

# Lippincott® Illustrated Reviews Pharmacology

South Asian Edition

Karen Whalen

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Sangeeta Sharma | Thirumurthy Velpandian

## Highlights

- Drug development and approval process
- Prescription writing
- Rational use of medicines and interventions
- Fixed-dose combinations
- Evaluation of response to drug therapy
- Drug–drug interactions
- Adverse drug reactions and their management
- Pharmacovigilance
- Updated treatment guidelines/goals—hypertension, hyperlipidemia, TB, snake bite, etc.
- Comprehensive tables on antipsychotic drugs, antiepileptic drugs, local anesthetics, antiarrhythmic drugs, antihypertensives, anticoagulants, etc.
- Updated drug list and drug information



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**Lippincott®**  
**Illustrated Reviews:**  
**Pharmacology**  
*South Asian Edition*



# Lippincott® Illustrated Reviews: Pharmacology

***South Asian Edition***

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# UNIT I

## Principles of Drug Therapy

# General Pharmacology, Pharmacotherapeutics, and Pharmacokinetics

1

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## I. GENERAL PHARMACOLOGY

The word “pharmacology” is derived from the words *pharmakon*, which means “drug” and *logus*, which means “science.” Pharmacology is the science of the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes. These substances may be chemicals administered to achieve a beneficial therapeutic effect on some process within the patient.

Pharmacology is the branch of medicine with a unique combination of several biomedical sciences—chemistry, biochemistry, physiology, and clinical medicine. Pharmacology is both a basic and an applied science. It forms the backbone of rational therapeutics. Pharmacology deals with the knowledge of drugs, their sources, biochemical and physiological effects, mechanism of action, and therapeutic uses of drug. Pharmacology studies the effects of drugs and how they exert their effects. For example, paracetamol can reduce body temperature in case of fever by inhibiting an enzyme known as cyclooxygenase in CNS, which is responsible for the synthesis of a number of inflammatory mediators. Penicillin cures certain bacterial infections by disrupting the synthesis of bacterial cell walls by inhibiting a key enzyme.

World Health Organization (WHO) in 1966 defined drugs as any substance or product which is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient, either therapeutic or diagnostic benefits.

Drugs are chemical substances which affect living organisms and are used by the clinician to diagnose, prevent, or cure diseases. So the safe use of drugs needs sound knowledge of their various aspects such as mechanism of action, doses, routes of administration, adverse drug affects, toxicity, and drug interactions.

The medicinal/organic chemists may create the candidate molecule or compound (also referred to as a new chemical entity [NCE]), and the pharmacologist test its pharmacological activity *in vitro*, in animals, and then in human beings, ultimately leading to the discovery of novel drugs for therapeutic intervention.

The general pharmacology involves the aspects of sources of drugs, route of administration of drugs, absorption of drugs and factors affecting them, their distribution, biotransformation, and excretion. It also involves the mechanism by which the drug is acting with receptor, toxicity of drug, and preclinical and clinical evaluation.

### A. Branches of pharmacology

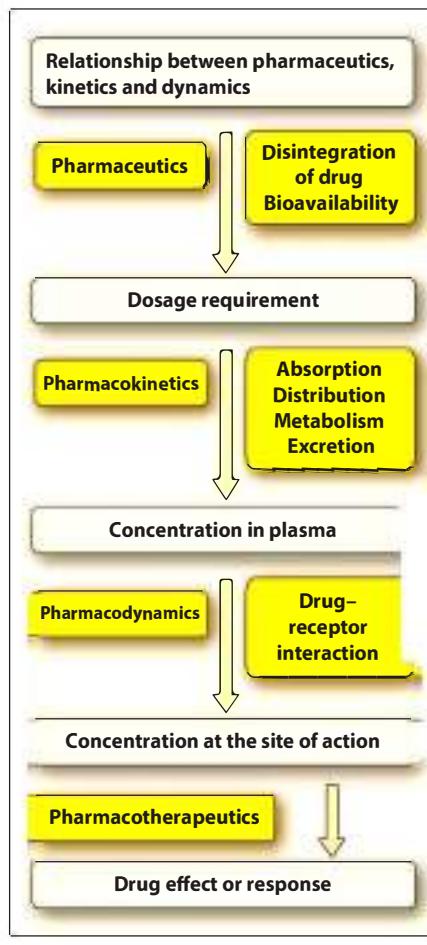
Pharmacology comprises two main branches: 1) pharmacokinetics and 2) pharmacodynamics.

- 1. Pharmacokinetics (what body does to drug):** It involves movement of drug and includes study of absorption, distribution, metabolism, and excretion of drugs. The study of what happens to the drug in the body is called pharmacokinetics. For example, *chlorpromazine* is absorbed at a faster rate by the parenteral route than the oral route; it binds with plasma and tissue protein and it is metabolized into the liver and is excreted in 15 to 30 hours.
- 2. Pharmacodynamics (what drug does to body):** It is a quantitative study of the biological and therapeutic effect of drug. For example, curare (a plant extract used by tribals as arrow poison) is a nondepolarizing blocker which rapidly produces muscle weakness and finally leads to skeletal muscle paralysis.

The relationship between pharmaceutics, pharmacokinetics, pharmacodynamics, and pharmacotherapeutics is depicted in [Figure 1.1](#).

### B. Other branches

- 1. Pharmacotherapeutics:** It is a branch of medicine which deals with clinical application of the pharmacokinetic and pharmacodynamic knowledge of the drug, in finding a cure of diseases or relief of symptoms. It includes use of drugs in the treatment, diagnosis, or prevention of a disease or their purposeful use in alteration of physiological functions for the benefit of the recipient.
- 2. Toxicology:** It is a science of poisons. Poisons are substances that are harmful and dangerous or show fatal symptoms in animals and human beings; many drugs in large dose act as poisons, for example, *aspirin* in less dose acts as an anticoagulant by inhibiting thromboxane A2; thus, it is useful for heart patients but in high dose causes ulceration and can lead to fatal bleeding.
- 3. Chemotherapy:** It is concerned with the effect of drug upon microorganisms and parasites, living and multiplying in living organisms. It is now also useful for the treatment of cancer by targeting cancerous cells.



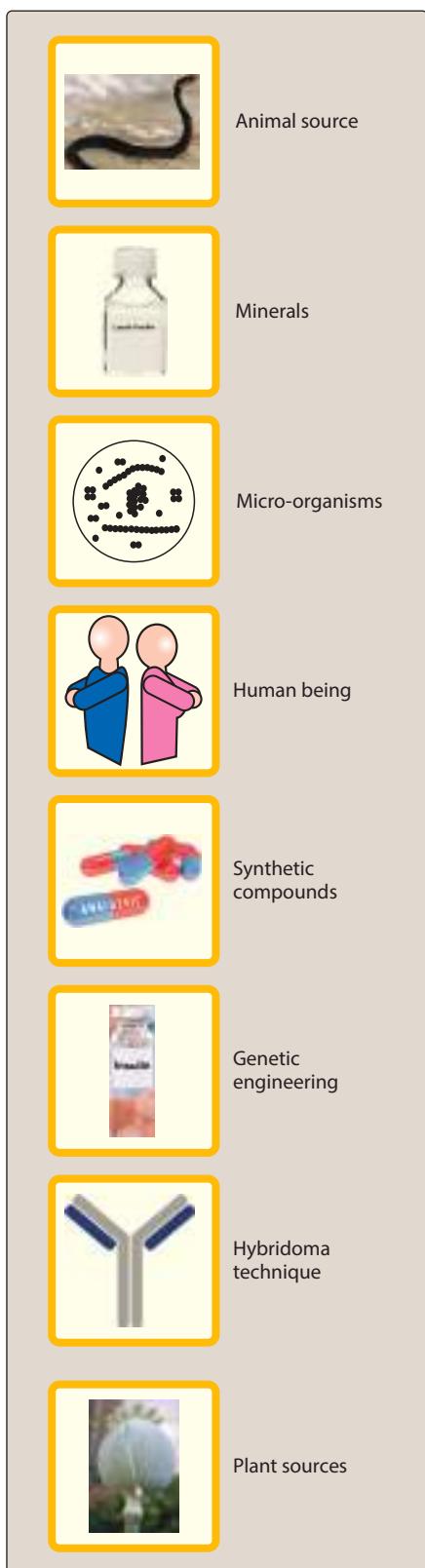
**Figure 1.1**

Relationship between pharmaceutics, pharmacokinetics, pharmacodynamics, and pharmacotherapeutics.

4. **Clinical pharmacology:** It is a branch of pharmacology dealing with drugs and their clinical use. It gives useful data about the potency, usefulness, doses, and toxicity of new drugs for their safe clinical use.
5. **Pharmacoepidemiology:** It is a study of the effect of the drugs on population.
6. **Pharmacoconomics:** It is a branch of pharmacology which studies the cost effectiveness of drug treatment and cost of medications, particularly among certain groups such as elderly and AIDS patients.
7. **Pharmacogenetics:** It is the study of the genetic variation that gives rise to differing response to drugs among individuals or populations. Some patients respond to certain drugs with greater than usual sensitivity to standard doses. Screening of individuals for a variety of such differences before prescribing may help in individualized therapy.
8. **Pharmacogenomics:** It is the application of genomic technologies to drug discovery and further characterization of older drugs.
9. **Pharmacognosy:** It deals with the study of the sources of drugs derived from plants and animal origin.
10. **Pharmacy:** It is the art and science of compounding or preparing suitable dosage forms for administration of drugs in man and animals and dispensing drugs. It also includes identification, selection, collection, purification, isolation, standardization, and quality control of medicinal substances.
11. **Clinical pharmacy:** It is a health science discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention.

### C. Definitions

1. **Pharmacopoeia:** It is an official reference containing a selected list of the established drugs and medicinal preparations with descriptions of their physical properties and tests for their identity, purity, and potency. It defines the standards of preparations. A few famous pharmacopoeia and other reference books are the British pharmacopoeia (BP), Indian Pharmacopoeia (IP), International Pharmacopoeia (IP), and United States Pharmacopoeia (USP).
2. **National formulary:** It provides product information on drugs available to prescribers in respective countries/states/health systems. For example, National Formulary of India is published by Government of India, and British National Formulary (BNF) is jointly published by British Medical Association (BMA) and the Royal Pharmaceutical Society.
3. **Essential medicines:** WHO defines Essential Medicines as those that satisfy the priority healthcare needs of the population. Essential medicines are intended to be available within the context of functioning health systems at all times and in adequate amounts, in appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford.
4. **Orphan drugs:** These are the drugs or vaccines or biological products for diagnosis, prevention, and treatment of a rare disease or

**Figure 1.2**

Sources of drugs.

a more common disease (but endemic only in poor countries) for which the pharmaceutical industry has little interest in developing and marketing products as they are intended for only a small number of patients. For drug companies, it means huge financial losses as this involves an extremely high cost of bringing a medicinal product to market which would not be recovered by the expected sales of the product. For ethical and legal reasons, clinical studies in children are severely restricted, but a number of rare diseases affect the very young population. Similarly, rare diseases which occur in small patient populations thus are “orphaned” by the pharmaceutical industry—that is, only a few approved drug treatment options available are called “orphan diseases.” Rare diseases or orphan diseases are those that manifest in patient populations representing at the maximum 6% to 8% of the world population, for example, genetic diseases—infantile spinal muscular atrophy, cystic fibrosis, patent ductus arteriosus (PDA), lysosomal storage disorders, familial adenomatous polyposis (FAP), and acute intermittent porphyria.

Some of the examples of orphaned drugs are *miglustat* used for Type 1 Gaucher disease, *iloprost* for pulmonary arterial hypertension in patients with NYHA Class III or IV symptoms, *bosantan* for WHO Class II–IV symptoms, *pegvisomant* used for acromegaly, and *busulfan* used for allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia. Various countries have enacted laws in this regard and provide incentives and support for drug development.

#### D. Sources of drugs (Figure 1.2)

Drugs are obtained mainly from plants, animals, microbes, and mineral sources. Nowadays, a majority of therapeutically used drugs are produced from synthetic or semisynthetic products. Various sources are given in the following text.

1. **Animal sources:** Insulin, heparin, gonadotrophins, thyroid extract, and antitoxic sera (for example, antivenom).
2. **Minerals:** Liquid paraffin, ferrous sulfate, magnesium sulfate, magnesium trisilicate, kaolin, etc.
3. **Microorganisms—bacteria and fungi:** *Penicillin*, *streptomycin*, *erythromycin*, *polymixin B*, *bacitracin*, *chloramphenicol*, *nystatin*, *griseofulvin*. Apart from antibiotics obtained from microorganisms, other products that are also produced by microorganisms include streptokinase, an enzyme from gram-positive cocci (*Streptococcus pyogenes*), and vitamin B<sub>12</sub> (cyanocobalamin), produced from *Streptomyces griseus*.
4. **Human beings:** These products are obtained from human beings. For example, immunoglobulins from blood, growth hormone from the pituitary gland, placental extract from placenta, and chorionic gonadotropin from the urine of pregnant women.
5. **Synthetic compounds:** Analgesics, antimicrobials, hypnotics, anticancer drugs, etc.
6. **Genetic engineering:** Human insulin, growth hormone, etc.
7. **Hybridoma technique:** Monoclonal antibodies, etc.

**8. Plant sources:** The pharmacologically active components in vegetable drugs are given in the following text.

**a. Alkaloids:** These are water-soluble salts of water-insoluble nitrogenous compounds. Some of the important alkaloids are as follows:

- Cinchona (Cinchona officinalis): *Quinine*, etc.
- Rauwolfia serpentina (root): *Reserpine*.
- Coca (Erythroxylum coca): *Cocaine*.
- Opium (Papaver somniferum): *Morphine group*.
- Belladonna (Atropa belladonna): *Atropine group*.
- Pilocarpus sp.: *Pilocarpine*.
- Vinca (Vinca rosea): *Vincristine, vinblastine*.

**b. Glycosides:** These are ether-like organic structure combined with sugars. The nonsugar component is called aglycone or genin. The important glycosides are as follows:

- Digitalis (Digitalis purpurea, Digitalis lanata): *Digoxin*, etc.
- Senna (Cassia acutifolia): *Sennoside*, etc.
- Strophanthus (Strophanthus kombe): *Strophanthin*, etc.

**c. Oils:**

**[1] Fixed oils:** These are glycerides of oleic, palmitic, and stearic acids. Mostly fixed oils are edible and used for cooking. The fixed oils used as drug are as follows:

- Castor (Ricinus communis): Castor oil.
- Olive (Olea europaea): Olive oil.
- Cocoa butter (Theobroma cacao): Theobroma oil used as emollient in skin cream and making suppositories.

**[2] Volatile oils:** These are essential oils which contain the hydrocarbon terpene. The important volatile oils are as follows:

- Turpentine oil, from species of pines, used as a counterirritant.
- Lemon oil (from citrus limon), used as a flavoring agent.
- Peppermint, cardamom, ginger, and fennel used as carminative and flavoring agents.
- Eucalyptus oil used for relieving congestion.
- Oil of clove mainly useful in toothache for relieving pain.

**d. Resins:** These are oxidized or polymerized volatile oils. The different types of resins are as follows:

- Oleoresins: A mixture of volatile oils and resins. Male fern extract used for tapeworm infestation.
- Gum resins: Asafetida, used as carminative and antispasmodic.
- Oleo gum resin: Myrrh—it has a local stimulant and anti-septic properties and generally used in mouthwash.
- Balsams: Benzoin, used internally as expectorant and externally as astringent.
- Balsam Tolu, used as stimulating expectorant.

- e. **Gums:** These are the secretory products of plants. On hydrolysis, they yield simple sugar-like polysaccharides. They are pharmacologically inert substances and mainly employed as a suspending and emulsifying agent in various pharmaceutical products. The widely used preparations are gum acacia and tragacanth.
- f. **Tannins:** These are non-nitrogenous constituents of plant. Chemically, these are phenolic derivatives and are characterized by their astringent action. Tannins are generally used in the treatment of diarrhea and burns. The important plants which contain tannins are Hirda (in combination form "Triphala"), Amla, Behera, Ashoka bark, Black catechu, etc.

### E. Drug nomenclature/naming of drugs

Drug nomenclature is a system of names that puts drugs into classification, as of anatomic structures, molecular entities, or organisms. The three broad name classifications of drugs are as follows:

- Chemical/molecular/scientific name
  - International nonproprietary/generic/approved name
  - Proprietary/brand/trade name
1. **Chemical/molecular/scientific name:** It depicts the chemical/molecular structure of the drug and states the structure in terms of atoms and molecules accompanied by a diagram of the chemical structure. Chemical or scientific names are complex, long, can be difficult to pronounce, and are useful to a few technically trained personnel. For example, acetyl-p-amino-phenol is a chemical name for *paracetamol*. This name is not suitable for routine use by medical professionals or common people. However, this name is very helpful for the discovery of new compounds.
  2. **International nonproprietary/generic/approved name:** The International Nonproprietary Name (INN) is an official generic and nonproprietary name given to a pharmaceutical drug—that is, this is the abbreviated and approved name of the drug. International nonproprietary names provide a unique standard name for each active ingredient, thus making communication more precise and avoid prescribing errors. Each drug's INN is unique. Drugs from the same therapeutic or chemical class are usually given names with the same stem. *-sartan* for angiotensin blockers (for example, *losartan*), *-azepam* suffix for benzodiazepines (for example, *lorazepam* and *diazepam*), *-pril* for ACE inhibitors (for example, *captopril*), and *ase* for enzymes (for example, *alteplase*). The nature of a drug can be easily identified by studying the suffix. WHO has laid down the general principles in naming a drug by the nonproprietary name. However, the nonproprietary name may sometimes vary from country to country. Usually, the British Approved Name (BAN) and the INN coincide, and where the two differed, the BAN was modified to match the INN with some exception where the nonproprietary name of some drugs in UK (BAN) and USA (USAN) is different (Figure 1.3).

BRITISH APPROVED NAME (BAN)	UNITED STATES APPROVED NAMES (USAN)
<i>Adrenaline</i>	<i>Epinephrine</i>
<i>Cinchocaine</i>	<i>Dibucaine</i>
<i>Dexamphetamine</i>	<i>Dextroamphetamine</i>
<i>Ergotametrine</i>	<i>Ergonovine</i>
<i>Glyceryl trinitrate</i>	<i>Nitroglycerin</i>
<i>Hyoscine</i>	<i>Scopolamine</i>
<i>Isoprenaline</i>	<i>Isoproterenol</i>
<i>Lignocaine</i>	<i>Lidocaine</i>
<i>Paracetamol</i>	<i>Acetaminophen</i>
<i>Pethidine</i>	<i>Meperidine</i>
<i>Phenobarbitone</i>	<i>Phenobarbital</i>
<i>Rifampicin</i>	<i>Rifampin</i>
<i>Suxamethonium</i>	<i>Succinylcholine</i>
<i>Thiopentone</i>	<i>Thiopental</i>
<i>Salbutamol</i>	<i>Albuterol</i>
<i>Furosemide</i>	<i>Furosemide</i>
<i>Paracetamol (Europe)</i>	<i>Acetaminophen</i>

**Figure 1.3**

Different nonproprietary names for the same drug by BAN and USAN.

The generic name can be used by anyone and it removes the confusion of giving several names to the same drug with the

same chemical structure regardless of who manufactures them. A generic drug name is not capitalized, for example, *aspirin* and *paracetamol*.

- 3. Proprietary/brand/trade name:** These are names given to the drug by the manufacturing and marketing company. The innovator company can then exclusively market and sell this “brand-name” product during the patent protection period. Copyright laws prevent any other person from using the brand name. On expiry of the patent life, a branded-name drug product is eligible to be manufactured and marketed as a “generic drug.” Trade name refers to a particular company and appears with the sign ® at its upper right corner which indicates that the name is registered and its production is restricted to that pharmaceutical company as the sole owner. For example, bronchodilator drug *salbutamol* is marketed as Asthalin; *metformin* is a generic name whereas Glyciphage is a brand name. In most cases, one drug could have so many trade/brand names, for example, *paracetamol* (*acetaminophen*) has more than 30 trade names; some of these are Crocin, Panadol, Calpol, etc.

A generic medicine is a legitimately produced medicine that is an exact copy of the innovator/originator product (branded medicine) and performs in exactly the same way. Though brand-name drug and its generic version must have the same active ingredient, dosage, strength, usage directions, safety, quality, performance, and use, it may differ in inactive ingredients, preservatives, color, shape, taste, and packaging. For example, generic and brand-name drugs must meet the exact same standards for equivalency in effectiveness, safety profile, and quality except cost. The difference in cost between a generic and a brand-name drug is mainly due to a difference in the development costs as manufacturers of the generic versions do not incur expenses on developing and marketing the generic version which is required for a new drug; thus, the manufacturers can produce the drug at a lower unit cost and sell it for less. Further, the competition keeps the prices of generic medicines down.

## F. Regulatory oversight

The Drug Regulatory Authority (DRA) oversees the approval and regulation of drugs. To market a prescription drug in any country, the manufacturer needs the approval of the DRA—that is, product licenses (known formally as Marketing Authorisations) permitting license holders to market medicinal products for specified indications under specified conditions. To get that approval, the manufacturer must demonstrate the drug’s safety and effectiveness according to criteria specified in law and agency regulations, ensure that its manufacturing plant passes DRA inspection, and obtain DRA approval for the drug’s labeling—that is, every license for a medicinal product contains information about the approved uses of the drug, including prescribing information for physicians, for example, dosage forms, packaging, therapeutic indications, doses, route of administration, contraindications, precautions for use or special warnings, adverse drug reactions, drug interactions, and patient brochures.

Almost all countries have established Drug Regulatory Authorities to assure the safety and effectiveness of Investigational New Drugs (IND)

through the evaluation of clinical pharmacology and biopharmaceutics data in support in the New Drug Application (NDA) and license application review programs.

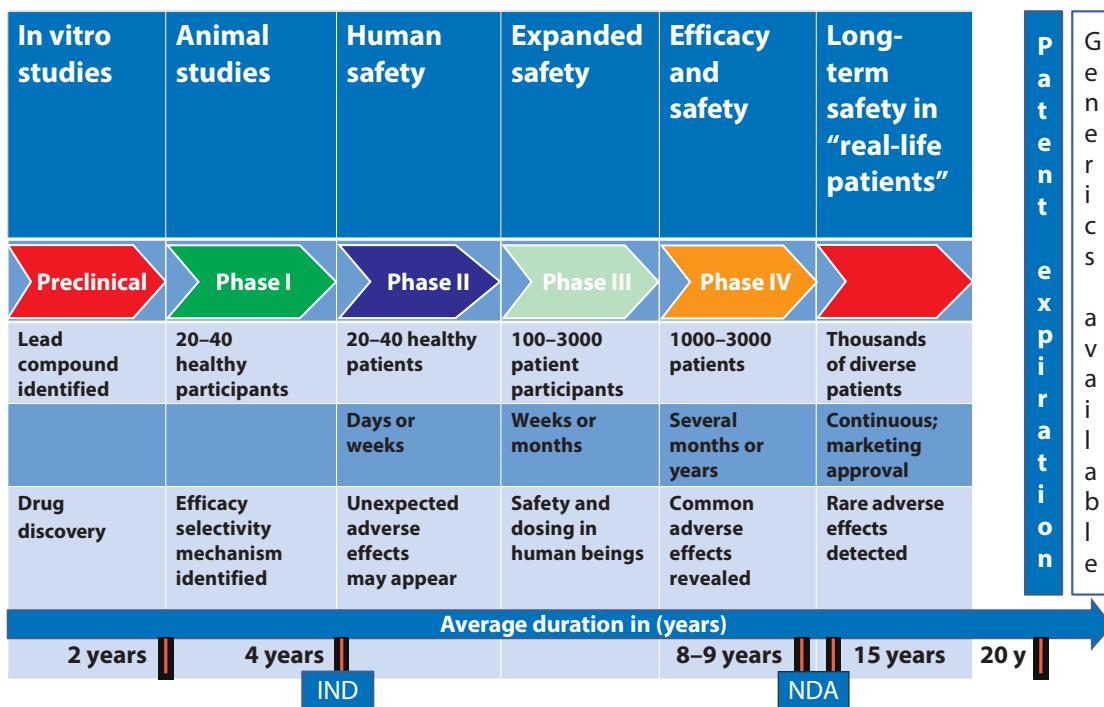
Regulatory oversight is necessary to prevent anyone from selling or freely advertising outrageous claims of benefit and safety including products containing *cocaine* or opioids (for example, *morphine*). Progressively stronger laws intended to ensure the effectiveness and safety of drugs sold in the country are needed. DRA is responsible for approval of new drugs, and medical devices as well as oversight of the drugs and medical devices already available in the market. This includes both prescription drugs and over-the-counter (OTC) drugs (drugs that do not require a prescription). Also, “dietary supplements” such as vitamins, amino acids, mineral, and herbal medication, even though most of these products have significant pharmacologic activity, are not regulated.

The states also participate in the process of drug regulation primarily by controlling the licensing of drug manufacturing premises and health professionals who can write drug prescriptions—that is, physicians, dentists, podiatrists, and veterinarians. Though nurse practitioners, physician's assistants, optometrists, and pharmacists can prescribe, they have limited prescribing authority.

## G. The drug development and approval process

The approval process for new drugs, especially drugs that are the first in a wholly new chemical class, is complex, time consuming, and expensive (up to \$100 to \$500 million dollars per new drug). Once a promising new candidate is identified, it is tested in preclinical studies (*in vitro* systems and experimental animals). Drugs that still look promising after these preclinical studies' application of investigational new drugs (IND) are filed with the DRA for testing in clinical trials first in healthy people (Phase 0 and I) and then in people with the target disease (Phases II and III). In phase 0, a very low dose of the drug is tested for the first time on human subjects (10 to 15 subjects). Based on the pharmacogenetic or pharmacodynamic properties, a decision on whether to start phase 1 or not is taken. These clinical trials assess safety and effectiveness in human beings. If the drug appears promising through three phases of clinical trials, the manufacturer files application for approval of NDA from DRA to market the drug. It is important that the manufacturer and the DRA continue postmarketing surveillance of new drugs (Phase IV) in real-life patients under diverse conditions for early detection of risk of toxicity that occurs rarely enough which escapes detection in the clinical trials setting.

1. **Preclinical and clinical phases of drug evaluation:** The drug development path and objectives of various phases of the clinical trials, the number of patients enrolled at each stage, and the approximate average time for each stage is shown in [Figure 1.4](#).
2. **Patent protection and generic drugs:** A company usually patents novel/new chemical entities early in the drug discovery process. Usually, patents provide 20 years of protection including the time from the filing of a patent application to NDA marketing approval which may be 5 years or longer. On expiry of the patent (that is, 20 years after filing application) companies other than the original patent holder can sell a generic drug, which is an exact copy of

**Figure 1.4**

Drug development path—phases of clinical trials. IND = Investigational new drug; NDA = new drug application.

a proprietary drug without paying license fees to the original patient owner. However, a trade name or the drug's proprietary name may be legally protected indefinitely. The process for approval by the DRA of a generic drug is much less cumbersome and less expensive than the process for approval of a new drug. Basically, generic product manufacturers just need to document that their drug has the same pharmacokinetic properties as the innovator/proprietary drug. Generic products usually cost significantly less than trade-named products; in some cases, the difference in the price of the trade-named products can be many folds higher.

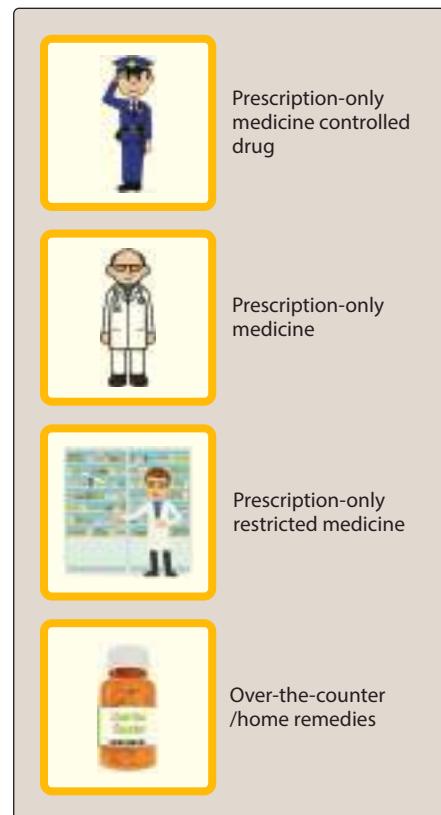
## H. Classification of drugs

A drug may be classified by the chemical structure of the active ingredient or according to its therapeutic use. Each drug can be classified into one or more drug classes (for example, laxative, analgesics, decongestants, relaxants, and antihypertensive) or system drugs affecting the cardiovascular system, gastrointestinal system, and neurological system.

### 1. Classification of drugs according to prescription (Figure 1.5):

Another classification system is according to prescription, based on the drug's potential for addiction and subsequent abuse. In India, medicines fall into four categories:

- Prescription-only medicine controlled drug (POM CD): Schedule X in India
- Prescription-only medicine (POM): Schedule H in India

**Figure 1.5**

Drugs according to prescription.

- Prescription-only restricted medicines: Schedule H1 in India
- Over-the-counter or home remedies: Tab. aspirin, paracetamol, analgesic balms, antacid preparations

The POM CD category is the most strictly controlled of the four, and the home remedy is the least strictly controlled. POM CD medicines have the potential for addiction, subsequent abuse, and causing harm and also have the potential of being obtained by illegal means. Narcotic and Psychotropic Substances (NDPS) Act prohibits certain activities in relation to "Controlled Drugs," in particular, their manufacture, purchase, transport, supply, and possession, and/or consume any narcotic drug or psychotropic substance. These legal controls govern how controlled medicines may be stored, supplied, and prescribed. Healthcare providers including nurses must follow standard operating procedures for procurement, storage, administration, and maintaining record of Schedule X medicines.

- a. **Prescription drugs:** A prescription drug is a pharmaceutical agent that legally requires a medical prescription from a healthcare professional to be dispensed or sold only to consumers possessing a valid prescription. In contrast, over-the-counter (nonprescription) drugs can be sold directly to a consumer or obtained without a prescription. In India, though there is no separate provision for OTC medicines in the Drugs and Cosmetics Act, the drugs, which have not been included in any of the Schedules, may be considered nonprescription or OTC drugs.

In India, Schedule H1 has been a newly introduced category imposing certain conditions in the dispensing of medicines in the list, which are somewhat midway between Schedule H (that stipulates retail dispensing only against a valid prescription) and Schedule X (that stipulates prescription in duplicate, separate license requirement, and meticulous storage and dispensing records). The schedule is primarily intended to control the rampant misuse through OTC dispensing of higher antibiotics, some of the reserved drugs such as second-line antitubercular drugs, and drugs with abuse/misuse potential in India.

- b. **Over-the-counter/home remedies:** These medicines have the least number of restrictions placed on them and can be sold in most shops or supermarkets without any intervention from a healthcare professional. These medicines tend to carry a low risk of harm if they are used according to the guidelines that accompany them, for example, vitamin supplements and mild analgesics. If they are used in larger than recommended doses, they can cause damage. However, for some medicines, such as *paracetamol*, there is a limit on the number of tablets that may be purchased at any one time.

## I. Pharmacotherapeutics

### 1. Rational use of medicines:

- a. **Definition:** Patients receive medications appropriate to their clinical needs, in doses that meet their own individual

requirements, for an adequate period of time, and at the lowest cost to them and their community (WHO, 1985).

Irrational or nonrational use is the use of medicines in a way that is not in accordance with the rational use of medicines as defined in the preceding text. Irrational use of medicines lead to ineffective and unsafe treatment, exacerbation or prolongation of illness, hospitalization sometimes, distress and harm to the patient, and higher cost of treatment. A wide variety of irrational drug uses that arise from prescription practices adopted by doctors are as follows:

- The use of too many medicines prescribed per patient (polypharmacy); often, these result in cross-reactions between different drugs prescribed.
- Inappropriate prescription of antimicrobials, often in inadequate dosage, for nonbacterial infections.
- Overprescription of injections when oral formulations would be more appropriate.
- Failure to prescribe in accordance with clinical guidelines: Wrong choice of drugs, inadequate dosages, incorrect frequency of administration of drug, improper duration of therapy, or failure to observe drug contraindications.
- Underuse of life-extending drugs for illnesses such as diabetes mellitus, hypertension, heart disease, asthma, epilepsy, and other chronic illnesses. Usually, these are situations where a small dose of the drug has to be taken in a fixed low periodicity, lifelong.
- Choice of more expensive drugs when less expensive drugs would be equally or more effective.
- Prescription of drugs which have no use, only for their placebo effect or for impressing the patient or for vested interests in the prescribed drugs.
- Inadequate consulting time and dispensing time along with poor communication of information regarding drugs to a patient in a verbal or written form leading to incorrect use by patients is of great public health concern too. Worldwide, more than 50% of all medicines are prescribed, dispensed, or sold inappropriately, while 50% of patients fail to take them correctly.
- Inappropriate self-medication of prescription-only medicines.

## **2. Impact of irrational use of medicines: Massive detrimental effects:**

- Ineffective treatment leading to serious morbidity and mortality, both in infections and in chronic diseases, such as hypertension, diabetes, epilepsy, and mental disorders. This would affect those more who are sicker or who are more vulnerable due to childhood, old age, or other morbidities.
- Iatrogenic diseases: Diseases caused by the choice of hazardous drugs or by the side effects of essential drugs and inessential drugs. As the number of drugs prescribed increases, the chances of adverse effects of drugs also increases.

- Inappropriate use and overuse of medicines leading to high out-of-pocket payments by patients and resulting in significant patient harm in terms of poor patient outcomes and adverse drug reactions and needless and avoidable impoverishment of the patient.
- Inappropriate use and overuse in the public sector facility, where the government pays the bills, leads to wastage of meager resources, and a shift of funds away from necessary expenditures to unnecessary areas.
- Availability of too many not-needed doubtful medicines in the market leads to lack of consistent supply of needed drugs and variation of individual prescribing preferences and inconsistent prescribing, leading to numerous prescribing and dispensing errors.
- Irrational overuse of medicines can further stimulate inappropriate patient demand, further compromising access to medicines and attendance rates due to medicine stock-outs and loss of patient confidence in the health system.
- Increasing antimicrobial resistance: Inappropriate use of antimicrobials is leading to increased antimicrobial resistance. Antimicrobial resistance (AMR) is one of the most serious public health problems globally resulting in prolonged illness and hospitalization, mortality, and higher costs. Use of drugs other than first-line drugs in such situations may increase costs (sometimes as high as 100-fold), makes treatment unaffordable for many governments/health systems, especially in developing countries, and increase in out-of-pocket expenditure by patients.

**Development and spread of antimicrobial resistance is due to:**

- overuse, misuse, and irrational use by doctors;
- noncompliance and self-medication by patients; and
- use in animal husbandry, aquaculture, and agriculture.

**3. Twelve core interventions to promote rational use of medicines:**

- Essential Medicines List and drug formulary based on that list
- Standard Treatment Guidelines
- Drugs and Therapeutics Committees in hospitals. This is a committee designated to ensure safe and effective use of medicines in hospital.
- In-service continuing medical and nursing and pharmacy education
- Rational drug use in undergraduate curricula
- Supervision, monitoring, audits
- Independent prescriber information on medicines
- Public education about medicines and awareness of essential drug concepts
- Procurement and logistics within the public health system
- Appropriate and enforced regulation
- Sufficient public health and public drug expenditure

**J. Drug information sources**

The quantity of medical information and medical literature available is growing at an overwhelming rate. Numerous resources of

information on medicines are available which include textbooks, medical journals, reference books, drug compendia, national medicines lists, essential medicines and treatment guidelines, drug formularies, drug bulletins, drug information centers, Internet, and the pharmaceutical industry. The technology by which this information can be accessed is also improving exponentially. The introduction of Internet resources, personal digital assistants (PDAs), and smartphones has radically changed the methods and technology of the way information is accessed. It is therefore important to evaluate the quality of information provided by each source.

Sources are considered primary, secondary, or tertiary depending on the originality of the information and their proximity or closeness to the source of information. Primary sources constitute papers or technical reports or case studies published in a journal article. Once published, the information may be commented on by other researchers and/or professionally indexed in a database that comprises secondary sources (for example, review article, textbook specialized to a narrow topic or a more broader overview, article indexes/databases such as Biological Abstracts/MEDLINE). Tertiary sources are when the information from primary and secondary sources is summarized into a textbook or full-text databases or reference book format, drug reference books, drug compendia, etc. Tertiary sources provide information about the established drugs as well as newer drugs and treatment options.

Generally, the best method to find authentic information includes a stepwise approach moving first through tertiary sources, then through secondary sources, and finally through primary source literature. The tertiary source initially provides the required information to familiarize the reader with the topic, the disease or drug in question, which will ultimately result in a more structured and productive and effective search. In case the information obtained from the tertiary resources is not recent or comprehensive enough, a secondary database may be employed.

Primary resources include published meta-analyses, randomized controlled trials, observational trials, and case reports. There is a wide range of journals available that can assist one in keeping up to date in the different aspects of medical practice. The information obtained from this literature is the basis for developing guidelines for evidence-based practice. Although good medical journals are peer-reviewed, a review article or researched study appearing in print does not necessarily mean good science. Though primary resources are most up-to-date information, they require critical skills in interpretation and evaluation of the strength of evidence (described as above). Moreover, decisions should not be based on a single piece of evidence, but rather on a compilation of all the available evidence.

**1. Internet sources of drug information:** The Internet is the most readily accessible and widely used source of information including primary, secondary, and tertiary data but due to the unregulated nature of the Internet, it is of utmost importance to critically evaluate information obtained by this method. With the increasing popularity of the Internet, many primary resources may be accessed directly from the web site of the publisher or medical or a pharmacy journal. The majority of journals require a subscription but some journals may be open access. Often, access to the abstract is free of charge even in subscription journals. Due to the

limited information provided and inherent bias in an abstract, it is critical to ascertain whether obtaining the article may be of value before making a therapeutic decision.

## K. Essential Medicines List

Essential medicines are those that satisfy the priority healthcare needs of the population. They are selected with due regard to disease prevalence, evidence on efficacy, safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford.

Implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains the responsibility of states within a national framework.

Essential drugs are neither to be understood as only consisting of life-saving drugs nor as medicines for the treatment of rare diseases. The concept of essential drugs includes all the drugs needed for most commonly encountered diseases including life-saving conditions. The concept was mentioned in 1 of the 10 points of the 1978 Alma Ata Declaration on primary health care.

**1. Impact of essential medicines:** A limited range of carefully selected essential medicines leads to

- better health care,
- better drug management and health outcome (including procurement, storage and distribution, and improved quality of prescribed medicines),
- cost-effective use of health resources.

Access to essential drugs, high expenditure on drugs, and irrational competition of unscientific or even hazardous drugs are the three problems people face and public systems are challenged to response to. Nonavailability of medicines can block the operation of the healthcare system. Attendance at health services, credibility, and effectiveness of the healthcare system depend to a large extent on the patient being able to obtain relevant drugs at the right time. A patient values services only if he/she obtains necessary treatment and medicines. A good diagnosis is of not much use if the patient cannot obtain the necessary treatment.

The WHO Model List of Essential Medicines is a list of essential medicines created by the World Health Organization (WHO) which serves as a guide for the development of national and institutional Essential Medicine Lists (EML). It is updated and revised every 2 years by the WHO Expert Committee on Selection and Use of Medicines. The list was first published in 1977. Since 2007, a separate list for children up to 12 years (WHO Model List of Essential Medicines for Children) is being brought out. The 18th edition for adults and the 4th edition for children were released in April 2013. The WHO EML has steadily grown in terms of the number of drugs included in the list with each update. Initially in

1977, the WHO EML had 204 molecules and the current list of 2013 includes 374 unique molecules. The 2013 WHO EML has 431 molecules with duplications across indications and includes both core and complimentary medicines.

Worldwide, the concept of essential medicines has been accepted as a powerful tool to promote health equity and its impact is remarkable, as essential medicines are considered to be one of the most cost-effective elements in health care. This model WHO EML is customizable to clinical guidelines for healthcare practice, to region-specific public health issues, to least costly or most accessible therapeutic equivalent, and can be implemented on a country, state, or institutional level.

2. **Formulary system:** The formulary system is a mechanism for the ongoing assessment of availability of medicines to assure safe and effective use of drugs in a cost-conscious manner. The formulary process is the cornerstone of good pharmaceutical management and safe use of medicines. A formulary list (also referred to as Essential Medicines List) is a limited list of the most cost-effective, safe, and available medicines of assured quality which meets the priority health needs of the population. A formulary manual is developed and maintained based on the recommended treatments from Standard Treatment Guidelines, using explicit drug selection criteria (relative efficacy, safety, suitability, and cost).

The formulary process consists of preparing, using, and updating a formulary list, a formulary manual (providing information on drugs in the formulary list), and Standard Treatment Guidelines (choosing the most appropriate therapies, STGs) in a hospital.

The benefits that arise from a limited range of carefully selected medicines are numerous and well known and include improved drug therapy, decreased adverse drug reactions (ADRs), better health care, better drug management and health outcome (including efficiency in procurement, inventory management, storage and distribution, and improved quality of prescribed medicines), and decreased overall healthcare cost. The advantages of the drug formulary list are given in **Figure 1.6**. Carefully selected essential medicines lead to cost-effective use of health resources. The formulary concept is intended to be flexible and adaptable to many different situations. Exactly which medicines are regarded as essential remains a national responsibility as well as an individual hospital responsibility. The selection of essential medicines, preferably linked to Standard Clinical Guidelines, is a crucial step in ensuring access to health care and in promoting rational use by health professionals and consumers.

The factors that are critical to the use of a hospital formulary by health workers are their involvement in the development and updating process, the quality of the content, a user-friendly format, and adequate distribution and follow-up supervision.

The process by which the medicines are selected is critical to its acceptance by the prescribers. An essential medicines list which is imposed from above and does not reflect the needs of the users will not be accepted and used by the prescribers. It is therefore very important that the formulary development process be consultative and transparent and that the selection be based on explicit criteria

### Improving Health Outcomes

The primary advantage is that it provides a systematic method to review scientific evidence on clinical effectiveness and cost effectiveness in drug selection decision, thus potentially improving health outcomes while reducing costs.

### Efficient Pharmacy Management

It is difficult to achieve efficiency in the hospital pharmaceutical system if there are too many brands of the same medicines. All aspects of drug management, including procurement, storage, distribution, and use, are easier if fewer items are to be dealt with, there are fewer stockouts, there is containment of inventory cost, and it can lead to improved drug availability in hospitals. It also improves efficiency and reduce confusion and thereby medication errors.

### Improved Quality of Care

Patients are treated with fewer but more cost-effective medicines for which information can be better provided. The doctors gain more experience with fewer drugs and recognize drug interactions and adverse drug reactions better. Quality of care will be further improved if medicine selection is based on evidence-based treatment guidelines.

**Figure 1.6**

Advantages of drug formulary list.

Drugs are selected depending on many factors, such as the pattern of prevalent diseases, treatment facilities, training and experience of available personnel, financial resources, and genetic, demographic, and environmental factors. WHO (1999) has developed the following selection criteria:

- Only those medicines should be selected for which sound adequate data on efficacy and safety are available from clinical studies and for which evidence of performance in general use in a variety of medical settings in terms of efficacy, suitability, safety, and cost effectiveness has been obtained (Figure 1.8).
- Each selected medicine must be available in a form in which adequate quality, including bioavailability, can be assured; its stability under the anticipated conditions of storage and use must be established.
- When two or more medicines appear to be similar in the above respects, the choice between them should be made on the basis of a careful evaluation of their relative efficacy, safety, quality, price, and availability.
- In cost comparison between medicines, not only the cost of the total treatment but also the unit cost of the medicine must be considered. In cases where drugs are not entirely similar, the selection should be made on the basis of a cost-effectiveness analysis.
- In some cases, the choice may also be influenced by other factors, such as pharmacokinetic properties, or by local considerations, such as the availability of facilities for storage or manufacturer.
- Most essential medicines should be formulated as single compounds. Fixed-ratio combination products are acceptable only when the dosage of each ingredient meets the requirements of a defined population and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, or compliance.
- Drugs are specified by the international nonproprietary name (INN) or generic name without reference to brand names or specific manufacturers.

**Figure 1.7**

Criteria in selection of medicines for hospital formulary.

For example, SIGN—Scottish Intercollegiate Guidelines Network

- (1++) High-quality meta analysis, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias.
- (1+) Well-conducted meta analysis, systematic reviews of RCTs, or RCTs with a low risk of bias.
- (1) Meta analysis or systematic reviews of RCTs or RCTs with a high risk of bias.
- (2++) High-quality systematic reviews of case-control or cohort studies; or high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.

**Figure 1.8**

Categories/levels of evidence.  
(Figure continues on next page)

(based on efficacy, safety, quality, cost [which will vary locally]) and cost-effectiveness. Figure 1.7 depicts the criteria for selection of medicines for hospital formulary. Finally, selection of the medicines should be linked to evidence-based Standard Clinical Guidelines. Evidence-Based Medicine (EBM) is defined as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient.” EBM is the integration of the best available clinical evidence with an individual’s clinical expertise and patient’s values and expectations. The hierarchy of evidence is shown in Figure 1.8. Figure 1.9 shows categories/levels of evidence. Grading of quality of evidence tells us the extent to which one can be confident that an estimate of the effect is correct and provides confidence that the estimates are adequate to support a particular recommendation (Figure 1.9).

## L. Prescription writing

Prescription is a medicolegal document written by a physician, dentist, or any other medical practitioner to the pharmacist giving directions to compound and dispense a specific medication for an individual patient. Prescription is actually a direct link between the physician, pharmacist, and patient. Over the years, the demand for individually compounded medicines has declined; therefore, pharmacists largely perform the role of filling prescription and patient education ensuring safe and appropriate use by the patient.

1. **The prescription:** The prescription must be accurately and legibly written and identify the patient, the prescriber, the medication to

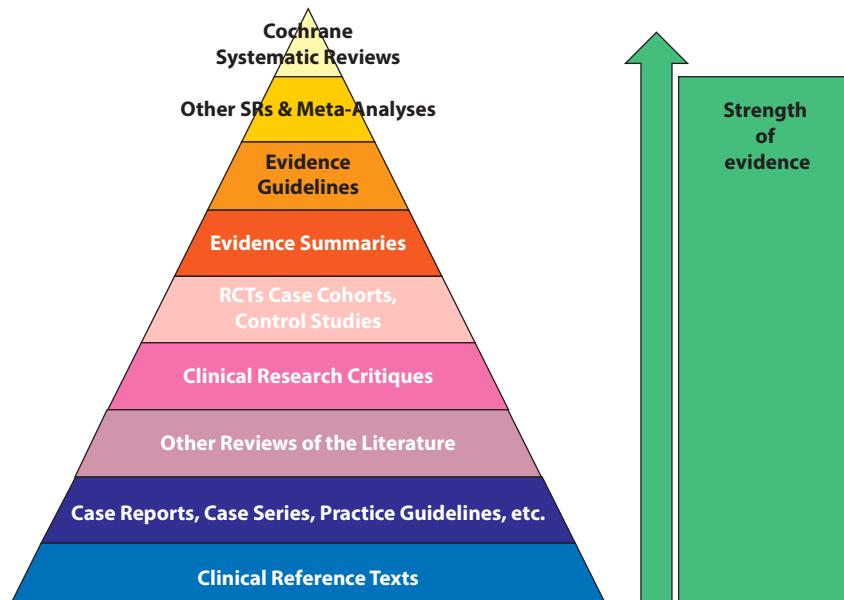
be dispensed, the mode of drug administration, and the duration of treatment. Avoid abbreviations and Latin as they lead to dispensing errors. The prescription should also include the therapeutic purpose in the subscription (for example, “for control of blood pressure”; use of *metformin* for the “control of sugar”; *losartan* for the treatment of hypertension) to prevent errors in dispensing. Further including the therapeutic purpose of the prescription can also empower patients and improve compliance with therapy. Moreover, inclusion of the patient’s weight on the prescription, especially in children, can be useful in avoiding dosing errors.

a. **Parts of prescription:** The prescription consists of the *superscription*, the *inscription*, the *subscription*, the *signa*, and the *name and signature of the prescriber*, all contained on a single form.

- [1] **Superscription:** The superscription includes the date of the prescription; personal data of the patient—name, address, weight, and age of the patient; and the Rx. Rx is an abbreviation for the Latin word “recipere” or “recipe,” which means “Take, thou.” The symbol is said to designate Jupiter “The God of Healing.”
  - [2] **Inscription:** It is a main part of the prescription. It contains the name, dosage form (such as “tablet,” “oral solution,” “injection,” “eye ointment”), amount or strength, and number of doses or quantity of the drug to be dispensed. It also contains a manner in which the medicine should be taken.
  - [3] **Subscription:** The *signa* or “Sig” is the instruction for the patient (for example, how to take the medicines, interpreted, and transposed onto the prescription label by the pharmacist).
- Historically, this was an instruction to the pharmacist to compound medications (for example, instructions

- (2+) Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
- (2) Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
- (3) Nonanalytic studies, for example, case reports.
- (4) Expert opinion.

**Figure 1.8** (Continued)  
Categories/levels of evidence.



LEVEL	DEFINITION
High	Very confident that the true effect lies close to that of the estimate of effect
Moderate	Moderately confident that the true effect is likely to be close to the estimate of effect; but there is a possibility that it is substantially different
Very low	Confidence in the effect estimate is limited: the true effect may be substantially different
Low	Very little confidence in the effect estimate: the true effect is likely to be substantially different

**Figure 1.9**

Evidence-based medicine pyramid.

Name: XYZ  
Age: 60 years  
Sex: Female  
Date: 7/05/18

Diagnosis: Parkinsonism

Rx

Tab Levodopa 100 mg plus  
Tab Carbidopa 25 mg 2 tablets  
by mouth 3 times daily for one  
month. Take with food.

Dr. XYZ

Assistant Professor of Neurology,  
Reg. No. 1345  
Date

regarding the fortification of *tobramycin* eye drops for treating a corneal ulcer) since these days, most medications are pre-compounded preparations. Subscription now indicates the quantity of medication (number of capsules or tablets) such as “dispense 30 tablets” or the size of the bottle to be dispensed (5 mL, 10 mL, or 15 mL). Typically, Latin or English abbreviations are used to provide specific instructions translated by the pharmacist for patient use. Typical instructions on the prescription used to include use of Latin abbreviations such as BD for twice daily, TDS for thrice daily, HS at night, and SOS for as and when required. It also provides for the number of refills the patient should need to complete the cycle of drug treatment. Most antibiotic and steroid prescriptions need no refills or one refill only.

- [4] **Signature of the physician:** The prescription must be signed in the prescriber's own hand and dated. Address, telephone number, and registration number should be clearly stated in the prescription which could either be preprinted on the prescription or stamped with all these details. This will allow either the patient or the dispenser to contact the prescriber for any clarification or potential problem with the prescription.

Prescriptions should preferably be written in the dominant language of the patient or English. Latin is no longer the international language of medicine, but a number of prescribers continue to use obsolete Latin usage. Avoid using them. Latin abbreviations, for example, “1 cap q1d,” should be interpreted by the pharmacist as “take one capsule once a day” but this can easily be mistaken for QID leading to four times the dose. Clear and explicit directions specifying the route, dose, and frequency should be written; avoid using of phrases such as “take as directed” or “take as before.” For medicines which are to be taken on an “as required” basis, the minimum dose interval should be stated together along with the maximum permissible daily dose. It is a good practice to qualify such prescriptions with the purpose of the medication (for example, “every 6 hours as required for pain” or “at night as required to sleep”). It is a good dispensing practice to explain these directions to the patient; these directions should then be reinforced by the label on the medicine.

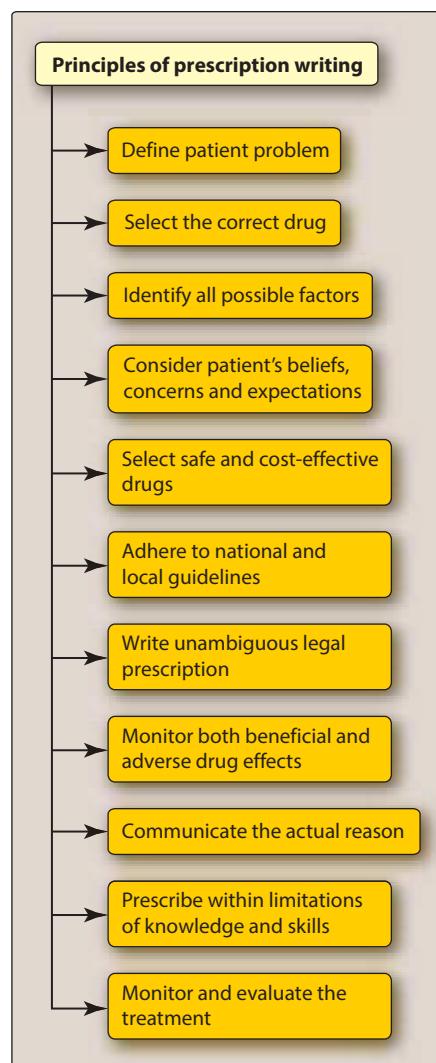
- [5] **Quantity to be dispensed:** The quantity of the medicine to be supplied should be clearly stated in such a manner that it does not get confused with either the strength of the product or the dosage directions. Alternatively, the length of the treatment course may be stated (for example, “for 5 days”). Whenever possible, the quantity dispensed should be adjusted to avoid strip cutting. Medicines with a single-dose regimen should be procured matching the pack size facilitating dispensing of single dose (without strip cutting) or in other cases adjusted to match the available pack size (for

example, if medicines are prescribed in a dose of three times a day for 7 days which makes the total quantity to be dispensed as 21 tablets and the available pack size is of 10 tablets in each strip, then 20 tablets could be dispensed to avoid strip cutting). Strip cutting is an error-prone activity and can be dangerous if it involves high-alert or look-alike, sound-alike drug. For liquid preparations, the quantity should be stated in milliliters (abbreviated as "ml") or liters (abbreviated as "L," since the letter "l" could be confused with the figure "1").

**[6] Narcotics and controlled substances:** The prescribing of a medicine that is liable to abuse requires special attention and may be subject to specific statutory requirements. Practitioners may need authorization to prescribe controlled substances; in such cases, it might be necessary to indicate details of the authority on the prescription. In particular, the strength, directions, and the quantity of the controlled substance to be dispensed should be stated clearly, with all quantities written in words as well as in figures to prevent alteration. Other details such as patient particulars and date should also be filled in carefully to avoid alteration and unauthorized refills. The prescription for controlled substances is valid for up to 14 days. The prescription for narcotics should be rewritten and should not be refilled by "continue same treatment as above."

**[7] Off-label prescribing:** "Off-label" means the licensed medicine is used in a manner not specified in the DRA's approved packaging label or insert. For example, botulinum toxin has been approved for use in treatment of spasm but its use to treat migraine is off-label use; chemotherapy is approved to treat one type of cancer, but if it is used to treat a different type of cancer or when given in a different way from the approved dose or dosage form, it would amount to off-label use.

**2. Principles of prescription writing (Figure 1.10):** In modern medicine, prescribing medicines is the main approach to the treatment and prevention of disease. Though medicines have the capacity to enhance health or sometimes are life-saving, at the same time all have the potential to cause harm and could be life-threatening, if used inappropriately (for example, adverse drug reactions, under- or overdose, and medication errors). One of the basic principles in treatment is "First do no harm" as stated by Hippocrates. Stories of medical remedies causing more harm than good have been recorded from time immemorial. An iatrogenic disorder occurs when the deleterious effects of the therapeutic or diagnostic regimen cause pathology independent of the condition for which the initial regimen was advised, for example, extrapyramidal symptoms seen with antipsychotic agents. Iatrogenic disease is one of the most frequent causes of hospital admissions and constitutes a growing public health problem. Polypharmacy (patients receiving multiple drugs) and potentially inappropriate medications have been associated with many negative health outcomes, including adverse drug reactions, falls, nonadherence, reduced quality of



**Figure 1.10**

Principles of prescription writing.

life, addiction, hospitalizations, and mortality. Efficacy and safety do not lie solely with the drug but the successful pharmacotherapy depends on the application of pharmacodynamic and pharmacokinetic principles in light of knowledge gained in clinical medicine. It requires critical thinking skills to maximize therapeutic benefits weighing drug- and patient-related variables.

Certain principles of prescription writing have been laid out as below for safe use of medicines:

**a. Define the patient's problem and be clear about the reasons for prescribing:**

- Establish an accurate diagnosis (although this may at times be difficult) whenever possible.
- Specify a clear therapeutic objective based on the underlying pathophysiology. Sometime, more than one therapeutic goal may be set for a given patient.
- Select the therapeutic strategy. It should be a shared decision involving patients.

The select treatment can be nonpharmacological and/or pharmacological. Nonpharmacological treatment is equally important as very often, health problems can be resolved by a change in lifestyle, diet, exercise, or psychological support.

**b. Select the correct drug considering the patient's history before prescribing:**

- Obtain an accurate list of current and recent medications (including over-the-counter and alternative medicines) and a history of prior adverse drug reactions and drug allergies and undertake medication reconciliation, especially at transition points.
- Drugs sometimes are a cause of a disease but withdrawal of drug, if abrupt, can also cause disease. For example, sudden withdrawal of benzodiazepines and antiepileptic agents can lead to withdrawal syndrome.
- The sources of this information/history may come from patients, family/carers, or other healthcare practitioners.

**c. Identify other factors that might alter the benefits and risks of treatment:**

- Consider individual risk factors that might influence the prescription (for example, genetics, physiological changes with age and pregnancy, concomitant diseases, or impaired liver, kidney, or heart function).

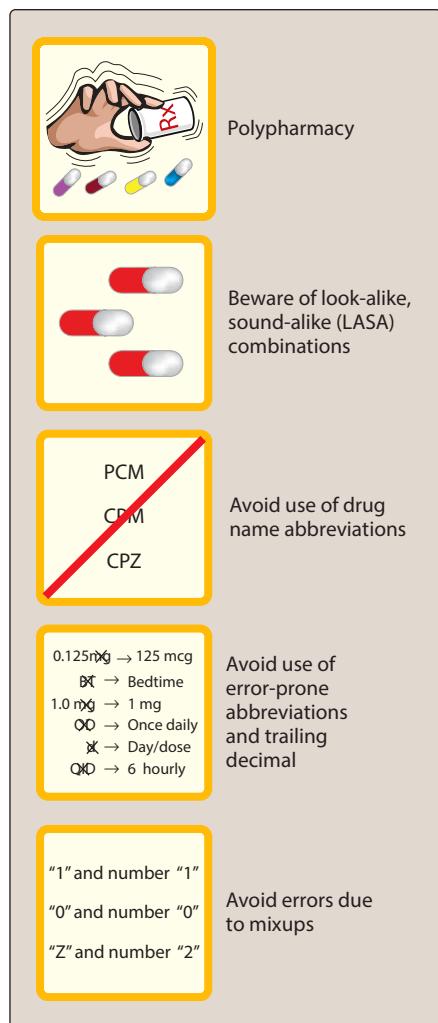
**d. Take into consideration the patient's beliefs, concerns, and expectations:**

- While selecting treatments, make sure that the patient understands and agrees with the reasons for taking the medication.

**e. Select efficacious, safe, and cost-effective drugs appropriate for the patient:**

- The likely beneficial effects of a drug should outweigh any potential harms. At the same time, also consider the likely harms of treating versus likely harms of not treating, whenever possible, this decision should be based on published evidence.

- Choose the most suitable formulation, dose, frequency, route of administration, and duration of treatment.
  - Prescribe medicines for their approved indications only. Pay special attention to drugs that are liable to abuse which come under specific statutory requirements. Do not prescribe medicines for conditions other than those approved by the DRA (also called “off-label” use) or outside standard practice as far as possible unless satisfied that no effective alternative is available or when available would not meet the patient’s needs. This decision should be based on explicit evidence and/or experience of the likely benefit-harm balance of all available options.
  - In most cases, treatment should be started with a low dose and the dose gradually increased by monitoring the patient’s response or a loading dose may be administered as may be needed (for example, glucocorticosteroids, *phenytoin*, *valproic acid*, *warfarin*, and *amiodarone*).
- f. **Adhere to the national or local guidelines where appropriate:**
- Be aware of evidence-based recommendations developed by respected professional organizations.
  - Balance specific drug selection considering the needs of the patient and cost and verify the suitability of the chosen medicine for each patient. Select medicine may be the best medicines for a given patient; however, a final decision while selecting medicines should be taken with regard to overall costs and needs of other patients considering public health requirements as healthcare resources are finite.
  - Access, identify, and use only reliable and validated sources of information, and evaluate potentially less reliable, such as Internet, information critically.
- g. **Write unambiguous legal prescriptions using the correct documentation:**
- Write the drug name by the generic name in Capitals.
  - Be aware of the medicines and common factors that cause medication errors (such as high-alert, look-alike and sound-alike medicine [LASA], and abbreviations) and know how to avoid them.
  - Avoid abbreviations and Latin to prevent dispensing errors. Do not write abbreviated drug names.
  - Do not use unapproved, nonstandard, or error-prone abbreviations, symbols, and dose designations. Avoid decimal wherever possible (write 125 micrograms instead of 1.25 mg) and do not write naked or trailing decimals (for example, “.5 or 1.0” mg). Do not abbreviate micrograms and nanograms. State strength in standard units using abbreviations those are consistent with the System Internationale (SI). Further, hand-written U can easily be mistaken for “0 or 4.”
- h. **Monitor both the beneficial and the adverse drug effects of medicines:**
- Understand how to alter the therapeutic regimen as a result of this information.
  - Know the system to report adverse drug reactions.

**Figure 1.11**

Risk factors of medication errors.

i. **Communicate the reasons for and document prescribing decisions:**

- Communicate clearly with the patient as well as the pharmacist in the language which the patient understands.
- Give information to patients about how to take the medicine correctly, its potential benefits, and adverse effects (especially those that will require urgent attention), and any monitoring that is required. Use patient education aids when possible, such as patient information leaflets, dose organizers, and posters.
- Document prescribing decisions in the health record accurately and in real time.

j. **Prescribe within your limitations of knowledge, skills, and experience:**

- Always keep relevant knowledge and skills up to date.
- Be prepared to seek the advice and support of qualified professional colleagues, if required.
- Verify all information on prescriptions before handing over to the patient.

k. **Monitoring treatment and de-prescribing or de-escalation when necessary:**

- Evaluate the outcome of treatment on follow-up visits to allow the stopping of the drug (if the patient's problem is solved) or to modify it when necessary providing important information about the adverse effects of drugs contributing to building up the body of knowledge of pharmacovigilance and promoting rational use of drugs.
- De-prescribing is a process of tapering, discontinuing, or withdrawing unnecessary drugs with the goal of managing polypharmacy and improving patient outcomes. The process of de-prescribing can be planned and supervised by healthcare professionals.

## M. Medication errors

Every step in patient care involves a potential for error and some degree of risk to patient safety. Errors in ambulatory and ICU prescribing are a major public health problem. On average, more than one medication error each day is expected. The real key to patient safety is reducing or eliminating harm to patients. Medication error can occur in the process of ordering, transcribing, dispensing, administering, and monitoring of medication. A medication error may or may not result in an actual adverse drug event.

1. **Risk factors (Figure 1.11):**

- Polypharmacy and irrational use of medicines:** Polypharmacy is the largest risk factor, which on one hand increases the chance of adverse drug reactions and on the other hand makes it vulnerable to medication errors.
- Look-alike, sound-alike (LASA) combinations:** Confusing drug names, particularly sound-alike names, is one of the most common causes of medication error and is of concern worldwide. This includes confusion between nonproprietary

names and proprietary (brand or trademarked) names. Many drug names look or sound like other drug names (for example, Glynase [glyburide], and Zinase [combination of diclofenac potassium and serratiopeptidase]; Daonil [*glibenclamide*], Duodil [*chlorzoxazone*], and Diovol [antacid]; Lasix [*furosemide*], and Lorax [*lorazepam*]). Illegible handwriting and incomplete knowledge of drug names further add to this confusion. Availability of the products with similar packaging or labeling, and the failure of manufacturers and regulatory authorities to recognize prior to approving new product names and packing continue to threaten prescribing and administration errors.

- c. **Use of abbreviations for drug names:** Acronyms such as PCM (*paracetamol*), CPM (*chlorpheniramine*), CPZ (*chlorpromazine*), CBZ (*carbamazepine*), THP (*trihexyphenidyl*), TFP (*trifluoperazine*), ASA (*aspirin*), and 5-ASA (5-amino salicylic acid) are an important source of errors. Moreover, a prescription is a medicolegal document, and these acronyms are not standard abbreviations used by all and may be interpreted differently, for example, MS (magnesium sulfate or morphine sulfate). The full drug name should be written out.
- d. **Use of error-prone abbreviations:** Use of error-prone abbreviations, symbols, and dose designations.
- e. **Errors due to mixups:** Between “l” and the number “1”; “O” and “0”; “Z” and “2”; “1” and “7.” For example, Q1d can easily be mistaken for QID leading to four times the dose and hand-written “U” could easily be interpreted as “0 or 4.” Therefore, “Unit” should always be written.

## N. Irrational, nonessential, and hazardous drugs in the market

Tremendous transformation has been witnessed in the pharmaceutical industry since the 1950s leading to its increasing profits; at the same time, huge numbers of irrational, nonessential, and hazardous drugs have flooded the market. It needs to be clearly understood that as little as about 300 to 400 pharmaceuticals are capable of providing all the useful therapeutic value that any medicine can provide for any type of illness. This is what the “Essential Medicines List” is really. Even if we include a number of drugs which are safe and efficacious but duplicate the effects provided by one of these 300 chemicals, still we should have maximum 750 to 1000 drugs on Essential Medicines List. Yet, it is estimated that there are as many as 70,000 formulations available in the market today. This is a source of tremendous confusion for both the doctors and the patients, since in any case the patients would have little knowledge of what drug has been prescribed to them and even doctors would not easily be able to interpret the prescription of another doctor. It is estimated that as many as 90% of the drugs sold in the market today and consumed by people are the same essential drugs being sold under different brand names, or they may be inessential drugs, or worse they may even be irrational/unscientific or hazardous drugs.

1. **Sources of these drugs:** Most formulations are brand names given by companies for the same drug. Another large set of

**Figure 1.12**

Commonly available fixed-dose combinations.

formulations are what are called fixed-dose combinations (FDCs) of one or more of the drugs.

It must be noted that except for about 10 drug combinations where there is a pharmacologic synergy in combining the drugs in a certain dosage form, most FDCs are irrational and inadvisable. This is because the dose of each of the drugs in the combination may have to be altered at different rates at different times, or because the combination is with an inessential or even hazardous drug.

Combinations of allopathic drugs with AYUSH drugs, almost all of which are neither tested nor certified, form another major group of irrational drugs. Another large set of formulations are made of drugs which have no therapeutic value or have much less value than the generic preparation of the active ingredient. A large number of cough syrups, pain killers, tonics, gripe waters, digestives, energizers, and so on are examples of this category (**Figure 1.12**).

Another large set are basically drugs which are minor and less effective drugs, or more hazardous drugs, or more costly variants of other active drugs available for that purpose. Most of these drugs comprise antibiotics, vitamins, and anti-inflammatory analgesics. There are also, surprisingly, a number of drugs that have been clearly banned by the Drug Control Authority of India, but which still continue to be available in the market and continue to be prescribed/used. Most of them are there through some weakness in the banning order or some technical device that has been used to contravene the order.

## O. Fixed-dose combinations

Fixed-dose combinations (FDCs) are formulations of two or more active ingredients combined in a single dosage form available in certain fixed doses. Fixed ratio combination products are acceptable only when the dosage of each ingredient meets the requirement of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, or compliance (*The Use of Essential Drugs. Model List of Essential Drugs [Seventh List]. Fifth report of the WHO Expert Committee. World Health Organ Tech Rep Ser. 1992; 825:1-75*). FDCs by simplifying the medication regimen may improve medication compliance by reducing the pill burden of patients. ***However the data on comparison of fixed-dose combination with free-drug regimen to improve a patient's medication compliance is limited*** except in some conditions only in patients with chronic conditions like hypertension for improving medication compliance which can translate into better clinical outcomes. On the other hand, there are concerns about increased adverse effects, particularly postural hypertension, among drug-naïve patients treated initially with two antihypertensive agents.

Most of the pharmaceutical companies manufacture a wide number of FDCs as novel products without adequate supporting evidence of proven better efficacy over single drugs, safety, and cost advantage.

- 1. Concerns with FDCs (Figure 1.13):** FDCs are highly popular in India and a large numbers of FDCs are available in the pharmaceutical market. Apart from these, most of the FDCs are not only unnecessary but are also big public health problems as they

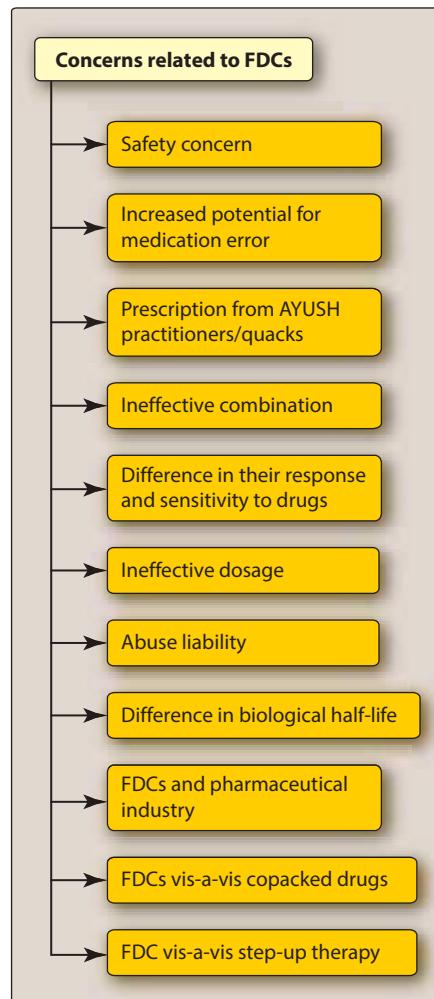
are heavily promoted and prescribed to cover up for diagnostic imprecision and lack of access to laboratory facilities. Such injudicious use of FDCs of antibiotics can rapidly give rise to resistant strains of organisms, which is a matter of serious concern, especially in resource-poor settings. The problem gets worsened as these FDCs are freely available as over-the-counter products.

- a. **Safety concern: Some fixed-dose combinations available in the market are unsafe and even dangerous:** The most serious concern with irrational FDCs is that they expose patients to an unnecessary risk of adverse drug reactions (ADRs). In case a patient suffers from any ADRs, it is difficult to pinpoint the offending agent, for example, in an FDC such as *phenacetin + aspirin + caffeine* (APC; additive toxicity potential, for example, with anti-TB drugs, *streptomycin*, *kanamycin*, and *capreomycin* when combined, as they have the same side effects [oto and nephrotoxicity]).

Some FDCs are unsafe and may be even dangerous when multiple drugs from the same therapeutic group are combined and particularly when centrally acting drugs are clubbed together. If the former compounds the risk of adverse effects, the latter makes it difficult to undertake separate dose adjustments of the drugs that are combined. FDCs containing two or more antiepileptic drugs to treat epilepsy; FDCs containing antipsychotics, antidepressants, and sedatives; antidepressants + antipsychotics + sedatives + anticholinergic; *paracetamol* and *codeine* in older people; and pediatric formulations of *nimesulide + paracetamol*. Nimesulide alone has greater antipyretic properties than aspirin, and equivalent in analgesia to any of the NSAIDs alone, so there is no gain in efficacy with the added paracetamol in the FDC. However, the patient may be subject to increased hepatotoxic effects from the combination. FDCs of *diclofenac + serratopeptidase* do not offer any particular advantage over the individual drugs given separately despite the claim of rapid resolution of inflammation with serratopeptidase. On the other hand, the patient is exposed to a greater risk of gastrointestinal (GI) irritation and serious bleeding from unsuspected peptic ulceration.

FDCs of *quinalones* and *nitroimidazoles* (for example, combinations of [antiamoebic] with *tinidazole + loperamide*; *norfloxacin + tinidazole + dicyclomine*; *norfloxacin + tinidazole*; *norfloxacin + metronidazole*; *ciprofloxacin + tinidazole*; *ofloxacin + ornidazole*) have not been recommended, but continue to be heavily prescribed drugs in GI infections, pelvic inflammatory disease, dental infection, etc., to cover up for diagnostic imprecision and lack of access to laboratory facilities. Such injudicious use of antibiotic FDCs can rapidly give rise to resistant strains of microorganisms, which is a matter of serious concern in a resource-poor setting. Emergence of *ciprofloxacin-resistant Salmonella typhi* strains made treatment of typhoid fever more difficult and expensive in India.

Absence of information on adverse effects of the FDCs available in market with the pharmacovigilance program being at



**Figure 1.13**

Concerns with fixed-dose combinations (FDCs).

a nascent stage and low reporting of adverse events further hamper safety data collection.

- b. **Increased potential for medication errors:** Multifold use of drugs compounded by confusion generated by multiple brand names, especially many FDC formulations, gave rise to multiple branded products. For example, 211 antipsychotic FDC products from 10 formulations to 2,739 NSAID FDC products from 124 formulations are available in the market.

Sometimes even approved FDC formulations contain banned, restricted, or never-approved drugs; for example, *phenylpropanolamine* is a banned drug in other countries due to the risk of stroke. *Nimesulide* containing formulations have been banned from use in children below 12 years of age in India. *Phenylpropanolamine* and its formulations have also been banned in India. Recently, *nimesulide* and *phenylpropanolamine* containing formulations has been banned from use in children below 12 years of age in India.

Irrational FDCs not only impose unnecessary financial burden on consumers but also are misleading. The patient has to pay for two drugs when one (or even none) may be needed for the patient. The FDCs are marketed with slogans such as “ibuprofen for pain and paracetamol for fever” and “ibuprofen for peripheral action and paracetamol for central action” which are misleading and unsafe. Similarly, there is no synergism when two drugs acting on the same enzyme are combined. Thus, combining two NSAIDs does not and cannot improve the efficacy of treatment.

- c. **Prescription from AYUSH quacks:** Ayush practitioners are not knowledgeable about the principles of modern medicine and do not have the capability to rationally choose and prescribe individual components separately.
- d. **Ineffective combinations:** Combination of Vitamin B series with an inadequate dose below RDA of each vitamin is an ineffective combination
- e. **Patients differ in their response and sensitivity to drugs:** Adjustment in dosage and dose interval may be necessary.
- f. **Ineffective dosage adjustments:** Dosage of some of the drugs needs to be adjusted depending on the response to drug therapy and stage of the disease. For example, epileptic and cardiovascular drugs are not suitable for patients who take different doses at different stages, such as initial and maintenance phases.
- g. **Abuse liability:** Some combinations have abuse liability, for example, FDCs containing *dextropropoxyphene*, *phenobarbitone*, and corticosteroid.
- h. **Difference in biological half-life and quality of FDCs:** *Rifampicin* has variable bioavailability from solid oral dosage forms; thus, its potency will be severely affected by using formulations with poor bioavailability.
- i. **FDCs and pharmaceutical industry:** FDCs is one of the ways to extend the patent and marketability of a drug product.

FDCs may be protected by patents, even though the individual active ingredients may be off-patent.

- j. **FDCs vis-a-vis copacked drugs:** FDCs should be distinguished from copacked drugs and combination therapy. For example, some medicines, such as for the treatment of AIDS and tuberculosis, are copackaged as unit-of-use to target a single disease to delay the emergence of resistance; *atorvastatin + amlodipine* is combined to target multiple diseases. Combination therapy refers to treatment with two or more active drugs, administered at one time in their individual formulations.
  - k. **FDC vis-a-vis step-up therapy:** Sometimes, FDCs are considered to be essential as a measure for improving compliance but should be delineated from step-up therapy where medicines are added to the regimen over time depending on the progress of the patient. However, physicians should be familiar with individual components. Switching to FDC may be considered once the dose of the individual medicines is established and the regimen is well tolerated to overcome compliance issue.
2. **Rationality of FDCs:** The rationality of FDCs is based on certain aspects which are as follows:
- The pharmacokinetics of the drugs combined in a formulation must not be widely different.
  - The fixed-dose combination should not have supra-additive toxicity of the ingredients as a combination of the two drugs may increase the side effects of both the drugs such as combinations of NSAIDs and cough and cold formulations.

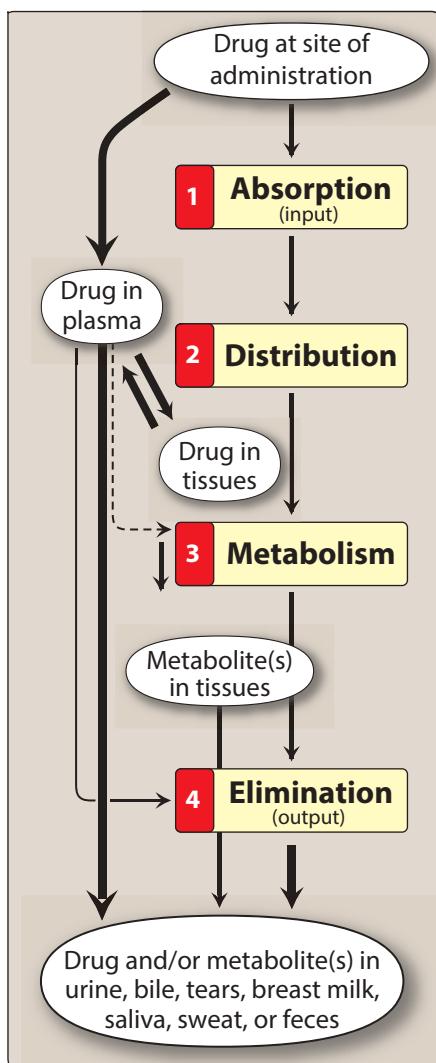
The World Health Organization's (WHO) model list of Essential Drugs provides examples of some rational FDCs such as:

- *sulfamethoxazole + trimethoprim*,
- antitubercular FDCs like *rifampicin + isoniazid + ethambutol*, and *pyrazinamide*
- antiparkinsonism FDCs like *levodopa + carbidopa*.

## P. The Menace of Fake Drugs: Consequences, Causes, and Possible Solutions:

Quality control and assurance play an essential role in the pharmaceutical manufacturing process, to ensure that safe, effective medications of good quality are available. Quality issues with medicines are a frequent occurrence, resulting in recalls, withdrawals, or harm to patients despite advances in technology in the manufacturing sector. Some commonly used terms are given in [Figure 1.14](#).

DRA maintains and enforces regulatory requirements for quality of pharmaceuticals manufactured through a group of regulations known collectively as Good Manufacturing Practices (GMP). Despite government control on the quality of production, import/export, storage, supply, and distribution through prescribed norms and standards, substandard and counterfeit drugs proliferate primarily in the environment where the drug regulation implementation is lax. Both branded and generic products are subject to counterfeiting. Both developed and developing countries face the problem of counterfeit

**Figure 1.15**

Schematic representation of drug absorption, distribution, metabolism, and elimination.

A **substandard medicine** is a drug that does not meet quality standards. It may contain too much or too little of the active ingredient, may be contaminated, may be poorly packaged, or fail to meet quality standards in other ways. These medicines may be a result of negligence or of mistakes during the manufacturing process or may have been deliberately produced. Both originator and generic medicines can be found to be substandard. Substandard medicines are products whose composition and ingredients do not meet the correct scientific specifications as per pharmacopoeia and which may consequently be ineffective and often dangerous to the patient.

A **fake medicine** is deliberately and fraudulently mislabeled medicine, giving false information on where it was made or by whom, in order to appear as a legitimate medicine. Fake medicines are unlikely to contain the active pharmaceutical ingredient needed to make the medicine effective and may even contain harmful substances.

**Spurious drugs:** If it is marketed under a name which belongs to another drug; or if it is an imitation of, or a substitute for, another drug or resembles another drug in a manner likely to deceive or bears upon it or upon its label or container the name of another drug.

**Counterfeit medicines** are part of the broader phenomenon of substandard pharmaceuticals. The difference is that they are deliberately and fraudulently mislabeled with respect to identity and/or source. The term **counterfeit medicine** is overly broad and creates confusion because it conflates intellectual property issues with public health problems.

**Spurious/false labeled/falsified/counterfeit (SFFC)** medicines may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient or too much active ingredient, or with fake packaging.

**Figure 1.14**

Commonly used terms for reflecting drug quality issues.

drugs but the magnitude of the problem is not really known because of nonavailability of global study and nonuniformity in the definitions used. Different countries and organizations use different definitions to define the quality of medicines, making it hard to know exactly which problem is being referred to when this term is used. For all practical purposes, WHO describes spurious/false labeled/falsified/counterfeit (SFFC) medicines that are deliberately and fraudulently mislabeled medicines with respect to identity and/or source.

## II. OVERVIEW OF PHARMACOKINETICS

Pharmacokinetics refers to what the body does to a drug, whereas pharmacodynamics (see Chapter 2) describes what the drug does to the body. Four pharmacokinetic properties determine the onset, intensity, and duration of drug action (Figure 1.15):

- **Absorption:** First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.

- **Distribution:** Second, the drug may reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.
- **Metabolism:** Third, the drug may be biotransformed through metabolism by the liver or other tissues.
- **Elimination:** Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces.

Using knowledge of pharmacokinetic parameters, clinicians can design optimal drug regimens, including the route of administration, dose, frequency, and duration of treatment.

### III. ROUTES OF DRUG ADMINISTRATION

The route of administration is determined by the properties of the drug (for example, water or lipid solubility, and ionization) and by the therapeutic objectives (for example, the need for a rapid onset, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical, among others (Figure 1.16).

#### A. Enteral

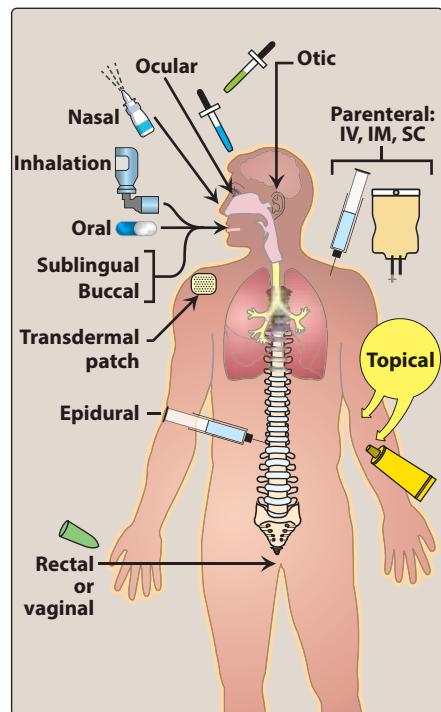
Enteral administration (administering a drug by mouth) is the most common, convenient, and economical method of drug administration. The drug may be swallowed, allowing oral delivery, or it may be placed under the tongue (sublingual) or between the gums and cheek (buccal), facilitating direct absorption into the bloodstream.

**1. Oral:** Oral administration provides many advantages and is the most convenient dosage form. Oral drugs are easily self-administered, and toxicities and/or overdose of oral drugs may be overcome with antidotes, such as activated charcoal. However, the pathways involved in oral drug absorption are the most complicated, and the low gastric pH inactivates some drugs.

A wide range of oral preparations is available including enteric-coated and extended-release preparations.

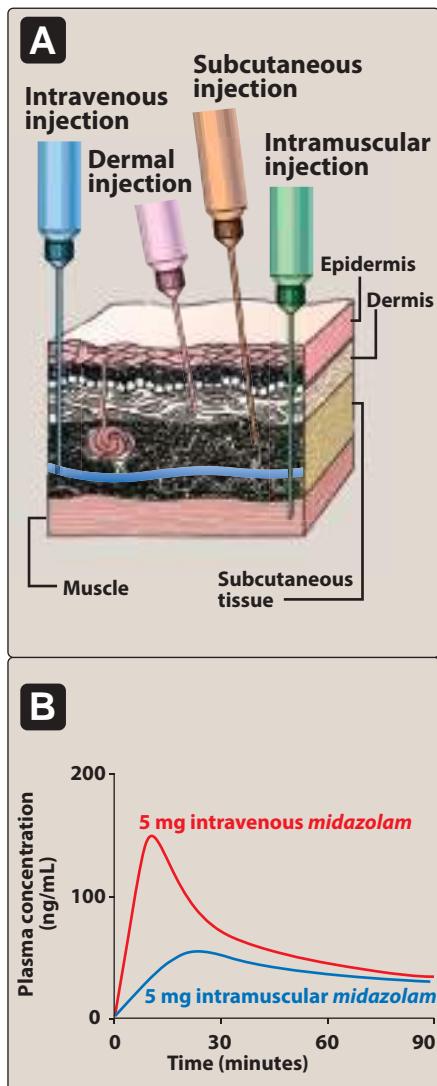
**a. Enteric-coated preparations:** An enteric coating is a chemical envelope that protects the drug from stomach acid, delivering it instead to the less acidic intestine, where the coating dissolves and releases the drug. Enteric coating is useful for certain drugs (for example, *erythromycin* and *omeprazole*) that are acid labile for drugs that are irritating to the stomach (for example, *aspirin*) and to delay the onset of action to a specific site within the gastrointestinal tract (*sulfasalazine* in the treatment of Crohn's disease).

**b. Extended-release preparations:** Extended-release (abbreviated SR, CR, ER, XR, XL, etc.) medications have special coatings or ingredients that control drug release, thereby allowing for slower absorption and prolonged duration of action. ER formulations can be dosed less frequently and may improve patient compliance. In addition, ER formulations may maintain concentrations within the therapeutic range over a longer duration, as opposed to immediate-release dosage forms, which may result in larger peaks and troughs in plasma concentration. ER formulations are advantageous for drugs with



**Figure 1.16**

Commonly used routes of drug administration. IM = intramuscular; IV = intravenous; SC = subcutaneous.



**Figure 1.17**

**A.** Schematic representation of subcutaneous and intramuscular injection. **B.** Plasma concentrations of *midazolam* after intravenous and intramuscular injection.

short half-lives. For example, the half-life of oral *morphine* is 2 to 4 hours, and it must be administered six times daily to provide continuous pain relief. However, only two doses are needed when extended-release tablets are used.

2. **Sublingual/buccal:** The sublingual route involves placement of drug under the tongue. The buccal route involves placement of drug between the cheek and gum. Both the sublingual and buccal routes of absorption have several advantages, including ease of administration, rapid absorption, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism (see discussion of first-pass metabolism in the following text).

## B. Parenteral

The parenteral route introduces drugs directly into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, *heparin*) or unstable in the GI tract (for example, *insulin*). Parenteral administration is also used for patients unable to take oral medications (unconscious patients) and in circumstances that require a rapid onset of action. Parenteral administration provides the most control over the dose of drug delivered to the body. However, this route of administration is irreversible and may cause pain, fever, local tissue damage, and infections. The four major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, subcutaneous, and intradermal (Figure 1.17). Other parenteral routes are intra-arterial, intraperitoneal, intra-articular, intramedullary, etc.

1. **Intravenous (IV):** IV injection is the most common parenteral route. It is useful for drugs that are not absorbed orally, such as the neuromuscular blocker *rocuronium*. IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered. When injected as a bolus, the full amount of drug is delivered to the systemic circulation almost immediately. If administered as an IV infusion, the drug is infused over a longer period, resulting in lower peak plasma concentrations and an increased duration of the circulating drug.
2. **Intramuscular (IM):** Drugs administered IM can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of drug in a nonaqueous vehicle, such as polyethylene glycol. As the vehicle diffuses out of the muscle, the drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended interval.
3. **Subcutaneous (SC):** Like IM injection, SC injection provides absorption via simple diffusion and is slower than the IV route. SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur.
4. **Intradermal (ID):** The intradermal (ID) route involves injection into the dermis, the more vascular layer of skin under the epidermis.

Agents for diagnostic determination and desensitization are usually administered by this route.

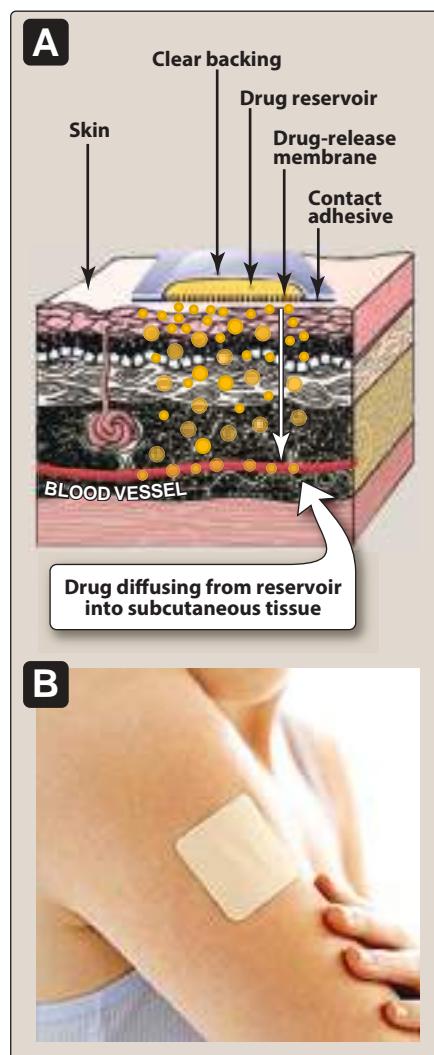
### C. Other

1. **Oral inhalation and nasal preparations:** Both the oral inhalation and nasal routes of administration provide rapid delivery of drug across the large surface area of mucous membranes of the respiratory tract and pulmonary epithelium. Drug effects are almost as rapid as those with IV bolus. Drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol are administered via inhalation. This route is effective and convenient for patients with respiratory disorders such as asthma or chronic obstructive pulmonary disease, because the drug is delivered directly to the site of action, thereby minimizing systemic side effects. The nasal route involves topical administration of drugs directly into the nose, and it is often used for patients with allergic rhinitis.
2. **Intrathecal/intraventricular:** The blood–brain barrier typically delays or prevents the absorption of drugs into the central nervous system (CNS). When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid.
3. **Topical:** Topical application is used when a local effect of the drug is desired, for example, skin, eye, ear, nose, vaginal, and urethral.
4. **Transdermal:** This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch (Figure 1.18). The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application, as well as the lipid solubility of the drug.
5. **Rectal:** Because 50% of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. The rectal route has the additional advantage of preventing destruction of the drug in the GI environment. This route is also useful, if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. Figure 1.19 summarizes characteristics of the common routes of administration, along with examples of drugs.

## IV. ABSORPTION OF DRUGS

Absorption is the transfer of a drug from the site of administration to the bloodstream. The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, dosage form, and route of administration (which influences bioavailability). Routes of administration other than intravenous may result in partial absorption and lower bioavailability. The choice of an appropriate route in a given situation depends on the drug and also depends on patient-related factors. For example,

- physical and chemical characteristics of the drug and its formulation (solid/liquid/gas or aqueous solution, suspension, or oil); accuracy of the dosage, and



**Figure 1.18**

**A.** Schematic representation of a transdermal patch. **B.** Transdermal nicotine patch applied to the arm.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Oral	● Variable; affected by many factors	● Safest and most common, convenient, and economical route of administration	● Limited absorption of some drugs ● Food may affect absorption ● Patient compliance is necessary ● Drugs may be metabolized before systemic absorption	● Acetaminophen tablets ● Amoxicillin suspension
Sublingual	● Depends on the drug: Few drugs (for example, <i>nitroglycerin</i> ) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	● Bypasses first-pass effect ● Bypasses destruction by stomach acid ● Drug stability maintained because the pH of saliva relatively neutral ● May cause immediate pharmacological effects	● Limited to certain types of drugs ● Limited to drugs that can be taken in small doses ● May lose part of the drug dose if swallowed	● Nitroglycerin ● Buprenorphine
Intravenous	● Absorption not required	● Can have immediate effects ● Ideal if dosed in large volumes ● Suitable for irritating substances and complex mixtures ● Valuable in emergency situations ● Dosage titration permissible ● Ideal for high molecular weight proteins and peptide drugs	● Unsuitable for oily substances ● Bolus injection may result in adverse effects ● Most substances must be slowly injected ● Strict aseptic techniques needed	● Vancomycin ● Heparin
Intramuscular	● Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	● Suitable if drug volume is moderate ● Suitable for oily vehicles and certain irritating substances ● Preferable to intravenous if patient must self-administer	● Affects certain lab tests (creatinine kinase) ● Can be painful ● Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)	● Haloperidol ● Depot medroxy-progesterone
Subcutaneous	● Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	● Suitable for slow-release drugs ● Ideal for some poorly soluble suspensions	● Pain or necrosis if drug is irritating ● Unsuitable for drugs administered in large volumes	● Epinephrine ● Insulin ● Heparin
Inhalation	● Systemic absorption may occur; this is not always desirable	● Absorption is rapid; can have immediate effects ● Ideal for gases ● Effective for patients with respiratory problems ● Dose can be titrated ● Localized effect to target lungs: lower doses used compared to that with oral or parenteral administration ● Fewer systemic side effects	● Most addictive route (drug can enter the brain quickly) ● Patient may have difficulty regulating dose ● Some patients may have difficulty using inhalers	● Albuterol ● Fluticasone
Topical	● Variable; affected by skin condition, area of skin, and other factors	● Suitable when local effect of drug is desired ● May be used for skin, eye, intra-vaginal, and intranasal products ● Minimizes systemic absorption ● Easy for patient	● Some systemic absorption can occur ● Unsuitable for drugs with high molecular weight or poor lipid solubility	● Clotrimazole cream ● Hydrocortisone cream ● Timolol eye drops
Transdermal (patch)	● Slow and sustained	● Bypasses the first-pass effect ● Convenient and painless ● Ideal for drugs that are lipophilic and have poor oral bioavailability ● Ideal for drugs that are quickly eliminated from the body	● Some patients are allergic to patches, which can cause irritation ● Drug must be highly lipophilic ● May cause delayed delivery of drug to pharmacological site of action ● Limited to drugs that can be taken in small daily doses	● Nitroglycerin ● Nicotine ● Scopolamine
Rectal	● Erratic and variable	● Partially bypasses first-pass effect ● Bypasses destruction by stomach acid ● Ideal if drug causes vomiting ● Ideal in patients who are vomiting, or comatose	● Drugs may irritate the rectal mucosa ● Not a well-accepted route	● Bisacodyl ● Promethazine

**Figure 1.19**

The absorption pattern, advantages, and disadvantages of the most common routes of administration.  
(Figure continues on next page)

FORMS	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES
Vaginal douche (for example, Betadine douche)	Washing or cleaning out the inside of the vagina with water or other mixtures of fluids	<ul style="list-style-type: none"> <li>Helps to remove unpleasant odors, wash away menstrual blood, avoid getting sexually transmitted diseases, and prevent pregnancy after intercourse</li> </ul>	<ul style="list-style-type: none"> <li>Vaginal infection as it upsets the natural balance of bacteria in the vagina—that is, vaginal flora</li> <li>Pelvic inflammatory disease</li> </ul>
Pharmaceutical pessary	It is a device that is placed into the vagina for local action (for example, Clotrimazole vaginal pessary)	<ul style="list-style-type: none"> <li>Easy to use</li> <li>Local action</li> </ul>	<ul style="list-style-type: none"> <li>Difficulty in getting pregnant in women who douche more than once a week. May increase the incidence of complications in pregnancy—ectopic pregnancy</li> </ul>
Support/therapeutic pessary (for example, Ring, Shaatz, Gellhorn, Ring with support)	It is a device to provide support to the uterus or bladder and rectum	<ul style="list-style-type: none"> <li>Vaginal support pessary is a useful nonsurgical treatment for the management of pelvic support defects such as cystocele, rectocele, stress, and urinary incontinence</li> <li>Support pessaries fit by trial and error of several sizes and/or styles. In patients who use a diaphragm, the size of the diaphragm does not correlate with the size of the pessary</li> </ul>	<ul style="list-style-type: none"> <li>Increased risk of vaginal discharge, vaginal irritation, ulceration, bleeding, and dyspareunia</li> <li>A neglected pessary can become embedded in the vaginal mucosa and may be difficult to remove</li> <li>Improperly fitted ring pessary can lead to strangulation and necrosis of the cervix and uterus</li> </ul>

**Figure 1.19** (Continued)

The absorption pattern, advantages, and disadvantages of the most common routes of administration.

- the speed with which the drug is absorbed and/or released; the time until effect for different routes of drugs is given in **Figure 1.20**.
- The desired action (local or systemic or to achieve high concentration at a particular site)
- Clinical emergency or routine treatment
- Condition of the patient (unconscious or vomiting)

Whether the drug is absorbed from the stomach and intestine or whether it is liable to first-pass degradation, knowledge of the characteristics of a drug is must for appropriate drug administration and improving patient compliance.

ROUTE OF ADMINISTRATION	VARIABLE (MINUTES TO HOURS)
Oral ingestion	30–90 minutes
Rectal	5–30 minutes
Subcutaneous	15–30 minutes
Intramuscular	10–20 minutes
Sublingual	3–5 minutes
Inhalation	2–3 minutes
Endotracheal	2–3 minutes
Intraosseous	30–60 seconds
Intravenous	30–60 seconds

**Figure 1.20**

Route of administration and time to effect.

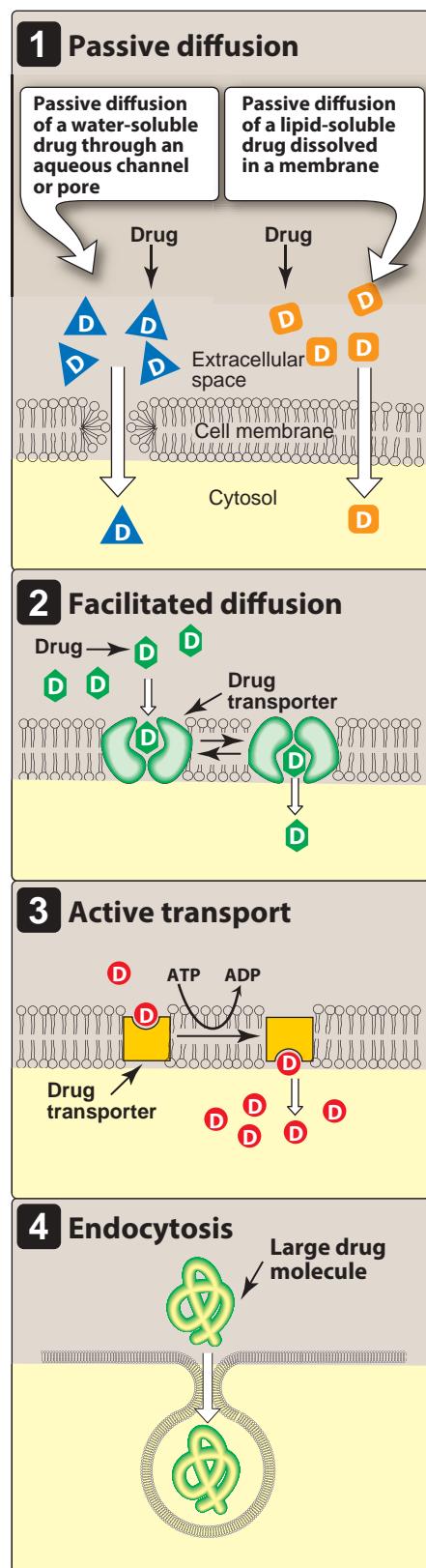
## A. Determinants of absorption

The general determinants of the absorption rate of drugs include the following:

- Routes of drug administration
- Dissolution into aqueous fluids at the absorption site
- Lipid solubility
- Concentration gradient
- Blood flow at the absorption site
- Surface area of the absorption site

## B. Mechanisms of absorption of drugs from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis (**Figure 1.21**).

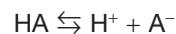
**Figure 1.21**

Schematic representation of drugs crossing a cell membrane.  
ADP = adenosine diphosphate;  
ATP = adenosine triphosphate.

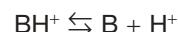
- 1. Passive diffusion:** The driving force for passive diffusion of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from an area of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows low structural specificity. The vast majority of drugs are absorbed by this mechanism. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to solubility in the membrane lipid bilayers.
- 2. Facilitated diffusion:** Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells. This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.
- 3. Active transport:** This mode of drug entry also involves specific carrier proteins that span the membrane. However, active transport is energy-dependent, driven by the hydrolysis of adenosine triphosphate (ATP). It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher concentration. The process is saturable. Active transport systems are selective and may be competitively inhibited by other cotransported substances.
- 4. Endocytosis and exocytosis:** This type of absorption is used to transport drugs of an exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug-filled vesicle. Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation. Vitamin B<sub>12</sub> is transported across the gut wall by endocytosis, whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular vesicles in the nerve terminal and released by exocytosis.

### C. Factors influencing absorption

- 1. Effect of pH on drug absorption:** Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a proton (H<sup>+</sup>), causing a charged anion (A<sup>-</sup>) to form:



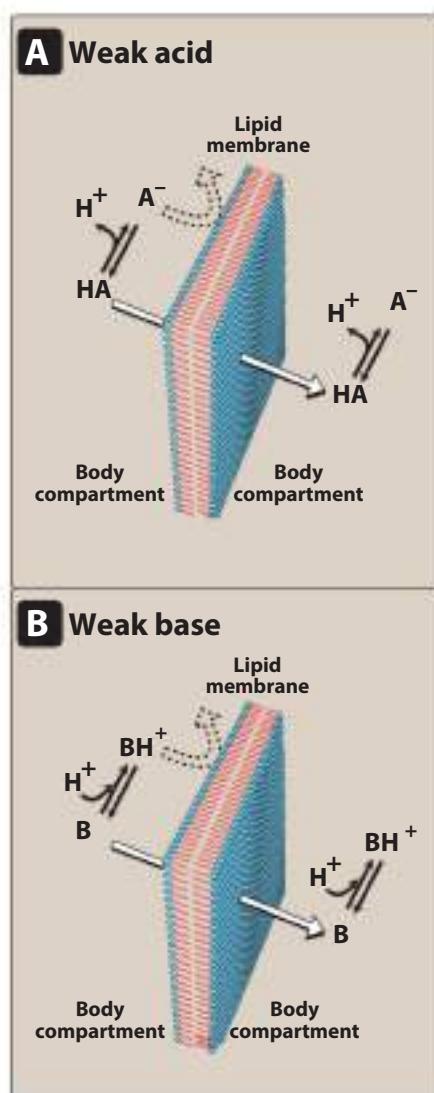
Weak bases (BH<sup>+</sup>) can also release an H<sup>+</sup>. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):



A drug passes through membranes more readily if it is uncharged (Figure 1.22). Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A<sup>-</sup> cannot. For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form BH<sup>+</sup> does not. Therefore,

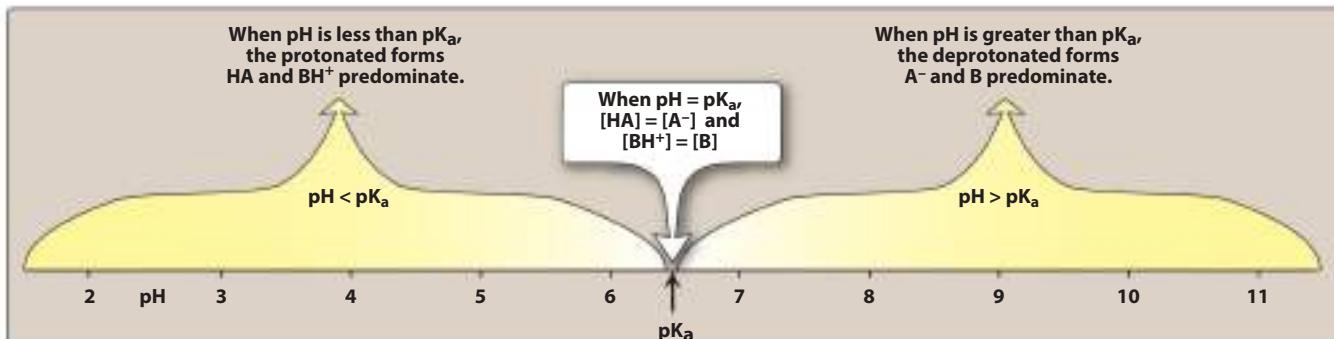
the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the ionization constant,  $pK_a$  (Figure 1.23). [Note: The  $pK_a$  is a measure of the strength of the interaction of a compound with a proton. The lower the  $pK_a$  of a drug, the more acidic it is. Conversely, the higher the  $pK_a$ , the more basic is the drug.] Distribution equilibrium is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces.

2. **Blood flow to the absorption site:** The intestines receive much more blood flow than the stomach, so absorption from the intestine is favored over the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thereby minimizing absorption from SC administration.]
3. **Total surface area available for absorption:** With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.
4. **Contact time at the absorption surface:** If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption. [Note: The presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.]
5. **Expression of P-glycoprotein:** P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes (Figure 1.24). It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. That is, it “pumps” drugs out of cells. Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance.



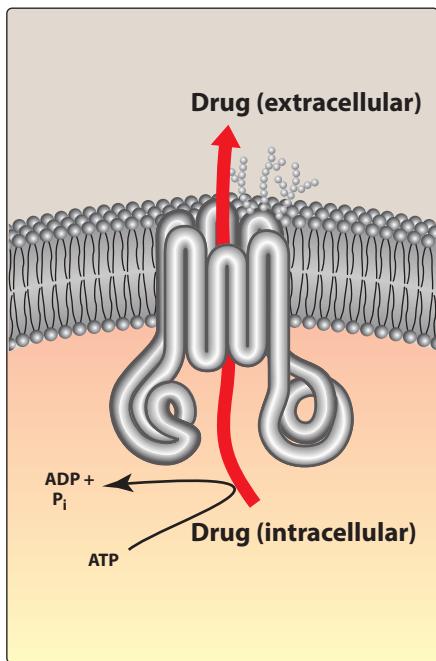
**Figure 1.22**

- A. Diffusion of the nonionized form of a weak acid through a lipid membrane.
- B. Diffusion of the nonionized form of a weak base through a lipid membrane.



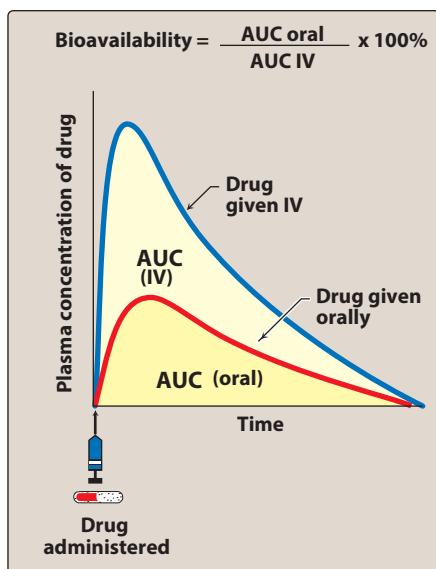
**Figure 1.23**

The distribution of a drug between its ionized and nonionized forms depends on the ambient pH and  $pK_a$  of the drug. For illustrative purposes, the drug has been assigned a  $pK_a$  of 6.5.



**Figure 1.24**

The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.



**Figure 1.25**

Determination of the bioavailability of a drug. AUC = area under curve; IV = intravenous

#### D. Bioavailability

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7% or 70%. Determining bioavailability is important for calculating drug dosages for nonintravenous routes of administration.

1. **Determination of bioavailability:** Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with levels achieved by IV administration. After IV administration, 100% of the drug rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured. A schematic depiction of determination of bioavailability is provided in [Figure 1.25](#).
2. **Factors that influence bioavailability:** In contrast to IV administration, which confers 100% bioavailability, orally administered drugs often undergo first-pass metabolism. This biotransformation, in addition to chemical and physical characteristics of the drug, determines the rate and extent to which the agent reaches the systemic circulation.
  - a. **First-pass hepatic metabolism (presystemic elimination):** When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation ([Figure 1.26](#)). If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased. This is referred to as first-pass metabolism. [Note: First-pass metabolism by the intestine or liver limits the efficacy of many oral medications. For example, more than 90% of *nitroglycerin* is cleared during first-pass metabolism. Hence, it is primarily administered via the sublingual or transdermal, or intravenous route.] Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action. For example, *propranolol* when given by the intravenous route requires much smaller doses compared to the oral dose as the intravenous route bypasses hepatic metabolism and the dose quickly reaches the systemic circulation.
  - b. **Solubility of the drug:** Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

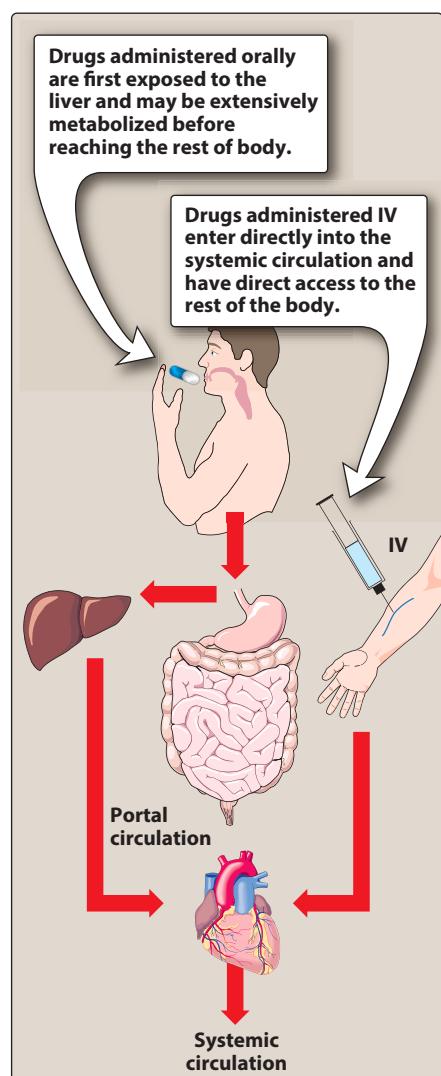
- c. **Chemical instability:** Some drugs, such as *penicillin G*, are unstable in the pH of gastric contents. Others, such as *insulin*, are destroyed in the GI tract by degradative enzymes.
- d. **Nature of the drug formulation:** Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

Sometimes, patients on their own may engage in changing the way in which a dosage form is to be taken such as splitting or crushing of tablets or opening of a capsule prior to administration. While many immediate-release tablets can be safely crushed into a fine powder and diluted prior to administration, certain dosage forms such as sublingual, enteric-coated, and extended or delayed-release medications should NOT be crushed. Any change in these oral dosage forms can alter its absorption characteristics, which may result in the medicine's instability, produce local irritant effects, result in a preparation with an unacceptable taste, cause failure to reach the site of action, and may produce occupational health and safety issues due to vaporization to the health workers. Crushing or opening enteric-coated tablets may result in the drug being released too early in the stomach, may be destroyed by stomach acid, or may irritate the stomach mucosa (for example, *nitrofurantoin*, *potassium chloride*, *alendronate*, and *diclofenac*). A sugar/film-coated dosage form is often used to help mask the unpleasant or bitter taste of some drugs (for example, *ibuprofen*, *quinine*, *cefuroxime axetil*, and *ciprofloxacin*). Coatings can also be added to photosensitive drugs to protect them from light (for example, *nifedipine*).

Crushing an extended-release preparation may also change the drug release characteristics and result in releasing unintended large bolus of a drug which otherwise is meant for controlled drug release over an intended time frame. The consequence of crushing not only would lead to overdosing (a potentially toxic dose of medication to be delivered upon administration in a short span) with an increased risk of adverse effects but also lack of clinical efficacy due to underdosing at later times. For example, extended release *nifedipine* may deliver the dose instantly and result in severe hypotension.

Buccal or sublingual preparations should also not be altered. These medications are also not designed for absorption in the GI tract, for example, *isosorbide mononitrate*, and crushing them for administration via the enteral tube may result in reduced drug absorption and lack of efficacy.

Different oral drug dose forms are discussed in [Figure 1.27](#). Excipients are included in dosage forms to aid manufacture (for example, add bulk to the active drug used in extremely



**Figure 1.26**

First-pass metabolism can occur with orally administered drugs.  
IV = intravenous.

DOSAGE FORM	DEFINITION	EXAMPLES
Tablet (TAB)	A solid dosage form containing medicinal substances with or without suitable diluents	-
Tablet, chewable (TAB CHEW)	A solid dosage form containing medicinal substances with or without suitable diluents that is intended to be chewed, producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste	Ibuprofen chewable tablets; Digene® (antacid) chewable tablets
Tablet, sugar coated	A solid dosage form that contains medicinal substances with or without suitable diluents and is coated with colored or uncolored water-soluble sugar to avoid the bitter taste of ingredients	Tablet <i>chloroquine</i> , tablet <i>metronidazole</i>
Tablet enteric coated	Coating is made of cellulose acid phthalate, shellac, or keratin which is resistant to gastric acid but dissolves at intestinal alkaline pH  The active drug is thus protected from destruction at acidic pH and the incidence of gastric irritation is reduced	Ecosprin® ( <i>aspirin</i> enteric coated) Diclofen 25/50® ( <i>diclofenac</i> enteric-coated tab) Enzar forte® (Enteric-coated enzyme preparation) Dynasprin encotabs (enteric-coated <i>aspirin</i> with <i>dipyridamol</i> )
Tablet, delayed release (TAB DR)	A solid dosage form which delays the release of a drug (or drugs) to a time other than promptly/immediate after administration. Enteric-coated articles are delayed release dosage forms	<i>Lansoprazole</i> delayed tablets
Tablet, dispersible (TAB DISP)/TAB suspension	A tablet that, prior to administration, is intended to be placed in liquid, where its contents will be distributed evenly throughout that liquid. Note: The term "tablet, dispersible" has now been replaced with "tablet, for suspension"	<i>Lamotrigine</i> dispersible tablets; <i>amoxicillin</i> dispersible tablets; <i>clonazepam</i> dispersible tablets
Tablet, effervescent (TAB EFFRV)	A solid dosage form containing mixtures of acids (for example, citric acid, and tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water; it is intended to be dissolved or dispersed in water before administration	<i>Aspirin</i> effervescent preparation
Tablet, extended release (TABER)	A solid dosage form containing a drug which allows at least a reduction in dosing frequency as compared to that drug which is presented in a conventional dosage form	Glucophage XR®. <i>Metformin</i> extended-release tablets, Dilantin® extended release Procardia XL ( <i>Nifedipine</i> extended release tablets)
Tablet retard	Aggregated drug particles have individual coating with different types of inert resins so that each type has different time intervals  Such tablets provide a uniform and sustained release of the drug over a period of 10–12 hours and hence have a lower incidence of side effects	Voveron SR® ( <i>diclofenac</i> ) Dicloflex Retard 100 mg of coating dissolves at ( <i>diclofenac</i> ) Depin Retard® ( <i>Nifedipine</i> retard tablet) K. Grad (Pot. chloride retard tabs)
Tablet, film coated	A solid dosage form that contains medicinal substances with or without suitable diluents and coated with a thin layer of a water-insoluble or water-soluble polymer (gelatin or cellulose derivatives) which masks unpleasant taste	Losartan Potassium 25 mg film-coated tablets Valsartan 320 film-coated tablets Ceftum® ( <i>cefuroxime</i> film-coated tab) Dilgard ( <i>diltiazem</i> film-coated tablet)
Tablet, for solution/suspension	A tablet that forms a solution or suspension when placed in a liquid	<i>Aspirin</i>
Tablet, multilayer	A solid dosage form containing medicinal substances that have been compressed to form a multiple-layered tablet or a tablet-within-a-tablet, the inner tablet being the core and the outer portion being the shell	Admixture containing Phenylephedrin HCl and ascorbic acid with <i>paracetamol</i>
Tablet, orally disintegrating	A solid dosage form containing medicinal substances which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue	<i>Olanzapine</i> , <i>clonazepam</i> orally distintegrating tablets

**Figure 1.27**

List of oral dosage forms and their definition with examples.

small quantities) or administration (to mask or lessen the unpleasant taste, for example, lactose and calcium lactate starch) or modulate absorption. Most excipients have no direct pharmacological action; they are pharmacologically inert. However, in some cases physical and chemical interactions between drugs and excipients can affect the chemical nature, the stability and bioavailability of drug products, and consequently their therapeutic efficacy and safety such as *phenytoin*, *lithium*, and *digoxin*. Therefore, switching of brands of these medications may lead to changes in the bioavailability and hence may need dose adjustment with a change in the brand. Also excipients in some oral solutions and suspensions, such as sweeteners, gums, stabilizers, and suspension agents, can increase viscosity and osmolality, causing diarrhea and clogged tubes.

### E. Bioequivalence and other types of equivalence

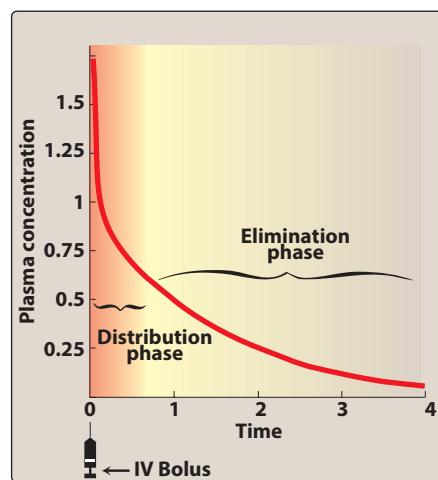
Two drug formulations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations. Two drug formulations are therapeutically equivalent if they are pharmaceutically equivalent (that is, they have the same dosage form, contain the same active ingredient at the same strength, and use the same route of administration) with similar clinical and safety profiles. Thus, therapeutic equivalence requires that drug products are bioequivalent and pharmaceutically equivalent. Bioequivalence can be an issue with generic versus branded/trade drugs. Although both generic and brand drugs may have the same amount of drug, the bioavailability of the drug may be different.

## V. DRUG DISTRIBUTION

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the extracellular fluid and tissues. For drugs administered IV, absorption is not a factor, and the initial phase immediately following administration represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues (Figure 1.28). The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, tissue volume, degree of binding of the drug to plasma and tissue proteins, and relative lipophilicity of the drug.

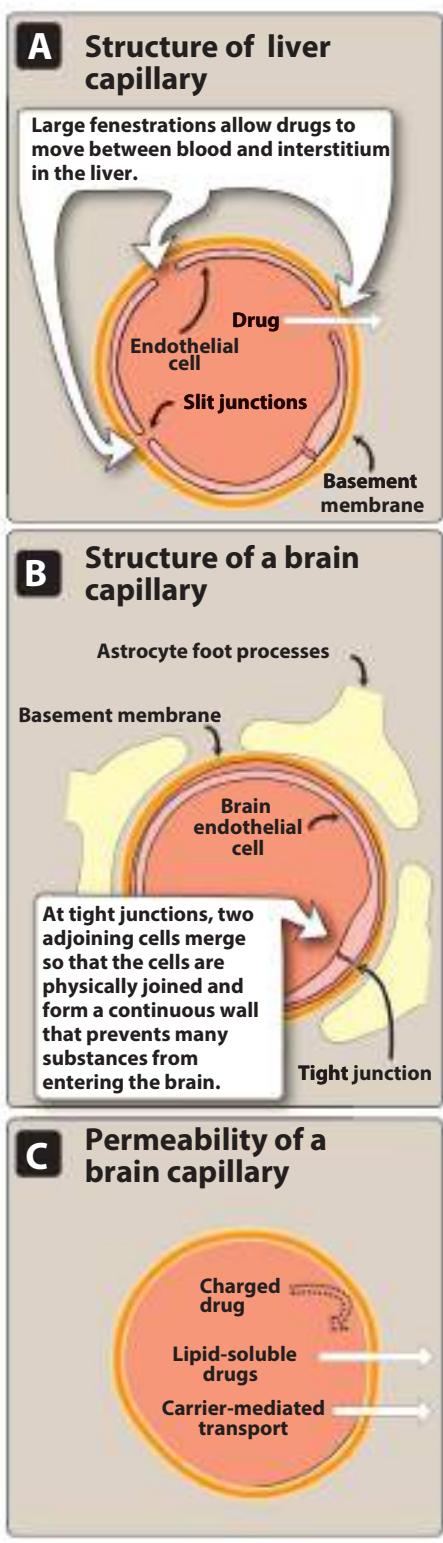
### A. Blood flow

The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to “vessel-rich organs” (brain, liver, and kidney) is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow. Variation in blood flow partly explains the short duration of hypnosis produced by an IV bolus of *propofol* (see Chapter 13). High blood flow, together with high lipophilicity of *propofol*, permits rapid distribution into the CNS and produces anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration so that



**Figure 1.28**

Drug concentrations in serum after a single injection of drug. Assume that the drug distributes and is subsequently eliminated.

**Figure 1.29**

Cross-section of liver and brain capillaries.

the drug diffuses out of the CNS, down the concentration gradient, and consciousness is regained.

### B. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug. Capillary structure varies in terms of the fraction of the basement membrane exposed by slit junctions between endothelial cells. In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass (Figure 1.29A). In the brain, the capillary structure is continuous, and there are no slit junctions (Figure 1.29B). To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or undergo active transport. For example, a specific transporter carries *levodopa* into the brain. Lipid-soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. By contrast, ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions (Figure 1.29C). These closely juxtaposed cells form tight junctions that constitute the blood-brain barrier.

### C. Binding of drugs to plasma proteins and tissues

**1. Binding to plasma proteins:** Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows transfer out of the vascular compartment. Many drugs reversibly bind to albumin, 1-acid glycoprotein, or other proteins in plasma. Albumin is the major drug-binding protein, and it may act as a drug reservoir. Drug bound to albumin is not filtered by renal glomerulus but may be cleared by the proximal renal tubule and liver. As the concentration of free drug decreases due to elimination, the bound drug dissociates from albumin—that is, free drug. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma. The extent of binding to proteins is dependent on several factors such as affinity, number of binding sites, and drug concentrations at the site. The factors which can displace a drug from the protein-binding site and lead to an increase of the fraction of the unbound (free) drug are as follows:

- Renal impairment (leaking albumin)
- Low plasma albumin levels (hypoproteinemia seen in chronic liver disease and malnutrition)
- Late pregnancy—increase in blood volume counters increased albumin production seen in pregnancy
- Displacement from the binding site by other drugs, for example, *aspirin*, *sodium valproate*, and *sulfonamides*
- Saturability of plasma protein-binding sites within therapeutic range, for example, *phenytoin*

**2. Binding to tissue proteins:** Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood. Drugs may accumulate because of binding to lipids, proteins, or nucleic acids. Drugs may also undergo active transport into tissues. Tissue reservoirs may serve as a major source

of the drug and prolong its actions or cause local drug toxicity. (For example, acrolein, the metabolite of *cyclophosphamide*, can cause hemorrhagic cystitis because it accumulates in the bladder.)

#### D. Lipophilicity

The chemical nature of a drug strongly influences its ability to cross cell membranes. Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. The major factor influencing the distribution of lipophilic drugs is blood flow to the area. By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

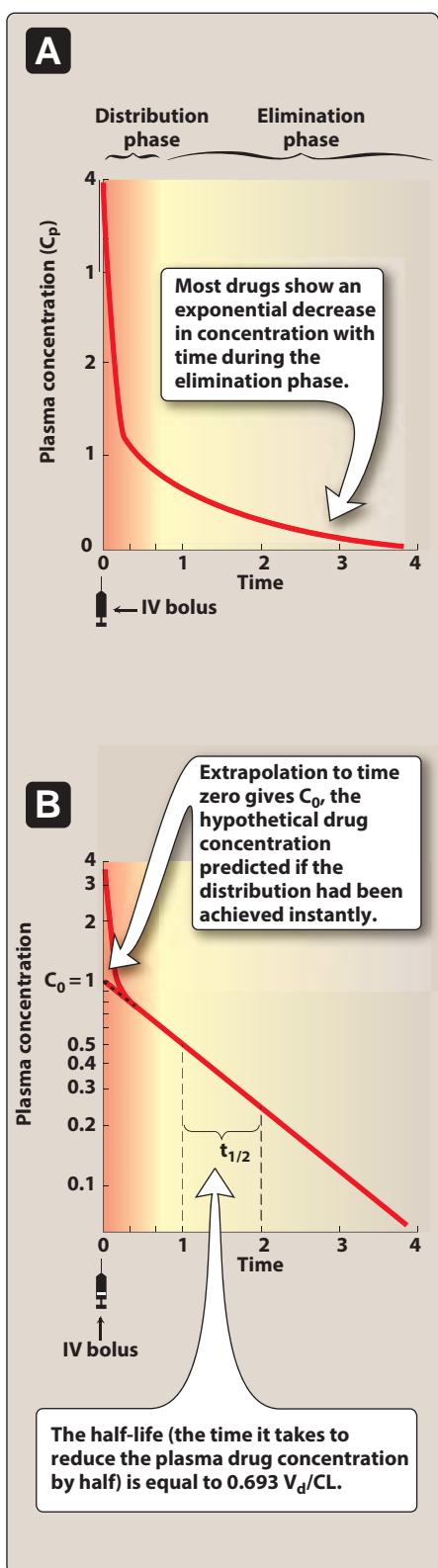
#### E. Volume of distribution

The apparent volume of distribution,  $V_d$ , is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero ( $C_0$ ).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

Although  $V_d$  has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

1. **Distribution into the water compartments in the body:** Once a drug enters the body, it has the potential to distribute into any one of the three functionally distinct compartments of body water or to become sequestered in a cellular site.
  - a. **Plasma compartment:** If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low  $V_d$  that approximates the plasma volume, or about 4 L in a 70-kg individual. *Heparin* (see Chapter 21) shows this type of distribution.
  - b. **Extracellular fluid:** If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into a volume that is the sum of the plasma volume and the interstitial fluid, which together constitute the extracellular fluid (about 20% of body weight or 14 L in a 70-kg individual). Aminoglycoside antibiotics (see Chapter 30) show this type of distribution.
  - c. **Total body water:** If a drug has a low molecular weight and has enough lipophilicity, it can move into the interstitium through the slit junctions and pass through the cell membranes into the intracellular fluid. These drugs distribute into



**Figure 1.30**

Drug concentrations in plasma after a single injection of drug at time = 0. **A.** Concentration data are plotted on a linear scale. **B.** Concentration data are plotted on a log scale.

a volume of about 60% of body weight or about 42 L in a 70-kg individual. *Ethanol* exhibits this apparent  $V_d$ . [Note: In general, a larger  $V_d$  indicates greater distribution into tissues; a smaller  $V_d$  suggests confinement to plasma or extracellular fluid.]

- Determination of  $V_d$ :** The fact that drug clearance is usually a first-order process allows calculation of  $V_d$ . First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration ( $C_p$ ) versus time (Figure 1.30). The concentration of drug in the plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine  $C_0$ , which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. This allows calculation of  $V_d$  as

$$V_d = \frac{\text{Dose}}{C_0}$$

For example, if 10 mg of drug is injected into a patient and the plasma concentration is extrapolated back to time zero, and  $C_0 = 1 \text{ mg/L}$  (from the graph in Figure 1.30B), then  $V_d = 10 \text{ mg}/1 \text{ mg/L} = 10 \text{ L}$ .

- Effect of  $V_d$  on drug half-life:**  $V_d$  has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the liver or kidney (or other organs where metabolism occurs) per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow, but also on the fraction of drug in the plasma. If a drug has a large  $V_d$ , most of the drug is in the extraplasma space and is unavailable to the excretory organs. Therefore, any factor that increases  $V_d$  can increase the half-life and extend the duration of action of the drug. [Note: An exceptionally large  $V_d$  indicates considerable sequestration of the drug in some tissues or compartments.]

## VI. DRUG CLEARANCE THROUGH METABOLISM

Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary excretion. [Note: Elimination is irreversible removal of drug from the body. It involves biotransformation (drug metabolism) and excretion. Excretion is removal of intact drug from the body.] Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug is eliminated in a given unit of time (Figure 1.30A). Metabolism results in products with increased polarity, which allows the drug to be eliminated. Clearance (CL) estimates the volume of blood from which the drug is cleared per unit of time. Total CL is a composite estimate reflecting all mechanisms of drug elimination and is calculated as follows:

$$CL = 0.693 \times V_d / t_{1/2}$$

where  $t_{1/2}$  is the elimination half-life,  $V_d$  is the apparent volume of distribution, and 0.693 is the natural log constant. Drug half-life is often used as a measure of drug CL, because, for many drugs,  $V_d$  is a constant.

## A. Kinetics of metabolism

- First-order kinetics:** The metabolic transformation of drugs is catalyzed by enzymes, and most of the reactions obey Michaelis-Menten kinetics, where  $K_m$  is Michaelis constant (the substrate concentration at half maximal velocity).

$$V = \text{Rate of drug metabolism} = \frac{V_{\max} [C]}{K_m + [C]}$$

In most clinical situations, the concentration of the drug,  $[C]$ , is much less than the Michaelis constant,  $K_m$ , and the Michaelis-Menten equation reduces to

$$V = \text{Rate of drug metabolism} = \frac{V_{\max} [C]}{K_m}$$

That is, the rate of drug metabolism and elimination is directly proportional to the concentration of free drug, and first-order kinetics is observed (Figure 1.31). This means that a constant fraction of drug is metabolized per unit of time (that is, with each half-life, the concentration decreases by 50%). First-order kinetics is also referred to as linear kinetics. Most of the drugs follow first-order kinetics.

- Zero-order kinetics:** With a few drugs, such as *aspirin*, *ethanol*, and *phenytoin*, the doses are very large. Therefore,  $[C]$  is much greater than  $K_m$ , and the velocity equation becomes

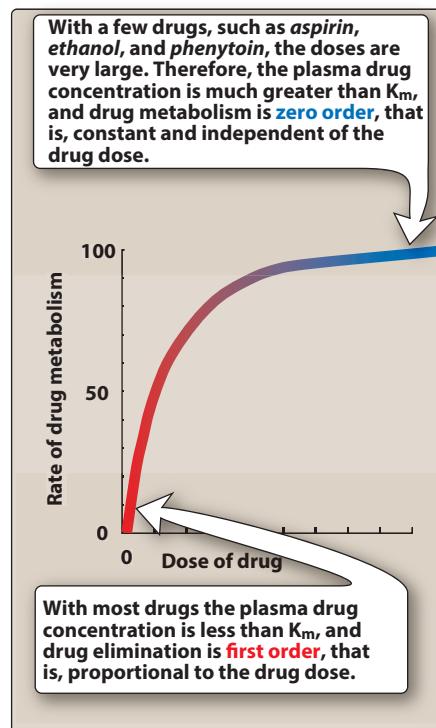
$$V = \text{Rate of drug metabolism} = \frac{V_{\max} [C]}{[C]} = V_{\max}$$

A fixed amount of the drug is eliminated per unit time. The amount of drug cleared is independent of the amount to be cleared. The rate of elimination is constant and does not depend on the drug concentration. This is called zero-order kinetics (also called non-linear kinetics), for example, *ethanol* and *phenytoin*. Repeated drug administration over short intervals in such drugs leads to toxicity. With these, the only way to speed the elimination process is to go for dialysis. The enzyme is saturated by a high free drug concentration, and the rate of metabolism remains constant over time.

## B. Reactions of drug metabolism

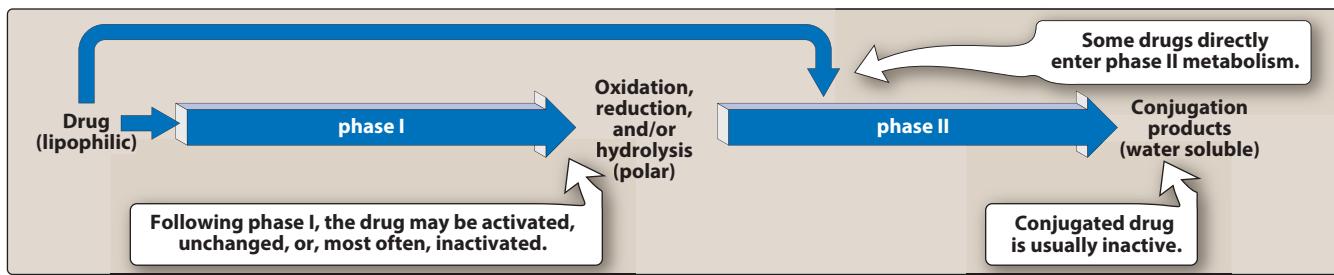
The kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II (Figure 1.32). The duration and intensity of pharmacological action(s) are determined by the rate they are metabolized to inactive products. Products of metabolism may have lesser, greater, or qualitatively different pharmacologic activity from the parent compound.

- Phase I:** Phase I reactions convert lipophilic drugs into more polar molecules by introducing or unmasking a polar functional group, such as  $-OH$  or  $-NH_2$ . Phase I reactions usually involve reduction,

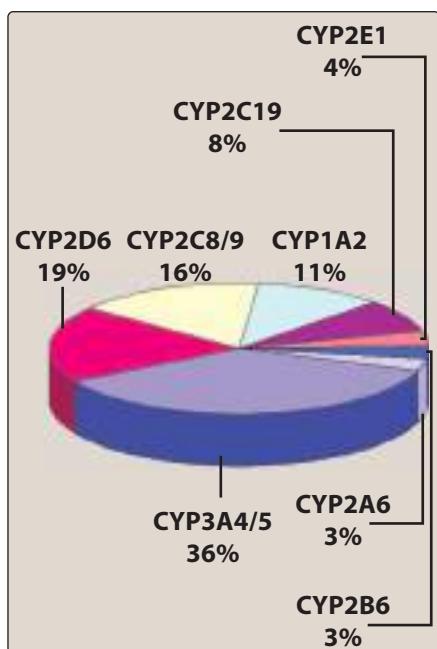


**Figure 1.31**

Effect of drug dose on the rate of metabolism.

**Figure 1.32**

The biotransformation of drugs.

**Figure 1.33**

Relative contribution of cytochrome P450 (CYP) isoforms to drug biotransformation.

oxidation, or hydrolysis. Phase I metabolism may increase, decrease, or have no effect on pharmacologic activity.

**a. Phase I reactions utilizing the P450 system:** The phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 system. The P450 system is important for the metabolism of many endogenous compounds (such as steroids and lipids) and for the biotransformation of exogenous substances (drugs, carcinogens, and environmental pollutants). Cytochrome P450 (CYP) is a superfamily of heme-containing isozymes located in most cells, but primarily in the liver and GI tract.

- [1] **Nomenclature:** The family name is indicated by the Arabic number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A (Figure 1.33). A second number indicates the specific isozyme, as in CYP3A4.
- [2] **Specificity:** Because there are many different genes that encode multiple enzymes, there are many different P450 isoforms. These enzymes have the capacity to modify a large number of structurally diverse substrates. In addition, an individual drug may be a substrate for more than one isozyme. Four isozymes (CYP3A4/5, CYP2D6, CYP2C8/9, and CYP1A2) are responsible for the vast majority of P450-catalyzed reactions (Figure 1.33). Considerable amounts of CYP3A4 are found in intestinal mucosa, accounting for first-pass metabolism of drugs such as *chlorpromazine* and *clonazepam*.
- [3] **Genetic variability:** P450 enzymes exhibit considerable genetic variability among individuals and racial groups. Variations in P450 activity may alter drug efficacy and the risk of adverse events. CYP2D6, in particular, exhibits genetic polymorphism. CYP2D6 mutations result in very low capacities to metabolize substrates. For example, some individuals obtain no benefit from the opioid analgesic *codeine*, because they lack the CYP2D6 enzyme that activates the drug. Similar polymorphisms have been characterized for the CYP2C subfamily of isozymes. For instance, *clopidogrel* carries a warning that patients who are CYP2C19 "poor metabolizers"

have a diminished antiplatelet effect when taking this drug and an alternative medication should be considered. *Clopidogrel* is a prodrug, and CYP2C19 activity is required to convert it to the active metabolite.

**[4] CYP inducers:** The CYP450-dependent enzymes are an important target for pharmacokinetic drug interactions. Certain drugs (for example, *phenobarbital*, *rifampin*, *phenytoin*, *carbamazepine*, and oral contraceptives) are capable of inducing CYP isozymes. This results in increased biotransformation of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, often with concurrent loss of pharmacologic effect. For example, *rifampin*, an antitubercular drug (see Chapter 32), significantly decreases the plasma concentrations of human immunodeficiency virus (HIV) protease inhibitors, thereby diminishing the ability to suppress HIV replication. Patients on antitubercular therapy when put on antiepileptic medications or oral contraceptive results in therapeutic failure, break through seizures, and/or contraception failure. **Figure 1.34** lists some of the more important inducers for representative CYP isozymes.

**[5] CYP inhibitors:** Inhibition of drug metabolism can lead to significant increases in plasma drug concentration and resultant adverse effects or drug toxicity. The most common form of inhibition is through competition for the same isozyme. Some drugs, however, are capable of inhibiting reactions for which they are not substrates (for example, *ketoconazole*), leading to drug interactions. Numerous drugs inhibit one or more of the CYP-dependent biotransformation pathways of *warfarin*. For example, *omeprazole* is a potent inhibitor of three CYP isozymes involved in *warfarin* metabolism. When taken with *omeprazole*, plasma concentrations of *warfarin* increase, which leads to greater anticoagulant effect and increased risk of bleeding. [Note: The more important CYP inhibitors are *erythromycin*, *ketoconazole*, and *ritonavir*, because they each inhibit several CYP isozymes.]

- b. **Phase I reactions not involving the P450 system:** These include amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, *ethanol* oxidation), esterases (for example, metabolism of *aspirin* in the liver), and hydrolysis (for example, of *procaine*).
- 2. **Phase II:** This phase consists of conjugation reactions. If the metabolite from phase I is sufficiently polar, it can be excreted by the kidneys. However, many phase I metabolites are still too lipophilic to be excreted. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble compounds that are often therapeutically inactive and more water-soluble metabolite which are readily excreted in urine or bile. A notable exception is *morphine-6-glucuronide*, which is more potent than *morphine*. Glucuronidation is the most common and the

<b>Isozyme: CYP2C9/10</b>	
COMMON SUBSTRATES	INDUCERS
<i>Celecoxib</i>	
<i>Glimepiride</i>	<i>Carbamazepine</i>
<i>Ibuprofen</i>	<i>Phenobarbital</i>
<i>Phenytoin</i>	<i>Rifampin</i>
<i>Warfarin</i>	

<b>Isozyme: CYP2D6</b>	
COMMON SUBSTRATES	INDUCERS
<i>Fluoxetine</i>	<i>None*</i>
<i>Haloperidol</i>	
<i>Paroxetine</i>	
<i>Propranolol</i>	

<b>Isozyme: CYP3A4/5</b>	
COMMON SUBSTRATES	INDUCERS
<i>Carbamazepine</i>	<i>Carbamazepine</i>
<i>Cyclosporine</i>	<i>Dexamethasone</i>
<i>Erythromycin</i>	<i>Phenobarbital</i>
<i>Nifedipine</i>	<i>Phenytoin</i>
<i>Simvastatin</i>	<i>Rifampin</i>
<i>Verapamil</i>	

**Figure 1.34**

Some representative cytochrome P450 isozymes. CYP = cytochrome P.

\*Unlike most other CYP450 enzymes, CYP2D6 is not very susceptible to enzyme induction.

most important conjugation reaction. [Note: Drugs already possessing an  $-OH$ ,  $-NH_2$ , or  $-COOH$  group may enter phase II directly and become conjugated without prior phase I metabolism (Figure 1.32).] The highly polar drug conjugates are then excreted by the kidney or in bile. Patients deficient in acetylation capacity (slow acetylators) may have prolonged or toxic responses to normal doses of certain drugs because of decreased metabolism (for example, *phenytoin*). The opposite may be seen with fast acetylators.

Other sources of individual variation in rates of metabolism are physiological factors such as age, gender, enterohepatic circulation, intestinal flora or chemical exposures (drugs, dietary constituents and supplements, smoke, alcohol), and disease state. In general, drugs are metabolized more slowly in elderly, neonates, and children than in adults.

## VII. DRUG CLEARANCE BY THE KIDNEY

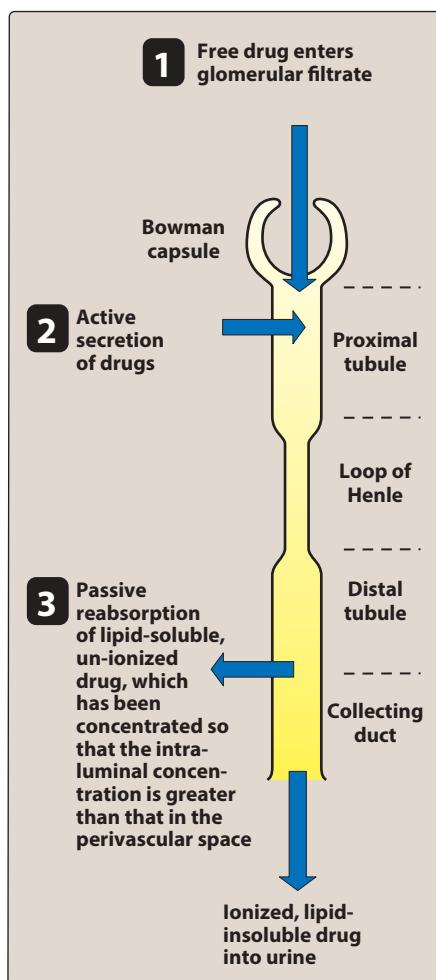
Drugs must be sufficiently polar to be eliminated from the body. Removal of drugs from the body occurs via a number of routes; the most important is elimination through the kidney into the urine. Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects, if the drug is mainly renally excreted. Drugs are also excreted in bile, sweat, lungs, breast milk, tears, genital secretions, and saliva.

### A. Renal elimination of a drug

A drug passes through several processes in the kidney before elimination: glomerular filtration, active tubular secretion, and passive tubular reabsorption.

**1. Glomerular filtration:** Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into the Bowman space as part of the glomerular filtrate (Figure 1.35). The glomerular filtration rate (GFR) is normally about 125 mL/min but may diminish significantly in renal disease or can be significantly compromised in elderly and diabetic patients. Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate. However, variations in GFR, renal blood flow, and protein binding of drugs do affect this process. Any decrease in circulating blood volume, nephrotoxic drugs, or certain diseases can precipitate acute renal failure which may influence the rate of delivery of a drug to the kidney for elimination. Renal excretion is significant with fluoroquinolones and gentamicin; therefore, the doses of these agents should be halved if GFR is below 30 mL/min.

**2. Proximal tubular secretion:** Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems: one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms



**Figure 1.35**

Drug elimination by the kidney.

of weak bases). Each of these transport systems shows low specificity and can transport many compounds. Thus, competition between drugs for these carriers can occur within each transport system. [Note: Premature infants and neonates have an incompletely developed tubular secretory mechanism and it is mostly reduced in elderly; thus, it may retain certain drugs in the blood.] It is affected by genetic polymorphisms of transporters.

Tubular secretion is especially important for drugs that are highly plasma protein bound, because these drugs are not excreted effectively by glomerular filtration, for example, NSAIDs, penicillins, cephalosporins, and glucuronic acid conjugates. Tubular secretion is important in delivering some drugs, such as diuretics, to their site of action in the renal tubule. Also, tubular secretion can be manipulated clinically via the use of inhibitors to extend the duration of action and increase the plasma concentration of drugs that are rapidly excreted by tubular secretion. For example, the drug *probenecid* blocks the transporter responsible for secretion of some penicillin and cephalosporin antibiotics into the renal tubule. *Probenecid* is usually prescribed along with antibiotics in the penicillin and cephalosporin families to prolong their duration of action.

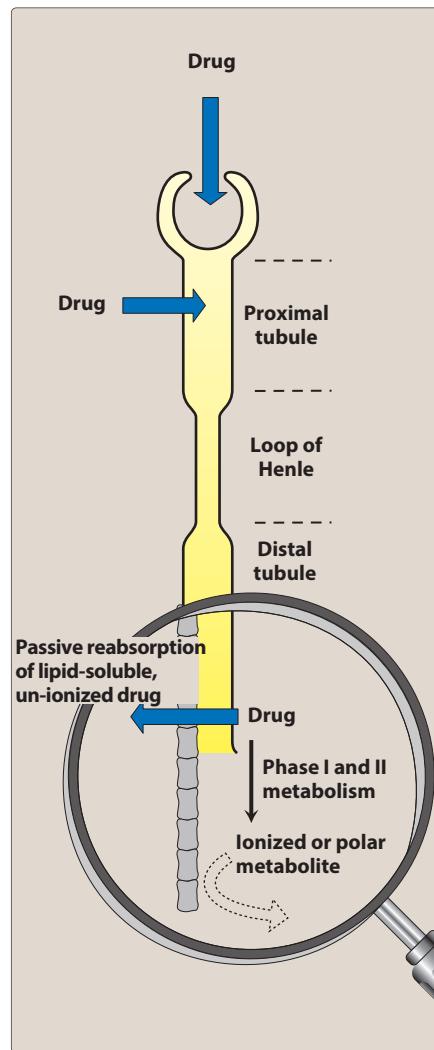
3. **Distal tubular reabsorption:** As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation (Figure 1.36). Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug. Generally, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called “ion trapping.” For example, a patient presenting with *phenobarbital* (weak acid) overdose can be given *bicarbonate*, which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

## VIII. EXCRETION BY OTHER ROUTES

Drug excretion may also occur via the intestines, bile, lungs, and breast milk, among others. Drugs that are not absorbed after oral administration or drugs that are secreted directly into the intestines or into bile are excreted in the feces. The lungs are primarily involved in the elimination of anesthetic gases (for example, *desflurane*). Elimination of drugs in breast milk may expose the breastfeeding infant to medications and/or metabolites being taken by the mother and is a potential source of undesirable side effects to the infant. Excretion of most drugs into sweat, saliva, tears, hair, and skin occurs only to a small extent. Total body clearance and drug half-life are important measures of drug clearance that are used to optimize drug therapy and minimize toxicity.

### A. Total body clearance

Clearance is the volume of plasma from which the drug is completely removed per unit time. The amount eliminated is proportional to the concentration of the drug in the blood stream.



**Figure 1.36**

Effect of drug metabolism on reabsorption in the distal tubule.

The total body (systemic) clearance,  $CL_{total}$ , is the sum of all clearances from the drug-metabolizing and drug-eliminating organs. The kidney is often the major organ of excretion. The liver also contributes to drug clearance through metabolism and/or excretion into the bile. Total clearance is calculated using the following equation:

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$$

where  $CL_{hepatic} + CL_{renal}$  are typically the most important.

Care should be exercised while administering:

- renally excreted drugs;
- drugs with a narrow therapeutic index—*digoxin*;
- drugs which produce active metabolites—benzodiazepines (*diazepam* + *chlordiazepoxide*), antipsychotics (*risperidone*, *thioridazine*), and opioids (*morphine*, *pethidine*, *dextropropoxyphene*); and
- drugs that may further reduce renal function—NSAIDs.

1. **Half-life ( $t_{1/2}$ ):** Half-life is the time required for the body to eliminate one-half the amount of drug in the body. This concept applies only to drugs eliminated by first-order kinetics. In first-order kinetics, a fixed proportion of the drug is eliminated in a unit time.

When a person is administered a drug on a continual basis, the drug will continue to accumulate in the body until a steady state is achieved. A steady state means that the drug has reached a stable concentration—that is, a consistent amount of drug is maintained in plasma. At a steady state, the drug is being eliminated at the same rate it is being administered. Steady-state levels are achieved after four to five half-lives of the drug have passed; therefore, the time to steady state ( $T_{ss}$ ) depends on the half-life of a drug. The half-life DOES NOT depend on dose or dosage interval.

a. **Significance of plasma  $t_{1/2}$ :**

- Plasma  $t_{1/2}$  helps in devising dose schedule and frequency of dosing.
- Plasma  $t_{1/2}$  is useful for rational prescribing or in understanding the time course of adverse events.
- In zero-order kinetics, where a fixed amount of the drug is eliminated per unit time, the amount of drug cleared is independent of the amount to be cleared, for example, *ethanol* and *phenytoin*. Repeated drug administration over short intervals in such drugs leads to toxicity. Hence, the only way to speed the elimination process is to go for dialysis.

**B. Clinical situations resulting in changes in drug half-life**

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. Patients who may have an increase in drug half-life include those with 1) diminished renal or hepatic blood flow, for example, in cardiogenic shock, heart failure, or hemorrhage; 2) decreased ability to extract drug from plasma, for example, in renal disease; and 3) decreased metabolism, for example, when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis. These patients may require a decrease in dosage or less frequent dosing intervals. In contrast, the half-life of a drug may be decreased by increased hepatic blood flow, decreased protein

binding, or increased metabolism. This may necessitate higher doses or more frequent dosing intervals.

## IX. DESIGN AND OPTIMIZATION OF DOSAGE REGIMENT

To initiate drug therapy, the clinician must select the appropriate route of administration, dosage, and dosing interval. Selection of a regimen depends on various patient and drug factors, including how rapidly therapeutic levels of a drug must be achieved. Therapy may consist of a single dose of a drug, for example, a sleep-inducing agent, such as *zolpidem*. More commonly, drugs are continually administered, either as an IV infusion or in IV or oral fixed-dose/fixed-time interval regimens (for example, “one tablet every 4 hours”). Continuous or repeated administration results in accumulation of the drug until a steady state occurs. Steady-state concentration is reached when the rate of drug elimination is equal to the rate of drug administration, such that plasma and tissue levels remain relatively constant.

### A. Continuous infusion regimens

With continuous IV infusion, the rate of drug entry into the body is constant. Most drugs exhibit first-order elimination, that is, a constant fraction of the drug is cleared per unit of time. Therefore, the rate of drug elimination increases proportionately as the plasma concentration increases.

#### 1. Plasma concentration of a drug following continuous IV infusion:

Following initiation of a continuous IV infusion, the plasma concentration of a drug rises until a steady state (rate of drug elimination equals rate of drug administration) is reached, at which point the plasma concentration of the drug remains constant.

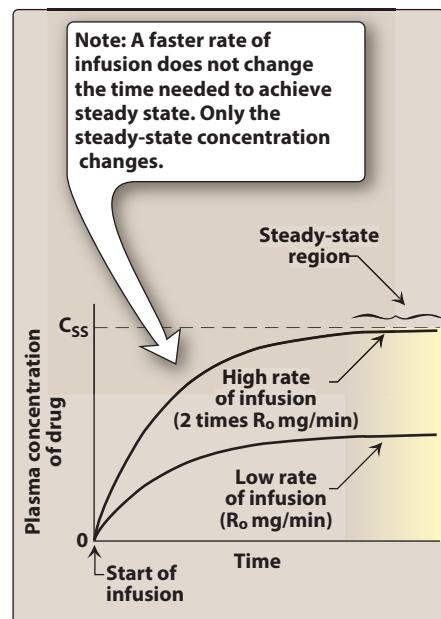
##### a. Influence of the infusion rate on steady-state concentration:

The steady-state plasma concentration ( $C_{ss}$ ) is directly proportional to the infusion rate. For example, if the infusion rate is doubled, the  $C_{ss}$  is doubled (Figure 1.37). Furthermore, the  $C_{ss}$  is inversely proportional to the clearance of the drug. Thus, any factor that decreases clearance, such as liver or kidney disease, increases the  $C_{ss}$  of an infused drug (assuming  $V_d$  remains constant). Factors that increase clearance, such as increased metabolism, decrease the  $C_{ss}$ .

##### b. Time to reach steady-state drug concentration:

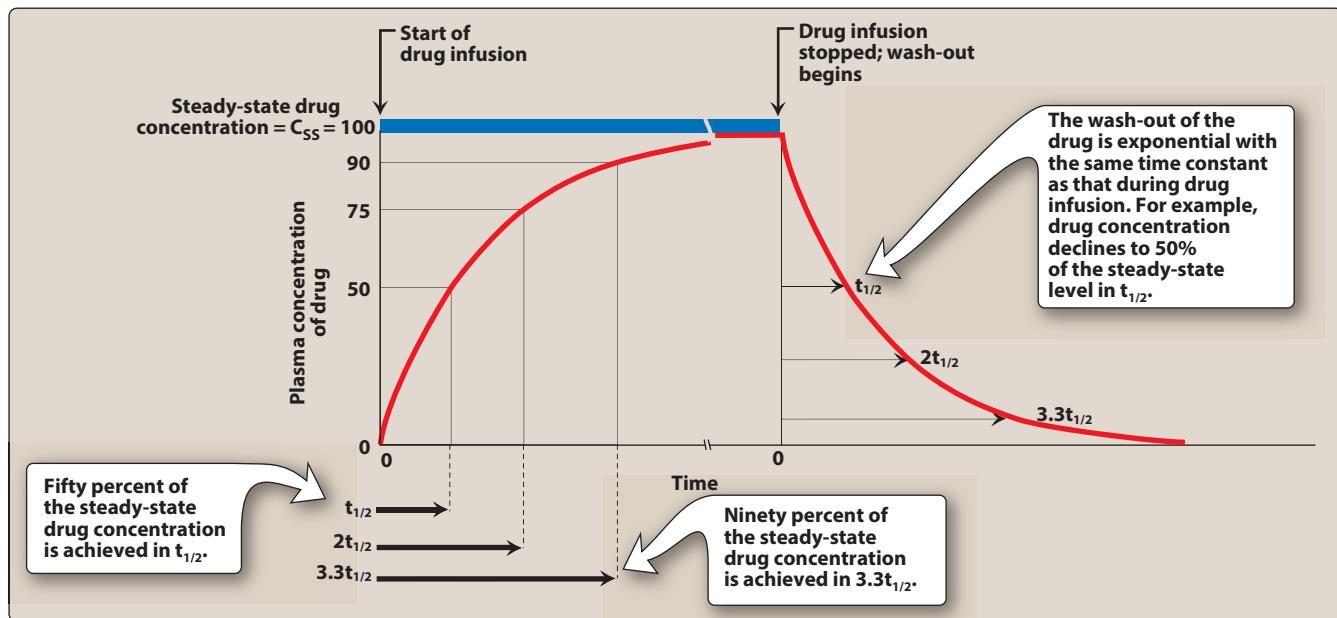
The concentration of a drug rises from zero at the start of the infusion to its ultimate steady-state level,  $C_{ss}$  (Figure 1.37). The rate constant for attainment of steady state is the rate constant for total body elimination of the drug. Thus, 50% of  $C_{ss}$  of a drug is observed after the time elapsed, since the infusion,  $t$ , is equal to  $t_{1/2}$ , where  $t_{1/2}$  (or half-life) is the time required for the drug concentration to change by 50%. After another half-life, the drug concentration approaches 75% of  $C_{ss}$  (Figure 1.38). The drug concentration is 87.5% of  $C_{ss}$  at 3 half-lives and 90% at 3.3 half-lives. Thus, a drug reaches steady state in about four to five half-lives.

The sole determinant of the rate that a drug achieves steady state is the half-life ( $t_{1/2}$ ) of the drug, and this rate is influenced only by factors that affect half-life. The rate of approach to



**Figure 1.37**

Effect of infusion rate on the steady-state concentration of drug in the plasma.  $R_o$  = rate of drug infusion;  $C_{ss}$  = steady-state concentration.  
Modified from H. P. Range, and M. M. Dale, *Pharmacology*, Churchill Livingstone (1987).

**Figure 1.38**

Rate of attainment of steady-state concentration of a drug in the plasma after intravenous infusion.

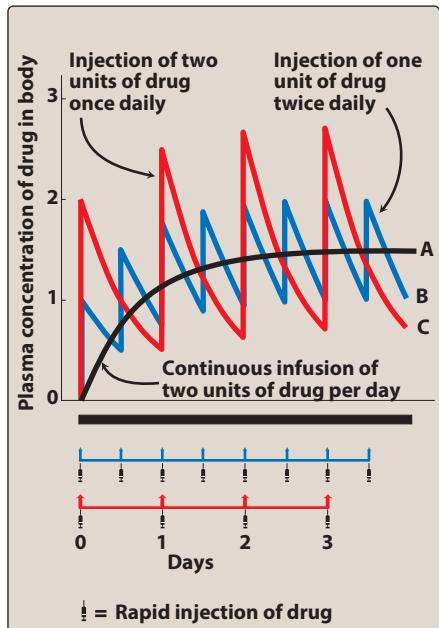
a steady state is not affected by the rate of infusion. When the infusion is stopped, the plasma concentration of a drug declines (washes out) to zero with the same time course observed in approaching a steady state (Figure 1.38).

## B. Fixed-dose/fixed-time regimens

Administration of a drug by fixed doses rather than by continuous infusion is often more convenient. However, fixed doses of IV or oral medications given at fixed intervals result in time-dependent fluctuations in the circulating level of drug, which contrasts with the smooth ascent of drug concentration with continuous infusion.

- Multiple IV injections:** When a drug is given repeatedly at regular intervals, the plasma concentration increases until a steady state is reached (Figure 1.39). Because most drugs are given at intervals shorter than five half-lives and are eliminated exponentially with time, some drug from the first dose remains in the body when the second dose is administered, some from the second dose remains when the third dose is given, and so forth. Therefore, the drug accumulates until, within the dosing interval, the rate of drug elimination equals the rate of drug administration and a steady state is achieved.

- Effect of dosing frequency:** With repeated administration at regular intervals, the plasma concentration of a drug oscillates about a mean. Using smaller doses at shorter intervals reduces the amplitude of fluctuations in drug concentration. However, the dosing frequency changes neither the magnitude of  $C_{ss}$  nor the rate of achieving  $C_{ss}$ .
- Example of achievement of a steady state using different dosage regimens:** Curve B of Figure 1.39 shows the amount of drug in the body when 1 unit of a drug is administered

**Figure 1.39**

Predicted plasma concentrations of a drug given by infusion (A), twice-daily injection (B), or once-daily injection (C). Model assumes rapid mixing in a single body compartment and a half-life of 12 hours.

IV and repeated at a dosing interval that corresponds to the half-life of the drug. At the end of the first dosing interval, 0.50 units of drug remain from the first dose when the second dose is administered. At the end of the second dosing interval, 0.75 units are present when the third dose is given. The minimal amount of drug remaining during the dosing interval progressively approaches a value of 1.00 unit, whereas the maximal value immediately following drug administration progressively approaches 2.00 units. Therefore, at the steady state, 1.00 unit of drug is lost during the dosing interval, which is exactly matched by the rate of administration. That is, the “rate in” equals the “rate out.” As in the case for IV infusion, 90% of the steady-state value is achieved in 3.3 half-lives.

- Multiple oral administrations:** Most drugs administered on an outpatient basis are oral medications taken at a specific dose one, two, or more times daily. In contrast to IV injection, orally administered drugs may be absorbed slowly, and the plasma concentration of the drug is influenced by both the rate of absorption and the rate of elimination (Figure 1.40).

### C. Optimization of dose

The goal of drug therapy is to achieve and maintain concentrations within a therapeutic response window while minimizing toxicity and/or adverse effects. With careful titration, most drugs can achieve this goal. If the therapeutic window (see Chapter 2) of the drug is small (for example, *digoxin* or *lithium*), extra caution should be taken in selecting a dosage regimen, and drug levels should be monitored to ensure attainment of the therapeutic range. Drug regimens are administered as a maintenance dose and may require a loading dose if rapid effects are warranted.

- Maintenance dose:** Drugs are generally administered to maintain a  $C_{ss}$  within the therapeutic window. It takes four to five half-lives for a drug to achieve  $C_{ss}$ . To achieve a given concentration, the rate of administration and the rate of elimination of the drug are important. The dosing rate can be determined by knowing the target concentration in plasma ( $C_p$ ), clearance (CL) of the drug from the systemic circulation, and the fraction (F) absorbed (bioavailability):

$$\text{Dosing rate} = \frac{(\text{Target } C_{\text{plasma}})(\text{CL})}{F}$$

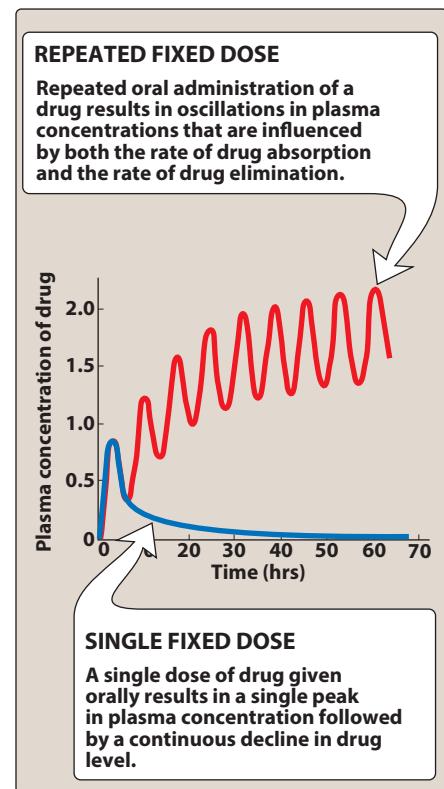
- Loading dose:** Sometimes, rapid obtainment of desired plasma levels is needed (for example, in serious infections, seizures, or arrhythmias). Therefore, a “loading dose” of drug is administered to achieve the desired plasma level rapidly, followed by a maintenance dose to maintain the steady state (Figure 1.41). In general, the loading dose can be calculated as

$$\text{Loading dose} = (V_d) \times (\text{desired steady-state plasma concentration})/F$$

For IV infusion, the bioavailability is 100%, and the equation becomes

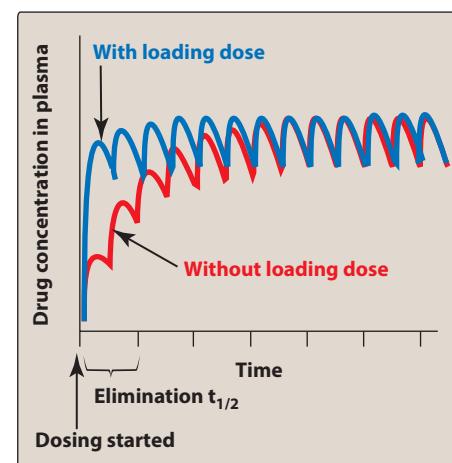
$$\text{Loading dose} = (V_d) \times (\text{desired steady-state plasma concentration})$$

The disadvantages of loading doses include increased risk of drug toxicity and a longer time for the plasma concentration to fall if excess levels occur.



**Figure 1.40**

Predicted plasma concentrations of a drug given by repeated oral administrations.



**Figure 1.41**

Accumulation of drug administered orally without a loading dose and with a single oral loading dose administered at  $t = 0$ .

**3. Dose adjustment:** The amount of a drug administered for a given condition is estimated based on an “average patient.” This approach overlooks interpatient variability in pharmacokinetic parameters such as clearance and  $V_d$ , which are quite significant in some cases. Knowledge of pharmacokinetic principles is useful in adjusting dosages to optimize therapy for a given patient. Monitoring drug therapy and correlating it with clinical benefits provides another tool to individualize therapy. For drugs with a defined therapeutic range, drug concentrations are measured, and the dosage and frequency adjusted to obtain the desired levels. When determining a dosage adjustment,  $V_d$  can be used to calculate the amount of drug needed to achieve a desired plasma concentration. For example, assume a heart failure patient is not well controlled due to inadequate plasma levels of *digoxin*. Suppose the concentration of *digoxin* in the plasma is  $C_1$  and the desired target concentration is  $C_2$ , a higher concentration. The following calculation can be used to determine how much additional *digoxin* should be administered to bring the level from  $C_1$  to  $C_2$ .

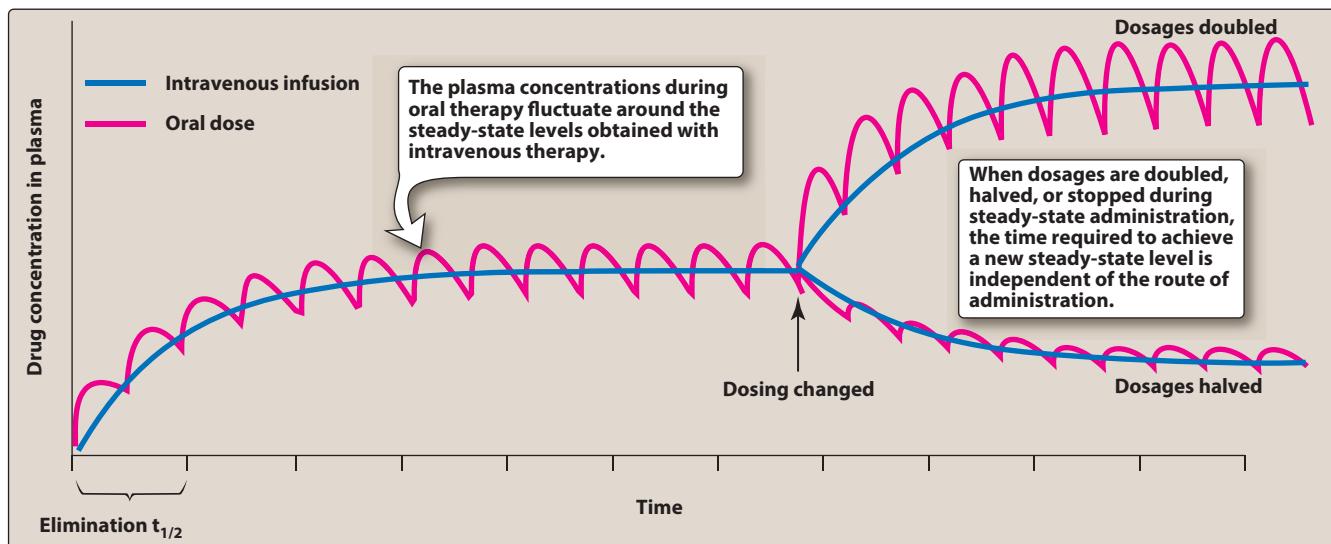
$$(V_d)(C_1) = \text{Amount of drug initially in the body}$$

$$(V_d)(C_2) = \text{Amount of drug in the body needed to achieve the desired plasma concentration}$$

The difference between the two values is the additional dosage needed, which equals  $V_d(C_2 - C_1)$ .

**Figure 1.42** shows the time course of drug concentration when treatment is started or dosing is changed.

**4. Prodrug:** A prodrug is a pharmacologically inactive drug originally but is biotransformed to an active therapeutic agent inside the body. For example, carbamazepine is metabolized to active



**Figure 1.42**

Accumulation of drug following sustained administration and following changes in dosing. Oral dosing was at intervals of 50% of  $t_{1/2}$ . Modified from Figure 6-3, Libby: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed., Philadelphia, PA, Saunders (2007).

metabolite *oxcarbamazepine*. The potential utility of this prodrug lies in its ability to retain its therapeutic action (by improving selectivity for the drug interaction with cells or processes or by protecting peptides against degradation by various proteolytic enzymes) while eliminating or reducing the adverse effects of a drug, for example, with chemotherapy.

## Study Questions

Choose the ONE best answer.

- 1.1 An 18-year-old female patient is brought to the emergency department due to drug overdose. Which of the following routes of administration is the most desirable for administering the antidote for the drug overdose?
- A. Intramuscular
  - B. Intravenous
  - C. Oral
  - D. Subcutaneous
  - E. Transdermal
- 1.2 Drug A is a weakly basic drug with a  $pK_a$  of 7.8. If administered orally, at which of the following sites of absorption will the drug be able to readily pass through the membrane?
- A. Mouth (pH approximately 7.0)
  - B. Stomach (pH of 2.5)
  - C. Duodenum (pH approximately 6.1)
  - D. Jejunum (pH approximately 8.0)
  - E. Ileum (pH approximately 7.0)
- 1.3 KR2250 is an investigational cholesterol-lowering agent. KR2250 has a high molecular weight and is extensively bound to albumin. KR2250 will have a(n) \_\_\_\_\_ apparent volume of distribution ( $V_d$ ).
- A. High
  - B. Low
  - C. Extremely high
  - D. Normal
- 1.4 A 40-year-old male patient (70 kg) was recently diagnosed with infection involving methicillin-resistant *S. aureus*. He received 2000 mg of vancomycin as an IV loading dose. The peak plasma concentration of vancomycin was 28.5 mg/L. The apparent volume of distribution is:
- A. 1 L/kg
  - B. 7 L/kg
  - C. 10 L/kg
  - D. 14 L/kg
  - E. 70 L/kg

Correct answer = B. The intravenous route of administration is the most desirable because it results in achievement of therapeutic plasma levels of the antidote rapidly.

Correct answer = D. Because Drug A is a weakly basic drug ( $pK_a = 7.8$ ), it will be predominantly in the nonionized form in the jejunum (pH of 8.0). For weak bases, the nonionized form will permeate through the cell membrane readily.

Correct answer = B. Because of its high molecular weight and high protein binding, KR2250 will be effectively trapped within the plasma (vascular) compartment and will have a low apparent volume of distribution.

Correct answer = A.  $V_d = \text{dose}/C = 2000 \text{ mg}/28.5 \text{ mg/L} = 70.1 \text{ L}$ . Because the patient is 70 kg, the apparent volume of distribution in L/kg will be approximately 1 L/kg ( $70.1 \text{ L}/70 \text{ kg}$ ).

- 1.5 A 55-year-old woman is brought to the emergency department because of seizures. She has a history of renal disease and currently undergoes dialysis. She receives an intravenous infusion of anti-seizure drug X. Which of the following is likely to be observed with use of drug X in this patient?

	<b>Half-life</b>	<b>Dosage</b>
A.	↑	↑
B.	↓	↓
C.	↑	↔
D.	↑	↓
E.	↔	↔

- 1.6 A 68-year-old woman is brought to the emergency department for treatment of a myocardial infarction. She is currently taking clopidogrel (antiplatelet agent) and aspirin daily, as well as omeprazole (potent CYP inhibitor) for heartburn. Which of the following is the most likely contributor to her myocardial infarction today?

- A. Reduced antiplatelet activity of clopidogrel due to aspirin
- B. Reduced antiplatelet activity of clopidogrel due to omeprazole
- C. Hypersensitivity reaction due to clopidogrel
- D. Increased antiplatelet activity of clopidogrel due to omeprazole
- E. Increased antiplatelet activity of clopidogrel due to aspirin

- 1.7 Which of the following reactions represents Phase II of drug metabolism?

- A. Amidation
- B. Hydrolysis
- C. Oxidation
- D. Reduction
- E. Sulfation

- 1.8 A pharmacokinetic study of a new antihypertensive drug is being conducted in healthy human volunteers. The half-life of the drug after administration by continuous intravenous infusion is 12 hours. Which of the following best approximates the time for the drug to reach steady state?

- A. 24 hours
- B. 48 hours
- C. 72 hours
- D. 120 hours
- E. 240 hours

Correct answer = D. Because the patient has a renal disorder, she may not be able to excrete the drug effectively. Therefore, the half-life of drug X will be prolonged. As the half-life is prolonged, the dosage must be reduced so the patient will not have serious toxic effects of drug X.

Correct answer = B. Clopidogrel is a prodrug and requires CYP2C19 activity for conversion to an active metabolite. Because omeprazole is a potent CYP inhibitor, clopidogrel is not converted to the active metabolite, and therefore the antiplatelet activity is reduced, potentially contributing to myocardial infarction.

Correct answer = E. Phase II metabolic reactions involve conjugation reactions to make phase I metabolites more polar. Sulfation and glucuronidation are the most common Phase II conjugation reactions.

Correct answer = B. A drug will reach steady state in about four to five half-lives. Therefore, for this drug with a half-life of 12 hours, the approximate time to reach steady state will be 48 hours.

- 1.9 A 64-year-old female patient (60 kg) is treated with experimental Drug A for type 2 diabetes. Drug A is available as tablets with an oral bioavailability of 90%. If the  $V_d$  is 2 L/kg and the desired steady-state plasma concentration is 3.0 mg/L, which of the following is the most appropriate oral loading dose of Drug A?
- A. 6 mg
  - B. 6.66 mg
  - C. 108 mg
  - D. 360 mg
  - E. 400 mg
- 1.10 A 74-year-old man was admitted to the hospital for treatment of heart failure. He received 160 mcg of digoxin intravenously, and the plasma digoxin level was 0.4 ng/mL. If the desired plasma concentration of digoxin for optimal therapeutic activity in heart failure is 1.2 ng/mL, and the patient has an estimated  $V_d$  of 400 L, calculate the additional dose of digoxin needed for this patient to achieve the desired plasma concentration.
- A. 128 mcg
  - B. 160 mcg
  - C. 320 mcg
  - D. 480 mcg
  - E. 640 mcg
- 1.11 Essential drugs list is a
- A. List of life-saving drugs
  - B. List of drugs by generic names
  - C. List of drugs required for common ailments
  - D. List of drugs required for majority of ailments and people
  - E. List of drugs required for priority needs of the population
- 1.12 All are criteria for selection of essential drugs EXCEPT
- A. Pattern of prevalent diseases
  - B. The training and experience of available personnel
  - C. Treatment facilities
  - D. Relative efficacy, cost, and suitability
  - E. Latest drug in the market

Correct answer = E. For oral dosing, Loading dose =  $[V_d] \times (\text{desired steady-state plasma concentration})/F$ . The  $V_d$  in this case is corrected to the patient's weight is 120 L. The F value is 0.9 (because bioavailability is 90%, i.e.,  $90/100 = 0.9$ ). Thus, Loading dose =  $(120 \text{ L} \times 3.0 \text{ mg/L})/0.9 = 400 \text{ mg}$ .

Correct answer = C. The additional dosage of digoxin needed to achieve the desired plasma concentration can be calculated using the equation  $V_d (C_2 - C_1)$ .  $C_1$  is the current plasma concentration (0.4 ng/mL) and  $C_2$  is the desired plasma concentration (1.2 ng/mL). Therefore, the additional dosage of digoxin is  $[400 \text{ L} \times (1.2 - 0.4) \text{ ng/mL}] = 320 \text{ mcg}$ .

Correct answer = E. Essential medicines are those that satisfy the priority healthcare needs of the population. They are selected with due regard to disease prevalence, evidence on efficacy, safety, and comparative cost-effectiveness.

Correct answer = E. Drugs are selected depending on many factors, such as the pattern of prevalent diseases, treatment facilities, training and experience of available personnel, financial resources, and genetic, demographic, and environmental factors.

1.13 Antimicrobial resistance is of public health concern because of:

- A. Higher cost of therapy.
- B. Increased risk of morbidity.
- C. Antimicrobial resistance.
- D. Reduced quality of care.
- E. All of the above.

Correct answer = E. Antimicrobial resistance (AMR) is one of the most serious public health problems globally resulting in prolonged illness and hospitalization, mortality, and higher costs. Use of drugs other than first-line drugs in such situations may increase costs (sometimes as high as 100-fold), makes treatment unaffordable for many governments/health systems, especially in developing countries, and increase in out-of-pocket expenditure by patients.

1.14 Development and spread of antimicrobial resistance is due to:

- A. Antimicrobial use.
- B. Overuse, misuse, and irrational use.
- C. Noncompliance and self-medication by patients.
- D. Use in animal husbandry, aquaculture, and agriculture.
- E. All of the above.

Correct answer = E. Development and spread of antimicrobial resistance is due to overuse, misuse, and irrational use by doctors; noncompliance and self-medication by patients; and use in animal husbandry, aquaculture, and agriculture.

# Pharmacodynamics

2

Joanna Peris and Sangeeta Sharma

## I. OVERVIEW

Pharmacodynamics describes the actions of a drug on the body. Most drugs exert effects, both beneficial and harmful, by interacting with specialized target macromolecules called receptors, which are present on or in the cell. The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction (Figure 2.1).

### A. Fundamentals of drug action

Any chemical agent that alters the biochemical or physiological process of tissues of organisms which is intended for diagnostic, preventive, and therapeutic purpose is called “drug.” The term “drug” is derived from the French term “Drogue” which means a medicament. Drugs are obtained from plant (for example, *atropine*), animal (for example, *insulin*), synthetic sources (for example, *ciprofloxacin*), mineral (for example, sodium chloride), and genetic means such as recombinant DNA technique (for example, *interferons*).

On the target site, a drug molecule is expected to exhibit its mechanism of action. The principles based on which the drug elicit such action can be broadly classified into the following types.

1. **Activation:** By binding to the target site if the drug molecule stimulates the process or selectively accelerates the process. For example, *caffeine* causes CNS stimulation and increased alertness.
2. **Inhibition:** On the target site a drug molecule exhibiting its action by inhibiting the process or selectively deaccelerating the process. For example, *aspirin* inhibits cyclooxygenase, thereby inhibiting the formation of prostaglandins.
3. **Complexation:** On the target site, the drug molecule exhibiting its action by making a complex, thereby making it inactive by sequesterization. For example, *deferoxamine* chelates ion.
4. **Neutralization:** The drug molecule binding to the target site and neutralizing the action of the existing molecule directly through a chemical reaction [for example, antacids (sodium bicarbonate, magnesium hydroxide)] or physical interaction (polyvalent antisnake venom).

## II. SIGNAL TRANSDUCTION

Drugs act as signals, and receptors act as signal detectors. A drug is termed an “agonist” if it binds to a site on a receptor protein and activates

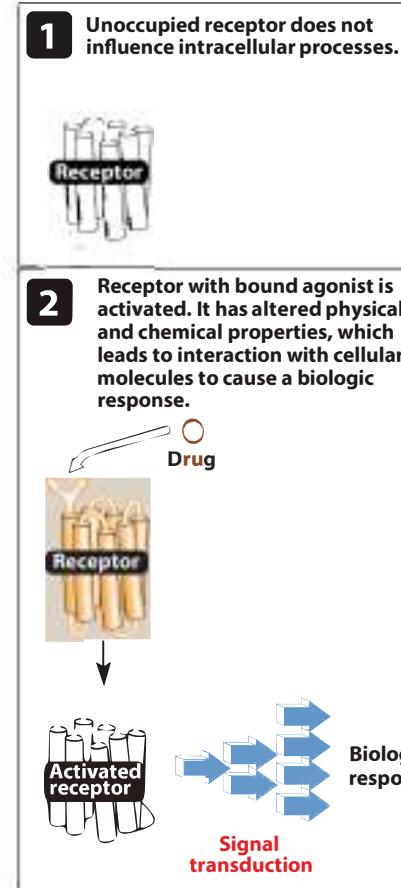


Figure 2.1

The recognition of a drug by a receptor triggers a biologic response.

it to initiate a series of reactions that ultimately result in a specific intracellular response. “Second messenger” or effector molecules are part of the cascade of events that translates agonist binding into a cellular response.

### A. The drug–receptor complex

Cells have many different types of receptors, each of which is specific for a particular agonist and produces a unique response. Cardiac cell membranes, for example, contain  $\beta$ -adrenergic receptors that bind and respond to *epinephrine* or norepinephrine. Cardiac cells also contain muscarinic receptors that bind and respond to acetylcholine. These two receptor populations dynamically interact to control the heart’s vital functions.

The magnitude of the cellular response is proportional to the number of drug–receptor complexes. This concept is conceptually similar to the formation of complexes between enzyme and substrate and shares many common features, such as specificity of the receptor for a given agonist. Although much of this chapter centers on the interaction of drugs with specific receptors, it is important to know that not all drugs exert effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing stomach upset.

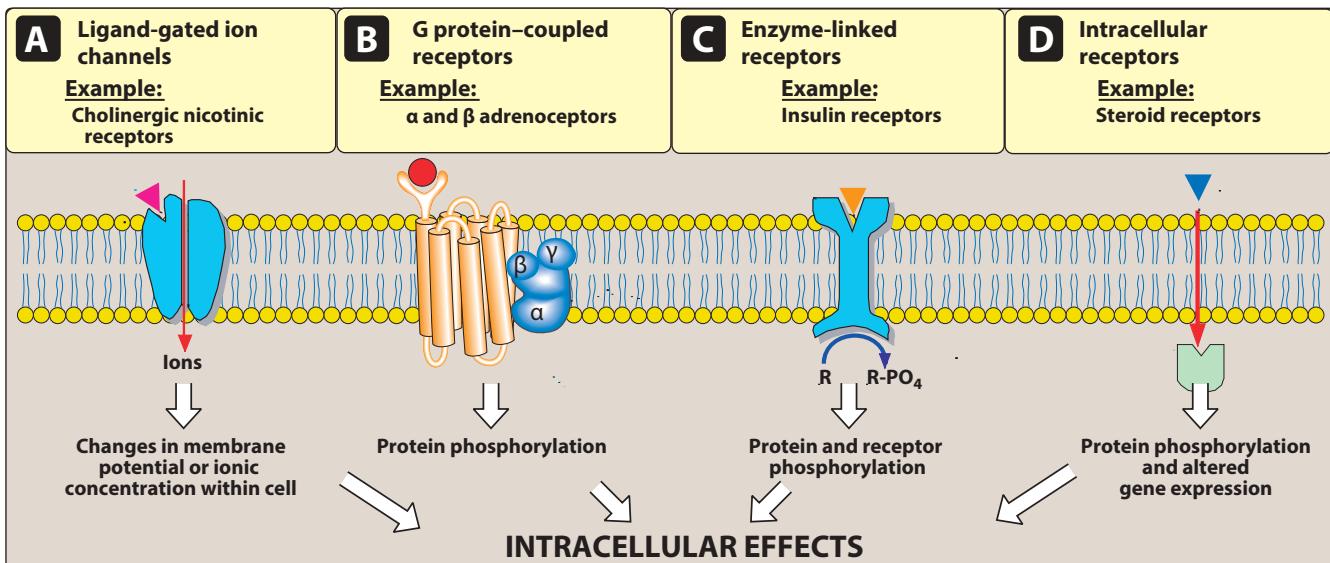
### B. Receptor states

Receptors exist in at least two states, inactive ( $R$ ) and active ( $R^*$ ), that are in reversible equilibrium with one another, usually favoring the inactive state. Binding of agonists causes the equilibrium to shift from  $R$  to  $R^*$  to produce a biologic effect. Antagonists are drugs that bind to the receptor but do not increase the fraction of  $R^*$ , instead stabilizing the fraction of  $R$ . Some drugs (partial agonists) shift the equilibrium from  $R$  to  $R^*$ , but the fraction of  $R^*$  is less than that caused by an agonist. The magnitude of biological effect is directly related to the fraction of  $R^*$ . In summary, agonists, antagonists, and partial agonists are examples of molecules or ligands that bind to the activation site on the receptor and can affect the fraction of  $R^*$ .

### C. Major receptor families

A receptor is defined as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes, nucleic acids, and structural proteins can act as receptors for drugs or endogenous agonists. However, the richest sources of receptors are membrane-bound proteins that transduce extracellular signals into intracellular responses. These receptors may be divided into four families: 1) ligand-gated ion channels, 2) G protein–coupled receptors, 3) enzyme-linked receptors, and 4) intracellular receptors (Figure 2.2). Generally, hydrophilic ligands interact with receptors that are found on the cell surface (Figure 2.2A, B, C). In contrast, hydrophobic ligands enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells (Figure 2.2D).

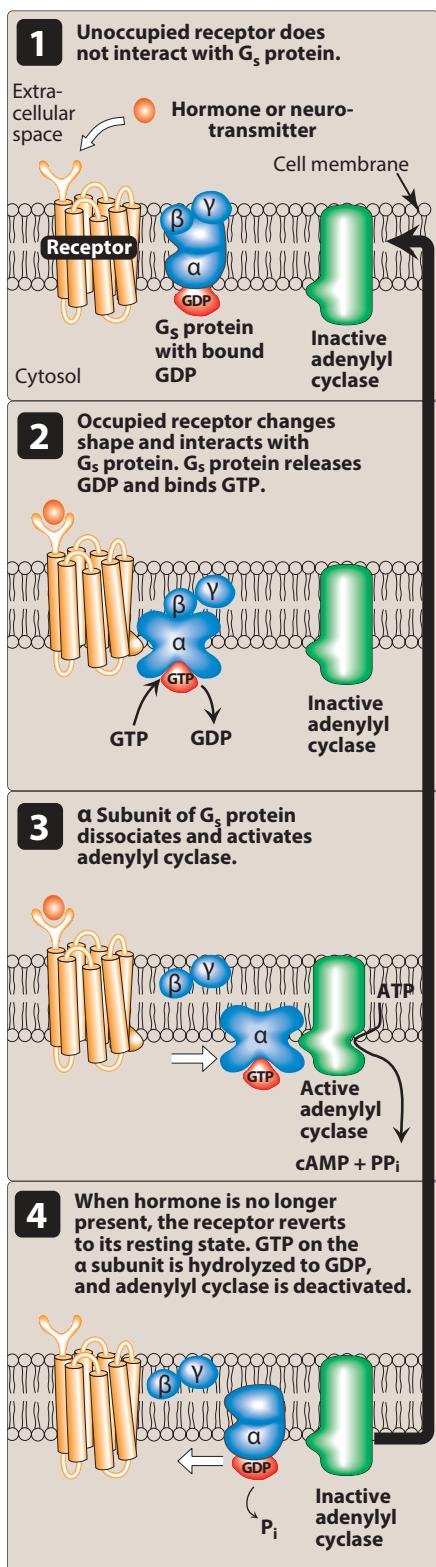
1. **Transmembrane ligand-gated ion channels:** The extracellular portion of ligand-gated ion channels contains the drug-binding

**Figure 2.2**

Transmembrane signaling mechanisms. **A.** Ligand binds to the extracellular domain of a ligand-gated channel. **B.** Ligand binds to a domain of a transmembrane receptor, which is coupled to a G protein. **C.** Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme. **D.** Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor. R = inactive protein.

site. This site regulates the opening of the pore through which ions can flow across cell membranes (Figure 2.2A). The channel is usually closed until the receptor is activated by an agonist, which opens the channel for a few milliseconds. Depending on the ion conducted through these channels, these receptors mediate diverse functions, including neurotransmission and muscle contraction. For example, stimulation of the nicotinic receptor by acetylcholine opens a channel that allows sodium influx and potassium outflux across the cell membranes of neurons or muscle cells. This change in ionic concentrations across the membrane generates an action potential in a neuron and contraction in skeletal and cardiac muscle. On the other hand, agonist stimulation of the  $\alpha$  subtype of the  $\gamma$ -aminobutyric acid (GABA) receptor increases chloride influx, resulting in hyperpolarization of neurons and less chance of generating an action potential. Drug-binding sites are also found on many voltage-gated ion channels where they can regulate channel function. For example, local anesthetics bind to the voltage-gated sodium channel, inhibiting sodium influx and decreasing neuronal conduction.

2. **Transmembrane G protein-coupled receptors:** The extracellular portion of this receptor contains the ligand-binding site, and the intracellular portion interacts (when activated) with a G protein. There are many kinds of G proteins (for example,  $G_s$ ,  $G_i$ , and  $G_q$ ), but all types are composed of three protein subunits. The  $\alpha$  subunit binds guanosine triphosphate (GTP), and the  $\beta$  and  $\gamma$  subunits anchor the G protein in the cell membrane

**Figure 2.3**

The recognition of chemical signals by G protein-coupled membrane receptors affects the activity of adenyl cyclase. PP<sub>i</sub> = inorganic pyrophosphate.

(Figure 2.3). Binding of an agonist to the receptor increases GTP binding to the  $\alpha$  subunit, causing dissociation of the  $\alpha$ -GTP complex from the  $\beta\gamma$  complex. The  $\alpha$  and  $\beta\gamma$  subunits are then free to interact with specific cellular effectors, usually an enzyme or an ion channel, that cause further actions within the cell. These responses usually last several seconds to minutes. Often, the activated effectors produce “second messenger” molecules that further activate other effectors in the cell, causing a signal cascade effect.

A common effector, activated by G<sub>s</sub> and inhibited by G<sub>i</sub>, is adenyl cyclase, which produces the second messenger cyclic adenosine monophosphate (cAMP). The effector phospholipase C, when activated by G<sub>q</sub>, generates two second messengers: inositol 1,4,5-trisphosphate (IP<sub>3</sub>) and diacylglycerol (DAG). DAG and cAMP activate specific protein kinases within the cell, leading to a myriad of physiological effects. IP<sub>3</sub> increases intracellular calcium concentration, which in turn activates other protein kinases.

3. **Enzyme-linked receptors:** This family of receptors undergoes conformational changes when activated by a ligand, resulting in increased intracellular enzyme activity (Figure 2.4). This response lasts for minutes to hours. The most common enzyme-linked receptors (for example, growth factors and insulin) possess tyrosine kinase activity. When activated, the receptor phosphorylates tyrosine residues on itself and other specific proteins (Figure 2.4). Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch. For example, the phosphorylated insulin receptor in turn phosphorylates other proteins that now become active. Thus, enzyme-linked receptors often cause a signal cascade effect similar to that caused by G protein-coupled receptors.
4. **Intracellular receptors:** The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and, therefore, the ligand (for example, steroid hormones) must have sufficient lipid solubility to diffuse into the cell to interact with the receptor (Figure 2.5). The primary targets of activated intracellular receptors are transcription factors in the cell nucleus that regulate gene expression. The activation or inactivation of transcription factors alters the transcription of DNA into RNA and subsequently translation of RNA into proteins. The effect of drugs or endogenous ligands that activate intracellular receptors takes hours to days to occur. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes. For example, tubulin is the target of antineoplastic agents such as paclitaxel (see Chapter 35), the enzyme dihydrofolate reductase is the target of antimicrobials such as trimethoprim (see Chapter 31), and the 50S subunit of the bacterial ribosome is the target of macrolide antibiotics such as erythromycin (see Chapter 30).

#### D. Characteristics of signal transduction

Signal transduction has two important features: 1) the ability to amplify small signals and 2) mechanisms to protect the cell from excessive stimulation.

**1. Signal amplification:** A characteristic of G protein-linked and enzyme-linked receptors is the ability to amplify signal intensity and duration via the signal cascade effect. Additionally, activated G proteins persist for a longer duration than does the original agonist–receptor complex. The binding of *albuterol*, for example, may only exist for a few milliseconds, but the subsequent activated G proteins may last for hundreds of milliseconds. Further prolongation and amplification of the initial signal are mediated by the interaction between G proteins and their respective intracellular targets. Because of this amplification, only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response. Systems that exhibit this behavior are said to have spare receptors. About 99% of insulin receptors are “spare,” providing an immense functional reserve that ensures that adequate amounts of glucose enter the cell. On the other hand, only about 5% to 10% of the total  $\beta$ -adrenoceptors in the heart are spare. Therefore, little functional reserve exists in the failing heart, because most receptors must be occupied to obtain maximum contractility.

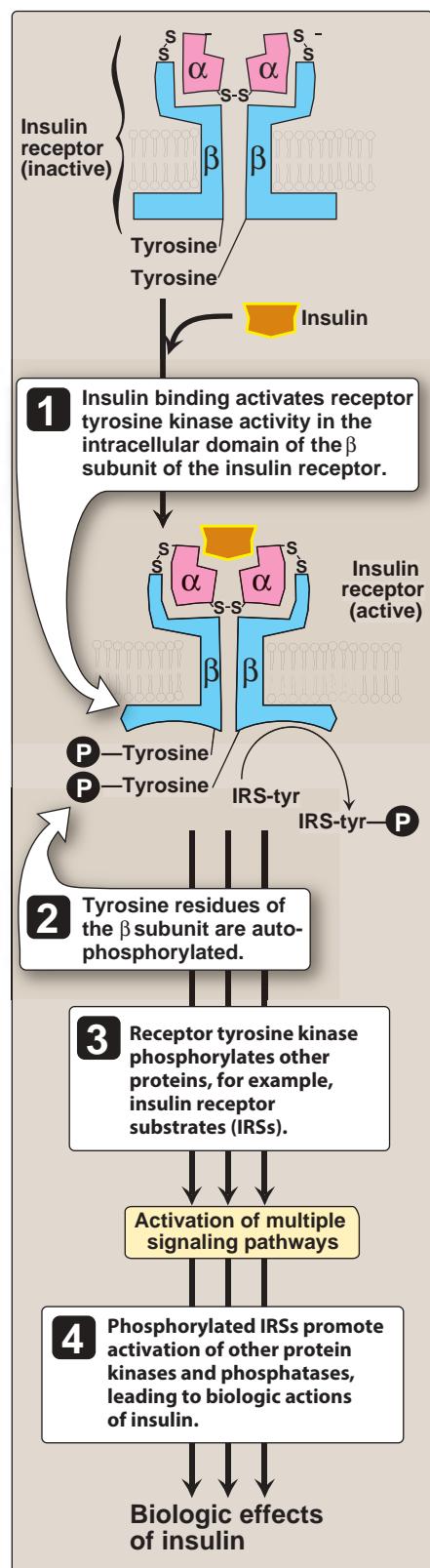
**2. Desensitization and down-regulation of receptors:** Repeated or continuous administration of an agonist or antagonist often leads to changes in the responsiveness of the receptor. The receptor may become desensitized due to too much agonist stimulation (Figure 2.6), resulting in a diminished response. This phenomenon, called tachyphylaxis, is often due to phosphorylation that renders receptors unresponsive to the agonist. In addition, receptors may be internalized within the cell, making them unavailable for further agonist interaction (down-regulation). Some receptors, particularly ion channels, require a finite time following stimulation before they can be activated again. During this recovery phase, unresponsive receptors are said to be “refractory.” Repeated exposure of a receptor to an antagonist, on the other hand, results in up-regulation of receptors, in which receptor reserves are inserted into the membrane, increasing the number of receptors available. Up-regulation of receptors can make cells more sensitive to agonists and/or more resistant to effects of the antagonist.

### III. DOSE–RESPONSE RELATIONSHIPS

Agonist drugs mimic the action of the endogenous ligand for the receptor (for example, *isoproterenol* mimics norepinephrine on  $\beta_1$  receptors of the heart). The magnitude of the drug effect depends on receptor sensitivity to the drug and the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug’s pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination.

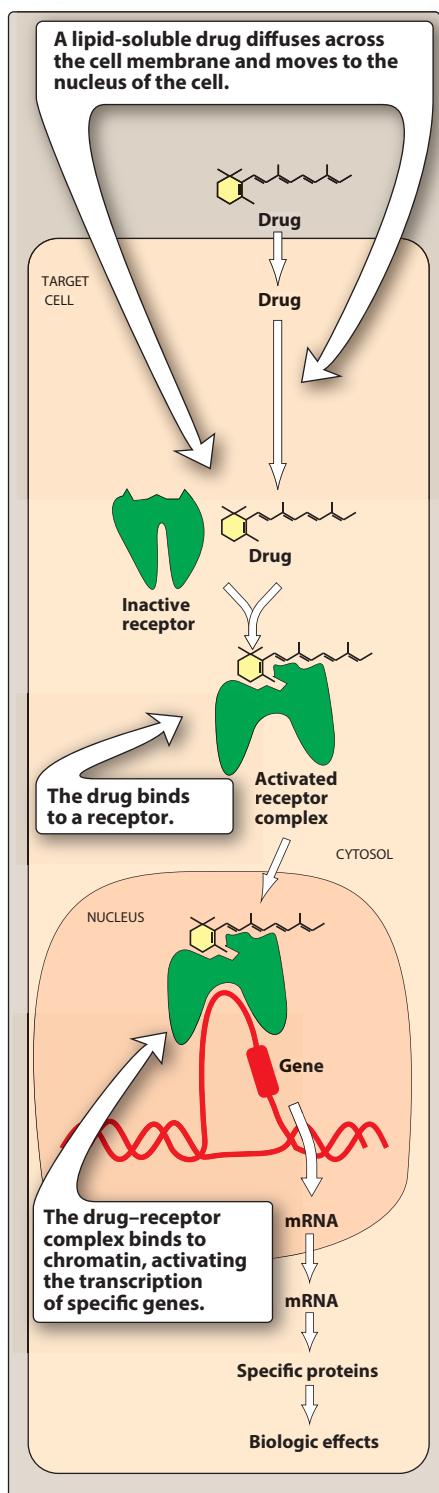
#### A. Graded dose–response relations

As the concentration of a drug increases, its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect). Plotting the magnitude of response against increasing doses of a drug produces a graded dose–response curve that



**Figure 2.4**

Insulin receptor.

**Figure 2.5**

Mechanism of intracellular receptors.  
mRNA = messenger RNA.

has the general shape depicted in **Figure 2.7A**. Two important drug characteristics, potency and efficacy, can be determined by graded dose-response curves.

- 1. Potency:** Potency is a measure of the amount of drug necessary to produce an effect. The concentration of drug producing 50% of the maximum effect ( $EC_{50}$ ) is often used to determine potency. In **Figure 2.7**, the  $EC_{50}$  for Drugs A and B indicate that Drug A is more potent than Drug B, because a lesser amount of Drug A is needed to obtain 50% effect. Therapeutic preparations of drugs reflect their potency. For example, *candesartan* and *irbesartan* are angiotensin receptor blockers used to treat hypertension. The therapeutic dose range for *candesartan* is 4 to 32 mg, as compared to 75 to 300 mg for *irbesartan*. Therefore, *candesartan* is more potent than *irbesartan* (it has a lower  $EC_{50}$  value). Since the range of drug concentrations that cause from 1% to 99% of maximal response usually spans several orders of magnitude, semilogarithmic plots are used to graph the complete range of doses. As shown in **Figure 2.7B**, the curves become sigmoidal in shape, which simplifies the interpretation of the dose-response curve.
- 2. Efficacy:** Efficacy is the magnitude of response a drug causes when it interacts with a receptor. Efficacy is dependent on the number of drug-receptor complexes formed and the intrinsic activity of the drug (its ability to activate the receptor and cause a cellular response). Maximal efficacy of a drug ( $E_{max}$ ) assumes that the drug occupies all receptors, and no increase in response is observed in response to higher concentrations of drug. The maximal response differs between full and partial agonists, even when the drug occupies 100% of the receptors. Similarly, even though an antagonist occupies 100% of the receptor sites, no receptor activation results and  $E_{max}$  is zero. Efficacy is a more clinically useful characteristic than potency, since a drug with greater efficacy is more therapeutically beneficial than one that is more potent. **Figure 2.8** shows the response to drugs of differing potency and efficacy.

## B. Effect of drug concentration on receptor binding

The quantitative relationship between drug concentration and receptor occupancy applies the law of mass action to the kinetics of the binding of drug and receptor molecules:



By making the assumption that the binding of one drug molecule does not alter the binding of subsequent molecules and applying the law of mass action, we can mathematically express the relationship between the percentage (or fraction) of bound receptors and the drug concentration:

$$\frac{[\text{DR}]}{[\text{R}_t]} = \frac{[\text{D}]}{K_d + [\text{D}]} \quad (1)$$

where  $[\text{D}]$  = the concentration of free drug,  $[\text{DR}]$  = the concentration of bound drug,  $[\text{R}_t]$  = the total number of receptors, and  $K_d$  = the equilibrium dissociation constant for the drug from the receptor. The value of  $K_d$  can be used to determine the affinity of a drug for its receptor.

Affinity describes the strength of the interaction (binding) between a ligand and its receptor. The higher the  $K_d$  value, the weaker the interaction and the lower the affinity, and vice versa. Equation (1) defines a curve that has the shapes shown in Figure 2.9 when plotted against drug concentration (Panel A) or log drug concentration (Panel B). As the concentration of free drug increases, the ratio of the concentrations of bound receptors to total receptors approaches unity, thereby producing the maximal effect. Thus, it is not surprising that the curves shown in Figure 2.9 and those representing the relationship between dose and effect (Figure 2.7) are similar.

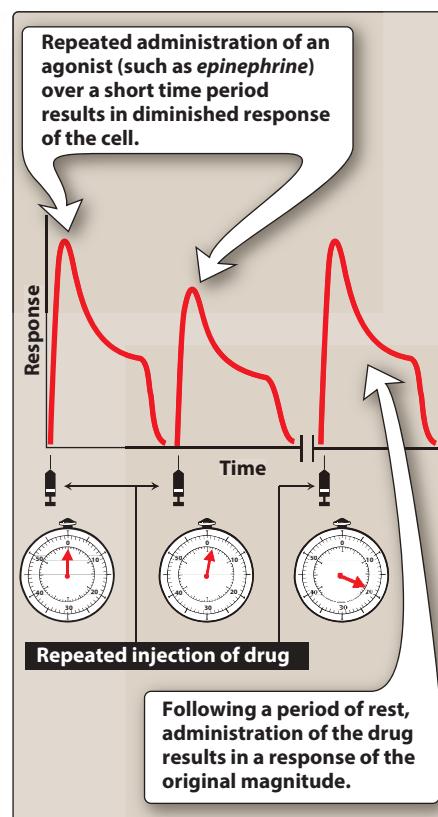
### C. Relationship of drug binding to pharmacologic effect

The law of mass action can be applied to drug concentration and response providing the following assumptions are met: 1) The magnitude of the response is proportional to the amount of receptors occupied by drug, 2) the  $E_{max}$  occurs when all receptors are bound, and 3) one molecule of drug binds to only one molecule of receptor. In this case,

$$\frac{[E]}{[E_{max}]} = \frac{[D]}{K_d + [D]} \quad (2)$$

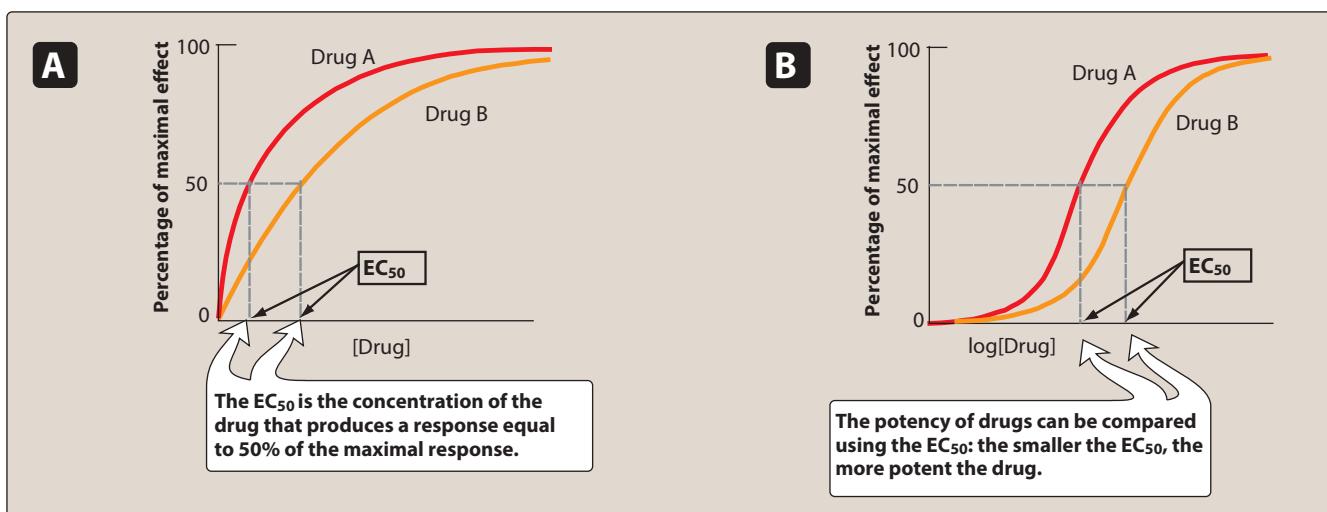
where  $[E]$  = the effect of the drug at concentration  $[D]$  and  $[E_{max}]$  = the maximal effect of the drug.

Thus, it follows that if a specific population of receptors is vital for mediating a physiological effect, the affinity of an agonist for binding to those receptors should be related to the potency of that drug for causing that physiological effect. Many drugs and most neurotransmitters can bind to more than one type of receptor, thereby causing both desired therapeutic effects and undesired adverse effects. In order to establish a relationship between drug occupation of a particular receptor subtype and the corresponding biological response to that drug, correlation curves of receptor affinity and drug potency are often constructed (Figure 2.10).



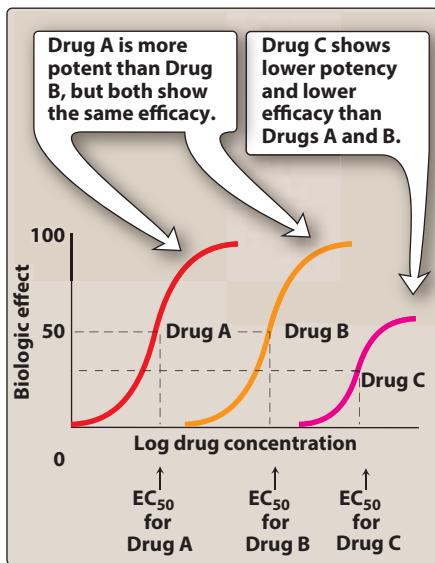
**Figure 2.6**

Desensitization of receptors.



**Figure 2.7**

The effect of dose on the magnitude of pharmacologic response. **Panel A** is a linear plot. **Panel B** is a semilogarithmic plot of the same data.  $EC_{50}$  = drug dose causing 50% of maximal response.



**Figure 2.8**

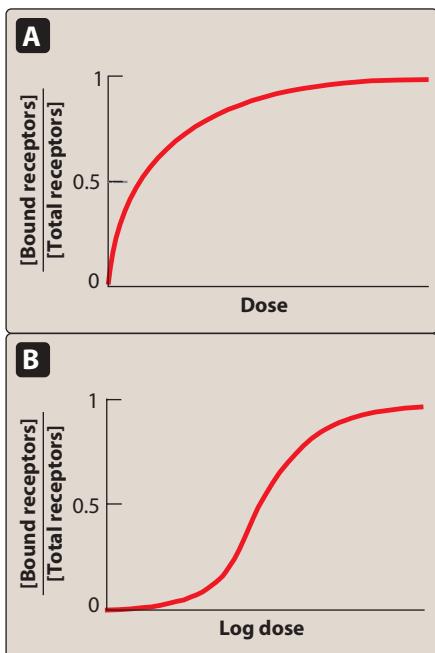
Typical dose–response curve for drugs showing differences in potency and efficacy.  $EC_{50}$  = drug dose that shows 50% of maximal response.

## IV. INTRINSIC ACTIVITY

As mentioned in the preceding text, an agonist binds to a receptor and produces a biologic response based on the concentration of the agonist, its affinity for the receptor and, hence, the fraction of occupied receptors. However, the intrinsic activity of a drug further determines its ability to fully or partially activate the receptors. Drugs may be categorized according to their intrinsic activity and resulting  $E_{max}$  values.

### A. Full agonists

If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is a full agonist (Figure 2.11). Full agonists bind to a receptor, stabilizing the receptor in its active state and are said to have an intrinsic activity of one. All full agonists for a receptor population should produce the same  $E_{max}$ . For example, *phenylephrine* is a full agonist at  $\alpha_1$ -adrenoceptors, because it produces the same  $E_{max}$  as the endogenous ligand, norepinephrine. Upon binding to  $\alpha_1$ -adrenoceptors on vascular smooth muscle, both norepinephrine and *phenylephrine* stabilize the receptor in its active state, thereby increasing  $G_q$  activation. Activation of  $G_q$  increases intracellular  $Ca^{2+}$ , causing interaction of actin and myosin filaments and shortening of the muscle cells. The diameter of the arteriole decreases, causing an increase in resistance to blood flow through the vessel and an increase in blood pressure. Thus, effects of agonists on intracellular molecules, cells, tissues, and intact organisms are all attributable to interaction of the drug with the receptor. For full agonists, the dose–response curves for receptor binding and each of the biological responses should be comparable.



**Figure 2.9**

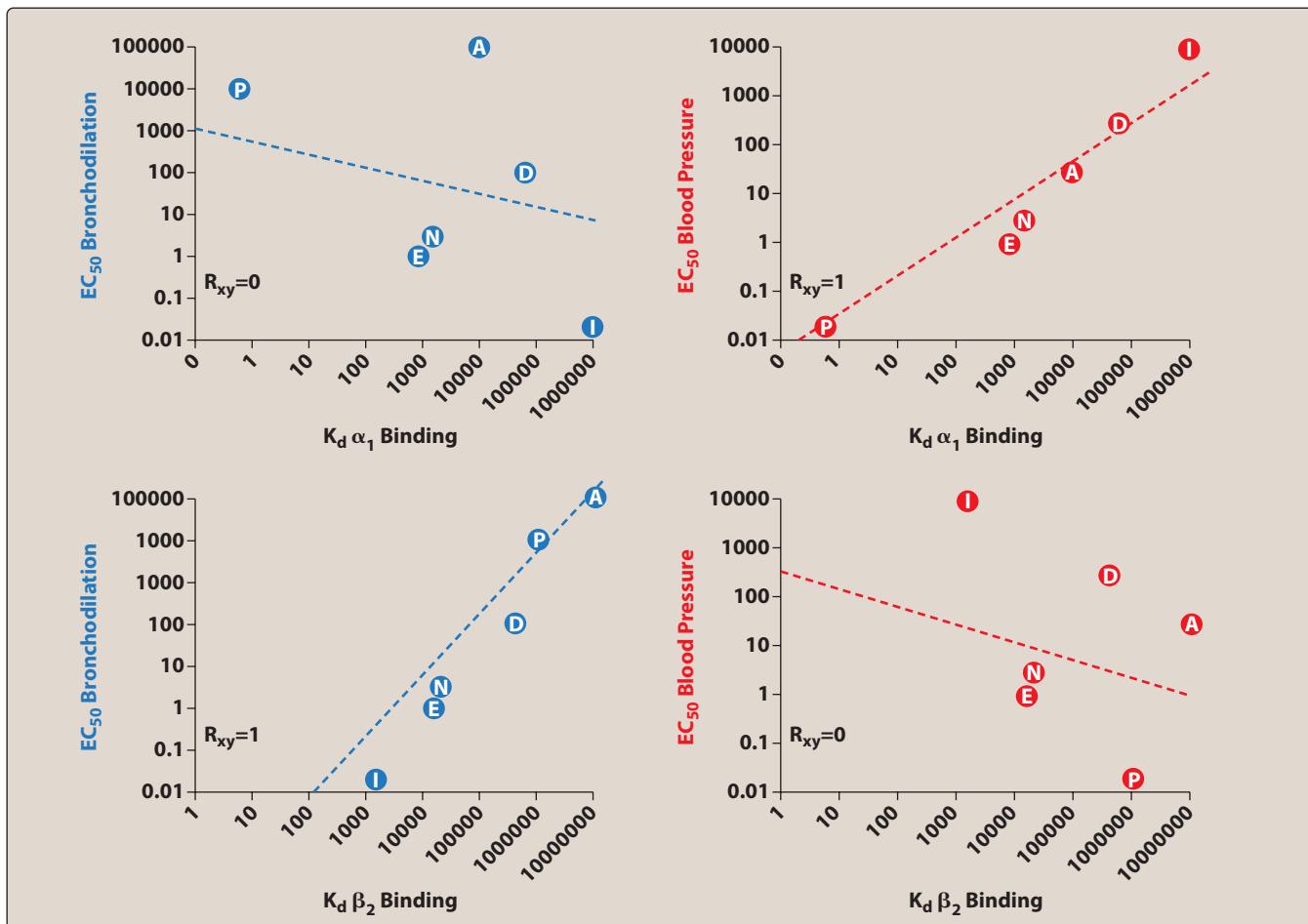
The effect of dose on the magnitude of drug binding.

### B. Partial agonists

Partial agonists have intrinsic activities greater than zero but less than one (Figure 2.11). Even when all the receptors are occupied, partial agonists cannot produce the same  $E_{max}$  as a full agonist. Even so, a partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist. A partial agonist may also act as a partial antagonist of a full agonist (Figure 2.12). As the number of receptors occupied by the partial agonist increases, the number of receptors that can be occupied by the full agonist decreases and therefore  $E_{max}$  would decrease until it reached the  $E_{max}$  of the partial agonist. This potential of partial agonists to act as both an agonist and an antagonist may have therapeutic utility. For example, *ariPIPrazole*, an atypical antipsychotic, is a partial agonist at selected dopamine receptors. Overactive dopaminergic pathways tend to be inhibited by *ariPIPrazole*, whereas underactive pathways are stimulated. This might explain the ability of *ariPIPrazole* to improve symptoms of schizophrenia, with a small risk of causing extrapyramidal adverse effects (see Chapter 11).

### C. Inverse agonists

Typically, unbound receptors are inactive and require interaction with an agonist to assume an active conformation. However, some receptors show a spontaneous conversion from R to  $R^*$  in the absence of

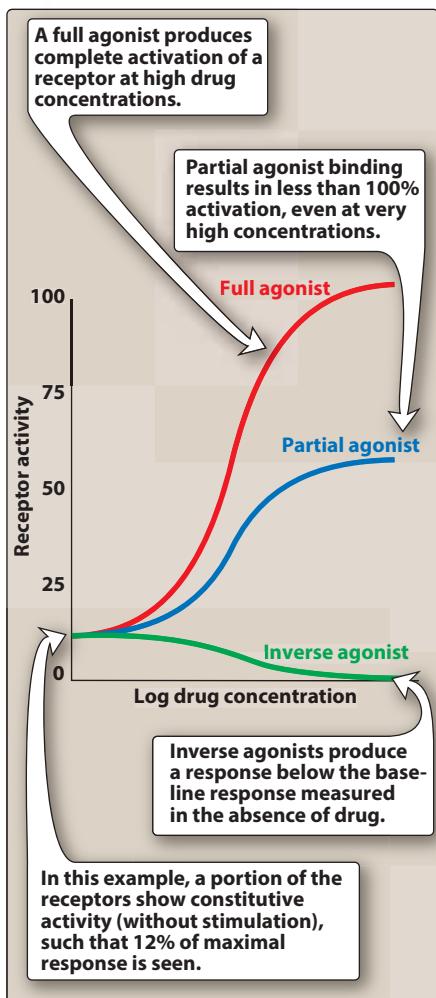
**Figure 2.10**

Correlation of drug affinity for receptor binding and potency for causing a physiological effect. A positive correlation should exist between the affinity ( $K_d$  value) of a drug for binding to a specific receptor subtype and the potency (EC<sub>50</sub> value) of that drug to cause physiological responses mediated by that receptor population. For example, many drugs have affinity for both  $\alpha_1$  and  $\beta_2$  adrenergic receptors. The circled letters in the figure represent agonists with varying affinities for  $\alpha_1$  and  $\beta_2$  receptors. However, from the data provided, it becomes clear that  $\alpha_1$  receptors only mediate changes in blood pressure, while  $\beta_2$  receptors only mediate changes in bronchodilation.

an agonist. Inverse agonists, unlike full agonists, stabilize the inactive R form and cause R\* to convert to R. This decreases the number of activated receptors to below that observed in the absence of drug (Figure 2.11). Thus, inverse agonists have an intrinsic activity less than zero, reverse the activation state of receptors, and exert the opposite pharmacological effect of agonists.

#### D. Antagonists

Antagonists bind to a receptor with high affinity but possess zero intrinsic activity. An antagonist has no effect on biological function in the absence of an agonist, but can decrease the effect of an agonist when present. Antagonism may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.



**Figure 2.11**

Effects of full agonists, partial agonists, and inverse agonists on receptor activity.

1. **Competitive antagonists:** If the antagonist binds to the same site on the receptor as the agonist in a reversible manner, it is “competitive.” A competitive antagonist interferes with an agonist binding to its receptor and maintains the receptor in its inactive state. For example, the antihypertensive drug *terazosin* competes with the endogenous ligand norepinephrine at  $\alpha_1$ -adrenoceptors, thus decreasing vascular smooth muscle tone and reducing blood pressure. However, increasing the concentration of agonist relative to antagonist can overcome this inhibition. Thus, competitive antagonists characteristically shift the agonist dose-response curve to the right (increased  $EC_{50}$ ) without affecting  $E_{max}$  (Figure 2.13).
2. **Irreversible antagonists:** Irreversible antagonists bind covalently to the active site of the receptor, thereby permanently reducing the number of receptors available to the agonist. An irreversible antagonist causes a downward shift of the  $E_{max}$ , with no shift of  $EC_{50}$  values (Figure 2.13). In contrast to competitive antagonists, addition of more agonist does not overcome the effect of irreversible antagonists. Thus, irreversible antagonists and allosteric antagonists (see below) are both considered noncompetitive antagonists. A fundamental difference between competitive and noncompetitive antagonists is that competitive antagonists reduce agonist potency (increase  $EC_{50}$ ) and noncompetitive antagonists reduce agonist efficacy (decrease  $E_{max}$ ).
3. **Allosteric antagonists:** An allosteric antagonist binds to a site (allosteric site) other than the agonist-binding site and prevents receptor activation by the agonist. This type of antagonist also causes a downward shift of the  $E_{max}$  of an agonist, with no change in the  $EC_{50}$  value. An example of an allosteric agonist is picrotoxin, which binds to the inside of the GABA-controlled chloride channel. When picrotoxin binds inside the channel, no chloride can pass through the channel, even when the GABA fully occupies the receptor.
4. **Functional antagonism:** An antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist. A classic example is the functional antagonism by *epinephrine* to histamine-induced bronchoconstriction. Histamine binds to  $H_1$  histamine receptors on bronchial smooth muscle, causing bronchoconstriction of the bronchial tree. Epinephrine is an agonist at  $\beta_2$ -adrenoceptors on bronchial smooth muscle, which causes the muscles to relax. This functional antagonism is also known as “physiologic antagonism.”

## V. QUANTAL DOSE-RESPONSE RELATIONSHIPS

Another important dose-response relationship is that between the dose of the drug and the proportion of a population of patients that responds to it. These responses are known as quantal responses, because, for any individual, either the effect occurs or it does not. Graded responses can be transformed to quantal responses by designating a predetermined level of the graded response as the point at which a response occurs or not. For example, a quantal dose-response relationship can be determined in a population for the antihypertensive drug *atenolol*. A positive response is defined as a fall of at least 5 mm Hg in diastolic blood pressure. Quantal

dose–response curves are useful for determining doses to which most of the population responds. They have similar shapes to log dose–response curves, and the  $ED_{50}$  is the drug dose that causes a therapeutic response in half of the population.

### A. Therapeutic index

The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population ( $TD_{50}$ ) to the dose that produces a clinically desired or effective response ( $ED_{50}$ ) in half the population:

$$TI = TD_{50} / ED_{50}$$

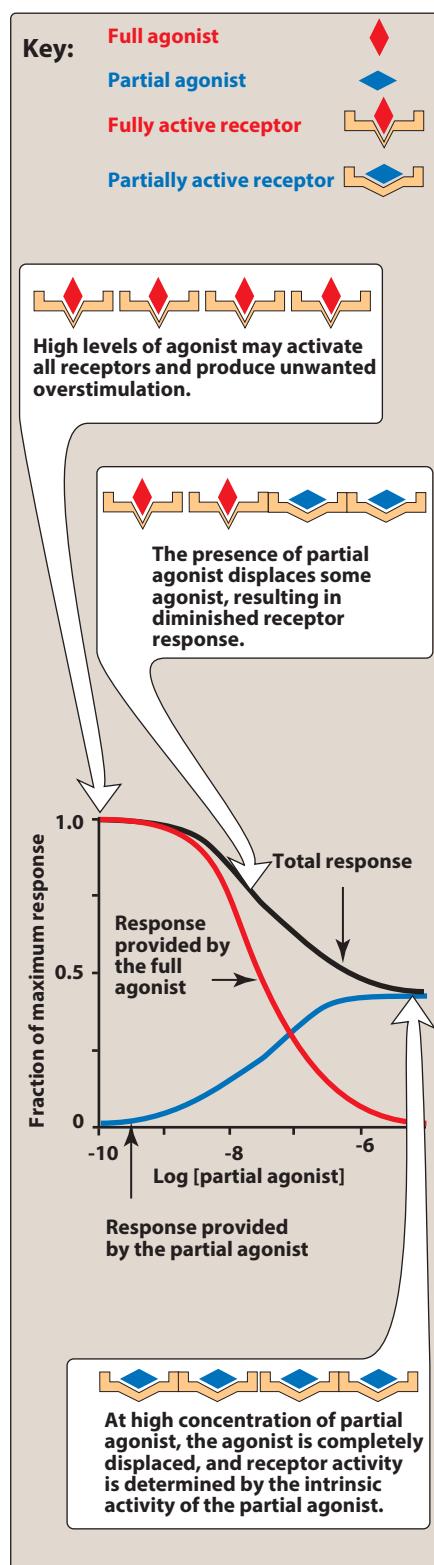
The TI is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

### B. Clinical usefulness of the therapeutic index

The TI of a drug is determined using drug trials and accumulated clinical experience. These usually reveal a range of effective doses and a different (sometimes overlapping) range of toxic doses. Although high TI values are required for most drugs, some drugs with low therapeutic indices are routinely used to treat serious diseases. In these cases, though more adverse effects may be experienced, the risk of experiencing adverse effects should be weighed against the risk of leaving the disease untreated. Cytotoxic agents, used in cancer chemotherapy and antiepileptic drugs, are examples of drugs where there is little difference between the therapeutic dose and the toxic dose. Thus, cytotoxic agents are said to have a small therapeutic index. Other examples of some drugs with a narrow therapeutic index are *lithium*, *digoxin*, *gentamicin*, *phenytoin*, and *carbamazepine*. These drugs have a recommended therapeutic range with lower and upper values of the concentration of the drug in blood at which majority of the users can expect a clinical effect with minimal adverse effects. If the concentration falls below the lower limit, the effect diminishes. If it rises above the upper limit, patients may experience adverse effects. The concentration range is called the recommended therapeutic range. Figure 2.14 shows the responses to *warfarin*, an oral anticoagulant with a low therapeutic index, and *penicillin*, an antimicrobial drug with a large therapeutic index.

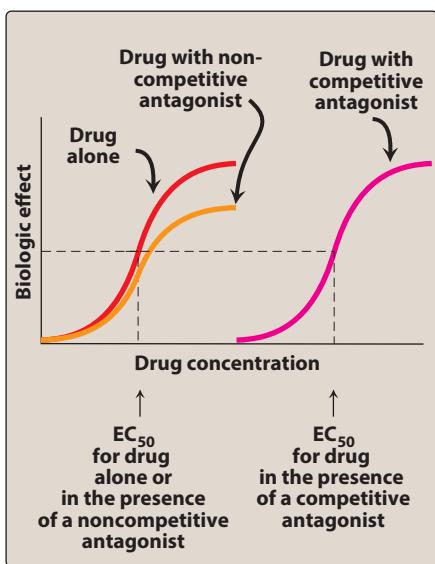
**1. Warfarin (example of a drug with a small therapeutic index):** As the dose of *warfarin* is increased, a greater fraction of the patients respond (for this drug, the desired response is a two- to threefold increase in the international normalized ratio [INR]) until, eventually, all patients respond (Figure 2.14A). However, at higher doses of *warfarin*, anticoagulation resulting in hemorrhage occurs in a small percent of patients. Agents with a low TI (that is, drugs for which dose is critically important) are those drugs for which bioavailability critically alters the therapeutic effects (see Chapter 1).

**2. Penicillin (example of a drug with a large therapeutic index):** For drugs such as *penicillin* (Figure 2.14B), it is safe and common to give doses in excess of that which is minimally required to achieve a desired response without the risk of adverse effects. In this case, bioavailability does not critically alter the therapeutic or clinical effects.

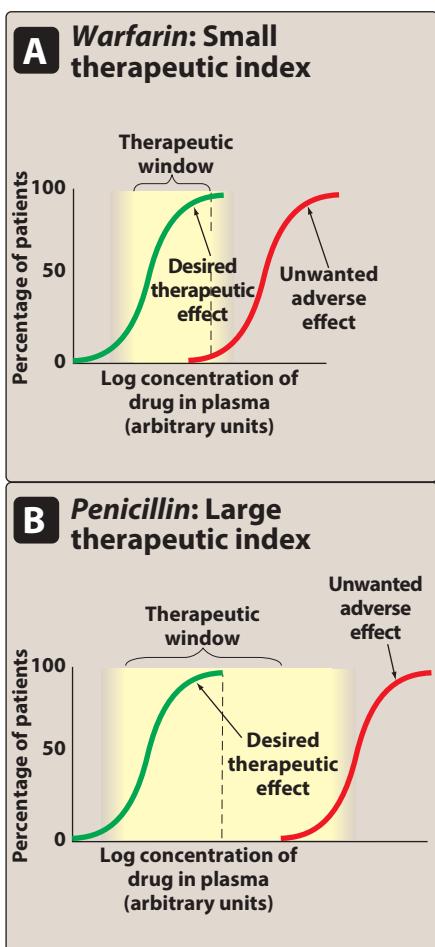


**Figure 2.12**

Effects of partial agonists.

**Figure 2.13**

Effects of drug antagonists.

 $EC_{50}$  = drug dose that shows 50% of maximal response.**Figure 2.14**

Cumulative percentage of patients responding to plasma levels of warfarin and penicillin.

## VI. EVALUATION OF RESPONSE TO THERAPY

The objective of drug therapy is to produce the desired therapeutic effect with minimum toxic effects. However, patients vary widely in their responses to drugs. This variability continues to be a major public health problem due to serious and apparently unpredictable adverse drug reactions. Therapy must be individualized—that is, a drug should be prescribed after careful consideration of its beneficial and minimal harmful effects including the patient's characteristics and comorbidities.

The reasons for failure of drug treatment can be due to interindividual variation in physiological and pharmacokinetic parameters, which cannot always be evaluated prior to initiation of drug therapy (for example, genetic metabolic differences) or pharmacodynamics (for example, drug hypersensitivity), and drug tolerance (diminished pharmacologic responsiveness to the drug). Response to a drug can be altered by disease state and draw attention to dosage individualization.

The usual dosage regimen approved by Drug Control Authorities suits an average patient's needs. As a principle, individualization of the dosing regimen is required considering the patient's characteristics (for example, weight and age) and comorbidities that affect the drug's pharmacokinetics (for example, liver and renal function).

To achieve an optimal effect, the patient's response to the drug must be evaluated from time to time. The dosage regimen needs to be further modified in case of no-response to therapy or due to the appearance of undesirable effects. Both clinical and laboratory tests (hemoglobin, INR prothrombin time) can help in evaluation of response to therapy, which may improve the monitoring of treatment.

### A. Factors affecting drug response

Variability in drug responses can be observed due to genetic difference and pharmacokinetic and pharmacodynamic variability. The most important factors responsible for variability of pharmacokinetic parameters are as follows:

- Genetic
- Disease
- Age and body size
- Concomitant drugs
- Environmental factors (for example, foods and pollutants)

Other factors include compliance, pregnancy, alcohol intake, seasonal variations, gender, or conditions of drug intake (Figure 2.15).

#### 1. Variation in response due to changes in pharmacokinetics:

Diseases of the liver and the kidneys are responsible for large variations in drug pharmacokinetics. Circulatory disorders and diminished vascular perfusion of one or more parts of the body as in cardiac failure are also an important cause of pharmacokinetic variability.

Age-induced variability can be seen in each of the four main pharmacokinetic mechanisms given in the following text.

- a. **Drug absorption:** Drug absorption rates may vary widely between individuals and in the same individual at different

times and in different physiological states. Drugs taken after a meal reach the small intestine much more slowly than in the fasting state, leading to much lower drug concentrations. In pregnancy, gastric emptying gets delayed while some drugs may also increase gastric emptying and affect absorption of other drugs.

Poorly formulated drugs may fail to disintegrate or dissolve and thus affect drug response. Enteric-coated drugs sometimes can pass through the gastrointestinal tract intact. In drugs with a narrow therapeutic range, changes in absorption can produce sudden changes in drug levels. For such drugs, quality control surveillance should be carried out.

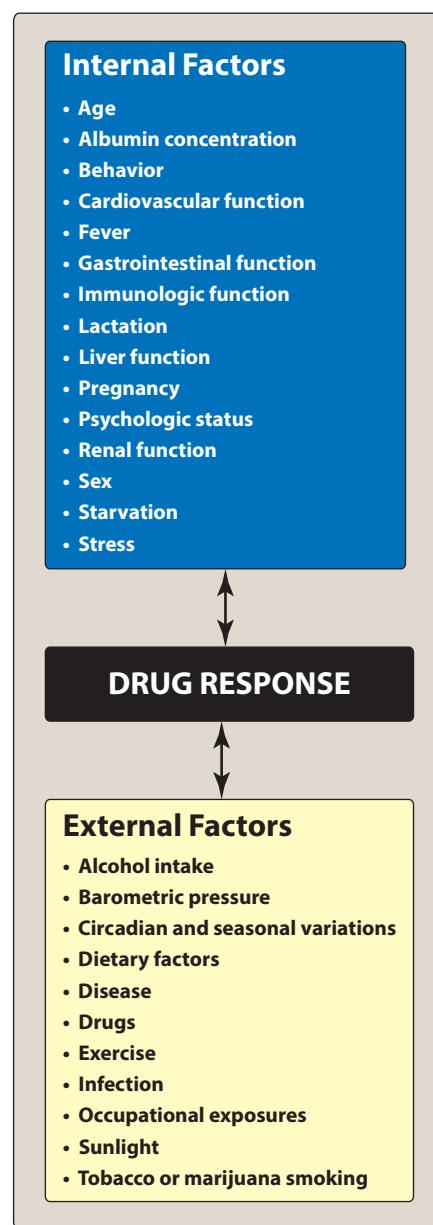
Though drug absorption does not appear to change dramatically with age, changes in the rate rather than in the extent of absorption are found. As exceptions, marked differences in absorption are observed in the neonatal period and in the elderly. In both cases, a decrease in hepatic metabolism and first-pass effect may lead to an increase in the oral bioavailability of some drugs.

Age-related physiologic changes in the gastrointestinal (GI) tract include elevated gastric pH, delayed gastric emptying, decreases in GI motility, intestinal blood flow, and absorptive surface area. Reduced gastric acid secretion can reduce tablet dissolution and decrease the solubility of basic drugs. The delay in gastric emptying allows more contact time in the stomach for potentially ulcerogenic drugs such as NSAIDs and bisphosphonates, increased absorption of poorly soluble drugs, and increased antacid drug interactions due to an increased opportunity for binding. A higher incidence of diarrhea and a delay in the onset of action of weak basic drugs also result from this physiologic effect. In the elderly patients, absorption of nutrients is often reduced, for example, vitamins (such as thiamine and folic acid), minerals (such as calcium and iron), and carbohydrates.

### b. Drug distribution

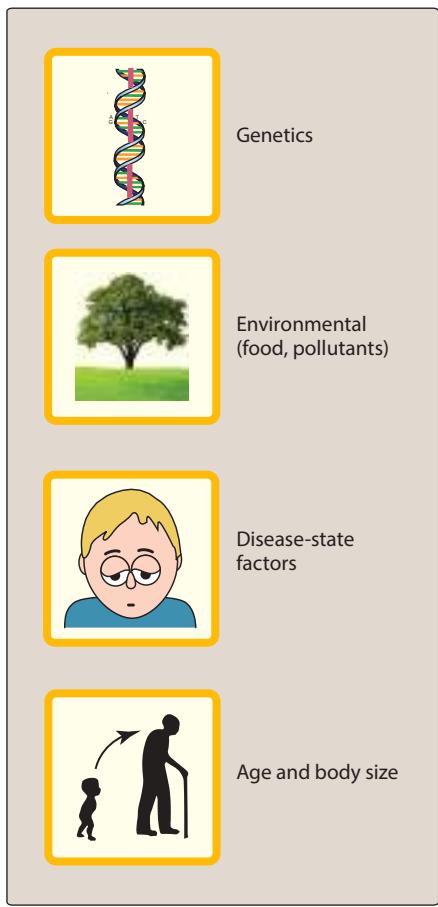
[1] **Wide variation in drug distribution:** Water-soluble drugs are distributed chiefly in the extracellular space, acidic drugs bind strongly to plasma albumin, basic drugs bind to muscle cells, and fat-soluble drugs are stored in adipose tissue. Hence, variation in plasma albumin concentration, fat content, or muscle mass may all contribute to dose variation. For very highly albumin-bound drugs such as *warfarin*, a small change in albumin concentration can double the levels of free drug in circulation with a dramatic change in the drug effect.

The volume of distribution is frequently directly proportional to body weight and modulated by age. Body fat content and water composition get altered with aging. Fat stores increase while total body water decreases. These changes can alter therapeutic drug levels, causing greater concentrations of water-soluble drugs (for example, alcohol, lithium, and morphine) and longer half-lives of fat-soluble drugs (for example, most tricyclic



**Figure 2.15**

Factors affecting drug response.

**Figure 2.16**

Factors affecting drug metabolism.

antidepressants, barbiturates, benzodiazepines, calcium channel blockers, and phenothiazines) which may have a delayed onset of action and can accumulate in adipose tissue, prolonging their action sometimes to the point of toxicity. All of these drugs are considered inappropriate in the elderly due to availability of safe alternatives.

Sometimes, age-related changes in drug binding (for example, decrease in extracellular fluid in the elderly) can affect the volume of distribution of a drug. In the elderly, if there is evidence of decreased serum albumin, the doses of most highly protein-bound drugs (>90% protein bound) should be reduced initially and then increased slowly. Seizure control may be seen at lower total *phenytoin* (bound plus unbound) concentrations in the elderly whose unbound fraction has increased. Similarly, decrease in serum albumin levels seen commonly in the elderly with chronic illnesses, malnutrition, or severe debilitation can lead to higher drug blood levels. For these reasons, elderly patients may be more sensitive to some drugs and less sensitive to others.

- c. **Drug metabolism:** Drug metabolism is affected by genetic, environmental, age, and disease-state factors (Figure 2.16). The enzymes involved in both phase I and phase II metabolism mature gradually following the postpartum period in the first 2 to 4 weeks. Full maturity in metabolism appears in the second decade of life with a subsequent slow decline in organ function (around 1% per year) associated with aging. Also, because the metabolism of many drugs (for example, most  $\beta$ -blockers, lidocaine, narcotic analgesics) takes place in liver, thus any age-related changes, or changes such as reduced hepatic blood flow and liver size may alter drug clearance, which in turn can increase the drug concentration leading to toxicity.

Most subjects have a normal distribution of drug metabolizing capacity; however, due to genetic polymorphism individuals, a small proportion of the population may be either of the fast or of the slow acetylator type (for example, *isoniazid* and *phenytoin*). Many drugs are eliminated by the kidneys unchanged (without being metabolized). Renal disease or toxicity of other drugs on the kidney can, therefore, slow the excretion of some drugs.

Hepatic disorders affect not only the metabolism (in cirrhosis) and excretion of drugs (in obstructive jaundice) but also their absorption (through first-pass effect) and distribution (through protein binding). In conditions such as cirrhosis, the oral bioavailability of drugs undergoing a substantial hepatic first-pass effect can be greatly increased. In patients with hepatic impairment, there is a decrease in plasma protein synthesis by the liver. This decrease in proteins may affect the volume of distribution of extensively protein-bound drugs.

- d. **Excretion:** Renal clearance normalized for body weight is lower in neonates but then it rapidly increases with the

maximum being at 6 months of age. Throughout adulthood, renal function declines at the rate of 1% per year approximately. In patients with a compromised renal function, urinary excretion of drugs is diminished. In the elderly, renal function is reduced by an average of 50% (due to age-related or chronic disease-related decrease in kidney size, renal blood flow, and glomerular filtration rates) limiting elimination of many drugs from the body which in turn results in higher drug concentrations and an enhanced pharmacologic response, or toxicity.

Therefore, special attention should be given to the evaluation of the patients with impaired renal and hepatic function. If the patient has lost more than 50% of the kidney function, the dosage regimen of many drugs primarily excreted by the kidney should be adapted accordingly to avoid toxic accumulation of the drug in the body.

- 2. Pharmacodynamic variables (Figure 2.17):** Significant variation in receptor response is seen with some drugs, especially central nervous system responses, for example, pain and sedation. This can be because of genetic factors, tolerance, concurrent diseases affecting the patient, drug interactions, and drug dependence.

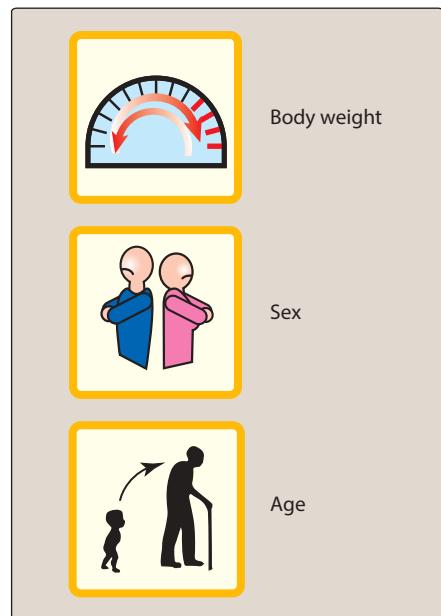
**a. Body weight and sex:** Although the concept of varying the dose with the body weight or age of children is widely followed, adult doses have been assumed to be the same irrespective of size or shape although adult weights may vary two- to threefold. A patient with a large fat mass can store large excesses of highly lipid-soluble drugs compared with a lean patient of the same weight. Females have a smaller body size and require doses on the lower side of the range. Some drugs interfere with the sexual function of males exclusively and should be avoided, if possible, for example, ketoconazole, statins and fibrates, antidepressants,  $\beta$ -blockers, and  $\alpha$ -blockers.

**b. Age:**

[1] **Children:** All children, and particularly neonates, differ from adults in their response to drugs. Some drugs are likely to cause problems in neonates (*morphine*), but are generally tolerated in children. *Valproic acid* is associated with increased risk of adverse drug reactions (ADRs) in children of all ages. Other drugs associated with problems in children include *chloramphenicol* (grey baby syndrome), *antiarrhythmics* (worsening of arrhythmias), and *acetylsalicylic acid* (Reye's syndrome).

Children's doses may be calculated from adult doses by using age, body weight, or body surface area or by a combination of these factors. The most reliable methods are those based on the body surface area as drug clearance is considered to correlate better with the body surface area than with the body weight.

Body weight may be used to calculate doses expressed in mg/kg. Young children may require a higher dose per kilogram than adults because of their higher metabolic



**Figure 2.17**

Pharmacodynamic variables.

rates. In an overweight child, calculation of dose on per kilo body weight may result in much higher doses being administered than necessary; in such cases, the dose should be calculated on the basis of an ideal weight, related to height and age. Nomograms allow body surface values to be calculated from a child's height and weight.

In case the dose for children is not readily available, the advice of a specialist should be sought before prescribing. In neonates, doses also should always be calculated with care as the risk of toxicity is increased by lack of maturation of renal and hepatic function, relative enzyme deficiencies, differing target organ sensitivity, and inadequate detoxifying systems causing delayed excretion.

#### **Young's formula**

$$\text{Child's dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{Adult dose}$$

#### **Dilling's formula**

$$\text{Child's dose} = \frac{\text{Age}}{20} \times \text{Adult dose}$$

The average body surface area of a 70-kg adult is about 1.8 m<sup>2</sup>.

$$\text{Approximate dose} = \frac{\frac{\text{Surface area}}{\text{of patient (m}^2\text{)}}}{1.8} \times \text{Adult dose}$$

- [2] **Elderly:** In the elderly, drug use generally requires significant reductions in drug dose reflecting the general decline in body function with age. Therefore, more attention should be given to both treatment failure and toxicity. Individuals become dissimilar as they age and react differently to medications than younger persons. Elderly have increased sensitivity to drugs and possible exaggerated pharmacodynamic responses (for example, central nervous system depressants [opioid analgesic, benzodiazepines, antipsychotics, antiparkinsonian drugs]) and also increased sensitivity to adverse effects such as high blood pressure with psychotropic medications and hemorrhage from anticoagulants. However, elderly may be less sensitive to some effects of β-adrenergic agonists (for example, *salbutamol*).

Also because of decreased physiological reserve, symptoms develop at an earlier stage of the disease. Mild hyperthyroidism or hyperparathyroidism can lead to heart failure; mild prostatic enlargement presents as urinary retention; and mild glucose intolerance may present as nonketotic hyperosmolar coma.

In the elderly, distinguishing subtle adverse drug effects from the effects of disease is often difficult which may thus lead to a prescribing cascade. A prescribing cascade occurs when the adverse effect of a drug is

misinterpreted as a symptom or a sign of a new disorder and a new drug is prescribed to treat it. The new, unnecessary drug may cause additional adverse effects, which may then be misinterpreted as yet another disorder and treated unnecessarily with medicines and so on, thus leading to potentially dangerous situations and overprescribing. For example, antipsychotics may cause symptoms that resemble Parkinson's disease and elderly patients may be put on antiparkinson drugs, thus exposing them to adverse effects of these drugs (for example, orthostatic hypotension, delirium, nausea). Another example is of patients on *donepezil*, a cholinesterase inhibitor for the treatment of dementia, who may develop diarrhea or urinary incontinence and receive *oxybutynin*, an anticholinergic drug given to treat these new symptoms. Thus, an unnecessary drug is added, increasing the risk of adverse drug effects and drug-drug interactions. A better strategy is to either reduce the dose of the *donepezil* or consider a different treatment for dementia with *memantine* having a different mechanism of action.

3. **Variation in drug response due to drug interactions:** Polypharmacy is common in elderly as they are likely to be receiving several medicines due to multiple comorbidities. Elderly patients take multiple medications concurrently to manage coexisting health problems, such as diabetes and hypertension. Polypharmacy becomes problematic when patients are prescribed too many medications by multiple healthcare providers working independent of each other. Thus, elderly, especially frail patients, have higher chances of experiencing more drug interactions and adverse drug reactions. The toxicity of certain drug combinations may sometimes be synergistic and greater than the sum of the risks of toxicity of either agent used alone (higher risk of peptic ulcer disease with concurrent oral corticosteroids and NSAIDs). For details, see Section IV.

The elderly also frequently use medicinal herbs and other dietary supplements and often do not inform them to their healthcare providers. Medicinal herbs can interact with prescribed drugs and lead to adverse effects. For example, ginkgo biloba extract taken with *warfarin* can increase the risk of bleeding and St. John's wort taken with an SSRI can increase the risk of serotonin syndrome.

4. **Pharmacogenetic variability:** Substantial ethnic differences in response to most drugs exist among patients, for example, genetic variability in the metabolism of isoniazid which is primarily acetylated in the liver to N-acetyl isoniazid, a precursor of a hepatotoxic compound. Large genetically controlled ethnic differences exist in the distribution of acetylator status (slow and rapid acetylators). Adverse effects may occur prevalently in slow acetylators whereas rapid acetylators may be more susceptible to adverse reactions such as isoniazid-induced hepatic damage and therapeutic failure.

5. **Environmental variables:** Many environmental toxins, pesticides, and anesthetic drugs can induce the hepatic cytochrome

P450 system, leading to more rapid metabolism and elimination of the drugs and thus making treatment less effective. Diet and nutritional status also affect pharmacokinetics. Chronic alcohol use induces oxidation of other drugs, but in the presence of high circulating alcohol concentrations, drug metabolism may be inhibited.

6. **Placebo effect:** Drugs are used based on their known pharmacological effects on somatic and psychological conditions. The term “placebo effect” refers to any therapeutic procedure, without any specific activity, given deliberately to have an effect on a patient, symptom, syndrome, or disease than can simply be explained on the basis of the drugs’ known pharmacological and therapeutic properties. “Nocebo effect” is used when the drug produces a worsening effect on the condition being treated, compared with the pharmacological properties indicated. Placebo effect can have a great impact on response to a medication. It is known, for example, that specific procedures or experiences that are associated with a treatment can influence the outcome of treatment. A prescriber’s behavior before, during, and after a treatment sends important signals to the patient, affecting compliance and response to therapy. If a prescriber provides treatment and simultaneously expresses the fact that it is doubtful that it will work, many patients become skeptical and some of the benefits of the treatment get lost. Likewise, a prescriber who exudes confidence will lessen anxiety more effectively than one who appears uncertain. In other words when positive signals about an effect reinforce the desired effect of a drug, a placebo effect is expressed. On the other hand, if signals concerning an effect weaken the desired effect of the drug, a nocebo effect is expressed.

## B. Clinical evaluation of beneficial and adverse effects

The most important element in the evaluation of positive effects and adverse effects of a drug is a thorough clinical evaluation of the patient. Evaluate each patient after initiating drug therapy, for example, the desired response (for example, analgesia) and the appearance of undesirable effects (for example, sleepiness). While evaluating the benefit of a drug, consider if the drug is necessary and also consider the risk of not taking it and carefully establish benefit versus risk in case of drugs that have serious adverse effects.

1. **Adherence (compliance) to drug treatment:** Very often, it is assumed that treatment will be successful once the appropriate drug treatment is chosen and it is taken correctly. Unfortunately, this is not always the case. One of the most important reasons for treatment failure—that is, poor adherence (compliance) to the treatment plan—is often overlooked by the physician.
2. **Noncompliance with drug treatment:** The reasons for noncompliance may be related to the patient, the disease, the doctor, the prescription, the pharmacist, or the health system and can often be avoided. Patients’ perceptions of the risk and severity of adverse drug reactions may differ from those of the healthcare provider and may affect adherence. Such limitations or attitudes

need to be discussed and taken account of. Specific education interventions have been shown to improve adherence.

a. **Causes of noncompliance (Figure 2.18):** There are many possible reasons for noncompliance. The common reasons are as follows:

- The patient suffers adverse effects.
- The patient does not think the drug is effective.
- The patient forgets to take the drug.
- The patient believes the disease is cured because the symptoms have abated.
- The patient has misunderstood the user instructions.
- The patient has run out of the drug.
- The patient does not master the administration technique, for example, inhalation
- The drug formulation is unsuitable.
- The drug is unacceptable, for example, unpleasant taste
- The patient uses many drugs simultaneously (polypharmacy).
- Frequent dosages
- The patient has other objections toward the use of a certain drug.

[1] **Polypharmacy:** Many chronically ill and elderly patients use several drugs simultaneously (polypharmacy). For some, it can be difficult to remember the different time intervals for taking different drugs. Elderly subjects may sometimes also have difficulty in understanding information and following user instructions. All drug prescriptions should be reviewed regularly to minimize the problems associated with polypharmacy and also to reduce the chances of misuse and adverse effects.

[2] **Disease-related reasons:** Conditions with a known worse prognosis (such as cancer) or painful conditions (such as rheumatoid arthritis) elicit better adherence than asymptomatic “perceived as benign” conditions such as hypertension.

[3] **Doctor reasons:** Doctors may cause poor adherence in many ways—by failing to inspire confidence in the treatment offered, by giving too little or no explanation, by thoughtlessly prescribing too many medicines, by making errors in prescribing, or by their overall attitude to the patient.

[4] **The doctor-patient interaction:** There is considerable evidence that the quality of the doctor-patient interaction is crucial to concordance. “Satisfaction with the consultation” is one of the best predictors of good adherence. Patients, who are well informed, expect a greater say in their health care. If they are in doubt or dissatisfied, they may turn to alternative options, including “complementary medicine.”



**Figure 2.18**

Causes of noncompliance with drug treatment.

3. **Situations where compliance is important:** There are several situations where compliance is of even greater importance than what is considered normal:
  - When using drugs with a narrow therapeutic range
  - When using drugs that may produce serious adverse effects (for example, cytotoxics, immunosuppressants, and anticoagulants)
  - With hormone supplementation (for example, metabolic disease, diabetes, and adrenal failure)
  - In the treatment of glaucoma and epilepsy
  - In the treatment of certain infections, for example, when treating multidrug-resistant tuberculosis and AIDS
4. **Strategies to improve compliance:** The interventions required to improve adherence rates may be classified into the following categories:
  - *Staff motivation and supervision*—includes training and management processes aimed at improving the way in which providers care for patients.
  - *Defaulter action*—the action to be taken when a patient fails to keep a prearranged appointment.
  - *Prompts*—routine reminders for patients to keep prearranged appointments/daily alerts.
  - *Health education*—provision of information about the disease and the need for treatment. Use of information education communication (IEC) material such as posters, leaflets, films, and street plays.
  - *Incentives and reimbursements*—money or cash in kind to reimburse the expenses of attending the treatment center such as DOTS center or to improve the attractiveness of visiting the treatment center.
  - *Peer assistance*—people from the same social group helping someone with the disease, such as tuberculosis, to return to the health center by prompting or accompanying him or her.
  - *Directly observed therapy (DOT)*—an identified, trained, and supervised agent (health worker, community volunteer, or family member) directly monitors patients swallowing their medicines as one of a range of measures to promote adherence, for example, TB treatment.

### C. Laboratory tests

Many drugs have organ-specific effects that cannot be detected by normal observation, patient history, or clinical examination. Therefore, laboratory tests are also sometimes an important component in the evaluation of drug therapy. For example, the effectiveness of oral hypoglycemic agents for diabetes mellitus can be measured by blood sugar levels and HbA1C levels. During treatment with the anticoagulant *warfarin*, it is useful to measure the clotting tendency of the blood (internationalized ratio [INR]) to evaluate its effect and monitor for adverse signs and decide the correct dose. In pneumonia, X-rays of the lungs before and after drug treatment are very useful in evaluating the effect of antibiotics. Stress electrocardiograms

(ECGs) in the treatment of angina pectoris and gastroscopies in the treatment of stomach ulcers can offer similar benefits.

In a number of chronic diseases and long-term drug therapy, it is sometimes difficult to monitor response to treatment by observation or surrogate clinical markers (laboratory test). In such situations, it can often be important to measure drug concentration levels directly to evaluate the need for dose adjustment.

#### D. Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) is the clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's bloodstream, thereby optimizing individual dosage regimens. Examples of drugs which do not require monitoring since clinical effect is easily measurable include antihypertensive, hypoglycemic, and antibacterials where the response can be easily observed by measuring BP or blood sugar or by resolving the infection. Some drugs are taken as prodrugs which get activated inside the body, so there is no need to monitor plasma levels as the latter will reflect an activated form. For drugs with irreversible action, for example, organophosphate compounds, there is no need to monitor plasma levels as the clinical response can be easily measured.

TDM is used selectively mainly for monitoring drugs with narrow therapeutic ranges, drugs with marked pharmacokinetic variability, medications for which target concentrations are difficult to monitor, and drugs known to cause adverse effects at therapeutic doses. When used properly, measurements of plasma drug levels in a clinical setting may provide valuable information. While there may be specific individual circumstances for TDM, most indications can be summarized as follows:

- Low therapeutic index, for example, *lithium*, *phenytoin*, *valproic acid*, and *phenobarbitone*, where a concentration range is established for which the majority of users experience the desired outcome without serious adverse effects
- Poorly defined clinical end point, for example, epilepsy
- Noncompliance, for example, to discover whether a patient is actually taking a prescribed drug, particularly a patient suffering from psychiatric illness
- Therapeutic failure to a particular drug without any apparent reason
- Drugs with saturable metabolism, for example, *phenytoin*
- Wide variation in the metabolism of drugs, for example, slow or fast metabolizers, *phenytoin*, and isoniazid
- Dose adjustment in major organ failure (liver or kidney failure), for example, *gentamicin*
- Prevention of adverse drug effects; for example, nephrotoxicity of aminoglycoside antibiotics is difficult to distinguish clinically from that caused by a severe generalized infection

For these reasons, drug analyses are only performed in a minority of cases. For the majority of drugs prescribed, dosage is modified according to standard dosage regimes and according to a clinical

evaluation of the drug's impact on the development of the disease and any adverse effects.

Measurement of drug concentration in urine is not suitable, since varying urine volumes will result in a varying concentration of the drug in the urine. In addition, drugs that are metabolized in the liver and which are largely eliminated in the bile through the intestine are not accurately measured in the urine. Blood tests that determine plasma drug concentrations are usually taken before the next planned dose (trough levels).

## VII. DRUG-DRUG INTERACTIONS

A drug interaction occurs when one drug is given with or shortly after another drug and alters the effect of one drug or both the drugs. Usually, the effect of one of the drugs gets either increased or decreased or cause unexpected side effects. The drugs involved can be prescription medications, over-the-counter medicines, and even vitamins and herbal products.

Drug interactions pose one of the common problems as patients often take more than one drug at a given time. It is estimated that a hospitalized patient receives an average of 5 to 10 drugs daily. When several drugs are given together, interactions are bound to occur.

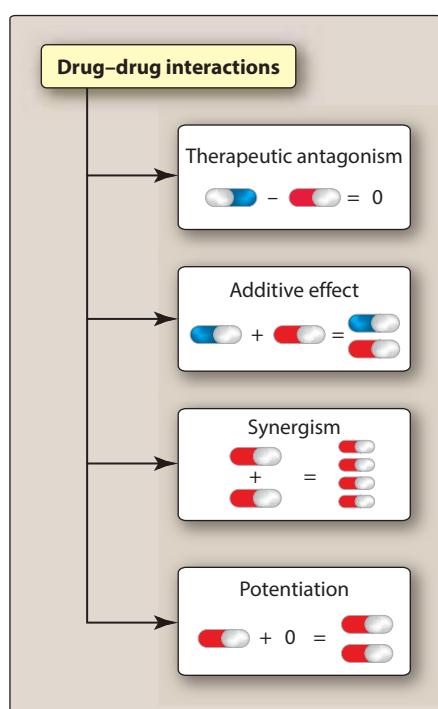
### A. Consequences of drug-drug interactions

The consequences of drug-drug interactions are usually divided into four groups: 1) therapeutic antagonism, 2) additive, 3) synergism, and 4) potentiation (Figure 2.19).

**1. Therapeutic antagonism:** Antagonism means that one drug reduces or blocks the effect of another. There are various ways in which this can happen. For instance, drugs can interfere with each other's absorption in the gut, circulation in the blood, or uptake by cells. For example, antagonistic action is seen if acetylsalicylic acid and ibuprofen and angiotensin converting enzyme inhibitors (ACEIs) and non-steroidal anti-inflammatory drugs (NSAIDs) are given together. Likewise, acetylcholine and noradrenaline have opposing effects on heart rate and hypoglycemic agents and corticosteroids have opposing effects on sugar levels.

**2. Additive effect:** Additive means when the effects of two drugs are simply additive—that is, the interacting drugs have similar actions and the resultant effect is the sum of individual drug responses (like one plus one getting two) NSAIDs and glucocorticoids—increase risk of bleeding; hyperkalemia with angiotensin-converting enzyme inhibitors (ACEI) such as spironolactone and amiloride. Other examples are quinolones given with *citalopram*, and macrolide antibiotic causes QT interval prolongation and *torse de pointes*.

**3. Synergism:** Synergism means that two or more drugs work together against one target, producing an effect that is greater than the individual effect of the two drugs together (like combining two plus two and getting five). Synergistic interactions can be beneficial and treatments may be deliberately chosen for this effect, for example, bactericidal effect of *sulfamethoxazole* and *trimethoprim* when given in combination whereas when given individually they have bacteriostatic activity only.



**Figure 2.19**

Consequences of drug interactions.

- 4. Potentiation:** Potentiation means that the effect of one drug is greatly increased by the intake of another drug itself without a notable effect. Like synergism, this may be useful in cases where the beneficial effects of drug B are enhanced. However, the toxicities of drug B may also be potentiated, leading to an increased level of side effects. Sedatives can potentiate each other. Alcohol enhances the analgesic activity of *aspirin* and increases the drowsiness of H1 receptor antagonists.

## B. Outcome of drug interactions

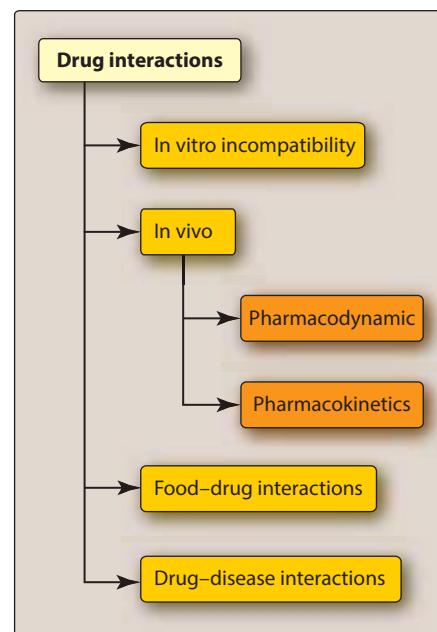
The outcome of drug interactions can be beneficial or harmful.

- 1. Beneficial effects:** Combination therapy in some cases is based on drug interactions. For example, use of codeine with paracetamol increases its analgesic effect or combination of clavulanic acid with amoxicillin overcomes bacterial resistance to the antibiotic. *Hydrochlorothiazide* and *spironolactone* are combined together to maintain potassium levels within a normal range. However, beneficial effects are very few; most are harmful.
- 2. Harmful effects:** These can be in terms of lack of efficacy or toxicity or increased adverse reactions. Whenever the levels of drugs in the body are increased due to interactions, the toxicity of that drug or adverse drug reactions get enhanced. If levels are decreased, namely, due to enhanced metabolism of the drug, it may result into lack of response. For example, both *aspirin* and blood thinners, such as *warfarin*, are used to protect one against heart attack by helping to prevent the formation of blood clots. Using these medications together, however, may cause excessive bleeding.
  - a. Lack of efficacy:** On the other hand, the overall effect of one or both of the drugs may be less than what is desired. For example, certain antacids can prevent many medicines (such as antibiotics, blood thinners, and heart medications) from being absorbed into the bloodstream resulting in loss of efficacy. In some case, the drug may not work at all.

## C. Mechanism of drug interaction (Figure 2.20)

Various types of drug interaction mechanisms are as follows:

- Drug interactions due to incompatibility (outside the body)
  - In vivo drug interactions
    - Pharmacodynamic interactions
    - Pharmacokinetic interactions
  - Food–drug interactions
- 1. In vitro drug interactions due to incompatibility:** It is also possible for interactions to occur outside an organism before administration of the drugs has taken place. These are also called incompatibility interactions. Interactions can occur during mixing of drugs for intravenous administrations such as saline and ringer lactate. Patients in intensive care units (ICU) often receive numerous medications by the parenteral route. Frequently, two



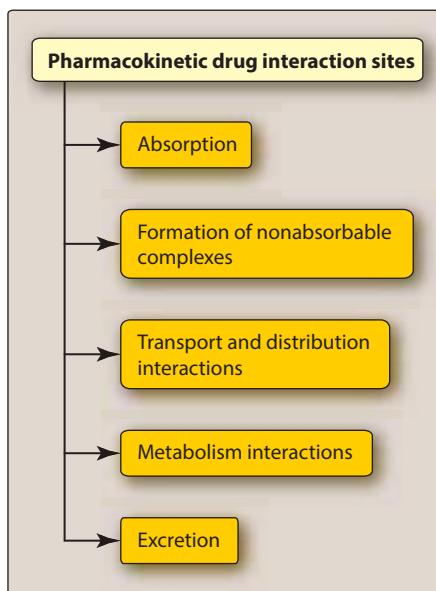
**Figure 2.20**

Mechanism of drug interactions.

IN VITRO DRUG-DRUG INCOMPATIBILITY	IN VITRO DRUG-VEHICLE INCOMPATIBILITY
Benzyl penicillin and heparin	Vancomycin with balanced salt solution
Protamine zinc insulin and plain insulin	Phenytoin with dextrose
Ketamine with barbiturates	Amphotericin B with saline
Thiopentone and suxamethonium	Ceftriaxone with ringer lactate
Ciprofloxacin with furosemide	Morphine with sodium bicarbonate solution

**Figure 2.21**

In vitro drug interactions.

**Figure 2.22**

Pharmacokinetic drug interactions.

or more drugs are delivered simultaneously through the same line and the risk of physicochemical incompatibilities is thus important. Physical or visual incompatibilities may be present in the form of precipitation, effervescence, color change, and related visual changes. Interactions can occur during formulation and mixing of drugs. Most of the precipitation-related incompatibilities are due to the change in drug solubility which is again due to a change in the pH of the solution due to mixing of drugs together. Therefore, chemical incompatibility makes the drugs vulnerable for precipitation and makes them unsuitable for injection. Examples for this kind of incompatibility are shown in **Figure 2.21**.

2. **In vivo drug interactions:** The drug interaction in the body after its administration either together or separately or through different routes can be broadly divided into pharmacodynamic and pharmacokinetic drug interactions.

a. **Pharmacodynamic drug interactions:** Interactions generally take place between drugs acting on the same type of receptors or on the physiological system; for example, the effect of antihistaminic such as *chlorpheniramine* on CNS is increased by alcohol as both cause CNS depression whereas coadministration of CNS stimulants such as *caffeine* or *theophylline* can decrease the effect or side effects of drugs causing CNS suppression. The effect of *propranolol* on the heart is increased by *verapamil*. Both of them cause depressive action on heart. Such interactions are predictable and it is important to observe them when such drugs are administered together.

Corticosteroid decreases the hypoglycemic response of oral hypoglycemics.  $\beta$ -Blockers mask the symptoms of hypoglycemia. Patient monitoring is very important for any hypoglycemic response.

*Furosemide* interacts with many drugs. When given with NSAIDs, *furosemide*'s clinical response is decreased. Concomitant administration of *furosemide* and *lithium* results into lithium toxicity. When *furosemide* is given with *gentamicin*, ototoxicity is potentiated.

- b. **Pharmacokinetic drug interactions (Figure 2.22):** Modifications in the effect of a drug are caused by differences in the absorption, transport, distribution, metabolism, or excretion of one or both of the drugs compared with the expected behavior of each drug when taken individually.

[1] **Absorption:** Most of the drugs in a tablet, liquid, or capsule form are absorbed from the small intestine. Once absorbed, they circulate in bloodstream and are available for action. The quantity of drug available is known as bioavailability. Drugs, food, and drinks can alter the absorption of drugs. The absorption of *ampicillin* decreases when it is taken with food. Therefore, it should be taken on an empty stomach. Antacids and laxatives reduce *INH* absorption from GIT; therefore, *INH* should be administered an hour before these drugs are given. Absorption of drugs can also be hindered by

the coadministration of bulk-forming laxatives such as psyllium husk.

- **Changes in motility:** Some drugs, such as the prokinetic agents, increase the speed with which a substance passes through the intestines. If a drug is present in the digestive tracts, its absorption will be fast and its blood concentration will decrease. The opposite will occur with drugs that decrease intestinal motility.
- **pH:** Certain drugs require an acidic stomach pH for absorption, for example, *omeprazole*. Others require the basic pH of the intestines. Any modification in the pH could change this absorption. Antacids increase pH and can inhibit the absorption of other drugs such as *zalcitabine* (absorption can be decreased by 25%), *tipranavir* (25%), and *amprenavir* (up to 35%). A gap of 2 to 4 hours between taking the two drugs is usually sufficient to avoid the interaction.
- **Drug solubility:** The absorption of some drugs can get drastically reduced if they are administered together with food with a high fat content, for example, oral anticoagulants and avocado. Avoid giving drugs after high-fat meals because of increased peak concentration. They should always be taken on an empty stomach. However, administration of *griseofulvin* after a fatty meal has been reported to increase the bioavailability.

## [2] Formation of nonabsorbable complexes:

**Chelation:** The presence of di- or trivalent cations can cause the chelation of certain drugs, making them harder to absorb. This interaction frequently occurs between drugs such as *tetracycline* or fluoroquinolones or iron preparation and dairy products (due to the presence of  $\text{Ca}^{2+}$ ).

**Binding with proteins:** Some drugs such as *sucralfate* binds to proteins, especially if they have a high bioavailability. For this reason, its administration is contraindicated in enteral feeding.

The drug is retained in the intestinal lumen forming large complexes impeding its absorption, for example, *cholestyramine* when given with *sulfamethoxazole*, *thyroxine*, *warfarin*, or *digoxin*.

**Acting on the P-glycoprotein of the enterocytes:** This appears to be one of the mechanisms promoted by the consumption of grapefruit juice in increasing the bioavailability of various drugs, regardless of its demonstrated inhibitory activity on first-pass metabolism. Drugs such as *cyclosporine*, *digoxin*, *erythromycin*, *itraconazole*, and *verapamil* are reported to interact with P-glycoprotein and alter the pharmacokinetics of drugs.

## [3] Transport and distribution interactions:

**Drug-binding site:** The drug moves from bloodstream into various fluids and tissues or the drug may get bound to plasma proteins. This is another site for drug

interactions. One drug may displace another drug from these sites based on their affinity for the site. Generally, acidic drugs bind to serum albumin and basic drugs bind to  $\alpha$ -glycoprotein. Steroidal drugs bind to serum steroid-binding proteins. The main interaction mechanism is competition for plasma protein transport. In these cases the drug that arrives first binds with the plasma protein, leaving the other drug dissolved in the plasma, which modifies its concentration. The organism has mechanisms to counteract these situations (by, for example, increasing plasma clearance), which means that they are not usually clinically relevant. However, these situations should be taken into account if there other associated problems are present such as when the method of excretion is affected. Moreover, increasing free drug levels in the plasma could be a matter of concern for drugs having a low therapeutic margin.

- [4] **Metabolism:** Most drugs are metabolized in the liver. The liver has many enzymes that metabolize the drugs. Many drug interactions are due to alterations in drug metabolism. As a result of these interactions, the function of the enzymes can either be stimulated (**enzyme induction**) or be inhibited (**enzyme inhibition**), thus causing increase or decrease in metabolism of other drugs. Antitubercular drug, such as *rifampicin*, and anti-convulsants, such as *phenobarbital*, *phenytoin*, and *carbamazepine*, are enzyme inducers which are reported to increase the clearance of the oral contraceptive steroids. *Paracetamol* coadministration has been reported to increase the blood concentrations of ethinyl estradiol due to competition for sulfation. Most of the drugs undergoing metabolism through CYP3A4 are known to have drug interaction with each other. *Cyclosporine* has been reported to have drug interaction with several drugs metabolized through CYP3A4.
- [5] **Excretion:** Drugs are excreted primarily by kidneys. One drug may decrease or increase the excretion of drugs. *INH* inhibits excretion of *diazepam*. Patient monitoring is important as diazepam response may be enhanced. All cephalosporines when given with aminoglycosides (*gentamicin*, *amikacin*) increase renal toxicity. Close patient monitoring is important for cases involving renal toxicity. It is recommended that renal function tests should be done frequently. The beneficial effects of such interaction such as probenecid decrease the active tubular secretion of *penicillin* through the kidney, thereby increasing the bioavailability and duration of action. Drug interaction-mediated displacement of drugs causing rise in free drug levels is quickly excreted either through metabolism or directly through the kidney according to their nature.

**3. Food-drug interactions:** Generally, administering oral medication along with food or at a meal time is a convenient manner of drug dosing. Foods and beverages can interfere with the stages of drug action in a number of ways, potentially making them less effective or causing side effects. The most common effect is for foods to interfere with drug absorption. With some drugs, it is important to avoid taking food and medication together because the food can make the drug less effective (for example, *thyroxine* and *omeprazole*). For other drugs, such as NSAIDS, it may be good to take the drug with food to prevent gastric irritation. Examples of drugs whose absorption is decreased when taken with food include *penicillin*, *tetracycline*, *erythromycin*, *levodopa*, *phenytoin*, and *digoxin*. Drugs whose absorption increases when taken with food include *spironolactone*, *griseofulvin*, and *itraconazole*.

Some drugs interfere with the absorption of a nutrient. Other drugs affect the body's use and/or excretion of nutrients, especially vitamins and minerals. If less nutrient is available to the body because of these effects, this may lead to a nutrient deficiency. Antacids neutralize stomach acid, and acid blockers reduce stomach acid production. Long-term use of these drugs may lead to certain nutrient deficiencies; for example, vitamin B<sub>12</sub> supplements are required in older people and in patients on *metformin* as they produce less stomach acid, leading to low absorption of vitamin B<sub>12</sub>. Regular use of antacids or acid blockers lowers B<sub>12</sub> absorption and drugs which cause chronic nausea may result in poor intake and weight loss. *Isoniazid* causes decrease in absorption of dietary pyridoxine (B<sub>6</sub>) during therapy.

Calcium-rich dairy products (such as milk, cheese, and ice cream), antacids, and vitamins containing iron can all lessen the effectiveness of antibiotics, particularly *tetracycline*. Mixing of calcium-rich dairy products or calcium supplement with a prescription antibiotic can cause a much slower absorption rate of the antibiotic into the bloodstream/body, causing it to have a decreased effect.

Iron binds to calcium found in dairy products and calcium supplements. Therefore, the dose of iron and calcium should be separated by 2 hours. This can decrease the absorption of the antibiotic. Other drugs such as *penicillin* and *erythromycin* are most effective when taken on an empty stomach. This is because they may be partially destroyed by stomach acid when taken with food. However, food can reduce the chance of stomach irritation from these drugs.

*Warfarin* (Coumadin) works by interfering with the use of vitamin K in blood clotting; therefore, people taking these anticoagulants should be advised to be consistent in the intake of amount of vitamin K they get from foods and avoid eating large amounts of foods high in vitamin K. Rich sources of vitamin K include liver and green vegetables such as broccoli, spinach, and other leafy greens.

Antihypertensives such as diuretics can affect body levels of minerals such as potassium, calcium, and zinc. For patients with diabetes, these drugs can cause problems in controlling blood

sugar. In addition, natural licorice, found in some imported candies, causes salt and water retention. This can lead to an increase in blood pressure.

Grapefruit juice blocks enzymes that normally metabolize certain drugs, leaving more of the compounds to be absorbed and thus increasing blood levels of the medications. For example, grapefruit juice should not be taken with certain blood pressure-lowering medications, the antihistamine *terfenadine*, and *cyclosporine*, a drug taken to prevent organ transplant rejection.

Concomitant intake of alcohol has been reported in the pharmacokinetic and pharmacodynamic preparation of several drugs. Administration of drugs such as *metronidazole* has been reported to cause several disulfiram types of reactions in patients. Coadministration of herbal supplements containing black pepper has been reported to alter the pharmacokinetics of drugs.

#### D. Red alert drugs and interactions

The following medicines should “ring alarm bells” as they often have important interactions:

- *Warfarin*
- Statins, particularly *simvastatin*
- Macrolide antibiotics, particularly *erythromycin* and *clarithromycin* (less with *roxithromycin* and minimal with *azithromycin*)
- Calcium channel blockers, particularly diltiazem and verapamil
- Azole antifungals, particularly ketoconazole and itraconazole
- SSRIs, particularly fluoxetine and paroxetine, and less so citalopram
- Amiodarone
- Digoxin
- Cyclosporin
- Antiepileptic medicines, particularly *carbamazepine* and *phenytoin* and less so valproate and gabapentin
- Oral contraceptives
- Antitubercular drugs

#### E. Severity rating of drug interactions

Due to drug interaction at any of the site or mechanism, the concentration of one drug in the body may either decrease or increase; if it is decreased, there is a lack of therapeutic response and if it is increased there may be toxicity. Though not all interactions are clinically important, slight change in drug concentration in the body may not produce significant alteration in drug response whereas some interactions may be significant. The drug-drug interactions are classified as mild, moderate, and severe according to their severity and undesirable effects.

1. **Mild drug-drug interactions:** Mild drug-drug interactions limit the clinical effects. The manifestations include an increase in the frequency or the severity of the adverse effects, for example, digestive disturbances, headaches, fatigue, vague muscle aches, malaise, discomfort, and changes in sleep patterns. No action is

usually needed but some patients may find it distressing and can affect compliance with medications, for example, bowel disturbance with iron therapy.

2. **Moderate drug–drug interactions:** Moderate drug–drug interactions may result in exacerbation of the disease of the patient or adverse effects which are considered distinctly annoying, distressing, or intolerable requiring dose change or a change in the therapy. Patients need to be monitored. Moderate reactions include rashes (especially if they are extensive and persistent), visual disturbances (especially in people who wear corrective lenses), muscle tremor, difficulty with urination particularly in elderly males, any perceptible change in mood or mental function, and temporary, reversible decrease in the white blood cell count or hypoglycemia.
3. **Major or severe drug–drug interactions:** Major or severe drug–drug interactions are life threatening (such as liver failure, abnormal heart rhythms, and certain types of allergic reactions) which result in persistent or significant disability, hospitalization, or birth defect. Severe reactions are relatively rare but require immediate action and discontinuation of the offending drug. However, sometimes doctors must continue giving high-risk drugs such as chemotherapy or immunosuppressants. **Statins** (cholesterol-lowering drugs) and **fluconazole** (an antifungal medication) can cause severe muscle weakness or kidney damage. SSRI antidepressants combined with OTC antihistamines or pain relievers or St. John's Wort, an over-the-counter herbal remedy used to treat depression, can cause a deadly reaction called serotonin syndrome. (Wide-ranging symptoms include delirium, restlessness, euphoria, shivering, diarrhea, etc.)

## F. Lethal reactions

Lethal reactions are those in which a drug reaction directly or indirectly causes death. These reactions are typically severe reactions that were not detected in time or did not respond to treatment. Combination of benzodiazepines with narcotic analgesics or with other CNS depressants can cause lethal respiratory depression.

## G. Reactions with contraindicated drugs

The drugs which are contraindicated for concurrent use, therefore, avoid such combinations.

## H. Benefits of minimizing drug interactions

- Better patient outcomes in terms of prevention of side effects, better patient compliance, continuation of drugs by patients, reduced need for additional medication, lesser disease complications, preservation of optimal nutritional status, and requirement of fewer caloric or nutrient supplements.
- The cost of healthcare services is reduced.
- Licensing agency requirements are met and lesser professional liability.

## VIII. ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRs) are the leading cause of morbidity, mortality, and increased healthcare cost. Despite drastic improvement in healthcare practices, ADRs are contributing toward poor clinical outcome, hospitalization, prolongation of hospital stay, and enhanced economic burden. All drugs are capable of producing adverse effects. 3% to 5% of hospital admissions are caused by ADRs. The incidence of serious and fatal adverse drug reactions has been reported in 5% to 7% of hospitalized patients.

### A. General definition

1. **ADR (Definition by WHO):** Adverse drug reaction (ADR) is a response to a drug that is noxious, unpleasant, and unintended and occurs at doses normally used in patients for prophylaxis diagnosis or therapy of a disease. It does not include therapeutic failures, overdose, drug abuse, noncompliance, and medication errors.
2. **Adverse event or experience:** Any unfavorable medical occurrence or injury temporally associated with the use of a pharmaceutical product at normal dosage and/or due to overdose or discontinuation of therapy, but which does not necessarily have a causal relationship with the treatment. Adverse drug events may result from medication errors or from ADRs in which there was no error.
3. **Medication error:** Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer.
4. **Life-threatening reaction:** A reaction in which the patient was at risk of death and does not refer to the underlying medical problem, which could have caused death.
5. **Serious adverse drug reaction:** A noxious and unintended response to a drug results in death, is life-threatening (such as Stevens–Johnson syndrome), requires patient hospitalization or prolongation of the existing hospitalization, causes a congenital anomaly or birth defect, results in persistent or significant disability or incapacity, or requires intervention to prevent permanent impairment or damage.
6. **Side effect:** Any unintended effect of a pharmaceutical product occurring at normal doses which is related to the pharmacological properties of the product and in which there is no deliberate overdose. However, when side effects are severe, the reaction is termed adverse drug reaction. It is often used interchangeably.
7. **Adverse drug reaction (ADR) case report:** This is a case report in ADR monitoring program which is a notification relating to a patient with an adverse effect or laboratory test abnormality suspected to be induced by a medicinal product.
8. **Benefit/risk analysis:** Examination of the favorable (benefit) and unfavorable results of undertaking a specific course of action.

9. **Signal:** Reported information (at least three spontaneous case reports) on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.
10. **Unexpected adverse drug reaction:** An adverse reaction, the nature or severity of which is not consistent with the applicable product or mentioned in the summary of product characteristic or market authorization, or expected from the characteristics of the drug.

## B. WHO definitions for causality assessment

Causality assessment provides a degree of likelihood to the relationship between a drug and an adverse reaction. Timing, pattern of illness, results of investigations, and rechallenge can help attribute causality to a suspected ADR.

ADR is classified into one of six category terms as per World Health Organization-Uppsala Monitoring Centre (WHO-UMC): 1) certain, 2) probable/likely, 3) possible, 4) unlikely, 5) inaccessible/unclassifiable, and 6) conditional/unclassified.

### 1. Certain

- Clinical event, lab test abnormality with plausible time relationship to drug intake
- Cannot be explained by concurrent disease or other drugs/chemicals
- Response to dechallenge—plausible
- Event must be definitive pharmacologically/immunologically
- Positive rechallenges (if performed)

### 2. Probable/likely

- Clinical event, lab test abnormality with reasonable time relationship to drug intake
- Unlikely to be due to concurrent disease, drugs/chemicals
- Clinically reasonable response to withdrawal (dechallenge)
- Rechallenge not required

### 3. Possible

- Clinical event, lab test abnormality with reasonable time relationship to drug intake
- Could also be explained by concurrent disease or other drugs or chemicals
- Information on drug withdrawal may be lacking or unclear

### 4. Unlikely

- Clinical event, lab test with improbable time relationship to drug intake
- Other drugs, chemicals, or underlying disease provide plausible explanations

### 5. Inaccessible/unclassifiable:

A report suggests ADR but there is insufficient/contradictory evidence which cannot be supplemented or verified.

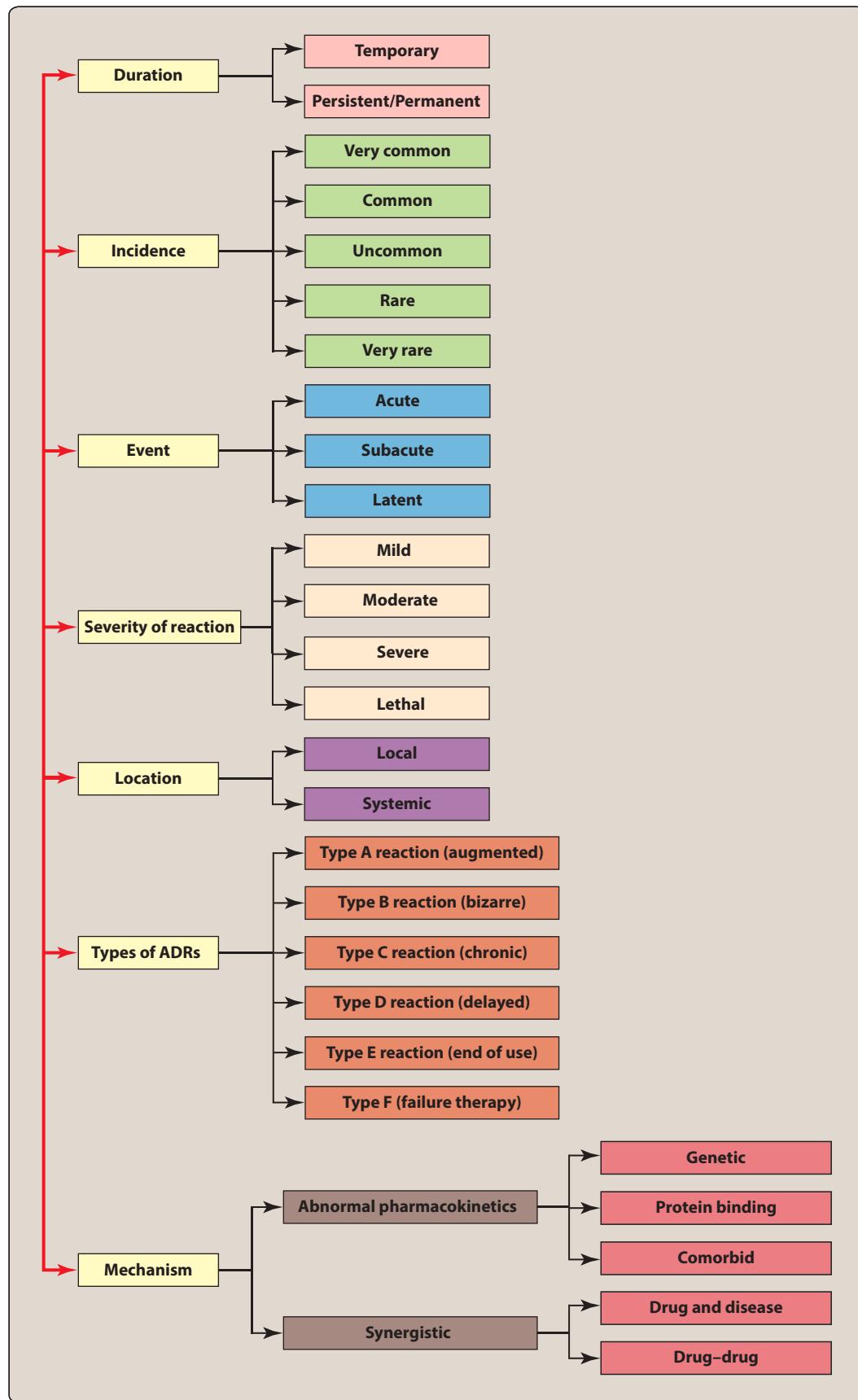
### 6. Conditional/unclassified:

Event or laboratory test abnormality reported but more data is essential for proper assessment or additional data are under examination.

### C. Classification of ADRs (Figure 2.23)

Adverse drug reactions can be categorized in a number of ways (for example, duration/incidence/frequency, severity, types of ADRs, location, body systems affected, or mechanism). The following categorization is often used.

1. **Based on duration:** Temporary, persistent, or permanent, for example, visual loss with *quinine*, *ethambutol*, and *amiodarone*
2. **Based on incidence (frequency)**
  - Very common (>1/10 patients)
  - Common (>1/100)
  - Uncommon (>1/1000)
  - Rare (>1/10,000)
  - Very rare (1/100,000)
3. **Based on onset of event**
  - Acute (<60 minutes)
  - Subacute (1–24 hours)
  - Latent (>2 days)
4. **Based on severity of reaction**
  - a. **Mild:** Adverse effects are transient in nature and generally do not interfere with normal activities. They require no change in therapy, for example, sedation due to antihistaminics.
  - b. **Moderate:** Adverse effects are sufficiently disturbing and interfere with normal activities of the patient. They require change in therapy, additional treatment, hospitalization, for example, vomiting, tachycardia or bradycardia seen with a drug; cough with angiotensin-converting enzyme inhibitors; and optic atrophy due to *ethambutol*.
  - c. **Severe:** These are incapacitating, disabling, or life-threatening adverse effects such as anaphylaxis, hypertension, and death. Seriousness is a measure of the degree of harmfulness of an adverse response to a drug whereas severity is a measure of the intensity of the effect or response to a drug.
  - d. **Lethal:** Directly or indirectly contributes to the death of the patient.
5. **Based on location:** Adverse effects may be local—that is, limited to a certain location—or systemic, where a medication has caused adverse effects throughout the systemic circulation. For example, some ocular antihypertensives, although administered topically as eye drops, cause systemic effects as a fraction is absorbed to the systemic circulation.
6. **Based on the types of ADRs:** ADRs have been broadly classified into the following.
  - a. **Type A (augmented) reactions:** These are the reactions that are related to the exaggerated pharmacological effects of the drugs and tend to be fairly common (usually more than 1 in 100), are often predictable and dose dependent (more frequent and more severe at higher dosage), and may often be avoided by using dosages that are appropriate for the individual patients, for example, hypoglycemia with insulin, hypotension with antihypertensive agents, constipation and respiratory depression with *morphine*, bleeding with anticoagulants, bradycardia with β-blockers, headache with nitrates,

**Figure 2.23**

Classification of adverse drug reactions.

postural hypotension with *prazosin*, and dry mouth with tricyclic antidepressants. Type A reactions are usually reproducible and can be studied experimentally and have high morbidity but low mortality.

- b. **Type B (bizarre) reactions:** These are the reactions that are unexpected and unpredictable and are often related to patient factors such as genetic predisposition and allergy. They occur in a minority of the patients (less than 1 per 100), are often serious, may show little or no relationship with dosage, and may be difficult to detect. For example, anaphylaxis to *penicillin*. These reactions are often suspected with their relationship to time and a low background frequency.

Common cutaneous allergic reactions include exanthema, urticaria, and fixed drug eruptions. More serious and potentially fatal forms of drug rashes hypersensitivity reactions include toxic epidermal necrolysis, Stevens–Johnson syndrome, and drug hypersensitivity syndrome. Drug hypersensitivity syndrome is potentially life threatening with significant morbidity. It is characterized by fever and rash and involves the internal organs. Prompt diagnosis is vital, along with identification and early withdrawal of suspect medicines. Avoidance of re-exposure to the responsible agent is essential. Cross-reactivity to structurally related medicines is common. First-degree relatives may be predisposed to developing this syndrome.

**Hypersensitivity:** This is a term sometimes used interchangeably with drug allergy. It is the result of antigen–antibody reactions that occur in the body. One of the most dangerous of all drug-hypersensitive reactions is *penicillin* allergy. In its more severe form, *penicillin* anaphylaxis becomes fatal. One should always remain well prepared to face anaphylaxis as it is fatal; however, the patient can be saved if the right drug is administered—that is, *adrenaline*. Parenteral administration of drugs carries greater risk of acute hypersensitivity reactions than oral administration.

**Rarely:** Idiosyncratic reaction occurs. These reactions are highly unpredictable, individual, and unusual. One of the best-known idiosyncratic reactions is *chloramphenicol*-induced aplastic anemia which occurs in 1 in 40,000 patients. Although rare but when occurs, it is mostly fatal.

- c. **Type C (chronic) reactions:** These reactions are associated with long-term use of a drug and involve dose accumulation, for example, ototoxicity, renal toxicity caused by aminoglycosides, analgesic nephropathy, interstitial nephritis caused by *phenacetin*, ocular toxicity caused by antimalarials, hypothalamic-pituitary-adrenal axis suppression by corticosteroids, osteonecrosis of the jaw with bisphosphonates, etc.

- d. **Type D (delayed) reactions:** These are delayed effects (dose independent), timing makes it more difficult to detect, e.g.—leucopenia after weeks of use of *lomustine*, teratogenesis, e.g. fetal hydantoin syndrome with *phenytoin*, carcinogenesis like clear cell carcinoma of the female reproductive tract in matured women whose mothers have received *diethylstilbestrol* during pregnancy, tardive dyskinesia with neuroleptics.

- e. **Type E (end-of-use) reactions:** These are the reactions that occur when the discontinuation of the drug is too abrupt, especially after long-term therapy with the drug, for example, adrenocortical insufficiency due to sudden withdrawal of corticosteroids, opioids,  $\beta$ -blockers, and rebound hypertension after sudden withdrawal of *clonidine*.
  - f. **Type F (failure of therapy):** Unexpected failure of therapy. It is common and often due to drug interactions, for example, inadequate dosage of an oral contraceptive when used with an enzyme inducer in antitubercular therapy, resistance to antimicrobial agents.
7. **Based on mechanisms:** Most ADRs (80%) are Type A and fewer ADRs are Type B. The common mechanisms are as given in the following text.
- a. **Abnormal pharmacokinetics due to:**
    - [1] **Genetic factors:** Abnormal drug metabolism may be due to inherited factors of either phase I oxidation or phase II conjugation. Inheriting abnormal butyrylcholinesterase (pseudocholinesterase) may affect succinylcholine metabolism. Inheriting abnormal *N*-acetyltransferase which conjugated (phase II reaction) some drugs to facilitate excretion may affect the metabolism of drugs such as *isoniazid*, *hydralazine*, and *procainamide*. Pharmacogenomics is the study of the inherited basis for abnormal drug reactions.
    - [2] **Protein binding:** Some drug interactions with *warfarin* are due to changes in protein binding.
    - [3] **Comorbid disease states:** Various diseases, which cause renal or hepatic insufficiency, may alter drug metabolism and produce ADRs.
  - b. **Synergistic effects between/either:**
    - [1] **Drug and disease interaction:** Interactions between a drug and a disease.
    - [2] **Drug-drug interactions:** Patients have abnormal metabolism by cytochrome P450 due to either inheriting abnormal alleles or due to drug interactions. The risk of drug interactions gets increased with polypharmacy. Two drugs may have synergistic actions. For example prolongation of the QT interval by *haloperidol*, selective serotonin reuptake inhibitors, and *astemizole*.

## D. Pharmacovigilance

Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding, and prevention of adverse reactions to medicines/drug with both short- and long-term adverse effects. The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health since most ADRs are preventable. All suspected adverse drug reactions should be reported using the suspected adverse drug reaction reporting form. WHO Programme for International Drug Monitoring began in 1968 as a pilot project in 10 countries to pool

existing data on ADRs. This network together with Uppsala Monitoring Center (UMC) has expanded, and currently 86 countries participate in the programme with a national pharmacovigilance center. Each country has its own reporting guidelines on pharmacovigilance.

1. **Rationale for ADRs' monitoring:** The process of collection of safety information begins with phase I of the clinical through phase III and even continues in the form of postmarket safety studies, referred to as postmarketing surveillance.

Some common ADRs may manifest during different phases of clinical trials as in each phase, an increasing number of patients would have been exposed to the investigational drug. Although a review of premarketing clinical trials (phases I, II, and III), animal tests, and other information in the product development process provides valuable information about ADRs, limitations exist as these trials are often of short duration and tested on a small number of patients, making ADRs that develop with long-term use and rare ADRs impossible to detect, especially ADRs with a frequency of 1:1000 or above.

Further, premarketing safety evaluation of pharmaceutical products at the time of registration is inherently limited due to the following three reasons.

- a. **Median population and limited exposure:** The population in phase III clinical trials is limited and very selective. The trials may have a narrow patient population as many types of patients with different characteristics are often excluded from studies such as children, elderly, and pregnant women; patients with diseases other than the one being treated; and patients using other drugs concomitantly. Although these populations are not included in the studies, they are often at risk of ADRs. This often prevents the identification of adverse effects caused by the interaction of two or more drugs given at the same time. Premarketing studies may not reveal ADRs because of small sample sizes that lack the power to detect rare ADRs. Statistically, reactions with an incidence of less than 1% are frequently not identified. These are often found many years after drug approval in postmarketing surveillance studies with much larger patient populations.
  - b. **Short duration of clinical trial:** The duration of a clinical trial is too short. Such studies do not allow the detection of adverse effects that appear after long periods of use or exposure, especially with chronic medication, for example, oral contraceptives.
  - c. **Geographical differences:** Differences between countries which lead to variation in patient factors, variation in drug utilization among healthcare professionals, and variation in drug manufacturing processes used can influence pharmaceutical quality and composition of locally produced products compared to those imported outside the country.
2. **Postmarketing surveillance:** For the above-stated reasons, it is obvious that not all safety-related problems associated with the drug may be detected during premarketing test and evaluation. The goal of evaluating ADRs is to increase patient safety by

preventing harm; therefore, safety monitoring of a drug is required throughout the life cycle of all medicinal products.

**3. Aims and objectives of the pharmacovigilance program:**

**a. Early detection of ADRs, their nature, and frequency of ADRs:** The pharmacovigilance program involves detection of increase in the frequency of (known) ADRs including periodic re-evaluation of the benefit-risk ratio of medicinal products in order to assist the drug regulatory authority, public health programs, and scientists and consumer society to take appropriate action to minimize the risks of ADRs to consumers by

- providing updated drug safety information to healthcare professionals and other stakeholders to improve drug prescribing including WHO ADRs monitoring centers;
- upgrading package insert and designing appropriate package insert information and dissemination of information which may constitute institution of recall or withdrawal of the product in the market or restrictions for marketing;
- dissemination of information by designing a proper education program to consumers and other users; and
- initiation of further studies for education value, for example, benefit of the drug especially in long term, and for prevention of relapse or study of new indication, overuse, and possible mechanism underlying the adverse reaction observed or misused (utilization pattern).

**b. Identification of risk factors:** Identification of risk factors and possible mechanisms underlying adverse reactions that may predispose, induce, or influence the development, severity, and incidence of adverse reactions in the population. For example:

- Patient factors: Genetics, racial differences, diets, diseases, prescribing practices, culture of drug use, and traditions of the people, for example, high carbohydrate and fat diet.
- Drug interactions, drug distribution, storage and use including indications, dose, availability, and other underlying conditions.

**4. Reporting of an adverse drug reaction:** ADR reporting covers all pharmaceutical products, biological, herbal drugs, cosmetics, and medical devices circulating in the market. The scope of the pharmacovigilance program has now been expanded to include hemovigilance (adverse events reported with blood and blood component/product administration). Biovigilance is adverse events/reactions during tissue, organ, and cell therapy transplantation. It is mandatory for all pharmaceutical manufacturers or product registrants to monitor their products during clinical trials as well as during marketing and report any suspected undesirable effects to appropriate authority. For those conducting clinical trials in phases I to IV, it is mandatory to report all adverse events encountered to the appropriate authority. These reports help in reduction of the harmful effects of medicinal products by early detection of drug safety problems in patients and timely warning to healthcare professionals. Moreover, drug monitoring is

important in detection of lack of efficacy, detection, and prevention of counterfeit and substandard products in clinical practice.

ADR reports are, for the most part, only suspected associations that a drug has caused a particular adverse event. Reporting an ADR does not imply a causal association between the drug and the adverse reaction. However, in a doubtful case it is better to report than not to report. Reporting of these reactions to a national agency strengthens the power of detecting a recurrent rare ADR, which could lead to changes in drug labeling, prescribing, or availability.

The following adverse drug reactions should be reported:

- All ADRs to newly marketed drugs or newly added drugs to the Essential Medicines List (EML)
- All serious reactions, whether expected or not, and drug interactions
- An observed increase in the frequency of a known reaction
- Unexpected ADRs regardless of their nature or severity, which are not clearly stated in the package insert
- Unusual ADRs or ADRs which are interesting
- ADRs in special populations such as drug abuse and drug use in pregnancy and during lactation, pediatrics, and geriatrics
- All adverse reactions or poisonings to traditional or herbal remedies

Report product quality problems such as

- suspected contamination,
- questionable stability,
- defective components,
- poor packaging or labeling, and
- therapeutic failures.

Pharmacovigilance uses spontaneous adverse reactions' reporting to generate hypothesis and signals about the potential hazards of marketed drugs that require further investigation. ADR reporting is integral to the duties; therefore, all suspected or unexpected adverse reactions should be reported according to the requirements, irrespective of causality assessment. The key players to this ADR monitoring are all healthcare professionals—doctors, pharmacists, nurses, and all those directly associated with the care of patients and consumers. It is the task of the national reporting centers to establish the causality between reported suspected ADRs and the drugs used.

The early detection of safety signals is increasingly becoming important and of great interest to the pharmaceutical industry, regulators, and the public. The disadvantage of not reporting may result in deleterious effects of a medicinal product not being noticeable for a long time, for example, the *thalidomide* tragedy which resulted in thousands of newborns born with congenital malformation before this ADR was recognized. Also, it may be too late before it is recognized that prolonged use of a medicinal product can produce deliberate health effects. Other examples include *phenacetin* in renal papillary necrosis.

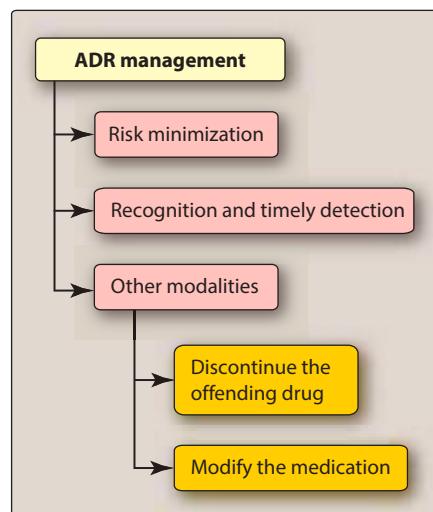
Safety signals are generated by various sources such as spontaneous reporting, case control and cohort studies, prescription event monitoring, registries, and periodic safety update reports (PSUR). Evaluation of ADR reports may lead to regulatory action by the DRA, including labeling changes, communicating new safety information to the public, restricting use of the drug, or removing the drug from the market. The DRA can also require a boxed warning on product information inserts and other drug literature when drug use presents potential serious risks that may outweigh the intended benefits. Boxed warnings are often based on serious ADRs reported by healthcare practitioners and patients. A black box warning is the strictest warning put in the labeling of prescription drugs or drug products by the FDA when there is reasonable evidence of an association of a serious hazard with the drug, for example, increased suicide risks with antidepressants, increased risk of bladder carcinoma in patients on *pioglitazone*. Boxed warnings inform the prescriber of appropriate use of the drug, such as in patient selection, monitoring, concomitant therapies or specific clinical situations to be avoided, or adjunctive therapies to administer.

## E. ADR management (Figure 2.24)

Noncompliance due to an ADR is a major issue. Actual, perceived, or even fear of ADRs increases the likelihood for medication noncompliance, leading to suboptimal treatment efficacy and adding to the burden of disease. Actual ADRs can result from inherent pharmacological characteristics of a drug, whereas perceived or fear of ADRs are influenced by psychological factors such as predetermined medication views, lack of belief in treatment necessity, anticipation of ADRs, conditioning based on past experiences, and misattributing symptoms as ADRs. Clinician awareness of these factors helps to reduce the risk for ADRs, early identification of ADRs, and optimizing its management, ultimately allowing patients to benefit from intended treatment.

### 1. Risk minimization

- Understand patient views about medication therapy.
- Educate about the benefits of treatment.
- Inform patients about potential ADRs and management strategies should any occur.
- Ensure an updated and accurate medication list.
- Use fewest drugs as possible.
- Utilize decision support software to help prevent ADRs.
- Start with low doses and frequencies and slowly titrate as tolerated.
- Initiate less-potent agents, agents with direct mechanisms of action, or alternatives with lower adverse event incidence.
- Avoid or reduce the use of interacting medications. Always elicit concomitant drug history such as over-the-counter medicines, medicines prescribed by other prescribers/providers including home remedies, herbal medicines, and alternative system of medicine.
- Prescribe dosage forms with minimal systemic exposure (for example, creams and patches).



**Figure 2.24**

Adverse drug reaction management.

**2. Recognition and detection:** Successful management of ADRs requires early identification.

- Anticipation of adverse reactions whenever treatment is started. Extremes of age—that is, elderly and neonates—are more prone to ADRs. The most commonly implicated medications include antibiotics, anticoagulants, *digoxin*, diuretics, hypoglycemics, antineoplastics, and NSAIDs.
- Eliciting drugs history that caused immunologic reactions, such as hypersensitivity reaction, in the past is essential to avoid inadvertent re-exposure to medicines. Predict hypersensitivity reactions by administering drug test dose whenever indicated.
- Listen to the patient's complaints about his reaction to a drug and consider each objectively. Be familiar with the known ADRs of the medication as well as the patient's pre-existing symptoms. For example, differentiate patients with bleeding tendency or overanticoagulation. Be alert to even minor changes in the patient's clinical status. Such minor changes may be an early warning to future reactions and may be hazardous and unacceptable and require discontinuation of the drugs.
- Always advise the patient to report ADR to the prescriber immediately.
- Evaluate new symptoms as possible ADRs, looking into health conditions, laboratory reports, or other factors which may explain the symptoms.
- Consider the temporal relationship between medication initiation and symptom onset. Symptoms which appear after starting a new medication or after an increase in dose are likely to be ADRs or symptoms appearing after stopping a drug could be withdrawal symptoms.
- Utilize lab tests for more evidence to identify an ADR—baseline liver, renal function, allergy testing, therapeutic drug levels.
- Dechallenge concepts such as stopping the medication or reducing the dose to see if the symptom subsides in absence of the medication.
- Apply probability tools such as the Naranjo Adverse Drug Reaction Probability Scale or WHO-UMC scale.
- Reassurance to patients in case of nonhazardous ADRs such as yellow/orange discoloration of the urine with *rifampicin* and urinary analgesic pyridine or black stools with iron therapy. An explanation of what ADR to expect may reduce the concern and fears of the patient. Further, some ADRs may be tolerated to obtain a necessary therapeutic effect or may subside with continuous use. For example, headache due to *amlodepine*, drowsiness caused by *paroxetine*, and orthostatic hypotension caused by *prazosin* usually subside after some days as the patient develops tolerance to these effects.
- Reduce dose or discontinue the offending medication. Many adverse reactions are dosage related and disappear after reduction in dose, for example, cough with *enalapril* may reduce after dose reduction.

- Schedule modification: Rescheduling of the drug administration time can help sometimes. For example, antihistamines produce sedation and administering them at bedtime can take care of this ADR.
- Switch to another agent or dosage form which is less likely to cause ADRs.
- Treat adverse effects when necessary (beware of prescribing cascades), for example, prescribing proton-pump inhibitor (PPI) *omeprazole* to treat NSAIDs-induced gastritis in the mistaken belief that a new medical condition requiring treatment has developed. The second drug places the patient at a risk of additional ADRs due to *omeprazole*. Prescribing cascades can exacerbate the harmful effects of an unrecognized ADR, for example, prescribing codeine-based cough suppressant to manage ACE inhibitor-induced cough. On persistence of cough, an antibiotic was started which led to antibiotic-induced *Clostridium difficile* diarrhea. This prescribing cascade culminated in the patient being hospitalized for severe diarrhea and delirium. The elderly, especially those using multiple medicines, women, and people using high-risk medicines are more likely to experience ADRs. Drugs usually involved in prescribing cascade are NSAIDs, diuretics, corticosteroids, ACE inhibitors, and antipsychotics.
- Document the ADR in the patient's medical record and report to appropriate authorities using prescribed forms. Return the filled ADR forms to the pharmacovigilance center.
- Follow up and re-evaluate the patient's progress, course of the event, delayed reactions, response to treatment, and specific monitoring parameters.
- Track and find trends in ADRs for ongoing process improvement.

**3. Other modalities of treating ADRs:** Other modalities of treating ADR include discontinuing the offending agent or continuing or modifying the medication depending on the patient's condition:

- Evaluate all medicines being taken by the patient for his/her benefits and harm and stop the nonessential drugs. Although the offending drug is usually discontinued or the dose is reduced, a necessary drug for which there is no satisfactory alternative may occasionally be continued depending on the favorable (benefit) and unfavorable results' (harm) evaluation of undertaking a specific course of action.
- If the patient is serious, discontinue all drugs which may possibly cause ADR and treat as necessary.
- In case of hypersensitivity reaction, timely recognition and prompt management of drug allergies or serious idiosyncratic reactions can sometime be life saving by using *epinephrine*, oxygen, and adequate fluid replacement; in some instances, vasopressors or corticosteroid drug therapy may be warranted. Emergency measures may be needed to maintain the airway.
- Although the offending drug is usually discontinued, as discussed earlier, hypersensitivity reactions can be often minimized through the use of other alternatives and

sometimes by using established protocols for premedication, for example, premedication with *epinephrine* in patients requiring antishake venom therapy. Sometimes when the drug is life saving or essential, though not widely advocated, desensitization may be achieved with graduated dosage schedules and maintained through continued administration of the drug, for example, patients hypersensitive to antishake venom.

## Study Questions

Choose the ONE best answer.

- 2.1 Which of the following best describes how a drug that acts as an agonist at the A subtype of GABA receptors affects signal transduction in a neuron?
- A. Activation of this receptor subtype alters transcription of DNA in the nucleus of the neuron.
  - B. Activation of this receptor subtype opens ion channels that allow sodium to enter cells and increases the chance of generating an action potential.
  - C. Activation of this receptor subtype opens ion channels that allow chloride to enter cells and decreases the chance of generating an action potential.
  - D. Activation of this receptor subtype results in G protein activation and increased intracellular second messenger levels.
- 2.2 If 1 mg of lorazepam produces the same anxiolytic response as 10 mg of diazepam, which is correct?
- A. Lorazepam is more potent than diazepam.
  - B. Lorazepam is more efficacious than diazepam.
  - C. Lorazepam is a full agonist, and diazepam is a partial agonist.
  - D. Lorazepam is a better drug to take for anxiety than diazepam.
- 2.3 If 10 mg of oxycodone produces a greater analgesic response than aspirin at any dose, which is correct?
- A. Oxycodone is more efficacious than aspirin.
  - B. Oxycodone is less potent than aspirin.
  - C. Aspirin is a full agonist, and oxycodone is a partial agonist.
  - D. Oxycodone and aspirin act on the same drug target.

Correct answer = C. The GABA-A receptor is a ligand-gated ion channel selective for chloride. Agonists for the GABA-A receptor increase opening of channels, resulting in chloride entry into the neuron, hyperpolarization, and decreased action potential events.

Correct answer = A. A drug that causes the same effect at a lower dose is more potent. B and C are incorrect because without information about the maximal effect of these drugs, no conclusions can be made about efficacy or intrinsic activity. D is incorrect because the maximal response obtained is often more important than the amount of drug needed to achieve it.

Correct answer = A. Drugs with greater maximal response are more efficacious than drugs with a lower maximal response. Choice B is incorrect since aspirin at any dose cannot produce the same analgesic effect as oxycodone. Choice B is incorrect because aspirin cannot produce maximal analgesic effect, even at higher doses. Choice D is incorrect since aspirin does not produce the same analgesic effects as oxycodone, even at higher doses.

- 2.4 In the presence of propranolol, a higher concentration of epinephrine is required to elicit full anti-asthmatic activity. Propranolol has no effect on asthma symptoms. Which is correct regarding these medications?
- Epinephrine is less efficacious than propranolol.
  - Epinephrine is a full agonist, and propranolol is a partial agonist.
  - Epinephrine is an agonist, and propranolol is a competitive antagonist.
  - Epinephrine is an agonist, and propranolol is a noncompetitive antagonist.
- 2.5 In the presence of picrotoxin, diazepam is less efficacious at causing sedation, regardless of the dose. Picrotoxin has no sedative effect, even at the highest dose. Which of the following is correct regarding these agents?
- Picrotoxin is a competitive antagonist.
  - Picrotoxin is a noncompetitive antagonist.
  - Diazepam is less efficacious than picrotoxin.
  - Diazepam is less potent than picrotoxin.
- 2.6 Haloperidol, chlorpromazine, and clozapine are antipsychotic medications that bind to the D<sub>2</sub> subtype of dopamine receptors, with a binding affinity of haloperidol > chlorpromazine > clozapine. Which statement would have to be correct to conclude that the mechanism of antipsychotic effects for these drugs is via binding to D<sub>2</sub> receptors?
- Haloperidol should have the lowest potency of the three antipsychotic drugs.
  - D<sub>2</sub> receptor binding should also be related to the potency of these drugs in causing Parkinson-like adverse effects.
  - A positive correlation should exist between the affinity of these drugs to bind to D<sub>2</sub> receptors and their potency for antipsychotic actions.
  - Clozapine would have to be more potent than chlorpromazine for decreasing psychosis.
- 2.7 If there were spare β<sub>1</sub> adrenergic receptors on cardiac muscle cells, which statement would be correct?
- The number of spare β<sub>1</sub> adrenergic receptors determines the size of the maximum effect of the agonist epinephrine.
  - Spare β<sub>1</sub> adrenergic receptors make the cardiac tissue less sensitive to epinephrine.
  - A maximal effect of epinephrine is seen when only a portion of β<sub>1</sub> adrenergic receptors are occupied.
  - Spare receptors are active even in the absence of epinephrine.

Correct answer = C. Since propranolol decreases the effect of epinephrine but the inhibition can be overcome by giving a higher dose of epinephrine, propranolol must be a competitive antagonist. If D were correct, even very high concentrations of epinephrine would not be able to elicit a maximal effect in the presence of propranolol. Since propranolol has no effect by itself, A and B are incorrect.

Correct answer = B. Since picrotoxin decreases the maximal effect of diazepam regardless of the diazepam dose, it is a noncompetitive antagonist. Picrotoxin has no efficacy alone, so C is incorrect. No information is provided about potency of either drug.

Correct answer = C. To conclude that the mechanism of antipsychotic effect for these drugs is via binding to D<sub>2</sub> receptors, there should be a positive correlation between the affinity of the drugs for D<sub>2</sub> receptors and their potency for antipsychotic actions. Haloperidol should have the highest antipsychotic potency and clozapine the lowest. There is no guarantee the therapeutic effects and adverse effects are mediated by the same receptor population, therefore a different correlation may exist for the adverse effects and D<sub>2</sub> receptor affinity.

Correct answer = C. Only a fraction of the total receptors need to be bound to elicit a maximum cellular response when spare receptors are present. The other choices do not accurately describe the effects of having spare receptors.

- 2.8 Which of the following up-regulates postsynaptic  $\alpha_1$  adrenergic receptors?
- Daily use of amphetamine that causes release of norepinephrine.
  - A disease that causes an increase in the activity of norepinephrine neurons.
  - Daily use of phenylephrine, an  $\alpha_1$  receptor agonist.
  - Daily use of prazosin, an  $\alpha_1$  receptor antagonist.
- 2.9 Methylphenidate helps patients with attention deficit hyperactivity disorder (ADHD) maintain attention and perform better at school or work, with an  $ED_{50}$  of 10 mg. However, methylphenidate can also cause significant nausea at higher doses ( $TD_{50} = 30$  mg). Which is correct regarding methylphenidate?
- The therapeutic index of methylphenidate is 3.
  - The therapeutic index of methylphenidate is 0.3.
  - Methylphenidate is more potent at causing nausea than treating ADHD.
  - Methylphenidate is more efficacious at causing nausea than treating ADHD.
- 2.10 Which is correct concerning the safety of using warfarin (with a small therapeutic index) versus penicillin (with a large therapeutic index)?
- Warfarin is a safer drug because it has a low therapeutic index.
  - Warfarin treatment has a high chance of resulting in dangerous adverse effects if bioavailability is altered.
  - The high therapeutic index makes penicillin a safe drug for all patients.
  - Penicillin treatment has a high chance of causing dangerous adverse effects if bioavailability is altered.
- 2.11 Which type of adverse drug reactions are serious?
- Type A: Augmented reactions such as hypotension with antihypertensives
  - Type B: Bizarre reactions such as hypersensitivity
  - Type C: Chronic reactions such as renal toxicity and ototoxicity
  - Type D: Delayed reactions such as cancer and teratogenicity
  - All of the above

Correct answer = D. Up-regulation of receptors occurs when receptor activation is lower than normal, such as when the receptor is continuously exposed to an antagonist for that receptor. Down-regulation of receptors occurs when receptor activation is greater than normal because of continuous exposure to an agonist, as described in A, B and C.

Correct answer = A. Therapeutic index is calculated by dividing  $TD_{50}$  by  $ED_{50}$  (30/10), making B incorrect. C is incorrect because methylphenidate is more potent at treating ADHD (it takes a lower dose) than causing nausea. D. No information about efficacy is provided.

Correct answer = B. Agents with a low TI (that is, drugs for which dose is critically important) are those drugs for which bioavailability critically alters the therapeutic and adverse effects. A is incorrect, because a drug with a low TI is not generally considered to be safe. C is incorrect because a high TI does not ensure safety across the entire patient population. D is incorrect because the high TI makes it unlikely that bioavailability alters the incidence of therapeutic or adverse effects.

Correct answer = B. Type B (bizarre) reactions are the reactions that are unexpected and unpredictable and are often related to patient factors such as genetic predisposition and allergy. More serious and potentially fatal forms of drug rashes hypersensitivity reactions include toxic epidermal necrolysis, Stevens–Johnson syndrome, and drug hypersensitivity syndrome. Drug hypersensitivity syndrome is potentially life threatening with significant morbidity.

2.12 Drug–drug interaction can lead to:

- A. Beneficial effects.
- B. Toxicity.
- C. Lack of response.
- D. All of the above.
- E. Both B and C.

2.13 Which of the following adverse drug reactions would you report to the pharmacovigilance center?

- A. A patient reports a skin rash after starting a course on amoxicillin capsules.
- B. A patient reports experiencing dyspepsia when they take their indomethacin capsules.
- C. A patient complains of a dry irritating cough since they have started taking ramipril.
- D. A patient complains they have experienced diarrhea since taking azilsartan

Correct answer = D. The outcome of drug interactions can be beneficial or harmful. However, beneficial effects are very few; most are harmful. Harmful effects can be in terms of lack of efficacy or toxicity or increased adverse reactions.

2.14 Which of the following patients are most at risk of suffering from an adverse drug reaction?

- A. A 2-month-old infant receiving a prescription for an antibiotic.
- B. A 22-year-old patient with asthma receiving prescriptions for inhalers to relieve and prevent their asthma.
- C. A 48-year-old patient who has hypertension and receives a prescription for an ACE inhibitor.
- D. A 50-year-old patient who has edema receiving a prescription for a diuretic.

Correct answer = D. The following adverse drug reactions should be reported: All ADRs to newly marketed drugs or newly added drugs to the Essential Medicines List (EML), azilsartan is a newly introduced drug and uncommon and rare side effects with this drug may not have been revealed in clinical trials. Reporting of side effects after marketing of the drug helps in improving the compilation and analysis of this side effect which in turn may influence drug label and warning precautions. In case a side effect is serious, the drug may be withdrawn from market. The following should be reported: All serious reactions, whether expected or not, and drug interactions; an observed increase in the frequency of a known reaction; unexpected ADRs regardless of their nature or severity, which are not clearly stated in the package insert; unusual ADRs or ADRs which are interesting; ADRs in special populations such as drug abuse and drug use in pregnancy and during lactation, pediatrics, and geriatrics; all adverse reactions or poisonings to traditional or herbal remedies.

Correct answer = A. Children and elderly patients are at a greater risk of suffering from side effects. Moreover, clinical trials for most drugs are done in adult population and children are excluded from the trials due to ethical concerns, but these drugs are often used in this age group; therefore, the side effects which may appear in children are not evident from clinical trial safety data. Study of the side effects mainly in this population is important.



## UNIT II

# Drugs Affecting the Autonomic Nervous System

# Autonomic Nervous System

Rajan Radhakrishnan

3

## I. OVERVIEW

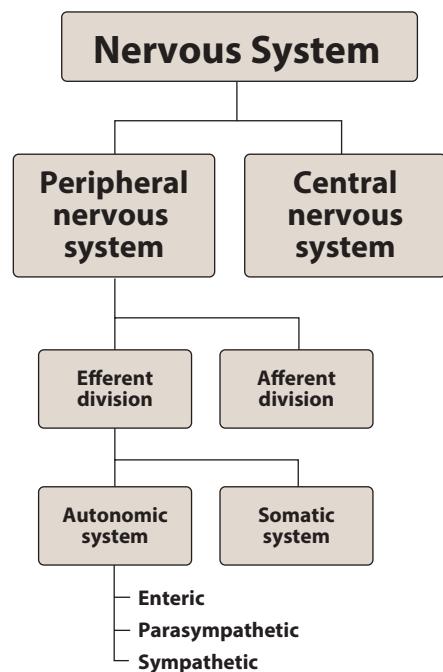
The autonomic nervous system (ANS), along with the endocrine system, coordinates the regulation and integration of bodily functions. The endocrine system sends signals to target tissues by varying the levels of blood-borne hormones. By contrast, the nervous system exerts effects by the rapid transmission of electrical impulses over nerve fibers that terminate at effector cells, which specifically respond to the release of neuromediator substances. Drugs that produce their primary therapeutic effect by mimicking or altering the functions of the ANS are called autonomic drugs and are discussed in Chapters 4 through 7. The autonomic agents act either by stimulating portions of the ANS or by blocking the action of the autonomic nerves. This chapter outlines the fundamental physiology of the ANS and describes the role of neurotransmitters in the communication between extracellular events and chemical changes within the cell.

## II. INTRODUCTION TO THE NERVOUS SYSTEM

The nervous system is divided into two anatomical divisions: the central nervous system (CNS), which is composed of the brain and spinal cord, and the peripheral nervous system, which includes neurons located outside the brain and spinal cord—that is, any nerves that enter or leave the CNS (Figure 3.1). The peripheral nervous system is subdivided into the efferent and afferent divisions. The efferent neurons carry signals away from the brain and spinal cord to the peripheral tissues, and the afferent neurons bring information from the periphery to the CNS. Afferent neurons provide sensory input to modulate the function of the efferent division through reflex arcs or neural pathways that mediate a reflex action.

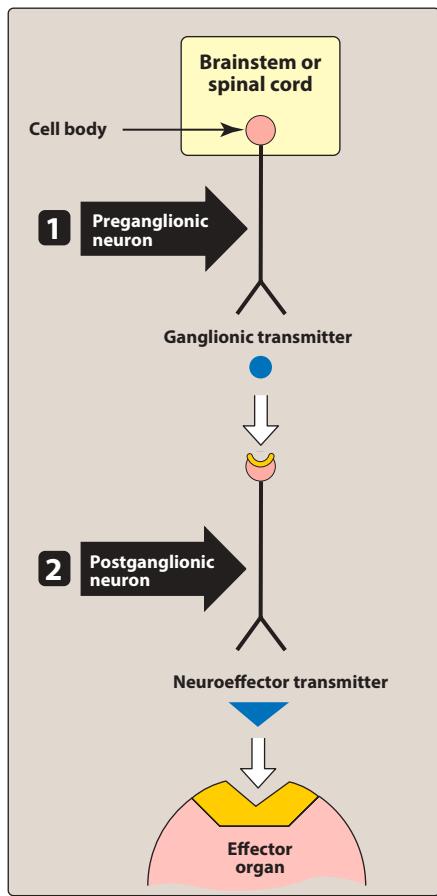
### A. Functional divisions within the nervous system

The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions: the somatic and the ANS (Figure 3.1).



**Figure 3.1**

Organization of the nervous system.



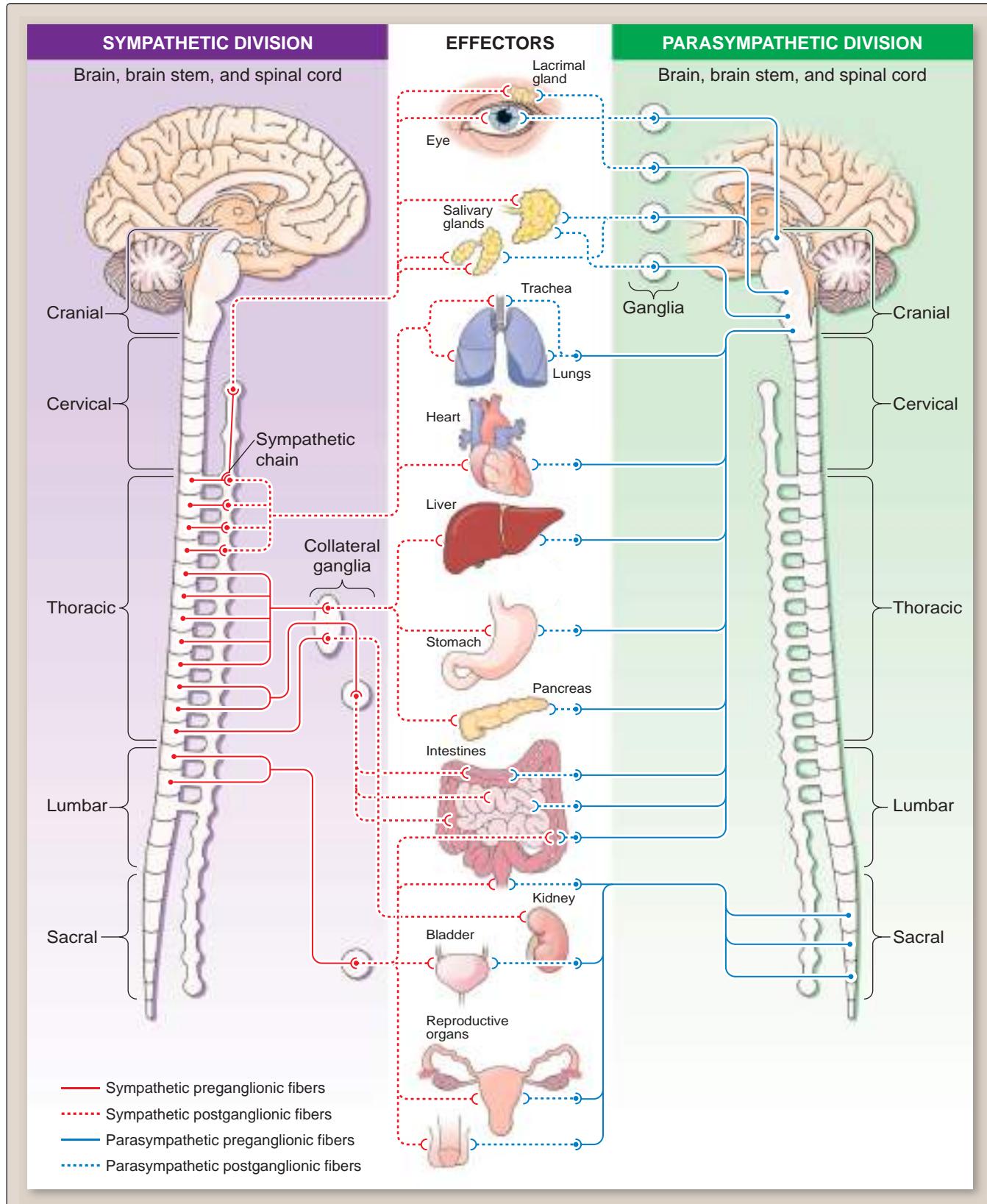
**Figure 3.2**

Efferent neurons of the autonomic nervous system.

The somatic efferent neurons are involved in the voluntary control of functions such as contraction of the skeletal muscles essential for locomotion. The ANS, conversely, regulates the everyday requirements of vital bodily functions without the conscious participation of the mind. Because of the involuntary nature of the ANS as well as its functions, it is also known as the visceral, vegetative, or involuntary nervous system. It is composed of efferent neurons that innervate visceral smooth muscle, cardiac muscle, vasculature, and the exocrine glands, thereby controlling digestion, cardiac output, blood flow, and glandular secretions.

## B. Anatomy of the ANS

- Efferent neurons:** The ANS carries nerve impulses from the CNS to the effector organs through two types of efferent neurons: the preganglionic neurons and the postganglionic neurons (Figure 3.2). The cell body of the first nerve cell, the preganglionic neuron, is located within the CNS. The preganglionic neurons emerge from the brainstem or spinal cord and make a synaptic connection in ganglia (an aggregation of nerve cell bodies located in the peripheral nervous system). The ganglia function as relay stations between the preganglionic neuron and the second nerve cell, the postganglionic neuron. The cell body of the postganglionic neuron originates in the ganglion. It is generally nonmyelinated and terminates on effector organs, such as visceral smooth muscle, cardiac muscle, and the exocrine glands.
- Afferent neurons:** The afferent neurons (fibers) of the ANS are important in the reflex regulation of this system (for example, by sensing pressure in the carotid sinus and aortic arch) and in signaling the CNS to influence the efferent branch of the system to respond.
- Sympathetic neurons:** The efferent ANS is divided into the sympathetic and the parasympathetic nervous systems, as well as the enteric nervous system (Figure 3.1). Anatomically, the sympathetic and the parasympathetic neurons originate in the CNS and emerge from two different spinal cord regions (Figure 3.3). The preganglionic neurons of the sympathetic system come from the thoracic and lumbar regions (T1 to L2) of the spinal cord, and they synapse in two cord-like chains of ganglia that run close to and in parallel on each side of the spinal cord. The preganglionic neurons are short in comparison to the postganglionic ones. The axons of the postganglionic neuron extend from the ganglia to tissues they innervate and regulate (see Chapter 6). In most cases, the preganglionic nerve endings of the sympathetic nervous system are highly branched, enabling one preganglionic neuron to interact with many postganglionic neurons. This arrangement enables activation of numerous effector organs at the same time. [Note: The adrenal medulla, like the sympathetic ganglia, receives preganglionic fibers from the sympathetic system. The adrenal medulla, in response to stimulation by the ganglionic neurotransmitter acetylcholine, secretes epinephrine (adrenaline), and lesser amounts of norepinephrine, directly into the blood.]
- Parasympathetic neurons:** The parasympathetic preganglionic fibers arise from cranial nerves III (oculomotor), VII (facial), IX (glossopharyngeal), and X (vagus), as well as from the sacral region (S2 to S4) of the spinal cord and synapse in ganglia near

**Figure 3.3**

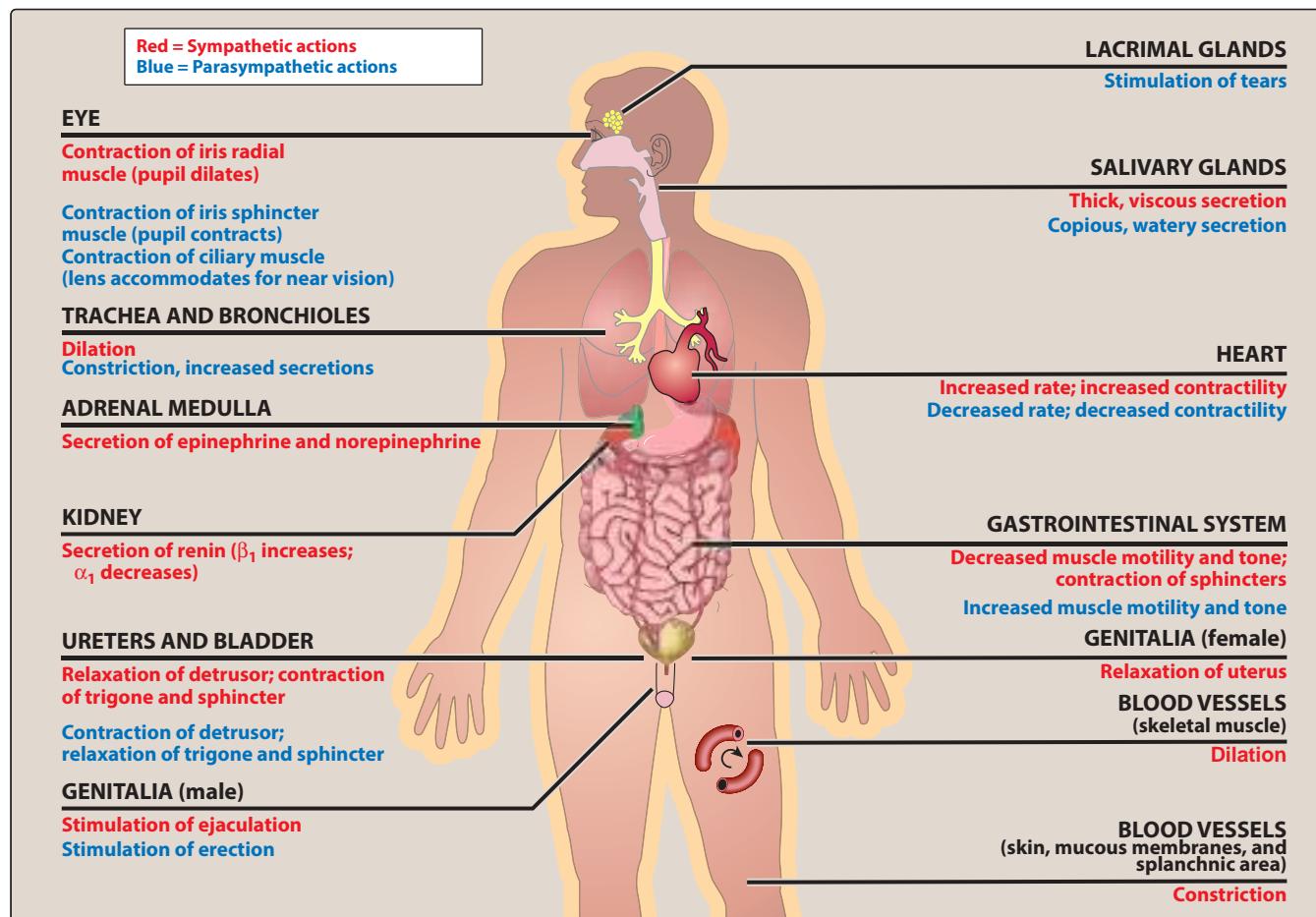
Autonomic nervous system. From Cohen BJ, Hull KL: Memmler's Structure and Function of the Human Body, 11th Ed. Philadelphia, Wolters Kluwer, 2016.

or on the effector organs. [Note: The vagus nerve accounts for 90% of preganglionic parasympathetic fibers. Postganglionic neurons from this nerve innervate most organs in the thoracic and abdominal cavity.] Thus, in contrast to the sympathetic system, the preganglionic fibers are long, and the postganglionic ones are short, with the ganglia close to or within the organ innervated. In most instances, there is a one-to-one connection between the preganglionic and postganglionic neurons, enabling discrete response of this system.

5. **Enteric neurons:** The enteric nervous system is the third division of the ANS. It is a collection of nerve fibers that innervate the gastrointestinal (GI) tract, pancreas, and gallbladder, and it constitutes the “brain of the gut.” This system functions independently of the CNS and controls motility, exocrine and endocrine secretions, and microcirculation of the GI tract. It is modulated by both the sympathetic and the parasympathetic nervous systems.

### C. Functions of the sympathetic nervous system

Although continually active to some degree (for example, in maintaining tone of vascular beds), the sympathetic division is responsible for adjusting in response to stressful situations, such as trauma, fear, hypoglycemia, cold, and exercise (Figure 3.4).



**Figure 3.4**

Actions of sympathetic and parasympathetic nervous systems on effector organs.

- Effects of stimulation of the sympathetic division:** The effect of sympathetic stimulation is an increase in heart rate and blood pressure, mobilization of energy stores, and increase in blood flow to skeletal muscles and the heart, while diverting flow from the skin and internal organs. Sympathetic stimulation results in dilation of the pupils and bronchioles (Figure 3.4). It also reduces GI motility and affects function of the bladder and sexual organs.
- Fight-or-flight response:** The changes experienced by the body during emergencies are referred to as the “fight or flight” response (Figure 3.5). These reactions are triggered both by direct sympathetic activation of effector organs and by stimulation of the adrenal medulla to release epinephrine and lesser amounts of norepinephrine. Hormones released by the adrenal medulla directly enter the bloodstream and promote responses in effector organs that contain adrenergic receptors (see Chapter 6). The sympathetic nervous system tends to function as a unit and often discharges as a complete system, for example, during severe exercise or in reactions to fear (Figure 3.5). This system, with its diffuse distribution of postganglionic fibers, is involved in a wide array of physiologic activities. Although it is not essential for survival, it is essential in preparing the body to handle uncertain situations and unexpected stimuli.

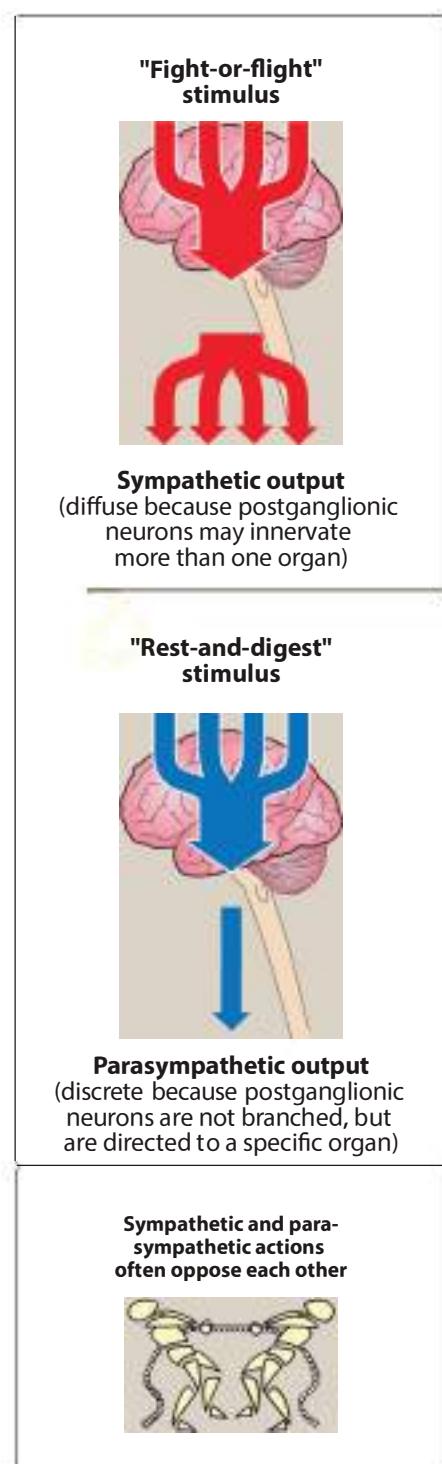
#### D. Functions of the parasympathetic nervous system

The parasympathetic division is involved with maintaining homeostasis within the body. It is required for life, since it maintains essential bodily functions, such as digestion and elimination. The parasympathetic division usually acts to oppose or balance the actions of the sympathetic division and generally predominates the sympathetic system in “rest-and-digest” situations. Unlike the sympathetic system, the parasympathetic system never discharges as a complete system. If it did, it would produce massive, undesirable, and unpleasant symptoms, such as involuntary urination and defecation. Instead, parasympathetic fibers innervating specific organs such as the gut, heart, or eye are activated separately, and the system affects these organs individually.

#### E. Role of the CNS in the control of autonomic functions

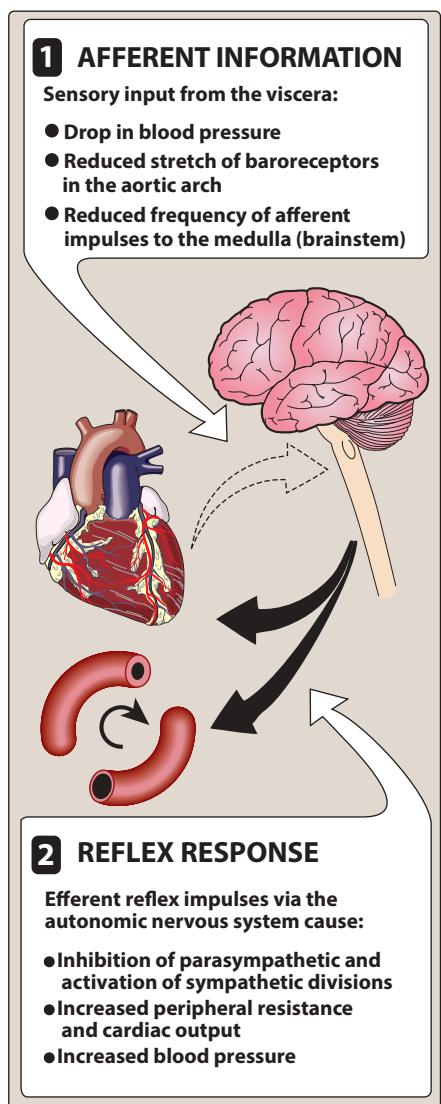
Although the ANS is a motor system, it does require sensory input from peripheral structures to provide information on the current state of the body. This feedback is provided by streams of afferent impulses, originating in the viscera and other autonomically innervated structures that travel to integrating centers in the CNS, such as the hypothalamus, medulla oblongata, and spinal cord. These centers respond to stimuli by sending out efferent reflex impulses via the ANS.

- Reflex arcs:** Most of the afferent impulses are involuntarily translated into reflex responses. For example, a fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the heart, vena cava, aortic arch, and carotid sinuses) to send fewer impulses to cardiovascular centers in the brain. This prompts a reflex response of increased sympathetic output to the heart and vasculature and decreased parasympathetic output to the heart, which results in a compensatory rise in blood pressure and heart rate (Figure 3.6). [Note: In each case, the reflex arcs of the ANS comprise a sensory (afferent) arm and a motor (efferent or effector) arm.]



**Figure 3.5**

Sympathetic and parasympathetic actions are elicited by different stimuli.



- 2. Emotions and the ANS:** Stimuli that evoke strong feelings, such as rage, fear, and pleasure, can modify activities of the ANS.

### F. Innervation by the ANS (Figure 3.7)

- 1. Dual innervation:** Most organs are innerved by both divisions of the ANS. Thus, vagal parasympathetic innervation slows the heart rate and sympathetic innervation increases heart rate. Despite this dual innervation, one system usually predominates in controlling the activity of a given organ. For example, the vagus nerve is the predominant factor for controlling heart rate. The dual innervation of organs is dynamic and fine-tuned continually to maintain homeostasis.

EFFECTOR	ACTIONS OF SYMPATHETIC DIVISION	ACTIONS OF PARASYMPATHETIC DIVISION
Eye (pupil)	Dilatation	Constriction
Eye (ciliary muscle)	Far vision	Near vision
Heart		
Rate	Acceleration	Slowing
Contractility	Increased	Decreased
Arterioles		
Skin and most others	Constriction	
Skeletal muscle	Dilation	
Glands		
Salivary	Viscid secretion	Watery secretion
Lacrimal		Secretion
Sweat	Secretion	Contraction
Bronchial muscle	Relaxation	Contraction
GI tract		
Muscle wall	Relaxation	Contractions
Sphincters	Contractions	Relaxation
Urinary bladder		
Fundus	Relaxation	Contraction
Trigone; Sphincters	Contraction	Relaxation
Penis	Ejaculation	Erection
Uterus	Relaxation	
Metabolism		
Liver	Gluconeogenesis Glycogenolysis	
Kidney	Renin secretion	
Fat cells	Lipolysis	

**Figure 3.7**

Actions of the autonomic nervous system on select effector organs.

- 2. Sympathetic innervation:** Although most tissues receive dual innervation, some effector organs, such as the adrenal medulla, kidney, pilomotor muscles, and sweat glands, receive innervation only from the sympathetic system.

## G. Somatic nervous system

The efferent somatic nervous system differs from the ANS in that a single myelinated motor neuron, originating in the CNS, travels directly to skeletal muscle without the mediation of ganglia. As noted earlier, the somatic nervous system is under voluntary control whereas the ANS is involuntary. The responses in the somatic division are generally faster than those in the ANS.

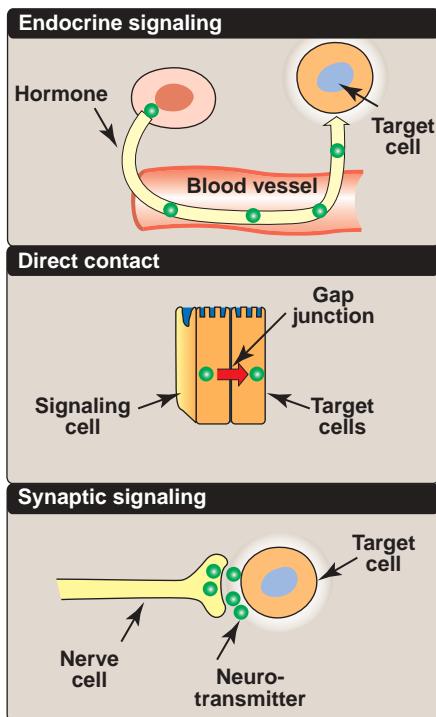
## H. Summary of differences between sympathetic, parasympathetic, and motor nerves

Major differences in the anatomical arrangement of neurons lead to variations of the functions in each division (Figure 3.8). The sympathetic nervous system is widely distributed, innervating practically all effector systems in the body. By contrast, the distribution of the parasympathetic division is more limited. The sympathetic preganglionic fibers have a much broader influence than the parasympathetic fibers and synapse with a larger number of postganglionic fibers. This type of organization permits a diffuse discharge of the sympathetic nervous system. The parasympathetic division is more circumscribed, with mostly one-to-one interactions, and the ganglia are also close to, or within, organs they innervate. This limits the amount of branching that can be done by this division. [A notable exception is found in the myenteric plexus (major nerve supply to the GI tract), where one preganglionic neuron has been shown to interact with 8000 or more postganglionic fibers.] The anatomical arrangement of the parasympathetic system results in the distinct functions of this division. The somatic nervous system innervates skeletal muscles. One somatic motor neuron axon is highly branched, and each branch innervates a single muscle fiber. Thus, one somatic motor neuron may innervate 100 muscle fibers. This arrangement leads to the formation of a motor unit. The lack of ganglia and the myelination of the motor nerves enable a fast response by the somatic nervous system.

	SYMPATHETIC	PARASYMPATHETIC
Sites of origin	Thoracic and lumbar region of the spinal cord (thoracolumbar)	Brain and sacral area of the spinal cord (craniosacral)
Length of fibers	Short preganglionic Long postganglionic	Long preganglionic Short postganglionic
Location of ganglia	Close to the spinal cord	Within or near effector organs
Preganglionic fiber branching	Extensive	Minimal
Distribution	Wide	Limited
Type of response	Diffuse	Discrete

**Figure 3.8**

Characteristics of the sympathetic and parasympathetic nervous systems.



**Figure 3.9**

Some commonly used mechanisms for transmission of regulatory signals between cells.

### III. CHEMICAL SIGNALING BETWEEN CELLS

Neurotransmission in the ANS is an example of chemical signaling between cells. In addition to neurotransmission, other types of chemical signaling include the secretion of hormones and the release of local mediators (Figure 3.9).

#### A. Hormones

Specialized endocrine cells secrete hormones into the bloodstream, where they travel throughout the body, exerting effects on broadly distributed target cells (see Unit V: Drugs Affecting the Endocrine System).

#### B. Local mediators

Most cells secrete chemicals that act locally on cells in the immediate environment. Because these chemical signals are rapidly destroyed or removed, they do not enter the blood and are not distributed throughout the body. Histamine (see Chapter 40) and prostaglandins are examples of local mediators.

#### C. Neurotransmitters

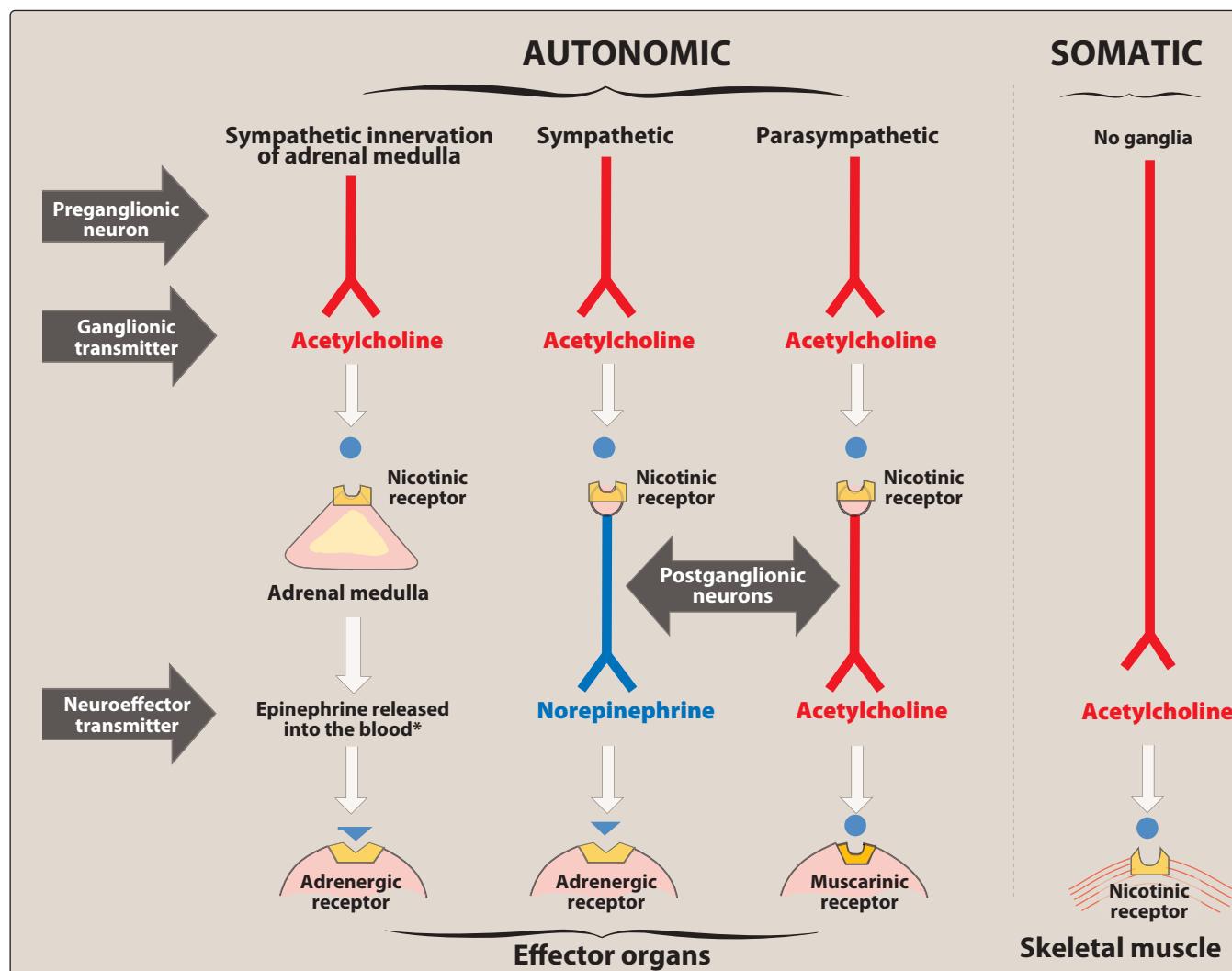
Communication between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical signals (neurotransmitters) from the nerve terminals. The release is triggered by arrival of the action potential at the nerve ending, leading to depolarization. An increase in intracellular  $\text{Ca}^{2+}$  initiates fusion of synaptic vesicles with the presynaptic membrane and release of their contents. The neurotransmitters rapidly diffuse across the synaptic cleft, or space (synapse), between neurons and combine with specific receptors on the postsynaptic (target) cell.

**1. Membrane receptors:** All neurotransmitters, and most hormones and local mediators, are too hydrophilic to penetrate the lipid bilayers of target cell plasma membranes. Instead, their signal is mediated by binding to specific receptors on the cell surface of target organs. [Note: A receptor is defined as a recognition site for a substance. It has a binding specificity and is coupled to processes that eventually evoke a response. Most receptors are proteins (see Chapter 1).]

**2. Types of neurotransmitters:** Although over 50 signal molecules in the nervous system have been identified, norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, glutamate, and  $\gamma$ -aminobutyric acid are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. Acetylcholine and norepinephrine are the primary chemical signals in the ANS, whereas a wide variety of neurotransmitters function in the CNS.

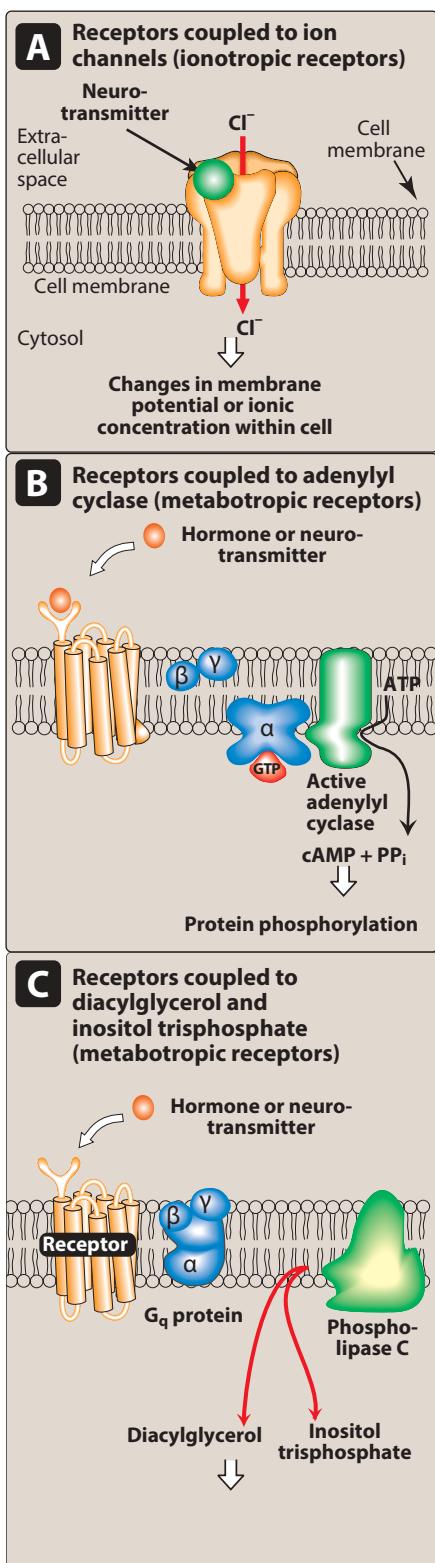
**a. Acetylcholine:** The autonomic nerve fibers can be divided into two groups based on the type of neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed cholinergic (Figure 3.10; Chapters 4 and 5).

Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. It is the neurotransmitter at the adrenal medulla. Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system, and a few sympathetic system organs, also involves the release of acetylcholine. In the somatic nervous system, transmission at the neuromuscular junction (the junction of nerve fibers and voluntary muscles) is also cholinergic (Figure 3.10).



**Figure 3.10**

Summary of the neurotransmitters released, types of receptors, and types of neurons within the autonomic and somatic nervous systems. Cholinergic neurons are shown in red and adrenergic neurons in blue. [Note: This schematic diagram does not show that the parasympathetic ganglia are close to or on the surface of the effector organs and that the postganglionic fibers are usually shorter than the preganglionic fibers. By contrast, the ganglia of the sympathetic nervous system are close to the spinal cord. The postganglionic fibers are long, allowing extensive branching to innervate more than one organ system. This allows the sympathetic nervous system to discharge as a unit.] \*Epinephrine 80% and norepinephrine 20% released from adrenal medulla.

**Figure 3.11**

Three mechanisms whereby binding of a neurotransmitter leads to a cellular effect.

- b. **Norepinephrine and epinephrine:** When norepinephrine is the neurotransmitter, the fiber is termed adrenergic ([Figure 3.10](#); Chapters 6 and 7). In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs. Epinephrine secreted by the adrenal medulla (not sympathetic neurons) also acts as a chemical messenger in the effector organs. [Note: A few sympathetic fibers, such as those involved in sweating, are cholinergic, and, for simplicity, they are not shown in [Figure 3.10](#).]
- 3. **Dissipation of the transmitter/termination of neurotransmitter action:** The action of the neurotransmitter is terminated either by destruction by enzymes (cholinesterase destroys acetyl choline whereas monoamine oxidase [MAO] and catechol-o-methyltransferase [COMT] destroy noradrenaline) or by reuptake of the neurotransmitter by tissues or axonal terminal (noradrenaline at adrenergic endings).

#### IV. SIGNAL TRANSDUCTION IN THE EFFECTOR CELL

The binding of chemical signals to receptors activates enzymatic processes within the cell membrane that ultimately results in a cellular response, such as the phosphorylation of intracellular proteins or changes in the conductivity of ion channels (see Chapter 1). A neurotransmitter can be thought of as a signal and a receptor as a signal detector and transducer. The receptors in the ANS effector cells are classified as adrenergic or cholinergic based on the neurotransmitters or hormones that bind to them. Epinephrine and norepinephrine bind to adrenergic receptors, and acetylcholine binds to cholinergic receptors. Cholinergic receptors are further classified as nicotinic or muscarinic. Some receptors, such as the postsynaptic cholinergic nicotinic receptors in skeletal muscle cells, are directly linked to membrane ion channels and are known as ionotropic receptors. Binding of neurotransmitter to ionotropic receptors directly affects ion permeability ([Figure 3.11A](#)). All adrenergic receptors and cholinergic muscarinic receptors are G protein-coupled receptors (metabotropic receptors). Metabotropic receptors mediate the effects of ligands by activating a second messenger system inside the cell. The two most widely recognized second messengers are the adenylyl cyclase system and the calcium/phosphatidylinositol system ([Figure 3.11B, C](#)).

#### V. AUTONOMIC DYSFUNCTION (DYSAUTONOMIA)

The autonomic nervous system controls a number of functions in the body, for example, heart rate, blood pressure, peristalsis of bowel and urinary system, and secretions such as sweat. Drugs can influence neurotransmitter function at the synapse and thereafter the conduction of impulses in nerve cells. Dysfunction of the ANS can involve any of these functions. Autonomic dysfunction may also result from diseases that affect primarily either the central nervous system or the peripheral autonomic nervous system. Autonomic dysfunction may be secondary to Parkinson's disease, diabetes, and alcoholism. The most common cause of disturbed autonomic function in the central nervous system diseases is degeneration of the intermediolateral cell columns (progressive dysautonomia) or disease or damage to descending pathways (spinal cord lesions, cerebrovascular disease, brainstem tumors, multiple sclerosis).

## Study Questions

Choose the ONE best answer.

- 3.1. Which is correct regarding the sympathetic nervous system?
- It generally mediates body functions in “rest-and-digest” mode.
  - The neurotransmitter at the sympathetic ganglion is norepinephrine (NE).
  - The neurotransmitter at the sympathetic ganglion is acetylcholine (ACh).
  - Sympathetic neurons release ACh in the effector organs.
- 3.2. Why does the somatic nervous system enable a faster response compared to the ANS?
- Somatic motor neurons have ganglia where neurotransmission is mediated by ACh.
  - Somatic motor neurons have ganglia where neurotransmission is mediated by NE.
  - Somatic motor neurons are not myelinated.
  - Somatic motor neurons are myelinated and do not have ganglia.
- 3.3. Which physiological change occurs when the parasympathetic system is activated?
- Increase in heart rate
  - Inhibition of lacrimation (tears)
  - Dilation of the pupil (mydriasis)
  - Increase in gastric motility
- 3.4. Which physiological change is expected when the sympathetic system is inhibited using a pharmacological agent?
- Reduction in heart rate
  - Increase in blood pressure
  - Decrease in fluid secretions
  - Constriction of blood vessels
- 3.5. Which is correct regarding activation of receptors on the effector organs in the ANS?
- Acetylcholine activates muscarinic receptors.
  - Acetylcholine activates adrenergic receptors.
  - Epinephrine activates nicotinic receptors.
  - Norepinephrine activates muscarinic receptors.

Correct answer = C. The neurotransmitter at the sympathetic and parasympathetic ganglia is acetylcholine. The sympathetic system generally mediates body functions in “fight-or-flight” mode and the parasympathetic system generally mediates body functions in “rest-and-digest” mode. Sympathetic neurons release NE, and parasympathetic neurons release ACh in the effector cells.

Correct answer = D. Somatic motor neurons are myelinated and have no ganglia. This enables faster transmission in the somatic neurons.

Correct answer = D. Activation of the parasympathetic system causes an increase in gastric motility, increase in fluid secretions, reduction in heart rate, and constriction of the pupil. In the “rest-and-digest” mode, the parasympathetic system is more active, which helps with digestion.

Correct answer = A. Activation of the sympathetic system causes an increase in heart rate, increase in blood pressure, reduction or thickening of fluid secretions, and constriction of blood vessels. Therefore, inhibition of the sympathetic system should theoretically cause a reduction in heart rate, decrease in blood pressure, increase in fluid secretions, and relaxation of blood vessels.

Correct answer = A. Acetylcholine is the neurotransmitter in the cholinergic system, and it activates both muscarinic and nicotinic cholinergic receptors, not adrenergic receptors. Norepinephrine and epinephrine activate adrenergic receptors, not muscarinic receptors.

- 3.6. Which statement concerning the parasympathetic nervous system is correct?
- The parasympathetic system often discharges as a single, functional system.
  - The parasympathetic division is involved in near vision, movement of food, and urination.
  - The postganglionic fibers of the parasympathetic division are long, compared to those of the sympathetic nervous system.
  - The parasympathetic system controls the secretion of the adrenal medulla.
- 3.7. Which is correct regarding neurotransmitters and neurotransmission?
- Neurotransmitters are released from the presynaptic nerve terminals.
  - Arrival of an action potential in the postsynaptic cell triggers release of neurotransmitter.
  - Intracellular calcium levels drop in the neuron before the release of neurotransmitter.
  - Serotonin and dopamine are the primary neurotransmitters in the ANS.
- 3.8. An elderly man is brought to the emergency room after ingesting a large quantity of prazosin tablets, a drug that blocks  $\alpha_1$  adrenergic receptors, which mediate effects of epinephrine and norepinephrine on the blood vessels and urinary bladder. Which symptom is most likely to be seen in this patient?
- Reduced heart rate (bradycardia)
  - Dilation of blood vessels (vasorelaxation)
  - Increased blood pressure
  - Reduction in urinary frequency
- 3.9. Which statement is correct regarding the autonomic nervous system?
- Afferent neurons carry impulses from the central nervous system (CNS) to the effector organs.
  - Preganglionic neurons of the sympathetic system arise from the cranial nerves, as well as from the sacral region.
  - When there is a sudden drop in blood pressure, the baroreceptors send signals to the brain to activate the parasympathetic system.
  - The heart receives both sympathetic and parasympathetic innervation.

Correct answer = B. The parasympathetic nervous system maintains essential bodily functions, such as vision, movement of food, and urination. It uses acetylcholine, not norepinephrine, as a neurotransmitter, and it discharges as discrete fibers that are activated separately. The postganglionic fibers of the parasympathetic system are short compared to those of the sympathetic division. The adrenal medulla is under the control of the sympathetic system.

Correct answer = A. Neurotransmitters are released from presynaptic neurons, triggered by the arrival of an action potential in the presynaptic neuron (not in the postsynaptic cell). When an action potential arrives in the presynaptic neuron, calcium enters the presynaptic neuron and calcium levels increase in the neuron before neurotransmitter is released. The main neurotransmitters in the ANS are norepinephrine and acetylcholine.

Correct answer = B. Activation of  $\alpha_1$  receptors causes vasoconstriction, reduction in urinary frequency, and an increase in blood pressure, without a direct effect on the heart rate. It may cause reflex tachycardia (increase in heart rate) in some patients. Thus blockade of  $\alpha_1$  receptors could theoretically cause dilation of blood vessels, reduction in blood pressure, and increase in urinary frequency. It should not cause a reduction in heart rate.

Correct answer = D. The heart receives both sympathetic and parasympathetic innervation. Activation of sympathetic neurons increases the heart rate and force of contraction, and activation of parasympathetic neurons reduces the heart rate and force of contraction (slightly). Afferent neurons carry impulses from the periphery to the CNS. Preganglionic neurons of the sympathetic system arise from thoracic and lumbar regions of the spinal cord, whereas the preganglionic neurons of the parasympathetic system arise from cranial nerves and the sacral region. When there is a sudden drop in blood pressure, the sympathetic system is activated, not the parasympathetic system.

3.10. Which is correct regarding membrane receptors and signal transduction?

- A. ANS neurotransmitters bind to membrane receptors on the effector cells, which leads to intracellular events.
- B. Cholinergic muscarinic receptors are ionotropic receptors.
- C. Cholinergic nicotinic receptors are metabotropic receptors.
- D. Metabotropic receptors activate ion channels directly.

Correct answer = A. Neurotransmitters generally bind to membrane receptors on the postsynaptic effector cells and cause cellular effects. Acetylcholine (ACh) binds to cholinergic muscarinic receptors and activates the second messenger pathway in effector cells, which in turn causes cellular events. Receptors that are coupled to second messenger systems are known as metabotropic receptors. Metabotropic receptors do not directly activate ion channels. ACh also binds to cholinergic nicotinic receptors and activates ion channels on the effector cells. The receptors that directly activate ion channels are known as ionotropic receptors.



# Cholinergic Agonists

4

Rajan Radhakrishnan

## I. OVERVIEW

Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in the mechanism of action. The cholinergic drugs, which are described in this and the following chapter, act on receptors activated by acetylcholine (ACh), whereas the adrenergic drugs (see Chapters 6 and 7) act on receptors stimulated by norepinephrine or epinephrine. Cholinergic and adrenergic drugs act by either stimulating or blocking receptors of the ANS. **Figure 4.1** summarizes cholinergic agonists discussed in this chapter.

## II. THE CHOLINERGIC NEURON

The preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia (both parasympathetic and sympathetic), and the postganglionic fibers of the parasympathetic division use ACh as a neurotransmitter (**Figure 4.2**). The postganglionic sympathetic division of sweat glands also uses acetylcholine. In addition, cholinergic neurons innervate the muscles of the somatic system and play an important role in the central nervous system (CNS).

### A. Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves six sequential steps: 1) synthesis of ACh, 2) storage, 3) release, 4) binding of ACh to the receptor, 5) degradation of ACh in the synaptic cleft (the space between the nerve endings and the adjacent receptors on nerves or effector organs), and 6) recycling of choline (**Figure 4.3**).

- Synthesis of acetylcholine:** Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system that cotransports sodium and can be inhibited by the drug *hemicholinium*. [Note: Choline has a quaternary nitrogen and carries a permanent positive charge and, thus, cannot diffuse through the membrane.] The uptake of choline is the rate-limiting step in ACh synthesis. Choline acetyl-transferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol.
- Storage of acetylcholine in vesicles:** ACh is packaged and stored into presynaptic vesicles by an active transport process. The mature vesicle contains not only ACh but also adenosine triphosphate (ATP) and proteoglycan. Cotransmission from autonomic

### DIRECT ACTING

*Acetylcholine*  
*Bethanechol (oral)*  
*Carbachol*  
*Nicotine*  
*Pilocarpine*  
*Methacholine*

### INDIRECT ACTING (REVERSIBLE)

*Short acting*  
*Edrophonium*  
*Medium acting*  
*Neostigmine*  
*Physostigmine*  
*Pyridostigmine*

### INDIRECT ACTING USED FOR ALZHEIMER'S DISEASE

*Tacrine (not used clinically due to ADR profile)*  
*Donepezil*  
*Galantamine*  
*Rivastigmine*

### INDIRECT ACTING (IRREVERSIBLE)

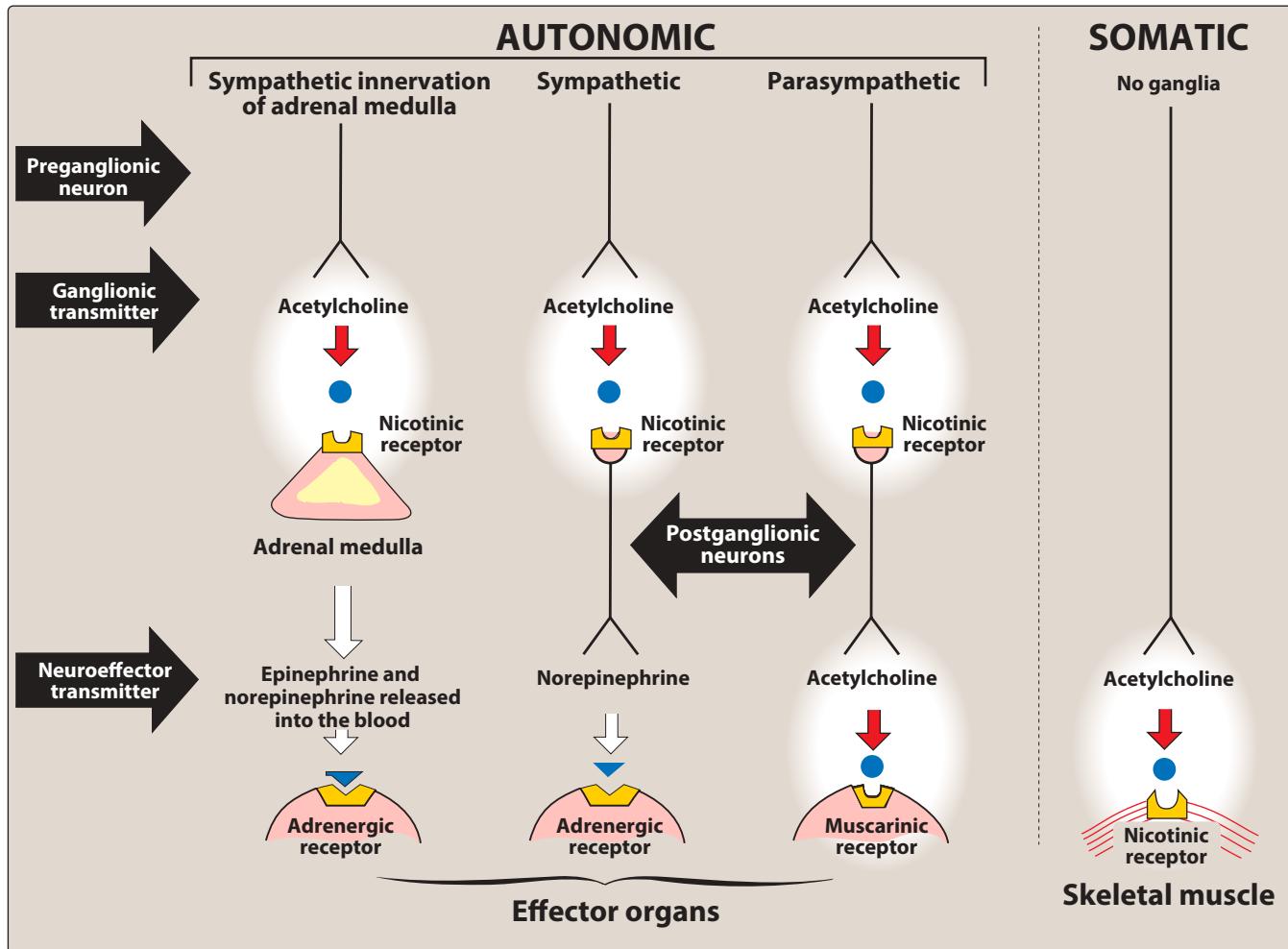
*Echothiophate*  
*Organophosphates*

### REACTIVATION OF ACETYLCHOLINESTERASE

*Pralidoxime*

**Figure 4.1**

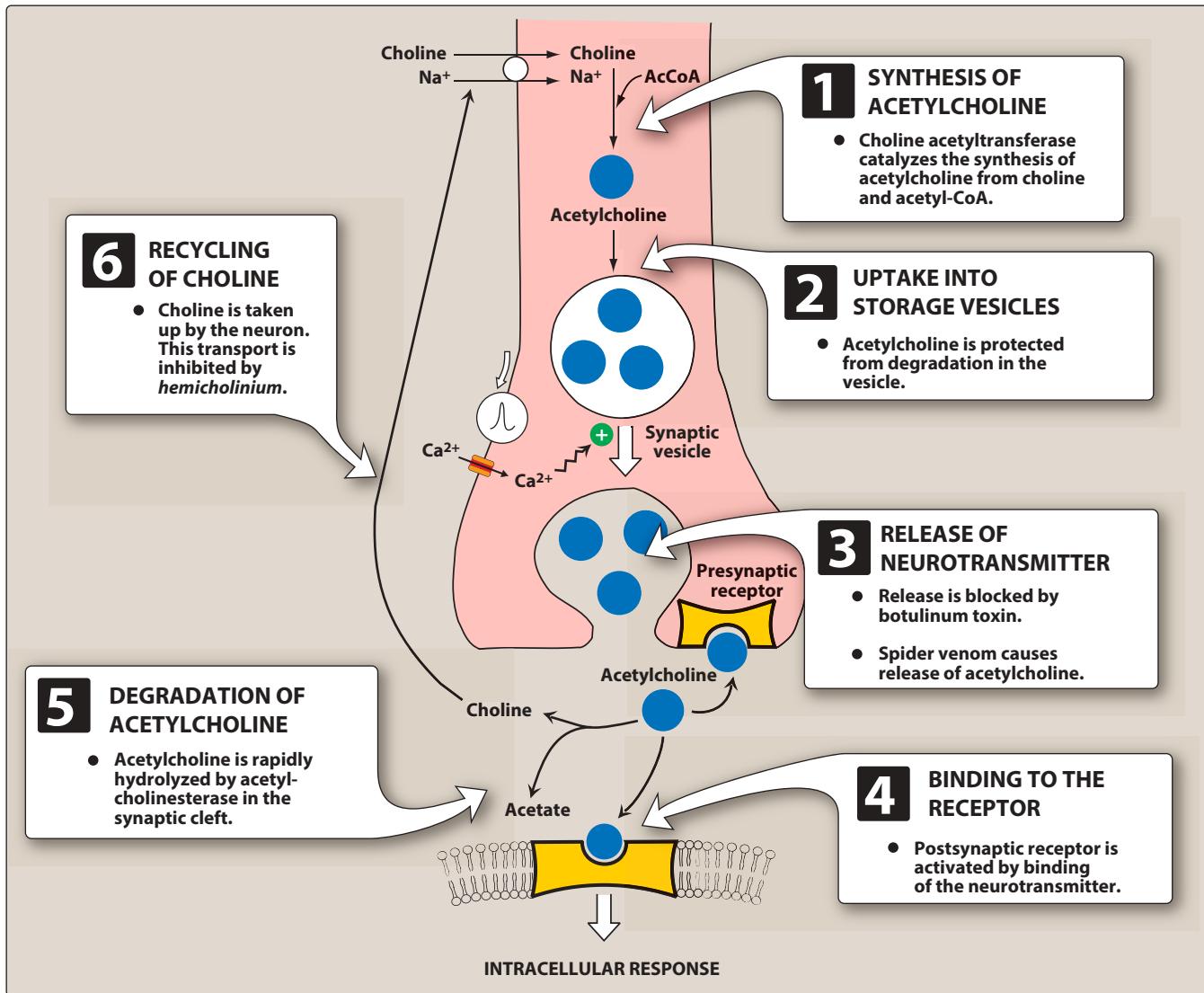
Summary of cholinergic agonists.

**Figure 4.2**

Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems.

neurons is the rule rather than the exception. This means that most synaptic vesicles contain the primary neurotransmitter (here, ACh) as well as a cotransmitter (here, ATP) that increases or decreases the effect of the primary neurotransmitter.

3. **Release of acetylcholine:** When an action potential propagated by voltage-sensitive sodium channels arrives at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of contents into the synaptic space. This release can be blocked by botulinum toxin. In contrast, the toxin in black widow spider venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap.
4. **Binding to the receptor:** ACh released from the synaptic vesicles diffuses across the synaptic space and binds to postsynaptic receptors on the target cell, to presynaptic receptors on the

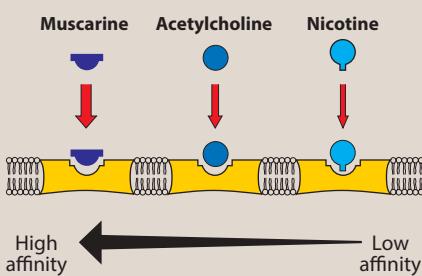
**Figure 4.3**

Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.

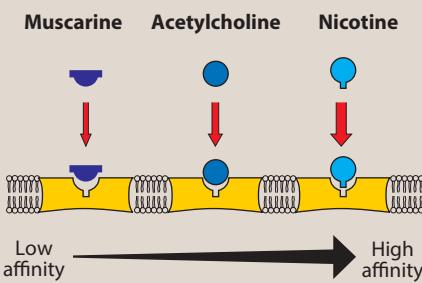
membrane of the neuron that released ACh, or to other targeted presynaptic receptors. The postsynaptic cholinergic receptors on the surface of effector organs are divided into two classes: muscarinic and nicotinic (Figure 4.2). Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells, as mediated by second messenger molecules.

- Degradation of acetylcholine:** The signal at the postjunctional effector site is rapidly terminated, because acetylcholinesterase (AChE) cleaves ACh to choline and acetate in the synaptic cleft.
- Recycling of choline:** Choline may be recaptured by a sodium-coupled, high-affinity uptake system that transports the molecule back into the neuron. There, it is available to be acetylated into ACh.

## A Muscarinic receptors



## B Nicotinic receptors



## **Figure 4.4**

### **III. CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)**

Two families of cholinoreceptors, designated muscarinic and nicotinic receptors, can be distinguished from each other on the basis of their different affinities for agents that mimic the action of ACh (cholinomimetic agents).

#### A. Muscarinic receptors

Muscarinic receptors belong to the class of G protein-coupled receptors (metabotropic receptors). These receptors, in addition to binding ACh, also recognize muscarine, an alkaloid in certain poisonous mushrooms. By contrast, the muscarinic receptors show only a weak affinity for nicotine, an alkaloid found in tobacco and other plants (Figure 4.4A). There are five subclasses of muscarinic receptors; however, only M<sub>1</sub>, M<sub>2</sub>, and M<sub>3</sub> receptors have been functionally characterized. These receptors, in addition to binding with acetylcholine, also recognize muscarine. Muscarine is an alkaloid that is present in certain poisonous mushrooms.

- 1. Location of muscarinic receptors:** These receptors are found on the autonomic effector organs, such as the heart, smooth muscle, brain, and exocrine glands. Although all five subtypes are found on neurons, M<sub>1</sub> receptors are also found on gastric parietal cells, M<sub>2</sub> receptors on cardiac cells and smooth muscle, and M<sub>3</sub> receptors on the bladder, exocrine glands, and smooth muscle. [Note: Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration, they may show some activity at nicotinic receptors.]
  - 2. Mechanism of acetylcholine signal transduction:** A number of different molecular mechanisms transmit the signal generated by ACh occupation of the receptor. For example, when M<sub>1</sub> or M<sub>3</sub> receptors are activated, the receptor undergoes a conformational change and interacts with a G protein that activates phospholipase C. This ultimately leads to production of second messengers inositol-1,4,5-trisphosphate (IP<sub>3</sub>) and diacylglycerol (DAG). IP<sub>3</sub> causes an increase in intracellular Ca<sup>2+</sup>. Calcium can then interact to stimulate or inhibit enzymes or to cause hyperpolarization, secretion, or contraction. Diacylglycerol activates protein kinase C, an enzyme that phosphorylates numerous proteins within the cell. In contrast, activation of the M<sub>2</sub> subtype on the cardiac muscle stimulates a G protein that inhibits adenylyl cyclase and increases K<sup>+</sup> conductance. The heart responds with a decrease in rate and force of contraction.
  - 3. Muscarinic agonists:** *Pilocarpine* is a nonselective muscarinic agonist used to treat xerostomia and glaucoma. Attempts are currently underway to develop muscarinic agents that are directed against specific receptor subtypes.

### B. Nicotinic receptors

These receptors, in addition to binding ACh, also recognize nicotine but show only a weak affinity for muscarine (Figure 4.4B). The nicotinic receptor is composed of five subunits, and it functions as a ligand-gated ion channel. Binding of two ACh molecules elicits a

conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell. Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor. Nicotinic receptors are located in the CNS, the adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles. Those at the NMJ are sometimes designated  $N_M$ , and the others,  $N_N$ . The nicotinic receptors of autonomic ganglia differ from those of the NMJ. For example, ganglionic receptors are selectively blocked by *hexamethonium* and *mecamylamine*, whereas NMJ receptors are specifically blocked by *tubocurarine* and *atracurium*.

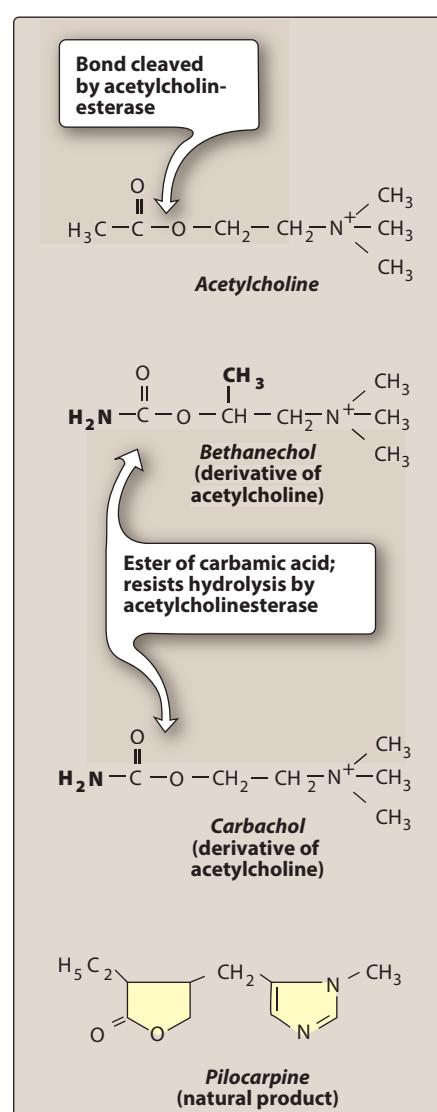
## IV. DIRECT-ACTING CHOLINERGIC AGONISTS

Cholinergic agonists mimic the effects of ACh by binding directly to cholinoreceptors (muscarinic or nicotinic). These agents may be broadly classified into two groups: 1) choline esters, which include endogenous ACh and synthetic esters of choline, such as *carbachol* and *bethanechol*, and 2) naturally occurring alkaloids, such as *nicotine* and *pilocarpine* (Figure 4.5). All direct-acting cholinergic drugs have a longer duration of action than ACh. The more therapeutically useful drugs (*pilocarpine* and *bethanechol*) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents. However, as a group, the direct-acting agonists show little specificity in their actions, which limits their clinical usefulness.

### A. Acetylcholine

Acetylcholine [ah-see-teel-KOE-leen] is a quaternary ammonium compound that cannot penetrate membranes. Although it is the neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases. ACh has both muscarinic and nicotinic activity. Its actions include the following:

- Decrease in heart rate and cardiac output:** The actions of ACh on the heart mimic the effects of vagal stimulation. For example, if injected intravenously, ACh produces a brief decrease in cardiac rate (bradycardia) and cardiac output, mainly because of a reduction in the rate of firing at the sinoatrial (SA) node. [Note: Normal vagal activity regulates the heart by the release of ACh at the SA node.]
- Decrease in blood pressure:** Injection of ACh causes vasodilation and lowering of blood pressure by an indirect mechanism of action. ACh activates  $M_3$  receptors found on endothelial cells lining the smooth muscles of blood vessels. This results in the production of nitric oxide from arginine. Nitric oxide then diffuses to vascular smooth muscle cells to stimulate protein kinase G production, leading to hyperpolarization and smooth muscle relaxation via phosphodiesterase-3 inhibition. In the absence of administered cholinergic agents, the vascular cholinergic receptors have no known function, because ACh is never released into the blood in significant quantities. *Atropine* blocks these muscarinic receptors and prevents ACh from producing vasodilation.

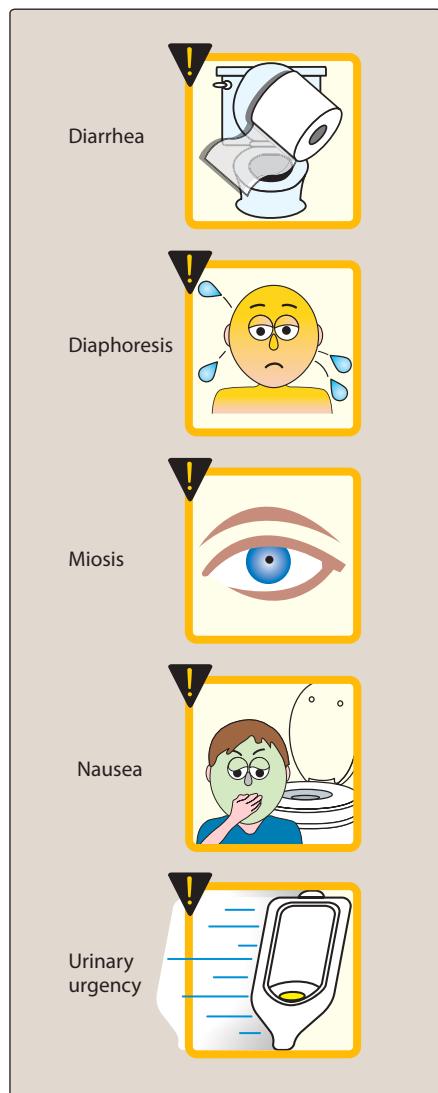


**Figure 4.5**

Comparison of the structures of some cholinergic agonists.

**3. Other actions:** In the gastrointestinal (GI) tract, acetylcholine increases salivary secretion, increases gastric acid secretion, and stimulates intestinal secretions and motility. It also enhances bronchiolar secretions and causes bronchoconstriction. [Note: *Methacholine*, a direct-acting cholinergic agonist, is used to assist in the diagnosis of asthma due to its bronchoconstricting properties.] In the genitourinary tract, ACh increases the tone of the detrusor muscle, causing urination. In the eye, ACh is involved in stimulation of ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil). ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

## B. Bethanechol



**Figure 4.6**

Some adverse effects observed with cholinergic agonists.

*Bethanechol* [be-THAN-e-kole] is an unsubstituted carbamoyl ester, structurally related to ACh (Figure 4.5). It is not hydrolyzed by AChE due to the esterification of carbamic acid, although it is inactivated through hydrolysis by other esterases. It lacks nicotinic actions (due to addition of the methyl group), but does have strong muscarinic activity. Its major actions are on the smooth musculature of the bladder and GI tract. It has about a 1-hour duration of action.

- Actions:** *Bethanechol* directly stimulates muscarinic receptors and selectively stimulates urinary and gastrointestinal tract. Its effect on the GI tract causes increased intestinal motility and tone. It also stimulates the detrusor muscle of the bladder, whereas the trigone and sphincter muscles are relaxed. These effects stimulate urination. It has persistent effects because it is resistant to cholinesterases.
- Therapeutic applications:** In urologic treatment, *bethanechol* is used to stimulate the atonic bladder, particularly seen in postpartum or postoperative or with spinal cord injury, and nonobstructive urinary retention to facilitate emptying of the neurogenic bladder. *Bethanechol* may also be used to treat neurogenic atony as well as megacolon.
- Adverse effects:** *Bethanechol* can cause generalized cholinergic stimulation (Figure 4.6), with sweating, salivation, flushing, decreased blood pressure (with reflex tachycardia), nausea, abdominal pain, diarrhea, and bronchospasm. *Atropine sulfate* may be administered to overcome severe cardiovascular or bronchoconstrictor responses to this agent.

## C. Carbachol (carbamylcholine)

*Carbachol* [KAR-ba-kole] has both muscarinic and nicotinic actions. Like *bethanechol*, *carbachol* is an ester of carbamic acid (Figure 4.5) and a poor substrate for AChE. It is biotransformed by other esterases, but at a much slower rate.

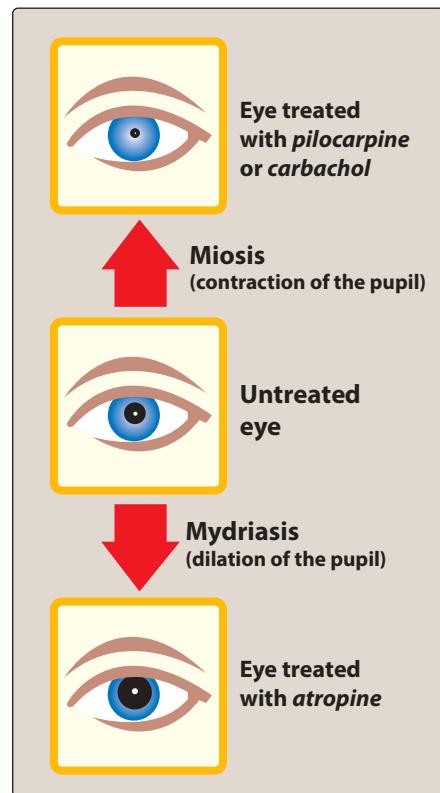
- Actions:** *Carbachol* has profound effects on both the cardiovascular and the GI systems because of its ganglion-stimulating activity, and it may first stimulate and then depress these systems. It can cause release of epinephrine from the adrenal medulla by its

nicotinic action. Locally instilled into the eye, it mimics the effects of ACh, causing miosis and a spasm of accommodation in which the ciliary muscle of the eye remains in a constant state of contraction. The vision becomes fixed at some particular distance, making it impossible to focus (Figure 4.7). [Note the opposing effects of *atropine*, a muscarinic blocker, on the eye.]

2. **Therapeutic uses:** Because of its high potency, receptor non-selectivity, and relatively long duration of action, *carbachol* is rarely used. Intraocular use provides rapid miosis for eye surgery and lowers intraocular pressure in the treatment of glaucoma. *Carbachol* is used in glaucoma when resistant to *pilocarpine* or *physostigmine*.
3. **Adverse effects:** With ophthalmologic use, few adverse effects occur due to lack of systemic penetration (quaternary amine).

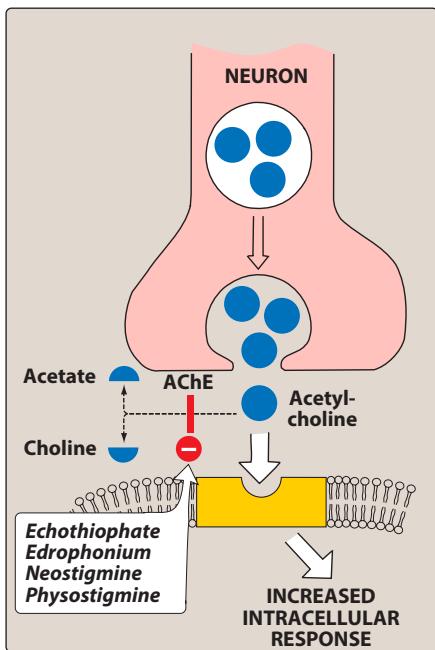
#### D. Pilocarpine

1. The alkaloid *pilocarpine* [pye-loe-KAR-peen] is a tertiary amine and is stable to hydrolysis by AChE (Figure 4.5). Compared with ACh and its derivatives, it is far less potent but is uncharged and can penetrate the CNS at therapeutic doses. *Pilocarpine* exhibits muscarinic activity and is used primarily in ophthalmology.
2. **Actions:** Applied topically to the eye, *pilocarpine* produces rapid miosis, contraction of the ciliary muscle, and spasm of accommodation. *Pilocarpine* is one of the most potent stimulators of secretions such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack of selectivity. The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. Sjögren syndrome, which is characterized by dry mouth and lack of tears, is treated with oral *pilocarpine* tablets and *cevimeline*, a cholinergic drug that also has the drawback of being nonspecific.
3. **Therapeutic use in glaucoma:** *Pilocarpine* is used to treat glaucoma and is the drug of choice for emergency lowering of intraocular pressure of both open-angle and angle-closure glaucoma. *Pilocarpine* is extremely effective in opening the trabecular meshwork around the Schlemm canal, causing an immediate drop in intraocular pressure because of the increased drainage of aqueous humor. This action occurs within a few minutes, lasts 4 to 8 hours, and can be repeated. [Note: Topical carbonic anhydrase inhibitors, such as *dorzolamide* and  $\beta$ -adrenergic blockers such as *timolol*, are effective in treating glaucoma but are not used for emergency lowering of intraocular pressure.] The miotic action of *pilocarpine* is also useful in reversing mydriasis due to *atropine*.
4. **Adverse effects:** *Pilocarpine* can cause blurred vision, night blindness, and brow ache. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects, including profuse sweating (diaphoresis) and salivation. The effects are similar to those produced by consumption of mushrooms of the genus *Inocybe*, which contain muscarine. Parenteral *atropine*, at doses that can cross the blood-brain barrier, is administered to counteract the toxicity of *pilocarpine*.



**Figure 4.7**

Actions of *pilocarpine*, *carbachol*, and *atropine* on the iris and ciliary muscle of the eye.



**Figure 4.8**

Mechanisms of action of indirect cholinergic agonists.  
AChE = acetylcholinesterase.

## V. INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (REVERSIBLE)

AChE is an enzyme that specifically cleaves ACh to acetate and choline and, thus, terminates its actions. It is located both pre- and postsynaptically in the nerve terminal where it is membrane bound. Inhibitors of AChE (anticholinesterase agents or cholinesterase inhibitors) indirectly provide cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space (Figure 4.8). Therefore, these drugs can provoke a response at all cholinoreceptors, including both muscarinic and nicotinic receptors of the ANS, as well as at the NMJ and in the brain. Reversible inhibitors are *physostigmine*, *neostigmine*, *pyridostigmine*, *edrophonium*, *rivastigmine*, and *donepezil*.

The reversible AChE inhibitors can be broadly classified as short-acting or intermediate-acting agents.

All are poorly absorbed from conjunctiva, skin, and lungs except *physostigmine* which is well absorbed from all sites. The effects are similar to direct-acting cholinergic agonists. Primary target organs of anticholinesterase drugs are eye, skeletal muscle, neuromuscular junctions, gastrointestinal tract, urinary tract, respiratory tract, and heart.

These agents are commonly used in the treatment of:

- glaucoma,
- myasthenia gravis,
- stimulation of gastrointestinal and urinary tract motility (for example, *neostigmine*)—same effects as with agonists,
- reversal of neuromuscular blockade, and
- atropine poisoning.

### A. *Edrophonium*

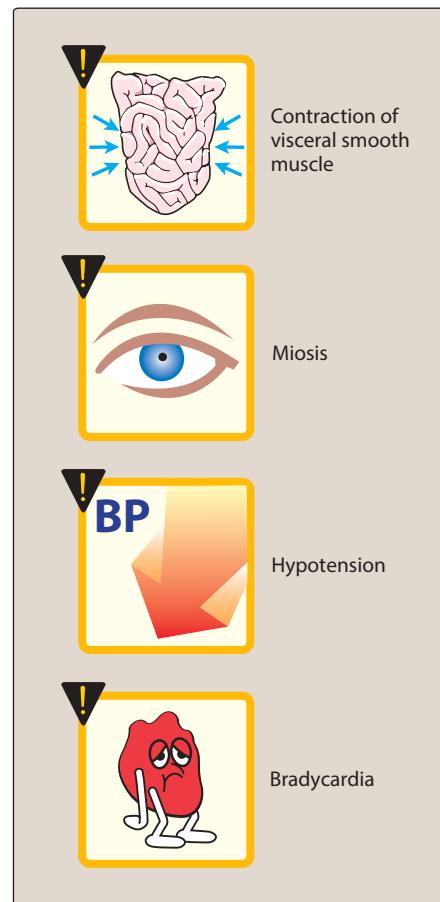
*Edrophonium* [ed-row-FOE-nee-um] is the prototype short-acting AChE inhibitor. *Edrophonium* binds reversibly to the active center of AChE, preventing hydrolysis of ACh. It is rapidly absorbed and has a short duration of action of 10 to 20 minutes due to rapid renal elimination. *Edrophonium* is a quaternary amine, and its actions are limited to the periphery. It is used in the diagnosis of myasthenia gravis, an autoimmune disease caused by antibodies to the nicotinic receptor at the NMJ. This causes the degradation of the nicotinic receptors, making fewer receptors available for interaction with ACh. Intravenous injection of *edrophonium* leads to a rapid increase in muscle strength in patients with myasthenia gravis. Care must be taken, because excess drug may provoke a cholinergic crisis (*atropine* is the antidote). *Edrophonium* may also be used to assess cholinesterase inhibitor therapy, for differentiating cholinergic and myasthenic crises, and for reversing the effects of nondepolarizing neuromuscular blockers after surgery. Due to the availability of other agents, *edrophonium* use has become limited.

*Edrophonium* is also used to diagnose myasthenia gravis.\* The Tensilon test uses the short-acting drug *edrophonium chloride*, which is given intravenously, to assess the adequacy of treatment with AChE inhibitors. Small doses of *edrophonium* improve weakness, especially in the eye muscles, briefly and temporarily in untreated myasthenia patients or in treated patients in whom AChE inhibition is inadequate. Worsening of muscle weakness indicates that the dose of AChE inhibitor is too high—that is, excessive ACh stimulation at the neuromuscular junction results in a depolarizing blockade). A trial use of oral *pyridostigmine bromide* is an alternative approach. Tolerance may develop to long-term use of the AChE inhibitors.

## B. Physostigmine

*Physostigmine* [fi-zoe-STIG-meen] is a nitrogenous carbamic acid ester found naturally in plants and is a tertiary amine. It is a substrate for AChE, and it forms a relatively stable carbamoylated intermediate with the enzyme, which then becomes reversibly inactivated. The result is potentiation of cholinergic activity throughout the body.

- Actions:** *Physostigmine* has a wide range of effects and stimulates not only the muscarinic and nicotinic sites of the ANS, but also the nicotinic receptors of the NMJ. Muscarinic stimulation can cause contraction of gastrointestinal smooth muscles, miosis, bradycardia, and hypotension (Figure 4.9). Nicotinic stimulation can cause skeletal muscle twitches, fasciculations, and skeletal muscle paralysis (at higher doses). Its duration of action is about 30 minutes to 2 hours, and it is considered an intermediate-acting agent. *Physostigmine* can enter and stimulate the cholinergic sites in the CNS.
- Therapeutic uses:** *Physostigmine* is used in the treatment of overdoses of drugs with anticholinergic actions, such as *atropine* and *scopolamine*, and to reverse the effects of neuromuscular blockers (NMBs).
- Adverse effects:** *Physostigmine* is well absorbed orally and it enters the CNS. High doses of *physostigmine* may lead to convulsions. Bradycardia and a fall in cardiac output may also occur. Inhibition of AChE at the NMJ causes the accumulation of ACh and, ultimately through continuous depolarization, results in paralysis of skeletal muscle. However, these effects are rarely seen with therapeutic doses.



**Figure 4.9**

Some actions of *physostigmine*.

\*Myasthenia gravis (MG) is an autoimmune disease in which antibodies complex with nicotinic receptors at the neuromuscular junction resulting in destruction of nicotinic receptors, resembling neuromuscular block by curare. The patient presents with progressive weakness, fatigue, drooping eyelids, and difficulty in breathing, speaking, and swallowing. Indirect AChE inhibitors, such as *neostigmine* and *pyridostigmine*, are used to increase ACh levels at the neuromuscular junction to fully activate the remaining receptors and increase strength of contraction of muscles.

MG can be difficult to diagnose because weakness is a common symptom of many disorders. In addition, symptoms may be vague, fluctuate, or only affect certain muscles. The diagnosis of MG can be established by clinical and serologic testing.

### C. Neostigmine

*Neostigmine* [nee-oh-STIG-meen] is a synthetic compound that is also a carbamic acid ester, and it reversibly inhibits AChE in a manner similar to *physostigmine*.

1. **Actions:** Unlike *physostigmine*, *neostigmine* has a quaternary nitrogen. Therefore, it is more polar, is absorbed poorly from the GI tract, and does not enter the CNS. Its effect on skeletal muscle is greater than *physostigmine*, and it can stimulate contractility before it paralyzes. *Neostigmine* has an intermediate duration of action, usually 30 minutes to 2 hours.
2. **Therapeutic uses:** *Neostigmine* is used to stimulate the bladder and GI tract and as an antidote for competitive neuromuscular-blocking agents. It is also used to manage symptoms of myasthenia gravis.
3. **Adverse effects:** Adverse effects of *neostigmine* include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. Unlike *physostigmine*, *neostigmine* is poorly absorbed from the GI tract and has negligible distribution into the CNS; therefore, it does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as *atropine*. *Neostigmine* is contraindicated when intestinal or urinary bladder obstruction is present.

### D. Pyridostigmine

*Pyridostigmine* [peer-id-oh-STIG-meen] is another cholinesterase inhibitor used in the chronic management of myasthenia gravis. Its duration of action is intermediate (3 to 6 hours) but longer than that of *neostigmine*. Adverse effects are similar to those of *neostigmine*.

### E. Tacrine, donepezil, rivastigmine, and galantamine

Patients with Alzheimer's disease have a deficiency of cholinergic neurons and therefore lower levels of ACh in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function. *Tacrine* [TAK-reen], the first agent in this category, has been replaced by others because of its hepatotoxicity. Despite the ability of *donepezil* [doe-NEP-e-zil], *rivastigmine* [ri-va-STIG-meen], and *galantamine* [ga-LAN-ta-meen] to delay the progression of Alzheimer's disease, none can stop its progression. GI distress is their primary adverse effect (see Chapter 8).

## VI. INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (IRREVERSIBLE)

A number of synthetic organophosphate compounds have the ability to bind covalently to AChE. The result is a long-lasting increase in ACh at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve agents. Related compounds, such as *parathion* and *malathion*, are used as insecticides.

### A. Echothiophate

*Ecothiopate* and *isofluorophate* are irreversible and toxic organophosphate cholinesterase inhibitors.

- Mechanism of action:** *Ecothiopate* [ek-oe-THI-oh-fate] is an organophosphate that covalently binds via its phosphate group at the active site of AChE (Figure 4.10). Once this occurs, the enzyme is permanently inactivated, and restoration of AChE activity requires the synthesis of new enzyme molecules. Following covalent modification of AChE, the phosphorylated enzyme slowly releases one of its ethyl groups. The loss of an alkyl group, which is called aging, and AChE becomes irreversibly inhibited. The enzyme can be reactivated within the first 30 minutes by chemical reactivators, such as *pralidoxime*, by breaking the bond between the remaining drug and the enzyme. Hydrolysis of the covalent alkylphosphoryl-serine bond takes days.
- Actions:** Actions include generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties), and convulsions. *Ecothiopate* is poorly absorbed from the GI tract and has negligible distribution into the CNS whereas *isofluorophate* is highly lipid soluble and is well absorbed across all membranes. *Ecothiopate* produces intense miosis and, thus, has found therapeutic use. Intraocular pressure falls from the facilitation of outflow of aqueous humor. *Atropine* in high dosages can reverse many of the peripheral and some of the central muscarinic effects of *echothiopate*.
- Therapeutic uses:** A topical ophthalmic solution of the drug is available for the treatment of open-angle glaucoma. However, *echothiopate* is rarely used due to its side effect profile, which includes the risk of cataracts. Figure 4.11 summarizes actions of some cholinergic agonists.

## VII. TOXICOLOGY OF ANTICHOLOLINESTERASE AGENTS

Irreversible AChE inhibitors (mostly organophosphate compounds) are commonly used as agricultural insecticides, which has led to numerous cases of accidental poisoning with these agents. In addition, they are frequently used for suicidal and homicidal purposes. Organophosphate nerve gases such as sarin are used as agents of warfare and chemical terrorism. Toxicity with these agents is manifested as nicotinic and muscarinic signs and symptoms (cholinergic crisis). Depending on the agent, the effects can be peripheral or can affect the whole body.

### A. Reactivation of acetylcholinesterase

*Pralidoxime* [pral-i-DOX-eem] (2-PAM) can reactivate inhibited AChE. However, it is unable to penetrate into the CNS and therefore is not useful in treating the CNS effects of organophosphates. The presence of a charged group allows it to approach an anionic site on the enzyme, where it essentially displaces the phosphate group of the organophosphate and regenerates the enzyme. *Pralidoxime* acts as an antidote for organophosphorus insecticide and nerve gas poisoning but must be administered intravenously within minutes of exposure to an AChE inhibitor because it is effective only prior to

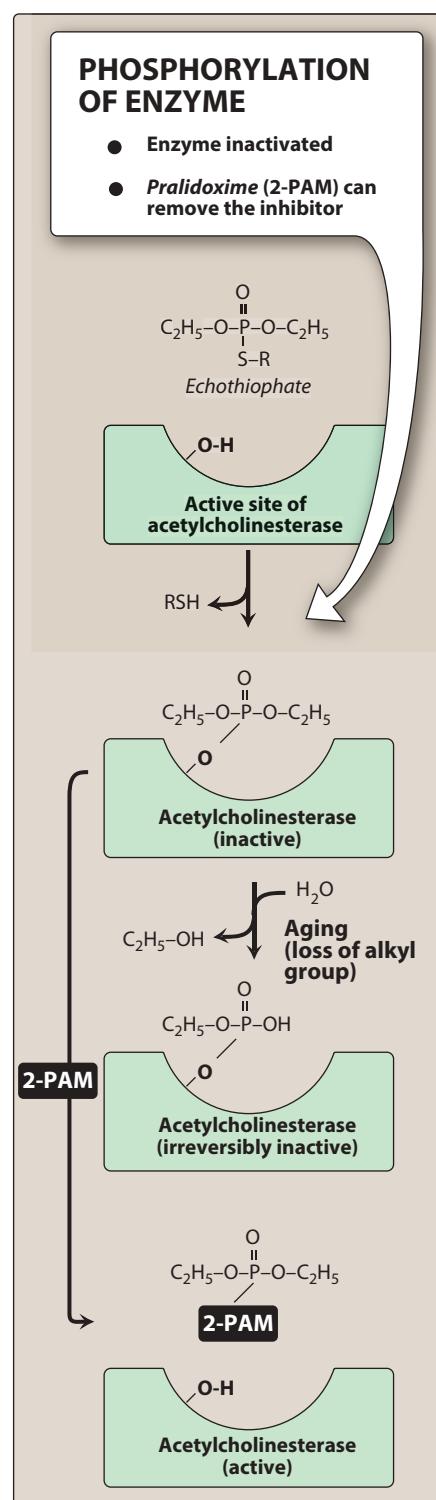


Figure 4.10

Covalent modification of acetylcholinesterase by *echothiophate*. Also shown is the reactivation of the enzyme with *pralidoxime*.  
 $\text{R}=(\text{CH}_3)_3\text{N}^+-\text{CH}_2-\text{CH}_2-$ ;  $\text{RSH}=(\text{CH}_3)_3\text{N}^+-\text{CH}_2-\text{CH}_2-\text{S}-\text{H}$ .

DIRECT-ACTING CHOLINERGIC DRUGS	INDIRECT ACTING CHOLINERGIC DRUGS (ANTICHOLINESTERASE AGENTS)	
<b>Acetylcholine</b> <ul style="list-style-type: none"> <li>Used to produce miosis in ophthalmic surgery</li> </ul>		
<b>Bethanechol</b> <ul style="list-style-type: none"> <li>Used in treatment of urinary retention; postoperative; postpartum urinary retention</li> <li>Binds preferentially at muscarinic receptors</li> <li>Postoperative abdominal distention, paralytic ileus, esophageal reflux; promotes increased esophageal motility (<i>cisapride</i> and <i>metoclopramide</i> are better alternatives)</li> </ul>	<b>Physostigmine</b> <ul style="list-style-type: none"> <li>Increases intestinal and bladder motility</li> <li>Reverses CNS and cardiac effects of tricyclic antidepressants' overdose</li> <li>Reverses CNS effects of <i>atropine</i> poisoning</li> <li>Uncharged, tertiary amine that can penetrate the CNS</li> </ul>	<b>Rivastigmine, galantamine, donepezil</b> <ul style="list-style-type: none"> <li>Used as first-line treatments for Alzheimer's disease,<sup>2</sup> though confers modest benefit</li> <li>Have not been shown to reduce healthcare costs or delay institutionalization</li> <li>Can be used with <i>memantine</i> (N-methyl-D-aspartate antagonist) with moderate to severe disease</li> </ul>
<b>Carbachol</b> <ul style="list-style-type: none"> <li>Produces miosis during ocular surgery</li> <li>Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to <i>pilocarpine</i></li> </ul>	<b>Neostigmine</b> <ul style="list-style-type: none"> <li>Prevents postoperative abdominal distention and urinary retention</li> <li>Used in treatment of myasthenia gravis<sup>1</sup> along with corticosteroids</li> <li>Used as an antidote for competitive neuromuscular blockers such as <i>tubocurarine</i> (postoperative)</li> <li>Has intermediate duration of action (0.5 to 2 hr)</li> </ul>	<b>Echothiophate</b> <ul style="list-style-type: none"> <li>Indirect acting (irreversible)</li> <li>Used in treatment of open-angle glaucoma<sup>4</sup></li> <li>Has long duration of action (100 hours)</li> </ul>
<b>Pilocarpine</b> <ul style="list-style-type: none"> <li>Reduces intraocular pressure in open-angle and narrow-angle glaucoma to break iris-lens adhesions (alternated with <i>atropine</i>)</li> <li>Binds preferentially at muscarinic receptors</li> <li>Uncharged, tertiary amine that can penetrate the CNS</li> </ul>	<b>Edrophonium</b> <ul style="list-style-type: none"> <li>Used for diagnosis of myasthenia gravis<sup>3</sup></li> <li>Used as an antidote for competitive neuromuscular blockers</li> <li>Has short duration of action (10 to 20 min)</li> </ul>	

<sup>1</sup>Myasthenia gravis is an autoimmune disorder due to the formation of antibodies to the muscle end-plate nicotinic receptors leading to muscular weakness and easy fatigability.

<sup>2</sup>Neurodegenerative disorder with progressive dementia due to deposition of amyloid plaques (neurofibrillary tangles) affecting cholinergic neurons of brain.

<sup>3</sup>Edrophonium 1–2 mg IV injection will result improvement in a myasthenia gravis patient, but will worsen the condition in a patient with cholinergic crises.

<sup>4</sup>Progressive optic nerve damage due to raised intraocular tension.

**Figure 4.11**

Summary of actions of some cholinergic agonists. CNS = central nervous system.

“aging.” If given before aging of the alkylated enzyme occurs, it can reverse both muscarinic and nicotinic peripheral effects of organophosphates, but not the CNS effects. With the newer nerve agents that produce aging of the enzyme complex within seconds, *pralidoxime* is less effective. In addition, it cannot overcome toxicity of reversible AChE inhibitors (for example, *physostigmine*). *Pralidoxime* produces few adverse effects in usual doses.

## B. Other treatments

*Atropine* is administered to prevent muscarinic side effects of these agents. Such effects include increased bronchial and salivary secretion, bronchoconstriction, and bradycardia. *Diazepam* is also administered to reduce the persistent convulsion caused by these agents. General supportive measures, such as maintenance of patent airway, oxygen supply, and artificial respiration, may be necessary as well.

## Study Questions

Choose the ONE best answer.

- 4.1 Botulinum toxin blocks the release of acetylcholine from cholinergic nerve terminals. Which is a possible effect of botulinum toxin?

- A. Skeletal muscle paralysis
- B. Improvement of myasthenia gravis symptoms
- C. Increased salivation
- D. Reduced heart rate

Correct answer = A. Acetylcholine released by cholinergic neurons acts on nicotinic receptors in the skeletal muscle cells to cause contraction. Therefore, blockade of ACh release causes skeletal muscle paralysis. Myasthenia gravis is an autoimmune disease where antibodies are produced against nicotinic receptors and inactivate nicotinic receptors. A reduction in ACh release therefore worsens (not improves) the symptoms of this condition. Reduction in ACh release by botulinum toxin causes reduction in secretions including saliva (not increase in salivation) causing dry mouth and an increase (not reduction) in heart rate due to reduced vagal activity.

- 4.2 A patient develops urinary retention after an abdominal surgery. Urinary obstruction was ruled out in this patient. Which strategy would be helpful in promoting urination?

- A. Activating nicotinic receptors
- B. Inhibiting the release of acetylcholine
- C. Inhibiting cholinesterase enzyme
- D. Blocking muscarinic receptors

Correct answer = C. Activation of muscarinic receptors in the detrusor muscles of urinary bladder can promote urination in patients where the tone of detrusor muscle is low. Inhibiting cholinesterase enzyme increases the levels of acetylcholine, and acetylcholine can increase the tone of the detrusor muscle. There are no nicotinic receptors in the detrusor muscles; therefore, activation of nicotinic receptors is not helpful. Inhibiting the release of acetylcholine or blocking muscarinic receptors worsens urinary retention.

- 4.3 Which of the following drugs could theoretically improve asthma symptoms?

- A. Bethanechol
- B. Pilocarpine
- C. Pyridostigmine
- D. Atropine

Correct answer = D. Muscarinic agonists and drugs that increase acetylcholine levels cause constriction of bronchial smooth muscles and could exacerbate asthma symptoms. Bethanechol and pilocarpine are muscarinic agonists, and pyridostigmine is a cholinesterase inhibitor that increases levels of acetylcholine. Atropine is a muscarinic antagonist and therefore does not exacerbate asthma. Theoretically, it should relieve symptoms of asthma (not used clinically for this purpose).

- 4.4 If an ophthalmologist wants to dilate the pupils for an eye examination, which drug/class of drugs is theoretically useful?

- A. Muscarinic receptor activator (agonist)
- B. Muscarinic receptor inhibitor (antagonist)
- C. Pilocarpine
- D. Neostigmine

Correct answer = B. Muscarinic agonists (for example, pilocarpine) contract the circular smooth muscles in the iris sphincter and constrict the pupil (miosis). Anticholinesterases (for example, neostigmine and physostigmine) also cause miosis by increasing the level of ACh. Muscarinic antagonists, on the other hand, relax the circular smooth muscles in the iris sphincter and cause dilation of the pupil (mydriasis).

4.5 In Alzheimer disease, there is a deficiency of cholinergic neuronal function in the brain. Theoretically, which strategy is useful in treating symptoms of Alzheimer disease?

- A. Inhibiting cholinergic receptors in the brain
- B. Inhibiting the release of acetylcholine in the brain
- C. Inhibiting the acetylcholinesterase enzyme in the brain
- D. Activating the acetylcholinesterase enzyme in the brain

4.6 An elderly female who lives in a farmhouse was brought to the emergency room in serious condition after ingesting a liquid from an unlabeled bottle found near her bed, apparently in a suicide attempt. She presented with diarrhea, frequent urination, convulsions, breathing difficulties, constricted pupils (miosis), and excessive salivation. Which of the following is correct regarding this patient?

- A. She most likely consumed an organophosphate pesticide.
- B. The symptoms are consistent with sympathetic activation.
- C. Her symptoms can be treated using an anticholinesterase agent.
- D. Her symptoms can be treated using a cholinergic agonist.

4.7 A patient who had received a nondepolarizing neuromuscular blocker (NMB) for skeletal muscle relaxation during surgery is experiencing mild skeletal muscle paralysis after the surgery. Which drug could reverse this effect of NMBs?

- A. Pilocarpine
- B. Bethanechol
- C. Neostigmine
- D. Atropine

4.8 A 60-year-old female who had a cancerous growth in the neck region underwent radiation therapy. Her salivary secretion was reduced due to radiation and she suffers from dry mouth (xerostomia). Which drug would be most useful in treating xerostomia in this patient?

- A. Acetylcholine
- B. Pilocarpine
- C. Echothiopate
- D. Atropine

Correct answer = C. Because there is already a deficiency in brain cholinergic function in Alzheimer disease, inhibiting cholinergic receptors or inhibiting the release of ACh worsens the condition. Activating the acetylcholinesterase enzyme increases the degradation of ACh, which also worsens the condition. However, inhibiting the acetylcholinesterase enzyme helps to increase the levels of ACh in the brain and thereby, relieve the symptoms of Alzheimer disease.

Correct answer = A. The symptoms are consistent with those of cholinergic crisis. Since the elderly female lives on a farm and the symptoms are consistent with a cholinergic crisis (usually caused by cholinesterase inhibitors), it may be assumed that she has consumed an organophosphate pesticide (irreversible cholinesterase inhibitor). Assuming that the symptoms are caused by organophosphate poisoning, administering an anticholinesterase agent or a cholinergic agonist will worsen the condition. The symptoms are not consistent with those of sympathetic activation, as sympathetic activation will cause symptoms opposite to those of cholinergic crisis seen in this patient.

Correct answer = C. Neuromuscular blockers act by blocking nicotinic receptors on the skeletal muscles. Increasing the levels of ACh in the neuromuscular junctions can reverse the effects of NMBs. Therefore, neostigmine, a cholinesterase inhibitor, could reverse the effects of NMBs. Pilocarpine and bethanechol are preferentially muscarinic agonists and have no effects on the nicotinic receptors. Atropine is a muscarinic antagonist and has no effects on nicotinic receptors.

Correct answer = B. Salivary secretion may be enhanced by activating muscarinic receptors in the salivary glands. This can be achieved in theory by using a muscarinic agonist or an anticholinesterase agent. Pilocarpine is a muscarinic agonist administered orally for this purpose. Acetylcholine has similar effects as that of pilocarpine; however, it cannot be used therapeutically as it is rapidly destroyed by cholinesterase in the body. Echothiopate is an irreversible cholinesterase inhibitor, but it cannot be used therapeutically because of its toxic effects. Atropine is a muscarinic antagonist and worsens dry mouth.

4.9 A 40-year-old male presents to his family physician with drooping eyelids, difficulty chewing and swallowing, and muscle fatigue even on mild exertion. Which agent could be used to diagnose myasthenia gravis in this patient?

- A. Atropine
- B. Edrophonium
- C. Pralidoxime
- D. Echothiophate

Correct answer = B. The function of nicotinic receptors in skeletal muscles is diminished in myasthenia gravis due to the development of antibodies to nicotinic receptors (autoimmune disease). Any drug that increases levels of ACh in the neuromuscular junction can improve symptoms in myasthenia gravis. Thus, edrophonium, reversible a cholinesterase inhibit or with a short duration of action can temporarily improve skeletal muscle weakness in myasthenia gravis, serving as a diagnostic tool. Atropine is a muscarinic antagonist, and has no role in skeletal muscle function. Pralidoxime is a drug that is used to reverse the binding of irreversible cholinesterase inhibitors with cholinesterase enzyme and helps to reactivate cholinesterase enzyme. Hence, pralidoxime will not be useful in improving skeletal muscle function in myasthenia gravis.

4.10 Atropa belladonna is a plant that contains atropine (a muscarinic antagonist). Which of the following drugs or classes of drugs will be most useful in treating poisoning with belladonna?

- A. Malathion
- B. Physostigmine
- C. Muscarinic antagonists
- D. Nicotinic antagonists

Correct answer = B. Atropine is a competitive muscarinic receptor antagonist that causes anticholinergic effects. Muscarinic agonists or any other drugs that increase the levels of ACh are able to counteract effects of atropine. Thus, anticholinesterases such as malathion and physostigmine can counteract the effects of atropine, in theory. However, since malathion is an irreversible inhibitor of acetylcholinesterase, it is not used for systemic treatment in patients. Muscarinic antagonists worsen the toxicity of atropine. Nicotinic antagonists can worsen the toxicity by acting on parasympathetic ganglionic receptors and thus reducing the release of ACh.



# Cholinergic Antagonists

5

Rajan Radhakrishnan and Carinda Feild

## I. OVERVIEW

Cholinergic antagonist is a general term for agents that bind to cholinoreceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists. The most clinically useful of these agents are selective blockers of muscarinic receptors. They are commonly known as anticholinergic agents (a misnomer, as they antagonize only muscarinic receptors), antimuscarinic agents (more accurate terminology), or parasympatholytics. The effects of parasympathetic innervation are thus, interrupted by these agents, and the actions of sympathetic innervation are left unopposed. A second group of drugs, the ganglionic blockers, shows a preference for nicotinic receptors of the sympathetic and parasympathetic ganglia. Clinically, they are the least important cholinergic antagonists. A third family of compounds, the neuromuscular-blocking agents (mostly nicotinic antagonists), interfere with transmission of efferent impulses to skeletal muscles. These drugs are used as skeletal muscle relaxants in surgical anesthesia and as agents to facilitate intubation in surgical and critical care patients. **Figure 5.1** shows the classification of the cholinergic antagonists discussed in this chapter.

NATURAL ALKALOIDS	SEMI SYNTHETIC DERIVATIVES	SYNTHETIC COMPOUNDS	MISCELLANEOUS
<ul style="list-style-type: none"><li>• <i>Atropine</i></li><li>• <i>Hyoscine (scopolamine)</i></li></ul>	<ul style="list-style-type: none"><li>• <i>Homatropine</i></li><li>• <i>Homatropine methyl bromide</i></li><li>• <i>Atropine methonitrate</i></li><li>• <i>Hyoscine methyl bromide</i></li><li>• <i>Hyoscine butyl bromide</i></li><li>• <i>Ipratropium bromide</i></li><li>• <i>Tiotropium bromide</i></li></ul>	<p><b>Mydriatics</b></p> <ul style="list-style-type: none"><li>• <i>Cyclopentolate</i></li><li>• <i>Tropicamide</i></li></ul> <p><b>Antisecretory—antispasmodics</b></p> <p><b>Quaternary ammonium compounds</b></p> <ul style="list-style-type: none"><li>• <i>Propantheline</i></li><li>• <i>Oxyphenonium</i></li><li>• <i>Clidinium</i></li><li>• <i>Pipenzolate</i></li><li>• <i>Glycopyrrolate</i></li></ul> <p><b>Tertiary amines</b></p> <ul style="list-style-type: none"><li>• <i>Dicyclomine</i></li><li>• <i>Pirenzepine</i></li><li>• <i>Telenzepine</i></li><li>• <i>Oxybutynin</i></li><li>• <i>Flevoxate</i></li></ul> <p><b>Antiparkinsonian drugs</b></p> <ul style="list-style-type: none"><li>• <i>Benzhexol</i></li><li>• <i>Procyclidine</i></li><li>• <i>Biperiden</i></li><li>• <i>Benztropine</i></li><li>• <i>Trihexiphenidyl</i></li></ul>	<p><b>Tricyclic antidepressants</b></p> <ul style="list-style-type: none"><li>• <i>Phenothiazines</i></li><li>• <i>Antihistamine</i></li><li>• <i>Disopyramide</i></li></ul>

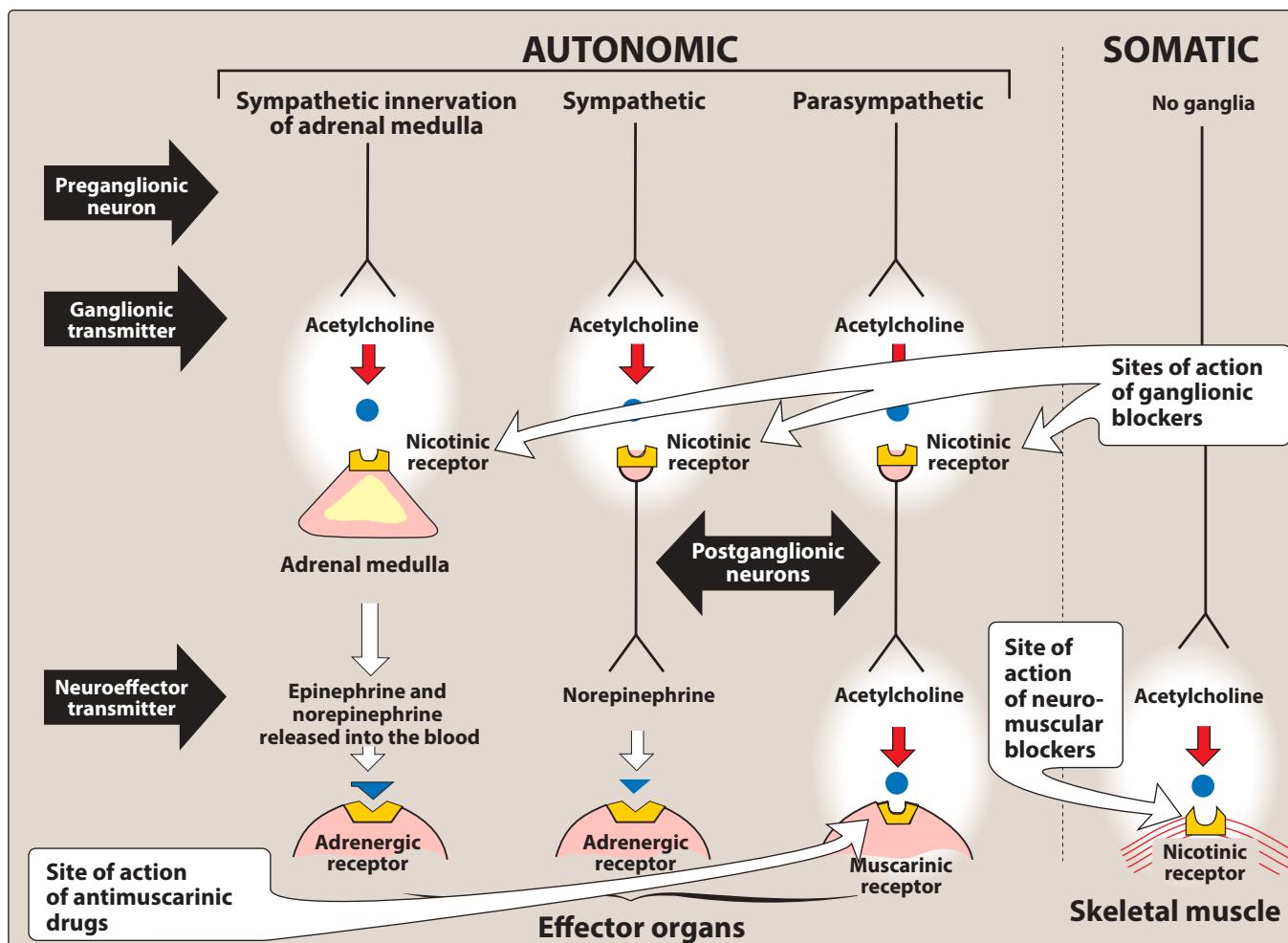
**Figure 5.1**

Classification of antimuscarinic agents.

The belladonna alkaloids are absorbed from the GI tract, the mucous membranes, the skin, and the eyes and they are widely distributed. Absorption of the synthetic derivatives is confined mainly to the GI tract. They are less lipid soluble and do not cross the blood–brain barrier. Some of the synthetic derivatives such as propantheline bromide undergo hydrolysis in the upper small intestine as well as metabolism in the liver and they are excreted in urine and feces. Unlike quaternary ammonium drugs (absorption 10% to 30%), tertiary muscarinic antagonists are well absorbed across the GI tract or mucosal surfaces and are distributed throughout the body, including the brain. *Atropine* and *scopolamine* have relatively long duration of action.

## II. ANTIMUSCARINIC AGENTS

Commonly known as anticholinergic drugs, these agents (for example, *atropine* and *scopolamine*) block muscarinic receptors (Figure 5.2), causing inhibition of muscarinic functions. In addition, these drugs block the



**Figure 5.2**

Sites of actions of cholinergic antagonists.

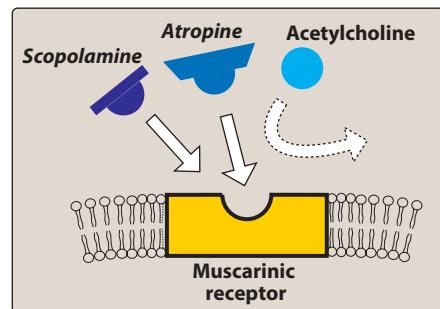
few exceptional sympathetic neurons that are cholinergic, such as those innervating the salivary and sweat glands. Because they do not block nicotinic receptors, the anticholinergic drugs (more precisely, antimuscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia. The anticholinergic drugs are beneficial in a variety of clinical situations. Tertiary amines are often used for their effects on the CNS whereas quaternary amines have minimal CNS actions and are often used for their effects on the peripheral systems. [Note: A number of anti-histamines and antidepressants (mainly tricyclic antidepressants) also have antimuscarinic activity.]

### A. Atropine

*Atropine* [A-troe-peen] is a tertiary amine extracted from belladonna alkaloid. It has a high affinity for muscarinic receptors and binds competitively to prevent ACh from binding (Figure 5.3). *Atropine* acts both centrally and peripherally. General actions last about 4 hours; however, effects of topical administration in the eye may persist for days. Neuroeffector organs have varying sensitivity to *atropine*. The greatest inhibitory effects are seen in bronchial tissue, salivary and sweat glands, and the heart.

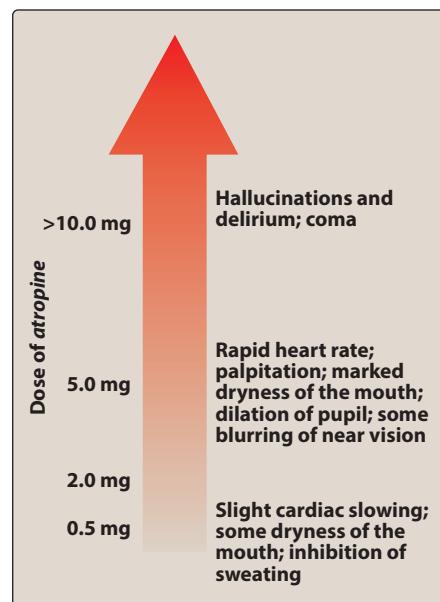
#### 1. Actions:

- Eye:** *Atropine* blocks muscarinic activity in the eye, resulting in mydriasis (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision). Photophobia and blurred vision due to pupil unresponsiveness and cycloplegia may last up to 2 weeks. *Atropine* is used principally in the management of anterior uveitis-induced miosis (iritocyclitis). In patients with angle-closure glaucoma, intraocular pressure may rise dangerously.
- Gastrointestinal (GI):** *Atropine* (as the active isomer, L-hyoscyamine [hi-oh-SYE-uh-meen]) can be used as an antispasmodic to reduce activity of the GI tract. *Atropine* and *scopolamine* (discussed in the following text) are probably the most potent antispasmodic drugs available. Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, *atropine* is not effective for the treatment of ulcers. Doses of *atropine* that reduce spasms also reduce saliva secretion, ocular accommodation, and urination. These effects decrease compliance with *atropine*.
- Cardiovascular:** *Atropine* produces divergent effects on the cardiovascular system, depending on the dose (Figure 5.4). At low doses, the predominant effect is a slight decrease in heart rate. This effect results from blockade of M<sub>1</sub> receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release. Higher doses of *atropine* cause a progressive increase in heart rate by blocking M<sub>2</sub> receptors on the sinoatrial node.
- Secretions:** *Atropine* blocks muscarinic receptors in the salivary glands, producing dryness of the mouth (xerostomia). The salivary glands are exquisitely sensitive to *atropine*. Sweat and lacrimal glands are similarly affected.



**Figure 5.3**

Competition of *atropine* and *scopolamine* with acetylcholine for the muscarinic receptor.



**Figure 5.4**

Dose-dependent effects of *atropine*.

[Note: Inhibition of secretions of sweat glands can cause elevated body temperature, which can be dangerous in children and the elderly.]

**2. Therapeutic uses:**

- a. **Ophthalmic:** Topical *atropine* exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors without interference by the accommodative capacity of the eye. Short-acting antimuscarinics (*cyclopentolate* [sye-kloe-PEN-toe-late] and *tropicamide* [troe-PIK-a-mide]) have largely replaced *atropine* due to prolonged mydriasis observed with *atropine* (7 to 14 days vs. 6 to 24 hours with other agents). [Note: *Phenylephrine* or similar  $\alpha$ -adrenergic drugs are preferred for pupillary dilation if cycloplegia is not required.]
- b. **Antispasmodic:** *Atropine* is used as an antispasmodic agent to relax the GI tract.
- c. **Cardiovascular:** The drug is used to treat bradycardia of varying etiologies.
- d. **Antisecretory:** *Atropine* is sometimes used as an antisecretory agent to block secretions in the respiratory tract prior to surgery. [Note: *Glycopyrrolate* (see in the following text) is also used for this indication.]
- e. **Antidote for cholinergic agonists:** *Atropine* is used for the treatment of organophosphate (insecticides, nerve gases) poisoning, of overdose of clinically used anticholinesterases such as *physostigmine*, and in some types of mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases). *Atropine*, *pralidoxime* (2-PAM), and benzodiazepines (*diazepam*) are the mainstays of medical therapy in organophosphate (OP) poisoning. Massive doses of *atropine* may be required over a long period to achieve adequate atropinization quickly. Typically a doubling approach is used, with escalation of doses from 1 to 2 mg, 4 mg, 8 mg, 16 mg, and so on. The main concern with OP toxicity is respiratory failure from excessive airway secretions; therefore, adequate oxygenation and dried pulmonary secretions are considered endpoint for atropinization. Tachycardia and mydriasis must not be used to limit or to stop subsequent doses of *atropine*. The ability of *atropine* to enter the central nervous system (CNS) is of particular importance in treating central toxic effects of anticholinesterases. *Glycopyrrolate* does not cross the blood-brain barrier and cannot treat the central effects of OP poisoning. *Pralidoxime*, an antidote for OP AChE pesticide poisoning, reactivates the phosphorylated AChE by binding to the OP molecule and reverses muscle paralysis but is not effective once the OP compound has aged. *Pralidoxime* is administered concomitantly with *atropine* within 48 hours of OP poisoning to reverse muscle paralysis. *Pralidoxime* does not significantly relieve depression of the respiratory center or decrease muscarinic effects of AChE poisoning. For further details, refer to the chapter on toxicology.

3. **Pharmacokinetics:** *Atropine* is readily absorbed, partially metabolized by the liver, and eliminated primarily in urine. It has a half-life of about 4 hours.
4. **Adverse effects:** Depending on the dose, *atropine* may cause dry mouth, blurred vision, “sandy eyes,” tachycardia, urinary retention, and constipation. Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death. Low doses of cholinesterase inhibitors, such as *physostigmine*, may be used to overcome *atropine* toxicity. *Atropine* may also induce troublesome urinary retention. The drug may be dangerous in children, because they are sensitive to its effects, particularly to rapid increases in body temperature.

The adverse effects of antimuscarinic agents are extensions of pharmacologic actions and include mydriasis, cycloplegia, dry eyes, tachycardia, dry mouth, elevated temperature, dry skin, urine retention, agitation, hallucinations, and delirium. A common mnemonic for the main features of anticholinergic syndrome is as follows:

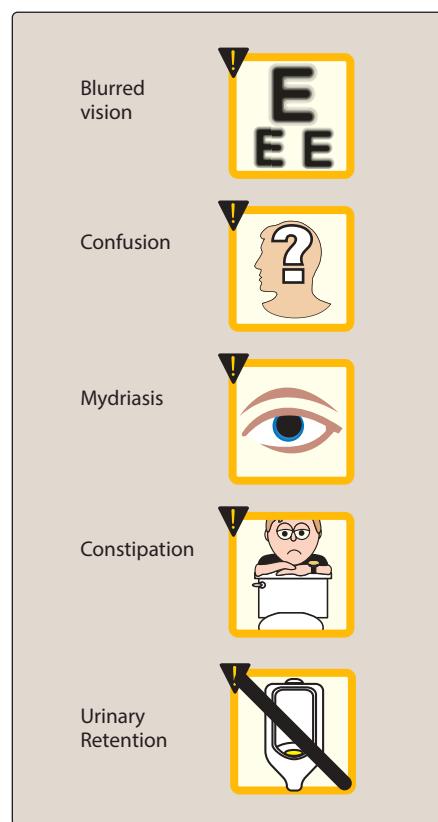
- Blind as a bat (dilated pupils)
- Red as a beet (vasodilation/flushing)
- Hot as a hare (hyperthermia)
- Dry as a bone (dry skin)
- Mad as a hatter (hallucinations/agitation)
- Bloated as a toad (ileus, urinary retention)
- And the heart runs alone (tachycardia)

The adverse effects of antimuscarinic drugs are more pronounced in children and the elderly, which limit tolerability of these agents. Extended-release formulations and the transdermal patch have a lower incidence of adverse effects and may be better tolerated. *Trospium* is a quaternary compound that minimally crosses the blood–brain barrier and has fewer CNS effects than do other agents, making it a preferred choice in treating overactive bladder in patients with dementia. Important characteristics of the muscarinic antagonists are summarized in **Figure 5.5**.

Acute anticholinergic syndrome is reversible and subsides once all of the causative agents have been excreted; therefore, symptomatic treatment is recommended. Reversible acetylcholinesterase inhibitor agents such as *physostigmine* can be used as an antidote in life-threatening cases. Its wider use is discouraged due to the significant side effects related to cholinergic excess including seizures, muscle weakness, bradycardia, bronchospasm, lachrymation, salivation, bronchorrhea, vomiting, and diarrhea. *Neostigmine* is used to treat poisoning with quaternary antimuscarinic agents.

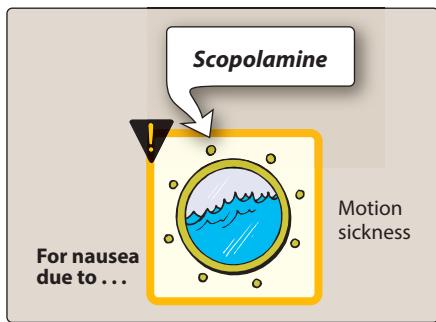
## B. Scopolamine

*Scopolamine* [skoe-POL-a-meen], another tertiary amine plant alkaloid, produces peripheral effects similar to those of *atropine*. However, *scopolamine* has greater action on the CNS (unlike *atropine*, CNS effects



**Figure 5.5**

Adverse effects commonly observed with muscarinic antagonists.



**Figure 5.6**

Scopolamine is an effective anti-motion sickness agent.

are observed at therapeutic doses) and a longer duration of action as compared to *atropine*. It has some special actions as indicated below.

- Actions:** *Scopolamine* is one of the most effective antimotion sickness drugs available (Figure 5.6). It also has the unusual effect of blocking short-term memory. In contrast to *atropine*, *scopolamine* produces sedation, but at higher doses, it can produce excitement. *Scopolamine* may produce euphoria and is susceptible to abuse.
- Therapeutic uses:** *Scopolamine* is used for the prevention of motion sickness and postoperative nausea and vomiting. For motion sickness, it is available as a topical patch that provides effects for up to 3 days. [Note: As with all drugs used for motion sickness, it is much more effective prophylactically than for treating motion sickness once it occurs.]
- Pharmacokinetics and adverse effects:** These aspects are similar to those of *atropine*, with the exception of longer half-life.

### C. Aclidinium, glycopyrrolate, ipratropium, and tiotropium

*Ipratropium* [i-pra-TROE-pee-um] and *tiotropium* [ty-oh-TROPE-ee-um] are quaternary derivatives of *atropine*, and *glycopyrrolate* [glye-koe-PYE-ro-e-late] and *aclidinium* [a-kli-DIN-ee-um] are synthetic quaternary compounds. *Ipratropium* is classified as a short-acting muscarinic antagonist (SAMA), while *glycopyrrolate*, *tiotropium*, and *aclidinium* are classified as long-acting muscarinic antagonists (LAMAs) based on the duration of action. These agents are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). *Ipratropium* and *tiotropium* are also used in the acute management of bronchospasm in asthma and chronic management of asthma, respectively (see Chapter 41). All of these agents are delivered via inhalation. Because of the positive charge, these drugs do not enter the systemic circulation or the CNS, restricting effects to the pulmonary system.

### D. Tropicamide and cyclopentolate

These agents are used as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of *atropine*. *Tropicamide* produces mydriasis for 6 hours and *cyclopentolate* for 24 hours.

### E. Benztropine and trihexyphenidyl

*Benztropine* and *trihexyphenidyl* are useful as adjuncts with other anti-parkinson agents to treat Parkinson disease (see Chapter 8) and other types of parkinsonian syndromes, including antipsychotic-induced extrapyramidal symptoms.

### F. Oxybutynin and other antimuscarinic agents for overactive bladder

*Oxybutynin* [ox-i-BYOO-ti-nin], *darifenacin* [dar-e-FEN-a-sin], *fesoterodine* [fes-oh-TER-oh-deen], *solifenacin* [sol-ee-FEN-a-sin], *tolterodine* [tol-TER-oh-deen], and *trospium* [TROSE pee um] are synthetic *atropine*-like drugs with antimuscarinic actions.

- 1. Actions:** By competitively blocking muscarinic ( $M_3$ ) receptors in the bladder, intravesical pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced. Antimuscarinic actions at  $M_3$  receptors in the GI tract, salivary glands, CNS, and eye may cause adverse effects. *Darifenacin* and *solifenacin* are relatively more selective  $M_3$  muscarinic receptor antagonists; however, the other drugs are mainly nonselective muscarinic antagonists, and binding to other muscarinic receptor subtypes may contribute to adverse effects.
- 2. Therapeutic uses:** These agents are used for the management of overactive bladder and urinary incontinence. *Oxybutynin* is also used in patients with neurogenic bladder.
- 3. Pharmacokinetics:** All of the agents are available in oral dosage forms. Most agents have a long half-life, which allows once-daily administration. [Note: Immediate-release *oxybutynin* and *tolterodine* must be dosed two or more times daily; however, extended-release formulations of these agents allow for once-daily dosing.] *Oxybutynin* is also available in a transdermal patch and topical gel formulation. These drugs are hepatically metabolized by the cytochrome P450 system (primarily CYP 3A4 and 2D6), with the exception of *trospium*, which is thought to undergo ester hydrolysis.
- 4. Contraindications:** The parasympathetic and sympathetic systems counterbalance each other in order to maintain physiological equilibrium. Depression of the parasympathetic system may inadvertently cause stimulation of the sympathetic system. This dual-opposing action warrants caution in many conditions which are as follows:
  - Glaucoma, particularly angle-closure glaucoma—the antimuscarinic drug effect of pupil dilatation may increase intraocular pressure.
  - Urinary obstruction and sphincter contraction may cause urinary retention in benign prostatic hypertrophy.
  - GI tract obstruction—paralytic ileus, stenosing peptic ulcer, and toxic megacolon may be intensified by slowing of the GI activity.
  - Compromised cardiac function—tachycardia may result from inhibition of the parasympathetic stimulation.

Antimuscarinic drugs should be used with caution in the elderly people and in those with autonomic neuropathy. Caution is also advised in hiatus hernia with reflux esophagitis and in hepatic impairment and renal impairment. The adverse effects of antimuscarinic agents may be exacerbated when given with antihistamines, antiparkinsonism drugs, monoamine oxidase inhibitors, or tricyclic antidepressants. **Figure 5.7** summarizes the therapeutic use of cholinergic antagonists.

### III. GANGLIONIC BLOCKERS

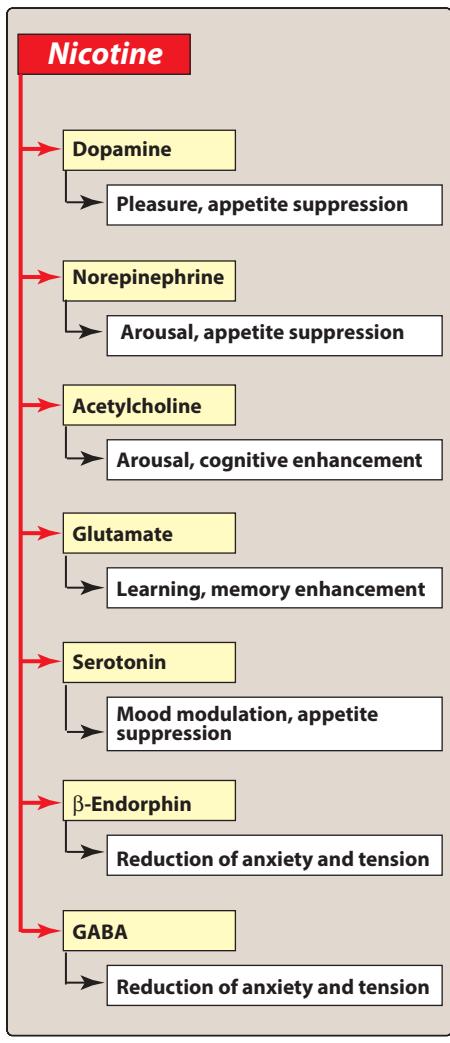
Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output

Drug	Therapeutic uses
<b>Muscarinic blockers</b>	
<i>Trihexyphenidyl</i> <i>Benztropine</i>	<ul style="list-style-type: none"> <li>• Treatment of Parkinson's disease</li> <li>• Management of antipsychotic-induced extrapyramidal effects</li> </ul>
<i>Darifenacin</i> <i>Fesoterodine</i> <i>Oxybutynin</i> <i>Solifenacin</i> <i>Tolterodine</i> <i>Trospium</i>	<ul style="list-style-type: none"> <li>• Treatment of overactive urinary bladder</li> </ul>
<i>Cyclopentolate</i> <i>Tropicamide</i> <i>Atropine*</i>	<ul style="list-style-type: none"> <li>• In ophthalmology, to produce mydriasis and cycloplegia prior to refraction</li> </ul>
<i>Atropine*</i>	<ul style="list-style-type: none"> <li>• To treat spastic disorders of the GI tract</li> <li>• To treat organophosphate poisoning</li> <li>• To suppress respiratory secretions prior to surgery</li> <li>• To treat bradycardia</li> </ul>
<i>Scopolamine</i>	<ul style="list-style-type: none"> <li>• To prevent motion sickness</li> </ul>
<i>Aclidinium</i> <i>Glycopyrrrolate</i> <i>Ipratropium</i> <i>Tiotropium</i>	<ul style="list-style-type: none"> <li>• Treatment of COPD</li> </ul>
<b>Ganglionic blockers</b>	
<i>Nicotine</i>	<ul style="list-style-type: none"> <li>• Smoking cessation</li> </ul>

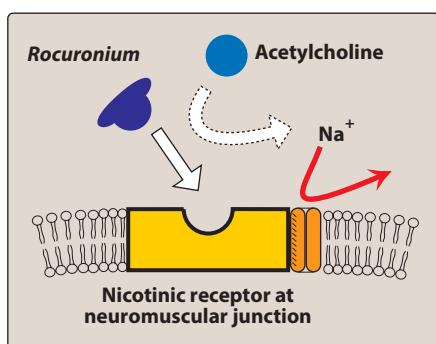
**Figure 5.7**

Summary of cholinergic antagonists.

\*Contraindicated in angle-closure glaucoma. GI = gastrointestinal; COPD = chronic obstructive pulmonary disease.

**Figure 5.8**

Neurochemical effects of *nicotine*.  
GABA =  $\gamma$ -aminobutyric acid.

**Figure 5.9**

Mechanism of action of competitive neuromuscular-blocking drugs.

of the autonomic nervous system at the nicotinic receptor. Except for nicotine, the other drugs mentioned in this category are nondepolarizing, competitive antagonists. The responses of the nondepolarizing blockers are complex and mostly unpredictable. Therefore, ganglionic blockade is rarely used therapeutically, but often serves as a tool in experimental pharmacology.

### A. Nicotine

A component of cigarette smoke, *nicotine* [NIK-oh-teen] is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health. Depending on the dose, *nicotine* depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia. The stimulatory effects are complex and result from increased release of neurotransmitters (Figure 5.8), due to effects on both sympathetic and parasympathetic ganglia (see Chapter 16 for a full discussion of *nicotine*).

## IV. NEUROMUSCULAR-BLOCKING AGENTS

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on skeletal muscle (Figure 5.2). They possess some chemical similarities to ACh, and act either as antagonists (nondepolarizing) or as agonists (depolarizing) at the receptors on the endplate of the NMJ. Neuromuscular blockers (NMBs) are clinically useful to facilitate rapid intubation when needed due to respiratory failure (rapid sequence intubation). During surgery, they are used to facilitate endotracheal intubation and provide complete muscle relaxation at lower anesthetic doses. This increases the safety of anesthesia by allowing patients to recover quickly and completely. NMBs should not substitute for inadequate anesthesia. NMBs are also used in the intensive care unit (ICU) as adjuvant therapy to facilitate intubation and mechanical ventilation in critically ill patients.

### A. Nondepolarizing (competitive) blockers

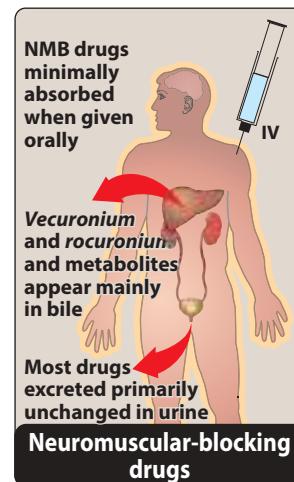
The first known NMB was *curare* [kyoo-RAH-ree], which Amazon hunters used to paralyze prey. The development of *tubocurarine* [too-boe-kyoo-AR-een] followed, but it has been replaced by agents with fewer adverse effects, such as *cisatracurium* [cis-a-trah-CURE-ih-um], *mivacurium* [mi-vah-KYOO-ree-um], *pancuronium* [pan-kure-OH-nee-um], *rocuronium* [roe-kyoor-OH-nee-um], and *vecuronium* [ve-KYOO-ro-nee-um].

#### 1. Mechanism of action:

- At low doses:** NMBs competitively block ACh at the nicotinic receptors (Figure 5.9). They compete with ACh at the receptor without stimulating it, thus preventing depolarization of the muscle cell membrane and inhibiting muscular contraction. Their competitive action can be overcome by administration of cholinesterase inhibitors, such as *neostigmine* and *edrophonium*, which increase the concentration of ACh in the neuromuscular junction. Clinicians employ this

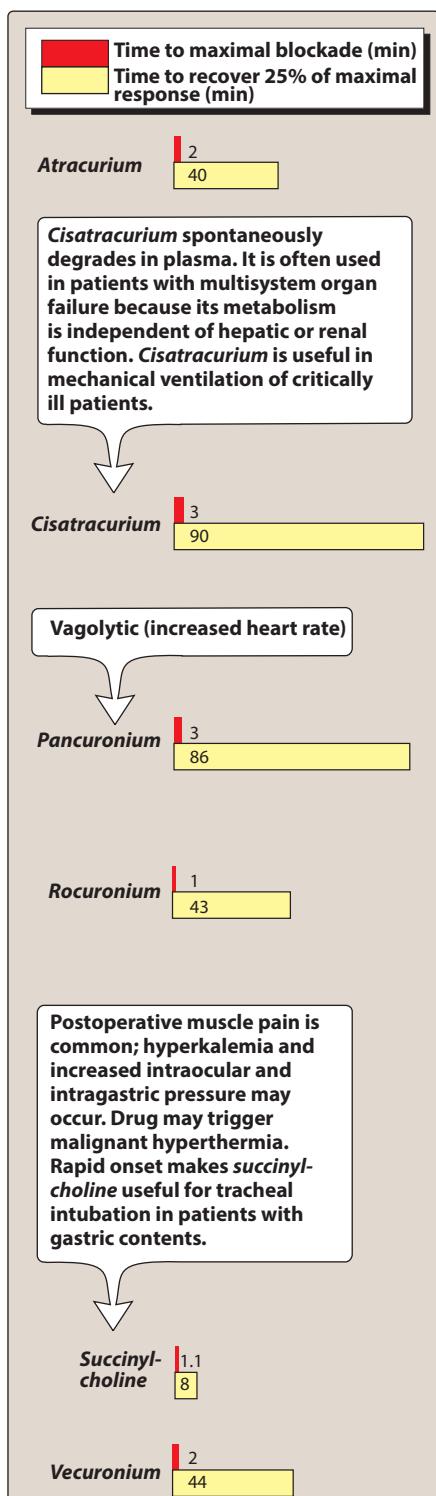
strategy to shorten the duration of neuromuscular blockade. In addition, at low doses the muscle responds to direct electrical stimulation from a peripheral nerve stimulator to varying degrees, allowing for monitoring of the extent of neuromuscular blockade.

- b. **At high doses:** Nondepolarizing agents can block the ion channels of the motor endplate. This leads to further weakening of neuromuscular transmission, reducing the ability of cholinesterase inhibitors to reverse the actions of the non-depolarizing blockers. With complete blockade, the muscle does not respond to direct electrical stimulation.
2. **Actions:** Muscles have differing sensitivity to blockade by competitive agents. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers, limbs, neck, and trunk muscles. Next, the intercostal muscles are affected and, lastly, the diaphragm. The muscles recover in the reverse manner. [Note: *Sugammadex* is a selective relaxant-binding agent that terminates the action of both *rocuronium* and *vecuronium* and can be used to speed recovery (see Chapter 13).]
3. **Pharmacokinetics:** All NMBs are injected intravenously or occasionally intramuscularly. These agents possess two or more quaternary amines in their bulky ring structure that prevent absorption from the gut. They penetrate membranes very poorly and do not enter cells or cross the blood–brain barrier. Drug action is terminated in a variety of ways. (Figure 5.10). *Pancuronium* is excreted unchanged in urine. *Cisatracurium* undergoes organ-independent metabolism (via Hofmann elimination) to laudanosine, which is further metabolized and renally excreted. The amino steroid drugs *vecuronium* and *rocuronium* are deacetylated in the liver and excreted unchanged in bile. *Mivacurium* is eliminated by plasma cholinesterase. The choice of agent depends on the desired onset and duration of muscle relaxation, and the route of elimination. Characteristics of the neuromuscular-blocking drugs are shown in Figure 5.11.
4. **Adverse effects:** In general, these agents are safe with minimal side effects. The adverse effects of the specific NMBs are shown in Figure 5.11.
5. **Drug interactions:**
  - a. **Cholinesterase inhibitors:** Drugs such as *neostigmine*, *physostigmine*, *pyridostigmine*, and *edrophonium* can overcome the action of nondepolarizing NMBs. However, with increased dosage, cholinesterase inhibitors can cause a depolarizing block due to elevated ACh concentrations at the end-plate membrane. If the NMB has entered the ion channel (is bound to the receptor), cholinesterase inhibitors are not as effective in overcoming blockade.
  - b. **Halogenated hydrocarbon anesthetics:** Drugs such as *desflurane* act to enhance neuromuscular blockade by exerting a stabilizing action at the NMJ. These agents sensitize the NMJ to the effects of NMBs.



**Figure 5.10**

Pharmacokinetics of the neuromuscular-blocking drugs. *Cisatracurium* undergoes organ-independent elimination. *Mivacurium* and *succinylcholine* are metabolized by plasma cholinesterase. IV = intravenous.



- c. **Aminoglycoside antibiotics:** Drugs such as *gentamicin* and *tobramycin* inhibit ACh release from cholinergic nerves by competing with calcium ions. They synergize with competitive blockers, enhancing neuromuscular blockade.
- d. **Calcium channel blockers:** These agents may increase the neuromuscular blockade of competitive blockers.

## B. Depolarizing agents

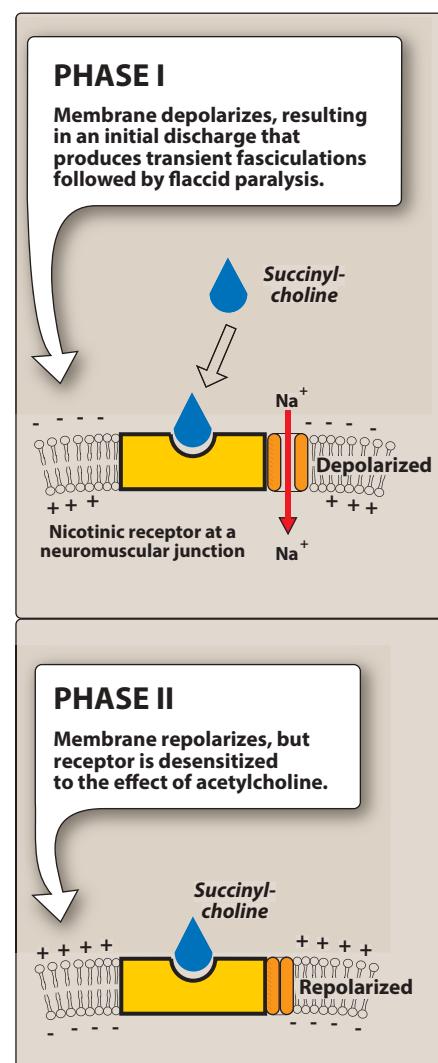
Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can more persistently depolarize the muscle fibers. *Succinylcholine* [suk-sin-il-KOE-leen] is the only depolarizing muscle relaxant in use today.

1. **Mechanism of action:** *Succinylcholine* attaches to the nicotinic receptor and acts like ACh to depolarize the junction (Figure 5.12). Unlike ACh, which is instantly destroyed by AChE, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a longer time and providing sustained depolarization of the muscle cell. [Note: The duration of action is dependent on diffusion from the motor endplate and hydrolysis by plasma cholinesterase (also called butyrylcholinesterase or pseudocholinesterase). Genetic variants in which plasma cholinesterase levels are low or absent lead to prolonged neuromuscular paralysis.] The depolarizing agent first causes opening of the sodium channel associated with nicotinic receptors, which results in depolarization of the receptor (Phase I). This leads to a transient twitching of the muscle (fasciculations). Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (Phase II) and flaccid paralysis.
2. **Actions:** As with the competitive blockers, the respiratory muscles are paralyzed last. *Succinylcholine* initially produces brief muscle fasciculations that cause muscle soreness. This may be prevented by administering a small dose of nondepolarizing NMB prior to *succinylcholine*. Normally, the duration of action of *succinylcholine* is extremely short, due to rapid hydrolysis by plasma cholinesterase. However, *succinylcholine* that reaches the NMJ is not metabolized, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism. In patients with pseudocholinesterase deficiency, abnormally slow metabolic degradation of *succinylcholine* and *mivacurium* leads to prolonged muscular paralysis, resulting in the extended need for mechanical ventilation. A variety of pathologic conditions, physiologic alterations, and medications also can lower plasma pseudocholinesterase activity.

**Figure 5.11**

Onset and duration of action of neuromuscular-blocking drugs.

3. **Therapeutic uses:** Because of its rapid onset of action, *succinylcholine* is useful when rapid endotracheal intubation is required. It is also used during electroconvulsive shock treatment.
4. **Pharmacokinetics:** *Succinylcholine* is injected intravenously. Its brief duration of action results from redistribution and rapid hydrolysis by plasma cholinesterase. Drug effects rapidly disappear upon discontinuation.
5. **Adverse effects:**
  - a. **Hyperthermia:** *Succinylcholine* can potentially induce malignant hyperthermia in susceptible patients (see Chapter 13).
  - b. **Apnea:** Administration of *succinylcholine* to a patient who is deficient in plasma cholinesterase or has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm. The rapid release of potassium may also contribute to prolonged apnea in patients with electrolyte imbalances. In patients with electrolyte imbalances receiving *digoxin* or diuretics (such as heart failure patients), *succinylcholine* should be used cautiously or not at all.
  - c. **Hyperkalemia:** *Succinylcholine* increases potassium release from intracellular stores. This may be particularly dangerous in burn patients, in patients with massive tissue damage in which potassium has been rapidly lost, or in patients with renal failure.

**Figure 5.12**

Mechanism of action of depolarizing neuromuscular-blocking drugs.

## Study Questions

Choose the ONE best answer.

- 5.1 During an ophthalmic surgical procedure, the surgeon wanted to constrict the pupil using a miotic drug. However, he accidentally used another drug that caused dilation of the pupil (mydriasis). Which drug was most likely used?
- A. Acetylcholine
  - B. Pilocarpine
  - C. Tropicamide
  - D. Bethanechol

Correct answer = C. Muscarinic agonists such as ACh, pilocarpine, and bethanechol contract the circular muscles of iris sphincter and cause constriction of the pupil (miosis), whereas muscarinic antagonists such as tropicamide prevent contraction of the circular muscles of the iris and cause dilation of the pupil (mydriasis).

5.2 Sarin is a nerve gas that is an organophosphate cholinesterase inhibitor. Which agent could be used as an antidote to sarin poisoning?

- A. Pilocarpine
- B. Carbachol
- C. Atropine
- D. Physostigmine

5.3 A patient with Alzheimer disease needs treatment for overactive bladder (OAB). Which drug is the best choice for this patient?

- A. Darifenacin
- B. Solifenacin
- C. Tolterodine
- D. Trospium

5.4 A patient with asthma was prescribed a  $\beta_2$  agonist for acute relief of bronchospasm, but did not respond to treatment. Which drug is the most likely next option for this patient?

- A. Benztropine
- B. Ipratropium
- C. Oxybutynin
- D. Physostigmine

5.5 A 50-year-old male who is noncompliant with medications was recently diagnosed with chronic obstructive pulmonary disease (COPD). His physician would like to prescribe an inhaled anticholinergic that is dosed once or twice daily. Which drug is most appropriate for this patient?

- A. Atropine
- B. Ipratropium
- C. Tiotropium
- D. Trospium

5.6 Which is the most effective anti-motion sickness drug for a person planning to go on a cruise?

- A. Atropine
- B. Fesoterodine
- C. Scopolamine
- D. Tropicamide

Correct answer = C. Sarin is an organophosphate cholinesterase inhibitor. It causes an increase in ACh levels in tissues that leads to cholinergic crisis through activation of muscarinic and nicotinic receptors. Most symptoms of cholinergic crisis are mediated by muscarinic receptors and, therefore, the muscarinic antagonist atropine is used as an antidote for sarin poisoning. Cholinergic agonists such as pilocarpine, carbachol, and physostigmine (indirect agonists) worsen symptoms of sarin poisoning.

Correct answer = D. All of agents for OAB except trospium cross the blood-brain barrier to various degrees, and could worsen dementia symptoms in Alzheimer disease. Trospium is a quaternary ammonium compound that minimally crosses the blood-brain barrier.

Correct answer = B. Major receptors present in the bronchial tissues are muscarinic and adrenergic- $\beta_2$  receptors. Muscarinic activation causes bronchoconstriction, and  $\beta_2$  receptor activation causes bronchodilation. Therefore, direct or indirect (physostigmine) muscarinic agonists worsen bronchospasm. Ipratropium is a muscarinic antagonist that can relax bronchial smooth muscles and relieve bronchospasm in patients who are not responsive to  $\beta_2$  agonists. Benztropine is used in the treatment of Parkinson disease or relief of extrapyramidal symptoms from antipsychotics. Oxybutynin is used for overactive bladder.

Correct answer = C. The physician should prescribe a long-acting muscarinic antagonist (LAMA) so that the patient has to inhale the medication only 1 or 2 times daily. Tiotropium is a LAMA, whereas ipratropium is a short-acting muscarinic antagonist (SAMA). Atropine and trospium are muscarinic antagonists, but are not indicated for pulmonary conditions such as asthma or COPD and are not available as inhaled formulations.

Correct answer = C. All muscarinic antagonists (anti-cholinergic drugs) listed above are theoretically useful as anti-motion sickness drugs; however, scopolamine is the most effective in preventing motion sickness. Tropicamide mostly has ophthalmic uses, and fesoterodine is used for overactive bladder.

5.7 Which is correct regarding ganglion-blocking drugs?

- A. Blockade of sympathetic ganglia could result in reduced blood pressure.
- B. Blockade of parasympathetic ganglia could result in reduced heart rate.
- C. Nicotine is a nondepolarizing ganglion blocker.
- D. Atropine is a nondepolarizing ganglion blocker.

Correct answer = A. Selective blockade (in theory) of the sympathetic ganglion causes reduction in norepinephrine release and, therefore, reduction in heart rate and blood pressure. Selective blockade (in theory) of the parasympathetic ganglion causes reduction in ACh release and an increase in heart rate. Receptors at both sympathetic and parasympathetic ganglia are of the nicotinic type. Nicotine is an agonist at nicotinic receptors and produces a depolarizing block in the ganglia. Atropine is a muscarinic antagonist and has no effect on the nicotinic receptors found in the ganglia.

5.8 Which drug is useful in treating sinus bradycardia?

- A. Atropine
- B. Cisatracurium
- C. Neostigmine
- D. Succinylcholine

Correct answer = A. Sinus bradycardia is a condition where the heart rate is below normal, and most often caused by increased vagal tone [increased release of ACh in the sinoatrial (SA) node that acts on muscarinic receptors to reduce heart rate]. A muscarinic antagonist such as atropine is useful in this situation to bring the heart rate back to normal. Succinylcholine and cisatracurium are nicotinic antagonists and have no effect on muscarinic receptors in the SA node. Neostigmine is a cholinesterase inhibitor and can worsen bradycardia by increasing the level of ACh in the SA node.

5.9 An ICU patient with severe lung injury requires a neuromuscular blocking agent to assist in his ventilator management. He has liver disease and is currently in renal failure. Which neuromuscular blocker is the best choice for this patient?

- A. Cisatracurium
- B. Pancuronium
- C. Vecuronium
- D. Rocuronium

Correct answer = A. Pancuronium is renally eliminated and the patient has renal failure. Vecuronium and rocuronium are hepatically metabolized and the patient has liver disease. Cisatracurium is cleared by organ-independent metabolism (Hofmann elimination).

5.10 Where would you expect to see the first return of function in skeletal muscles following discontinuation of a nondepolarizing neuromuscular blocking agent?

- A. Arms
- B. Diaphragm
- C. Fingers
- D. Pupils

Correct answer = C. Following administration of a neuromuscular blocker, the facial muscles are impacted first, but the pupils are not controlled by skeletal muscle and are not affected. The fingers and arms would be next, with the diaphragm function lost last. Function returns in the opposite order, so function of the diaphragm returns first.



# Adrenergic Agonists

6

Rajan Radhakrishnan

## I. OVERVIEW

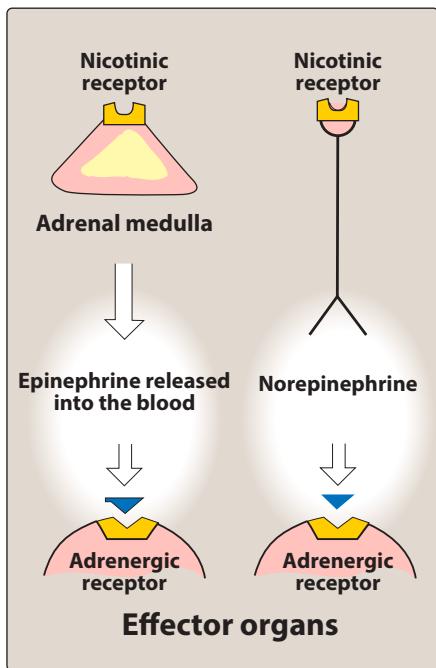
The adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline). These receptors are known as adrenergic receptors or adrenoceptors. Drugs that activate adrenergic receptors are termed sympathomimetics, and drugs that block activation of adrenergic receptors are termed sympatholytics. Some sympathomimetics directly activate adrenergic receptors (direct-acting agonists), while others act indirectly by enhancing release or blocking reuptake of norepinephrine (indirect-acting agonists). This chapter describes agents that either directly or indirectly stimulate adrenoceptors (Figure 6.1). Sympatholytic drugs are discussed in Chapter 7.

ADRENERGIC DRUGS		
DIRECT ACTING	MIXED ACTING	INDIRECT ACTING
<b><math>\alpha</math> Agonists</b>  Nonselective ( $\alpha_1, \alpha_2$ ) <ul style="list-style-type: none"><li>• <i>Epinephrine</i></li><li>• <i>Norepinephrine</i></li></ul> Selective ( $\alpha_1, \alpha_2$ ) <ul style="list-style-type: none"><li>• <math>\alpha_1</math> agonists<ul style="list-style-type: none"><li>- <i>Phenylephrine</i></li><li>- <i>Methhexamine</i></li></ul></li><li>• <math>\alpha_2</math> agonists<ul style="list-style-type: none"><li>- <i>Clonidine</i></li><li>- <i>Guanfacine</i></li><li>- <i>Guanabenz</i></li></ul></li></ul>	<ul style="list-style-type: none"><li>• <i>Ephedrine</i></li><li>• <i>Mephentermine</i></li><li>• <i>Metaraminol</i></li></ul>	<b>Releasing agents</b> <ul style="list-style-type: none"><li>• <i>Ammphetamines</i></li><li>• <i>Tyramine</i></li></ul> <b>Uptake inhibitor</b> <ul style="list-style-type: none"><li>• <i>Cocaine</i></li><li>MAO inhibitor<ul style="list-style-type: none"><li>• <i>Selegiline</i></li></ul></li><li>COMT inhibitor<ul style="list-style-type: none"><li>• <i>Entacapone</i></li></ul></li></ul>
<b><math>\beta</math> Agonists</b>  Nonselective ( $\beta_1, \beta_2$ ) <ul style="list-style-type: none"><li>• <i>Isoproterenol</i></li><li>• <i>Epinephrine</i></li></ul> Selective <ul style="list-style-type: none"><li>• <math>\beta_1</math> agonist<ul style="list-style-type: none"><li>- <i>Dopamine</i></li></ul></li><li>• <math>\beta_2</math> agonists<ul style="list-style-type: none"><li>- <i>Terbutaline</i></li><li>- <i>Salbutamol</i></li><li>- <i>Ritodrine</i></li><li>- <i>Salmeterol</i></li><li>- <i>Fenoterol</i></li></ul></li></ul>		

COMT = catechol-O-methyltransferase; MAO = monoamine oxidase inhibitor; Selective  $\approx$  50–100 fold.

Figure 6.1

Summary of adrenergic agonists.

**Figure 6.2**

Sites of actions of adrenergic agonists.

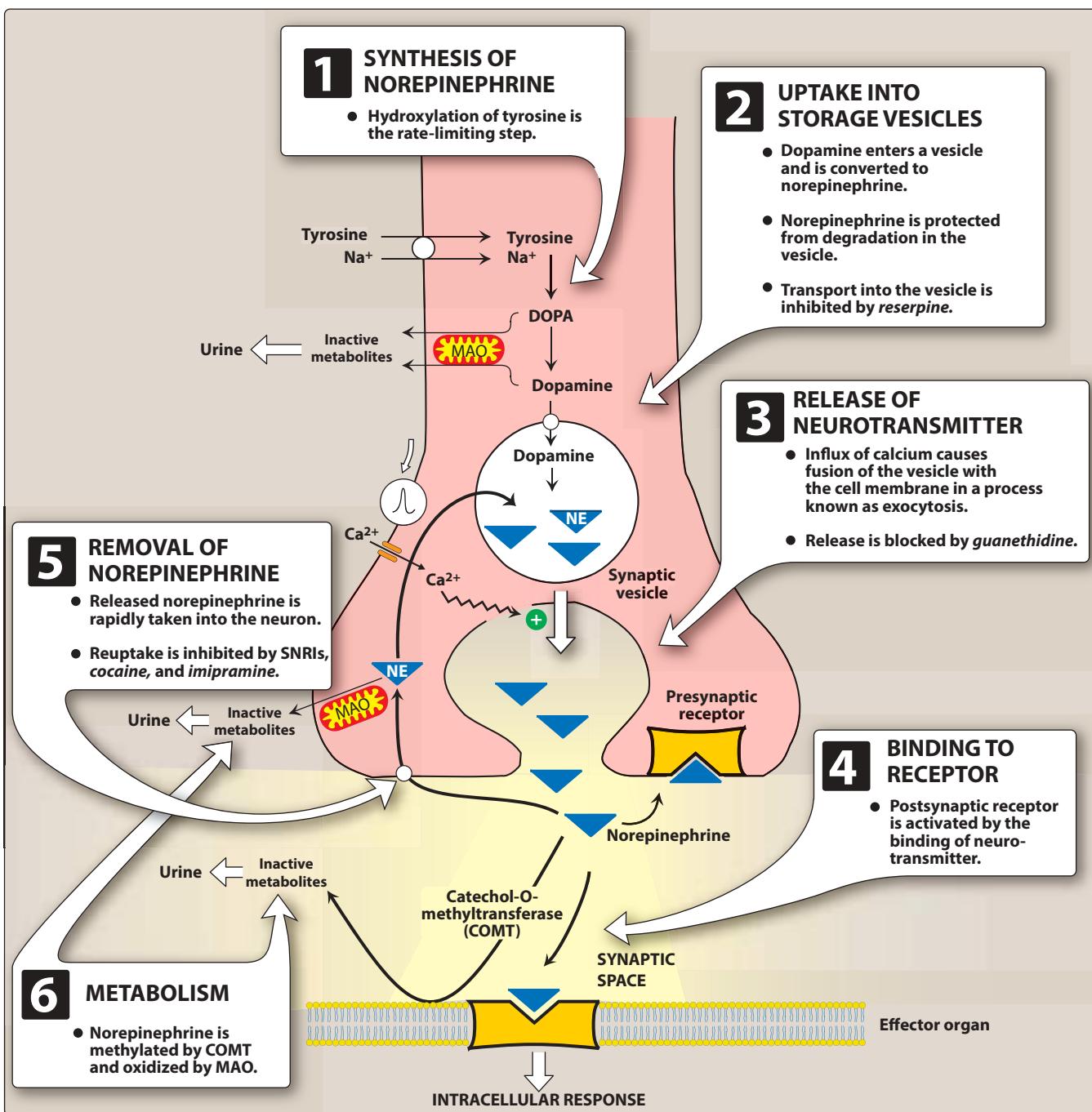
## II. THE ADRENERGIC NEURON

Adrenergic neurons release norepinephrine as the primary neurotransmitter. These neurons are found in the central nervous system (CNS) and in the sympathetic nervous system, where they serve as links between ganglia and the effector organs. Adrenergic drugs act on adrenergic receptors, located either presynaptically on the neuron or postsynaptically on the effector organ (Figure 6.2).

### A. Neurotransmission at adrenergic neurons

Neurotransmission in adrenergic neurons closely resembles that described for the cholinergic neurons (see Chapter 4), except that norepinephrine is the neurotransmitter instead of acetylcholine. Neurotransmission involves the following steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap (Figure 6.3).

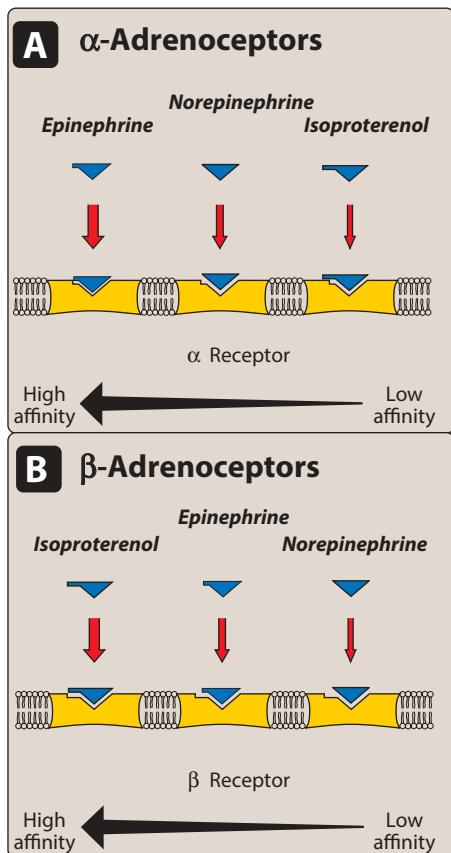
- Synthesis of norepinephrine:** Tyrosine is transported by a carrier into the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the formation of norepinephrine. DOPA is then decarboxylated by the enzyme aromatic L-amino acid decarboxylase to form dopamine in the presynaptic neuron.
- Storage of norepinephrine in vesicles:** Dopamine is then transported into synaptic vesicles by an amine transporter system. This carrier system is blocked by *reserpine* (see Chapter 7). Next, dopamine is hydroxylated to form norepinephrine by the enzyme dopamine  $\beta$ -hydroxylase.
- Release of norepinephrine:** An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes synaptic vesicles to fuse with the cell membrane and to undergo exocytosis and expel their contents into the synapse. Drugs such as *guanethidine* block this release.
- Binding to receptors:** Norepinephrine released from the synaptic vesicles diffuses into the synaptic space and binds to postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. Binding of norepinephrine to receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second messenger system and the phosphatidylinositol cycle to transduce the signal into an effect. Norepinephrine also binds to presynaptic receptors (mainly  $\alpha_2$  subtype) that modulate the release of the neurotransmitter.
- Removal of norepinephrine:** Norepinephrine may 1) diffuse out of the synaptic space and enter the systemic circulation; 2) be metabolized to inactive metabolites by catechol-O-methyltransferase (COMT) in the synaptic space; or 3) undergo reuptake back into the neuron. The reuptake by the neuronal membrane involves a sodium-chloride ( $\text{Na}^+/\text{Cl}^-$ )-dependent norepinephrine transporter that can be inhibited by tricyclic antidepressants (TCAs) such as *imipramine*, by

**Figure 6.3**

Synthesis and release of norepinephrine from the adrenergic neuron. MAO = monoamine oxidase, SNRI = serotonin-norepinephrine reuptake inhibitor.

serotonin–norepinephrine reuptake inhibitors such as *duloxetine*, or by *cocaine*. Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

- Potential fates of recaptured norepinephrine: Once norepinephrine re-enters the adrenergic neuron, it may be taken up into synaptic vesicles via the amine transporter system and be sequestered for

**Figure 6.4**

Types of adrenergic receptors.

release by another action potential, or it may persist in a protected pool in the cytoplasm. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.

### B. Adrenergic receptors (adrenoceptors)

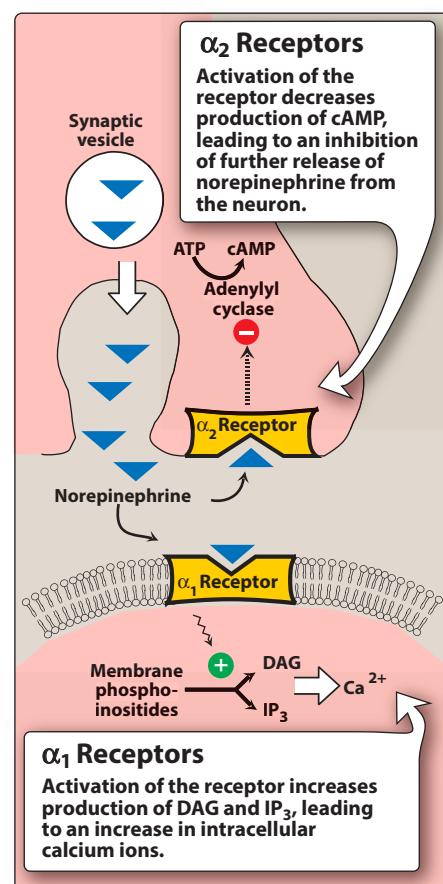
In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two main families of receptors, designated  $\alpha$  and  $\beta$ , are classified based on response to the adrenergic agonists *epinephrine*, *norepinephrine*, and *isoproterenol*. Both the  $\alpha$  and  $\beta$  receptor types have a number of specific receptor subtypes. Alterations in the primary structure of the receptors influence their affinity for various agents.

**1.  $\alpha$ -Adrenoceptors:** The  $\alpha$ -adrenoceptors show a weak response to the synthetic agonist *isoproterenol*, but they are responsive to the naturally occurring catecholamines *epinephrine* and *norepinephrine* (Figure 6.4). For  $\alpha$  receptors, the rank order of potency and affinity is *epinephrine*  $\geq$  *norepinephrine*  $>>$  *isoproterenol*. The  $\alpha$ -adrenoceptors are divided into two subtypes,  $\alpha_1$  and  $\alpha_2$ , based on their affinities for  $\alpha$  agonists and antagonists. For example,  $\alpha_1$  receptors have a higher affinity for *phenylephrine* than  $\alpha_2$  receptors. Conversely, the drug *clonidine* selectively binds to  $\alpha_2$  receptors and has less effect on  $\alpha_1$  receptors.

**a.  $\alpha_1$  Receptors:** These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as  $\alpha$ -adrenergic, involving constriction of smooth muscle. Activation of  $\alpha_1$  receptors initiates a series of reactions through the G protein activation of phospholipase C, ultimately resulting in the generation of second messengers inositol-1,4,5-trisphosphate ( $IP_3$ ) and diacylglycerol (DAG).  $IP_3$  initiates the release of  $Ca^{2+}$  from the endoplasmic reticulum into the cytosol, and DAG turns on other proteins within the cell (Figure 6.5).

**b.  $\alpha_2$  Receptors:** These receptors are located primarily on sympathetic presynaptic nerve endings and control the release of norepinephrine. When a sympathetic adrenergic nerve is stimulated, a portion of the released norepinephrine “circles back” and reacts with  $\alpha_2$  receptors on the presynaptic membrane (Figure 6.5). Stimulation of  $\alpha_2$  receptors causes feedback inhibition and inhibits further release of norepinephrine from the stimulated adrenergic neuron. This inhibitory action serves as a local mechanism for modulating norepinephrine output when there is high sympathetic activity. [Note: In this instance, by inhibiting further output of norepinephrine from the adrenergic neuron, these receptors are acting as inhibitory autoreceptors.]  $\alpha_2$  Receptors are also found on presynaptic parasympathetic neurons. Norepinephrine released from a presynaptic sympathetic neuron can diffuse to and interact with these receptors, inhibiting acetylcholine release. [Note: In these instances, these receptors are behaving as inhibitory heteroreceptors.] This is another mechanism to modulate autonomic activity in a given area. In contrast to  $\alpha_1$  receptors, the effects of binding at  $\alpha_2$  receptors are mediated by inhibition of adenyl cyclase and by a fall in the levels of intracellular cAMP.

- c. **Further subdivisions:** The  $\alpha_1$  and  $\alpha_2$  receptors are further divided into  $\alpha_{1A}$ ,  $\alpha_{1B}$ ,  $\alpha_{1C}$ , and  $\alpha_{1D}$  and into  $\alpha_{2A}$ ,  $\alpha_{2B}$ , and  $\alpha_{2C}$ . This extended classification is necessary for understanding the selectivity of some drugs. For example, *tamsulosin* is a selective  $\alpha_{1A}$  antagonist that is used to treat benign prostatic hyperplasia. The drug has fewer cardiovascular side effects because it targets  $\alpha_{1A}$  subtype receptors found primarily in the urinary tract and prostate gland and does not affect the  $\alpha_{1B}$  subtype found in the blood vessels.
2.  **$\beta$ -Adrenoceptors:** Responses of  $\beta$  receptors differ from those of  $\alpha$  receptors and are characterized by a strong response to *isoproterenol*, with less sensitivity to *epinephrine* and *norepinephrine* (Figure 6.4). For  $\beta$  receptors, the rank order of potency is *isoproterenol* > *epinephrine* > *norepinephrine*. The  $\beta$ -adrenoceptors can be subdivided into three major subgroups,  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$ , based on their affinities for adrenergic agonists and antagonists.  $\beta_1$  receptors have approximately equal affinities for *epinephrine* and *norepinephrine*, whereas  $\beta_2$  receptors have a higher affinity for *epinephrine* than for *norepinephrine*. Thus, tissues with a predominance of  $\beta_2$  receptors (such as the vasculature of skeletal muscle) are particularly responsive to the effects of circulating *epinephrine* released by the adrenal medulla.  $\beta_3$  receptors are involved in lipolysis and also have effects on the detrusor muscle of the bladder. Binding of a neurotransmitter at any of the three types of  $\beta$  receptors results in activation of adenylyl cyclase and increased concentrations of cAMP within the cell.
3. **Distribution of receptors:** Adrenergically innervated organs and tissues usually have a predominant type of receptor. For example, tissues such as the vasculature of skeletal muscle have both  $\alpha_1$  and  $\beta_2$  receptors, but the  $\beta_2$  receptors predominate. Other tissues may have one type of receptor almost exclusively. For example, the heart contains predominantly  $\beta_1$  receptors.
4. **Characteristic responses mediated by adrenoceptors:** It is useful to organize the physiologic responses to adrenergic stimulation according to receptor type, because many drugs preferentially stimulate or block one type of receptor. Figure 6.6 summarizes

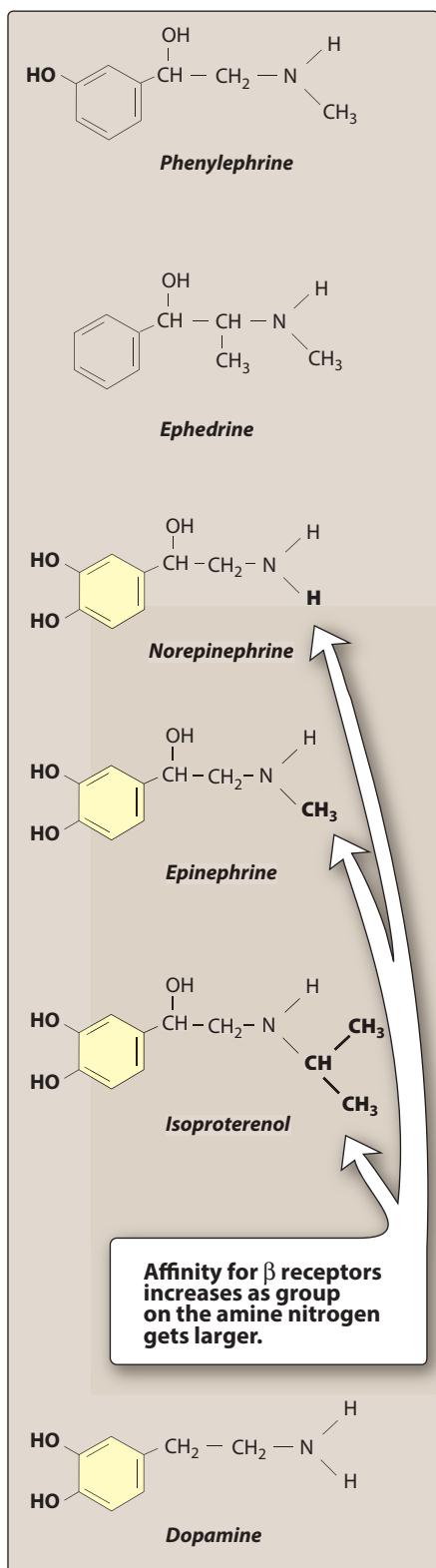
**Figure 6.5**

Second messengers mediate the effects of  $\alpha$  receptors. DAG = diacylglycerol; IP<sub>3</sub> = inositol trisphosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate.

ADRENOCEPTORS			
$\alpha_1$	$\alpha_2$	$\beta_1$	$\beta_2$
Vasoconstriction	Inhibition of norepinephrine release	Tachycardia	Vasodilation
Increased peripheral resistance	Inhibition of acetylcholine release	Increased lipolysis	Decreased peripheral resistance
Increased blood pressure	Inhibition of insulin release	Increased myocardial contractility	Bronchodilation
Mydriasis		Increased release of renin	Increased muscle and liver glycogenolysis
Increased closure of internal sphincter of the bladder			Increased release of glucagon
			Relaxed uterine smooth muscle

**Figure 6.6**

Major effects mediated by  $\alpha$ - and  $\beta$ -adrenoceptors.

**Figure 6.7**

Structures of several important adrenergic agonists. Drugs containing the catechol ring are shown in yellow.

the most prominent effects mediated by the adrenoceptors. As a generalization, stimulation of  $\alpha_1$  receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure. Stimulation of  $\beta_1$  receptors characteristically causes cardiac stimulation (increase in heart rate and contractility), whereas stimulation of  $\beta_2$  receptors produces vasodilation (in skeletal muscle vascular beds) and smooth muscle relaxation.

5. **Desensitization of receptors:** Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization. Three mechanisms have been suggested to explain this phenomenon: 1) sequestration of the receptors so that they are unavailable for interaction with the ligand; 2) down-regulation—that is, a disappearance of the receptors either by destruction or by decreased synthesis; and 3) an inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side.

### III. CHARACTERISTICS OF ADRENERGIC AGONISTS

Most adrenergic drugs are derivatives of  $\beta$ -phenylethylamine (Figure 6.7). Substitutions on the benzene ring or on the ethylamine side chains produce a variety of compounds with varying abilities to differentiate between  $\alpha$  and  $\beta$  receptors and to penetrate the CNS. Two important structural features of these drugs are 1) the number and location of OH substitutions on the benzene ring and 2) the nature of the substituent on the amino nitrogen.

#### A. Catecholamines

Sympathomimetic amines that contain the 3,4-dihydroxybenzene group (such as epinephrine, norepinephrine, isoproterenol, and dopamine) are called catecholamines. These compounds share the following properties:

1. **High potency:** Catecholamines show the highest potency in directly activating  $\alpha$  or  $\beta$  receptors.
2. **Rapid inactivation:** Catecholamines are metabolized by COMT postsynaptically and by MAO intraneuronally, as well as by COMT and MAO in the gut wall, and by MAO in the liver. Thus, catecholamines have only a brief period of action when given parenterally, and they are inactivated (ineffective) when administered orally.
3. **Poor penetration into the CNS:** Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most catecholamines have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS.

#### B. Noncatecholamines

Compounds lacking the catechol hydroxyl groups have longer half-lives, because they are not inactivated by COMT. These include phenylephrine, ephedrine, and amphetamine (Figure 6.7). These agents are poor substrates for MAO (an important route of metabolism) and, thus, show a prolonged duration of action. Increased lipid solubility of

many of the noncatecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS.

### C. Substitutions on the amine nitrogen

The nature of the substituent on the amine nitrogen is important in determining  $\beta$  selectivity of the adrenergic agonist. For example, *epinephrine*, with a  $-CH_3$  substituent on the amine nitrogen, is more potent at  $\beta$  receptors than *norepinephrine*, which has an unsubstituted amine. Similarly, *isoproterenol*, which has an isopropyl substituent  $-CH(CH_3)_2$  on the amine nitrogen (Figure 6.7), is a strong  $\beta$  agonist with little  $\alpha$  activity (Figure 6.4).

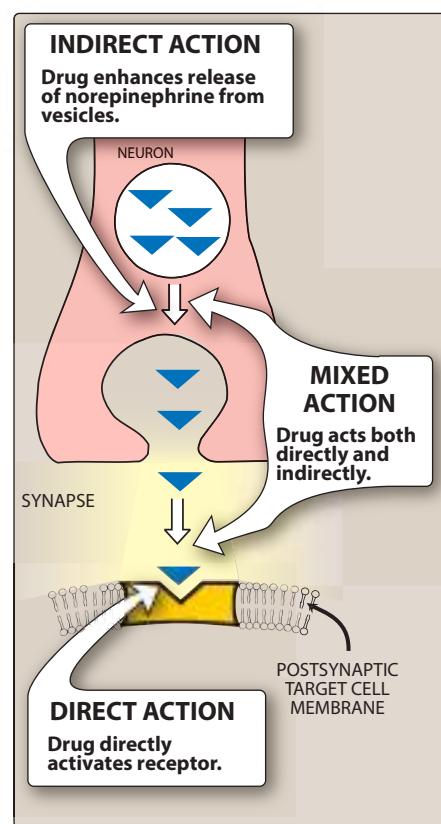
### D. Mechanism of action of adrenergic agonists

- Direct-acting agonists:** These drugs act directly on  $\alpha$  or  $\beta$  receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of epinephrine from the adrenal medulla (Figure 6.8). Examples of direct-acting agonists include *epinephrine*, *norepinephrine*, *isoproterenol*, *dopamine*, and *phenylephrine*.
- Indirect-acting agonists:** These agents may block the reuptake of norepinephrine or cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron (Figure 6.8). The norepinephrine then traverses the synapse and binds to  $\alpha$  or  $\beta$  receptors. Examples of reuptake inhibitors and agents that cause norepinephrine release include *cocaine* and *amphetamine*, respectively.
- Mixed-action agonists:** *Ephedrine* and its stereoisomer, *pseudoephedrine*, both stimulate adrenoceptors directly and enhance release of norepinephrine from the adrenergic neuron (Figure 6.8).

### E. Indications and contraindications of adrenergic agonists (sympathomimetics)

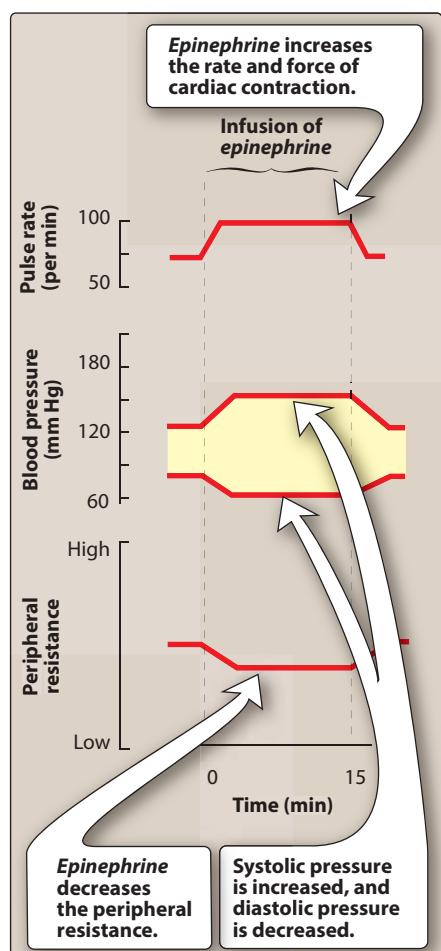
Sympathomimetics are used in conditions where it is appropriate to raise blood pressure by stimulating the heart and inducing vasoconstriction. They are used for short-term treatment only in refractory heart failure, cardiogenic shock, and hypotension caused by hemorrhage or sepsis because of deleterious long-term adverse effects. The adverse effects are generally extensions of their pharmacological activity—that is, stimulation of the sympathetic adrenergic system. Overdose with epinephrine or other pressor agents may result in severe hypertension, cardiac arrhythmias due to excessive cardiac stimulation with possible cerebral hemorrhage, and pulmonary edema. Because of these reasons, most of these drugs are high-alert drugs and are only used for short-term cardiovascular therapy with clinical supervision and monitoring. Their long-term use increases mortality in heart failure patients.

These drugs are contraindicated in patients with coronary artery disease because of the risk of precipitating myocardial ischemia and angina due to decreased myocardial oxygen supply–demand ratio. These drugs can also precipitate myocardial infarction and cerebrovascular stroke.



**Figure 6.8**

Sites of action of direct-, indirect-, and mixed-acting adrenergic agonists.



## IV. DIRECT-ACTING ADRENERGIC AGONISTS

Direct-acting agonists bind to adrenergic receptors on effector organs without interacting with the presynaptic neuron. As a group, these agents are widely used in clinical practice.

### A. Epinephrine

*Epinephrine* [ep-i-NEF-rin] is one of the four catecholamines (*epinephrine*, *norepinephrine*, *dopamine*, and *dobutamine*) commonly used in therapy. The first three are naturally occurring neurotransmitters, and the latter is a synthetic compound. In the adrenal medulla, *norepinephrine* is methylated to yield *epinephrine*, which is stored in chromaffin cells along with *norepinephrine*. On stimulation, the adrenal medulla releases about 80% *epinephrine* and 20% *norepinephrine* directly into the circulation. *Epinephrine* interacts with both  $\alpha$  and  $\beta$  receptors. At low doses,  $\beta$  effects (vasodilation) on the vascular system predominate, whereas at high doses,  $\alpha$  effects (vasoconstriction) are the strongest.

#### 1. Actions:

a. **Cardiovascular:** The major actions of *epinephrine* are on the cardiovascular system. *Epinephrine* strengthens the contractility of the myocardium (positive inotrope:  $\beta_1$  action) and increases its rate of contraction (positive chronotrope:  $\beta_1$  action). Therefore, cardiac output increases. These effects increase oxygen demands on the myocardium. *Epinephrine* activates  $\beta_1$  receptors on the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor. *Epinephrine* constricts arterioles in the skin, mucous membranes, and viscera ( $\alpha$  effects), and it dilates vessels going to the liver and skeletal muscle ( $\beta_2$  effects). These combined effects result in a decrease in renal blood flow. Therefore, the cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure due to  $\beta_2$  receptor-mediated vasodilation in the skeletal muscle vascular bed (Figure 6.9).

b. **Respiratory:** *Epinephrine* causes powerful bronchodilation by acting directly on bronchial smooth muscle ( $\beta_2$  action). It also inhibits the release of allergy mediators such as histamine from mast cells.

c. **Hyperglycemia:** *Epinephrine* has a significant hyperglycemic effect because of increased glycogenolysis in the liver ( $\beta_2$  effect), increased release of glucagon ( $\beta_2$  effect), and a decreased release of insulin ( $\alpha_2$  effect).

d. **Lipolysis:** *Epinephrine* initiates lipolysis through agonist activity on the  $\beta$  receptors of adipose tissue. Increased levels of cAMP stimulate a hormone-sensitive lipase, which hydrolyzes triglycerides to free fatty acids and glycerol.

#### 2. Therapeutic uses:

a. **Bronchospasm:** *Epinephrine* is the primary drug used in the emergency treatment of respiratory conditions when bronchoconstriction has resulted in diminished respiratory function. Thus, in treatment of anaphylactic shock, *epinephrine*

is the drug of choice and can be life-saving in this setting. Within a few minutes after subcutaneous administration, respiratory function greatly improves.

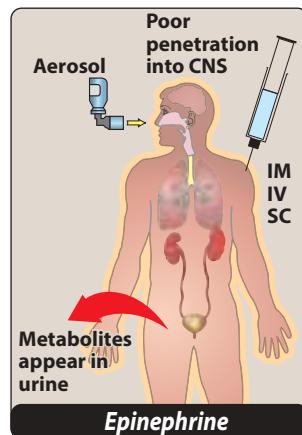
- b. **Anaphylactic shock:** *Epinephrine* is the drug of choice for the treatment of type I hypersensitivity reactions (including anaphylaxis) in response to allergens.
  - c. **Cardiac arrest:** *Epinephrine* may be used to restore cardiac rhythm in patients with cardiac arrest.
  - d. **Local anesthesia:** Local anesthetic solutions may contain low concentrations (for example, 1:100,000 parts) of *epinephrine*. *Epinephrine* greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection. *Epinephrine* also reduces systemic absorption of the local anesthetic and promotes local hemostasis.
  - e. **Intraocular surgery:** *Epinephrine* is used in the induction and maintenance of mydriasis during intraocular surgery.
3. **Pharmacokinetics:** *Epinephrine* has a rapid onset but a brief duration of action (due to rapid degradation). The preferred route for anaphylaxis in the outpatient setting is intramuscular (anterior thigh) due to rapid absorption. In emergencies, *epinephrine* is given intravenously (IV) for the most rapid onset of action. It may also be given subcutaneously, by the endotracheal tube, and by inhalation (Figure 6.10). It is rapidly metabolized by MAO and COMT, and the metabolites metanephrine and vanillylmandelic acid (VMA) are excreted in urine.
4. **Adverse effects:** *Epinephrine* can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor. It can trigger cardiac arrhythmias, particularly if the patient is receiving *digoxin*. *Epinephrine* can also induce pulmonary edema due to increased afterload caused by vasoconstrictive properties of the drug. Patients with hyperthyroidism may have an increased production of adrenergic receptors in the vasculature, leading to an enhanced response to *epinephrine*, and the dose must be reduced in these individuals. Inhalation anesthetics also sensitize the heart to the effects of *epinephrine*, which may lead to tachycardia. *Epinephrine* increases the release of endogenous stores of glucose. In diabetic patients, dosages of *insulin* may have to be increased. Nonselective  $\beta$ -blockers prevent vasodilatory effects of *epinephrine* on  $\beta_2$  receptors, leaving  $\alpha$  receptor stimulation unopposed. This may lead to increased peripheral resistance and increased blood pressure.

## B. Norepinephrine

Because *norepinephrine* [nor-ep-ih-NEF-rin] is the neurotransmitter in the adrenergic neurons, it should, theoretically, stimulate all types of adrenergic receptors. However, when administered in therapeutic doses, the  $\alpha$ -adrenergic receptor is most affected.

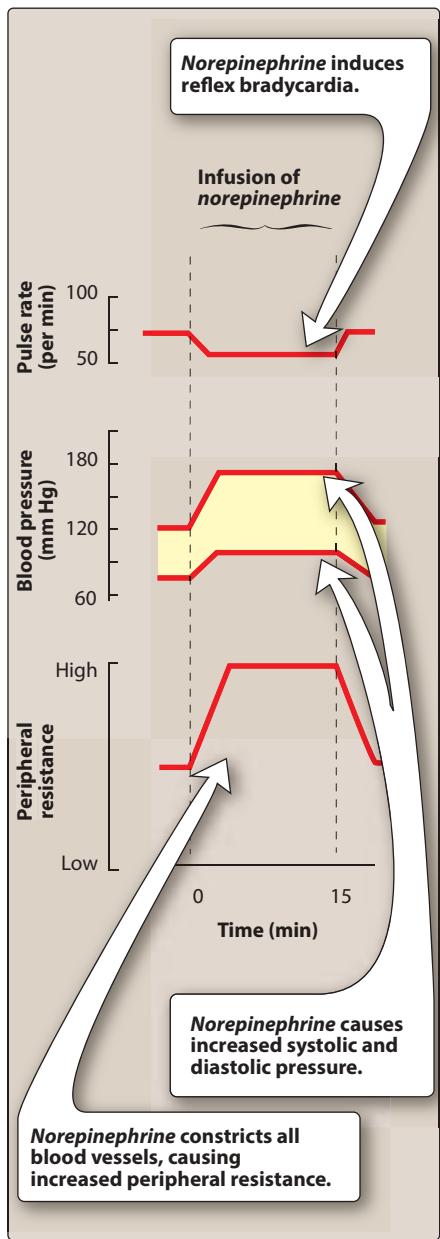
### 1. Cardiovascular actions:

- a. **Vasoconstriction:** Norepinephrine causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney ( $\alpha_1$  effect). Both systolic



**Figure 6.10**

Pharmacokinetics of *epinephrine*.  
CNS = central nervous system.



**Figure 6.11**

Cardiovascular effects of intravenous infusion of *norepinephrine*. Modified from M. J. Allwood, A. F. Cobbold, and J. Ginsburg. Peripheral vascular effects of noradrenaline, isopropylnoradrenaline and dopamine. Br. Med. Bull. 19: 132 (1963).

and diastolic blood pressures increase (Figure 6.11). [Note: Norepinephrine causes greater vasoconstriction than *epinephrine*, because it does not induce compensatory vasodilation via  $\beta_2$  receptors on blood vessels supplying skeletal muscles. The weak  $\beta_2$  activity of *norepinephrine* also explains why it is not useful in the treatment of bronchospasm or anaphylaxis.]

- b. **Baroreceptor reflex:** Norepinephrine increases blood pressure, and this stimulates the baroreceptors, inducing a rise in vagal activity. The increased vagal activity produces a reflex bradycardia, which is sufficient to counteract the local actions of *norepinephrine* on the heart, although the reflex compensation does not affect the positive inotropic effects of the drug (Figure 6.11). When *atropine*, which blocks the transmission of vagal effects, is given before *norepinephrine*, stimulation of the heart by *norepinephrine* is evident as tachycardia.
2. **Therapeutic uses:** Norepinephrine is used to treat shock (for example, septic shock), because it increases vascular resistance and, therefore, increases blood pressure. It has no other clinically significant uses.
3. **Pharmacokinetics:** Norepinephrine is given IV for rapid onset of action. The duration of action is 1 to 2 minutes, following the end of the infusion. It is rapidly metabolized by MAO and COMT, and inactive metabolites are excreted in the urine.
4. **Adverse effects:** These are similar to *epinephrine*. In addition, *norepinephrine* is a potent vasoconstrictor and may cause blanching and sloughing of skin along an injected vein. If extravasation (leakage of drug from the vessel into tissues surrounding the injection site) occurs, it can cause tissue necrosis. It should not be administered in peripheral veins, if possible. Impaired circulation from *norepinephrine* may be treated with the  $\alpha$  receptor antagonist *phentolamine*. Alternatives to *phentolamine* include intradermal *terbutaline* and topical *nitroglycerin*.

### C. Isoproterenol

*Isoproterenol* [eye-soe-proe-TER-e-nole] is a direct-acting synthetic catecholamine that stimulates both  $\beta_1$ - and  $\beta_2$ -adrenergic receptors. Its nonselectivity is a disadvantage and the reason why it is rarely used therapeutically. Its action on  $\alpha$  receptors is insignificant. *Isoproterenol* produces intense stimulation of the heart ( $\beta_1$  effect), increasing heart rate, contractility, and cardiac output (Figure 6.12). It is as active as *epinephrine* in this action. *Isoproterenol* also dilates the arterioles of skeletal muscle ( $\beta_2$  effect), resulting in decreased peripheral resistance. Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressures (Figure 6.12). *Isoproterenol* is also a potent bronchodilator ( $\beta_2$  effect). The adverse effects of *isoproterenol* are similar to the  $\beta$  receptor-related side effects of *epinephrine*.

## D. Dopamine

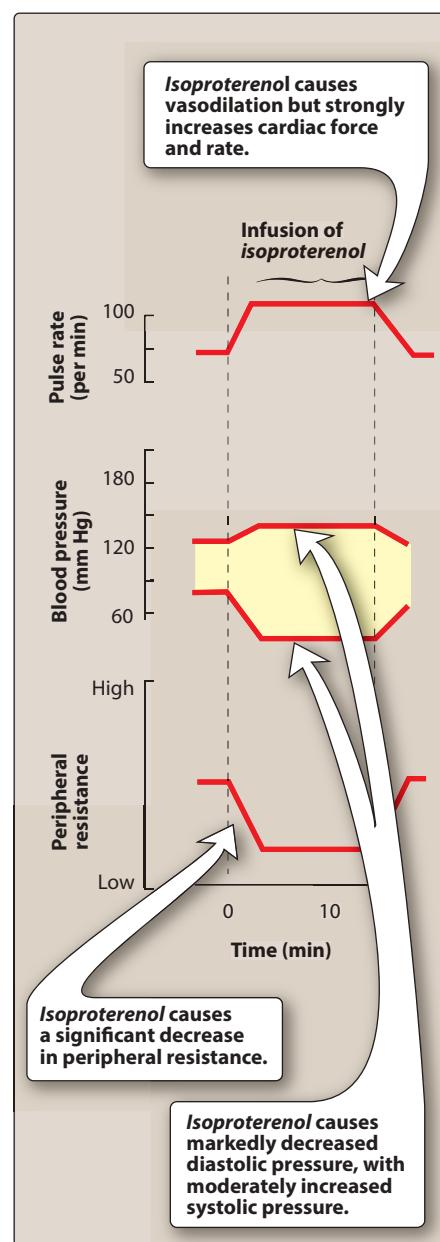
*Dopamine* [DOE-pa-meen], the immediate metabolic precursor of norepinephrine, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. *Dopamine* can activate  $\alpha$ - and  $\beta$ -adrenergic receptors. For example, at higher doses, it causes vasoconstriction by activating  $\alpha_1$  receptors, whereas at lower doses, it stimulates  $\beta_1$  cardiac receptors. In addition,  $D_1$  and  $D_2$  dopaminergic receptors, distinct from the  $\alpha$ - and  $\beta$ -adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of *dopamine* produces vasodilation.  $D_2$  receptors are also found on presynaptic adrenergic neurons, where their activation interferes with norepinephrine release.

### 1. Actions:

- Cardiovascular:** *Dopamine* exerts a stimulatory effect on the  $\beta_1$  receptors of the heart, having both positive inotropic and chronotropic effects (Figure 6.13). At very high doses, *dopamine* activates  $\alpha_1$  receptors on the vasculature, resulting in vasoconstriction.
- Renal and visceral:** *Dopamine* dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera (Figure 6.13). These receptors are not affected by  $\alpha$ - or  $\beta$ -blocking drugs, and in the past low-dose ("renal-dose") *dopamine* was often used in the prevention or treatment of acute renal failure. However, more recent data suggest there is limited clinical utility in the renal protective effects of *dopamine*.
- Therapeutic uses:** *Dopamine* can be used for cardiogenic and septic shock and is given by continuous infusion. It raises blood pressure by stimulating the  $\beta_1$  receptors on the heart to increase cardiac output and  $\alpha_1$  receptors on blood vessels to increase total peripheral resistance. It enhances perfusion to the kidney and splanchnic areas, as described above. Increased blood flow to the kidney enhances the glomerular filtration rate and causes diuresis. By contrast, *norepinephrine* can diminish blood supply to the kidney and may reduce renal function. *Dopamine* is also used to treat hypotension, severe heart failure, and bradycardia unresponsive to other treatments.
- Adverse effects:** An overdose of *dopamine* produces the same effects as sympathetic stimulation. *Dopamine* is rapidly metabolized by MAO or COMT, and its adverse effects (nausea, hypertension, and arrhythmias) are, therefore, short-lived.

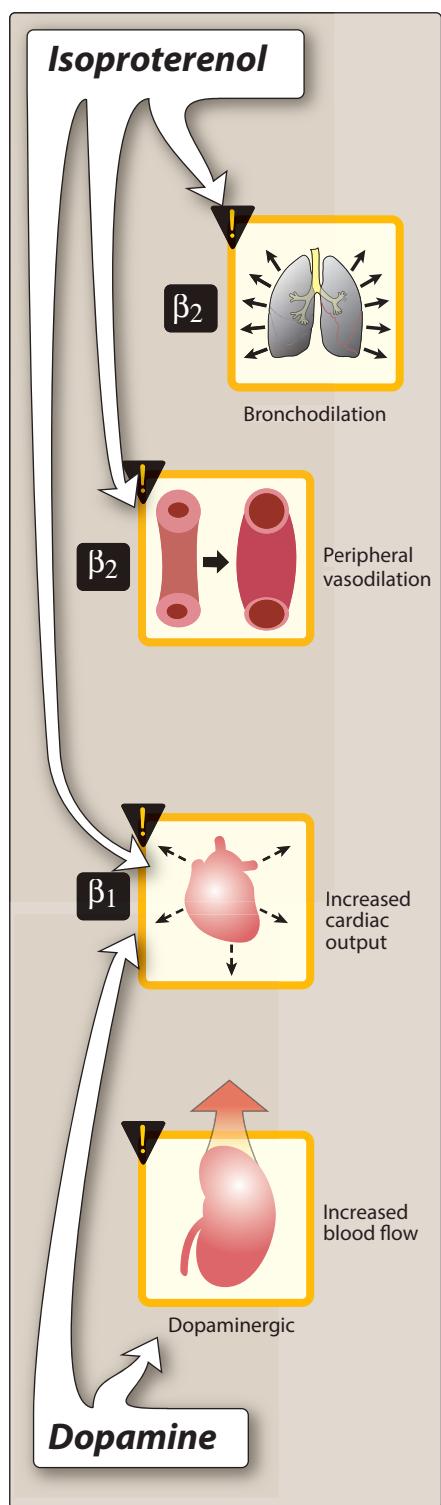
## E. Fenoldopam

*Fenoldopam* [fen-OL-de-pam] is an agonist of peripheral dopamine  $D_1$  receptors. It is used as a rapid-acting vasodilator to treat severe hypertension in hospitalized patients, acting on coronary arteries, kidney arterioles, and mesenteric arteries. *Fenoldopam* is a racemic mixture, and the R-isomer is the active component. It undergoes extensive first-pass metabolism and has a 10-minute elimination half-life after IV infusion. Headache, flushing, dizziness, nausea, vomiting, and tachycardia (due to vasodilation) may occur with this agent.



**Figure 6.12**

Cardiovascular effects of intravenous infusion of isoproterenol.

**Figure 6.13**

Clinically important actions of isoproterenol and dopamine.

## F. Dobutamine

*Dobutamine* [doe-BYOO-ta-meen] is a synthetic, direct-acting catecholamine that is primarily a  $\beta_1$  receptor agonist with minor  $\beta_2$  and  $\alpha_1$  effects. It increases heart rate and cardiac output with few vascular effects. *Dobutamine* is used to increase cardiac output in acute heart failure (see Chapter 18), as well as for inotropic support after cardiac surgery. The drug increases cardiac output and does not elevate oxygen demands of the myocardium as much as other sympathomimetic drugs. *Dobutamine* should be used with caution in atrial fibrillation, because it increases AV conduction. Other adverse effects are similar to *epinephrine*. Tolerance may develop with prolonged use.

## G. Oxymetazoline

*Oxymetazoline* [OX-ee-mee-TAZ-ih-leen] is a direct-acting synthetic adrenergic agonist that stimulates both  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors. *Oxymetazoline* is found in many over-the-counter nasal spray decongestants, as well as in ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, and contact lenses. *Oxymetazoline* directly stimulates  $\alpha$  receptors on blood vessels supplying the nasal mucosa and conjunctiva, thereby producing vasoconstriction and decreasing congestion. It is absorbed in the systemic circulation regardless of the route of administration and may produce nervousness, headaches, and trouble sleeping. Local irritation and sneezing may occur with intranasal administration. Use for greater than 3 days is not recommended, as rebound congestion and dependence may occur.

## H. Phenylephrine

*Phenylephrine* [fen-ill-EF-reen] is a direct-acting, synthetic adrenergic drug that binds primarily to  $\alpha_1$  receptors. *Phenylephrine* is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but, rather, induces reflex bradycardia when given parenterally, making it useful in the treatment of paroxysmal supraventricular tachycardia. The drug is used to treat hypotension in hospitalized or surgical patients (especially those with a rapid heart rate). Large doses can cause hypertensive headache and cardiac irregularities. *Phenylephrine* acts as a nasal decongestant when applied topically or taken orally. Although data suggest it may not be as effective, *phenylephrine* has replaced *pseudoephedrine* in many oral decongestants, since *pseudoephedrine* has been misused to make *methamphetamine*. *Phenylephrine* is also used in ophthalmic solutions for mydriasis.

## I. Midodrine

*Midodrine*, a prodrug, is metabolized to the pharmacologically active desglymidodrine. It is a selective  $\alpha_1$  agonist, which acts in the periphery to increase arterial and venous tone. *Midodrine* is indicated for the treatment of orthostatic hypotension. The drug should be given three times daily, with doses at 3- or 4-hour intervals. To avoid supine hypertension, doses within 4 hours of bedtime are not recommended.

### J. Clonidine

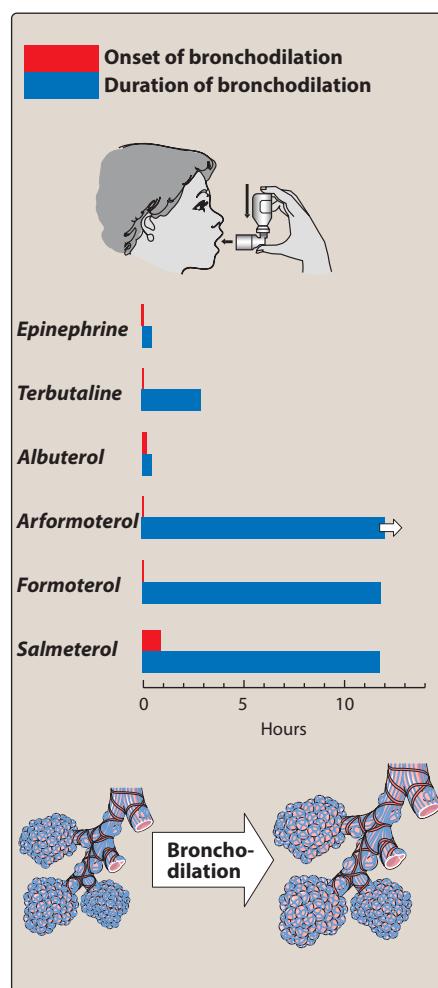
*Clonidine* [KLOE-ni-deen] is an  $\alpha_2$  agonist used for the treatment of hypertension. It can also be used to minimize symptoms of withdrawal from opiates, tobacco smoking, and benzodiazepines. Both *clonidine* and the  $\alpha_2$  agonist *guanfacine* [GWAHN-fa-seen] may be used in the management of attention-deficit hyperactivity disorder. *Clonidine* acts centrally on presynaptic  $\alpha_2$  receptors to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. The most common side effects of *clonidine* are lethargy, sedation, constipation, and xerostomia. Other adverse effects are bradycardia (because of increased vagal stimulation of the SA node as well as sympathetic withdrawal), orthostatic hypotension, and impotence. Fluid retention and edema are problems with chronic therapy; therefore, concurrent therapy with a diuretic is necessary. Abrupt discontinuance must be avoided to prevent rebound hypertension. *Clonidine* and another  $\alpha_2$  agonist *methyldopa* are discussed with antihypertensives in Chapter 16.

### K. Albuterol, metaproterenol, and terbutaline

*Albuterol* [al-BYOO-ter-ole], *metaproterenol* [MET-a-proe-TER-e-nol] and *terbutaline* [ter-BYOO-te-leen] are short-acting  $\beta_2$  agonists (SABAs) used primarily as bronchodilators and administered by a metered-dose inhaler (Figure 6.14). *Albuterol* is the SABA of choice for the management of acute asthma symptoms, because it is more selective for  $\beta_2$  receptors than *metaproterenol*. Inhaled *terbutaline* is no longer available in the United States, but is still used in other countries. Injectable *terbutaline* is used off-label as a uterine relaxant to suppress premature labor, and use for this indication should not exceed 72 hours. One of the most common side effects of these agents is tremor, but patients tend to develop tolerance to this effect. Other side effects include restlessness, apprehension, and anxiety. When these drugs are administered orally, they may cause tachycardia or arrhythmia (due to  $\beta_1$  receptor activation), especially in patients with underlying cardiac disease. Monoamine oxidase inhibitors (MAOIs) also increase the risk of adverse cardiovascular effects, and concomitant use should be avoided.

### L. Salmeterol, formoterol, and indacaterol

*Salmeterol* [sal-ME-ter-ole], *formoterol* [for-MOH-ter-ole], *arformoterol* (the [R,R]-enantiomer of *formoterol*), and *indacaterol* [IN-da-KA-ter-ol] are long-acting  $\beta_2$  selective agonists (LABAs) used for the management of respiratory disorders such as asthma and chronic obstructive pulmonary disease (see Chapter 41). A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for *albuterol*. Unlike *formoterol*, however, *salmeterol* has a somewhat delayed onset of action (Figure 6.14). LABAs are not recommended as monotherapy for the treatment of asthma, because they have been shown to increase the risk of



**Figure 6.14**

Onset and duration of bronchodilation effects of inhaled adrenergic agonists.

asthma-related deaths; however, these agents are highly efficacious when combined with an asthma controller medication such as an inhaled corticosteroid.

#### M. Mirabegron

*Mirabegron* [mir-a-BEG-ron] is a  $\beta_3$  agonist that relaxes the detrusor smooth muscle and increases bladder capacity. It is used for patients with overactive bladder. *Mirabegron* may increase blood pressure and should not be used in patients with uncontrolled hypertension. It increases levels of *digoxin* and inhibits the CYP2D6 isozyme, which may enhance the effects of other medications metabolized by this pathway (for example, *metoprolol*).

### V. INDIRECT-ACTING ADRENERGIC AGONISTS

Indirect-acting adrenergic agonists cause the release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine (Figure 6.8). They potentiate the effects of epinephrine or norepinephrine produced endogenously, but do not directly affect postsynaptic receptors.

#### A. Amphetamine

The marked central stimulatory action of *amphetamine* [am-FET-a-meen] is often mistaken by drug abusers as its only action. However, the drug can also increase blood pressure significantly by  $\alpha_1$  agonist action on the vasculature, as well as  $\beta_1$ -stimulatory effects on the heart. Its actions are mediated primarily through an increase in non-vesicular release of catecholamines such as dopamine and norepinephrine from nerve terminals. Thus, *amphetamine* is an indirect-acting adrenergic drug. The actions and therapeutic uses of *amphetamine* and its derivatives are discussed with CNS stimulants (see Chapter 15).

#### B. Tyramine

*Tyramine* [TIE-ra-meen] is not a clinically useful drug, but it is important because it is found in fermented foods, such as aged cheese and Chianti wine. It is a normal by-product of tyrosine metabolism. Normally, it is oxidized by MAO in the gastrointestinal tract, but, if the patient is taking MAOIs, it can precipitate serious vasoconstrictor episodes. Like *amphetamines*, *tyramine* can enter the nerve terminal and displace stored norepinephrine. The released catecholamine then acts on adrenoceptors.

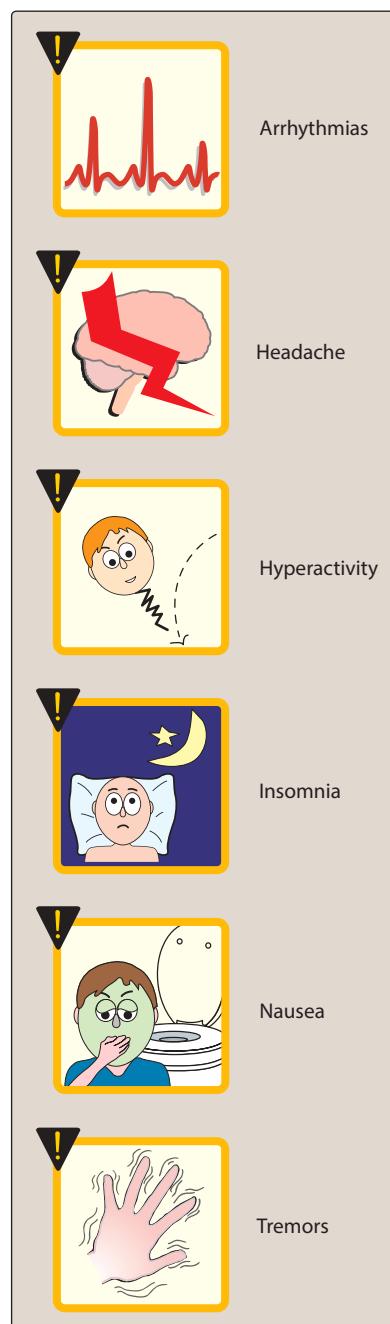
#### C. Cocaine

*Cocaine* [koe-KANE] is unique among local anesthetics in having the ability to block the sodium-chloride ( $\text{Na}^+/\text{Cl}^-$ )-dependent norepinephrine transporter required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Therefore, small doses of the catecholamines produce

greatly magnified effects in an individual taking cocaine. In addition, the duration of action of epinephrine and norepinephrine is increased. Like amphetamines, it can increase blood pressure by  $\alpha_1$  agonist actions and  $\beta$  stimulatory effects. Cocaine as a drug of abuse is discussed in Chapter 48.

## VI. MIXED-ACTION ADRENERGIC AGONISTS

*Ephedrine* [eh-FED-rin] and *pseudoephedrine* [soo-doe-eh-FED-rin] are mixed-action adrenergic agents. They not only enhance release of stored norepinephrine from nerve endings (Figure 6.8) but also directly stimulate both  $\alpha$  and  $\beta$  receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of epinephrine, although less potent. *Ephedrine* and *pseudoephedrine* are not catecholamines and are poor substrates for COMT and MAO. Therefore, these drugs have a long duration of action. *Ephedrine* and *pseudoephedrine* have excellent absorption after oral administration and penetrate the CNS, but *pseudoephedrine* has fewer CNS effects. *Ephedrine* is eliminated largely unchanged in urine, and *pseudoephedrine* undergoes incomplete hepatic metabolism before elimination in urine. *Ephedrine* raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation and it is indicated in anesthesia-induced hypotension. *Ephedrine* produces bronchodilation, but it is less potent and slower acting than *epinephrine* or *isoproterenol*. It was previously used to prevent asthma attacks but has been replaced by more effective medications. *Ephedrine* produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. [Note: The clinical use of *ephedrine* is declining because of the availability of better, more potent agents that cause fewer adverse effects. *Ephedrine*-containing herbal supplements (mainly ephedra-containing products) have been banned by most drug regulatory authorities because of life-threatening cardiovascular reactions.] Oral *pseudoephedrine* is primarily used to treat nasal and sinus congestion. *Pseudoephedrine* has been illegally used to produce *methamphetamine*. Therefore, products containing *pseudoephedrine* have certain restrictions and must be kept behind the sales counter in the United States. Important characteristics of the adrenergic agonists are summarized in Figures 6.15 to 6.17.



**Figure 6.15**

Some adverse effects observed with adrenergic agonists.

TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart	$\beta_1$	$\uparrow$ Automaticity	Cholinergic receptors
		$\uparrow$ Conduction velocity, automaticity	
		$\uparrow$ Contractility, automaticity	
Vascular smooth muscle	$\beta_2$	Vasodilation	$\alpha$ -Adrenergic receptors
Bronchial smooth muscle	$\beta_2$	Bronchodilation	Cholinergic receptors
Kidneys	$\beta_1$	$\uparrow$ Renin release	$\alpha_1$ -Adrenergic receptors
Liver	$\beta_2, \alpha_1$	$\uparrow$ Glycogenolysis and gluconeogenesis	—
Adipose tissue	$\beta_3$	$\uparrow$ Lipolysis	$\alpha_2$ -Adrenergic receptors
Skeletal muscle	$\beta_2$	Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor	—
Eye-ciliary muscle	$\beta_2$	Relaxation	Cholinergic receptors
GI tract	$\beta_2$	$\downarrow$ Motility	Cholinergic receptors
Gall bladder	$\beta_2$	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	$\beta_2, \beta_3$	Relaxation	Cholinergic receptors
Uterus	$\beta_2$	Relaxation	Oxytocin

AV = atrioventricular; GI = gastrointestinal.

**Figure 6.16**

Summary of  $\beta$ -adrenergic receptors.

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
<i>Epinephrine</i>	$\alpha_1, \alpha_2$ $\beta_1, \beta_2$	Anaphylactic shock Cardiac arrest In local anesthetics to increase duration of action
<i>Norepinephrine</i>	$\alpha_1, \alpha_2$ $\beta_1$	Treatment of shock
<i>Isoproterenol</i>	$\beta_1, \beta_2$	As a cardiac stimulant
<i>Dopamine</i>	Dopaminergic $\alpha_1, \beta_1$	Treatment of shock Treatment of congestive heart failure Raise blood pressure
<i>Dobutamine</i>	$\beta_1$	Treatment of acute heart failure
<i>Oxymetazoline</i>	$\alpha_1$	As a nasal decongestant
<i>Phenylephrine</i>	$\alpha_1$	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
<i>Clonidine</i>	$\alpha_2$	Treatment of hypertension
<i>Albuterol</i> <i>Metaproterenol</i> <i>Terbutaline</i>	$\beta_2$	Treatment of bronchospasm (short acting)
<i>Arformoterol</i> <i>Formoterol</i> <i>Indacaterol</i> <i>Salmeterol</i>	$\beta_2$	Treatment of bronchospasm (long acting)
<i>Amphetamine</i>	$\alpha, \beta$ , CNS	As a CNS stimulant in treatment of children with ADHD, narcolepsy, and for appetite control
<i>Ephedrine</i> <i>Pseudoephedrine</i>	$\alpha, \beta$ , CNS	Raise blood pressure As a nasal decongestant

ADHD = attention-deficit hyperactivity disorder; CNS = central nervous system.

**Figure 6.17**

Summary of the therapeutic uses of adrenergic agonists.

## Study Questions

**Choose the ONE best answer.**

6.1 Which of the following is correct regarding adrenergic neurotransmission?

- A. Norepinephrine is the major neurotransmitter released from sympathetic nerve terminals.
- B. Norepinephrine is mainly released from the adrenal glands.
- C. Tricyclic antidepressants and cocaine prevent the release of norepinephrine from the nerve terminals.
- D. Monoamine oxidase (MAO) converts dopamine to norepinephrine in the nerve terminal.

6.2 Which of the following adrenergic drugs is used in the treatment of overactive bladder?

- A. Epinephrine
- B. Dobutamine
- C. Phenylephrine
- D. Mirabegron

6.3 Which of the following classes of adrenergic agents has utility in the management of hypertension?

- A.  $\alpha_1$  agonist
- B.  $\alpha_2$  agonist
- C.  $\beta_1$  agonist
- D.  $\beta_3$  agonist

6.4 Which of the following is correct regarding responses mediated by adrenergic receptors?

- A. Stimulation of  $\alpha_1$  receptors increases blood pressure.
- B. Stimulation of sympathetic presynaptic  $\alpha_2$  receptors increases norepinephrine release.
- C. Stimulation of  $\beta_2$  receptors increases heart rate (tachycardia).
- D. Stimulation of  $\beta_2$  receptors causes bronchoconstriction.

Correct answer = A. Norepinephrine (NE) is the major neurotransmitter released from sympathetic nerve terminals. Epinephrine, not norepinephrine, is mainly released from the adrenal glands. Tricyclic antidepressants (TCAs) and cocaine inhibit the reuptake of norepinephrine into the sympathetic nerve terminals, but they do not prevent the release of NE. Dopamine is converted to norepinephrine by dopamine  $\beta$ -hydroxylase, not by MAO.

Correct answer = D. Detrusor muscles in the urinary bladder wall have  $\beta_3$  receptors. Stimulation of these receptors relaxes the urinary bladder wall and relieves overactive bladder. Mirabegron is a  $\beta_3$  agonist and therefore used in treating overactive bladder. None of the other drugs listed have  $\beta_3$  agonist activity.

Correct answer = B.  $\alpha_2$  agonists activate  $\alpha_2$  receptors located in the presynaptic terminal of sympathetic neurons and cause a reduction in the release of norepinephrine from sympathetic nerve terminals. This leads to a reduction in blood pressure.  $\alpha_2$  agonists such as clonidine and methyldopa are therefore used as antihypertensive agents.  $\alpha_1$  agonists cause vasoconstriction, and  $\beta_1$  agonists cause increased cardiac output and renin release, so these agents may increase blood pressure.  $\beta_3$  agonists are not used in the management of hypertension.

Correct answer = A. Stimulation of  $\alpha_1$  receptors, mostly found in the blood vessels, causes vasoconstriction and an increase in blood pressure. Stimulation of  $\alpha_2$  receptors on the sympathetic presynaptic terminal reduces the release of norepinephrine.  $\beta_2$  receptors are not found in the heart, so activation of  $\beta_2$  receptors does not affect heart rate. Stimulation of  $\beta_2$  receptors found in the bronchial tissues causes bronchodilation, not bronchoconstriction.

- 6.5 An asthma patient was given a nonselective  $\beta$  agonist to relieve bronchoconstriction. Which adverse effect would you expect in this patient?
- A. Bradycardia
  - B. Tachycardia
  - C. Hypotension (reduction in blood pressure)
  - D. Worsening bronchoconstriction
- 6.6 A 22-year-old male is brought to the emergency room with suspected cocaine overdose. Which of the following symptoms is most likely in this patient?
- A. Hypertension
  - B. Bronchoconstriction
  - C. Bradycardia
  - D. Miosis (constriction of pupil).
- 6.7 A 12-year-old boy with a peanut allergy is brought to the emergency room after accidental consumption of peanuts. He is in anaphylactic shock. Which of the following drugs is most appropriate to treat this patient?
- A. Norepinephrine
  - B. Phenylephrine
  - C. Dobutamine
  - D. Epinephrine
- 6.8 An elderly patient is brought to the emergency room with a blood pressure of 76/60 mm Hg, tachycardia, and low cardiac output. He is diagnosed with acute heart failure. Which of the following drugs is most appropriate to improve his cardiac function?
- A. Epinephrine
  - B. Fenoldopam
  - C. Dobutamine
  - D. Isoproterenol
- 6.9 Which of the following adrenergic agonists is commonly present in nasal sprays available over-the-counter (OTC) to treat nasal congestion?
- A. Clonidine
  - B. Albuterol
  - C. Oxymetazoline
  - D. Formoterol

Correct answer = B. A nonselective  $\beta$  agonist activates both  $\beta_1$  and  $\beta_2$  receptors.  $\beta_1$  activation causes an increase in heart rate (tachycardia), contractility, and subsequent increase in blood pressure. It relieves bronchoconstriction because of the  $\beta_2$  receptor activation.

Correct answer = A. Cocaine is an indirect adrenergic agonist that prevents the reuptake of norepinephrine into the nerve terminals, thus increasing the levels of NE in the synaptic cleft. The increase in NE leads to an increase in blood pressure (hypertension), tachycardia (not bradycardia), mydriasis (not miosis) and other symptoms of sympathetic overactivity.

Correct answer = D. Norepinephrine has more  $\alpha$  agonistic effects and activates mainly  $\alpha_1$ ,  $\alpha_2$ , and  $\beta_1$  receptors. Epinephrine has more  $\beta$  agonistic effects and activates mainly  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ , and  $\beta_2$  receptors. Phenylephrine has predominantly  $\alpha$  effects and activates mainly  $\alpha_1$  receptors. Dobutamine mainly activates  $\beta_1$  receptors and has no significant effects on  $\beta_2$  receptors. Thus, epinephrine is the drug of choice in anaphylactic shock that can both stimulate the heart ( $\beta_1$  activation) and dilate bronchioles ( $\beta_2$  activation).

Correct answer = C. Among the choices, the ideal drug to increase contractility in acute heart failure is dobutamine, since it is a selective  $\beta_1$ -adrenergic agonist. Fenoldopam is a dopamine agonist used to treat severe hypertension. The other drugs are nonselective adrenergic agonists that could cause unwanted side effects.

Correct answer = C. Drugs with selective  $\alpha_1$  agonistic activity are commonly used as nasal decongestants because of their ability to cause vasoconstriction in the nasal vessels. Oxymetazoline is an  $\alpha_1$  agonist and therefore the preferred drug among the choices as a nasal decongestant. Clonidine is an  $\alpha_2$  agonist, albuterol is a  $\beta_2$  agonist, and formoterol is a long-acting  $\beta_2$  agonist.

6.10 A patient who has hypertension and mild asthma attacks bought an herbal remedy for asthma online. He does not take any prescription medications for asthma, but takes a  $\beta_1$ -selective blocker for hypertension. The herbal remedy relieves the asthma attacks, but his blood pressure seems to increase despite the  $\beta$ -blocker therapy. Which of the following drugs is most likely present in the herbal remedy?

- A. Phenylephrine
- B. Norepinephrine
- C. Ephedrine
- D. Salmeterol

Correct answer = C. Both ephedrine and salmeterol can relieve asthma symptoms, as they activate  $\beta_2$  receptors in the bronchioles and cause bronchodilation. However, salmeterol is a selective  $\beta_2$  agonist and should not increase blood pressure. By contrast, ephedrine stimulates the release of norepinephrine and acts as a direct agonist at  $\alpha$ - and  $\beta$ -adrenergic receptors, thus causing an increase in blood pressure. Phenylephrine (a nonselective  $\alpha$  agonist) does not cause bronchodilation, so it would not relieve asthma symptoms. Norepinephrine is a nonselective adrenergic agonist that does not have any stimulatory effects on  $\beta_2$  receptors. In addition, norepinephrine is not active when given orally.

# Adrenergic Antagonists

7

Rajan Radhakrishnan and Sandhya Jinesh

## I. OVERVIEW

The adrenergic antagonists (also called adrenergic blockers or sympatholytics) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the adrenoceptors, thus preventing activation by endogenous or exogenous agonists. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for  $\alpha$  or  $\beta$  receptors in the sympathetic nervous system. Adrenergic antagonists have varying degrees of specificity and are therefore classified into five: 1) nonselective adrenergic antagonists, 2) and 3) nonselective  $\alpha$ - and  $\beta$ -adrenergic antagonists, and 4) and 5) selective  $\alpha_1$ - and  $\beta$ -adrenergic antagonists.

Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system. [Note: Antagonists that block dopamine receptors are most important in the central nervous system (CNS) and are, therefore, considered in Unit III, Drugs Affecting the Central Nervous System.] The adrenergic antagonists discussed in this chapter are summarized in [Figure 7.1](#).

## II. $\alpha$ -ADRENERGIC BLOCKING AGENTS

$\alpha$ -Adrenergic blocking agents antagonize the subtype(s) of  $\alpha$ -adrenergic receptors ( $\alpha_1$  or  $\alpha_2$ ), depending on the specificity of the agent for the receptor subtype(s). Drugs that block  $\alpha_1$  adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on  $\alpha_1$ -adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This lowered blood pressure induces reflex tachycardia. The magnitude of the response depends on the sympathetic tone of the individual when the agent is given. Selective  $\alpha_2$ -adrenergic blockers have limited clinical utility.

### A. Phenoxybenzamine

*Phenoxybenzamine* [fen-ox-ee-BEN-za-meen] is a nonselective, irreversible, noncompetitive blocker of  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors. The body can overcome the block by synthesis of the new adrenoceptors, which requires a day or longer. Therefore, the action of *phenoxybenzamine* last about 24 hours.

### $\alpha$ -BLOCKERS

#### Nonselective

*Phenoxybenzamine (irreversible)*

*Phentolamine*

#### $\alpha_1$ Selective

*Prazosin*

*Doxazosin*

*Terazosin*

*Alfuzosin*

#### $\alpha_{1A}$ Selective

*Tamsulosin*

#### $\alpha_2$ Selective

*Yohimbine*

### $\beta$ -BLOCKERS

#### Nonselective $\beta_1$ and $\beta_2$

*Propranolol*

*Carvedilol*

*Labetolol*

*Nadolol*

*Penbutolol*

*Pindolol*

*Sotalol*

*Timolol*

*Carteolol*

#### $\beta_1$ Selective

*Atenolol*

*Metoprolol*

*Betaxolol*

*Bisoprolol*

*Celiprolol*

*Esmolol (ultra short acting)*

*Nabivolol (vasodilatory)*

*Acebutalol (partial agonist)*

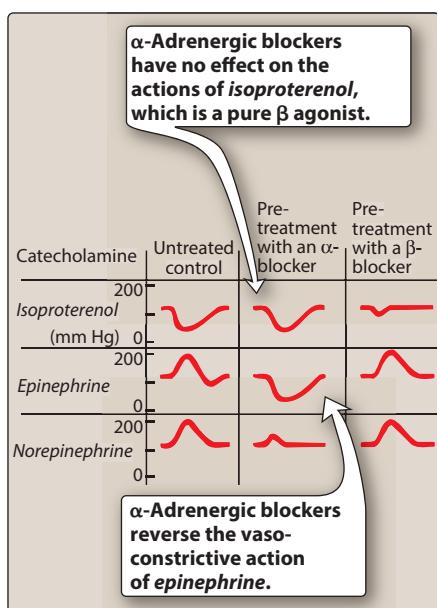
#### $\alpha_1$ and $\beta$ Selective

*Labetalol*

*Carvedilol (at high concentration calcium channel blocker)*

### Figure 7.1

Classes and drugs available of adrenergic antagonists. (For drug dosages, refer to Appendix at the end of the book.)



**Figure 7.2**

Summary of effects of adrenergic blockers on the changes in blood pressure induced by *isoproterenol*, *epinephrine*, and *norepinephrine*.

### 1. Actions:

- Cardiovascular effects:** The drug prevents  $\alpha_1$  receptor vasoconstriction of peripheral blood vessels caused by endogenous catecholamines, which leads to decreased peripheral resistance and resultant reflex tachycardia. However, by blocking presynaptic  $\alpha_2$  receptors on the sympathetic nerve terminals in the heart, *phenoxybenzamine* causes an increase in the release of norepinephrine, which in turn increases heart rate and cardiac output (mediated by  $\beta_1$  receptors). This may also lead to cardiac arrhythmias and anginal pain. Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and it is no longer used for this purpose.
- Epinephrine reversal:** All  $\alpha$ -adrenergic blockers reverse the  $\alpha$  agonist actions of *epinephrine*. For example, the vasoconstrictive action of *epinephrine* is interrupted, but vasodilation of other vascular beds caused by stimulation of  $\beta_2$  receptors is not blocked. Therefore, in the presence of *phenoxybenzamine*, the systemic blood pressure decreases in response to *epinephrine* (Figure 7.2). [Note: The actions of *norepinephrine* are not reversed but are diminished because *norepinephrine* lacks significant  $\beta$  agonist action on the vasculature.] *Phenoxybenzamine* has no effect on the actions of *isoproterenol*, which is a pure  $\beta$  agonist (Figure 7.2).

- Therapeutic uses:** *Phenoxybenzamine* is used in the treatment of sweating and hypertension associated with pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. *Phenoxybenzamine* is sometimes effective in treating Raynaud disease and frostbite.
- Adverse effects:** *Phenoxybenzamine* can cause postural hypotension, nasal stuffiness, nausea, and vomiting. It may inhibit ejaculation. It may also induce reflex tachycardia, which is mediated by the baroreceptor reflex. *Phenoxybenzamine* should be used with caution in patients with cerebrovascular or cardiovascular disease.

### B. Phentolamine

In contrast to *phenoxybenzamine*, *phentolamine* [fen-TOLE-a-meen] produces a competitive block of  $\alpha_1$  and  $\alpha_2$  receptors. Effects last for approximately 4 hours after a single injection. Pharmacological effects of *phentolamine* are very similar to those of *phenoxybenzamine*. *Phentolamine* is used for the diagnosis and short-term management of pheochromocytoma. It is also used locally to prevent dermal necrosis following extravasation of *norepinephrine*. *Phentolamine* is useful to treat hypertensive crisis due to abrupt withdrawal of *clonidine* or ingestion of tyramine-containing foods in patients taking monoamine oxidase inhibitors.

### C. Prazosin, terazosin, and doxazosin

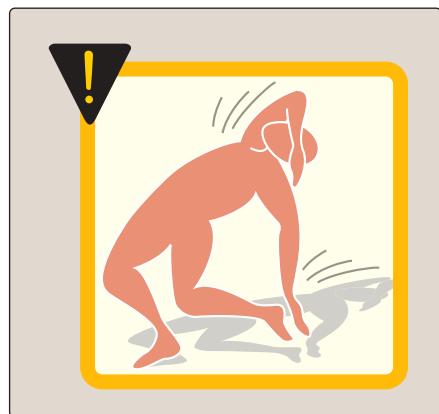
*Prazosin* [PRAY-zoe-sin], *terazosin* [ter-AY-zoe-sin], and *doxazosin* [dox-AY-zoe-sin] are selective competitive blockers of the  $\alpha_1$  receptor.

In contrast to *phenoxybenzamine* and *phentolamine*, they are useful in the treatment of hypertension. [Note: *Tamsulosin* [tam-SUE-loh-sin], *alfuzosin* [al-FYOO-zoe-sin], and *silodosin* [sye-LOE-doe-sin] are examples of other selective  $\alpha_1$  antagonists indicated for the treatment of benign prostatic hyperplasia (see Chapter 43).] Metabolism leads to inactive products that are excreted in urine except for those of *doxazosin*, which appear in feces. *Doxazosin* is the longest acting of these drugs.

- Mechanism of action:** These agents decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle. Unlike *phenoxybenzamine* and *phentolamine*, these drugs cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate. *Tamsulosin*, *alfuzosin*, and *silodosin* have less pronounced effects on blood pressure because they are less selective for  $\alpha_{1B}$  receptors found in the blood vessels and more selective for  $\alpha_{1A}$  receptors in the prostate and bladder. Blockade of the  $\alpha_{1A}$  receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow.
- Therapeutic uses:** Individuals with elevated blood pressure treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs may produce an exaggerated orthostatic hypotensive response (Figure 7.3) that can result in syncope (fainting). This action, termed a “first-dose” effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime. These drugs may cause modest improvement in lipid profiles and glucose metabolism in hypertensive patients. Because of inferior cardiovascular outcomes as compared to other antihypertensives,  $\alpha_1$  antagonists are not used as monotherapy for the treatment of hypertension (see Chapter 16).
- Adverse effects:**  $\alpha_1$ -Blockers such as *prazosin* and *doxazosin* may cause dizziness, lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension (although to a lesser degree than that observed with *phenoxybenzamine* and *phentolamine*). An additive antihypertensive effect occurs when  $\alpha_1$  antagonists are given with vasodilators such as nitrates or PDE-5 inhibitors (for example, *sildenafil*), thereby necessitating cautious dose titration and use at the lowest possible doses. These agents may cause “floppy iris syndrome,” a condition in which the iris billows in response to intraoperative eye surgery. Figure 7.4 summarizes some adverse effects observed with  $\alpha$ -blockers.

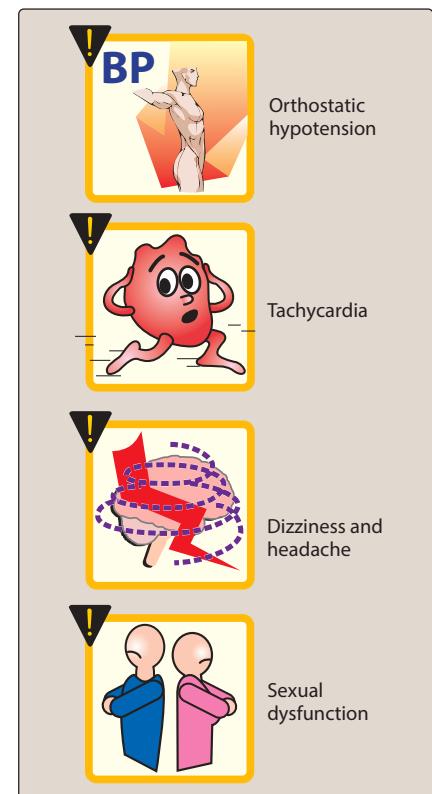
#### D. Yohimbine

*Yohimbine* [yo-HIM-bean] is a selective competitive  $\alpha_2$ -blocker that works at the level of the CNS to increase sympathetic outflow to the periphery. It is found as a component of the bark of the yohimbe tree (*Pausinystalia yohimbe*) and has been used as a sexual stimulant and in the treatment of erectile dysfunction. Its use in the treatment of these disorders is not recommended due to lack of demonstrated efficacy.



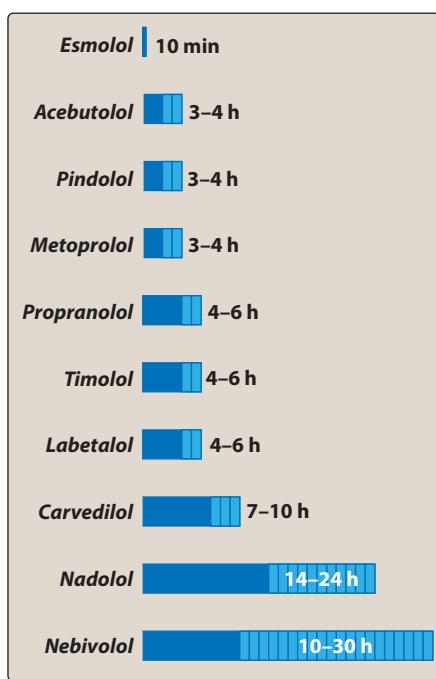
**Figure 7.3**

First dose of  $\alpha_1$  receptor blocker may produce an orthostatic hypotensive response that can result in syncope (fainting).



**Figure 7.4**

Some adverse effects commonly observed with nonselective  $\alpha$ -adrenergic blocking agents.

**Figure 7.5**

Elimination half-lives for some  $\beta$ -blockers.

### III. $\beta$ -ADRENERGIC BLOCKING AGENTS

All of the clinically available  $\beta$ -blockers are competitive antagonists. Nonselective  $\beta$ -blockers act at both  $\beta_1$  and  $\beta_2$  receptors, whereas cardioselective  $\beta$  antagonists primarily block  $\beta_1$  receptors. [Note: There are no clinically useful  $\beta_2$  selective antagonists.] These drugs also differ in intrinsic sympathomimetic activity, CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics (Figure 7.5). Although all  $\beta$ -blockers lower blood pressure, they do not induce postural hypotension, because the  $\alpha$  adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained.  $\beta$ -Blockers are effective in treating systemic as well as portal hypertension, angina, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism, and glaucoma. They are also used for the prophylaxis of migraine headaches. [Note: The names of all  $\beta$ -blockers end in “-olol” except for *labetalol* and *carvedilol*.]

#### A. Propranolol: A nonselective $\beta$ antagonist

*Propranolol* [proe-PRAN-oh-lole] is the prototype  $\beta$ -adrenergic antagonist and blocks both  $\beta_1$  and  $\beta_2$  receptors with equal affinity. Sustained-release preparations for once-a-day dosing are available. Nonselective  $\beta$ -blockers, including *propranolol*, have the ability to block the actions of *isoproterenol* ( $\beta_1$ ,  $\beta_2$  agonist) on the cardiovascular system. Thus, in the presence of a  $\beta$ -blocker, *isoproterenol* does not produce cardiac stimulation ( $\beta_1$  mediated) or reductions in mean arterial pressure and diastolic pressure ( $\beta_2$  mediated; Figure 7.2). [Note: In the presence of a nonselective  $\beta$ -blocker, *epinephrine* no longer lowers diastolic blood pressure or stimulates the heart, but its vasoconstrictive action (mediated by  $\alpha$  receptors) remains unimpaired. The actions of *norepinephrine* on the cardiovascular system are mediated primarily by  $\alpha$  receptors and are, therefore, mostly unaffected.]

##### 1. Actions:

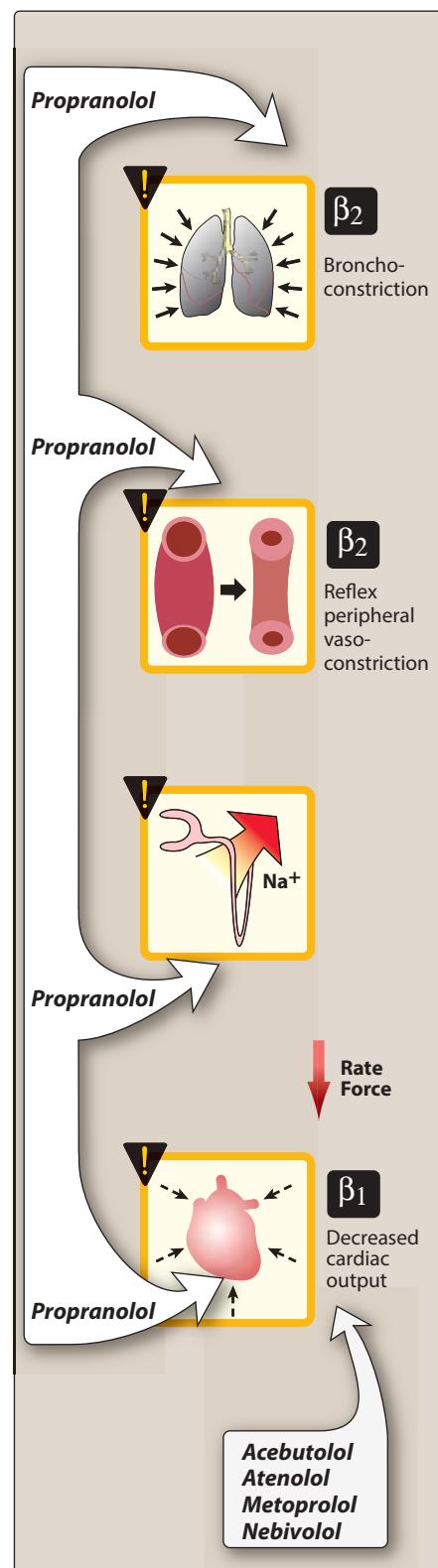
- Cardiovascular:** *Propranolol* diminishes cardiac output, having both negative inotropic and chronotropic effects (Figure 7.6). It directly depresses sinoatrial and atrioventricular nodal activity. The resulting bradycardia usually limits the dose of the drug. During exercise or stress, when the sympathetic nervous system is activated,  $\beta$ -blockers attenuate the expected increase in heart rate. Cardiac output, workload, and oxygen consumption are decreased by blockade of  $\beta_1$  receptors, and these effects are useful in the treatment of angina (see Chapter 20). The  $\beta$ -blockers are effective in attenuating supraventricular cardiac arrhythmias, but generally are not effective against ventricular arrhythmias (except those induced by exercise).
- Peripheral vasoconstriction:** Nonselective blockade of  $\beta$  receptors prevents  $\beta_2$ -mediated vasodilation in skeletal muscles, increasing peripheral vascular resistance (Figure 7.6). The reduction in cardiac output produced by all  $\beta$ -blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. In patients with hypertension, total peripheral resistance returns to normal or decreases with long-term use of propranolol as a result of down-regulation of the  $\beta$  receptors.

There is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

- c. **Bronchoconstriction:** Blocking  $\beta_2$  receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle (Figure 7.6). This can precipitate an exacerbation in patients with chronic obstructive pulmonary disease (COPD) or asthma. Therefore,  $\beta$ -blockers, particularly nonselective ones, are contraindicated in patients with asthma and should be avoided in COPD.
- d. **Disturbances in glucose metabolism:**  $\beta$  Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Therefore, if *propranolol* is given to a diabetic patient receiving *insulin*, careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after *insulin* injection.  $\beta$ -Blockers also attenuate the normal physiologic response to hypoglycemia. [Note: Diaphoresis with hypoglycemia still occurs, as this is mediated through the neurotransmitter acetylcholine.]

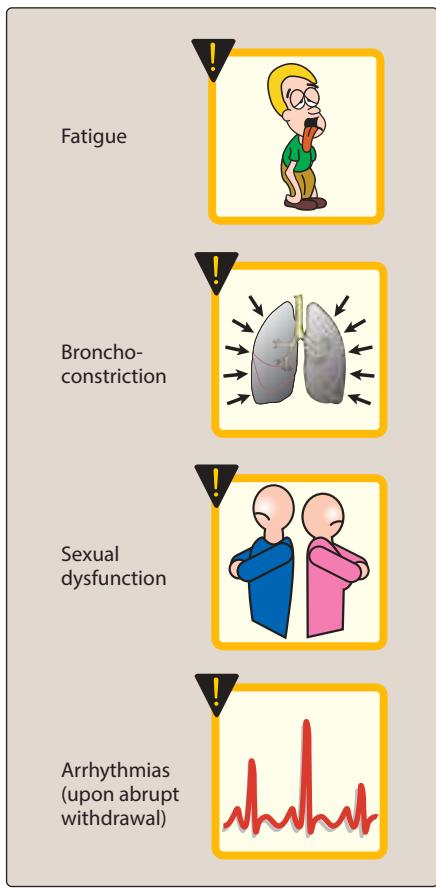
## 2. Therapeutic uses:

- a. **Hypertension:** *Propranolol* does not reduce blood pressure in people with normal blood pressure. *Propranolol* lowers blood pressure in hypertension by several different mechanisms of action. Decreased cardiac output is the primary mechanism, but inhibition of renin release from the kidney, decrease in total peripheral resistance with long-term use, and decreased sympathetic outflow from the CNS also contribute to the anti-hypertensive effects (see Chapter 16).
- b. **Angina pectoris:** *Propranolol* decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing chest pain on exertion that is common in angina. *Propranolol* is therefore useful in the management of chronic stable angina.
- c. **Myocardial infarction:** *Propranolol* and other  $\beta$ -blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction seem to be protected against a second heart attack by prophylactic use of  $\beta$ -blockers. In addition, administration of a  $\beta$ -blocker immediately following a myocardial infarction reduces infarct size and early mortality. The mechanism for these effects may be a reduction in the actions of circulating catecholamines that increase the oxygen demand in an already ischemic heart muscle. *Propranolol* also reduces the incidence of sudden arrhythmic death after myocardial infarction.
- d. **Migraine:** *Propranolol* is effective in reducing migraine episodes when used prophylactically (see Chapter 40). It is one of the more useful  $\beta$ -blockers for this indication, due to its lipophilic nature that allows it to penetrate the CNS. [Note: For the acute management of migraine, serotonin agonists such as *sumatriptan* are used, as well as other drugs.]
- e. **Hyperthyroidism:** *Propranolol* and other  $\beta$ -blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm),  $\beta$ -blockers may be lifesaving in protecting against serious cardiac arrhythmias.



**Figure 7.6**

Actions of *propranolol* and other  $\beta$ -blockers.

**Figure 7.7**

Adverse effects commonly observed in individuals treated with *propranolol*.

**3. Pharmacokinetics:** After oral administration, *propranolol* is almost completely absorbed. It is subject to first-pass effect, and only about 25% of an administered dose reaches the circulation. The volume of distribution of *propranolol* is quite large (4 L/kg), and the drug readily crosses the blood–brain barrier due to its high lipophilicity. *Propranolol* is extensively metabolized, and most metabolites are excreted in the urine.

**4. Adverse effects:**

- Bronchoconstriction:** *Propranolol* has the potential to cause significant bronchoconstriction due to blockade of  $\beta_2$  receptors (Figure 7.7). Death by asphyxiation has been reported for patients with asthma whom were inadvertently administered the drug. Therefore, *propranolol* is contraindicated in patients with COPD or asthma.
- Arrhythmias:** Treatment with  $\beta$ -blockers must never be stopped abruptly because of the risk of precipitating cardiac arrhythmias, which may be severe. The  $\beta$ -blockers must be tapered off gradually over a period of at least a few weeks. Long-term treatment with a  $\beta$  antagonist leads to up-regulation of the  $\beta$  receptor. On suspension of therapy, the increased receptors can precipitate worsened angina or hypertension through action of endogenous catecholamines on the up-regulated  $\beta$  receptors.
- Sexual impairment:** Impaired sexual activity has been reported in male patients taking propranolol. The reasons for this are not clear and may be independent of  $\beta$  receptor blockade. However,  $\beta$  blockers do not affect ejaculation (mediated by  $\alpha$  receptors).
- Metabolic disturbances:**  $\beta$  Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. In addition,  $\beta$ -blockers can prevent the counter-regulatory effects of catecholamines during hypoglycemia. Thus, the perception of symptoms of hypoglycemia such as tremor, tachycardia, and nervousness are blunted by  $\beta$ -blockers. A major role of  $\beta$  receptors is to mobilize energy molecules such as free fatty acids. [Note: Lipases in fat cells are activated mainly by  $\beta_2$  and  $\beta_3$  receptor stimulation, leading to the metabolism of triglycerides into free fatty acids.] Patients administered nonselective  $\beta$ -blockers have increased low-density lipoprotein (“bad” cholesterol), increased triglycerides, and reduced high-density lipoprotein (“good” cholesterol) through  $\beta_2$  blockade. These effects on the serum lipid profile may be less pronounced with the use of  $\beta_1$ -selective antagonists such as *metoprolol*.
- CNS effects:** *Propranolol* has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), and depression. Fewer CNS effects may be seen with more hydrophilic  $\beta$ -blockers (for example, *atenolol*) because they do not cross the blood–brain barrier as readily.
- Drug interactions:** Drugs that interfere with, or inhibit, the metabolism of *propranolol*, such as *cimetidine*, *fluoxetine*,

*paroxetine*, and *ritonavir*, may potentiate its antihypertensive effects. Conversely, those that stimulate or induce its metabolism, such as barbiturates, *phenytoin*, and *rifampin*, can decrease its effects. Nonselective  $\beta$ -blockers such as *propranolol* may prevent the rescue effects of *epinephrine* in anaphylaxis.

### B. Nadolol and timolol: Nonselective $\beta$ antagonists

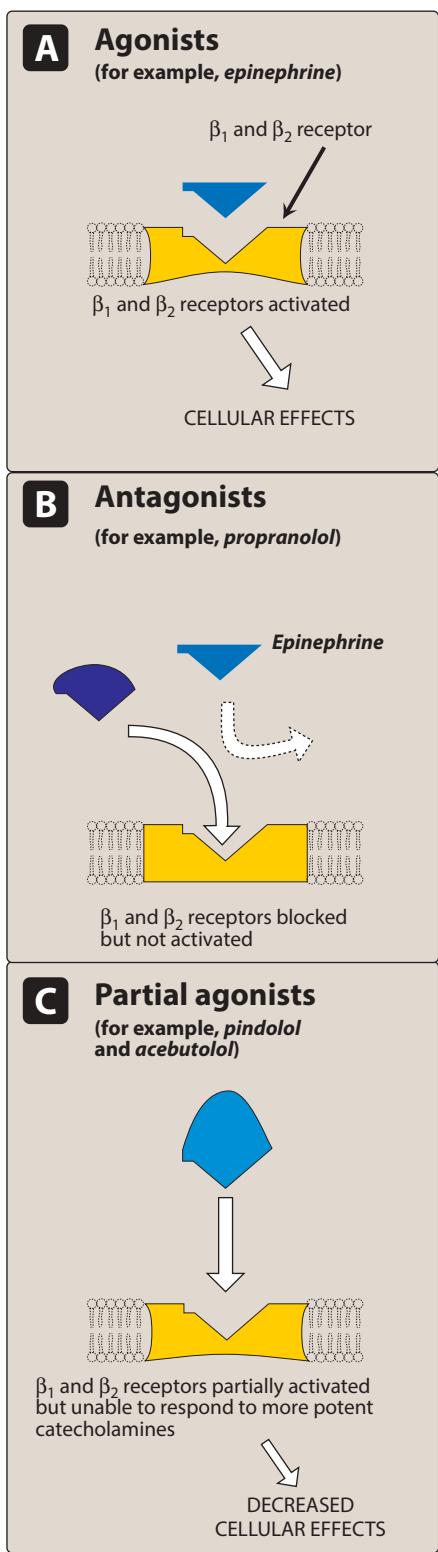
*Nadolol* [NAH-doh-lole] and *timolol* [TIM-o-lole] also block  $\beta_1$ - and  $\beta_2$ -adrenoceptors and are more potent than *propranolol*. *Nadolol* has a very long duration of action (Figure 7.5). *Timolol* reduces the production of aqueous humor in the eye. It is used topically in the treatment of chronic open-angle glaucoma.

**1. Treatment of glaucoma:**  $\beta$ -Blockers, such as topically applied *timolol*, are effective in diminishing intraocular pressure in glaucoma (Figure 7.8). This occurs by decreasing the secretion of aqueous humor by the ciliary body. *Carteolol* [kar-TEE-oh-lole], *levobunolol* [lee-voe-BYOO-noe-lole], and *metipranolol* [met-i-PRAN-oh-lole] are nonselective  $\beta$  antagonists, whereas *betaxolol* [be-TAKS-oh-lole] is a  $\beta_1$ -selective agent. Unlike the cholinergic drugs, these agents neither affect the ability of the eye to focus for near vision nor change pupil size. When administered intraocularly, the onset is about 30 minutes, and the effects last for 12 to 24 hours. The  $\beta$ -blockers are only used for chronic management of glaucoma. In an acute attack of glaucoma, *pilocarpine* is still the drug of choice for emergency lowering of intraocular pressure. Other agents used in the treatment of glaucoma are summarized in Figure 7.8.

CLASS OF DRUG	DRUG NAMES	MECHANISM OF ACTION	SIDE EFFECTS
$\beta$ -Adrenergic antagonists (topical)	<i>Betaxolol, carteolol, levobunolol, metipranolol, timolol</i>	Decrease of aqueous humor production	Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure
$\alpha$ -Adrenergic agonists (topical)	<i>Apraclonidine, brimonidine</i>	Decrease of aqueous humor production and increase of aqueous outflow	Red eye and ocular irritation, allergic reactions, malaise, and headache
Cholinergic agonists (topical)	<i>Pilocarpine, carbachol</i>	Increase of aqueous outflow	Eye or brow pain, increased myopia, and decreased vision
Prostaglandin-like analogs (topical)	<i>Latanoprost, travoprost, bimatoprost</i>	Increase of aqueous humor outflow	Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes
Carbonic anhydrase inhibitors (topical and systemic)	<i>Dorzolamide and brinzolamide (topical), acetazolamide, and methazolamide (oral)</i>	Decrease of aqueous humor production	Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs)

**Figure 7.8**

Classes of drugs used to treat glaucoma.

**Figure 7.9**

Comparison of agonists, antagonists, and partial agonists of  $\beta$  adrenoceptors.

### C. Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol: Selective $\beta_1$ antagonists

Drugs that preferentially block the  $\beta_1$  receptors minimize the unwanted bronchoconstriction ( $\beta_2$  effect) seen with the use of non-selective agents in asthma patients. Cardioselective  $\beta$ -blockers, such as *acebutolol* [a-se-BYOO-toe-lole], *atenolol* [a-TEN-oh-lole], and *metoprolol* [me-TOE-proe-lole], antagonize  $\beta_1$  receptors at doses 50- to 100-fold less than those required to block  $\beta_2$  receptors. This cardioselectivity is most pronounced at low doses and is lost at high doses. [Note: Because  $\beta_1$  selectivity of these agents is lost at high doses, they may antagonize  $\beta_2$  receptors.]

- Actions:** These drugs lower blood pressure in hypertension and increase exercise tolerance in angina (Figure 7.6). *Esmolol* [EZ-moe-lole], with a rapid onset of action of 90 seconds, has a very short duration of action (half-life of only 9 to 10 minutes) (Figure 7.5) due to rapid hydrolysis by red blood cell esterase. It is only available intravenously and is used to control blood pressure or heart rhythm in critically ill patients and those undergoing surgery or diagnostic procedures.  $\beta_1$ -Selectivity allows esmolol to be used safely in patients with bronchospastic and vascular disease. In addition to its cardioselective  $\beta$  blockade, *nebivolol* [ne-BIV-oh-lole] releases nitric oxide from endothelial cells and causes vasodilation. In contrast to *propranolol*, the cardioselective  $\beta$ -blockers have fewer effects on pulmonary function, peripheral resistance, and carbohydrate metabolism. Nevertheless, asthma patients treated with these agents must be carefully monitored to make certain that respiratory activity is not compromised. Because these drugs have less effect on peripheral vascular  $\beta_2$  receptors, coldness of extremities (Raynaud phenomenon), a common side effect of  $\beta$ -blockers, is less frequent.
- Therapeutic uses:** The cardioselective  $\beta$ -blockers are useful in hypertensive patients with impaired pulmonary function. These agents are also first-line therapy for chronic stable angina. *Bisoprolol* and the extended-release formulation of *metoprolol* are indicated for the management of chronic heart failure.

### D. Acebutolol and pindolol: Antagonists with partial agonist activity

- Actions:**
  - Cardiovascular:** *Acebutolol* ( $\beta_1$ -selective antagonist) and *pindolol* (nonselective  $\beta$ -blocker) [PIN-doe-lole] are not pure antagonists. These drugs can also weakly stimulate both  $\beta_1$  and  $\beta_2$  receptors (Figure 7.9) and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists stimulate the  $\beta$  receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, epinephrine and norepinephrine. The result of these opposing actions is a diminished effect on reduction of cardiac rate and cardiac output compared to that of  $\beta$ -blockers without ISA.

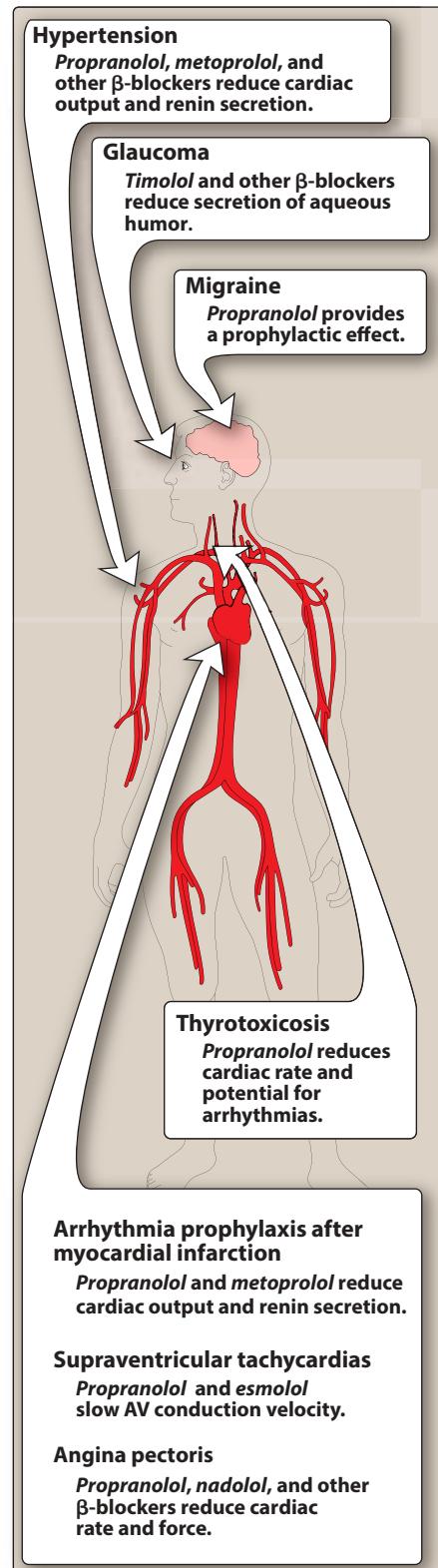
- b. Decreased metabolic effects:**  $\beta$ -Blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism that are seen with other  $\beta$ -blockers. For example, these agents do not decrease plasma HDL levels.
- 2. Therapeutic use:**  $\beta$ -Blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs. [Note:  $\beta$ -Blockers with ISA are not used for stable angina or arrhythmias due to their partial agonist effect.] Overall,  $\beta$ -blockers with ISA are infrequently used in clinical practice. **Figure 7.10** summarizes some of the indications for  $\beta$ -blockers.

## E. Labetalol and carvedilol: Antagonists of both $\alpha$ and $\beta$ adrenoceptors

- 1. Actions:** *Labetalol* [lah-BET-a-lole] and *carvedilol* [CAR-ve-dil-oil] are nonselective  $\beta$ -blockers with concurrent  $\alpha_1$ -blocking actions that produce peripheral vasodilation, thereby reducing blood pressure, and does not cause reflex tachycardia. They contrast with the other  $\beta$ -blockers that produce initial peripheral vasoconstriction, and these agents are, therefore, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. *Carvedilol* also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.
- 2. Therapeutic use in hypertension and heart failure:** *Labetalol* is used as an alternative to *methyldopa* in the treatment of pregnancy-induced hypertension. Intravenous *labetalol* is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure (see Chapter 16). The peak hypotensive effect from intravenous labetalol occurs within 5 to 15 minutes and the duration of action is 4 to 6 hours.  $\beta$ -Blockers should not be given to patients with an acute exacerbation of heart failure, as they can worsen the condition. However, *carvedilol* as well as *metoprolol* and *bisoprolol* are beneficial in patients with stable chronic heart failure. These agents work by blocking the effects of sympathetic stimulation on the heart, which causes worsening heart failure over time (see Chapter 18).
- 3. Adverse effects:** Orthostatic hypotension and dizziness are associated with  $\alpha_1$  blockade. **Figure 7.11** summarizes the receptor specificities and uses of the  $\beta$ -adrenergic antagonists.

## IV. DRUGS AFFECTING NEUROTRANSMITTER RELEASE OR UPTAKE

Some agents act on the adrenergic neuron, either to interfere with neurotransmitter release from storage vesicles or to alter the uptake of the neurotransmitter into the adrenergic neuron. However, due to the advent of newer and more effective agents with fewer side effects, these agents are seldom used therapeutically. *Reserpine* [re-SER-peen] is one of the remaining agents in this category.



**Figure 7.10**

Some clinical applications of  $\beta$ -blockers. AV = atrioventricular.

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
<i>Propranolol</i>	$\beta_1, \beta_2$	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
<i>Nadolol</i> <i>Pindolol</i> <sup>1</sup>	$\beta_1, \beta_2$	Hypertension
<i>Timolol</i>	$\beta_1, \beta_2$	Glaucoma, hypertension
<i>Atenolol</i> <i>Bisoprolol</i> <sup>2</sup> <i>Esmolol</i> <i>Metoprolol</i> <sup>2</sup>	$\beta_1$	Hypertension Angina Myocardial infarction
<i>Acebutolol</i> <sup>1</sup>	$\beta_1$	Hypertension
<i>Nebivolol</i>	$\beta_1$ , NO ↑	Hypertension
<i>Carvedilol</i> <sup>2</sup> <i>Labetalol</i>	$\alpha_1, \beta_1, \beta_2$	Hypertension

NO = nitric oxide.

<sup>1</sup>Acebutolol and pindolol are partial agonists, as well.

<sup>2</sup>Bisoprolol, metoprolol, and carvedilol are also used for the treatment of heart failure.

**Figure 7.11**

Summary of  $\beta$ -adrenergic antagonists.

*Reserpine*, a plant alkaloid, blocks the  $Mg^{2+}$ /adenosine triphosphate-dependent transport of biogenic amines (norepinephrine, dopamine, and serotonin) from the cytoplasm into storage vesicles in the adrenergic nerve terminals in all body tissues. This causes the ultimate depletion of biogenic amines. Sympathetic function, in general, is impaired because of decreased release of norepinephrine. *Reserpine*-mediated depletion of monoamine neurotransmitters in the synapses causes subsequent depression in humans. There has been much concern about *reserpine* causing depression leading to suicide. *Reserpine* has a slow onset, a long duration of action, and effects that persist for many days after discontinuation as it may take the body days to weeks to replenish the depleted vesicular monoamine transporter. It was used for the management of hypertension but has largely been replaced with newer agents with better adverse effect profiles and fewer drug interactions. *Reserpine* passes into breast milk and is harmful to breast-fed infants and should therefore be avoided during breastfeeding if possible. It also produces a dangerous decline in blood pressure at doses needed for treatment.

## Study Questions

Choose the ONE best answer.

- 7.1. A 60-year-old patient started a new antihypertensive medication. His blood pressure is well controlled, but he complains of fatigue, drowsiness, and fainting when he gets up from the bed (orthostatic hypotension). Which of the following drugs is he most likely taking?
- A. Metoprolol
  - B. Propranolol
  - C. Prazosin
  - D. Alfuzosin
- 7.2. A 30-year-old male patient was brought to the ER with amphetamine overdose. He presented with high blood pressure and arrhythmias. Which drug is the most appropriate to treat the cardiovascular symptoms of amphetamine overdose in this patient?
- A. Metoprolol
  - B. Prazosin
  - C. Labetalol
  - D. Nebivolol
- 7.3. A new antihypertensive drug was tested in an animal model of hypertension. The drug when given alone reduces blood pressure in the animal. Norepinephrine when given in the presence of this drug did not cause any significant change in blood pressure or heart rate in the animal. The mechanism of action of the new drug is similar to which of the following agents?
- A. Doxazosin
  - B. Clonidine
  - C. Atenolol
  - D. Carvedilol
- 7.4. A  $\beta$ -blocker was prescribed for hypertension in a patient with asthma. After a week of treatment, the asthma attacks got worse, and the patient was asked to stop taking the  $\beta$ -blocker. Which  $\beta$ -blocker would you suggest as an alternative that is less likely to worsen the asthma?
- A. Propranolol
  - B. Metoprolol
  - C. Labetalol
  - D. Carvedilol

Correct answer = C. Because they block  $\alpha_1$ -mediated vasoconstriction,  $\alpha$ -blockers (prazosin) are more likely to cause orthostatic hypotension, as compared to  $\beta$ -blockers (metoprolol, propranolol). Alfuzosin is a more selective antagonist for  $\alpha_{1A}$  receptors in the prostate and bladder and is less likely to cause hypotension than prazosin.

Correct answer = C. Amphetamine is an indirect adrenergic agonist that mainly enhances the release of norepinephrine from peripheral sympathetic neurons. Therefore, it activates all types of adrenergic receptors (that is,  $\alpha$  and  $\beta$  receptors) and causes an increase in blood pressure. Since both  $\alpha$  and  $\beta$  receptors are activated indirectly by amphetamine,  $\alpha$ -blockers (prazosin) or  $\beta$ -blockers (metoprolol, nebivolol) alone cannot relieve the cardiovascular effects of amphetamine poisoning. Labetalol blocks both  $\alpha_1$  and beta receptors and can minimize the cardiovascular effects of amphetamine overdose.

Correct answer = D. Norepinephrine activates both  $\alpha_1$  and  $\beta_1$  receptors and causes an increase in heart rate and blood pressure. A drug that prevents the increase in blood pressure caused by norepinephrine should be similar to carvedilol that antagonizes both  $\alpha_1$  and  $\beta_1$  receptors. Doxazosin is an  $\alpha_1$  antagonist, clonidine is an  $\alpha_2$  agonist, and atenolol is a  $\beta$  antagonist, and these drugs cannot completely prevent the cardiovascular effects of norepinephrine.

Correct answer = B. The patient was most likely given a nonselective  $\beta$ -blocker (antagonizes both  $\beta_1$  and  $\beta_2$  receptors) that made the asthma worse due to  $\beta_2$  antagonism. An alternative is to prescribe a cardioselective (antagonizes only  $\beta_1$ )  $\beta$ -blocker that does not antagonize  $\beta_2$  receptors in the bronchioles. Metoprolol is a cardioselective  $\beta$ -blocker. Propranolol, labetalol, and carvedilol are nonselective  $\beta$ -blockers and could worsen the asthma.

7.5. A 70-year-old male is treated with doxazosin for overflow incontinence due to his enlarged prostate. He complains of dizzy spells while getting up from bed at night. Which drug would you suggest as an alternative that may not cause dizziness?

- A. Propranolol
- B. Phentolamine
- C. Tamsulosin
- D. Terazosin

Correct answer = C. Dizziness in this elderly patient could be due to orthostatic hypotension caused by doxazosin. Tamsulosin is an  $\alpha_1$  antagonist that is more selective to the  $\alpha_1$  receptor subtype ( $\alpha_{1A}$ ) present in the prostate and less selective to the  $\alpha_1$  receptor subtype ( $\alpha_{1B}$ ) present in the blood vessels. Therefore, tamsulosin should not affect blood pressure significantly and may not cause dizziness. Terazosin and phentolamine antagonize both these subtypes and cause significant hypotension as a side effect. Propranolol is a non-selective beta blocker that is not indicated in overflow incontinence.

7.6. A 50-year-old male was in anaphylactic shock after being stung by a hornet. The medical team tried to reverse the bronchoconstriction and hypotension using epinephrine; however, the patient did not fully respond to the treatment. The patient's wife mentioned that he is taking a prescription medication for blood pressure. Which medication is he most likely taking that contributed to a reduced response to epinephrine?

- A. Doxazosin
- B. Propranolol
- C. Metoprolol
- D. Acebutolol

Correct answer = B. Epinephrine reverses hypotension by activating  $\beta_1$  receptors and relieves bronchoconstriction by activating  $\beta_2$  receptors in anaphylaxis. Since epinephrine was not effective in reversing hypotension or bronchoconstriction in this patient, it could be assumed that the patient was on a nonselective  $\beta$ -blocker (propranolol). Doxazosin ( $\alpha_1$ -blocker), metoprolol, or acebutolol (both  $\beta_1$ -selective blockers) would not have completely prevented the effects of epinephrine.

7.7. Which of the following is correct regarding  $\alpha$ -adrenergic blockers?

- A.  $\alpha$ -Adrenergic blockers are used in the treatment of hypotension in anaphylactic shock.
- B.  $\alpha$ -Adrenergic blockers are used in the treatment of benign prostatic hyperplasia (BPH).
- C.  $\alpha$ -Adrenergic blockers may cause bradycardia.
- D.  $\alpha$ -Adrenergic blockers reduce the frequency of urination.

Correct answer = B.  $\alpha$ -Adrenergic blockers are used in the treatment of BPH because of their relaxant effect on prostate smooth muscles. Being antihypertensive agents, they are not useful in treating hypotension in anaphylaxis.  $\alpha$ -Adrenergic blockers generally cause reflex tachycardia (not bradycardia) due to the significant drop in blood pressure caused by them. They increase (not reduce) the frequency of urination by relaxing the internal sphincter of the urinary bladder, which is controlled by  $\alpha_1$  receptors.

7.8. Which of the following is correct regarding  $\beta$ -blockers?

- A. Treatment with  $\beta$ -blockers should not be stopped abruptly.
- B. Propranolol is a cardioselective  $\beta$ -blocker.
- C. Cardioselective  $\beta$ -blockers worsen asthma.
- D.  $\beta$ -Blockers decrease peripheral resistance by causing vasorelaxation.

Correct answer = A. If  $\beta$ -blocker therapy is stopped abruptly, that could cause angina and rebound hypertension. This could be due to the up-regulation of  $\beta$  receptors in the body.  $\beta$ -Blockers do not cause direct vasorelaxation. Therefore, they do not decrease peripheral resistance with short-term use. Propranolol is a nonselective  $\beta$ -blocker (not cardioselective). Cardioselective  $\beta$ -blockers antagonize only  $\beta_1$  receptors and do not worsen asthma, as they do not antagonize  $\beta_2$  receptors.

7.9. Which of the following drugs is commonly used topically in the treatment of glaucoma?

- A. Esmolol
- B. Timolol
- C. Silodosin
- D. Yohimbine

Correct answer = B.  $\beta$ -Blockers reduce the formation of aqueous humor in the eye and therefore reduce intraocular pressure, thus relieving glaucoma. Timolol is a nonselective  $\beta$ -blocker that is commonly used topically to treat glaucoma. Esmolol is a short-acting  $\beta$ -blocker that is used intravenously for hypertension or arrhythmias. Silodosin is an  $\alpha_1$  antagonist used for BPH, and yohimbine is a  $\alpha_2$  antagonist used for sexual dysfunction.

7.10. Which of the following drugs has the highest potential to worsen orthostatic hypotension when given together with prazosin?

- A. Propranolol
- B. Atenolol
- C. Nebivolol
- D. Labetalol

Correct answer = D. Labetalol is a nonselective  $\beta$ -blocker with  $\alpha_1$ -blocking activity. Prazosin causes orthostatic hypotension due to its  $\alpha_1$  blockade, which could be enhanced by adding labetalol. Propranolol, atenolol, and nebivolol do not have  $\alpha_1$ -blocking effects.



## UNIT III

# Drugs Affecting the Central Nervous System

# Drugs for Neurodegenerative Diseases

Jose A. Rey

8

## I. OVERVIEW

Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process. Drugs affecting the CNS may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors. This chapter provides an overview of the CNS, with a focus on those neurotransmitters that are involved in the actions of the clinically useful CNS drugs. These concepts are useful in understanding the etiology and treatment strategies for the neurodegenerative disorders that respond to drug therapy: Parkinson's disease, Alzheimer's disease, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) (Figure 8.1).

## II. NEUROTRANSMISSION IN THE CNS

The basic functioning of neurons in the CNS is similar to that of the autonomic nervous system (ANS) described in Chapter 3. For example, transmission of information in both the CNS and in the periphery involves the release of neurotransmitters that diffuse across the synaptic cleft to bind to specific receptors on the postsynaptic neuron. In both systems, the recognition of the neurotransmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes. However, several major differences exist between neurons in the peripheral ANS and those in the CNS. The circuitry of the CNS is more complex than that of the ANS, and the number of synapses in the CNS is far greater. The CNS, unlike the peripheral ANS, contains networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission. In addition, the CNS communicates through the use of multiple neurotransmitters, whereas the ANS uses only two primary neurotransmitters, acetylcholine and norepinephrine.

DRUGS AFFECTING DOPAMINERGIC SYSTEM	DRUGS AFFECTING CHOLINERGIC SYSTEM	ANTIALZHEIMER DRUGS	ANTI-MULTIPLE SCLEROSIS (ALS) DRUGS	ANTI-AMYOTROPHIC LATERAL SCLEROSIS (ALS) DRUGS
Dopamine precursors • <i>Levodopa</i> • <i>Levodopa (with carbidopa)</i>	Central anticholinergic agents • <i>Trihexiphenidyl</i> • <i>Biperiden</i> • <i>Benztropine</i> • <i>Procyclidine</i>	Acetylcholinesterase (AChE) inhibitors • <i>Tacrine</i> • <i>Donepezil</i> • <i>Galantamine</i> • <i>Rivastigmine</i>	Disease-modifying agents Interferon $\beta_{1a}$ and interferon $\beta_{1b}$ • <i>Glatiramer</i> • <i>Fingolimod</i> • <i>Teriflunamide</i> • <i>Dimethyl fumarate</i> • <i>Natalizumab</i> • <i>Mitoxantrone</i>	<i>Riluzole</i>
Peripheral decarboxylase inhibitors • <i>Carbidopa</i> • <i>Benserazide</i>	Antihistamines • <i>Promethazine</i> • <i>Orphenadrine</i>	NMDA receptor antagonist • <i>Memantine</i>	Immunosuppressants • <i>Azathioprine</i> • <i>Cyclophosphamide</i>	
Dopamine agonists • <i>Bromocriptine</i> • <i>Pramipexole</i> • <i>Pergolide</i> • <i>Lisuride</i> • <i>Ropinirole</i> • <i>Rotigotine</i>			Corticosteroids • <i>Dexamethasone</i> • <i>Prednisolone</i>	
MAOB inhibitors • <i>Selegiline</i> • <i>Rasagiline</i>			Symptomatic treatment • <i>Dalfampridine</i>	
COMT inhibitors • <i>Entacapone</i> • <i>Tolcapone</i>				
Dopamine facilitators • <i>Amantadine1</i> • <i>Apomorphine</i>				

<sup>1</sup>Amantadine has multiple mechanism of actions—by increasing the release of dopamine, blocking cholinergic receptors, and inhibiting the N-methyl-d-aspartate (NMDA) type of glutamate receptors.

**Figure 8.1**

Drugs used for Parkinson's disease.

### III. SYNAPTIC POTENTIALS

In the CNS, receptors in most synapses are coupled to ion channels. Binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels. Open channels allow specific ions inside and outside the cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or hyperpolarization of the postsynaptic membrane, depending on the specific ions and the direction of their movement.

#### A. Excitatory pathways

Neurotransmitters can be classified as either excitatory or inhibitory, depending on the nature of the action they elicit. Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. These excitatory postsynaptic potentials (EPSP) are generated by the following: 1) Stimulation of an excitatory neuron causes the release of neurotransmitters, such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium ( $Na^+$ ) ions. 2) The influx of  $Na^+$  causes a weak depolarization,

or EPSP, that moves the postsynaptic potential toward its firing threshold. 3) If the number of stimulated excitatory neurons increases, more excitatory neurotransmitter is released. This ultimately causes the EPSP depolarization of the postsynaptic cell to pass a threshold, thereby generating an all-or-none action potential. [Note: The generation of a nerve impulse typically reflects the activation of synaptic receptors by thousands of excitatory neurotransmitter molecules released from many nerve fibers.] **Figure 8.2** shows an example of an excitatory pathway.

## B. Inhibitory pathways

Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane. These inhibitory postsynaptic potentials (IPSP) are generated by the following:

- 1) Stimulation of inhibitory neurons releases neurotransmitters, such as  $\gamma$ -aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of specific ions, such as potassium ( $K^+$ ) and chloride ( $Cl^-$ ).
- 2) The influx of  $Cl^-$  and efflux of  $K^+$  cause a weak hyperpolarization, or IPSP, that moves the postsynaptic potential away from its firing threshold. This diminishes the generation of action potentials. **Figure 8.3** shows an example of an inhibitory pathway.

## C. Combined effects of the EPSP and IPSP

Most neurons in the CNS receive both EPSP and IPSP input. Thus, several different types of neurotransmitters may act on the same neuron, but each binds to its own specific receptor. The overall action is the summation of the individual actions of the various neurotransmitters on the neuron. The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons, the axons of which may synapse with specific regions of the brain. Many neuronal tracts, thus, seem to be chemically coded, and this may offer greater opportunity for selective pharmacological modulation of certain neuronal pathways.

## IV. NEURODEGENERATIVE DISEASES

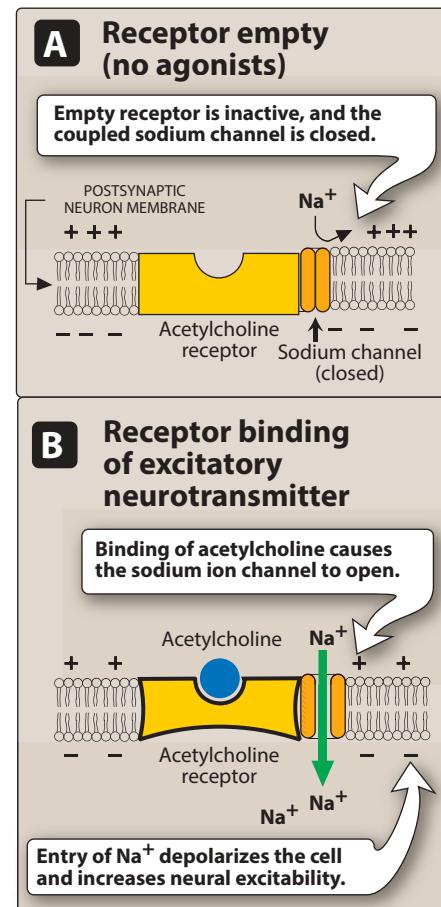
Neurodegenerative diseases of the CNS include Parkinson's disease, Alzheimer's disease, MS, and ALS. These devastating illnesses are characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both.

## V. OVERVIEW OF PARKINSON'S DISEASE

Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia, and postural and gait abnormalities. Most cases involve people over the age of 65 years. The exact etiology is unknown. The disease often manifests itself between the ages of 50 and 60 years, among whom the incidence is about 1 in 100 individuals. It was first described by James Parkinson in 1817; therefore, it is named after him.

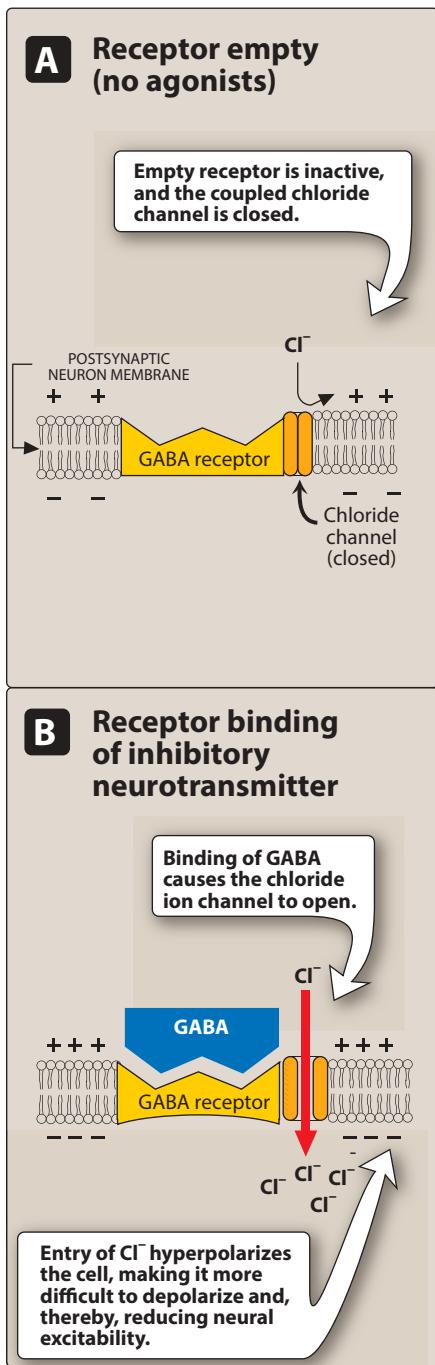
### A. Etiology

The cause of Parkinson's disease is unknown for most patients. The disease is correlated with destruction of dopaminergic neurons in the



**Figure 8.2**

Binding of the excitatory neurotransmitter, acetylcholine, causes depolarization of the neuron.

**Figure 8.3**

Binding of the inhibitory neurotransmitter,  $\gamma$ -aminobutyric acid (GABA), causes hyperpolarization of the neuron.

substantia nigra with a consequent reduction of dopamine actions in the corpus striatum, parts of the basal ganglia system that are involved in motor control.

- 1. Substantia nigra:** The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons (shown in red in Figure 8.4) that terminate in the neostriatum. Each dopaminergic neuron makes thousands of synaptic contacts within the neostriatum and therefore modulates the activity of a large number of cells. These dopaminergic projections from the substantia nigra fire tonically rather than in response to specific muscular movements or sensory input. Thus, the dopaminergic system appears to serve as a tonic, sustaining influence on motor activity, rather than participating in specific movements.
- 2. Neostriatum:** Normally, the neostriatum is connected to the substantia nigra by neurons (shown in orange in Figure 8.4) that secrete the inhibitory transmitter GABA at their termini. In turn, cells of the substantia nigra send neurons back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini. This mutual inhibitory pathway normally maintains a degree of inhibition of both areas. In Parkinson's disease, destruction of cells in the substantia nigra results in the degeneration of the nerve terminals that secrete dopamine in the neostriatum. Thus, the normal inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction, or a relative overactivity, of acetylcholine by the stimulatory neurons (shown in green in Figure 8.4). This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.
- 3. Secondary parkinsonism:** Antipsychotic drugs such as the phenothiazines and *haloperidol*, whose major pharmacologic action is blockade of dopamine receptors in the brain, may produce parkinsonian symptoms (also called pseudoparkinsonism or drug-induced parkinsonism). These drugs should be used with caution in patients with Parkinson's disease.

## B. Strategy of treatment

In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons that oppose the action of dopamine (Figure 8.4). Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons. Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.

## VI. DRUGS USED IN PARKINSON'S DISEASE

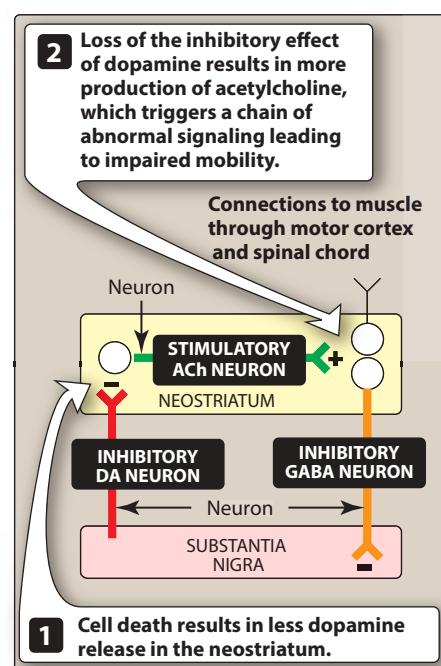
Many currently available drugs aim to maintain CNS dopamine levels, or signaling, as constant as possible. These agents offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration caused by the disease.

## A. Levodopa and carbidopa

*Levodopa* [lee-voe-DOE-pa] is a metabolic precursor of dopamine (Figure 8.5). It restores dopaminergic neurotransmission in the neostriatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra. In early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20% of normal) is adequate for conversion of *levodopa* to dopamine. Thus, in new patients, the therapeutic response to *levodopa* is consistent, and the patient rarely complains that the drug effects "wear off." Unfortunately, with time, the number of neurons decreases, and fewer cells are capable of converting exogenously administered *levodopa* to dopamine. Consequently, motor control fluctuation develops. Relief provided by *levodopa* is only symptomatic, and it lasts only while the drug is present in the body.

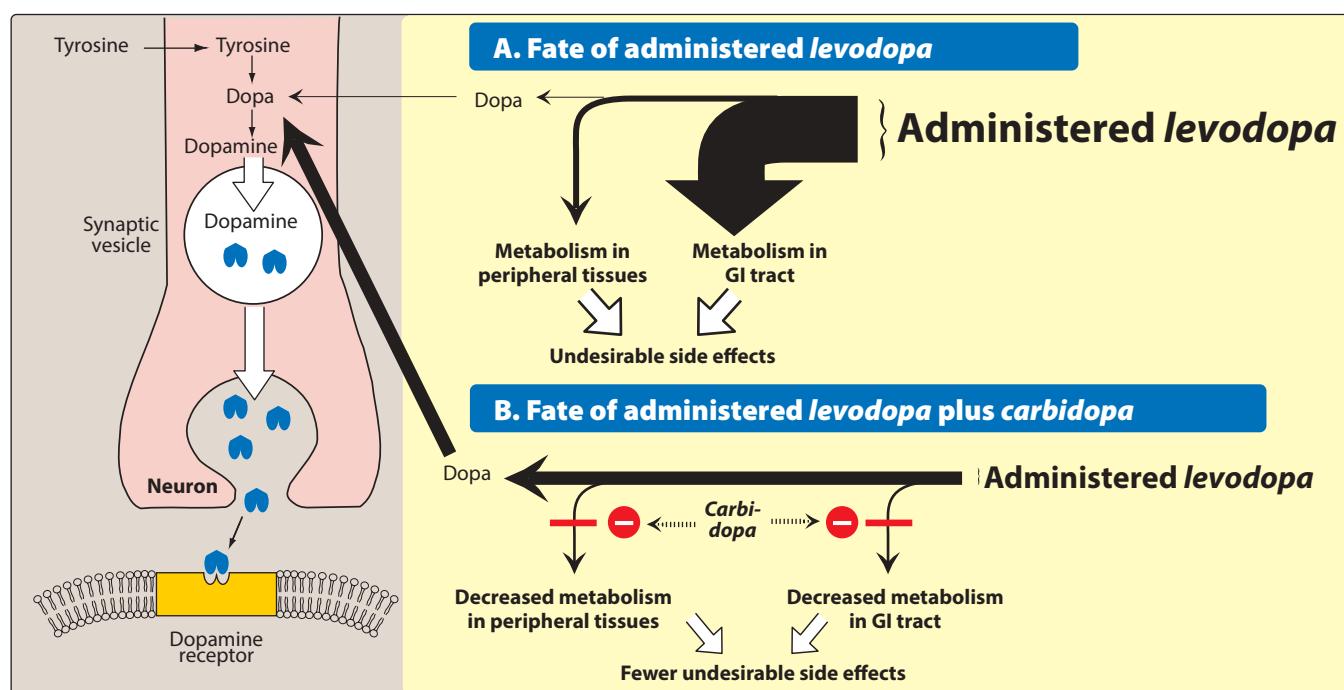
### 1. Mechanism of action:

- Levodopa:** Dopamine does not cross the blood–brain barrier, but its immediate precursor, *levodopa*, is actively transported into the CNS and converted to dopamine (Figure 8.5). *Levodopa* must be administered with *carbidopa* [kar-bi-DOE-pa]. Without *carbidopa*, much of the drug is decarboxylated to dopamine in the periphery, resulting in diminished effect, nausea, vomiting, cardiac arrhythmias, and hypotension.
- Carbidopa:** *Carbidopa*, a dopamine decarboxylase inhibitor, diminishes the metabolism of *levodopa* in the periphery,



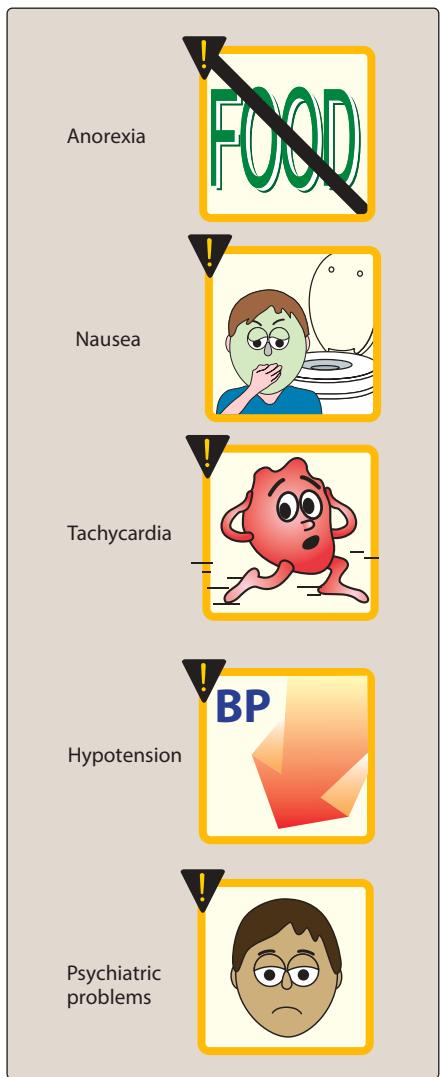
**Figure 8.4**

Role of substantia nigra in Parkinson's disease. ACh = acetylcholine; DA = dopamine; GABA =  $\gamma$ -aminobutyric acid.



**Figure 8.5**

Synthesis of dopamine from *levodopa* in the absence and presence of *carbidopa*, an inhibitor of dopamine decarboxylase in the peripheral tissues. GI = gastrointestinal.

**Figure 8.6**Adverse effects of *levodopa*.

thereby increasing the availability of *levodopa* to the CNS. The addition of *carbidopa* lowers the dose of *levodopa* needed by four- to five-fold and, consequently, decreases the severity of adverse effects arising from peripherally formed dopamine.

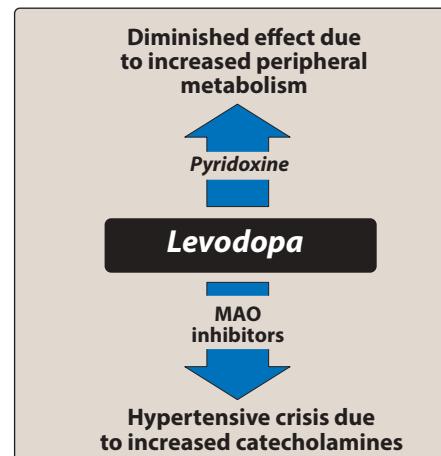
2. **Therapeutic uses:** *Levodopa* in combination with *carbidopa* is an efficacious drug regimen for the treatment of Parkinson's disease. It decreases rigidity, tremors, and other symptoms of parkinsonism. In approximately two-thirds of patients with Parkinson's disease, *levodopa–carbidopa* substantially reduces the severity of symptoms for the first few years of treatment. Patients typically experience a decline in response during the 3rd to 5th year of therapy. Withdrawal from the drug must be gradual.
  3. **Absorption and metabolism:** The drug is absorbed rapidly from the small intestine (when empty of food). *Levodopa* has an extremely short half-life (1 to 2 hours), which causes fluctuations in plasma concentration. This may produce fluctuations in motor response, which generally correlate with the plasma concentration of *levodopa*, or perhaps give rise to the more troublesome "on-off" phenomenon, in which the motor fluctuations are not related to plasma levels in a simple way. Motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility. Ingestion of meals, particularly if high in protein, interferes with the transport of *levodopa* into the CNS. Thus, *levodopa* should be taken on an empty stomach, typically 30 minutes before a meal.
  4. **Adverse effects:**
    - a. **Peripheral effects:** Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone (Figure 8.6). Tachycardia and ventricular extrasystole result from dopaminergic action on the heart. Hypotension may also develop. Adrenergic action on the iris causes mydriasis. In some individuals, blood dyscrasias and a positive reaction to the Coombs test are seen. Saliva and urine may turn brownish color because of the melanin pigment produced from catecholamine oxidation.
    - b. **CNS effects:** Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur. These effects are the opposite of parkinsonian symptoms and reflect overactivity of dopamine in the basal ganglia. *Levodopa* can also cause behavioral effects such as mood changes, depression, psychosis, and anxiety due to exacerbation of pre-existing psychotic symptoms. There are also occasional late-onset dream alterations, visual hallucinations, and drug-induced psychoses characterized by paranoia and confusional states.
- [1] Dyskinesias:** Dyskinesias are the major limiting factor in therapy with *levodopa* and may occur in 80% of patients. They are characterized by a variety of repetitive involuntary abnormal movements affecting the face, trunk, and limbs. Dyskinesias may be relieved by decreasing the dose of *levodopa*, but parkinsonian symptoms may deteriorate. Akinesia paradoxa, a sudden freezing of movement, may follow an episode of dyskinesia and is often precipitated by stress.

Some patients may experience an end-of-dose akinesia or “wearing-off” (worsening of symptoms) before the next dose is due. Each dose of *levodopa* improves mobility for a period of time and is followed by the rapid return of muscle rigidity and akinesia before the end of the dosing interval. Increase in dose and frequency of *levodopa* administration usually relieves these symptoms but may also induce dyskinesia. An “on-off” effect might also occur, in which rapid fluctuation between showing no beneficial effects of *levodopa* and showing beneficial effects with dyskinesias occurs. Clinical improvement may be seen with sustained release formulation of *levodopa*/*carbidopa*. Hence, *levodopa*/*carbidopa* should never be stopped suddenly.

- Interactions and contraindications:** The vitamin pyridoxine ( $B_6$ ) increases the peripheral breakdown of *levodopa* and diminishes its effectiveness (Figure 8.7). Concomitant administration of *levodopa* and nonselective monoamine oxidase inhibitors (MAOIs), such as *phenelzine*, can produce a hypertensive crisis caused by enhanced catecholamine production. Therefore, concomitant administration of these agents is contraindicated. In many psychotic patients, *levodopa* exacerbates symptoms, possibly through the buildup of central catecholamines. Cardiac patients should be carefully monitored for the possible development of arrhythmias. Antipsychotic drugs are generally contraindicated in Parkinson's disease, because they potently block dopamine receptors and may augment parkinsonian symptoms. However, low doses of atypical antipsychotics, such as *quetiapine* or *clozapine*, are sometimes used to treat *levodopa*-induced psychotic symptoms. The use of *levodopa* is also contraindicated in patients with narrow-angle glaucoma and peptic ulcer disease.

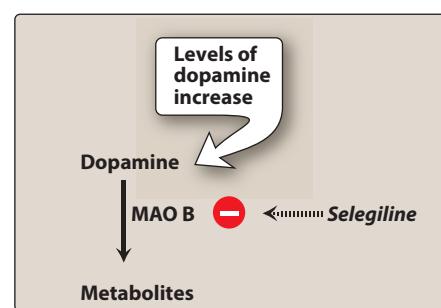
## B. Selegiline, rasagiline, and safinamide

*Selegiline* [seh-LEDGE-ah-leen], also called *deprenyl* [DE-pre-nill], selectively inhibits monoamine oxidase (MAO) type B, the enzyme that metabolizes dopamine. It does not inhibit MAO type A (metabolizes norepinephrine and serotonin) unless given above the recommended doses, where it loses its selectivity. By decreasing the metabolism of dopamine, *selegiline* increases dopamine levels in the brain (Figure 8.8). When *selegiline* is administered with *levodopa*, it enhances the actions of *levodopa* and substantially reduces the required dose. Unlike non-selective MAOIs, *selegiline* at recommended doses has little potential for causing hypertensive crises. However, the drug loses selectivity at high doses, and there is a risk for severe hypertension. Otherwise these drugs are well tolerated. *Selegiline* is metabolized to *methamphetamine* and *amphetamine*, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon. *Rasagiline* [ra-SA-gi-leen], an irreversible and selective inhibitor of brain MAO type B, has five times the potency of *selegiline*. Unlike *selegiline*, *rasagiline* is not metabolized to an *amphetamine*-like substance. *Safinamide* [sa-FIN-a-mide] is also a selective inhibitor of MAO type B indicated for use as an adjunct to *levodopa*-*carbidopa*. These drugs should be avoided in patients taking selective serotonin re-uptake



**Figure 8.7**

Some drug interactions observed with *levodopa*. MAO = monoamine oxidase.



**Figure 8.8**

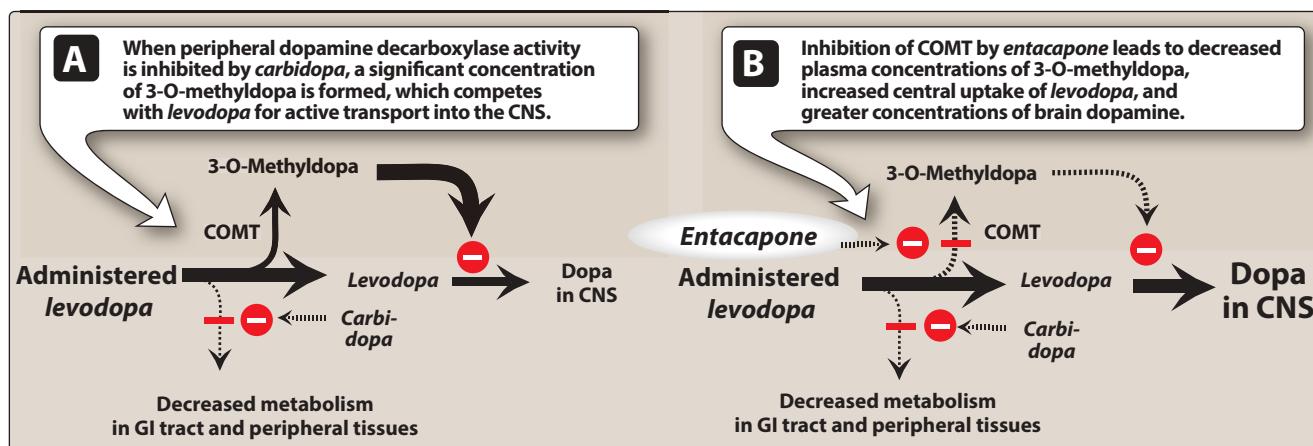
Action of *selegiline* (*deprenyl*) in dopamine metabolism. MAO B = monoamine oxidase type B.

inhibitors (SSRIs), tricyclic antidepressants, and meperidine, as concomitant therapy may precipitate serotonin syndrome (described later in Chapter 10).

### C. Catechol-O-methyltransferase inhibitors

Normally, the methylation of *levodopa* by catechol-O-methyltransferase (COMT) to 3-O-methyldopa is a minor pathway for *levodopa* metabolism. However, when peripheral dopamine decarboxylase activity is inhibited by *carbidopa*, a significant concentration of 3-O-methyldopa is formed that competes with *levodopa* for active transport into the CNS (Figure 8.9). *Entacapone* [en-TAK-a-pone] and *tolcapone* [TOLE-ka-pone] selectively and reversibly inhibit COMT. Inhibition of COMT by these agents leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of *levodopa*, and greater concentrations of brain dopamine. Both of these agents reduce the symptoms of “wearing-off” phenomena seen in patients on *levodopa–carbidopa*. The two drugs differ primarily in their pharmacokinetic and adverse effect profiles. *Entacapone* acts only in the periphery. It decreases the metabolism of *levodopa* and makes more *levodopa* available to the brain. *Tolcapone* acts in both the periphery and the brain by inhibiting the degradation of dopamine.

- 1. Pharmacokinetics:** Oral absorption of both drugs occurs readily and is not influenced by food. They are extensively bound to plasma albumin, with a limited volume of distribution. *Tolcapone* has a relatively long duration of action (probably due to its affinity for the enzyme) compared to *entacapone*, which requires more frequent dosing. Both drugs are extensively metabolized and eliminated in feces and urine. The dosage may need to be adjusted in patients with moderate or severe cirrhosis.
- 2. Adverse effects:** Both drugs exhibit adverse effects that are observed in patients taking *levodopa–carbidopa*, including diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders. Most seriously, fulminating hepatic



**Figure 8.9**

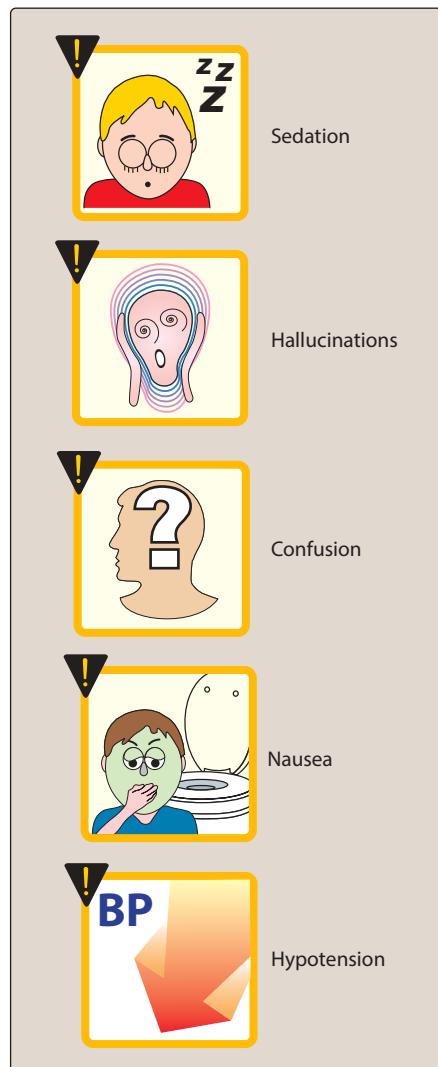
Effect of *entacapone* on dopa concentration in the central nervous system (CNS). COMT = catechol-O-methyltransferase.

necrosis is associated with *tolcapone* use. Therefore, it should be used, along with appropriate hepatic function monitoring, only in patients in whom other modalities have failed. *Entacapone* does not exhibit this toxicity and has largely replaced *tolcapone* in clinical practice.

#### D. Dopamine receptor agonists

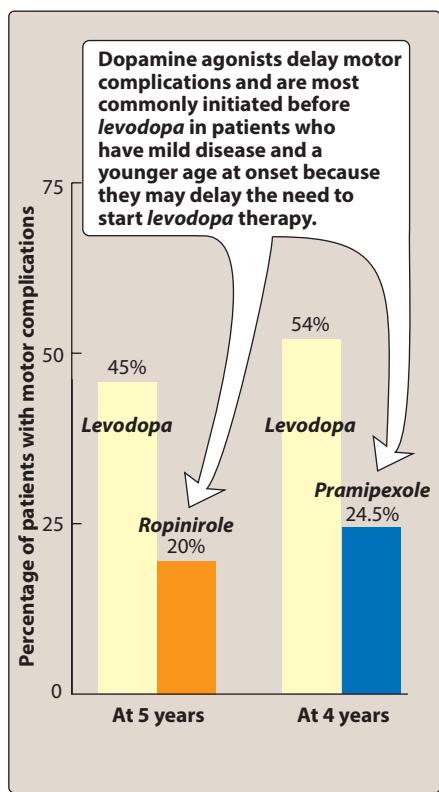
This group of antiparkinsonian compounds includes *bromocriptine* [broe-moe-KRIP-teen], an ergot derivative, and the nonergot drugs, *ropinirole* [roe-PIN-i-role], *pramipexole* [pra-mi-PEX-ole], *rotigotine* [ro-TIG-oh-teen], and *apomorphine* [A-poe-more-fee-en]. These agents have a longer duration of action than that of *levodopa* and are effective in patients exhibiting fluctuations in response to *levodopa*. Initial therapy with these drugs is associated with less risk of developing dyskinesias and motor fluctuations as compared to patients started on *levodopa*. *Bromocriptine*, *pramipexole*, and *ropinirole* are effective in patients with Parkinson's disease complicated by motor fluctuations and dyskinesias. However, these drugs are ineffective in patients who have not responded to *levodopa*. *Apomorphine* is an injectable dopamine agonist that is used in severe and advanced stages of the disease to supplement oral medications. Adverse effects severely limit the utility of the dopamine agonists (Figure 8.10).

- Bromocriptine:** The actions of the ergot derivative *bromocriptine* are similar to those of *levodopa*, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent. In psychiatric illness, *bromocriptine* may cause the mental condition to worsen. It should be used with caution in patients with a history of myocardial infarction or peripheral vascular disease due to the risk of vasospasm. Because *bromocriptine* is an ergot derivative, it has the potential to cause pulmonary and retroperitoneal fibrosis.
- Apomorphine, pramipexole, ropinirole, and rotigotine:** These are nonergot dopamine agonists that are approved for the treatment of Parkinson's disease. *Pramipexole* and *ropinirole* are orally active agents. *Apomorphine* and *rotigotine* are available in injectable and transdermal delivery systems, respectively. *Apomorphine* is used for acute management of the hypomobility "off" phenomenon in advanced Parkinson's disease. *Rotigotine* is administered as a once-daily transdermal patch that provides even drug levels over 24 hours. These agents alleviate the motor deficits in patients who have never taken *levodopa* and also in patients with advanced Parkinson's disease who are treated with *levodopa*. Dopamine agonists may delay the need to use *levodopa* in early Parkinson's disease and may decrease the dose of *levodopa* in advanced Parkinson's disease. Unlike the ergotamine derivatives, these agents do not exacerbate peripheral vascular disorders or cause fibrosis. Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are adverse effects of these drugs, but dyskinesias are less frequent than with *levodopa* (Figure 8.11). *Pramipexole* is mainly excreted unchanged in the urine, and dosage adjustments are needed in renal dysfunction. *Cimetidine* inhibits renal tubular secretion of organic bases and may significantly increase the half-life of *pramipexole*. The



**Figure 8.10**

Some adverse effects of dopamine agonists.

**Figure 8.11**

Motor complications in patients treated with *levodopa* or dopamine agonists.

fluoroquinolone antibiotics and other inhibitors of the cytochrome P450 (CYP450) 1A2 isoenzyme (for example, *fluvoxamine*) may inhibit the metabolism of *ropinirole*, requiring an adjustment in *ropinirole* dosage. **Figure 8.12** summarizes some properties of dopamine agonists.

### E. Amantadine

It was accidentally discovered that the antiviral drug *amantadine* [a-MAN-ta-deen] has an antiparkinsonian action. *Amantadine* has several effects on a number of neurotransmitters implicated in parkinsonism, including increasing the release of dopamine, blocking cholinergic receptors, and inhibiting the *N*-methyl-D-aspartate (NMDA) type of glutamate receptors. The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. *Amantadine* is less efficacious than *levodopa*, and tolerance develops more readily. However, *amantadine* has fewer adverse effects.

### F. Antimuscarinic agents

The antimuscarinic agents are much less efficacious than *levodopa* and play only an adjuvant role in antiparkinsonism therapy. The actions of *benztropine* [BENZ-troe-peen] and *trihexyphenidyl* [tri-hex-ee-FEN-i-dil] are similar, although individual patients may respond more favorably to one drug or the other. Blockade of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission, since it helps to correct the imbalance in the dopamine/acetylcholine activity (Figure 8.4). The antimuscarinic agents have a significant effect on tremors and rigidity but little effect on bradykinesia and postural reflexes. These drugs are often used in the tremor-predominant Parkinson's disease. These can also be used in combination with *levodopa*. These agents can induce mood changes and confusion and produce xerostomia, constipation, and visual problems typical of muscarinic blockers (see Chapter 5). They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis. To avoid precipitating these conditions, these agents should not be administered to patients who are taking other drugs

CHARACTERISTIC	PRAMIPEXOLE	ROPINIROLE	ROTIGOTINE
Bioavailability	> 90%	55%	45%
V <sub>d</sub>	7 L/kg	7.5 L/kg	84 L/kg
Half-life	8 hours <sup>1</sup>	6 hours	7 hours <sup>3</sup>
Metabolism	Negligible	Extensive	Extensive
Elimination	Renal	Renal <sup>2</sup>	Renal <sup>2</sup>

V<sub>d</sub> = volume of distribution.

<sup>1</sup>Increases to 12 hours in patients older than 65 years.

<sup>2</sup>Less than 10% excreted unchanged.

<sup>3</sup>Administered as a once-daily transdermal patch.

**Figure 8.12**

Pharmacokinetic properties of dopamine agonists *pramipexole*, *ropinirole*, and *rotigotine*.

with anticholinergic activity such as tricyclic antidepressants and antihistamines. They can also cause urinary retention in elderly males.

Any of the drugs used for the treatment of Parkinson's disease can be given as monotherapy or in combination depending on the stage of Parkinsonism. The choice of the drug first prescribed depends on the clinical and lifestyle characteristics and patient preferences.

## VII. DRUGS USED IN ALZHEIMER'S DISEASE

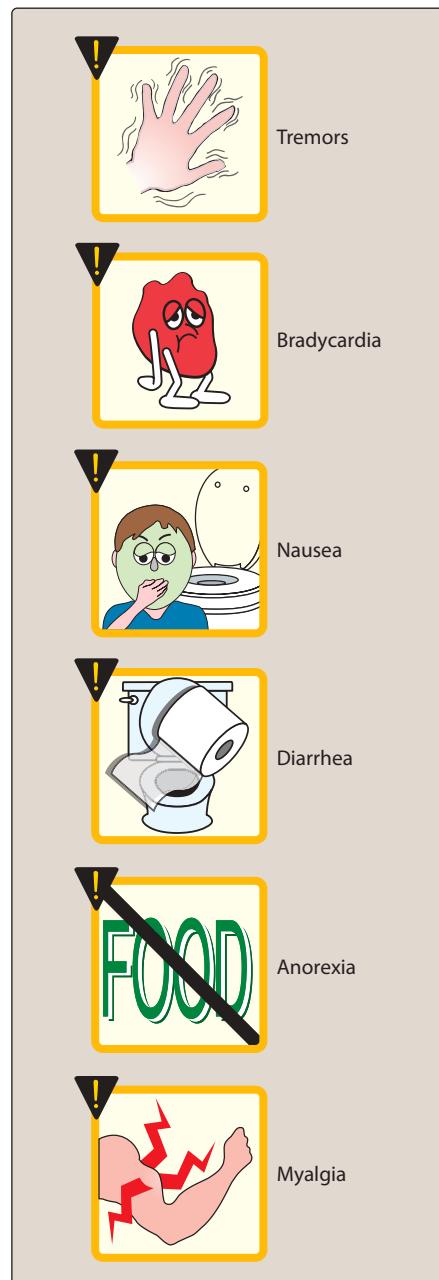
Dementia of the Alzheimer type has three distinguishing features: 1) accumulation of senile plaques ( $\beta$ -amyloid accumulations), 2) formation of numerous neurofibrillary tangles, and 3) loss of cortical neurons, particularly cholinergic neurons. Current therapies aim to either improve cholinergic transmission within the CNS or prevent excitotoxic actions resulting from overstimulation of NMDA-glutamate receptors in selected areas of the brain. Pharmacologic intervention for Alzheimer's disease is only palliative and provides modest short-term benefit. None of the available therapeutic agents alter the underlying neurodegenerative process.

### A. Acetylcholinesterase inhibitors

Numerous studies have linked the progressive loss of cholinergic neurons and, presumably, cholinergic transmission within the cortex to the memory loss that is a hallmark symptom of Alzheimer's disease. It is postulated that inhibition of acetylcholinesterase (AChE) within the CNS improves cholinergic transmission, at least at those neurons that are still functioning. The reversible AChE inhibitors approved for the treatment of Alzheimer's disease include *donepezil* [doe-NE-peh-zil], *galantamine* [ga-LAN-ta-meen], and *rivastigmine* [ri-va-STIG-meen]. These agents have some selectivity for AChE in the CNS, as compared to the periphery. *Galantamine* may also augment the action of acetylcholine at nicotinic receptors in the CNS. At best, these compounds may provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer patients. *Rivastigmine* is the only agent approved for the management of dementia associated with Parkinson's disease and also the only AChE inhibitor available as a transdermal formulation. *Rivastigmine* is hydrolyzed by AChE to a carbamylate metabolite and has no interactions with drugs that alter the activity of CYP450 enzymes. The other agents are substrates for CYP450 and have a potential for such interactions. Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps (Figure 8.13).

### B. NMDA receptor antagonist

Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain memories. However, overstimulation of glutamate receptors, particularly of the NMDA type, may result in excitotoxic effects on neurons and is suggested as a mechanism for neurodegenerative or apoptotic (programmed cell death) processes. Binding of glutamate to the NMDA receptor assists in the opening of an ion channel that allows  $\text{Ca}^{2+}$  to enter the neuron. Excess intracellular  $\text{Ca}^{2+}$  can activate a number of processes that ultimately damage neurons and lead to apoptosis. *Memantine* [meh-MAN-teen]



**Figure 8.13**

Adverse effects of AChE inhibitors.  
Modified from R. Young. Update on Parkinson's disease. Am. Fam. Physician 59: 2155 (1999).

is an NMDA receptor antagonist indicated for moderate-to-severe Alzheimer's disease. It acts by blocking the NMDA receptor and limiting  $\text{Ca}^{2+}$  influx into the neuron, such that toxic intracellular levels are not achieved. *Memantine* is well tolerated, with few dose-dependent adverse events. Expected adverse effects, such as confusion, agitation, and restlessness, are often indistinguishable from the symptoms of Alzheimer's disease. Given its different mechanism of action and possible neuroprotective effects, *memantine* is often given in combination with an AChE inhibitor.

1. **Other cognitive enhancers:** Drugs such as *pyritinol*, *dihydroergotoxine*, *piribedil*, *citicholine*, and extract of the plant *Ginkgo biloba* are reported to enhance cognitive functions by improving cerebral blood flow. Therefore, they have supporting value in the treatment of cognitive impairment.

## VIII. DRUGS USED IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the CNS. The course of MS is variable. For some, MS may consist of one or two acute neurologic episodes. In others, it is a chronic, relapsing, or progressive disease that may span 10 to 20 years. Medications are used to modify the disease course, treat relapses (exacerbations or attacks), and manage symptoms. Historically, high-dose intravenous corticosteroids (for example, *dexamethasone* and *prednisone*) for 3 to 5 days have been used to treat acute exacerbations of the disease as they reduce inflammation and end the relapse more quickly. Corticosteroids do not have any long-term benefit on the disease. Chemotherapeutic agents, such as *cyclophosphamide* and *azathioprine*, have also been used. There is currently no cure for MS, but it is possible to treat the symptoms with medications and other treatments. Along with the other essential components of comprehensive MS care, the medications discussed below help people manage their MS and enhance their comfort and quality of life.

Treatment for MS depends on the specific symptoms and difficulties the person has with daily activities. It may include the following:

- Treating relapses of MS symptoms (with steroid medication)
- Treating specific MS symptoms
- Treatment to reduce the number of relapses (disease-modifying therapies)

### A. Disease-modifying therapies

Drugs currently approved for MS are indicated to decrease the number and severity of relapses and slow the worsening disability in MS cases. The major target of these medications is to modify the immune response through inhibition of white blood cell-mediated inflammatory processes that eventually lead to myelin sheath damage and decreased or inappropriate axonal communication between cells. Disease-modifying agents are useful in certain patients with relapse remitting MS or secondary progressive MS.

1. **Interferon  $\beta_{1a}$  and interferon  $\beta_{1b}$ :** The immunomodulatory effects of *interferon* [in-ter-FEER-on] help to diminish the inflammatory responses that lead to demyelination of the axon sheaths.

Adverse effects of these medications may include depression, local injection site reactions, increases in hepatic enzymes, and flu-like symptoms.

2. **Glatiramer:** *Glatiramer* [gluh-TEER-a-mur] is a synthetic polypeptide that resembles myelin protein and may act as a decoy to T-cell attack. Some patients experience a postinjection reaction that includes flushing, chest pain, anxiety, and itching. It is usually self-limiting.
3. **Fingolimod:** *Fingolimod* [fin-GO-li-mod] is an oral drug that alters lymphocyte migration, resulting in fewer lymphocytes in the CNS. *Fingolimod* may cause first-dose bradycardia and is associated with an increased risk of infection and macular edema.
4. **Teriflunomide:** *Teriflunomide* [te-ree-FLOO-no-mide] is an oral pyrimidine synthesis inhibitor that leads to a lower concentration of active lymphocytes in the CNS. *Teriflunomide* may cause elevated liver enzymes. It should be avoided in pregnancy.
5. **Dimethyl fumarate:** *Dimethyl fumarate* [dye-METH-il FOO-mate] is an oral agent that may alter the cellular response to oxidative stress to reduce disease progression. Flushing and abdominal pain are the most common adverse events.
6. **Monoclonal antibodies:** *Alemtuzumab* [AL-em-TOOZ-ue-mab], *daclizumab* [dah-KLIH-zyoo-mab], *natalizumab* [na-ta-LIZ-oo-mab], and *ocrelizumab* [OK-re-LIZ-ue-mab] are monoclonal antibodies indicated for the treatment of MS. *Ocrelizumab* is the first agent to be approved for primary progressive forms of the disease. These agents can be associated with significant toxicities, such as progressive multifocal leukoencephalopathy with *natalizumab*, serious infections with *daclizumab* and *alemtuzumab*, and autoimmune disorders with *alemtuzumab*. As such, these agents may be reserved for patients who have failed other therapies.

## B. Symptomatic treatment

Many different classes of drugs are used to manage symptoms of MS such as spasticity, constipation, bladder dysfunction, and depression. *Dalfampridine* [DAL-fam-pre-deen], an oral potassium channel blocker, improves walking speeds in patients with MS. It is the first drug approved for this use.

# IX. DRUGS USED IN AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is characterized by progressive degeneration of motor neurons, resulting in the inability to initiate or control muscle movement. *Riluzole* [RIL-ue-zole] and *edaravone* [e-DAR-a-vone] are indicated for the management of ALS. *Riluzole*, an oral NMDA receptor antagonist, is believed to act by inhibiting glutamate release and blocking sodium channels. *Riluzole* may improve survival time in patients suffering from ALS. *Edaravone* is an intravenous free radical scavenger and antioxidant that may slow the progression of ALS.

## Study Questions

**Choose the ONE best answer.**

- 8.1. Which one of the following combinations of antiparkinsonian drugs is an appropriate treatment plan?

- A. Amantadine, carbidopa, and entacapone
- B. Levodopa, carbidopa, and entacapone
- C. Pramipexole, carbidopa, and entacapone
- D. Ropinirole, selegiline, and entacapone

Correct answer = B. To reduce the dose of levodopa and its peripheral adverse effects, the peripheral decarboxylase inhibitor, carbidopa, is coadministered. As a result of this combination, more levodopa is available for metabolism by catechol-O-methyltransferase (COMT) to 3-O-methyldopa, which competes with levodopa for the active transport processes into the CNS. By administering entacapone (an inhibitor of COMT), the competing product is not formed, and more levodopa enters the brain. The other choices are not appropriate, because neither peripheral decarboxylase nor COMT nor monoamine oxidase metabolizes amantadine or the direct-acting dopamine agonists, ropinirole and pramipexole.

- 8.2. Peripheral adverse effects of levodopa, including nausea, hypotension, and cardiac arrhythmias, can be diminished by including which of the following drugs in the therapy?

- A. Amantadine
- B. Ropinirole
- C. Carbidopa
- D. Entacapone

Correct answer = C. Carbidopa inhibits the peripheral decarboxylation of levodopa to dopamine, thereby diminishing the gastrointestinal and cardiovascular adverse effects of levodopa. The other agents listed do not ameliorate adverse effects of levodopa.

- 8.3. Which of the following antiparkinsonian drugs may cause vasospasm?

- A. Amantadine
- B. Bromocriptine
- C. Carbidopa
- D. Entacapone

Correct answer = B. Bromocriptine is a dopamine receptor agonist that may cause vasospasm. It is contraindicated in patients with peripheral vascular disease. The other drugs do not act directly on dopamine receptors.

- 8.4. Modest improvement in the memory of patients with Alzheimer's disease may occur with drugs that increase transmission at which of the following receptors?

- A. Adrenergic
- B. Cholinergic
- C. Dopaminergic
- D. GABAergic

Correct answer = B. AChE inhibitors, such as galantamine, increase cholinergic transmission in the CNS and may cause a modest delay in the progression of Alzheimer's disease. Increased transmission at the other types of receptors listed does not result in improved memory.

- 8.5. Which medication is a glutamate receptor antagonist that can be used in combination with an acetylcholinesterase inhibitor to manage the symptoms of Alzheimer's disease?

- A. Rivastigmine
- B. Pramipexole
- C. Memantine
- D. Galantamine

Correct answer = C. When combined with an acetylcholinesterase inhibitor, memantine has modest efficacy in keeping patients with Alzheimer's disease at or above baseline for at least 6 months and may delay disease progression.

8.6. Which of the following agents is available as a patch for once-daily use and is likely to provide steady drug levels to treat Alzheimer's disease?

- A. Rivastigmine
- B. Donepezil
- C. Memantine
- D. Galantamine

Correct answer = A. Rivastigmine is the only agent available as a transdermal delivery system for the treatment of Alzheimer's disease. It may also be used for dementia associated with Parkinson's disease.

8.7. Which of the following is approved for the management of amyotrophic lateral sclerosis?

- A. Pramipexole
- B. Selegiline
- C. Riluzole
- D. Glatiramer

Correct answer = C. Riluzole is approved for the debilitating and lethal illness of ALS. It is used to, ideally, delay the progression and need for ventilator support in severe patients.

8.8. Which of the following medications reduces immune system-mediated inflammation via inhibition of pyrimidine synthesis to reduce the number of activated lymphocytes in the CNS?

- A. Riluzole
- B. Rotigotine
- C. Teriflunomide
- D. Dexamethasone

Correct answer = C. Teriflunomide is believed to exert its disease modifying and anti-inflammatory effects by inhibiting the enzyme dihydro-orotate dehydrogenase to reduce pyrimidine synthesis.

8.9. Which of the following agents may cause tremors as an adverse effect and, thus, should be used with caution in patients with Parkinson's disease, even though it is also indicated for the treatment of dementia associated with Parkinson's disease?

- A. Benztropine
- B. Rotigotine
- C. Rivastigmine
- D. Dimethyl fumarate

Correct answer = C. Though rivastigmine is an acetylcholinesterase inhibitor, which can cause tremors as an adverse effect, its use is not contraindicated in patients with Parkinson's disease, as this agent is also the only medication approved for dementia associated with Parkinson's disease. It should be used with caution, as it may worsen the parkinsonian-related tremors. A risk-benefit discussion should occur with the patient and the caregiver before rivastigmine is used.

8.10. Which of the following agents exerts its therapeutic effect in multiple sclerosis via potassium channel blockade?

- A. Dalfampridine
- B. Donepezil
- C. Riluzole
- D. Bromocriptine

Correct answer = A. Dalfampridine is a potassium channel blocker and is the only agent that is indicated to improve walking speed in patients with MS.



# Anxiolytic/Hypnotic Drugs

Jose A. Rey

9

## I. OVERVIEW

Disorders involving anxiety are among the most common mental disorders. Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that arises from either a known or an unknown source). The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, severe, chronic, debilitating anxiety may be treated with antianxiety drugs (sometimes called anxiolytics) and/or some form of psychotherapy. Because many antianxiety drugs also cause some sedation, they may be used clinically as both anxiolytic and hypnotic (sleep-inducing) agents. *Sedation* is characterized by decreased anxiety, motor activity, and cognitive acuity. *Hypnosis* is characterized by drowsiness and an increased tendency to sleep. Figure 9.1 summarizes the anxiolytic and hypnotic agents. Some antidepressants are also indicated for certain anxiety disorders; however, they are discussed with the antidepressants (see Chapter 10).

## II. BENZODIAZEPINES

Benzodiazepines are widely used anxiolytic drugs. They have largely replaced barbiturates and *meprobamate* in the treatment of anxiety and insomnia, because benzodiazepines are generally considered to be safer and more effective (Figure 9.2). Though benzodiazepines are commonly used, they are not necessarily the best choice for anxiety or insomnia. Certain antidepressants with anxiolytic action, such as the selective serotonin reuptake inhibitors, are preferred in many cases, and nonbenzodiazepine hypnotics and antihistamines may be preferable for insomnia.

### A. Mechanism of action

The targets for benzodiazepine actions are the  $\gamma$ -aminobutyric acid ( $GABA_A$ ) receptors. [Note: GABA is the major inhibitory neurotransmitter in the central nervous system (CNS).] The  $GABA_A$  receptors are composed of a combination of five  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits that span the postsynaptic membrane (Figure 9.3). For each subunit, many subtypes exist (for example, there are six subtypes of the  $\alpha$  subunit). Binding of

### BENZODIAZEPINES

Long-acting  
*Chlordiazepoxide*  
*Diazepam*  
*Flurazepam*

Intermediate-acting  
*Alprazolam*  
*Clonazepam*  
*Clorazepate*  
*Estazolam*  
*Lorazepam*  
*Oxazepam*  
*Quazepam*  
*Temazepam*

### Short-acting

*Triazolam*

*Midazolam*

### BENZODIAZEPINE ANTAGONIST

*Flumazenil*

### NONBENZODIAZEPINE HYPNOTICS

*Zaleplon*  
*Zolpidem*  
*Eszopiclone*

### MELATONIN AGONISTS

*Ramelteon*  
*Tasimelteon*

### OTHER ANXIOLYTIC DRUGS

*Antidepressants*  
*Buspirone*  
*Meprobamate*

### BARBITURATES

*Amobarbital*  
*Pentobarbital*  
*Phenobarbital*  
*Secobarbital*

### Figure 9.1

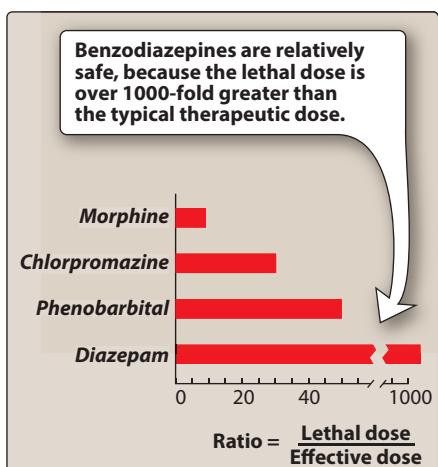
Summary of anxiolytic and hypnotic drugs. (Figure continues on next page)

### OTHER HYPNOTIC AGENTS

Antihistamines  
Doxepin  
Suvorexant (orexin receptor antagonist)  
Melatonin agonist  
Ramelteon  
Tasimelteon

**Figure 9.1** (Continued)

Summary of anxiolytic and hypnotic drugs.



**Figure 9.2**

Ratio of lethal dose to effective dose for morphine (an opioid, see Chapter 14), chlorpromazine (an antipsychotic, see Chapter 11), and the anxiolytic, hypnotic drugs, phenobarbital and diazepam.

GABA to its receptor triggers an opening of the central ion channel, allowing chloride through the pore. The influx of chloride ions causes hyperpolarization of the neuron and decreases neurotransmission by inhibiting the formation of action potentials. Benzodiazepines modulate GABA effects by binding to a specific, high-affinity site (distinct from the GABA-binding site) located at the interface of the  $\alpha$  subunit and the  $\gamma$  subunit on the GABA<sub>A</sub> receptor (Figure 9.3). Benzodiazepines increase the frequency of channel openings produced by GABA. The clinical effects of individual benzodiazepines correlate well with the binding affinity of each drug for the GABA receptor–chloride ion channel complex.

### B. Actions

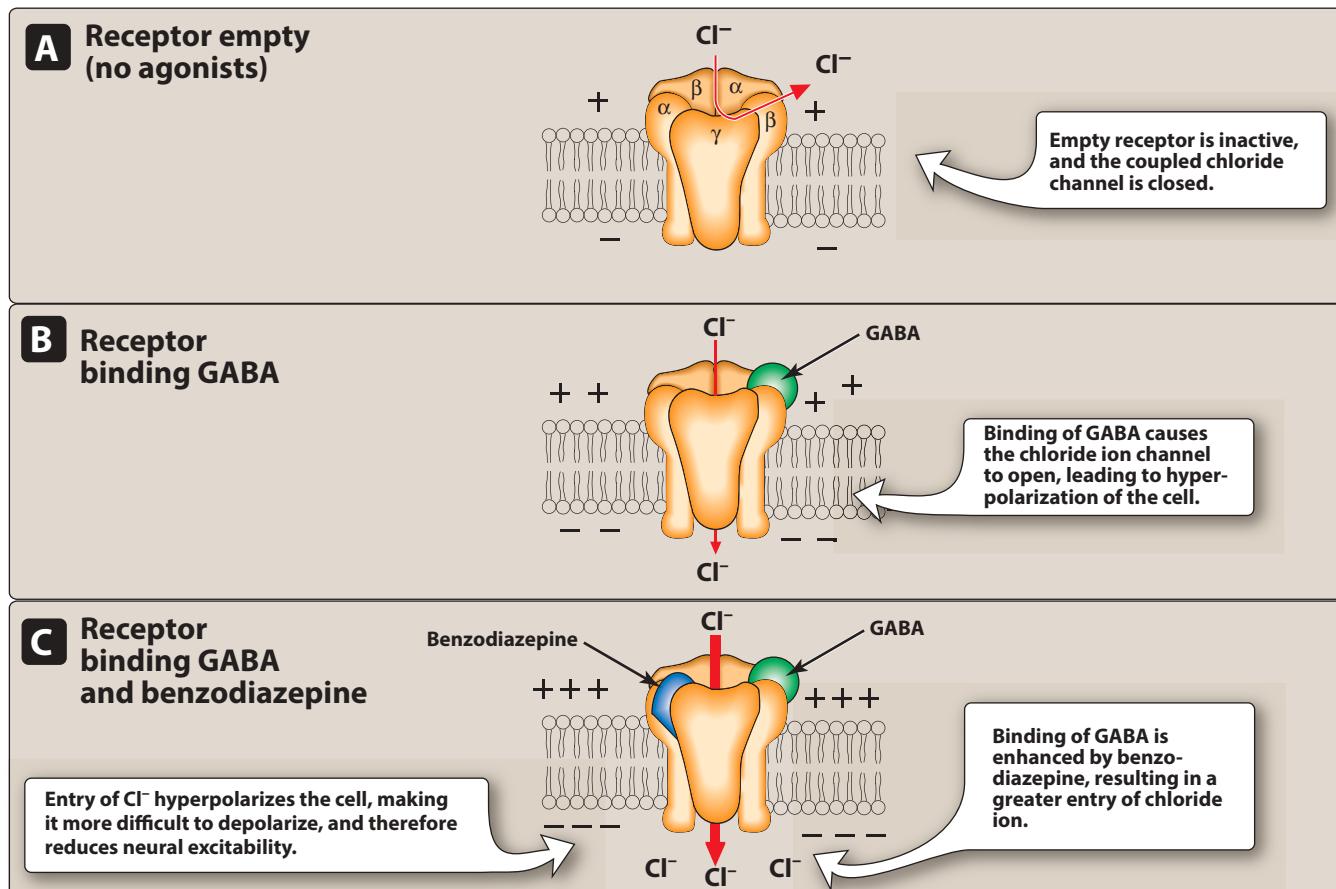
Most benzodiazepines exhibit qualitatively similar therapeutic actions to some extent but differ in their relative lipid solubility, biotransformation, and elimination half-life.

- Reduction of anxiety:** At low doses, the benzodiazepines are anxiolytic. They reduce anxiety by selectively enhancing GABAergic transmission in neurons having the  $\alpha_2$  subunit in their GABA<sub>A</sub> receptors, thereby inhibiting neuronal circuits in the limbic system of the brain.
- Sedative/hypnotic:** All benzodiazepines have sedative and calming properties, and some can produce hypnosis (artificially produced sleep) at higher doses. The hypnotic effects are mediated by the  $\alpha_1$ -GABA<sub>A</sub> receptors.
- Anterograde amnesia:** Temporary impairment of memory with use of the benzodiazepines is also mediated by the  $\alpha_1$ -GABA<sub>A</sub> receptors. The ability to learn and form new memories is also impaired.
- Anticonvulsant:** This effect is partially, although not completely, mediated by  $\alpha_1$ -GABA<sub>A</sub> receptors.
- Muscle relaxant:** At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord, where the  $\alpha_2$ -GABA<sub>A</sub> receptors are largely located. [Note: Baclofen [BAK-loe-fen] is a muscle relaxant that is believed to affect GABA receptors at the level of the spinal cord.]

### C. Therapeutic uses

The individual benzodiazepines show small differences in their relative anxiolytic, anticonvulsant, and sedative properties. However, pharmacokinetic considerations are often important in choosing one benzodiazepine over another.

- Anxiety disorders:** Benzodiazepines are effective for the treatment of anxiety associated with panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, and extreme phobias, such as fear of flying. The benzodiazepines are also useful in treating anxiety related to depression and schizophrenia. These drugs should be reserved for severe anxiety and should not be used to manage the stress of everyday life. Because of their addictive potential, they should only be used for short periods of time. The long-acting agents, such as clonazepam [kloe-NAZ-e-pam], lorazepam [lor-AZ-e-pam],

**Figure 9.3**

Schematic diagram of benzodiazepine–GABA–chloride ion channel complex. GABA =  $\gamma$ -aminobutyric acid.

and *diazepam* [dye-AZ-e-pam], are often preferred in patients with anxiety that require prolonged treatment. The antianxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects. [Note: Tolerance is decreased responsiveness to repeated doses of the drug that occurs when used for more than 1 to 2 weeks.] For panic disorders, *alprazolam* [al-PRAY-zoe-lam] is effective for short- and long-term treatment, although it may cause withdrawal reactions in approximately 30% of patients.

2. **Sleep disorders:** Benzodiazepine hypnotics decrease the latency to sleep onset and increase stage II of non-rapid eye movement (REM) sleep. Both REM sleep and slow-wave sleep are decreased. In the treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation ("hangover") upon awakening. Short-acting *triazolam* [try-AY-zoe-lam] is effective in treating individuals who have problems falling asleep. The risk of withdrawal and rebound insomnia is higher with *triazolam* than with other agents. Intermediate-acting *temazepam* [te-MAZ-e-pam] is useful for patients who experience frequent awakenings and have difficulty staying asleep. *Temazepam* should be administered 1 to 2 hours before the desired bedtime.

Long-acting *flurazepam* [flure-AZ-e-pam] is rarely used, due to its extended half-life, which may result in excessive daytime sedation and accumulation of the drug, especially in the elderly. *Estazolam* [eh-STAY-zoe-lam] and *quazepam* [QUAY-ze-pam] are considered intermediate- and long-acting agents, respectively. In general, hypnotics should be used for only a limited time, usually 1 to 3 weeks. Nonbenzodiazepine agents are now preferred due to reduced potential for tolerance, abuse, and physical dependence (see below).

3. **Amnesia:** The short-acting agents are often employed as pre-medication for anxiety-provoking and unpleasant procedures, such as endoscopy, bronchoscopy, dental procedures, and angioplasty. They cause a form of conscious sedation, allowing the patient to be receptive to instructions during these procedures. *Midazolam* [mi-DAY-zoe-lam] is a benzodiazepine used to facilitate anterograde amnesia while providing sedation prior to anesthesia.
4. **Seizures:** Benzodiazepines elevate seizure threshold. *Clonazepam* is occasionally used as an adjunctive therapy for certain types of seizures, whereas *lorazepam* and *diazepam* given by the intravenous or rectal route are the drugs of choice in terminating status epilepticus (see Chapter 12). Due to cross-tolerance, *chlordiazepoxide* [klor-di-az-e- POX-ide], *clorazepate* [klor-AZ-e-pate], *diazepam*, *lorazepam*, and *oxazepam* [ox-AZ-e-pam] are useful in the acute treatment of alcohol withdrawal and reduce the risk of withdrawal-related seizures.
5. **Muscular disorders:** *Diazepam* is useful in the treatment of skeletal muscle spasms and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.
6. **Physical dependence:** Long-acting benzodiazepines (*diazepam*, *chlordiazepoxide*) are used to reduce the withdrawal symptoms of physical dependence associated with alcohol and long-term use of short-acting benzodiazepines and barbiturates.

#### D. Pharmacokinetics

1. **Absorption and distribution:** The benzodiazepines are lipophilic. They are rapidly and completely absorbed after oral administration, distribute throughout the body, and penetrate into the CNS. The onset of action of benzodiazepines is related to a relative degree of lipid solubility which can vary 50-fold or more. Highly lipid-soluble compounds (*midazolam*, *triazolam*, *diazepam*) have a rapid onset of action than relatively less lipid-soluble benzodiazepines. Most benzodiazepines are available in oral dosage forms; *diazepam* and *midazolam* can be given both parenterally and by the rectal route.
2. **Duration of action:** The half-lives of the benzodiazepines are important clinically, because the duration of action may determine the therapeutic usefulness. The benzodiazepines can be roughly divided into short-, intermediate-, and long-acting groups (Figure 9.4). The long-acting agents form active metabolites with long half-lives. However, with some benzodiazepines, the clinical duration of action does not correlate with the actual half-life (otherwise, a

dose of *diazepam* could conceivably be given only every other day, given its long half-life and active metabolites). This may be due to receptor dissociation rates in the CNS and subsequent redistribution to fatty tissues and other areas. Short-acting benzodiazepines are more useful as they prevent preanesthetic anxiety and insomnia, without causing hangover on awakening. Long-acting benzodiazepines are generally more useful in managing anxiety, withdrawal states, seizures, and insomnia.

DRUG	PEAK BLOOD LEVEL (HOURS)	ELIMINATION HALF-LIFE (HOURS) <sup>1</sup>	DURATION OF ACTION	COMMENTS
<b>Benzodiazepines (short-acting):</b>				
<i>Oxazepam</i>	2–4	10–40	3–8 hours	No active metabolites; useful in sleep onset
<i>Triazolam</i>	1	2–3	3–8 hours	Rapid onset; short duration of action
<b>Benzodiazepines (intermediate-acting):</b>				
<i>Alprazolam</i>	1–2	12–15	10–20 hours	Rapid oral absorption; useful in sleep maintenance
<i>Lorazepam</i>	1–6	10–20	10–20 hours	No active metabolites; useful in sleep maintenance
<i>Temazepam</i>	2–3	10–40	10–20 hours	Slow oral absorption
<i>Estazolam</i>	1–6	8–31	10–20 hours	Useful in sleep maintenance
<b>Benzodiazepines (long-acting):</b>				
<i>Chlordiazepoxide</i>	2–4	15–40	1–3 days	Active metabolites; erratic bioavailability from injection
<i>Clorazepate</i>	1–2 ( <i>nordiazepam</i> )	50–100	1–3 days	Prodrug; hydrolyzed to active form in stomach
<i>Diazepam</i>	1–2	20–80	1–3 days	Active metabolites; erratic bioavailability from injection; useful in sleep maintenance
<i>Flurazepam</i>	1–2	40–100	1–3 days	Active metabolites with long half-lives; useful in sleep maintenance
<b>Nonbenzodiazepines:</b>				
<i>Eszopiclone</i>	<1	6	7 hours	Minor active metabolites; fast acting (20 min); useful in sleep maintenance
<i>Zaleplon</i>	<1	1–2	2–3 hours	Metabolized via aldehyde dehydrogenase; ultra short-acting; useful for sleep onset
<i>Zolpidem</i> <sup>2</sup>	1–3	1.5–3.5	5 hours	No active metabolites; fast acting (10–15 min of oral administration); short duration of action
<i>Ramelteon</i>	<1	1–3	7 hours	Promotes sleep initiation and maintenance

<sup>1</sup>Includes half-lives of major metabolites.

<sup>2</sup>Extended release preparation useful in sleep maintenance.

**Figure 9.4**

Pharmacokinetic properties of some benzodiazepines and newer hypnotics.

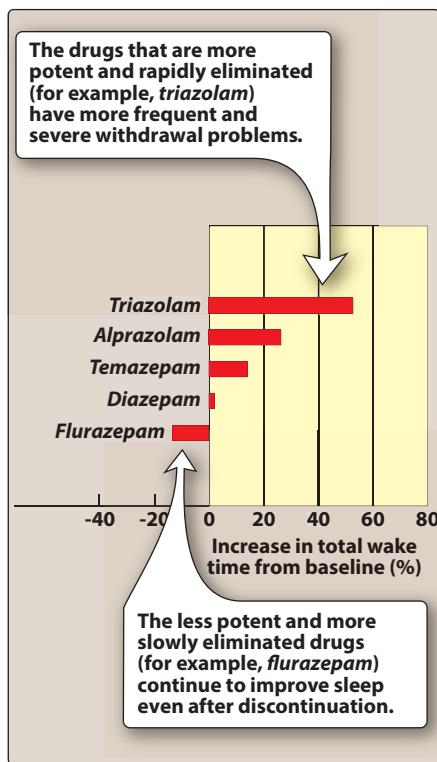
**3. Fate:** Most benzodiazepines, including *chlordiazepoxide* and *diazepam*, are metabolized by phase I hepatic microsomal oxidation to compounds that are also active. For these benzodiazepines, the apparent half-life of the drug represents the combined actions of the parent drug and its metabolites to as long as 60 hours or more accounting for hangover and other cumulative effects when administered repeatedly. *Clorazepate*, a prodrug, is hydrolyzed in stomach. The benzodiazepines are excreted in the urine as glucuronides or oxidized metabolites. Short- and intermediate-acting benzodiazepines are biotransformed by hydroxylation (*estazolam*) and/or direct glucuronidation (*lorazepam*, *oxazepam*, *temazepam*) to inactive metabolites followed by renal clearance. Clearance of benzodiazepines is reduced in the elderly and in patients with impaired hepatic function; therefore, the dose should be reduced in these patients. All benzodiazepines cross the placenta and may depress the CNS of the newborn if given before birth. The benzodiazepines are not recommended for use during pregnancy. Nursing infants may also be exposed to the drugs in breast milk.

### E. Tolerance, abuse, and dependence

Tolerance develops to the sedative, hypnotic, and anticonvulsant actions of benzodiazepines though to a lesser extent to the anxiolytic action. Cross-tolerance also occurs with other hypnotic and sedative agents, including alcohol and barbiturates. Psychological and physical dependence can develop if high doses of benzodiazepines are given for a prolonged period. All benzodiazepines are controlled substances. Abrupt discontinuation of these agents results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures. Benzodiazepines with a short elimination half-life, such as *triazolam*, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated such as *flurazepam* (Figure 9.5). The withdrawal reaction can be minimized by tapering the dose gradually or by substituting the long-acting benzodiazepines, for example, *diazepam* and *chlordiazepoxide*.

### F. Adverse effects

Daytime drowsiness, sedation, and confusion are the most common adverse effects of the benzodiazepines. Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile, or tasks that require skill, particularly in the elderly and with long-acting benzodiazepines. Cognitive impairment (decreased recall and retention of new knowledge) can occur with use of benzodiazepines, especially in the elderly. Benzodiazepines should be used cautiously in patients with liver disease. They may depress respiration at higher doses than hypnotic doses and may be exaggerated in patients with obstructive sleep apnea and chronic obstructive pulmonary disease. Alcohol and other CNS depressants enhance the sedative-hypnotic effects of the benzodiazepines. Benzodiazepines are, however, considerably less dangerous than the older anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal unless other central depressants, such as alcohol or opioids, are taken concurrently. Benzodiazepines when administered



**Figure 9.5**

Frequency of rebound insomnia resulting from discontinuation of benzodiazepine therapy. Modified from A. Kales, Excerpta Medical Congress Series 899: 149 (1989).

by the parenteral route may cause hypotension and bradycardia in patients with impaired cardiovascular function. These drugs may rarely cause paradoxical excitement. CYP3A4 enzyme inhibitors and grapefruit juice can extend the duration of action of benzodiazepines.

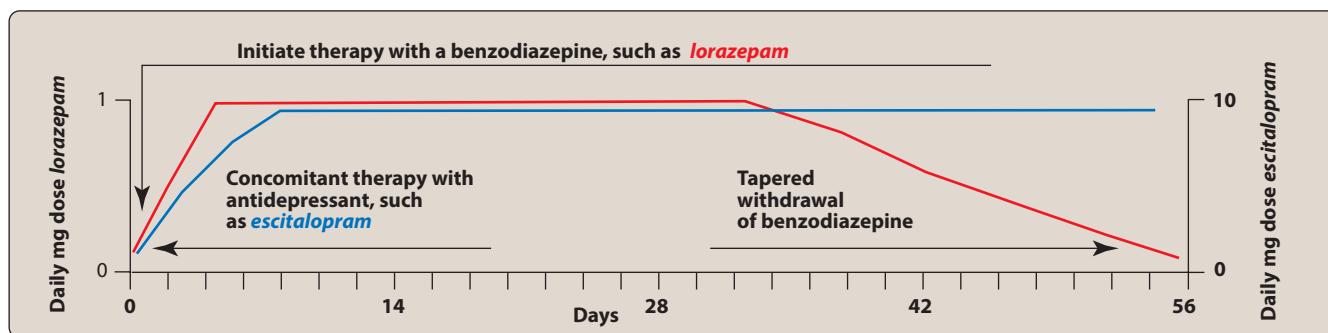
### III. BENZODIAZEPINE ANTAGONIST

*Flumazenil* [floo-MAZ-eh-nill] is a competitive GABA receptor antagonist that rapidly reverses the effects of benzodiazepines. The drug is available for intravenous (IV) administration only. Onset is rapid, but the duration is short, with a half-life of about 1 hour. Accidental ingestion of benzodiazepines is treated with supportive care, emetics, and/or activated charcoal. Frequent administration may be necessary in patients with marked central nervous system depression to maintain reversal of a long-acting benzodiazepine. Administration of *flumazenil* may precipitate withdrawal in dependent patients or cause seizures if a benzodiazepine is used to control seizure activity. Seizures may also result if the patient has a mixed ingestion with tricyclic antidepressants or antipsychotics. Dizziness, nausea, vomiting, and agitation are the most common adverse effects.

## IV. OTHER ANXIOLYTIC AGENTS

### A. Antidepressants

Many antidepressants are effective in the treatment of chronic anxiety disorders and should be considered as first-line agents, especially in patients with concerns for addiction or dependence. Selective serotonin reuptake inhibitors (SSRIs, such as *escitalopram* or *paroxetine*) or serotonin/norepinephrine reuptake inhibitors (SNRIs, such as *venlafaxine* or *duloxetine*) may be used alone or prescribed in combination with a benzodiazepine during the first weeks of treatment (Figure 9.6). After 4 to 6 weeks, when the antidepressant begins to produce an anxiolytic effect, the benzodiazepine dose can be tapered. While only certain SSRIs or SNRIs have been approved for the treatment of anxiety disorders such as GAD, the efficacy of these drugs is most likely a class effect. Long-term use of antidepressants and benzodiazepines for anxiety disorders is often required to maintain ongoing benefit and prevent relapse.



**Figure 9.6**

Treatment guideline for persistent anxiety. From data of E. C. Dimitrion, A. J. Parashos, and J. S. Giouzepas, Drug Invest. 4: 316 (1992).

## B. Buspirone

*Buspirone* [byoo-SPYE-rone] is a nonbenzodiazepine partial agonist at serotonin receptors. The actions of *buspirone* appear to be mediated by serotonin (5-HT<sub>1A</sub>) receptors, although it also displays some affinity for D<sub>2</sub> dopamine receptors and 5-HT<sub>2A</sub> serotonin receptors. Thus, its mode of action differs from that of the benzodiazepines. *Buspirone* is useful for the chronic treatment of generalized anxiety disorder (GAD) and has an efficacy comparable to that of benzodiazepines as it is devoid of sedation, hypnosis, and general CNS depression or drug abuse liability of benzodiazepines (Figure 9.7). It has a slow onset of action and is not effective for short-term or “as-needed” treatment of acute anxiety. In addition, *buspirone* lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines. *Buspirone* usually requires therapy of 3 to 6 weeks to demonstrate efficacy. The frequency of adverse effects is low, with the most common effects being headache, dizziness, nervousness, nausea, and light-headedness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely, a benefit that is particularly important in elderly patients. *Buspirone* does not potentiate the CNS depression of alcohol.

Figure 9.8 compares the common adverse effects of *buspirone* and the benzodiazepine *alprazolam*.

SEDATION		HYPNOSIS	
DRUG	DOSAGE	DRUG	DOSAGE (mg) (AT BEDTIME)
<b>Benzodiazepines (short-acting):</b>			
<i>Alprazolam</i>	0.25–0.5 mg, 2 to 3 times daily		
<i>Oxazepam</i>	15–30 mg, 3 to 4 times daily		
<i>Halazepam</i>	20–40 mg, 3 to 4 times daily	<i>Triazolam</i>	0.125–0.5
<b>Benzodiazepines (intermediate-acting):</b>			
<i>Lorazepam</i>	1–2 mg, once or twice daily	<i>Temazepam</i>	7.5–30
<i>Chlordiazepoxide</i>	10–20 mg, 2 to 3 times daily	<i>Lorazepam</i>	2–4
		<i>Choral hydrate</i>	500–1000
<b>Benzodiazepines (long-acting):</b>			
<i>Chlorazepate</i>	5–7.5 mg twice daily	<i>Estazolam</i>	0.5–2
<i>Diazepam</i>	5 mg twice daily	<i>Quazepam</i>	7.5–15
<b>Nonbenzodiazepines:</b>			
<i>Phenobarbital</i>	15–30 mg, 2 to 3 times daily	<i>Secobarbital</i>	100–200
<i>Buspirone</i>	5–10 mg, 2 to 3 times daily	<i>Zaleplon</i>	5–20
<i>Z drugs</i>		<i>Zolpidem</i>	5–10
		<i>Eszopiclone</i>	1–3

Benzodiazepines are associated with less adverse respiratory and cardiovascular effects than most alternative tranquilizers or sedatives.

**Note:** Fast-acting drug with short duration of action are preferred in insomnia characterized by difficulty in falling asleep (as opposed to difficulty in staying asleep); extended release preparations used for sleep maintenance.

**Figure 9.7**

Dosages of drugs used commonly for sedation and hypnosis.

## V. BARBITURATES

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. They have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance and physical dependence, are lethal in overdose, and are associated with severe withdrawal symptoms. All barbiturates are controlled substances.

### A. Mechanism of action

The sedative-hypnotic action of the barbiturates is due to their interaction with GABA<sub>A</sub> receptors, which enhances GABAergic transmission. The binding site of barbiturates on the GABA receptor is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings. In addition, barbiturates can block excitatory glutamate receptors. These molecular actions lead to decreased neuronal activity.

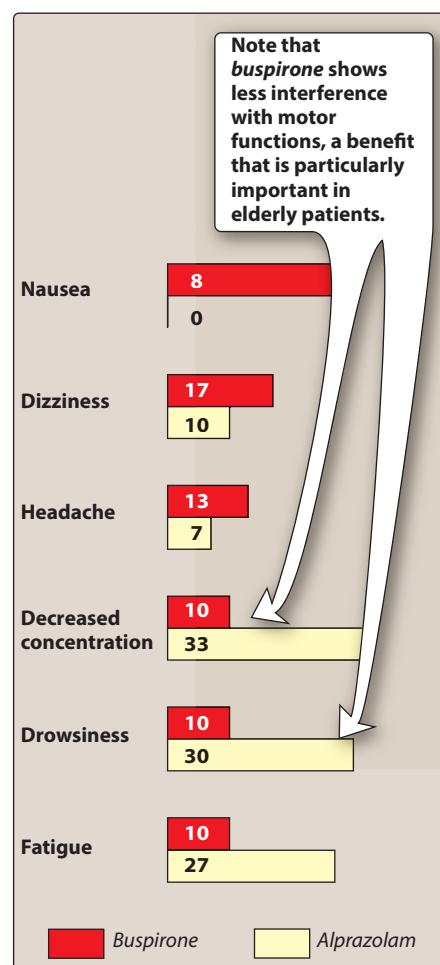
### B. Actions

Barbiturates are classified according to their duration of action (Figure 9.9). Long-acting *phenobarbital* [fee-noe-BAR-bi-tal] has a duration of action greater than a day. *Pentobarbital* [pen-toe-BAR-bi-tal], *secobarbital* [see-koe-BAR-bi-tal], *amobarbital* [am-oh-BAR-bi-tal], and *butilbarbital* [bu-TAL-bi-tal] are short-acting barbiturates.

- Depression of CNS:** At low doses, the barbiturates produce sedation (have a calming effect and reduce excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation) and, finally, coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose. Barbiturates do not raise the pain threshold and have no analgesic properties. They may even exacerbate pain. Chronic use leads to tolerance.
- Respiratory depression:** Barbiturates suppress the hypoxic and chemoreceptor response to CO<sub>2</sub>, and overdose is followed by respiratory depression and death.

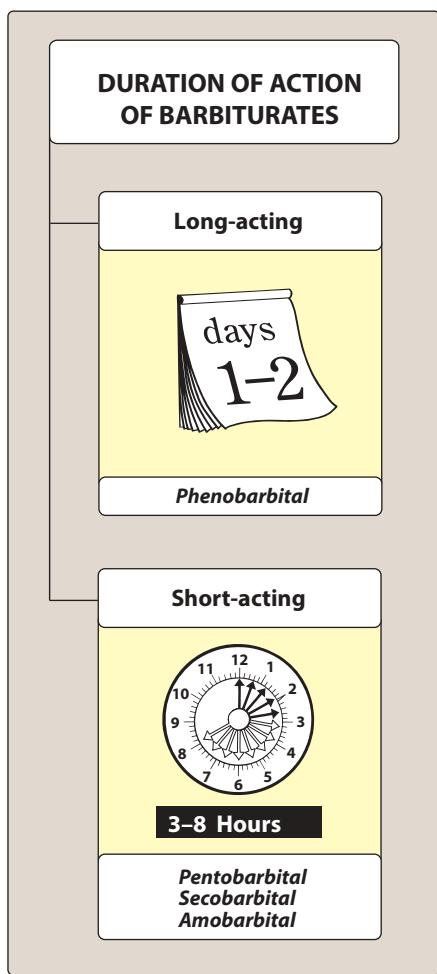
### C. Therapeutic uses

- Anesthesia:** The ultra short-acting barbiturates have been historically used intravenously to induce anesthesia but have been replaced by other agents.
- Anticonvulsant:** *Phenobarbital* has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression. However, *phenobarbital* can depress cognitive development in children and decrease cognitive performance in adults, and it should be used for seizures only if other therapies have failed. Similarly, *phenobarbital* may be used for the treatment of refractory status epilepticus.



**Figure 9.8**

Comparison of common adverse effects of *buspirone* and *alprazolam*. Results are expressed as the percentage of patients showing each symptom.

**Figure 9.9**

Barbiturates classified according to their durations of action.

**3. Sedative/hypnotic:** Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. When used as hypnotics, they suppress REM sleep more than other stages. However, the use of barbiturates for insomnia is no longer generally accepted, given their adverse effects and potential for tolerance. *Butalbital* is commonly used in combination products (with *acetaminophen* and *caffeine* or *aspirin* and *caffeine*) as a sedative to assist in the management of tension or migraine headaches.

#### D. Pharmacokinetics

Barbiturates are well absorbed after oral administration and distribute throughout the body. All barbiturates redistribute from the brain to the splanchnic areas, to skeletal muscle, and, finally, to adipose tissue. Barbiturates readily cross the placenta and can depress the fetus. These agents are metabolized in the liver, and inactive metabolites are excreted in urine.

#### E. Adverse effects

Barbiturates cause drowsiness, impaired concentration, and mental and psychomotor impairment (Figure 9.10). The CNS depressant effects of barbiturates synergize with those of *ethanol*.

Hypnotic doses of barbiturates produce a drug “hangover” that may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur. Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are metabolized by the CYP450 system. Barbiturates are contraindicated in patients with acute intermittent porphyria. Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opioids and can result in death. Death may also result from overdose. Severe depression of respiration and central cardiovascular depression results in a shock-like condition with shallow, infrequent breathing. Treatment includes supportive care and gastric decontamination for recent ingestions.

## VI. NONBENZODIAZEPINE HYPNOTIC AGENTS

Nonbenzodiazepine (*zolpidem*, *zaleplon*, and *eszopiclone*), often referred to as “Z-drugs,” are similar to benzodiazepine in nature though they are unrelated to benzodiazepines on a molecular level as they have dissimilar or entirely different chemical structures. However, the pharmacodynamics of nonbenzodiazepine is almost entirely the same as that of benzodiazepine and therefore employs similar benefits, adverse effects, and risks. Like the benzodiazepines, nonbenzodiazepines exert their effects by binding to and activating the benzodiazepine site of the receptor complex. Their actions are blocked and reversed by the benzodiazepine antagonist *flumazenil*. These drugs are widely used for short-term management of insomnia. Unlike the benzodiazepines, at usual hypnotic doses, the nonbenzodiazepine drugs, *zolpidem*, *zaleplon*, and *eszopiclone*, do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics. All the three agents are controlled substances. Unlike benzodiazepines, these drugs have reduced potential for tolerance, abuse, physical dependence, or

rebound insomnia. The side effects of each of these drugs can differ due to differences in onset of action and metabolism.

### A. Zolpidem

The hypnotic *zolpidem* [ZOL-pi-dem] is not structurally related to benzodiazepines, but it binds to GABA<sub>A</sub>, with relative selectivity for those with the  $\alpha_1$  subunit. *Zolpidem* has no anticonvulsant or muscle-relaxing properties at hypnotic doses. It shows few withdrawal effects, exhibits minimal rebound insomnia, and little tolerance occurs with prolonged use. *Zolpidem* is rapidly absorbed after oral administration. It has a rapid onset of action and short elimination half-life (about 2 to 3 hours). The drug provides a hypnotic effect for approximately 5 hours (Figure 9.11). [Note: A lingual spray and an extended-release formulation are also available. A sublingual tablet formulation may be used for middle-of-the-night awakening.] *Zolpidem* undergoes hepatic oxidation by the CYP450 system to inactive products. Thus, drugs such as *rifampin*, which induce this enzyme system, shorten the half-life of *zolpidem*, and drugs that inhibit the CYP3A4 isoenzyme may increase the half-life. Adverse effects of *zolpidem* include headache, dizziness, anterograde amnesia, and next-morning impairment (especially with extended-release formulations). Sleepwalking, sleep driving, and performing other activities while not fully awake have been reported.

### B. Zaleplon

*Zaleplon* [ZAL-e-plon] is an oral nonbenzodiazepine hypnotic similar to *zolpidem*; however, *zaleplon* causes fewer residual effects on psychomotor and cognitive function compared to *zolpidem* or the benzodiazepines. This may be due to its rapid elimination, with a half-life of approximately 1 hour. The drug is metabolized by CYP3A4.

### C. Eszopiclone

*Eszopiclone* [es-ZOE-pi-clone] is an oral nonbenzodiazepine hypnotic that has been shown to be effective for insomnia for up to 6 months; therefore, unlike both *zolpidem* and *zaleplon*, its use is not restricted to short-term use. *Eszopiclone* is rapidly absorbed (time to peak, 1 hour), extensively metabolized by oxidation and demethylation via the CYP450 system to inactive metabolites, and mainly excreted in urine. Elimination half-life is approximately 6 hours. *Eszopiclone* is well tolerated. The main adverse events associated with *eszopiclone* include unpleasant taste, anxiety, dry mouth, headache, peripheral edema, and somnolence.



**Figure 9.10**

Adverse effects of barbiturates.

## VII. OTHER HYPNOTIC AGENTS

### A. Melatonin and melatonin receptor agonists

Melatonin is a hormone secreted by the pineal gland that helps to maintain the circadian rhythm underlying the normal sleep-wake cycle. At an oral dose of 80 mg, melatonin induces sleep, but at lower doses of 2–10 mg it slightly induces the propensity to fall asleep without CNS depression. Therefore, it is used to treat jetlag in international

**Figure 9.11**

Onset and duration of action of the commonly used nonbenzodiazepine hypnotic agents.

travelers and to counter the disturbance in the sleep cycle in night workers.

*Ramelteon* [ram-EL-tee-on] and *tasimelteon* [tas-i-MEL-tee-on] are selective agonists at the MT<sub>1</sub> and MT<sub>2</sub> subtypes of melatonin receptors involved in promotion of sleep. Stimulation of MT<sub>1</sub> and MT<sub>2</sub> receptors by *ramelteon* and *tasimelteon* is thought to induce and promote sleep. They have minimal potential for abuse, and no evidence of dependence or withdrawal effects have been observed. Therefore, *ramelteon* and *tasimelteon* can be administered long term. *Ramelteon* is indicated for the treatment of insomnia characterized by difficulty falling asleep (increased sleep latency). Common adverse effects of *ramelteon* include dizziness, fatigue, and somnolence. *Ramelteon* may also increase prolactin levels. *Tasimelteon* is indicated for non-24-hour sleep-wake disorder, often experienced by patients who are blind. The most common adverse effects of *tasimelteon* are headache, abnormal dreams, increase in liver function tests, and possible upper respiratory tract infections. CYP450 1A2 and 3A4 are the principal isoenzymes required for metabolism of *ramelteon* and *tasimelteon*, and, thus, drug-drug interactions are possible with inducers or inhibitors of these enzymes.

## B. Antihistamines

Some antihistamines with sedating properties, such as *diphenhydramine*, *hydroxyzine*, and *doxylamine*, are effective in treating mild types of situational insomnia. However, they have undesirable adverse effects (such as anticholinergic effects) that make them less useful than the benzodiazepines and the nonbenzodiazepines. Sedative antihistamines are marketed in numerous over-the-counter products.

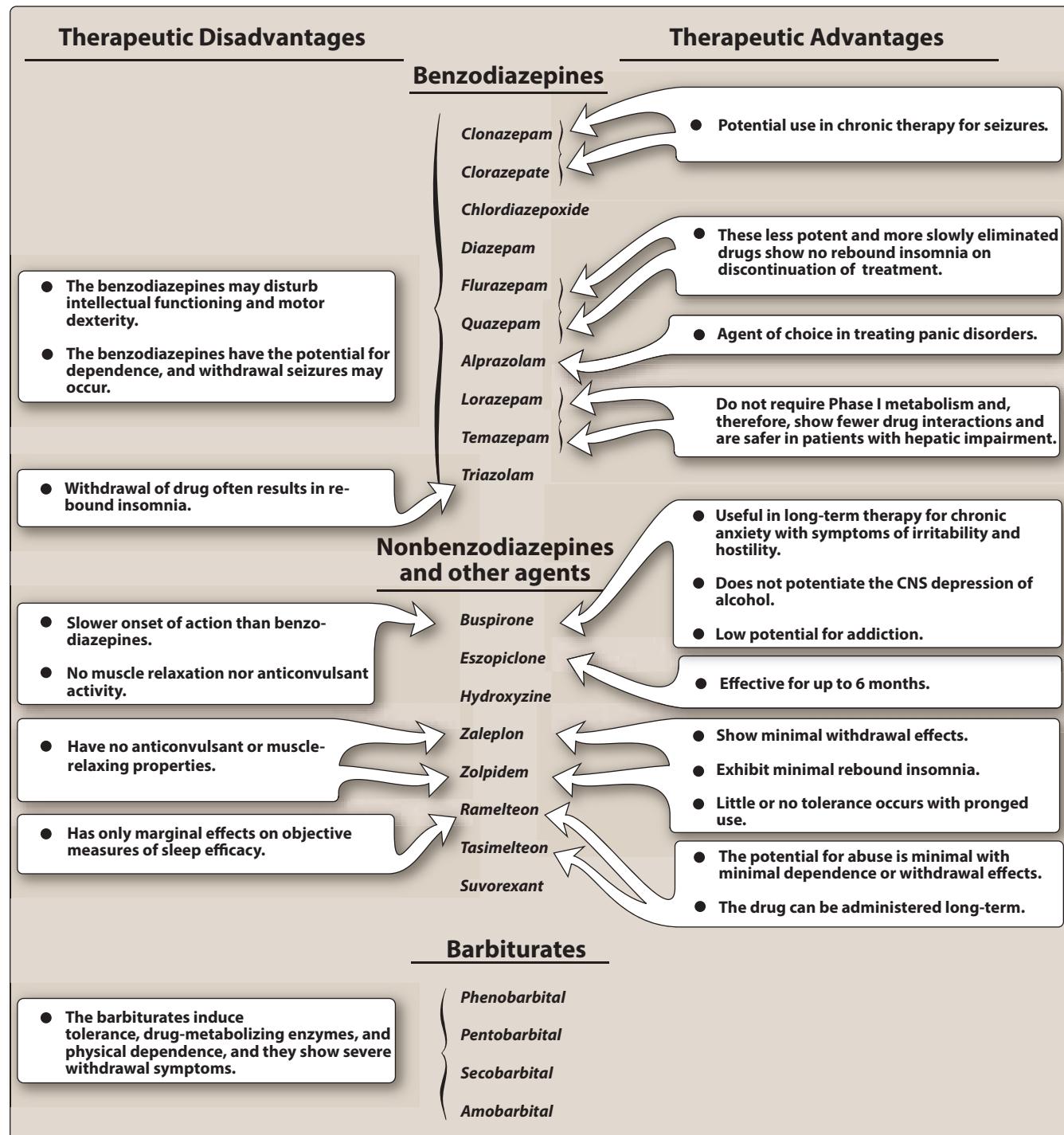
## C. Antidepressants

The use of sedating antidepressants with strong antihistamine profiles has been ongoing for decades. *Doxepin* [DOX-e-pin], an older tricyclic agent with SNRI mechanisms of antidepressant and anxiolytic action, is approved at low doses for the management of insomnia. Other antidepressants, such as *trazodone* [TRAZ-oh-done], *mirtazapine* [mir-TAZ-a-pine], and other older tricyclic antidepressants with strong antihistamine properties are used off-label for the treatment of insomnia (see Chapter 10).

## D. Suvorexant

*Suvorexant* [soo-voe-REX-ant] is an antagonist of the orexin receptor. Orexin is a neuropeptide that promotes wakefulness. Antagonism of the effects of orexin suppresses the wake drive from this neuropeptide. This antagonism may also explain the adverse events that are similar to signs of narcolepsy and cataplexy. The loss of orexin-producing neurons is believed to be an underlying pathology for narcolepsy. Daytime somnolence and increased suicidal ideation are other reported adverse effects. *Suvorexant* is mainly metabolized by CYP4503A4 enzyme, and thus it may have drug interactions with CYP3A4 inducers or inhibitors.

Figure 9.12 summarizes the therapeutic disadvantages and advantages of some of the anxiolytic and hypnotic drugs.

**Figure 9.12**

Therapeutic disadvantages and advantages of some anxiolytic and hypnotic agents. CNS = central nervous system.

## Study Questions

Choose the ONE best answer.

9.1. Which one of the following statements is correct regarding benzodiazepines?

- A. Benzodiazepines directly open chloride channels.
- B. Benzodiazepines show analgesic actions.
- C. Clinical improvement of anxiety requires 2 to 4 weeks of treatment with benzodiazepines.
- D. All benzodiazepines have some sedative effects.

Correct answer = D. Although all benzodiazepines can cause sedation, the drugs labeled "benzodiazepines" in Figure 9.1 are promoted for the treatment of sleep disorder. Benzodiazepines enhance the binding of GABA<sub>A</sub> to its receptor, which increases the permeability of chloride. The benzodiazepines do not relieve pain but may reduce the anxiety associated with pain. Unlike the tricyclic antidepressants and the monoamine oxidase inhibitors, the benzodiazepines are effective within hours of administration. Benzodiazepines do not produce general anesthesia and therefore are relatively safe drugs with a high therapeutic index.

9.2. Which one of the following is a short-acting hypnotic?

- A. Phenobarbital
- B. Diazepam
- C. Chlordiazepoxide
- D. Triazolam

Correct answer = D. Triazolam is a short-acting hypnotic agent. It causes little daytime sedation. The other medications listed are longer acting with longer half-lives.

9.3. Which one of the following statements is correct regarding the anxiolytic and hypnotic agents?

- A. Diazepam and phenobarbital induce the cytochrome P450 enzyme system.
- B. Phenobarbital is useful in the treatment of acute intermittent porphyria.
- C. Phenobarbital induces respiratory depression, which is enhanced by the consumption of ethanol.
- D. Buspirone has actions similar to those of benzodiazepines.

Correct answer = C. Barbiturates and ethanol are a potentially lethal combination because of a high risk for respiratory depression. Only phenobarbital strongly induces the synthesis of the hepatic cytochrome P450 drug-metabolizing system. Phenobarbital is contraindicated in the treatment of acute intermittent porphyria. Buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation.

9.4. A 45-year-old man who has been injured in a car accident is brought into the emergency department. His blood alcohol level at admission is 275 mg/dL. Hospital records show a prior hospitalization for alcohol-related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal?

- A. No pharmacological treatment is necessary.
- B. Lorazepam
- C. Phenytoin
- D. Buspirone

Correct answer = B. It is important to treat the seizures associated with alcohol withdrawal. Benzodiazepines such as chlordiazepoxide, diazepam, or the short-acting lorazepam are effective in controlling this problem. They are less sedating than phenytoin, have fewer adverse effects, and are cross-tolerant with alcohol. Buspirone will not prevent the seizures associated with alcohol withdrawal.

9.5. A 36-year-old male patient reports difficulty falling asleep for the past 2 weeks, but needs to be able to wake up at 6 am for work and doesn't want any daytime sedation. Which medication is best to recommend for the treatment of his insomnia?

- A. Temazepam
- B. Flurazepam
- C. Zaleplon
- D. Buspirone

Correct answer = C. Zaleplon has the shortest half-life and duration of action. Buspirone is not effective as a hypnotic agent. Temazepam and flurazepam have a longer duration of action and reduce nighttime awakenings, but have a greater risk of daytime sedation or hangover effect compared with zaleplon.

9.6. A 45-year-old woman reports constant daytime anxiety about work and family problems. This is causing difficulties functioning and participating in necessary daily activities. Which of the following agents has a rapid anxiolytic effect and is best for the acute management of her anxiety?

- A. Buspirone
- B. Venlafaxine
- C. Lorazepam
- D. Escitalopram

Correct answer = C. The benzodiazepines have same-day, first-dose efficacy for anxiety, whereas the other agents require 2 to 8 weeks for clinically significant improvement in anxiety to occur.

9.7. Which of the following sedative-hypnotic agents utilizes melatonin receptor agonism as the mechanism of action to induce sleep?

- A. Zolpidem
- B. Eszopiclone
- C. Estazolam
- D. Tasimelteon

Correct answer = D. Tasimelteon is a melatonin receptor agonist to promote sleep, especially in those individuals with non-24-hour sleep-wake disorder. Zolpidem, eszopiclone, and estazolam all utilize the benzodiazepine receptor.

9.8. A 50-year-old man presents with insomnia not responsive to sleep hygiene interventions. He has a long history of alcohol and opioid abuse. He has been successfully sober for 10 years but is very concerned about future addiction and dependence. Which is most appropriate to address insomnia and minimize the risk for dependence in this patient?

- A. Zaleplon
- B. Flurazepam
- C. Doxepin
- D. Zolpidem

Correct answer = C. Only doxepin, a tricyclic agent with significant antihistaminergic properties, is considered to have no risk of addiction or dependence. The other agents are all controlled substances with some risk for addiction or dependence, especially when used for extended periods.

9.9. A 68-year-old female patient is demonstrating signs and symptoms of insomnia, especially difficulty falling asleep. She is afraid of taking a medication that can negatively affect her memory and concentration, as she is still working as a bookkeeper. She has been taking temazepam for the past 4 days and has noticed a memory problem and would like to discontinue this medication. Which medication is most appropriate to treat the insomnia and minimize the risk for cognitive impairment?

- A. Diphenhydramine
- B. Zolpidem
- C. Alprazolam
- D. Ramelteon

Correct answer = D. All of these agents, except ramelteon, have been associated with cognitive impairments, including memory impairment. Diphenhydramine likely causes its cognitive problems from its anticholinergic and antihistaminergic effects. Zolpidem and alprazolam are well-known causes of cognitive impairment, including anterograde amnesia. Ramelteon is a noncontrolled hypnotic agent acting as a melatonin receptor agonist. It is not considered to have a risk for cognitive impairment compared with the other agents listed.

9.10. An 18-year-old woman is admitted to the emergency room after an accidental overdose of alprazolam. She is unconscious and not considered a regular user of any medications or illicit drugs. Which treatment could be used to reverse the effect of the alprazolam overdose?

- A. Diazepam
- B. Ramelteon
- C. Flumazenil
- D. Naloxone

Correct answer = C. Flumazenil is only indicated to reverse the effects of benzodiazepines via antagonism of the benzodiazepine receptor. It should be used with caution because of a risk of seizures if the patient has been a long-time recipient of benzodiazepines or if the overdose attempt was with mixed drugs. Naloxone is an opioid receptor antagonist. The other agents are not efficacious in reversing effects of benzodiazepines.

# Antidepressants

Jose A. Rey

10

## I. OVERVIEW

The symptoms of depression are feelings of sadness and hopelessness, as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts. Mania is characterized by the opposite behavior: enthusiasm, anger, rapid thought and speech patterns, extreme self-confidence, and impaired judgment. This chapter provides an overview of drugs used for the treatment of depression and mania.

## II. MECHANISM OF ANTIDEPRESSANT DRUGS

Most antidepressant drugs (Figure 10.1) potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin (5-HT) in the brain. This, along with other evidence, led to the biogenic amine theory, which proposes that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain. Conversely, the theory proposes that mania is caused by an overproduction of these neurotransmitters. However, the biogenic amine theory of depression and mania is overly simplistic. It fails to explain the time course for a therapeutic response, which usually occurs over several weeks compared to the immediate pharmacodynamic effects of the agents, which is usually immediate. This suggests that decreased reuptake of neurotransmitters is only an initial effect of the drugs, which may not be directly responsible for the antidepressant effects.

## III. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The selective serotonin reuptake inhibitors (SSRIs) are a group of antidepressant drugs that specifically inhibit serotonin reuptake, having 300- to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter. This contrasts with the tricyclic antidepressants (TCAs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) that nonselectively inhibit the reuptake of norepinephrine and serotonin (Figure 10.2). Moreover, the SSRIs have little blocking activity at muscarinic,  $\alpha$ -adrenergic, and histaminic H<sub>1</sub> receptors. Because they have different adverse effects and are relatively safe in overdose, the SSRIs have largely replaced TCAs and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression. The SSRIs include *fluoxetine* [floo-OX-e-teen] (the prototypic drug), *citalopram* [sye-TAL-oh-pram], *escitalopram* [es-sye-TAL-oh-pram], *fluvoxamine* [floo-VOX-e-meen], *paroxetine* [pa-ROX-e-teen], and *sertraline* [SER-tra-leen]. *Escitalopram* is the pure S-enantiomer of *citalopram*.

### SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

*Fluoxetine*  
*Paroxetine*  
*Citalopram*  
*Escitalopram*  
*Fluvoxamine*  
*Sertraline*

### SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

*Duloxetine*  
*Venlafaxine*  
*Desvenlafaxine*  
*Levomilnacipran*

### ATYPICAL ANTIDEPRESSANTS

*Bupropion*  
*Mirtazapine*  
*Nefazodone*  
*Trazodone*  
*Vilazodone*  
*Vortioxetine*

### TRICYCLIC ANTIDEPRESSANTS (TCAs)

*Amitriptyline*  
*Nortriptyline*  
*Protriptyline*  
*Doxepin*  
*Amoxapine*  
*Imipramine*  
*Desipramine*  
*Clomipramine*  
*Trimipramine*  
*Maprotiline*

### MONOAMINE OXIDASE INHIBITORS (MAOIs)

*Isocarboxazid*  
*Phenelzine*  
*Selegiline*  
*Tranylcypromine*

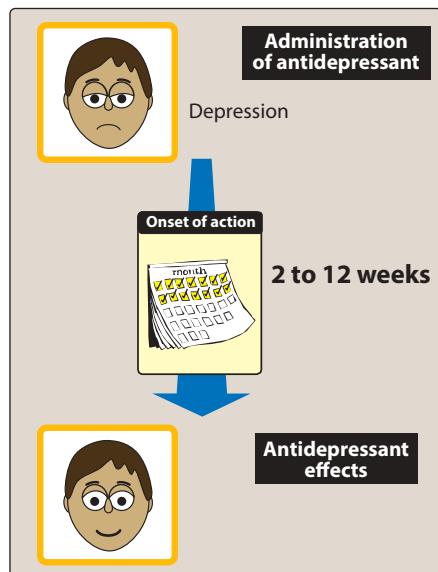
Figure 10.1

Summary of antidepressants.

DRUG AND CLASSIFICATION	UPTAKE INHIBITORS	UPTAKE INHIBITION
	Norepinephrine	Serotonin
<b>Tricyclic antidepressants:</b>		
Tertiary amines		
<i>Amitriptyline</i>	++	+++
<i>Imipramine</i>	++	+++
<i>Trimipramine</i>	+	0
<i>Doxepin</i>	+	++
<i>Clomipramine</i>	+++	+++
Secondary amines		
<i>Desipramine</i>	+++	0
<i>Nortriptyline</i>	++	+++
<i>Protriptyline</i>	+++	0
Dibenzoxazepine		
<i>Amoxapine</i>	++	+
<b>Selective serotonin reuptake inhibitors:</b>		
<i>Fluoxetine</i>	0/+	+++
<i>Paroxetine</i>	0	+++
<i>Sertraline</i>	0	+++
<i>Citalopram</i>	0	+++
<i>Escitalopram</i>	0	+++
<i>Fluvoxamine</i>	0	+++
<b>Other antidepressants:</b>		
<i>Trazodone</i>	0	++
<i>Maprotiline</i>	+++	0
<i>Bupropion</i>	0/+	0/+
<i>Venlafaxine</i>	++	+++
<i>Nefazodone</i>	0	0/+
<i>Mirtazapine</i>	0	0
<i>Duloxetine</i>	+++	+++

**Figure 10.2**

Relative activity of selected antidepressant drugs on prejunctional neuronal uptake of norepinephrine and serotonin.

**Figure 10.3**

Onset of therapeutic effects of the major antidepressant drugs requires several weeks.

### A. Actions

The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft. Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more (Figure 10.3).

A patient must be treated with an adequate dosage for at least 6 weeks before considering changing the treatment, although adverse effects due to their synaptic effects occur soon after taking the drug (Figure 10.4). However, with long-term administration of the drug, adaptive changes may occur. These changes can result in an adjustment to certain adverse effects, the development of new adverse effects, and the onset of therapeutic effects. Marked interindividual variations in the blood levels of an antidepressant with a given dose may be observed due to individual differences in the activity of drug-metabolizing enzymes. Clinically, these differences likely underlie the observed differences in the rates of response and of adverse effects. The dose of antidepressants could be tailored to achieve therapeutic effects and avoid adverse effects.

PHARMACOLOGIC PROPERTY/ RECEPTOR SUBTYPE	ADVERSE CLINICAL CONSEQUENCES
Blockade of norepinephrine uptake at nerve endings	Tremors Tachycardia Erectile and ejaculatory dysfunction Blockade of antihypertensive effects of clonidine, $\alpha$ -methyldopa Augmentation of pressor effects of sympathomimetic amines
Blockade of serotonin uptake at nerve endings	Gastrointestinal disturbances—nausea Increase or decrease in anxiety (dose-dependent) Drowsiness Sexual dysfunction Extrapyramidal side effects Drug interactions with L-tryptophan, monoamine oxidase inhibitors, and fenfluramine
Blockade of dopamine uptake at nerve endings	Psychomotor activation Antiparkinsonian effect Aggravation of psychosis
Blockade of dopamine D2 receptors	Extrapyramidal movement disorders Sexual dysfunction (males) Endocrine changes—increased secretions, breast enlargement, galactorrhea
Histamine H-receptors	Sedation Weight gain Hypotension Potentiation of CNS depressants
Muscarinic receptors	Dry mouth Blurred vision Constipation Urinary retention Sinus tachycardia Memory dysfunction
$\alpha_1$ Adrenoceptors	Postural hypotension Potentiation of the antihypertensive effect of prazosin, doxazosin, terazosin, and labetalol Reflex tachycardia Dizziness

**Figure 10.4**

Pharmacologic properties of antidepressants and their possible adverse clinical consequences.

## B. Therapeutic uses

The primary indication for SSRIs is depression. A number of other psychiatric disorders also respond favorably to SSRIs, including obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder, and bulimia nervosa (only *fluoxetine* is approved for bulimia).

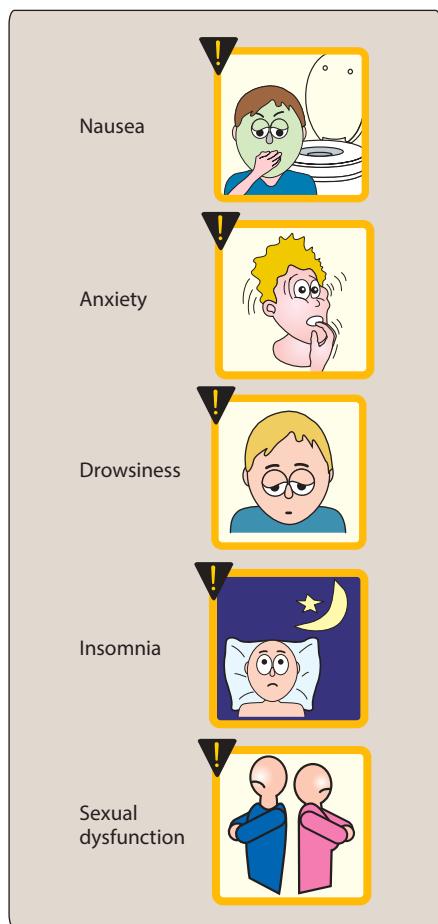
### C. Pharmacokinetics

All of the SSRIs are well absorbed after oral administration. Peak levels are seen in approximately 2 to 8 hours on average. Food has little effect on absorption (except with *sertraline*, for which food increases its absorption). The majority of SSRIs have plasma half-lives that range between 16 and 36 hours. Metabolism by cytochrome P450 (CYP450)-dependent enzymes and glucuronide or sulfate conjugation occurs extensively. *Fluoxetine* has the longest half-life (50 hours), and the half-life of its active metabolite S-norfluoxetine is quite long, averaging 10 days. *Fluoxetine* and *paroxetine* are potent inhibitors of a CYP450 isoenzyme (CYP2D6). Other CYP450 isoenzymes (CYP2C9/19, CYP3A4, CYP1A2) are involved with SSRI metabolism and may also be inhibited to various degrees by the SSRIs.

### D. Adverse effects

The most adverse effects of antidepressants can be explained by their synaptic effects. Although the SSRIs are considered to have fewer and less severe adverse effects than the TCAs and MAOIs, the SSRIs are not without adverse effects, such as headache, sweating, anxiety and agitation, hyponatremia, transient gastrointestinal (GI) effects (nausea, vomiting, diarrhea), weakness and fatigue, sexual dysfunction, changes in weight (weight loss followed by weight gain in some patients, especially with *paroxetine*), sleep disturbances (insomnia and somnolence), and the above-mentioned potential for drug–drug interactions (Figure 10.5).

- Sleep disturbances:** *Paroxetine* and *fluvoxamine* are generally more sedating than activating, and they may be useful in patients who have difficulty in sleeping. Conversely, patients who are fatigued or complaining of excessive somnolence may benefit from one of the more activating SSRIs, such as *fluoxetine* or *sertraline*.
- Sexual dysfunction:** Sexual dysfunction, which may include loss of libido, delayed ejaculation, and anorgasmia, is common with the SSRIs.
- Use in children and teenagers:** Antidepressants should be used cautiously in children and teenagers, because of reports of suicidal ideation as a result of SSRI treatment. Pediatric patients should be observed for worsening depression and suicidal thinking with initiation or dosage change of any antidepressant. *Fluoxetine*, *sertraline*, and *fluvoxamine* are approved for use in children to treat obsessive-compulsive disorder, and *fluoxetine* and *escitalopram* are approved to treat childhood depression.
- Overdose and toxicity:** Overdose with SSRIs does not usually cause cardiac arrhythmias, with the exception of *citalopram*, which may cause QT prolongation. Seizures are a possibility because all antidepressants may lower the seizure threshold. SSRIs have the potential to cause serotonin syndrome, especially when used in the presence of an MAOI or other highly serotonergic drug. Serotonin syndrome may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs. SSRIs including all other antidepressants may increase suicidal ideation; therefore, they have a black box warning especially for children, adolescents, and young adults.



**Figure 10.5**

Some commonly observed adverse effects of selective serotonin reuptake inhibitors.

- 5. Discontinuation syndrome:** SSRIs have the potential to cause a discontinuation syndrome after their abrupt withdrawal, particularly the agents with shorter half-lives and inactive metabolites. *Fluoxetine* has the lowest risk of causing an SSRI discontinuation syndrome due to its longer half-life and active metabolite. Possible signs and symptoms of SSRI discontinuation syndrome include headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern. These effects may persist up to 2 months. SSRIs should be gradually withdrawn to minimize these effects.
- 6. Drug interactions:** SSRIs have been reported to cause though rarely but potentially fatal reaction with other drugs that increase serotonin activity called “serotonin syndrome.” *Fluoxetine* and *paroxetine* inhibit CYP2D6 isozyme potentiating the action of other drugs metabolized by this isozyme.

## IV. SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS

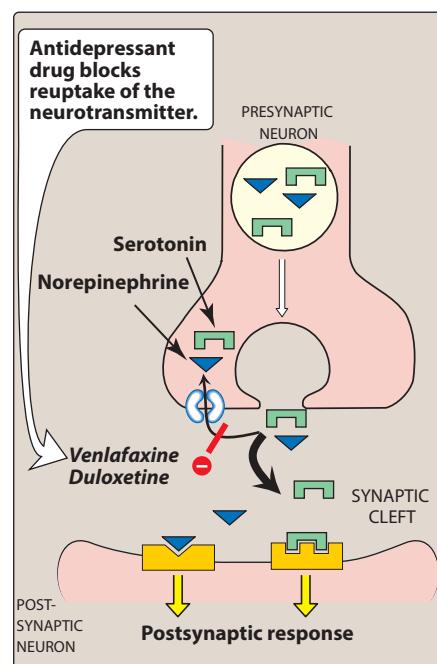
*Venlafaxine* [VEN-la-fax-een], *desvenlafaxine* [dez-VEN-la-fax-een], *levomilnacipran* [leevoh-mil-NA-si-pran], and *duloxetine* [doo-LOX-e-teen] inhibit the reuptake of both serotonin and norepinephrine (Figure 10.6) and, thus, are termed SNRIs. Depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which SSRIs are also relatively ineffective. This pain is, in part, modulated by serotonin and norepinephrine pathways in the central nervous system. Both SNRIs and the TCAs, with their dual inhibition of both serotonin and norepinephrine reuptake, are sometimes effective in relieving pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, and low back pain. The SNRIs, unlike the TCAs, have little activity at  $\alpha$ -adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the TCAs. The SNRIs may precipitate a discontinuation syndrome if treatment is abruptly stopped.

### A. Venlafaxine and desvenlafaxine

*Venlafaxine* is an inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake. *Venlafaxine* has minimal inhibition of the CYP450 isoenzymes and is a substrate of the CYP2D6 isoenzyme. *Desvenlafaxine* is the active, demethylated metabolite of *venlafaxine*. The most common side effects of *venlafaxine* are nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation. At high doses, there may be an increase in blood pressure and heart rate. The clinical activity and adverse effect profile of *desvenlafaxine* are similar to those of *venlafaxine*.

### B. Duloxetine

*Duloxetine* inhibits serotonin and norepinephrine reuptake at all doses. It is extensively metabolized in the liver to inactive metabolites and should be avoided in patients with liver dysfunction. GI side effects are common with *duloxetine*, including nausea, dry mouth, and constipation. Insomnia, dizziness, somnolence, sweating, and



**Figure 10.6**

Proposed mechanism of action of selective serotonin/norepinephrine reuptake inhibitor antidepressant drugs.

sexual dysfunction are also seen. *Duloxetine* may increase blood pressure or heart rate. *Duloxetine* is a moderate inhibitor of CYP2D6 isoenzymes and may increase concentrations of drugs metabolized by this pathway, such as antipsychotics. *Duloxetine* may rarely cause hepatotoxicity.

### C. Levomilnacipran

*Levomilnacipran* is an enantiomer of *milnacipran* (an older SNRI used for the treatment of depression in Europe and fibromyalgia in the United States). The adverse effect profile of *levomilnacipran* is similar to other SNRIs. It is primarily metabolized by CYP3A4, and, thus, activity may be altered by inducers or inhibitors of this enzyme system.

## V. ATYPICAL ANTIDEPRESSANTS

The atypical antidepressants are a mixed group of agents that have actions at several different sites. This group includes *bupropion* [byoo-PROE-pe-on], *mirtazapine* [mir-TAZ-a-peen], *nefazodone* [ne-FAZ-oh-done], *trazodone* [TRAZ-oh-done], *vilazodone* [vil-AZ-oh-done], and *vortioxetine* [vor-TEE-ox-e-teen].

### A. Bupropion

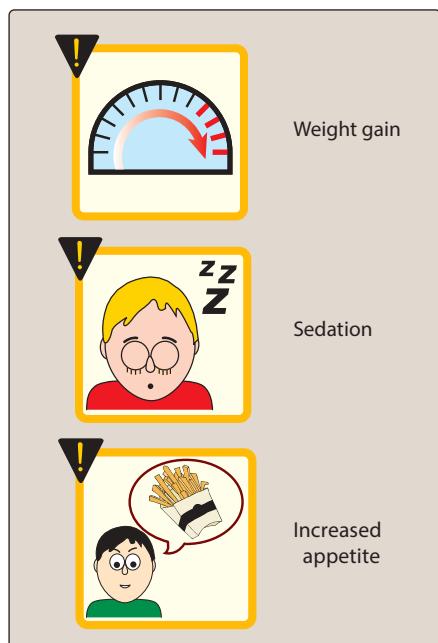
*Bupropion* is a weak dopamine and norepinephrine reuptake inhibitor that is used to alleviate the symptoms of depression. *Bupropion* is also useful for decreasing cravings and attenuating withdrawal symptoms of nicotine in patients trying to quit smoking. Side effects may include dry mouth, sweating, nervousness, tremor, and a dose-dependent increased risk for seizures. It has a very low incidence of sexual dysfunction. *Bupropion* is metabolized by the CYP2B6 pathway and has a relatively low risk for drug–drug interactions, given the few agents that inhibit/induce this enzyme. Use of *bupropion* should be avoided in patients at risk for seizures or those who have eating disorders such as bulimia.

### B. Mirtazapine

*Mirtazapine* enhances serotonin and norepinephrine neurotransmission by serving as an antagonist at central presynaptic  $\alpha_2$  receptors. Additionally, some of the antidepressant activity may be related to antagonism at 5-HT<sub>2</sub> receptors. It is sedating because of its potent antihistaminic activity, but it does not cause the antimuscarinic side effects of the TCAs, or interfere with sexual function like the SSRIs. Sedation, increased appetite, and weight gain frequently occur (Figure 10.7).

### C. Nefazodone and trazodone

These drugs are weak inhibitors of serotonin reuptake and are also antagonists at the postsynaptic 5-HT<sub>2a</sub> receptor. Both agents are highly sedating, probably because of their potent histamine



**Figure 10.7**

Some commonly observed adverse effects of *mirtazapine*.

$H_1$ -blocking activity. *Trazodone* is commonly used off-label for the management of insomnia. These drugs cause gastrointestinal disturbances. Sexual effects are limited except that *trazodone* has been associated with priapism in men. *Nefazodone* has been associated with a rare risk for hepatotoxicity. Both agents also have mild-to-moderate  $\alpha_1$  receptor antagonism, contributing to orthostasis and dizziness.

#### D. Vilazodone

*Vilazodone* is a serotonin reuptake inhibitor and a 5-HT<sub>1a</sub> receptor partial agonist. Although the extent to which the 5-HT<sub>1a</sub> receptor activity contributes to its therapeutic effects is unknown, this possible mechanism of action renders it unique from that of the SSRIs. The adverse effect profile of *vilazodone* is similar to the SSRIs, including a risk for discontinuation syndrome if abruptly stopped.

#### E. Vortioxetine

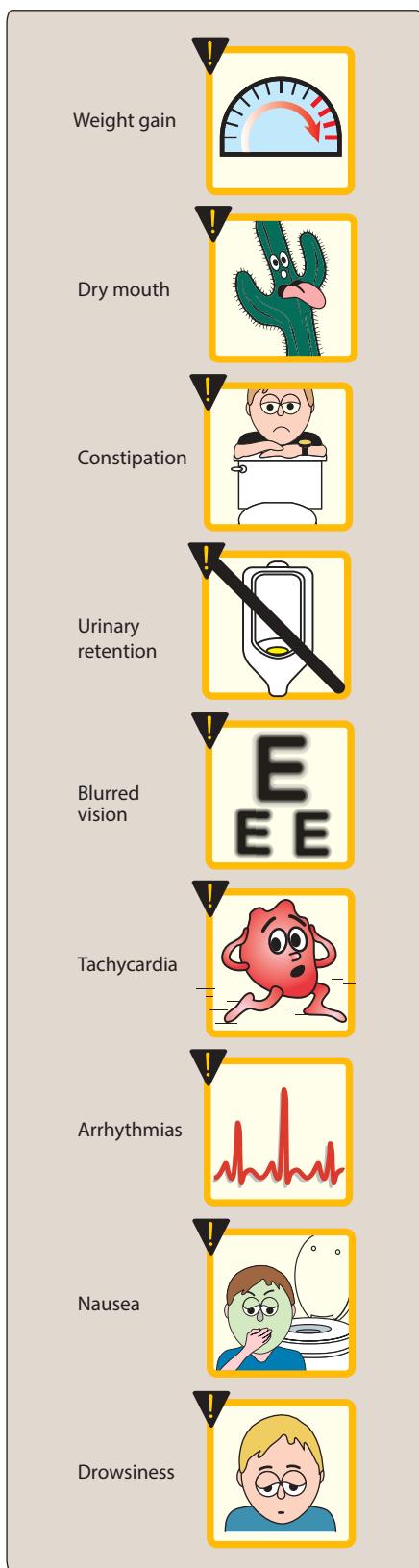
*Vortioxetine* utilizes a combination of serotonin reuptake inhibition, 5-HT<sub>1a</sub> agonism, and 5-HT<sub>3</sub> and 5-HT<sub>7</sub> antagonism as its suggested mechanisms of action to treat depression. It is unclear to what extent the activities other than inhibition of serotonin reuptake influence the overall effects of *vortioxetine*. The common adverse effects include nausea, constipation, and sexual dysfunction, which may be expected due to its serotonergic mechanisms.

## VI. TRICYCLIC ANTIDEPRESSANTS

The TCAs inhibit norepinephrine and serotonin reuptake into the presynaptic neuron and, thus, if discovered today, might have been referred to as SNRIs, except for their differences in adverse effects relative to this newer class of antidepressants. The TCAs include the tertiary amines *imipramine* [ee-MIP-ra-meen] (the prototype drug), *amitriptyline* [a- mee-TRIP-ti-leen], *clomipramine* [kloe-MIP-ra-meen], *doxepin* [DOX- e-pin], and *trimipramine* [trye-MIP-ra-meen], and the secondary amines *desipramine* [dess-IP-ra-meen] and *nortriptyline* [nor-TRIP-ti-leen] (the N-demethylated metabolites of *imipramine* and *amitriptyline*, respectively) and *protriptyline* [proe-TRIP-ti-leen]. *Maprotiline* [ma-PROE-ti-leen] and *amoxapine* [a-MOX-a-peen] are related “tetracyclic” antidepressant agents and are commonly included in the general class of TCAs.

#### A. Mechanism of action

1. **Inhibition of neurotransmitter reuptake:** TCAs and *amoxapine* are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. *Maprotiline* and *desipramine* are relatively selective inhibitors of norepinephrine reuptake.
2. **Blocking of receptors:** TCAs also block serotonergic,  $\alpha$ -adrenergic, histaminic, and muscarinic receptors. It is not known if any of these actions produce the therapeutic benefit of the TCAs. However, actions at these receptors are likely responsible for many of their adverse effects. *Amoxapine* also blocks 5-HT<sub>2</sub> and dopamine D<sub>2</sub> receptors.

**Figure 10.8**

Some commonly observed adverse effects of tricyclic antidepressants.

## B. Actions

The TCAs improve mood, in 50% to 70% of individuals with major depression. The onset of the mood elevation is slow, requiring 2 weeks or longer (Figure 10.3). Patient response can be used to adjust dosage. Tapering of these agents is recommended to minimize discontinuation syndromes and cholinergic rebound effects.

## C. Therapeutic uses

The TCAs are effective in treating moderate to severe depression. Some patients with panic disorder also respond to TCAs. *Imipramine* is used as an alternative to *desmopressin* or nonpharmacologic therapies (enuresis alarms) in the treatment of bedwetting in children. The TCAs, particularly *amitriptyline*, have been used to help prevent migraine headache and treat chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of pain is unclear. Low doses of TCAs, especially *doxepin*, can be used to treat insomnia.

## D. Pharmacokinetics

TCAs are well absorbed upon oral administration. As a result of their variable first-pass metabolism in the liver, TCAs have low and inconsistent bioavailability. These drugs are metabolized by the hepatic microsomal system (and, thus, may be sensitive to agents that induce or inhibit the CYP450 isoenzymes) and conjugated with glucuronic acid. Ultimately, the TCAs are excreted as inactive metabolites via the kidney. These drugs are highly lipid soluble and have a relatively long half-life.

## E. Adverse effects

Blockade of muscarinic receptors leads to blurred vision, xerostomia, urinary retention, sinus tachycardia, constipation, and aggravation of angle-closure glaucoma (Figure 10.8). These agents affect cardiac conduction similar to typical of class IA antiarrhythmics (*quinidine*) and may precipitate life-threatening arrhythmias in an overdose situation. They thus contribute toward the narrow therapeutic index of tricyclic antidepressants. This property is a major pharmacological distinction between the older tricyclic compounds and the newer generation compounds. The TCAs also block  $\alpha$ -adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia. Sedation is related to the ability of these drugs to block histamine H<sub>1</sub> receptors. Weight gain is a common adverse effect of the TCAs. Sexual dysfunction occurs in a minority of patients, and the incidence is lower than that associated with the SSRIs.

All antidepressants, including TCAs, should be used with caution in patients with bipolar disorder, even during their depressed state, because antidepressants may cause a switch to manic behavior. The TCAs have a narrow therapeutic index (for example, five- to six-fold the maximal daily dose of *imipramine* can be lethal). Depressed patients who are suicidal should be given only limited quantities of these drugs and be monitored closely. Drug interactions with the TCAs are shown in Figure 10.9. The TCAs may exacerbate certain medical conditions, such as benign prostatic hyperplasia, epilepsy, and pre-existing arrhythmias.

## VII. MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver. In the neuron, MAO functions as a “safety valve” to oxidatively deaminate and inactivate any excess neurotransmitters (for example, norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest. The MAOIs may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitters to escape degradation and, therefore, to accumulate within the pre-synaptic neuron and leak into the synaptic space. The four MAOIs currently available for the treatment of depression include *phenelzine* [FEN-el-zeen], *tranylcypromine* [tran-il-SIP-roe-meen], *isocarboxazid* [eye-soe-car-BOX-ih-zid], and *selegiline* [seh-LEDGE-ah-leen]. [Note: *Selegiline* is also used for the treatment of Parkinson’s disease. It is the only antidepressant available in a transdermal delivery system.] Use of MAOIs is limited due to the complicated dietary restrictions required while taking these agents.

### A. Mechanism of action

Most MAOIs, such as *phenelzine*, form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into the synaptic space (Figure 10.10). These drugs inhibit not only MAO in the brain but also MAO in the liver and gut that catalyzes oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods. The MAOIs, therefore, show a high incidence of drug–drug and drug–food interactions. *Selegiline* administered as the transdermal patch may produce less inhibition of gut and hepatic MAO at low doses because it avoids first-pass metabolism.

### B. Actions

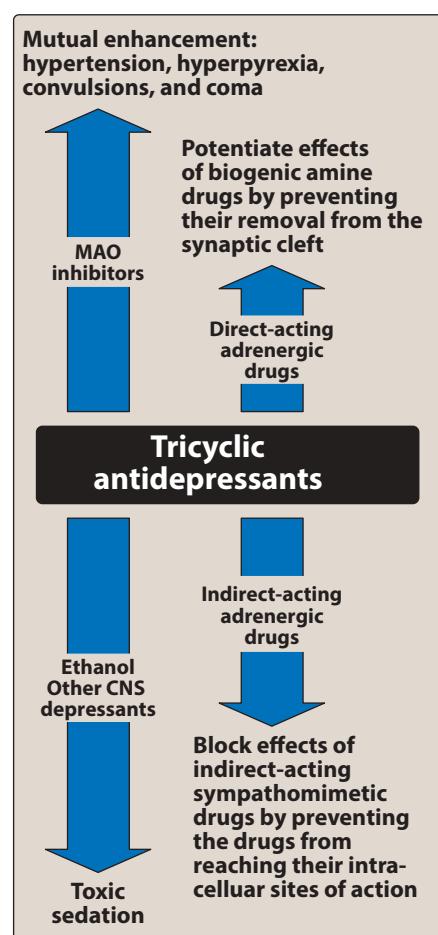
Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs, SNRIs, and TCAs, is delayed several weeks. *Selegiline* and *tranylcypromine* have an amphetamine-like stimulant effect that may produce agitation or insomnia.

### C. Therapeutic uses

The MAOIs are indicated for depressed patients who are unresponsive or intolerant of other antidepressants. Because of their risk for drug–drug and drug–food interactions, the MAOIs are considered last-line agents in many treatment settings.

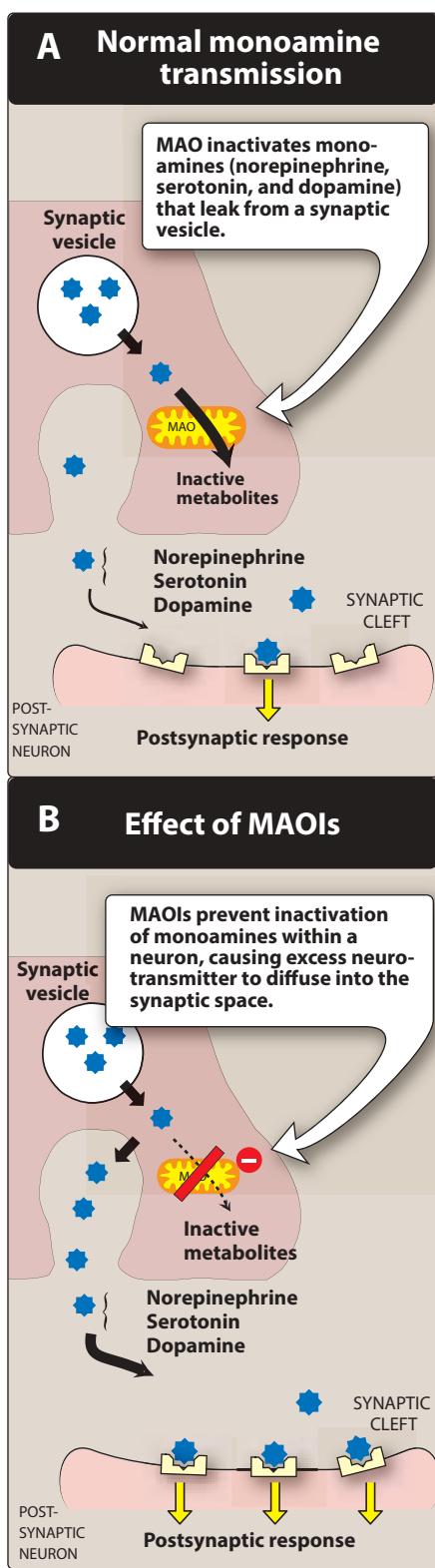
### D. Pharmacokinetics

These drugs are well absorbed after oral administration. Enzyme regeneration, when irreversibly inactivated, varies, but it usually occurs several weeks after termination of the drug. Thus, when switching antidepressant agents, a minimum of 2 weeks of delay must be allowed after termination of MAOI therapy and the initiation of another antidepressant from any other class. MAOIs are hepatically metabolized and excreted rapidly in urine.



**Figure 10.9**

Drugs interacting with tricyclic antidepressants. CNS = central nervous system; MAO = monoamine oxidase.

**Figure 10.10**

Mechanism of action of monoamine oxidase inhibitors (MAOIs).

### E. Adverse effects

Severe and often unpredictable side effects, due to drug-food and drug-drug interactions, limit the widespread use of MAOIs. For example, tyramine, which is contained in foods, such as aged cheeses and meats, liver, pickled or smoked fish, and red wines, is normally inactivated by MAO in the gut. Individuals receiving an MAOI are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in a hypertensive crisis, with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and, possibly, stroke. Patients must, therefore, be educated to avoid tyramine-containing foods. Other possible adverse effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation. SSRIs should not be coadministered with MAOIs due to the risk of serotonin syndrome. Both SSRIs and MAOIs require a washout period of at least 2 weeks before the other type is administered, with the exception of *fluoxetine*, which should be discontinued at least 6 weeks before an MAOI is initiated. In addition, the MAOIs have many other critical drug interactions, and caution is required when administering these agents concurrently with other drugs. *Figure 10.11* summarizes the side effects of the antidepressant drugs. *Figure 10.12* depicts the commonly used antidepressants, their dosage, and adverse effects.

## VIII. SEROTONIN-DOPAMINE ANTAGONISTS

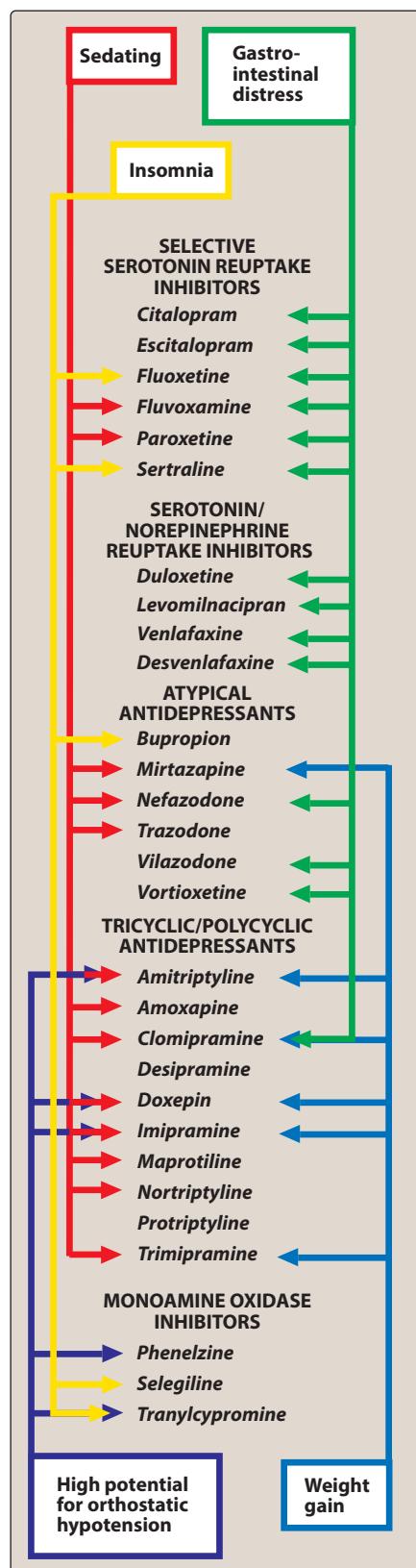
While 60% to 80% of patients respond favorably to antidepressants, 20% to 40% experience a partial or poor response to monotherapy. The serotonin-dopamine antagonists (SDAs), or atypical antipsychotics, are occasionally used as adjunctive treatments to antidepressants in partial responders. *Aripiprazole*, *brexpiprazole*, *quetiapine*, and the combination of *fluoxetine* and *olanzapine* are approved for use as adjuncts in major depressive disorder (MDD).

## IX. TREATMENT OF MANIA AND BIPOLAR DISORDER

The treatment of bipolar disorder has increased in recent years due to increased recognition of the disorder and also an increase in the number of available medications for the treatment of mania.

### A. Lithium

*Lithium salts* are used acutely and prophylactically for managing bipolar patients. *Lithium* normalizes mood and is effective in treating 60% to 80% of patients exhibiting mania and hypomania. The onset of therapeutic effect takes 2 to 3 weeks. Antipsychotic drugs and benzodiazepines can be used in the initial stages of the disease to control acute agitation. Anticonvulsants such as *valproic acid*, *carbamazepine*, and *lamotrigine* have been used extensively either alone or as adjunct to lithium therapy. Although many cellular processes are altered by treatment with *lithium*, the mode of action is unknown. The therapeutic index of *lithium* is extremely low (0.5 to 1.4 mmol/L), and levels above 2 mmol/L can be toxic. The levels of *lithium* should be monitored regularly. Common adverse effects at therapeutic levels may include headache, dry mouth, polydipsia, polyuria, polyphagia, edema, weight gain, GI distress fine hand tremor, dizziness, fatigue, dermatologic reactions,

**Figure 10.11**

Side effects of some drugs used to treat depression.

CLASS AND EXAMPLES	TYPICAL DAILY DOSE	MAXIMUM DOSE	THERAPEUTIC USES	ADVERSE EFFECTS
<b>Tricyclic antidepressants (TCAs):</b>				
<i>Amitriptyline</i> <i>Imipramine</i> <i>Clomipramine</i> <i>Nortriptyline</i>	25–150 mg 25–150 mg 25–150 mg 25–150 mg	300 mg <sup>1,2</sup> 300 mg 300 mg 200 mg	Major depression; chronic pain with or without depression	Orthostatic hypotension Weight gain GI disturbance Sexual dysfunction Seizures Irregular heart Suicidal thoughts and behavior
<b>Selective serotonin reuptake inhibitors (SSRIs):</b>				
<i>Fluoxetine</i> <i>Paroxetine</i> <i>Sertraline</i> <i>Citalopram</i> <i>Escitalopram</i> <i>Vilazodone</i> <sup>3</sup>	10–40 mg 20–40 mg 50–200 mg 10–40 mg 10–20 mg 10–40 mg	80 mg 50 mg 200 mg 40 mg 30 mg 80 mg	Anxiety and depression disorder, obsessive compulsive disorder, post-traumatic stress disorder (PTSD)	GI disturbance Sexual dysfunction Increased suicidal thoughts or behavior Serotonin syndrome with MAOIs Some CYP interactions Reduce dose with concomitant CYP3A4 inhibitors (for example, <i>itraconazole</i> , <i>clarithromycin</i> , and <i>voriconazole</i> ) Increase dose with concomitant CYP3A4 inducers (for example, <i>carbamazepine</i> , <i>phenytoin</i> , and <i>rifampin</i> )
<b>Serotonin-norepinephrine reuptake inhibitors (SNRIs):</b>				
<i>Duloxetine</i> <i>Desvenlafaxine</i> <i>Venlafaxine</i>	30–90 mg 50–100 mg 37.5–225 mg	120 mg 100 mg 375 mg	Anxiety and depression, attention deficit, hyperactivity disorder (ADHD), autism fibromyalgia, PTSD, menopause symptoms	Nausea Dizziness Increased suicidal thoughts and behavior Sexual dysfunction <i>Duloxetine</i> contraindicated in uncontrolled glaucoma

**Figure 10.12**

Dosage of antidepressants and their adverse effects. (Figure continues on next page)

CLASS AND EXAMPLES	TYPICAL DAILY DOSE	MAXIMUM DOSE	THERAPEUTIC USES	ADVERSE EFFECTS
<b>Atypical antidepressants:</b>				
<i>Bupropion</i> <i>Nefazodone</i> <i>Trazodone</i>	100–300 mg 200–600 mg 25–200 mg for sleep <sup>1</sup> 150 mg for depression	400–450 mg 600 mg <sup>4</sup> >600 mg	Anxiety and depression disorder	Priapism with <i>trazodone</i> Hepatotoxicity with <i>nefazodone</i>
<b><math>\alpha_2</math> Agonist:</b>				
<i>Mirtazapine</i>	15–30 mg <sup>1</sup>	45 mg	Major depression	Dry mouth, sweating, nervousness, tremors, dose-dependent increase in seizures, no weight gain
<b>Monoamine oxidase (MAO) inhibitors:</b>				
<i>Phenelzine</i> <i>Selegiline</i> <sup>5</sup> <i>Tranylcypromine</i>	10–30 mg	60–90 mg 12 mg/24 hr 60 mg	Resistant depression and atypical depression	Weight gain Sexual dysfunction Suicidal thoughts Hypertensive crisis with tyramine-containing food Orthostatic hypotension

<sup>1</sup>At bedtime<sup>2</sup>Can be divided<sup>3</sup>Not associated with sexual dysfunction or weight gain<sup>4</sup>In divided doses<sup>5</sup>Selegiline transdermal patch available**Figure 10.12 (Continued)**

Dosage of antidepressants and their adverse effects.

and sedation. Thyroid function may be decreased and should be monitored. Adverse effects due to higher plasma levels may indicate toxicity and include ataxia, slurred speech, and coarse tremors. Plasma levels above  $>2.5$  mmol/L show effects such as clonic movements of limbs, confusion, circulatory collapse, and convulsions. Treatment of toxicity includes discontinuation of lithium, hemodialysis, and the use of anticonvulsants. *Lithium* is renally eliminated; 80% is reabsorbed in the proximal renal tubule. Therefore, caution should be used when dosing this drug in renally impaired patients. It may be the best choice in patients with hepatic impairment. Sodium depletion results in increased renal reabsorption of *lithium* and increased chance for toxicity. Sodium depletion is increased by low-salt diets, thiazide diuretics, furosemide, ethacrynic acid, or severe diarrhea or vomiting. Chances of *lithium* toxicity increase by some nonsteroidal anti-inflammatory drugs such as *indomethacin* due to decreased renal clearance of lithium. *Lithium* is contraindicated during the first trimester of pregnancy and lactation because of the possible fetal congenital abnormalities and neonatal dysfunction.

## B. Other drugs

Several antiepileptic drugs, including *carbamazepine*, *valproic acid*, and *lamotrigine*, are approved as mood stabilizers for bipolar disorder. Other agents that may improve manic symptoms include the older (*chlorpromazine* and *haloperidol*) and newer antipsychotics. The atypical antipsychotics *risperidone*, *olanzapine*, *ziprasidone*, *ariprazole*, *asenapine*, *cariprazine*, and *quetiapine* (see Chapter 11) are also used for the management of mania. *Quetiapine*, *lurasidone*, and the combination of *clonazepam* and *fluoxetine* have been approved for bipolar depression.

## Study Questions

Choose the ONE best answer.

10.1 A 55-year-old teacher was diagnosed with depression. After 6 weeks of therapy with fluoxetine, his symptoms improved, but he complains of sexual dysfunction. Which of the following drugs might be useful for management of depression in this patient?

- A. Sertraline
- B. Citalopram
- C. Mirtazapine
- D. Lithium

Correct answer = C. Mirtazapine is largely free from sexual side effects. However, sexual dysfunction commonly occurs with SSRIs (sertraline and citalopram), as well as with TCAs, and SNRIs. Lithium is used for the treatment of mania and bipolar disorder.

10.2 A 25-year-old woman has a long history of depressive symptoms accompanied by body aches and pain secondary to a car accident. Which of the following drugs might be useful in this patient?

- A. Fluoxetine
- B. Sertraline
- C. Phenelzine
- D. Duloxetine

Correct answer = D. Duloxetine is an SNRI that can be used for depression accompanied by symptoms of pain. SSRIs (fluoxetine and sertraline) and MAOIs (phenelzine) have little activity against pain syndromes.

10.3 A 51-year-old woman with symptoms of major depression also has angle-closure glaucoma. Which antidepressant should be avoided in this patient?

- A. Amitriptyline
- B. Bupropion
- C. Mirtazapine
- D. Fluvoxamine

Correct answer = A. Because of its potent antimuscarinic activity, amitriptyline should not be given to patients with glaucoma because of the risk of acute increases in intraocular pressure. The other antidepressants all lack antagonist activity at the muscarinic receptor.

10.4 A 36-year-old man presents with symptoms of compulsive behavior. He realizes that his behavior is interfering with his ability to accomplish his daily tasks, but cannot seem to stop himself. Which drug would be most helpful to this patient?

- A. Desipramine
- B. Paroxetine
- C. Amitriptyline
- D. Selegiline

Correct answer = B. SSRIs are particularly effective in treating obsessive-compulsive disorder, and paroxetine is approved for this condition. The other drugs are less effective in the treatment of obsessive-compulsive disorder.

- 10.5 Which antidepressant has, as its two proposed principal mechanisms of action, 5-HT<sub>1a</sub> receptor partial agonism and 5-HT reuptake inhibition?
- A. Fluoxetine
  - B. Aripiprazole
  - C. Maprotiline
  - D. Vilazodone
- 10.6 Which antidepressant is the most sedating?
- A. Bupropion
  - B. Duloxetine
  - C. Doxepin
  - D. Venlafaxine
- 10.7 Which mood stabilizer is completely renally eliminated and may be beneficial for patients with hepatic impairment?
- A. Valproic acid
  - B. Carbamazepine
  - C. Lithium
  - D. Risperidone
- 10.8 Which antidepressant has, as its two principal mechanisms of action, 5-HT<sub>2A</sub> receptor antagonism and  $\alpha_2$  receptor antagonism?
- A. Fluoxetine
  - B. Doxepin
  - C. Maprotiline
  - D. Mirtazapine
- 10.9 Which mood stabilizing agent is most likely to decrease the thyroid function?
- A. Carbamazepine
  - B. Lithium
  - C. Valproic acid
  - D. Chlorpromazine
- 10.10 Which antidepressant agent has significant  $\alpha_1$  receptor antagonism and, thus, is a poor choice in an elderly female with depressive symptoms due to a higher risk of falls related to orthostatic hypotension?
- A. Venlafaxine
  - B. Bupropion
  - C. Escitalopram
  - D. Amitriptyline

Correct answer = D. In addition to inhibition of serotonin reuptake, the antidepressant activity of vilazodone may be related to its 5-HT<sub>1a</sub> receptor agonism. Though aripiprazole is also proposed to have 5-HT<sub>1a</sub> partial agonism, it is not a serotonin reuptake inhibitor.

Correct answer = C. Doxepin is the most sedating of the list due to its histamine-blocking activity.

Correct answer = C. Lithium is the only agent for bipolar disorder that does not require hepatic metabolism and, thus, may be dosed without issue in a hepatically impaired patient. However, if the patient had renal impairment, the lithium dosage would have to be adjusted.

Correct answer = D. Mirtazapine is the only antidepressant with this combination of mechanisms of action that are believed to contribute to its therapeutic effects.

Correct answer = B. Lithium is best known for causing a drug-induced hypothyroidism in patients after long-term use. Though it is possible with other mood stabilizers, lithium has the most reported cases, and thus, thyroid function tests should be performed at baseline and during follow-up to monitor for this possible effect.

Correct answer = D. Venlafaxine, bupropion, and escitalopram have very little effect on decreasing blood pressure (no  $\alpha_1$  receptor antagonism) and are considered acceptable choices for treatment of depression in the elderly. Amitriptyline is associated with a high risk for orthostasis in the elderly and should be avoided due to its adverse effect profile and risk for falls.

# Antipsychotics

Jose A. Rey

11

## I. OVERVIEW

The antipsychotic drugs are used primarily to treat schizophrenia, but they are also effective in other psychotic and manic states. The use of antipsychotic medications involves a difficult trade-off between the benefit of alleviating psychotic symptoms and the risk of a wide variety of adverse effects. Antipsychotic drugs (Figure 11.1) are not curative and do not eliminate chronic thought disorders, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment.

## II. SCHIZOPHRENIA

Schizophrenia is a type of chronic psychosis characterized by delusions, hallucinations (often in the form of voices), and disturbances in thought. The onset of illness is often during late adolescence or early adulthood. It occurs in about 1% of the population and is a chronic and disabling disorder. Schizophrenia has a strong genetic component and probably reflects some fundamental developmental and biochemical abnormality, possibly a dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways.

## III. ANTIPSYCHOTIC DRUGS

The antipsychotic drugs are usually divided into first- and second-generation agents. The first-generation drugs are further classified as “low potency” or “high potency.” This classification does not indicate clinical effectiveness of the drugs, but rather specifies affinity for the dopamine D<sub>2</sub> receptor, which, in turn, may influence the adverse effect profile of the drug.

### A. First-generation antipsychotics

The first-generation antipsychotic drugs (also called conventional) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blockade of dopamine D<sub>2</sub> receptors. First-generation antipsychotics are more likely to be associated with movement disorders known as extrapyramidal symptoms (EPS), particularly drugs that bind tightly to dopaminergic neuroreceptors, such as *haloperidol* [HAL-oh-PER-i-dol]. Movement disorders are somewhat less likely with medications that bind less potently, such as *chlorpromazine* [klor-PROE-ma-zeen]. No one drug is clinically more effective than another.

#### FIRST-GENERATION ANTIPSYCHOTIC (low potency)

*Chlorpromazine*  
*Thioridazine*

#### FIRST-GENERATION ANTIPSYCHOTIC (high potency)

*Fluphenazine*  
*Haloperidol*  
*Loxapine*  
*Molindone*  
*Perphenazine*  
*Pimozide*  
*Prochlorperazine*  
*Thiothixene*  
*Trifluoperazine*

#### SECOND-GENERATION ANTIPSYCHOTIC (atypical antipsychotic)

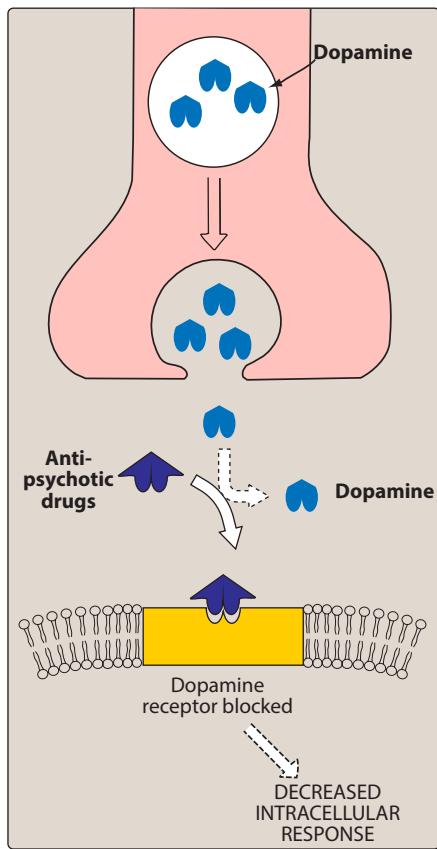
*Risperidone*  
*Ziprasidone*  
*Paliperidone*  
*Iloperidone*  
*Lurasidone*  
*Olanzapine*  
*Quetiapine*  
*Clozapine*  
*Asenapine*

#### THIRD-GENERATION ANTIPSYCHOTICS

*Aripiprazole*  
*Brexpiprazole*  
*Cariprazine*

Figure 11.1

Summary of antipsychotic agents.



**Figure 11.2**

Dopamine-blocking actions of antipsychotic drugs.

## B. Second-generation antipsychotic drugs

The second-generation antipsychotic drugs (also called “atypical” antipsychotics) have a lower incidence of EPS than the first-generation agents, but are associated with a higher risk of metabolic adverse effects, such as diabetes, hypercholesterolemia, and weight gain. The second-generation drugs owe their unique activity to blockade of both serotonin and dopamine receptors.

- 1. Drug selection:** Second-generation agents are generally used as first-line therapy for schizophrenia to minimize the risk of debilitating EPS associated with the first-generation drugs that act primarily at the dopamine D<sub>2</sub> receptor. The second-generation antipsychotics exhibit an efficacy that is equivalent to, and occasionally exceeds, that of the first-generation antipsychotic agents. Differences in therapeutic efficacy among the second-generation drugs have not been established, and individual patient response and comorbid conditions must often be used to guide drug selection.
- 2. Refractory patients:** Approximately 10% to 20% of patients with schizophrenia have an insufficient response to first- and second-generation antipsychotics. For these patients, *clozapine* [KLOE-za-peer] has shown to be an effective antipsychotic with a minimal risk of EPS. However, its clinical use is limited to refractory patients because of serious adverse effects. *Clozapine* can produce bone marrow suppression, seizures, and cardiovascular side effects, such as orthostasis. The risk of severe agranulocytosis necessitates frequent monitoring of white blood cell counts.

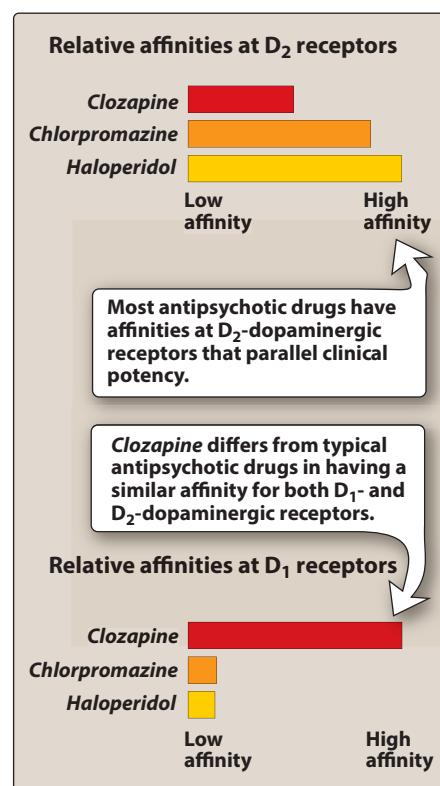
## C. Mechanism of action

- 1. Dopamine antagonism:** All of the first-generation and most of the second-generation antipsychotic drugs block D<sub>2</sub> dopamine receptors in the brain and the periphery (Figure 11.2).
- 2. Serotonin receptor-blocking activity:** Most of the second-generation agents exert part of their action through inhibition of serotonin receptors (5-HT), particularly 5-HT<sub>2A</sub> receptors. *Clozapine* has high affinity for D<sub>1</sub>, D<sub>4</sub>, 5-HT<sub>2</sub>, muscarinic, and α-adrenergic receptors, but it is also a weak dopamine D<sub>2</sub> receptor antagonist (Figure 11.3). *Risperidone* [ris-PEAR-ih-dohn] blocks 5-HT<sub>2A</sub> receptors to a greater extent than it does D<sub>2</sub> receptors, as does *olanzapine* [oh-LANZ-ah-peer]. The second-generation antipsychotics *ariPIPrazole* [a-rih-PIP-ra-zole], *brexPIPrazole* [brex-PIP-ra-zole], and *cariprazine* [kar-IP-ra-zeen] are partial agonists at D<sub>2</sub> and 5-HT<sub>1A</sub> receptors, as well as antagonists of 5-HT<sub>2A</sub> receptors. *Quetiapine* [qwe-TY-uh-peer] is relatively weak at blockade of D<sub>2</sub> and 5-HT<sub>2A</sub> receptors. Its low risk for EPS may also be related to the relatively short period of time it binds to the D<sub>2</sub> receptor. *Pimavanserin* [pim-a-VAN-ser-in] appears to act as an inverse agonist and antagonist at the 5-HT<sub>2A</sub> receptor and the 5-HT<sub>2C</sub> receptor, with no appreciable affinity for dopamine receptors. *Pimavanserin* is indicated for psychosis associated with Parkinson disease.

## D. Actions

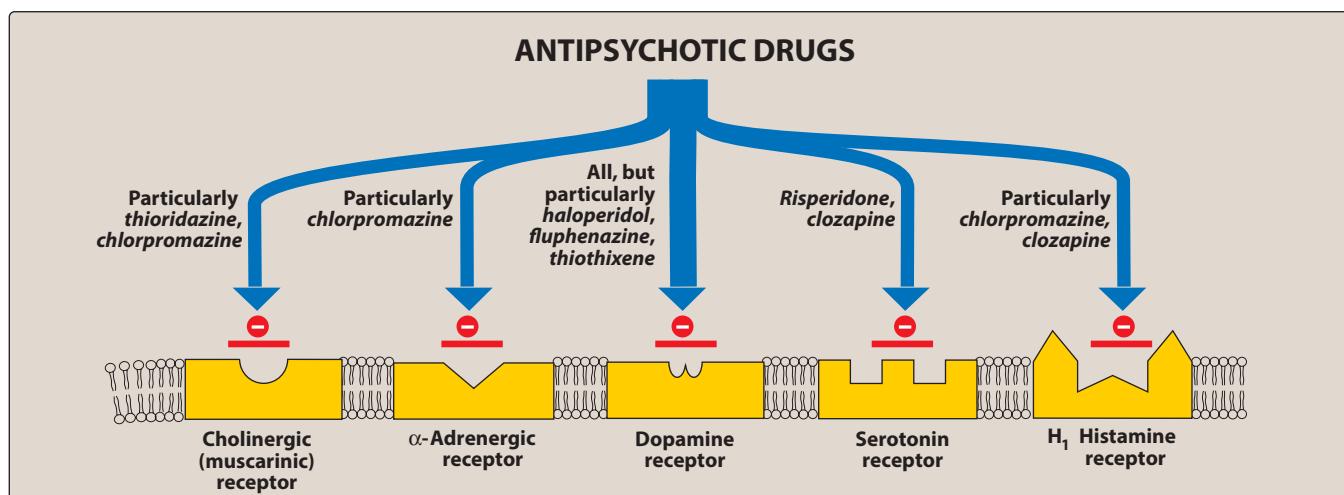
The clinical effects of antipsychotic drugs reflect a blockade at dopamine and/or serotonin receptors. However, many antipsychotic agents also block cholinergic, adrenergic, and histaminergic receptors (Figure 11.4). It is unknown what role, if any, these actions have in alleviating the symptoms of psychosis. However, the undesirable adverse effects of antipsychotic drugs often result from pharmacological actions at these other receptors.

- Antipsychotic effects:** All antipsychotic drugs can reduce hallucinations and delusions associated with schizophrenia (known as “positive” symptoms) by blocking D<sub>2</sub> receptors in the mesolimbic system of the brain. The “negative” symptoms, such as blunted affect, apathy, and impaired attention, as well as cognitive impairment, are not as responsive to therapy, particularly with the first-generation antipsychotics. Many second-generation agents, such as *clozapine*, can ameliorate the negative symptoms to some extent.
- Extrapyramidal effects:** Dystonias (sustained contraction of muscles leading to twisting, distorted postures), Parkinson-like symptoms, akathisia (motor restlessness), and tardive dyskinesia (involuntary movements, usually of the tongue, lips, neck, trunk, and limbs) can occur with both acute and chronic treatment. Blockade of dopamine receptors in the nigrostriatal pathway is believed to cause these unwanted movement symptoms. The second-generation antipsychotics exhibit a lower incidence of EPS.
- Antiemetic effects:** The antipsychotic drugs have antiemetic effects that are mediated by blocking D<sub>2</sub> receptors of the chemoreceptor trigger zone of the medulla (see Chapter 42). Figure 11.5 summarizes the antiemetic uses of antipsychotic agents, as well as other drugs that combat nausea.



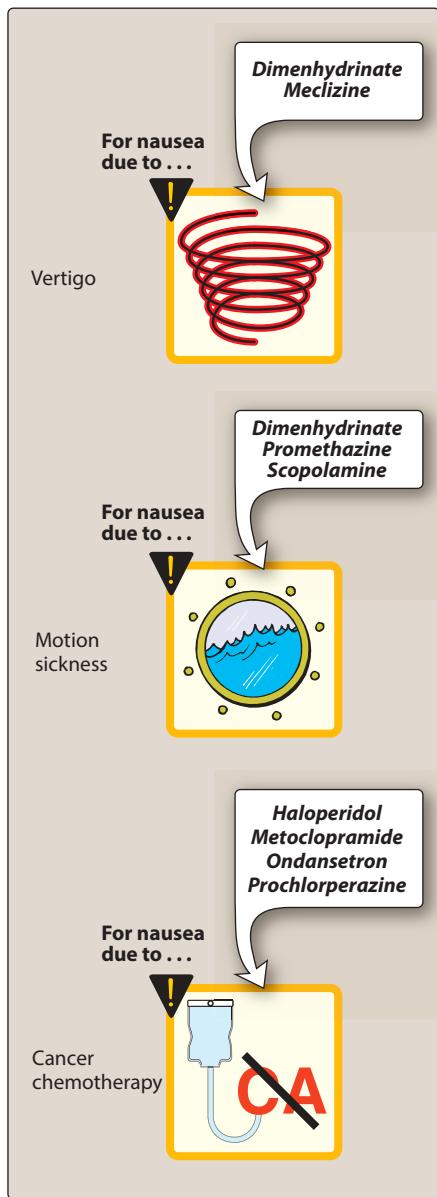
**Figure 11.3**

Relative affinity of *clozapine*, *chlorpromazine*, and *haloperidol* at D<sub>1</sub> and D<sub>2</sub> dopaminergic receptors.



**Figure 11.4**

Antipsychotic drugs block at dopaminergic and serotonergic receptors as well as at adrenergic, cholinergic, and histamine-binding receptors.

**Figure 11.5**

Therapeutic application of antiemetic agents.

**4. Anticholinergic effects:** Some of the antipsychotics, particularly *thioridazine* [THYE-oh-RID-a-zeen], *chlorpromazine*, *clozapine*, and *olanzapine*, produce anticholinergic effects. These effects include blurred vision, dry mouth (the exception is *clozapine*, which increases salivation), confusion, and inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention. The anticholinergic effects may actually assist in reducing the risk of EPS with these agents.

**5. Other effects:** Blockade of  $\alpha$ -adrenergic receptors causes orthostatic hypotension and light-headedness. The antipsychotics also alter temperature-regulating mechanisms and can produce poikilothermia (condition in which body temperature varies with the environment). In the pituitary, antipsychotics that block D<sub>2</sub> receptors may cause an increase in prolactin release. Sedation occurs with those drugs that are potent antagonists of the H<sub>1</sub>-histamine receptor, including *chlorpromazine*, *olanzapine*, *quetiapine*, and *clozapine*. Sexual dysfunction may also occur with the antipsychotics due to various receptor-binding characteristics. Weight gain is also a common adverse effect of antipsychotics and is more significant with the second-generation agents.

### E. Therapeutic uses

- Treatment of schizophrenia:** The antipsychotics are the only efficacious pharmacological treatment for schizophrenia. The first-generation antipsychotics are generally most effective in treating the positive symptoms of schizophrenia. The atypical antipsychotics with 5-HT<sub>2A</sub> receptor-blocking activity may be effective in many patients who are resistant to the traditional agents, especially in treating the negative symptoms of schizophrenia.
- Prevention of nausea and vomiting:** The older antipsychotics (most commonly, *prochlorperazine* [PROE-clor-PEAR-a-zeen]) are useful in the treatment of drug-induced nausea.
- Other uses:** The antipsychotic drugs can be used as tranquilizers to manage agitated and disruptive behavior secondary to other disorders. *Chlorpromazine* is used to treat intractable hiccups. *Pimozide* [PIM-oh-zide] is primarily indicated for treatment of the motor and phonic tics of Tourette disorder. However, *risperidone* and *haloperidol* are also commonly prescribed for this tic disorder. Also, *risperidone* and *ariPIPRAZOLE* are approved for the management of disruptive behavior and irritability secondary to autism. Many antipsychotic agents are approved for the management of the manic and mixed symptoms associated with bipolar disorder. *Lurasidone* [loo-RAS-i-done] and *quetiapine* are indicated for the treatment of bipolar depression. *Paliperidone* [pal-ee-PEAR-i-dohn] is approved for the treatment of schizoaffective disorder. Some antipsychotics (*ariPIPRAZOLE*, *brexpiprazole*, and *quetiapine*) are used as adjunctive agents with antidepressants for treatment-refractory depression.

## F. Absorption and metabolism

After oral administration, the antipsychotics show variable absorption that is unaffected by food (except for *ziprasidone* [zi-PRAS-i-done], *lurasidone*, and *paliperidone*, the absorption of which is increased with food). These agents readily pass into the brain and have a large volume of distribution. They are metabolized to many different metabolites, usually by the cytochrome P450 system in the liver, particularly the CYP2D6, CYP1A2, and CYP3A4 isoenzymes. Some metabolites are active and have been developed as pharmaceutical agents themselves (for example, *paliperidone* is the active metabolite of *risperidone*, and the antidepressant *amoxapine* is the active metabolite of *loxpiprazole*). *Fluphenazine decanoate*, *haloperidol decanoate*, *risperidonemicrospheres*, *paliperidone palmitate*, *ariPIPrazole monohydrate*, *ariPIPrazole lauroxil*, and *olanzapine pamoate* are long-acting injectable (LAI) formulations of antipsychotics. These formulations usually have a therapeutic duration of action of 2 to 4 weeks, with some having a duration of 6 to 12 weeks. Therefore, these LAI formulations are often used to treat outpatients and individuals who are nonadherent with oral medications.

## G. Adverse effects

Adverse effects of the antipsychotic drugs can occur in practically all patients and are significant in about 80% of them (Figure 11.6).

**1. Extrapyramidal effects:** The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects. The appearance of the movement disorders is generally time- and dose-dependent, with dystonias occurring within a few hours to days of treatment, followed by akathisias occurring within

TYPE	MECHANISM	MANIFESTATIONS
<b>Autonomic nervous system</b>	<b>Muscarinic cholinceptor blockade</b>	<b>Loss of accommodation, dry mouth, difficulty in urinating, constipation</b>
	<b><math>\alpha</math>-Adrenoceptor blockade</b>	<b>Orthostatic hypotension, impotence, failure to ejaculate</b>
<b>Central nervous system</b>	<b>Dopamine receptor blockade</b>	<b>Parkinson's syndrome, akathisia, dystonia</b>
	<b>Super-sensitivity of dopamine receptors</b>	<b>Tardive dyskinesia</b>
	<b>Muscarinic blockade</b>	<b>Toxic confusional state</b>
<b>Endocrine system</b>	<b>Dopamine receptor blockade resulting in hyperprolactinemia</b>	<b>Amenorrhea-galactorrhea, infertility, impotence</b>
<b>Other</b>	<b>Possibly combined H<sub>1</sub> and 5-HR<sub>2</sub> blockade</b>	<b>Weight gain</b>

**Figure 11.6**

Adverse pharmacologic effects of antipsychotic drugs and their mechanism.

days to weeks. Parkinson-like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment. Tardive dyskinesia (see below), which can be irreversible, may occur after months or years of treatment. If cholinergic activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal effects are minimized. This can be achieved by administration of an anticholinergic drug, such as *benztropine* [BENZ-troe-peen]. The therapeutic trade-off is a lower incidence of EPS in exchange for the adverse effect of muscarinic receptor blockade. Akathisia may respond better to  $\beta$  blockers (for example, *propranolol*) or benzodiazepines, rather than anticholinergic medications.

2. **Tardive dyskinesia:** Long-term treatment with antipsychotics can cause this motor disorder. Patients display involuntary movements, including bilateral and facial jaw movements and “fly-catching” motions of the tongue. A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear within a few months. However, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy. Tardive dyskinesia is postulated to result from an increased number of dopamine receptors that are synthesized as a compensatory response to long-term dopamine receptor blockade. This makes the neuron supersensitive to the actions of dopamine, and it allows the dopaminergic input to this structure to overpower the cholinergic input, causing excess movement in the patient. Traditional anti-EPS medications may actually worsen this condition. *Valbenazine* [val-BEN-a-zeen] and *deutetrabenazine* [doo-TET-ra-BEN-a-zeen] are inhibitors of the vesicular monoamine transporter and they are indicated for the management of tardive dyskinesia. These agents cause a decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores, ideally focused on dopamine, to address the symptoms of tardive dyskinesia.
3. **Neuroleptic malignant syndrome:** This potentially fatal reaction to antipsychotic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myoglobinemia. Treatment necessitates discontinuation of the antipsychotic agent and supportive therapy. Administration of *dantrolene* or *bromocriptine* may be helpful.
4. **Other effects:** Drowsiness occurs during the first few weeks of treatment. These agents may also cause confusion. Those antipsychotics with potent antimuscarinic activity often produce dry mouth, urinary retention, constipation, and loss of visual accommodation. Others may block  $\alpha$ -adrenergic receptors, resulting in lowered blood pressure and orthostatic hypotension. The antipsychotics depress the hypothalamus, thereby affecting thermoregulation and causing amenorrhea, galactorrhea, gynecomastia, infertility, and erectile dysfunction. Significant weight gain is often a reason for nonadherence. Glucose and lipid profiles should be monitored in patients taking antipsychotics, as the second-generation agents may increase these laboratory parameters and

possibly exacerbate pre-existing diabetes or hyperlipidemia. Some antipsychotics have been associated with mild to significant QT prolongation. *Thioridazine* has the highest risk, and *ziprasidone* and *iloperidone* [eye-low-PEAR-ee-dohn] also have cautions with their use due to this effect. Other antipsychotics have a general precaution regarding QT prolongation, even if the risk is relatively low.

5. **Cautions and contraindications:** All antipsychotics may lower the seizure threshold and should be used cautiously in patients with seizure disorders or those with an increased risk for seizures, such as withdrawal from alcohol. These agents also carry the warning of increased risk for mortality when used in elderly patients with dementia-related behavioral disturbances and psychosis. Antipsychotics used in patients with mood disorders should also be monitored for worsening of mood and suicidal ideation or behaviors.

#### H. Maintenance treatment

Considerable variability is expected in optimal dose ranges between individual patients; typical therapeutic ranges are provided in **Figure 11.7**. Lower doses are generally recommended in first-episode patients, who tend to be more responsive and more sensitive to side effects, and in the elderly, who may metabolize antipsychotic drugs at substantially lower rates and are also more sensitive to side effects. In addition, lower doses may be effective for maintenance treatment. Therefore, the dose should be increased gradually especially in patients who display no response or only partial response, provided compliance has been established and there is absence of dose-limiting side effects (particularly extrapyramidal syndrome [EPS]). Patients who have had two or more psychotic episodes secondary to schizophrenia should receive maintenance therapy for at least 5 years, and some experts prefer indefinite therapy. The rate of relapse may be lower with second-generation drugs. **Figure 11.8** summarizes the therapeutic uses, advantages, and disadvantages of some of the antipsychotic drugs

DRUGS	ORAL DOSE (mg)	EXTRAPYRAMIDAL EFFECTS <sup>1</sup>	AUTONOMIC EFFECTS (HYPOTENSIVE)	SEDATION	METABOLIC SIDE EFFECTS			INCREASED PROLACTIN
					Weight gain	Lipid	Glucose	
<b>Conventional or first-generation drugs:</b>								
<b>Alipathic phenothiazines</b>								
<i>Chlorpromazine</i>	100–600	++	+++	+++	+	+++	++	++
<i>Triflupromazine</i>	5–30	++	+++	+++	+			
<b>Piperidine phenothiazines</b>								
<i>Thioridazine<sup>2</sup></i>	100	+	+++	+++		-	-	++
<i>Mesondazine</i>	50	+	+++	+++	+			
<b>Piperazine phenothiazines</b>								
<i>Trifluoperazine</i>	5–30	+++	++	++	+	-	-	++
<i>Fluphenazine<sup>3</sup></i>	2.5–15	+++	++	++	+			
<b>Butyrophenones</b>								
<i>Haloperidol</i>	2–10	+++	+	+	+	-	-	++
<b>Other related drugs</b>								
<i>Loxapine</i>	15–50	+++	++	++	-	-	-	++
<b>Atypical or second-generation drugs:</b>								
<i>Clozapine<sup>4</sup></i>	200–600	±	++	+	+++	+++	+++	+
<i>Olanzapine<sup>1,3</sup></i>	5–20	±	+	++	+++	+++	+++	+
<i>Quetiapine<sup>3</sup></i>	200–600	±	++	++	++	+	±	+
<i>Risperidone<sup>3,5</sup></i>	4–8	++	+	+	+	±	±	++
<i>Ziprasidone<sup>6</sup></i>	120–160	±	±	±	±	-	-	+
<b>Third-generation drug:</b>								
<i>Aripiprazole</i>	10–20	±	+	±	±	-	-	+

<sup>1</sup>Excluding tardive dyskinesia.

<sup>2</sup>Cardiotoxicity.

<sup>3</sup>Depot form (long-acting injectables) available.

<sup>4</sup>Start at a low dose with monitoring blood counts as it may cause agranulocytosis in ~2% patients

<sup>5</sup>Little extrapyramidal effects at low doses.

<sup>6</sup>QTc prolongation.

### Figure 11.7

Potency and selected adverse effects of representative conventional and atypical antipsychotic drugs.

DRUG	ADVANTAGES	DISADVANTAGES
<b>First generation:</b>		
<i>Chlorpromazine</i>	Generic inexpensive	Many adverse effects, especially moderate-to-high potential for extrapyramidal syndrome, orthostasis, and sedation; moderate-to-high potential for weight gain
<i>Thioridazine</i>	Slight extrapyramidal syndrome, generic drug	800 mg/d limit, no parenteral form, cardiotoxicity
<i>Fluphenazine</i>	Depot form also available (enanthate, decanoate); effect lasts for 2 to 3 weeks, especially in noncompliant patients; least expensive	Oral formulation has high potential for EPS; low potential for weight gain, sedation, orthostasis, or muscarinic adverse events; weight gain Increased tardive dyskinesia
<i>Thiothixene</i>	Parenteral form also available  Decreased tardive dyskinesia	Uncertain
<i>Haloperidol</i>	Parenteral form also available; long-acting injection administered every 4 weeks; low potential for antiadrenergic (orthostasis) or antimuscarinic adverse events, weight gain, or sedation	Severe extrapyramidal syndrome
<b>Second generation:</b>		
<i>Loxapine</i>	No weight gain	Uncertain
<i>Clozapine</i>	May benefit treatment-resistant patients; little extrapyramidal toxicity	May cause agranulocytosis in up to 2% of patients, dose-related lowering of seizure threshold; risk of myocarditis; high potential for sialorrhea, weight gain, antimuscarinic effects, orthostasis, and sedation
<i>Risperidone</i>	Broad efficacy; little or no extrapyramidal system dysfunction at low doses; low-to-moderate risk of weight gain, orthostasis, and sedation; long-acting injection administered every 2 weeks (expensive); also used in BPAD	Extrapyramidal system dysfunction and hypotension with higher doses
<i>Olanzapine</i>	Effective against negative as well as positive symptoms; little or no extrapyramidal system dysfunction; low potential for orthostasis; also approved for BPAD; long-acting injection administered every 2 to 4 weeks	Weight gain; dose-related lowering of seizure threshold
<i>Quetapine</i>	Similar to olanzapine, perhaps less weight gain; also approved for BPAD and as an adjunctive treatment for depression	May require high doses if there is associated hypotension; short t½ and twice-daily dosing
<i>Ziprasidone</i>	Minimal weight gain, parenteral form available; less potential for EPS; used in BPAD	QT prolongation; therefore contraindicated in patients with cardiac arrhythmia
<i>Asenapine</i>	Low potential for EPS, weight gain, sedation, orthostasis; also approved for BPAD; available as sublingual formulation	Uncertain
<b>Third generation:</b>		
<i>Aripiprazole</i>	Lower weight gain liability, sedation, and antimuscarinic effects; long half-life; novel mechanism; also approved for BPAD, autistic disorders in children and as an adjunctive treatment for depression	Uncertain, novel toxicities possible

BPAD = bipolar affective disorder.

**Figure 11.8**

Summary of representative antipsychotic drugs commonly used to treat schizophrenia.

## Study Questions

Choose the ONE best answer.

11.1 An adolescent male is newly diagnosed with schizophrenia. Which antipsychotic agent may have the best chance to improve his apathy and blunted affect?

- A. Chlorpromazine
- B. Fluphenazine
- C. Haloperidol
- D. Risperidone

11.2 Which of the following antipsychotics is a partial agonist at the dopamine D<sub>2</sub> receptor?

- A. Brexpiprazole
- B. Clozapine
- C. Haloperidol
- D. Risperidone

11.3 A 21-year-old man has recently begun pimozide therapy for Tourette's disorder. He has been having "different-appearing tics," such as prolonged contraction of the facial muscles, and he experiences opisthotonus (extrapyramidal spasm of the body in which the head and heels are bent backward and the body is bowed forward). Which of the following drugs would be beneficial in reducing these symptoms?

- A. Benztropine
- B. Bromocriptine
- C. Prochlorperazine
- D. Risperidone

11.4 A 28-year-old woman with schizoaffective disorder (combination of mood and psychotic symptoms) reports difficulty falling asleep. Which of the following would be most beneficial in this patient?

- A. Olanzapine
- B. Haloperidol
- C. Paliperidone
- D. Ziprasidone

Correct answer = D. Risperidone is the only antipsychotic on the list that has some reported benefit in improving the negative symptoms of schizophrenia. All of the agents have the potential to diminish the hallucinations and delusional thought processes (positive symptoms).

Correct answer = A. Brexpiprazole is the only agent listed that acts as a partial agonist at D<sub>2</sub> receptors. Theoretically, the drug enhances action at these receptors when there is a low concentration of dopamine and blocks the actions of high concentrations of dopamine. All of the other drugs are antagonistic at D<sub>2</sub> receptors.

Correct answer = A. The patient is experiencing EPS due to pimozide, and a muscarinic antagonist such as benztropine would be effective in reducing the symptoms. The other drugs would have no effect or, in the case of prochlorperazine and risperidone, might increase the adverse symptoms.

Correct answer = C. Paliperidone is the only agent that is approved by the FDA for schizoaffective disorder. Olanzapine has significant sedative activity as well as antipsychotic properties and is the drug most likely to alleviate this patient's report of insomnia. Although other antipsychotics may benefit this patient's disorder, paliperidone has the indication for this disorder, and if the underlying disorder is improved, then the symptom of insomnia may also improve without risking other unwanted adverse effects, such as the weight gain effects of olanzapine.

11.5 Which of the following antipsychotic agents is considered to be the *most potent* and thus have the highest risk of extrapyramidal symptoms?

- A. Thioridazine
- B. Haloperidol
- C. Quetiapine
- D. Chlorpromazine

Correct answer = B. Among the older, conventional, or typical antipsychotics on this list, haloperidol is the most potent and would thus be expected to have the highest incidence of EPS. The atypical antipsychotics listed (quetiapine) could be considered low potency based on their common dosing and are considered to have the lowest risk for EPS.

11.6 Which antipsychotic has the most sedative potential and is sometimes, questionably, used as a hypnotic agent in certain clinical settings?

- A. Fluphenazine
- B. Thiothixene
- C. Quetiapine
- D. Haloperidol

Correct answer = C. Quetiapine has strong antihistaminergic effects causing sedation and is sometimes used at low doses as a sedative-hypnotic, even though this use is considered off-label. The other antipsychotic agents listed are weaker at blocking the histamine receptor and therefore are not as sedating.

11.7 A 30-year-old male patient is treated with haloperidol for schizophrenia. His psychotic symptoms are well managed with haloperidol; however, he is reporting restlessness, the inability to sit still at the dinner table, and his family notices that he frequently paces the hallway. Which is the best agent to treat this antipsychotic-induced akathisia?

- A. Benztrapine
- B. Dantrolene
- C. Bromocriptine
- D. Propranolol

Correct answer = D. Propranolol, a  $\beta$ -blocker, is considered the drug of choice for the management of antipsychotic-induced akathisia. Benztrapine is more effective for pseudoparkinsonism and acute dystonias. Bromocriptine is more effective for Parkinson-like symptoms, and dantrolene is a muscle relaxant that is best reserved for managing some symptoms of neuroleptic malignant syndrome.

11.8 Which antipsychotic agent is available in a LAI formulation that may be useful for patients with difficulty adhering to therapy?

- A. Asenapine
- B. Chlorpromazine
- C. Clozapine
- D. Aripiprazole

Correct answer = D. Aripiprazole is available in two different LAI formulations. The other agents listed do not have LAI formulations. Risperidone, fluphenazine, haloperidol, olanzapine, and paliperidone are other antipsychotics that are available in LAI formulations.

11.9 Which antipsychotic agent is most associated with the possibility of a hematological dyscrasia such as agranulocytosis in a patient being treated for schizophrenia?

- A. Chlorpromazine
- B. Buspirone
- C. Lithium
- D. Clozapine

Correct answer = D. Clozapine is the only antipsychotic medication that has a black box warning and a risk of agranulocytosis in approximately 1% of the patients treated. This requires regular monitoring of white blood cell counts. Although other antipsychotics have case reports of blood dyscrasias, clozapine is considered to have the highest risk.

11.10 Which antipsychotic agent has been most associated with significant QT interval prolongation and should be used with caution in patients with preexisting arrhythmias or patients taking other drugs associated with QT prolongation?

- A. Thioridazine
- B. Risperidone
- C. Asenapine
- D. Lurasidone

Correct answer = A. Of the antipsychotic drugs listed, thioridazine has the highest risk for causing QT interval prolongation. Although this is a general warning for many antipsychotics, thioridazine has been issued a “black box warning,” suggesting that it is associated with the greatest risk.

# Drugs for Epilepsy

Jeannine M. Conway and Angela K. Birnbaum

12

## I. OVERVIEW

Approximately 10% of the population has at least one seizure in their lifetime. Globally, epilepsy is the fourth most common neurologic disorder after migraine, cerebrovascular disease (stroke), and Alzheimer disease. Epilepsy is not a single entity but an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons. This abnormal electrical activity may result in a variety of events, including loss of consciousness, abnormal movements, atypical or odd behavior, and distorted perceptions that are of limited duration but recur if untreated. The site of origin of abnormal neuronal firing determines the symptoms that occur. For example, if the motor cortex is involved, the patient may experience abnormal movements or a generalized convulsion. Seizures originating in the parietal or occipital lobe may include visual, auditory, and olfactory hallucinations. Medications are the most widely used mode of treatment for patients with epilepsy. In general, seizures can be controlled with one medication in approximately 75% of patients. Patients may require more than one medication in order to optimize seizure control, and some patients may never obtain total seizure control. A summary of anti-seizure medications is shown in [Figure 12.1](#).

## II. ETIOLOGY OF SEIZURES

Epilepsy can be due to an underlying genetic, structural, or metabolic cause or an unknown cause. In most cases, epilepsy has no identifiable cause. The neuronal discharge in epilepsy results from firing of a small population of neurons in a specific area of the brain referred to as the “primary focus.” Focal areas that are functionally abnormal may be triggered into activity by changes in physiologic factors, such as an alteration in blood gases, pH, electrolytes, and blood glucose and changes in environmental factors, such as sleep deprivation, alcohol intake, and stress. A number of causes, such as illicit drug use, tumor, head injury, hypoglycemia, meningeal infection, and the rapid withdrawal of alcohol from an alcoholic, can precipitate seizures. In cases when the cause of a seizure can be determined and corrected, medication may not be necessary. For example, a seizure that is caused by a drug reaction is not epilepsy and does not require chronic therapy. In other situations, antiseizure medications, also called antiepileptic drugs (AEDs), may be needed when the primary cause of the seizures cannot be corrected. Though multiple specific epilepsy syndromes that include symptoms other than seizures have been classified, a discussion of these syndromes is beyond the scope of this chapter.

### FIRST-GENERATION AEDs

*Phenobarbital  
Primidone  
Phenytoin  
Ethosuximide  
Carbamazepine  
Valproic acid*

### SECOND-GENERATION AEDs

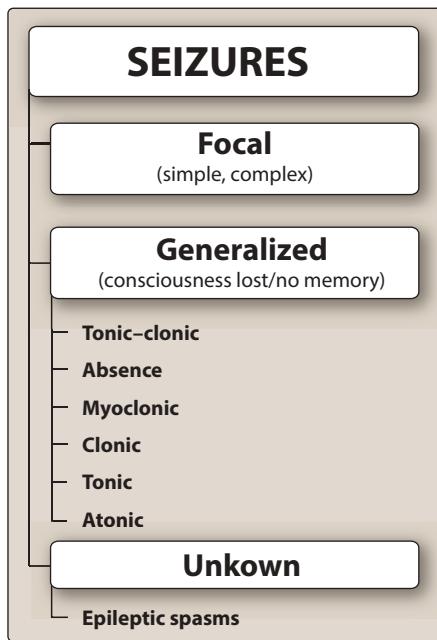
*Felbamate  
Gabapentin  
Lamotrigine  
Topiramate  
Tiagabine  
Levetiracetam  
Oxcarbazepine  
Zonisamide  
Pregabalin*

### NEWEST DRUGS

*Rufinamide  
Stiripentol  
Lacosamide  
Retigabine  
Eslicarbazepine  
Perampanel*

**Figure 12.1**

Summary of antiseizure medications.  
AEDs = antiepileptic drugs.

**Figure 12.2**

Classification of epilepsy.

### III. CLASSIFICATION OF SEIZURES

It is important to correctly classify seizures to determine appropriate treatment. Seizures have been categorized by site of origin, etiology, electrophysiologic correlation, and clinical presentation. The nomenclature developed by the International League Against Epilepsy is considered the standard classification for seizures and epilepsy syndromes (Figure 12.2). Seizures have been classified into two broad groups: focal and generalized.

#### A. Focal

Focal seizures involve only a portion of one hemisphere of the brain. The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain. Focal seizures may progress to become bilateral tonic-clonic seizures. Patients may lose consciousness or awareness. This seizure type may begin with a motor or nonmotor activity.

#### B. Generalized

Generalized seizures may begin locally and then progress to include abnormal electrical discharges throughout both hemispheres of the brain. Primary generalized seizures may be convulsive or nonconvulsive, and the patient usually has an immediate loss of consciousness.

1. **Tonic-clonic:** These seizures result in loss of consciousness, followed by tonic (continuous contraction) and clonic (rapid contraction and relaxation) phases. The seizure may be followed by a period of confusion and exhaustion due to depletion of glucose and energy stores.
2. **Absence:** These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond. The patient stares and exhibits rapid eye-blinking, which lasts for 3 to 5 seconds. An absence seizure has a very distinct three-per-second spike and wave discharge seen on electroencephalogram.
3. **Myoclonic:** These seizures consist of short episodes of muscle contractions that may recur for several minutes. They generally occur after wakening and exhibit as brief jerks of the limbs. Myoclonic seizures occur at any age but usually begin around puberty or early adulthood.
4. **Clonic:** These seizures consist of short episodes of muscle contractions that may closely resemble myoclonic seizures. Consciousness is more impaired with clonic seizures as compared to myoclonic.
5. **Tonic:** These seizures involve increased tone in the extension muscles and are generally less than 60 seconds long.
6. **Atonic:** These seizures are also known as drop attacks and are characterized by a sudden loss of muscle tone.

#### C. Mechanism of action of antiseizure medications

Many structures and processes are involved in the development of a seizure, including neurons, ion channels, receptors, glia, and inhibitory and excitatory synapses. The AEDs are designed to modify

these processes to favor inhibition over excitation in order to stop or prevent seizure activity. Narrow-spectrum AEDs mostly work for specific types of seizures (such as partial, focal, or absence, myoclonic seizures). Broad-spectrum AEDs additionally have some effectiveness for a wide variety of seizures (partial plus absence myoclonic seizures) (Figure 12.3). Drugs reduce seizures through mechanisms such as blocking voltage-gated channels ( $\text{Na}^+$  or  $\text{Ca}^{2+}$ ), enhancing inhibitory  $\gamma$ -aminobutyric acid (GABA)-ergic impulses, and interfering with excitatory glutamate transmission. Some antiseizure medications appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined (Figure 12.4). Antiseizure medications suppress seizures but do not “cure” or “prevent” epilepsy.

## IV. DRUG SELECTION

Choice of drug treatment is based on the classification of the seizures, patient-specific variables (for example, age, comorbid medical conditions, lifestyle, and personal preference), and characteristics of the drug (such as cost and drug interactions). For example, focal-onset seizures are treated with a different set of medications than primary generalized seizures, although the list of effective agents overlaps. The toxicity of the agent and characteristics of the patient are major considerations in drug selection. In newly diagnosed patients, monotherapy is instituted with a single agent and the dose is gradually increased until seizures are controlled or toxicity occurs (Figure 12.5). Avoid changing AED as long as seizures are controlled. Compared with those receiving combination therapy, patients receiving monotherapy exhibit better medication adherence and fewer side effects. If seizures are not controlled with the first medication, monotherapy with an alternate medication or the

NARROW-SPECTRUM AEDs	BROAD-SPECTRUM AEDs
<i>Phenytoin</i>	<i>Valproic acid</i>
<i>Phenobarbital</i>	<i>Lamotrigine</i>
<i>Carbamazepine</i>	<i>Topiramate</i>
<i>Oxcarbazepine</i>	<i>Zonisamide</i>
<i>Gabapentin</i>	<i>Levetiracetam</i>
<i>Pregabalin</i>	<i>Clonazepam</i>
<i>Vigabatrin</i>	<i>Clobazam</i>
<i>Tiagabine</i>	<i>Felbamate</i>

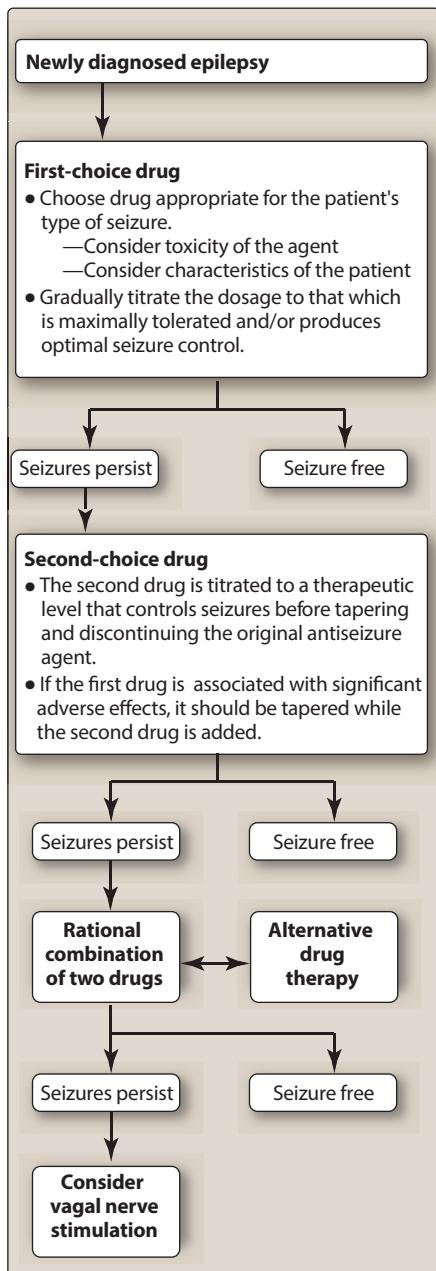
**Figure 12.3**

Spectrum of antiepileptic activity of antiseizure or antiepileptic drugs (AEDs)

MECHANISM OF ACTION	ANTIEPILEPTIC DRUG
<b>Sodium channel blockers:</b>	
<b>Fast-inactivated state</b>	<i>Phenytoin, carbamazepine, lamotrigine, oxcarbazepine, eslicarbazepine</i>
<b>Slow-inactivated state</b>	<i>Lacosamide</i>
<b>Calcium channel blockers:</b>	
<b>Low voltage-activated channel</b>	<i>Ethosuximide</i>
<b>High voltage-activated channel</b>	<i>Gabapentin, pregabalin</i>
<b>GABA-ergic drugs:</b>	
<b>Prolong chloride channel opening</b>	<i>Barbiturates</i>
<b>Increase frequency of chloride channel opening</b>	<i>Benzodiazepines</i>
<b>Inhibit GABA-transaminase</b>	<i>Vigabatrin</i>
<b>Block synaptic GABA reuptake</b>	<i>Tiagabine</i>
<b>Synaptic vesicle protein 2A modulation</b>	<i>Levetiracetam</i>
<b>Carbonic anhydrase inhibition</b>	<i>Acetazolamide, topiramate, zonisamide</i>
<b>Multiple pharmacological targets</b>	<i>Sodium valproate, felbamate, topiramate, zonisamide, rufinamide</i>

**Figure 12.4**

Mechanism of action of antiepileptic drugs.

**Figure 12.5**

Therapeutic strategies for managing newly diagnosed epilepsy.

addition of medications should be considered (Figure 12.6). The following prescribing guidelines are to be followed while adding or switching between antiepileptic drugs:

- If the initial drug was partially effective, it should be continued until reasonable levels of the new AED are achieved.
- Attempt tapering the first drug, if seizures are controlled.
- Switch to another AED, if the initial drug is not effective and is not tolerated well.
- Withdraw AEDs gradually that are not effective.
- Arbitrarily never prescribe a patient more than three AEDs at a time.
- Stress on the importance of regular AED usage to avoid loss of seizure control before starting therapy and assess adherence to medication regimens at every visit thereafter.
- Review diagnosis (confirm diagnosis of true seizure) and adherence to treatment in patients not responding to treatment.
- The goal of therapy should be complete seizure freedom with a single, first-line AED taken once or twice a day and without significant adverse effects.

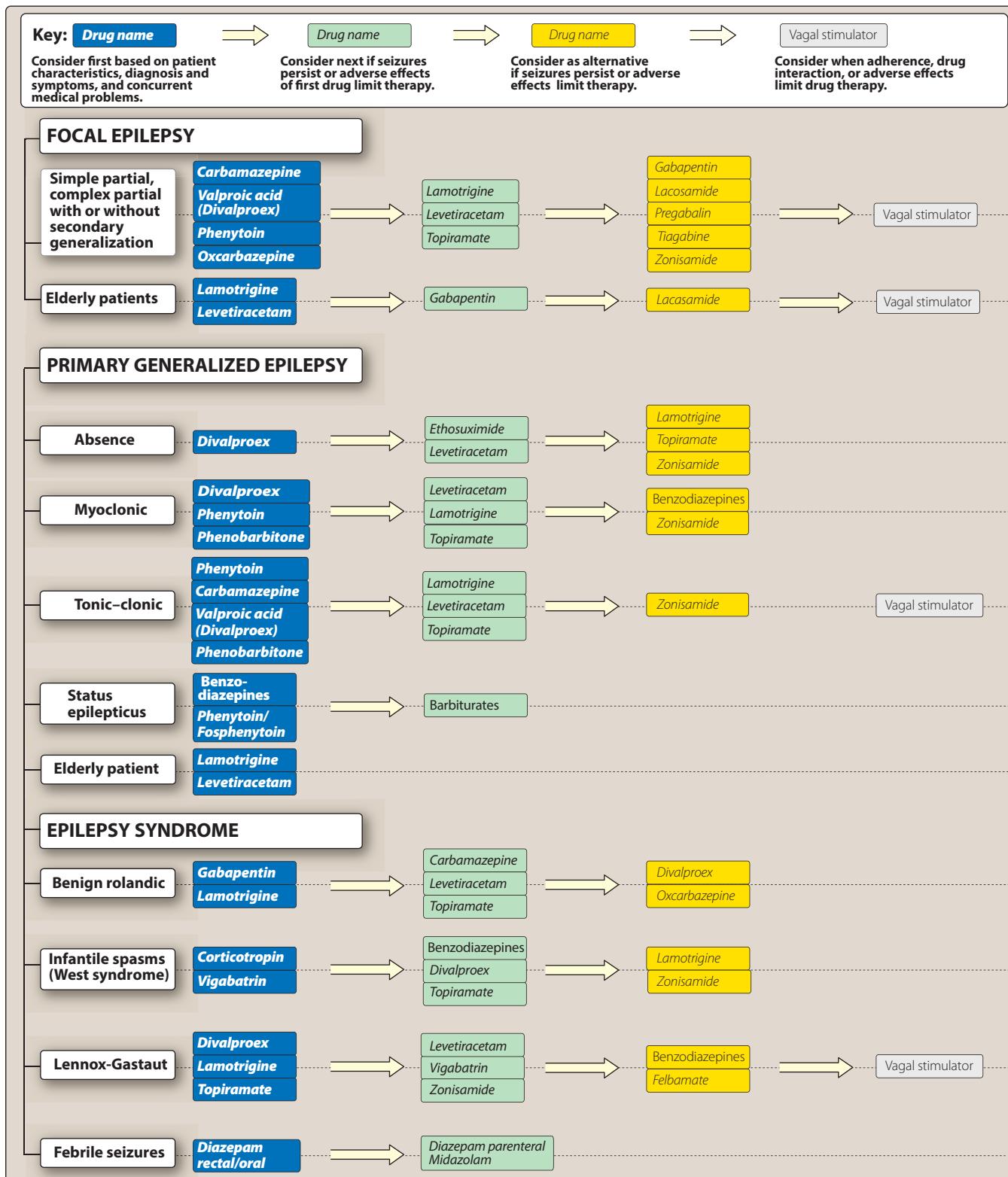
Awareness of the antiseizure medications available and their mechanisms of action, pharmacokinetics, potential for drug–drug interactions, and adverse effects is essential for successful treatment of the patient. There are many physiologic differences between neonates, infants, children, and adults which can affect the absorption, distribution, metabolism, and excretion of antiepileptic drugs. These pharmacokinetic differences may play a part in the age-related differences in the incidence of adverse effects; therefore, select dose and monitor these patients accordingly. Children on AED should be followed up regularly for compliance, recurrence of seizures, and also side effects. Monitor growth of the child, and suitable adjustment of the dose should be done with changing weight. Failing that, other medical management (vagal nerve stimulation, surgery, etc.) should be considered.

### A. Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) of antiepileptic drugs seeks to optimize patient outcome by managing their medication regimen with the assistance of information on the concentration of AEDs in serum or plasma. Many a times, identification of the optimal dose for an individual on purely clinical grounds can be difficult; therefore, TDM is required in the following situations:

- Prescribed dosage:** Since AED treatment is prophylactic and seizures occur at irregular intervals, it is often difficult to determine rapidly whether the prescribed dosage will be sufficient to produce long-term seizure control.
- Clinical symptoms:** Clinical symptoms and signs of toxicity may be subtle or difficult to differentiate from the manifestations of the underlying disorders.
- Laboratory markers:** There are no direct laboratory markers for clinical efficacy or for the most common manifestations of AED toxicity, such as adverse CNS effects.

However, monitoring of blood levels of AEDs is not routinely indicated; “routine” drug levels on controlled, nontoxic patients are not indicated.

**Figure 12.6**

Therapeutic indications for the antiseizure agents. Benzodiazepines = diazepam and lorazepam.

### B. Discontinuing antiepileptic drugs

Treatment of epilepsy is usually prolonged for a period of 2 to 3 years; however, the duration of therapy may be variable depending on the cause and type of seizures. Abrupt cessation of antiepileptic drugs is always risky and may precipitate not only a return of seizures, but also a bout of prolonged or status seizures. Therefore, withdrawal should be gradual, tapering the AED in fraction, over a period of 3 to 6 months or even more depending on the dose and number of AEDs. In particular, benzodiazepines and barbiturates are associated with withdrawal seizures and should be discontinued very gradually.

## V. ANTISEIZURE MEDICATIONS

The Food and Drug Administration has approved many new antiseizure medications in the last few decades. Some of these agents are thought to have potential advantages over older drugs in terms of pharmacokinetics, tolerability, and reduced risk for drug–drug interactions. However, studies have failed to demonstrate that the newer drugs are significantly more efficacious than the older agents. [Figure 12.7](#) summarizes pharmacokinetic properties of the antiseizure medications, and [Figure 12.8](#) shows common adverse effects. Suicidal behavior and suicidal ideation have been identified as a risk with antiseizure medications. In addition, virtually, all antiseizure medications have been associated with multiorgan hypersensitivity reactions, a rare idiosyncratic reaction characterized by rash, fever, and systemic organ involvement.

### A. Benzodiazepines

Benzodiazepines bind to GABA inhibitory receptors to reduce the firing rate. Most benzodiazepines are reserved for emergency or acute seizure treatment due to tolerance. However, *clonazepam* [kloe-NAY-ze-pam] and *clobazam* [KLOE-ba-zam] may be prescribed as adjunctive therapy for particular types of seizures. *Diazepam* [dye-AZ-e-pam] is also available for rectal administration to avoid or interrupt prolonged generalized tonic-clonic seizures or clusters when oral administration is not possible.

### B. Brivaracetam

*Brivaracetam* [briv-a-RA-se-tam] is approved for treatment of focal onset seizures in adults. It demonstrates high and selective affinity for a synaptic vesicle protein (SV2A); however, the exact mechanism of anti-seizure action is unknown. The drug is well absorbed after oral administration, and metabolized by both hydrolysis and CYP2C19 (minor). Comedication with strong CYP-inducing medications may lead to lower plasma concentrations. *Brivaracetam* is a moderate inhibitor of epoxide hydrolase, resulting in increased levels of the active metabolite of *carbamazepine* when the drugs are coadministered.

### C. Carbamazepine

*Carbamazepine* [kar-ba-MAZ-a-peen] blocks sodium channels, thereby possibly inhibiting the generation of repetitive action potentials in the

ANTIEPILEPSY MEDICATION	PROTEIN BINDING <sup>1</sup>	HALF-LIFE <sup>2</sup>	ACTIVE METABOLITE	MAJOR ORGAN OF ELIMINATION	DRUG INTERACTIONS
<i>Brivaracetam</i>	Low	0		Liver	✓
<i>Carbamazepine</i>	Moderate	6–15	CBZ-10,11-epoxide	Liver	✓
<i>Eslicarbazepine acetate<sup>3</sup></i>	Low	8–24	<i>Eslicarbazepine</i> (S-licarbazepine)	Kidney	✓
<i>Ethosuximide</i>	Low	25–26		Liver	✓
<i>Felbamate</i>	Low	20–23		Kidney/Liver	✓
<i>Fosphenytoin<sup>3</sup></i>	High	12–60	<i>Phenytoin</i>	Liver	✓
<i>Gabapentin</i>	Low	5–9		Kidney	
<i>Lacosamide</i>	Low	13		Various	
<i>Lamotrigine</i>	Low	25–32		Liver	✓
<i>Levetiracetam</i>	Low	6–8		Hydrolysis	
<i>Oxcarbazepine<sup>3</sup></i>	Low	5–13	Monohydroxy metabolite (MHD)	Liver	✓
<i>Perampanel</i>	High	105		Liver	✓
<i>Phenobarbital</i>	Low	72–124		Liver	✓
<i>Phenytoin</i>	High	12–60		Liver	✓
<i>Primidone</i>	High	72–124	<i>Phenobarbital</i> , PEMA	Liver	✓
<i>Pregabalin</i>	Low	5–6.5		Kidney	
<i>Rufinamide</i>	Low	6–10		Liver	✓
<i>Tiagabine</i>	High	7–9		Liver	✓
<i>Topiramate</i>	Low	21		Various	✓
<i>Valproic acid (Divalproex)</i>	Moderate/ High	6–18	Various	Liver	✓
<i>Vigabatrin</i>	Low	7.5		Kidney	✓
<i>Zonisamide</i>	Low	63		Liver	✓

PEMA = phenylethylmalonamide.

<sup>1</sup>Low = 60% or less, Moderate = 61%–85%, High = >85%.

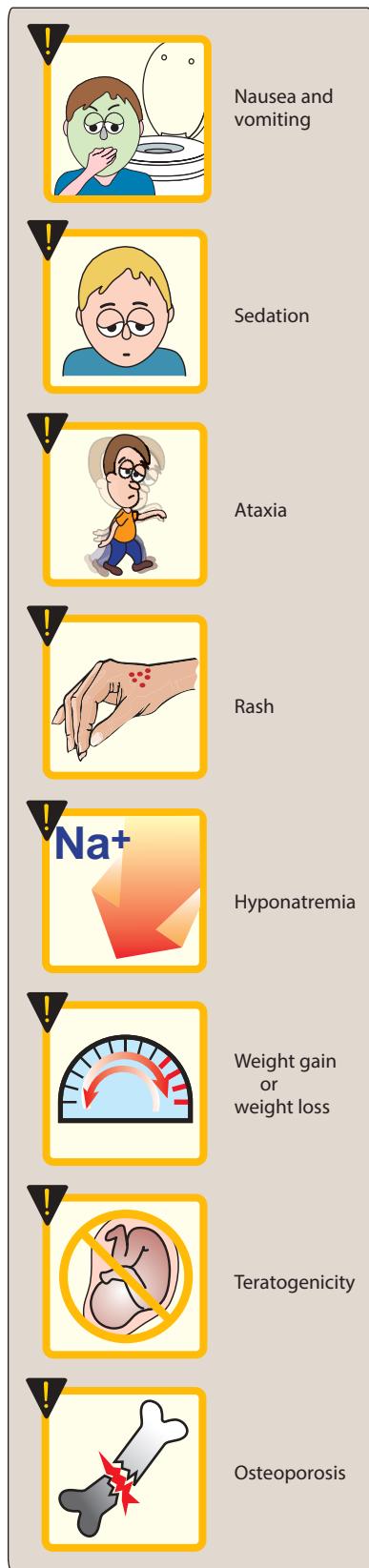
<sup>2</sup>Half-life in hours.

<sup>3</sup>Prodrug.

### Figure 12.7

Summary of the pharmacokinetics of antiseizure medications used as chronic therapy.

epileptic focus and preventing spread. *Carbamazepine* is a first-line drug for treatment of focal seizures, generalized tonic–clonic seizures, trigeminal neuralgia, and bipolar disorder. It induces its own metabolism (autoinduction), resulting in lower total carbamazepine blood concentrations at higher doses. It should be introduced in low dosage (100 to 200 mg daily) to allow tolerance to develop to its CNS side effects. The dose can then be increased (1 to 2 every week)

**Figure 12.8**

Notable adverse effects of antiseizure medications.

to a maintenance dose of 200 mg/day for complete control of seizures. *Carbamazepine* is an inducer of the CYP1A2, CYP2C, CYP3A, and UDP glucuronosyltransferase (UGT) enzymes, which increases the clearance of other drugs (Figure 12.9). Common side effects include diplopia, headache, dizziness, nausea, and vomiting. Some of these side effects may be due to its active epoxide metabolite. Peak levels often result in intermittent side effects occurring around 2 hours after dosing, necessitating administration three or four times daily in some. Peak dose-related side effects can often be overcome by prescribing the dose twice daily for a controlled-release formulation. *Carbamazepine* can cause a range of idiosyncratic reactions, the most common of which is a skin rash. Slow-dosage titration reduces the risk. Rarely, it may cause more severe skin eruptions including erythema multiforme and Stevens–Johnson syndrome, a dermatological emergency. Reversible mild leucopenia often occurs and has no clinical significance. At high levels, *carbamazepine* has an antidiuretic hormone–like action that can result in fluid retention in people with cardiac failure, especially in the elderly. Mild hyponatremia is usually asymptomatic, but if serum sodium falls below 125 mmol/L there might be confusion, peripheral edema, and worsening seizure control. Cardiac arrhythmia is also an occasional complication. *Carbamazepine* should not be prescribed for patients with absence seizures because it may cause an increase in seizures. *Carbamazepine* is a strong enzyme inducer and can accelerate its own clearance (referred to as autoinduction) and clearance of a number of other lipid-soluble drugs including the oral contraceptive pill (resulting in contraceptive failure) necessitating, for most women, a higher daily estrogen dose. Other affected drugs include *sodium valproate*, *ethosuximide*, corticosteroids, anticoagulants, antipsychotics, and *cyclosporin*. Drugs that inhibit carbamazepine metabolism and may result in toxicity include *phenytoin*, *isoniazid*, *cimetidine*, *danazol*, *dextropropoxyphene*, *erythromycin*, *verapamil*, *diltiazem*, and *vi洛xazine*.

#### D. Oxcarbazepine

*Oxcarbazepine* [ox-kar-BAY-zeh-peen] is a prodrug that is rapidly reduced to the 10-monohydroxy (MHD) metabolite responsible for its anticonvulsant activity. MHD blocks sodium channels and is thought to modulate calcium channels. It is approved for use in adults and children with focal seizures. *Oxcarbazepine* is a less potent inducer of CYP3A4 and UGT than *carbamazepine*. The adverse effect of hyponatremia limits its use in the elderly.

#### E. Eslicarbazepine

UGT *Eslicarbazepine* [es-li-kar-BAZ-a-peen] acetate is a prodrug that is converted to the active metabolite *eslicarbazepine* (S-licarbazepine) by hydrolysis. S-licarbazepine is the active metabolite of *oxcarbazepine*. It is a voltage-gated sodium channel blocker and is approved for focal seizures in adults. *Eslicarbazepine* exhibits linear pharmacokinetics and is eliminated via glucuronidation. The side effect profile includes dizziness, somnolence, diplopia, and headache. Serious adverse reactions such as rash, psychiatric side effects, and hyponatremia occur rarely.

## F. Ethosuximide

*Ethosuximide* [eth-oh-SUX-i-mide] reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels. It is most effective in treating absence seizures.

## G. Felbamate

*Felbamate* [FEL-ba-mate] has a broad spectrum of anticonvulsant action with multiple proposed mechanisms including the blocking of voltage-dependent sodium channels, competing with the glycine binding site on the *N*-methyl-D-aspartate (NMDA) glutamate receptor, blocking of calcium channels, and potentiating GABA action. It is an inhibitor of drugs metabolized by CYP2C19 and induces drugs metabolized by CYP3A4. It is reserved for use in refractory epilepsies (particularly Lennox–Gastaut syndrome) because of the risk of aplastic anemia (about 1:4000) and hepatic failure.

## H. Gabapentin

*Gabapentin* [GA-ba-pen-tin] is an analog of GABA. However, it does not act at GABA receptors, enhance GABA actions, or convert to GABA. Although *gabapentin* binds to the  $\alpha 2\delta$  subunit of voltage-gated calcium channels, the precise mechanism of action is not known. It is approved as adjunct therapy for focal seizures and treatment of postherpetic neuralgia. *Gabapentin* exhibits nonlinear pharmacokinetics (see Chapter 1) due to its uptake by a saturable transport system from the gut. *Gabapentin* does not bind to plasma proteins and is excreted unchanged through the kidneys. Reduced dosing is required in renal disease. *Gabapentin* is well tolerated by the elderly population with focal seizures due to its relatively mild adverse effects. *Gabapentin* is not metabolized, exhibits no protein binding, and does not induce hepatic enzymes. Its potential for drug interaction is small. It may also be a good choice for people with a high risk of drug interactions such as an older patient. Side effects of *gabapentin* are mainly related to the CNS and these include drowsiness, dizziness, diplopia, ataxia, and headaches. *Gabapentin*, at high doses, is associated with weight gain. It may also occasionally worsen seizures, particularly myoclonic seizures. No serious idiosyncratic reaction to *gabapentin* has been reported till now.

## I. Lacosamide

*Lacosamide* [la-KOE-sa-mide] affects voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. *Lacosamide* binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein involved in neuronal differentiation and control of axonal outgrowth. The role of CRMP-2 binding in seizure control is unknown. *Lacosamide* is approved for adjunctive treatment of focal seizures. The most common adverse events that limit treatment include dizziness, headache, and fatigue.

## J. Lamotrigine

*Lamotrigine* [la-MOE-tri-jeen] blocks sodium channels and high-voltage-dependent calcium channels. *Lamotrigine* is effective in a wide

<b>CYP1A2</b>	<i>Carbamazepine</i>
<b>CYP2C8</b>	<i>Carbamazepine</i>
<b>CYP2C9</b>	<i>Carbamazepine</i> <i>Divalproex</i> <i>Phenobarbital</i> <i>Phenytoin</i>
<b>CYP2C19</b>	<i>Clobazam</i> <i>Divalproex</i> <i>Felbamate</i> <i>Phenobarbital</i> <i>Phenytoin</i> <i>Zonisamide</i>
<b>CYP3A4</b>	<i>Carbamazepine</i> <i>Clobazam</i> <i>Ethosuximide</i> <i>Perampanel</i> <i>Tiagabine</i> <i>Zonisamide</i>
<b>UDP-glucuronosyltransferase</b>	<i>Divalproex</i> <i>Ezogabine</i> <i>Lamotrigine</i> <i>Lorazepam</i>

**Figure 12.9**

CYP metabolism of the antiseizure medications.

variety of seizure types, including focal, generalized, absence seizures, and Lennox–Gastaut syndrome. It is also used to treat bipolar disorder. *Lamotrigine* is metabolized primarily to the 2-N-glucuronide metabolite through the UGT1A4 pathway. As with other antiseizure medications, general inducers increase *lamotrigine* clearance leading to lower *lamotrigine* concentrations, whereas *divalproex* results in a significant decrease in *lamotrigine* clearance (higher *lamotrigine* concentrations). *Lamotrigine* dosages should be reduced when adding *valproate* to therapy. Slow titration is necessary with *lamotrigine* (particularly when adding *lamotrigine* to a regimen that includes *valproate*) due to risk of rash, which may progress to a serious, life-threatening reaction. Common side effects include headache, drowsiness, ataxia, diplopia, insomnia, nausea, and dizziness seen particularly during dose escalation.

### K. **Levetiracetam**

*Levetiracetam* [lee-ve-tye-RA-se-tam] is approved for adjunct therapy of focal onset, myoclonic, and primary generalized tonic–clonic seizures in adults and children. It demonstrates high affinity for a synaptic vesicle protein (SV2A). The drug is well absorbed after oral administration and is excreted in urine mostly unchanged, resulting in few to no drug interactions. *Levetiracetam* can cause mood alterations that may require a dose reduction or a change of medication.

### L. **Perampanel**

*Perampanel* [per-AM-pa-nel] is a selective  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonist resulting in reduced excitatory activity. *Perampanel* has a long half-life enabling once-daily dosing. It is approved for adjunctive treatment of focal and generalized tonic–clonic seizures. This medication has a warning for serious psychiatric and behavioral reactions including aggression, hostility, irritability, anger, and homicidal ideation.

### M. **Phenobarbital and primidone**

The primary mechanism of action of *phenobarbital* [fee-noe-BAR-bih-tal] is enhancement of the inhibitory effects of GABA-mediated neurons (see Chapter 9). *Primidone* is metabolized to *phenobarbital* (major) and phenylethylmalonamide, both with anticonvulsant activity. *Phenobarbital* is a first-line established treatment for focal and tonic–clonic seizures but is seldom currently used in developed countries due to its effect on cognition, mood, and behavior. It can produce fatigue, listlessness, and tiredness in adults and insomnia, hyperactivity, and aggression in children (and sometimes in the elderly). *Phenobarbital* is an enzyme inducer and can accelerate the metabolism of many lipid-soluble drugs and has an impact on bone health. To minimize sedation, it should be started in a low dose (30 mg in adolescents and adults) and increased gradually (15 mg) according to clinical requirements (usual therapeutic daily dose is 60 to 120 mg). The value of measuring drug levels is limited, as it has a relatively wider therapeutic range (15 to 45 mg/L), and the concentration associated with seizure control varies considerably. In addition, the development of tolerance to its CNS side effects makes the toxic threshold

imprecise. *Phenobarbital* is used primarily in the treatment of status epilepticus when other agents fail.

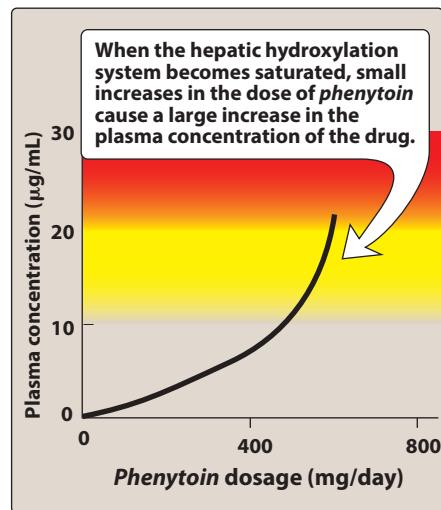
## N. Phenytoin and fosphenytoin

*Phenytoin* [FEN-i-toin] blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery. It is effective for treatment of focal and generalized tonic-clonic seizures and in the treatment of status epilepticus. *Phenytoin* induces CYP2C and CYP3A families and the UGT enzyme system. *Phenytoin* exhibits saturable enzyme metabolism resulting in nonlinear pharmacokinetic properties (small increases in the daily dose can produce large increases in plasma concentration, resulting in drug-induced toxicity; **Figure 12.10**). *Phenytoin* is one of the few examples of switching from first order to saturation kinetics at therapeutic dosage. Accordingly, at higher levels a moderate increment in dose can produce an unexpectedly large rise in the level with accompanying neurotoxicity. Conversely, levels can fall precipitously when the dose is reduced modestly, sometimes resulting in unexpected deterioration in seizure control. The dosage producing the same levels, therefore, varies substantially among different individuals. Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia. The elderly are highly susceptible to this effect. Reversible cosmetic changes include gum hyperplasia, acne, hirsutism, and facial coarsening. Gingival hyperplasia may cause the gums to grow over the teeth (**Figure 12.11**). Long-term use may lead to development of peripheral neuropathies and osteoporosis. Although *phenytoin* is advantageous due to its low cost, it exhibits a narrow therapeutic range (10 to 20 mmol/L). Symptoms of neurotoxicity (drowsiness, dysarthria, tremor, ataxia, cognitive difficulties) become increasingly likely with higher levels, but the diagnosis of *phenytoin* toxicity should be made on clinical grounds and not assumed from a high level of dosage. Permanent cerebellar damage may be a consequence of chronic toxicity (mental slowing and unsteadiness, and neurological examination may show cerebellar signs). Therefore, *phenytoin* levels should be measured regularly. A paradoxical increase in seizure frequency may also occur with marked *phenytoin* toxicity. *Phenytoin* can accelerate the metabolism of a number of lipid-soluble drugs, including *carbamazepine*, *sodium valproate*, *ethosuximide*, anticoagulants, steroids, and *cyclosporin*. Protein-binding displacement interactions with AEDs are only clinically relevant when there is concomitant enzyme inhibition, as is the case with the combination of *phenytoin* and *sodium valproate*.

*Fosphenytoin* [FOS-phen-i-toin] is a prodrug that is rapidly converted to *phenytoin* in the blood within minutes. Whereas *fosphe-nytoin* may be administered intramuscularly (IM), *phenytoin sodium* should never be given IM, as it causes tissue damage and necrosis. *Fosphenytoin* is the drug of choice and standard of care for IV and IM administration of *phenytoin*.

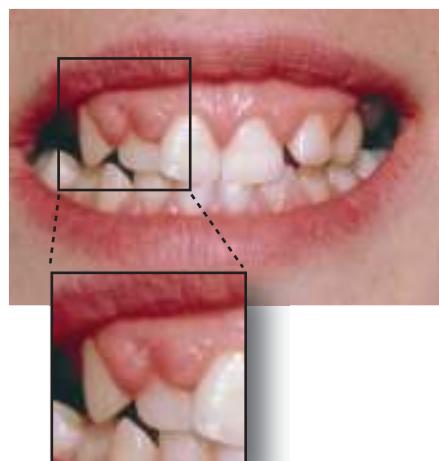
## O. Pregabalin

*Pregabalin* [pree-GA-ba-lin] binds to the  $\alpha_2\delta$  site, an auxiliary subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory



**Figure 12.10**

Nonlinear effect of *phenytoin* dosage on the plasma concentration of the drug.



**Figure 12.11**

Gingival hyperplasia in patient treated with *phenytoin*. Science Source, New York, NY.

neurotransmitter release. The drug has proven effects on focal-onset seizures, diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. More than 90% of *pregabalin* is eliminated renally. It has no significant effects on drug metabolism and few drug interactions. Dosage adjustments are needed in renal dysfunction.

#### P. Rufinamide

*Rufinamide* [roo-FIN-a-mide] acts at sodium channels. It is approved for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children over age 4 years and in adults. *Rufinamide* is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 enzymes. Food increases absorption and peak serum concentrations. Serum concentrations of *rufinamide* are affected by other antiseizure medications. *Carbamazepine* and *phenytoin* can reduce, and *valproate* can increase the serum concentrations of *rufinamide*. Adverse effects include the potential for shortened QT intervals. Patients with familial short QT syndrome should not be treated with *rufinamide*.

#### Q. Tiagabine

*Tiagabine* [ty-AG-a-been] blocks GABA uptake into presynaptic neurons permitting more GABA to be available for receptor binding, and thereby enhancing inhibitory activity. *Tiagabine* is effective as adjunctive treatment in focal seizures. In postmarketing surveillance, seizures have occurred in patients using *tiagabine* who did not have epilepsy. *Tiagabine* should not be used for indications other than epilepsy.

#### R. Topiramate

*Topiramate* [toe-PEER-a-mate] has multiple mechanisms of action. It blocks voltage-dependent sodium channels, reduces high-voltage calcium currents (L type), is a carbonic anhydrase inhibitor, and may act at glutamate (NMDA) sites. *Topiramate* is effective for use in focal and primary generalized epilepsy. It is also approved for prevention of migraine. It mildly inhibits CYP2C19, and coadministration with *phenytoin* and *carbamazepine* may reduce serum concentrations of *topiramate*. Adverse effects include somnolence, weight loss, and paresthesias. Renal stones, glaucoma, oligohidrosis (decreased sweating), and hyperthermia have also been reported.

#### S. Valproic acid and divalproex

Possible mechanisms of action include sodium channel blockade, blockade of GABA transaminase, and action at the T-type calcium channels. These varied mechanisms provide a broad spectrum of activity against seizures. It is effective for the treatment of focal and primary generalized epilepsies. *Valproic acid* [val-PRO-ik A-sid] is available as a free acid. *Divalproex* [dye-val-PRO-ex] sodium is a combination of *sodium valproate* [val-PROE-ate] and *valproic acid* that is converted to *valproate* when it reaches the gastrointestinal tract. It was developed to improve gastrointestinal tolerance of *valproic acid*.

All of the available salt forms are equivalent in efficacy (*valproic acid* and *sodium valproate*). Commercial products are available in multiple-salt dosage forms and extended-release formulations. Therefore, the risk for medication errors is high, and it is essential to be familiar with all preparations. The initial dose is 10 to 15 mg/kg per day. The dose should be increased by 5 to 10 mg/kg per week according to the clinical need to achieve optimal clinical response. The controlled release formulation can be given once daily. Frequent dosage adjustments shortly after initiating therapy may be unwarranted as the drug can take several weeks to become fully effective. *Valproate* inhibits metabolism of the CYP2C9, UGT, and epoxide hydrolase systems (Figure 12.9). Rare hepatotoxicity may cause a rise in liver enzymes, which should be monitored frequently. Use in children under age 2 years and women should be avoided if possible. Side effects of *sodium valproate* include dose-related tremor, weight gain due to appetite stimulation, thinning or loss of hair (usually temporary), and menstrual irregularities including amenorrhea. *Sodium valproate* can inhibit a range of hepatic metabolic processes, including oxidation, conjugation, and epoxidation reactions. It is involved in a number of drug interactions with other AEDs, particularly *phenytoin*, *phenobarbital*, *carbamazepine epoxide*, and *lamotrigine*. *Aspirin* displaces *sodium valproate* from its binding sites on plasma protein and inhibits its metabolism. *Valproic acid* does not interfere with the hormonal components of the oral contraceptive pill. Its use in women of childbearing potential is not recommended in view of its potential teratogenicity.

#### T. Vigabatrin

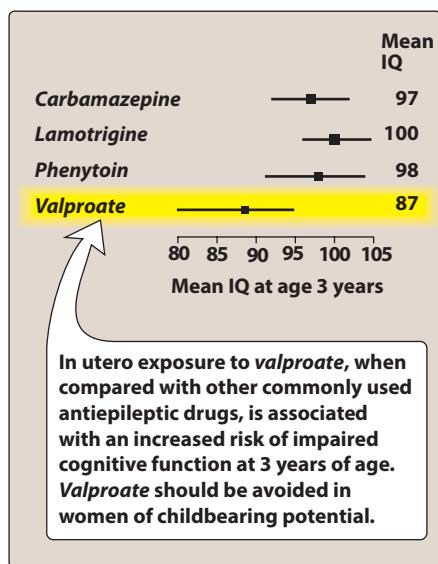
*Vigabatrin* [vye-GA-ba-trin] acts as an irreversible inhibitor of GABA transaminase (GABA-T). GABA-T is the enzyme responsible for metabolism of GABA. *Vigabatrin* is associated with visual field loss ranging from mild to severe in 30% or more of patients. *Vigabatrin* is only available through physicians and pharmacies that participate in the REMS (risk evaluation and mitigation strategies) program.

#### U. Zonisamide

*Zonisamide* [zoe-NIS-a-mide] is a sulfonamide derivative that has a broad spectrum of action. The compound has multiple effects, including blockade of both voltage-gated sodium channels and T-type calcium currents. It has a limited amount of carbonic anhydrase activity. *Zonisamide* is approved for use in patients with focal epilepsy. It is metabolized by the CYP3A4 isozyme and may, to a lesser extent, be affected by CYP3A5 and CYP2C19. In addition to typical CNS adverse effects, *zonisamide* may cause kidney stones. Oligohidrosis has been reported, and patients should be monitored for increased body temperature and decreased sweating. *Zonisamide* is contraindicated in patients with sulfonamide or carbonic anhydrase inhibitor hypersensitivity.

### VI. STATUS EPILEPTICUS

In status epilepticus, two or more seizures occur without recovery of full consciousness in between episodes. These may be focal or generalized, convulsive or nonconvulsive. Status epilepticus is life threatening and requires

**Figure 12.12**

Cognitive function at 3 years of age after fetal exposure to doses of antiepileptic drugs. The means (black squares) and 95% confidence intervals (horizontal lines) are given for the children's IQ as a function of the antiepileptic drugs.

emergency treatment usually consisting of parenteral administration of a fast-acting medication such as a benzodiazepine, followed by a slow-acting medication such as *phenytoin*, *fosphenytoin*, *divalproex*, or *levetiracetam*.

## VII. WOMEN'S HEALTH AND EPILEPSY

Women of childbearing potential with epilepsy require assessment of their antiseizure medications in regard to contraception and pregnancy planning. Several antiseizure medications increase the metabolism of hormonal contraceptives, potentially rendering them ineffective. These include *phenytoin*, *phenobarbital*, *carbamazepine*, *topiramate*, *oxcarbazepine*, *rufinamide*, and *clobazam*. These medications increase the metabolism of contraceptives regardless of the delivery system used (for example, patch, ring, implants, and oral tablets). Pregnancy planning is vital, as many antiseizure medications have the potential to affect fetal development and cause birth defects. All women considering pregnancy should be on high doses (1 to 5 mg) of folic acid prior to conception. *Divalproex* and barbiturates should be avoided. If possible, women already taking *divalproex* should be placed on other therapies before pregnancy and counseled about the potential for birth defects, including cognitive (Figure 12.12) and behavioral abnormalities and neural tube defects. The pharmacokinetics of antiseizure medications and the frequency and severity of seizures may change during pregnancy. Regular monitoring by both an obstetrician and a neurologist is important. All women with epilepsy should be encouraged to register with the Antiepileptic Drug Pregnancy Registry. Figure 12.13 summarizes important characteristics of the antiseizure medications.

DRUG	MECHANISM OF ACTION	USES	MAX DAILY DOSE/ADULTS	ADVERSE EFFECTS AND COMMENTS
<i>Phenytoin</i>	Blocks Na <sup>+</sup> channels	Mono/adjunctive for partial and GTCS and status epilepticus	200–500 mg daily Single dose	Gingival hyperplasia, confusion, slurred speech, double speech, ataxia, sedation, dizziness and hirsutism. Stevens–Johnson syndrome—potentially life threatening. Hence, not recommended for primary treatment
<i>Carbamazepine</i>	Blocks Na <sup>+</sup> channels	Mono/adjunctive therapy  Partial and GTCS; worsens myoclonic and absence seizures	2000 mg daily in divided doses	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has been associated with Stevens–Johnson syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias
<i>Oxcarbazepine</i>	Blocks Na <sup>+</sup> channels	Mono/adjunctive for partial onset seizures ± secondary generalization  Partial and GTCS	2000 mg daily in divided doses	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia
<i>Eslicarbazepine acetate</i>	Blocks Na <sup>+</sup> channels			Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia
<i>Divalproex</i>	Multiple mechanisms of action	All generalized seizures  Partial seizures	80 mg daily	Weight gain, easy bruising, nausea, tremor, hair loss, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects have been observed. Broad spectrum of antiseizure activity

AMPA =  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CBC = complete blood count; GABA =  $\gamma$ -aminobutyric acid; GABA-T =  $\gamma$ -aminobutyric acid transaminase; GI = gastrointestinal; GTCS = generalized tonic-clonic seizures; SLE = systemic lupus erythematosus.

**Figure 12.13**

Summary of antiepileptic drugs. (Figure continues on next page)

DRUG	MECHANISM OF ACTION	USES	MAX DAILY DOSE/ADULTS	ADVERSE EFFECTS AND COMMENTS
<i>Levetiracetam</i>	Multiple mechanisms of action	Mono/adjunctive for all seizure types	300 mg daily in two divided doses	Sedation, dizziness, headache, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity
<i>Topiramate</i>	Multiple mechanisms of action	Mono/adjunctive for all Partial and generalized seizures	400 mg daily (mono in two divided doses) 800 mg daily (adjunctive in two divided doses)	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity
<i>Gabapentin</i>	Unknown	Mono/adjunctive therapy in partial seizures	3600 mg daily in divided doses	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One hundred percent renal elimination
<i>Pregabalin</i>	Multiple mechanisms of action	Adjunctive for partial seizure ± secondary generalization	600 mg daily in divided doses	Weight gain, somnolence, dizziness, headache, diplopia, and ataxia. One hundred percent renal elimination
<i>Tiagabine</i>	Blocks GABA uptake	Adjunctive for partial seizure ± secondary generalization	30.45 mg daily in divided three doses	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions
<i>Vigabatrin</i>	Irreversible binding of GABA-T Infantile spasms	Adjunctive for partial seizures	3000 mg daily	Vision loss, anemia, somnolence, fatigue, peripheral neuropathy, weight gain. Available only through SHARE pharmacies
<i>Zonisamide</i>	Multiple mechanisms of action	Adjunctive for partial onset seizures ± secondary generalization	500 mg daily	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia, and oligohidrosis. Broad spectrum of antiseizure activity
<i>Felbamate</i>	Multiple mechanisms of action	Adjunctive for all seizure types	3600 mg daily in divided doses	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia and hepatic failure. Broad spectrum of seizure activity. Requires patient to sign informed consent at dispensing
<i>Ezogabine</i>	Enhances K <sup>+</sup> channels			Urinary retention, neuropsychiatric symptoms, dizziness, somnolence, OT prolongation, reports of blue skin discoloration, and retina changes
<i>Rufinamide</i>	Unknown	Adjunctive for Lennox-Gastaut seizures	1600 mg twice daily	Shortened OT interval Multiple drug interactions
<i>Perampanel</i>	Blocks AMPA glutamate receptors			Serious psychiatric and behavioral reactions, dizziness, somnolence, fatigue, gait disturbance, and falls; long half-life.
<i>Ethosuximide</i>	Block Ca <sup>2+</sup> channels	Mono/adjunctive therapy in absence seizures	2000 mg daily	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may cause seizures
<i>Lacosamide</i>	Multiple mechanisms of action	Adjunctive for partial onset seizures ± secondary generalization	200 mg twice daily	Dizziness, fatigue, and headache Few drug interactions
<i>Phenobarbital</i>	Drowsiness	Mono/adjunctive in partial and generalized seizures, newborn seizures, and status epilepticus	180 mg daily	Drowsiness

**Figure 12.13 (Continued)**

Summary of antiepileptic drugs.

## Study Questions

Choose the ONE best answer.

- 12.1 A 9-year-old boy is sent for neurologic evaluation because of episodes of apparent inattention. Over the past year, the child has experienced episodes during which he develops a blank look on his face and his eyes blink for 15 seconds. He immediately resumes his previous activity. Which best describes seizures in this patient?

- A. Focal
- B. Tonic-clonic
- C. Absence
- D. Myoclonic

- 12.2 A child is experiencing absence seizures that interrupt his ability to pay attention during school and activities. Which therapy is most appropriate for this patient?

- A. Ethosuximide
- B. Carbamazepine
- C. Diazepam
- D. Watchful waiting

- 12.3 Which drug is most useful for the treatment of absence seizures?

- A. Topiramate
- B. Tiagabine
- C. Levetiracetam
- D. Lamotrigine

- 12.4 A 25-year-old woman with generalized seizures is well controlled on valproate. She indicates that she is interested in becoming pregnant in the next year. With respect to her antiseizure medication, which of the following should be considered?

- A. Leave her on her current therapy.
- B. Consider switching to lamotrigine.
- C. Consider adding a second antiseizure medication.
- D. Decrease her valproate dose.

- 12.5 A woman with generalized seizures is well controlled with lamotrigine. She becomes pregnant and begins to have breakthrough seizures. What is most likely happening?

- A. Her epilepsy is getting worse.
- B. Lamotrigine concentrations are increasing.
- C. Lamotrigine concentrations are decreasing.
- D. Lamotrigine is no longer efficacious for this patient.

Correct answer = C. The patient is experiencing episodes of absence seizures where consciousness is impaired briefly. Absence seizures generally begin in children aged 4 to 12 years. Diagnosis includes obtaining an electroencephalogram that shows generalized 3-Hz waves.

Correct answer = A. The patient has had many seizures that interrupt his ability to pay attention during school and activities, so therapy is justified. Carbamazepine may make the seizures more frequent. Diazepam is not indicated for absence seizures.

Correct answer = D. Of the drugs listed, lamotrigine has the best data for use in absence seizures and is the best choice. Tiagabine is only used for focal seizures. Topiramate and levetiracetam may be options if lamotrigine does not work.

Correct answer = B. Valproate is a poor choice in women of child-bearing age and should be avoided if possible. A review of the medication history of this patient is warranted. If she has not tried any other antiseizure medication, then consideration of another antiseizure medication may be beneficial. Studies show that valproate taken during pregnancy can have a detrimental effect on cognitive abilities in children.

Correct answer = C. Pregnancy alters the pharmacokinetics of lamotrigine. As pregnancy progresses, women can require increased dosages to maintain blood concentrations and seizure control.

12.6 A 42-year-old man undergoes a neurologic evaluation because of episodes of apparent confusion. Over the past year, the man has experienced episodes during which he develops a blank look on his face and fails to respond to questions. Moreover, it appears to take several minutes before the man recovers from the episodes. Which best describes this type of seizure?

- A. Focal (aware)
- B. Focal (impaired awareness)
- C. Tonic-clonic
- D. Absence

12.7 A 52-year-old man has had several focal seizures with impaired consciousness over the last year. Which is the most appropriate initial therapy for this patient?

- A. Ethosuximide
- B. Levetiracetam
- C. Diazepam
- D. Carbamazepine plus primidone

12.8 A patient with focal seizures has been treated for 6 months with carbamazepine but, recently, has been experiencing breakthrough seizures on a more frequent basis. You are considering adding a second drug to the antiseizure regimen. Which of the following drugs is least likely to have a pharmacokinetic interaction with carbamazepine?

- A. Topiramate
- B. Tiagabine
- C. Levetiracetam
- D. Lamotrigine

12.9 Which is a first-line medication for generalized tonic-clonic seizures?

- A. Ethosuximide
- B. Felbamate
- C. Vigabatrin
- D. Topiramate

Correct answer = B. The patient is experiencing episodes of focal seizures with impaired consciousness. Typically, staring is accompanied by impaired consciousness and recall. If asked a question, the patient might respond with an inappropriate or unintelligible answer. Automatic movements are associated with most focal seizures and involve the mouth and face (lip-smacking, chewing, tasting, and swallowing movements), upper extremities (fumbling, picking, tapping, or clasping movements), vocal apparatus (grunts or repetition of words and phrases), as are complex acts (such as walking or mixing foods in a bowl).

Correct answer = B. The patient has had many seizures, and the risks of not starting drug therapy would be substantially greater than the risks of treating his seizures. Because the patient has impaired consciousness during the seizure, he is at risk for injury during an attack. Monotherapy with primary agents is preferred for most patients. The advantages of monotherapy include reduced frequency of adverse effects, absence of interactions between antiepileptic drugs, lower cost, and improved compliance. Ethosuximide and diazepam are not indicated for focal seizures.

Correct answer = C. Of the drugs listed, all of which are approved as adjunct therapy for refractory focal seizures, only levetiracetam does not affect the pharmacokinetics of other antiepileptic drugs, and other drugs do not significantly alter its pharmacokinetics. However, any of the listed drugs could be added depending on the plan and the patient characteristics. Treatment of epilepsy is complex, and diagnosis is based on history and may need to be reevaluated when drug therapy fails or seizures increase.

Correct answer = D. Topiramate is a broad-spectrum antiseizure medication that is indicated for primary generalized tonic-clonic seizures. Ethosuximide should only be used for absence seizures. Felbamate is reserved for refractory seizures due to the risk of aplastic anemia and liver failure. Vigabatrin is not indicated for generalized seizures and is associated with visual field defects.

12.10 A 75-year-old woman had a stroke approximately 1 month ago. She is continuing to have small focal seizures where she fails to respond appropriately while talking. Which is the most appropriate treatment for this individual?

- A. Phenytoin
- B. Oxcarbazepine
- C. Levetiracetam
- D. Phenobarbital

Correct answer = C. Levetiracetam is renally cleared and prone to very few drug interactions. Elderly patients usually have more comorbidities and take more medications than younger patients. Oxcarbazepine may cause hyponatremia, which is more symptomatic in the elderly. Phenytoin and phenobarbital have many drug interactions and a side effect profile that may be especially troublesome in the elderly age group, including dizziness that may lead to falls, cognitive issues, and bone health issues.

# Anesthetics

Brandon Lopez and Chris Giordano

13

## I. OVERVIEW

For patients undergoing surgical or medical procedures, different levels of sedation can provide important benefits to facilitate procedural interventions. These levels of sedation range from anxiolysis to general anesthesia and can create:

- sedation and reduced anxiety,
- lack of awareness and amnesia,
- skeletal muscle relaxation,
- suppression of undesirable reflexes, and
- analgesia.

Because no single agent provides all desired objectives, several categories of drugs are combined to produce the optimum level of sedation required (Figure 13.1). Anesthetics are agents that bring about reversible loss of sensation and consciousness. They are divided into two main groups: general anesthetics (Figure 13.2) and local anesthetics. Drugs are chosen to provide safe and efficient sedation based on the type and duration of

	TYPES OF GENERAL ANESTHETICS	
Inhalational anesthetics	Gas	Liquids
	Nitrous oxide	<i>Halothane Methoxyflurane Enflurane Isoflurane Desoflurane</i>
Intravenous anesthetics	Barbiturates: <i>Thiopentone Methohexitone</i> Nonbarbiturates: <i>Propofol Etomidate</i> Benzodiazepines: <i>Diazepam Lorazepam Midazolam</i>	
Dissociative anesthetics	<i>Ketamine</i>	

Figure 13.2

Types of general anesthetics.

### PREOPERATIVE MEDICATIONS

*Analgesics  
Antacids  
Antiemetics  
Benzodiazepines\**

### ANALGESICS

*Acetaminophen  
Celecoxib  
Gabapentin  
Ketamine  
Opioids*

### GENERAL ANESTHETICS: INHALED

*Desflurane  
Isoflurane  
Nitrous oxide  
Sevoflurane*

### GENERAL ANESTHETICS: INTRAVENOUS

*Barbiturates  
Dexmedetomidine  
Etomidate  
Propofol*

### NEUROMUSCULAR BLOCKERS (see Chapter 5)

*Cisatracurium  
Mivacurium  
Pancuronium  
Rocuronium  
Succinylcholine  
Vecuronium*

### LOCAL ANESTHETICS: AMIDES

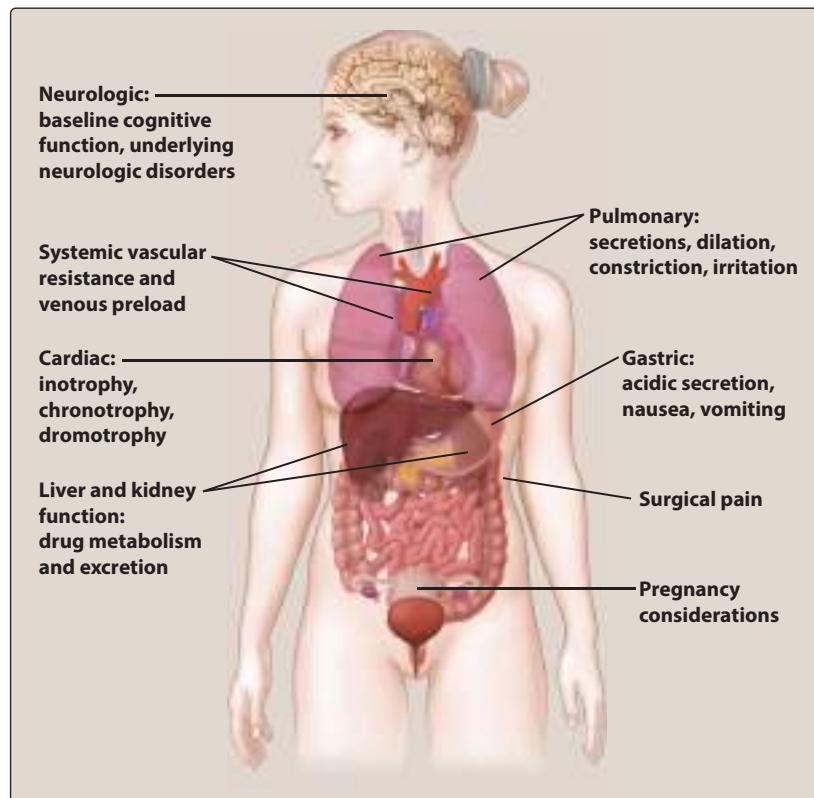
*Bupivacaine  
Lidocaine  
Mepivacaine  
Ropivacaine*

### LOCAL ANESTHETICS: ESTERS

*Chloroprocaine  
Tetracaine*

Figure 13.1

Summary of common drugs used for anesthesia. \*Can create general anesthesia with high dose. See Chapter 5 for summary of neuromuscular-blocking agents.



**Figure 13.3**

Overall considerations when delivering an anesthetic.

the procedure and patient characteristics, such as organ function, medical conditions, and concurrent medications (Figure 13.3). Preoperative medications provide anxiolysis and analgesia, and mitigate unwanted side effects of the anesthetic or the procedure itself. Neuromuscular blockers enable endotracheal intubation and muscle relaxation to facilitate surgery. Potent general anesthetic medications are delivered via inhalation and/or intravenously. Except for *nitrous oxide*, inhaled anesthetics are volatile, halogenated hydrocarbons, while intravenous (IV) anesthetics consist of several chemically unrelated drug classes commonly used to rapidly induce and/or maintain a state of general anesthesia.

## II. PATIENT FACTORS IN SELECTION OF ANESTHESIA

Drugs are chosen to provide safe and efficient anesthesia based on the type of procedure and patient characteristics such as organ function, medical conditions, and concurrent medications.

### A. Status of organ systems

- 1. Cardiovascular system:** Anesthetic agents suppress cardiovascular function to varying degrees. This is an important consideration in patients with coronary artery disease, heart failure, dysrhythmias, valvular disease, and other cardiovascular disorders. Hypotension may develop during anesthesia, resulting in reduced perfusion pressure and ischemic injury to tissues.

Treatment with vasoactive agents may be necessary. Some anesthetics, such as *halothane*, sensitize the heart to arrhythmogenic effects of sympathomimetic agents.

2. **Respiratory system:** Respiratory function must be considered for all anesthetics. Asthma and ventilation or perfusion abnormalities complicate control of inhalation anesthetics. Inhaled agents depress respiration but also act as bronchodilators. IV anesthetics and opioids suppress respiration. These effects may influence the ability to provide adequate ventilation and oxygenation during and after surgery.
3. **Liver and kidney:** The liver and kidneys influence long-term distribution and clearance of drugs and are also target organs for toxic effects. Release of fluoride, bromide, and other metabolites of halogenated hydrocarbons can affect these organs, especially if they accumulate with frequently repeated administration of anesthetics.
4. **Nervous system:** The presence of neurologic disorders (for example, epilepsy, myasthenia gravis, neuromuscular disease, compromised cerebral circulation) influences the selection of anesthetic.
5. **Pregnancy:** Special precautions should be observed when anesthetics and adjunctive agents are administered during pregnancy. Effects of fetal organogenesis are a major concern in early pregnancy. Transient use of *nitrous oxide* may cause aplastic anemia in the fetus. Oral clefts have occurred in fetuses when mothers received benzodiazepines in early pregnancy. Benzodiazepines should not be used during labor because of resultant temporary hypotonia and altered thermoregulation in the new born.

## B. Concomitant use of drugs

1. **Multiple adjunct agents:** Commonly, patients receive one or more of these preanesthetic medications:  $H_2$  blockers (*famotidine*, *ranitidine*) to reduce gastric acidity, benzodiazepines (*midazolam*, *diazepam*) to allay anxiety and facilitate amnesia; nonopioids (*acetaminophen*, *celecoxib*) or opioids (*fentanyl*) for analgesia; antihistamines (*diphenhydramine*) to prevent allergic reactions; antiemetics (*ondansetron*) to prevent nausea; and/or anticholinergics (*glycopyrrolate*) to prevent bradycardia and secretion of fluids into the respiratory tract (Figure 13.2). Premedications facilitate smooth induction of anesthesia and lower required anesthetic doses. However, they can also enhance undesirable anesthetic effects (hypoventilation) and, when coadministered, may produce negative effects not observed when given individually.
2. **Concomitant user of other drugs:** Patients may take medications for underlying diseases or abuse drugs that alter response to anesthetics. For example, alcoholics have elevated levels of liver enzymes that metabolize anesthetics, and drug abusers may be tolerant to opioids.

## III. LEVELS OF SEDATION

The levels of sedation occur in a dose-related continuum, which is variable and depends on individual patient response to various drugs. These "artificial" levels of sedation start with light sedation (anxiolysis), continue

	MINIMAL (ANXIOLYSIS)	MODERATE	DEEP	GENERAL
Mentation	Responds normally to verbal stimuli	Responds purposefully to verbal or tactile stimuli	Responds purposefully to repeated verbal or painful stimuli	Unarousable to painful stimuli
Airway competency	Unaffected	Adequate	Intervention may be required	Intervention usually required
Respiratory system	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular system	Unaffected	Usually maintained	Usually maintained	May be impaired

**Figure 13.4**

Anesthetic levels of sedation.

to moderate sedation, then deep sedation, and finally to a state of general anesthesia. The hallmarks of escalation from one level to the next are recognized by changes in mentation, hemodynamic stability, and respiratory competency (Figure 13.4). This escalation in levels is often very subtle and unpredictable; therefore, the sedation provider must always be ready to manage the unanticipated next level of sedation.

## IV. STAGES OF GENERAL ANESTHESIA

General anesthesia is a reversible state of central nervous system (CNS) depression, causing loss of response to and perception of stimuli. The state of general anesthesia can be divided into three stages: induction, maintenance, and recovery. Induction is the time from administration of a potent anesthetic to development of unconsciousness, while maintenance is the sustained period of general anesthesia. Recovery starts with the discontinuation of the anesthetic and continues until the return of consciousness and protective reflexes. Induction of anesthesia depends on how fast effective concentrations of anesthetic reach the brain. Recovery is essentially the reverse of induction and depends on how fast the anesthetic diffuses from the brain. The depth of general anesthesia is the degree to which the CNS is depressed, as evident in electroencephalograms.

### A. Induction

General anesthesia in adults is normally induced with an IV agent such as *propofol*, producing unconsciousness in 30 to 40 seconds. Often an IV neuromuscular blocker such as *rocuronium*, *vecuronium*, or *succinylcholine* is administered to facilitate endotracheal intubation by eliciting muscle relaxation. For children without IV access, nonpungent volatile agents, such as *sevoflurane*, are administered via inhalation to induce general anesthesia.

### B. Maintenance of anesthesia

After administering the induction drug, vital signs and response to stimuli are vigilantly monitored to balance the amount of drug continuously inhaled or infused to maintain general anesthesia. Maintenance is commonly provided with volatile anesthetics, although total

intravenous anesthesia (TIVA) with drugs such as *propofol* can be used to maintain general anesthesia. Opioids such as *fentanyl* are used for analgesia along with inhalation agents, because the latter alter consciousness but not perception of pain.

### C. Recovery

After cessation of the maintenance anesthetic drug, the patient is evaluated for return of consciousness. For most anesthetic agents, redistribution from the site of action (rather than metabolism of the drug) underlies recovery. Neuromuscular blocking drugs are typically reversed after completion of surgery, unless enough time has elapsed for their metabolism. The patient is monitored to assure full recovery of all normal physiologic functions (spontaneous respiration, blood pressure, heart rate, and all protective reflexes).

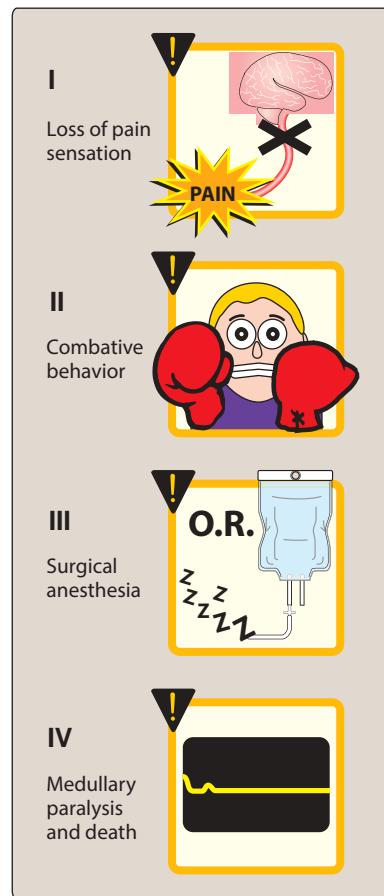
### D Depth of anesthesia

The depth of anesthesia has four sequential stages characterized by increasing CNS depression as the anesthetic accumulates in the brain (Figure 13.5). [Note: These stages were defined for the original anesthetic *ether*, which produces a slow onset of anesthesia. With modern anesthetics, the stages merge because of the rapid onset of stage III.]

- Stage I—Analgesia:** Loss of pain sensation results from interference with sensory transmission in the spinothalamic tract. The patient progresses from conscious and conversational to drowsy. Amnesia and reduced awareness of pain occur as stage II is approached.
- Stage II—Excitement:** The patient displays delirium and possibly combative behavior. A rise and irregularity in blood pressure and respiration occur, as well as a risk of laryngospasm. To shorten or eliminate this stage, rapid-acting IV agents are given before inhalation anesthesia is administered.
- Stage III—Surgical anesthesia:** There is gradual loss of muscle tone and reflexes as the CNS is further depressed. Regular respiration and relaxation of skeletal muscles with eventual loss of spontaneous movement occur. This is the ideal stage of surgery. Careful monitoring is needed to prevent undesired progression to stage IV.
- Stage IV—Medullary paralysis:** Severe depression of the respiratory and vasomotor centers occurs. Ventilation and/or circulation must be supported to prevent death.

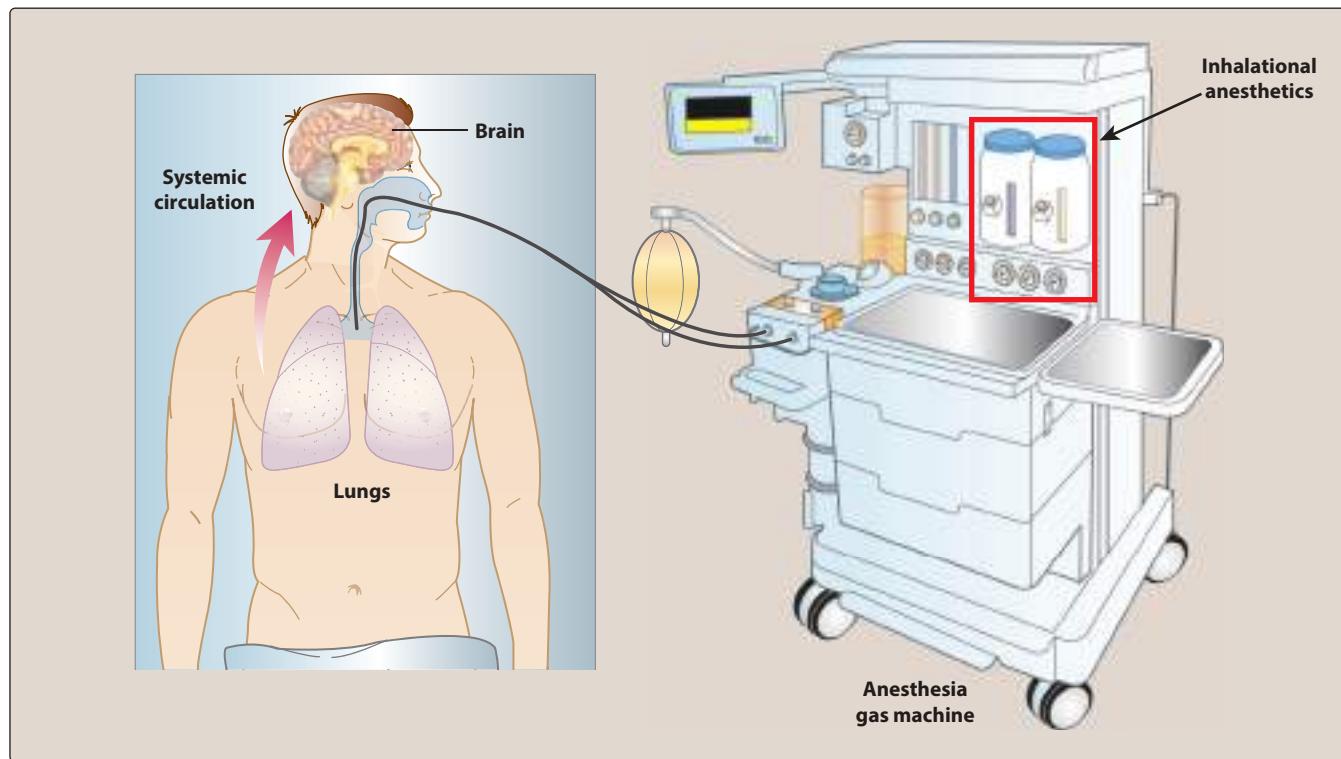
## V. INHALATION ANESTHETICS

Inhaled gases are used primarily for maintenance of anesthesia after administration of an IV drug (Figure 13.6). Depth of anesthesia can be rapidly altered by changing the inhaled gas concentration. Inhalational agents have steep dose-response curves with very narrow therapeutic indices, so the difference in concentrations from eliciting general anesthesia to cardiopulmonary collapse is small. No antagonists exist. To minimize waste, inhaled gases are delivered in a recirculation system that contains absorbents to remove carbon dioxide and allow rebreathing of the gas. Recently



**Figure 13.5**

Stages of anesthesia.  
O.R. = operating room.



**Figure 13.6**

Volatile anesthetics delivered to the patient are absorbed via the lungs into the systemic circulation causing dose-dependent CNS depression.

there has been greater attention to the anthropogenic emissions of these potent greenhouse gases, which are typically released from hospital rooftops after each procedure.

#### A. Common features of inhalation anesthetics

Modern inhalation anesthetics are nonflammable, nonexplosive agents, which include *nitrous oxide* and volatile, halogenated hydrocarbons. These agents decrease cerebrovascular resistance, resulting in increased brain perfusion. They cause bronchodilation but also decrease both respiratory drive and hypoxic pulmonary vasoconstriction (increased pulmonary vascular resistance in poorly oxygenated regions of the lungs, redirecting blood flow to better oxygenated regions). Movement of these gases from the lungs to various body compartments depends upon their solubility in blood and tissues, as well as on blood flow. The following factors play a role in induction and recovery.

#### B. Potency

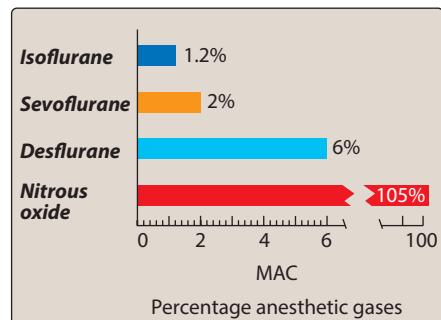
Potency is defined quantitatively as the minimum alveolar concentration (MAC), which is the end-tidal concentration of inhaled anesthetic needed to eliminate movement in 50% of patients exposed to a noxious stimulus. MAC is the median effective dose ( $ED_{50}$ ) of the anesthetic, expressed as the percentage of gas in a mixture required to achieve that effect. Numerically, MAC is small for potent anesthetics

such as *isoflurane* and large for less potent agents such as *nitrous oxide*. Thus, the inverse of MAC is an index of potency (Figure 13.7). *Nitrous oxide* alone cannot produce general anesthesia because any admixture with a survivable oxygen percentage cannot reach its MAC value. The more lipid soluble an anesthetic, the lower the concentration needed to produce anesthesia and, therefore, the higher the potency. Factors that can increase MAC (make the patient more resistant) include hyperthermia, drugs that increase CNS catecholamines, and chronic ethanol abuse. Factors that can decrease MAC (make the patient more sensitive) include increased age, hypothermia, pregnancy, sepsis, acute intoxication, concurrent IV anesthetics, and  $\alpha_2$ -adrenergic receptor agonists (*clonidine* and *dexmedetomidine*).

### C. Uptake and distribution of inhalation anesthetics

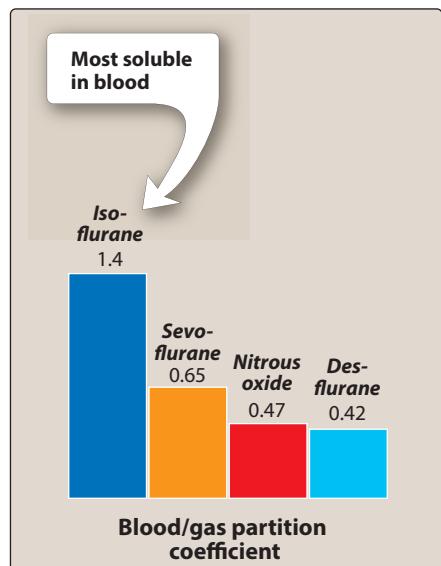
The principal objective of inhalation anesthesia is a constant and optimal brain partial pressure ( $P_{br}$ ) of inhaled anesthetic (to create a partial pressure equilibrium between alveoli [ $P_{alv}$ ] and brain [ $P_{br}$ ]). Measuring the  $P_{alv}$  is the most practical and feasible way to ascertain the  $P_{br}$  for the inhaled anesthetic concentration, but this necessitates adequate time for the two compartments to reach equilibrium. The partial pressure of an anesthetic gas that originates by pulmonary entry is the driving force moving the gas from the alveolar space into the bloodstream ( $P_a$ ), which transports the drug to the brain and other body compartments. Because gases move from one body compartment to another according to partial pressure gradients, a steady state is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture. [Note: At equilibrium,  $P_{alv} = P_a = P_{br}$ ] The time course for attaining this steady state is determined by the following factors:

- 1. Alveolar wash-in:** This refers to replacement of normal lung gases with the inspired anesthetic mixture. The time required for this process is directly proportional to the functional residual capacity of the lung (volume of gas remaining in the lungs at the end of a normal expiration) and inversely proportional to the ventilatory rate. It is independent of the physical properties of the gas. As the partial pressure builds within the lung, anesthetic gas transfer from the lung begins.
- 2. Anesthetic uptake (removal to peripheral tissues other than the brain):** Uptake is the product of the gas solubility in the blood, cardiac output (CO), and gradient between alveolar and blood anesthetic partial pressures.
  - Solubility in blood:** This is determined by a physical property of the anesthetic called the blood:gas partition coefficient (the ratio of the concentration of anesthetic in the liquid [blood] phase to the concentration of anesthetic in the gas phase when the anesthetic is in equilibrium between the two phases; Figure 13.8). For inhaled anesthetics, think of the blood as a pharmacologically inactive reservoir. Drugs with low versus high blood solubility differ in their rate of induction of anesthesia. When an anesthetic gas with low blood solubility such as *nitrous oxide* diffuses from the alveoli into the circulation, little anesthetic dissolves in the blood. Therefore, equilibrium between the inspired anesthetic and arterial blood occurs rapidly with relatively few additional molecules



**Figure 13.7**

Minimal alveolar concentrations (MAC) for anesthetic gases are used to compare pharmacologic effects of different agents (high MAC = low potency).



**Figure 13.8**

Blood/gas partition coefficients for some inhalation anesthetics.

of anesthetic required to raise the arterial anesthetic partial pressure. By contrast, anesthetic gases with high blood solubility, such as *isoflurane*, dissolve more fully in the blood; therefore, greater amounts of gas and longer periods of time are required to raise blood partial pressure. This results in longer periods for induction, recovery, and slower changes in depth of anesthesia in response to changes in the drug concentration. The solubility in blood is ranked as follows: *isoflurane* > *sevoflurane* > *nitrous oxide* > *desflurane*.

- b. **Cardiac output:** CO is inversely correlated with induction time for inhaled anesthetics. This counterintuitive phenomenon is explained by the threshold of drug concentration required to alter neuronal activity and the time neurons are exposed to the drug in the passing blood. During low CO, a longer period of time permits a larger concentration of gas to dissolve in the slowly moving bloodstream. Furthermore, this large bolus of drug has longer contact time to diffuse into neuronal tissue when it traverses the blood-brain barrier. Although a high CO will quickly transport the drug to the brain, a lower concentration of the drug with a shorter exposure time slows down the rate of induction.
  - c. **Alveolar-to-venous partial pressure gradient:** This gradient between the alveolar and returning venous gas partial pressure results from the tissue uptake from the arterial delivery. The arterial circulation distributes the anesthetic to various tissues, and tissue uptake is dependent on the tissue blood flow, blood to tissue partial pressure difference, and blood:tissue solubility coefficient. As venous circulation returns to the lung blood with low or no dissolved anesthetic gas, this high gradient causes gas to move from the alveoli into the blood. If a large alveolar-to-venous partial pressure gradient persists, the peripheral tissue gas uptake must be high, and, therefore, the induction time is longer. Over time, as the partial pressure of gas in venous blood approximates the inspired mixture and subsequent alveolar concentration, no further uptake from the lung occurs.
3. **Effect of different tissue types on anesthetic uptake:** The time required for a tissue compartment to reach a steady state with the partial pressure of the inspired anesthetic gas is inversely proportional to the blood flow to that tissue (greater flow equals less time to reach equilibrium). The time to a steady state is directly proportional to the capacity of that tissue to store anesthetic (greater storage capacity equals longer time to reach equilibrium). Furthermore, capacity is directly proportional to the volume of tissue and the tissue:blood solubility coefficient of the gas. Four major tissue compartments determine the time course of anesthetic uptake.
    - a. **Vessel-rich group (brain, heart, liver, kidney, and endocrine glands):** Highly perfused tissues rapidly attain a steady state with the partial pressure of anesthetic in the blood.
    - b. **Skeletal muscles:** These tissues are moderately perfused with a large storage capacity, which lengthens the time required to achieve a steady state.
    - c. **Fat:** Fat is poorly perfused, but has a very large storage capacity for the highly lipophilic volatile anesthetics. This poor perfusion to a high-capacity compartment drastically prolongs the time required to achieve a steady state.

- d. **Vessel-poor group (bone, ligaments, and cartilage):** These are very poorly perfused and have a low capacity to store anesthetic gas. Therefore, these tissues have minimal impact on the time course of anesthetic distribution in the body.
4. **Washout:** When an inhalation anesthetic gas is removed from the inspired admixture, the body becomes the repository of anesthetic gas to be circulated back to the alveolar compartment. The same factors that influence uptake and equilibrium of the inspired anesthetic determine the time course of its exhalation from the body. Thus, *nitrous oxide* exits the body faster than *isoflurane* (Figure 13.9).

#### D. Mechanism of action

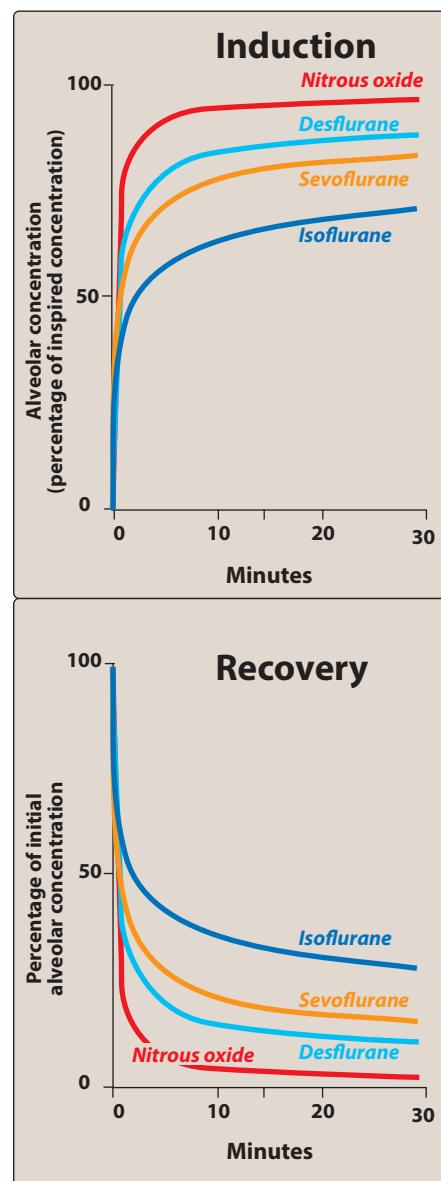
No specific receptor has been identified as the locus to create a state of general anesthesia. The fact that chemically unrelated compounds produce unconsciousness argues against the existence of a single receptor, and it appears that a variety of molecular mechanisms may contribute to the activity of anesthetics. At clinically effective concentrations, general anesthetics increase the sensitivity of the  $\gamma$ -aminobutyric acid ( $GABA_A$ ) receptors to the inhibitory neurotransmitter GABA. This increases chloride ion influx and hyperpolarization of neurons. Postsynaptic neuronal excitability and, thus, CNS activity are diminished (Figure 13.10). Unlike other anesthetics, *nitrous oxide* and *ketamine* do not have actions on  $GABA_A$  receptors. Their effects are mediated via inhibition of *N*-methyl-D-aspartate (NMDA) receptors. [Note: The NMDA receptor is a glutamate receptor, which is the body's main excitatory neurotransmitter.] Receptors other than GABA that are affected by volatile anesthetics include the inhibitory glycine receptors found in the spinal motor neurons. Additionally, inhalation anesthetics block excitatory postsynaptic currents found on nicotinic receptors. However, the mechanisms by which anesthetics perform these modulatory roles are not fully understood.

#### E. Isoflurane

*Isoflurane* [eye-so-FLOOR-ane], like other halogenated gases, produces dose-dependent hypotension predominantly from relaxation of systemic vasculature. Hypotension can be treated with a direct-acting vasoconstrictor, such as *phenylephrine* (see Chapter 6). Because it undergoes little metabolism, *isoflurane* is considered nontoxic to the liver and kidney. Its pungent odor stimulates respiratory reflexes (breath holding, salivation, coughing, laryngospasm), so it is not used for inhalation induction. With a higher blood solubility than *desflurane* and *sevoflurane*, *isoflurane* takes longer to reach equilibrium, making it less ideal for short procedures; however, its low cost makes it a good option for longer surgeries.

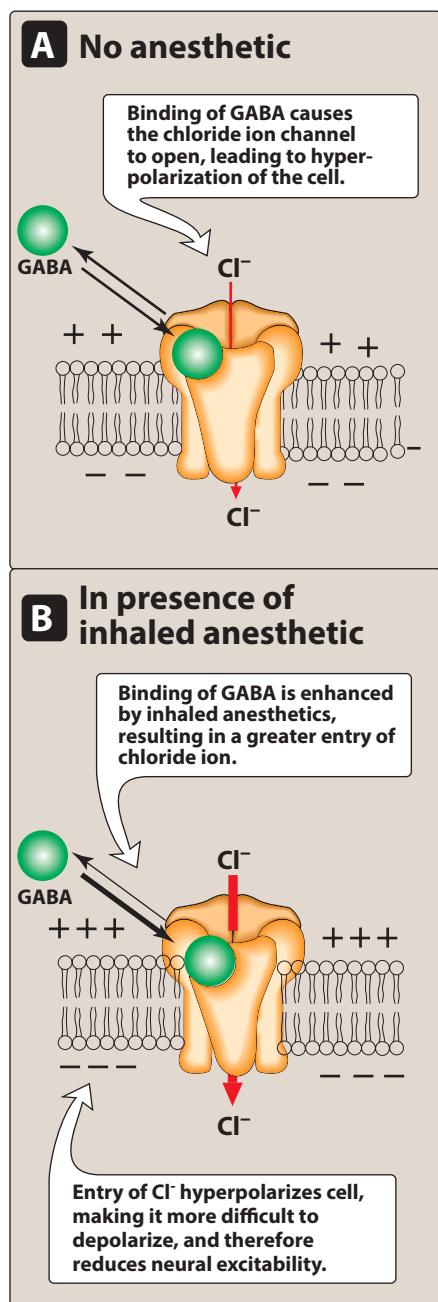
#### F. Desflurane

*Desflurane* [DES-floor-ane] provides very rapid onset and recovery due to low blood solubility. This makes it a popular anesthetic for short procedures. It has a low volatility, which requires administration via a special heated vaporizer. Like *isoflurane*, it decreases vascular resistance and perfuses all major tissues very well. *Desflurane* has significant respiratory irritation like *isoflurane* so it should not be used



**Figure 13.9**

Changes in the alveolar blood concentrations of some inhalation anesthetics over time.

**Figure 13.10**

An example of modulation of a ligand-gated membrane channel modulated by inhaled anesthetics.  
 Cl<sup>-</sup> = chloride ion;  
 GABA =  $\gamma$ -aminobutyric acid.

for inhalation induction. Its degradation is minimal and tissue toxicity is rare. Higher cost occasionally prohibits its use.

### G. Sevoflurane

Sevoflurane [see-voe-FLOOR-ane] has low pungency or respiratory irritation. This makes it useful for inhalation induction, especially with pediatric patients who do not tolerate IV placement. It has a rapid onset and recovery due to low blood solubility. Sevoflurane has low hepatotoxic potential, but compounds formed from reactions in the anesthesia circuit (soda lime) may be nephrotoxic with very low fresh gas flow that allows longer chemical reaction time.

### H. Nitrous oxide

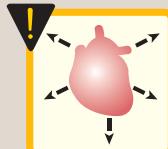
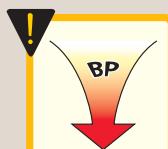
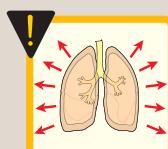
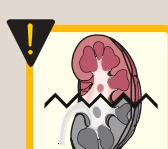
Nitrous oxide [NYE-truss OX-ide] ("laughing gas") is a nonirritating potent sedative that is unable to create a state of general anesthesia. It is frequently used at concentrations of 30% to 50% in combination with oxygen to create moderate sedation, particularly in dentistry. Nitrous oxide does not depress respiration and maintains cardiovascular hemodynamics as well as muscular strength. Nitrous oxide can be combined with other inhalational agents to establish general anesthesia, which lowers the required concentration of the combined volatile agent. This gas admixture further reduces many unwanted side effects of the other volatile agent that impact cardiovascular output and cerebral blood flow. Nitrous oxide is poorly soluble in blood and other tissues, allowing it to move very rapidly in and out of the body. This can be problematic in closed body compartments because nitrous oxide can increase the volume (exacerbating a pneumothorax) or pressure (sinus or middle ear pressure); it replaces nitrogen in various air spaces faster than the nitrogen leaves. Its speed of movement allows nitrous oxide to retard oxygen uptake during recovery, thereby causing "diffusion hypoxia." This can be overcome by delivering high concentrations of inspired oxygen during recovery. Some characteristics of the inhalation anesthetics are summarized in Figure 13.11.

### I. Ether

Diethyl ether (ether) is one of the old anesthetic methods used for anesthesia. It is a highly volatile and inflammable liquid. The vapors of ethers cause irritation causing increased bronchial secretions; therefore, atropine is used in the preanesthetic medication. However, ether is a potent anesthetic. Due to this property, it reduces the dose of competitive neuromuscular blockers while on administration it produces adequate muscle relaxation. For ether anesthesia, no major equipment is required and it is relatively simple. Since it is a highly lipophilic substance, recovery is slow. Respiration and blood pressure do not get affected during the anesthesia. Use of ether is limited only whereas it is completely banned from use in developed countries.

### J. Halothane

Halothane is a noninflammable, nonirritant, photosensitive volatile agent with a sweet smell. It is a liquid at room temperature and it is administered with a special vaporizer at a concentration of 2% to 4% for

	<i>Isoflurane</i>	<i>Desflurane</i>	<i>Sevoflurane</i>
	Decreased minimally	Decreased minimally	Decreased minimally
	Dose dependent decreased	Dose dependent decreased	Dose dependent decreased
	Initial stimulation	Initial stimulation	Inhibited
	Low risk	Low risk	Low risk
	Low risk	Low risk	Some risk

**Figure 13.11**

Characteristics of some inhalation anesthetics.

induction followed by 0.5% to 1% for maintenance. A precise control of the concentration of *halothane* is essential as it can cause direct effect on heart by interfering with calcium, thus causing depression of myocardial contractility. Dose-dependent fall in blood pressure is known during *halothane* anesthesia. It directly suppresses respiratory centers, thereby reducing ventilatory response to blood carbon dioxide levels. Decreased alveolar ventilation can cause increase in arterial CO<sub>2</sub> levels without compensatory increase in ventilation. Therefore, continuous arterial gas monitoring is essential during its usage. *Halothane* dilates cerebral blood vessels and increases cerebral blood flow which in turn causes increased intracranial pressure, especially in patients with other

susceptible comorbid conditions in the brain. It causes relaxation of skeletal muscle and potentiates the actions of competitive neuromuscular blockers. *Halothane* causes uterine smooth muscle relaxation. Although it is useful for the manipulation of fetus orientation, it is not used due to its action of inhibiting uterine contraction during parturition. Therefore, it is not used for vaginal delivery. More than 60% of the inhalationally administered *halothane* is eliminated through lungs on recovery within 24 hours. The rest of *halothane* is metabolized by liver. Trifluoroacetic acid is a major metabolite which can cause hepatic injury (*halothane*-induced hepatic necrosis). This syndrome of hepatic necrosis is reported in 1 in 10,000 patients and it is referred to as “*halothane hepatitis*.”

#### K. Malignant hyperthermia

In a very small percentage of susceptible patients, exposure to halogenated hydrocarbon anesthetics (or *succinylcholine*) may induce malignant hyperthermia (MH), a rare life-threatening condition. MH causes a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, overwhelming the body's capacity to supply oxygen, remove carbon dioxide, and regulate temperature, eventually leading to circulatory collapse and death if not treated immediately. Strong evidence indicates that MH is due to an excitation-contraction coupling defect. Burn victims and individuals with muscular dystrophy, myopathy, myotonia, and osteogenesis imperfecta are susceptible to MH-like events and caution should be taken. Susceptibility to MH is often inherited as an autosomal dominant disorder. Should a patient exhibit symptoms of MH, *dantrolene* is given as the anesthetic mixture is withdrawn, and measures are taken to rapidly cool the patient. *Dantrolene* [DAN-troe-leen] blocks release of  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum of muscle cells, reducing heat production and relaxing muscle tone. It should be available whenever triggering agents are administered. In addition, the patient must be monitored and supported for respiratory, circulatory, and renal problems. Use of *dantrolene* and avoidance of triggering agents such as halogenated anesthetics in susceptible individuals have markedly reduced mortality from MH. A more soluble formulation of *dantrolene* has become commercially available that drastically reduces the constitution time needed to make this drug in emergencies.

### VI. INTRAVENOUS ANESTHETICS

IV anesthetics cause rapid induction of anesthesia often occurring in 1 minute or less. It is the most common way to induce anesthesia before maintenance of anesthesia with an inhalation agent. IV anesthetics may be used as single agents for short procedures or administered as infusions (TIVA) to help maintain anesthesia during longer surgeries. In lower doses, they may be used solely for sedation.

#### A. Induction

After entering the blood, a percentage of drug binds to plasma proteins, and the rest remains unbound or “free.” The degree of protein binding depends upon the physical characteristics of the drug, such as the

degree of ionization and lipid solubility. The majority of CO flows to the brain, liver, and kidney (“vessel-rich organs”). Thus, a high proportion of initial drug bolus is delivered to the cerebral circulation and then passes along a concentration gradient from blood into the brain. The rate of this transfer is dependent on the arterial concentration of the unbound free drug, the lipid solubility of the drug, and the degree of ionization. Unbound, lipid-soluble, nonionized molecules cross into the brain most quickly. Like inhalational anesthetics, the exact mode of action of IV anesthetics is unknown; however, GABA likely plays a large role.

## B. Recovery

The recovery phase is short as these drugs are rapidly redistributed from the CNS into the various compartments of the body. After initial flooding of the CNS and other vessel-rich tissues with nonionized molecules, the drug diffuses into other tissues with less blood supply. With secondary tissue uptake, predominantly skeletal muscle, plasma concentration of the drug falls. This allows the drug to diffuse out of the CNS, down the resulting reverse concentration gradient. This initial redistribution of drug into other tissues leads to the rapid recovery seen after a single IV dose of the induction agent. The final elimination occurs via kidneys or liver. Metabolism and plasma clearance become important only following infusions and repeat doses of a drug. Adipose tissue makes little contribution to the early redistribution of free drug following a bolus, due to its poor blood supply. However, following repeat doses or infusions, equilibration with fat tissue forms a drug reservoir, often leading to delayed recovery.

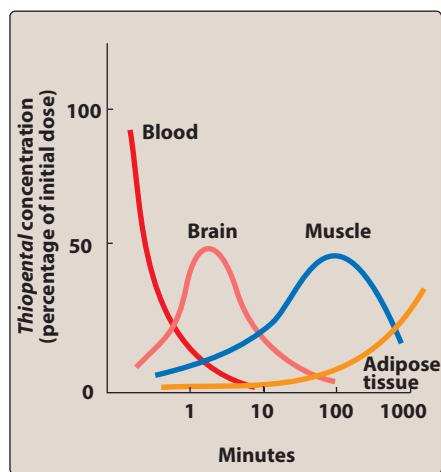
## C. Effect of reduced cardiac output on IV anesthetics

When CO is reduced (for example, in certain types of shock, the elderly, cardiac disease), the body compensates by diverting more CO to the cerebral circulation. A greater proportion of the IV anesthetic enters the cerebral circulation under these circumstances. Therefore, the dose of the drug must be reduced. Further, decreased CO causes prolonged circulation time. As global CO is reduced, it takes a longer time for an induction drug to reach the brain and exert its effects. The slow titration of a reduced dose of an IV anesthetic is key to a safe induction in patients with reduced CO.

## D. Propofol

*Propofol* [PRO-puh-fol] is an IV sedative/hypnotic used for induction and/or maintenance of anesthesia. It is widely used and has replaced *thiopental* as the first choice for induction of general anesthesia and sedation. Because *propofol* is poorly water soluble, it is supplied as an emulsion containing soybean oil and egg phospholipid, giving it a milk-like appearance.

- 1. Onset:** Induction is smooth and occurs 30 to 40 seconds after administration. Plasma levels decline rapidly as a result of redistribution, followed by a more prolonged period of hepatic metabolism and renal clearance. The initial redistribution half-life is 2 to 4 minutes. The pharmacokinetics of *propofol* are not altered by moderate hepatic or renal failure.



**Figure 13.12**

Redistribution of *thiopental* from the brain to muscle and adipose tissue.

**2. Actions:** Although *propofol* depresses the CNS, it occasionally contributes to excitatory phenomena, such as muscle twitching, spontaneous movement, yawning, and hiccups. Transient pain at the injection site is common. *Propofol* decreases blood pressure without significantly depressing the myocardium. It also reduces intracranial pressure, mainly due to decreased cerebral blood flow and oxygen consumption. It has less of a depressant effect than volatile anesthetics on CNS-evoked potentials, making it useful for surgeries in which spinal cord function is monitored. It does not provide analgesia, so supplementation with narcotics is required. *Propofol* is commonly infused in lower doses to provide sedation. The incidence of postoperative nausea and vomiting is very low secondary to its antiemetic properties.

### E. Barbiturates

*Thiopental* [thigh-oh-PEN-tahl] is an ultra short-acting barbiturate with high lipid solubility. It is a potent anesthetic but a weak analgesic. Barbiturates require supplementary analgesic administration during anesthesia. When given IV, agents such as *thiopental* and *methohexitol* [meth-oh-HEX-uh-tall] quickly enter the CNS and depress function, often in less than 1 minute. However, diffusion out of the brain can also occur very rapidly because of redistribution to other tissues (Figure 13.12). These drugs may remain in the body for relatively long periods, because only about 15% of a dose entering the circulation is metabolized by the liver per hour. Thus, metabolism of *thiopental* is much slower than its redistribution. Barbiturates tend to decrease blood pressure, which may cause a reflex tachycardia. They decrease intracranial pressure through reductions in cerebral blood flow and oxygen consumption. *Methohexitol* is still commonly used for electroconvulsive therapy.

### F. Benzodiazepines

The benzodiazepines are used in conjunction with anesthetics for sedation and amnesia. The most commonly used is *midazolam* [meh-DAZ-o-lam]. *Diazepam* [dye-AZ-uh-pam] and *lorazepam* [lore-AZ-uh-pam] are alternatives. All three facilitate amnesia while causing sedation, enhancing the inhibitory effects of various neurotransmitters, particularly GABA. Minimal cardiovascular depressant effects are seen, but all are potential respiratory depressants (especially when administered IV). They are metabolized by the liver with variable elimination half-lives, and *erythromycin* may prolong effects of *midazolam*. Benzodiazepines can induce a temporary form of anterograde amnesia in which the patient retains memory of past events, but new information is not transferred into long-term memory. Therefore, important treatment information should be repeated to the patient after the effects of the drug have worn off.

### G. Opioids

Because of their analgesic property, opioids are commonly combined with other anesthetics. The choice of opioid is based primarily on the duration of action needed. The most commonly used opioids are *fentanyl* [FEN-ta-nil] and its congeners, *sufentanil* [SOO-fen-ta-nil] and *remifentanil* [REMI-fen-ta-nil], because they induce analgesia more rapidly than *morphine*. They may be administered intravenously, epidurally, or intrathecally.

(into the cerebrospinal fluid). Opioids are not good amnestics, and they can all cause hypotension and respiratory depression, as well as nausea and vomiting. Opioid effects can be antagonized by *naloxone*.

#### H. Etomidate

*Etomidate* [ee-TOM-uh-date] is a hypnotic agent used to induce anesthesia, but it lacks analgesic activity. Its water solubility is poor, so it is formulated in a propylene glycol solution. Induction is rapid, and the drug is short-acting. Among its benefits are little to no effect on the heart and systemic vascular resistance. *Etomidate* is usually only used for patients with cardiovascular dysfunction or patients who are acutely critically ill. It inhibits 11- $\beta$  hydroxylase involved in steroidogenesis, and adverse effects may include decreased plasma cortisol and aldosterone levels. *Etomidate* should not be infused for an extended time, because prolonged suppression of these hormones is dangerous. Injection site pain, involuntary skeletal muscle movements, and nausea and vomiting are common.

#### I. Ketamine

*Ketamine* [KET-uh-meen], a short-acting anti-NMDA receptor anesthetic and analgesic, induces a dissociated state in which the patient is unconscious (but may appear to be awake) with profound analgesia. *Ketamine* stimulates central sympathetic outflow, causing stimulation of the heart with increased blood pressure and CO. It is also a potent bronchodilator. Therefore, it is beneficial in patients with hypovolemic or cardiogenic shock as well as asthmatics. Conversely, it is contraindicated in hypertensive or stroke patients. The drug is lipophilic and enters the brain very quickly. Like the barbiturates, it redistributes to other organs and tissues. *Ketamine* has become popular as an adjunct to reduce opioid consumption during surgery. Of note, it may induce hallucinations, particularly in young adults, but pretreatment with benzodiazepines may help. *Ketamine* may be used illicitly, since it causes a dream-like state and hallucinations similar to *phencyclidine* (PCP).

#### J. Dexmedetomidine

*Dexmedetomidine* [dex-med-eh-TOM-uh-deen] is a sedative used in intensive care settings and surgery. Like *clonidine*, it is an  $\alpha_2$  receptor agonist in certain parts of the brain. *Dexmedetomidine* has sedative, analgesic, sympatholytic, and anxiolytic effects that blunt many cardiovascular responses. It reduces volatile anesthetic, sedative, and analgesic requirements without causing significant respiratory depression. It has gained popularity for its ability to blunt emergence delirium in the pediatric population. [Figure 13.13](#) depicts the characteristics of anesthetic agents. Some therapeutic advantages and disadvantages of the anesthetic agents are summarized in [Figure 13.14](#).

## VII. NEUROMUSCULAR BLOCKERS

Neuromuscular blockers are crucial to the practice of anesthesia and used to facilitate endotracheal intubation and provide muscle relaxation when needed for surgery. Their mechanism of action is via blockade of nicotinic acetylcholine receptors on the skeletal muscle cell membrane. These

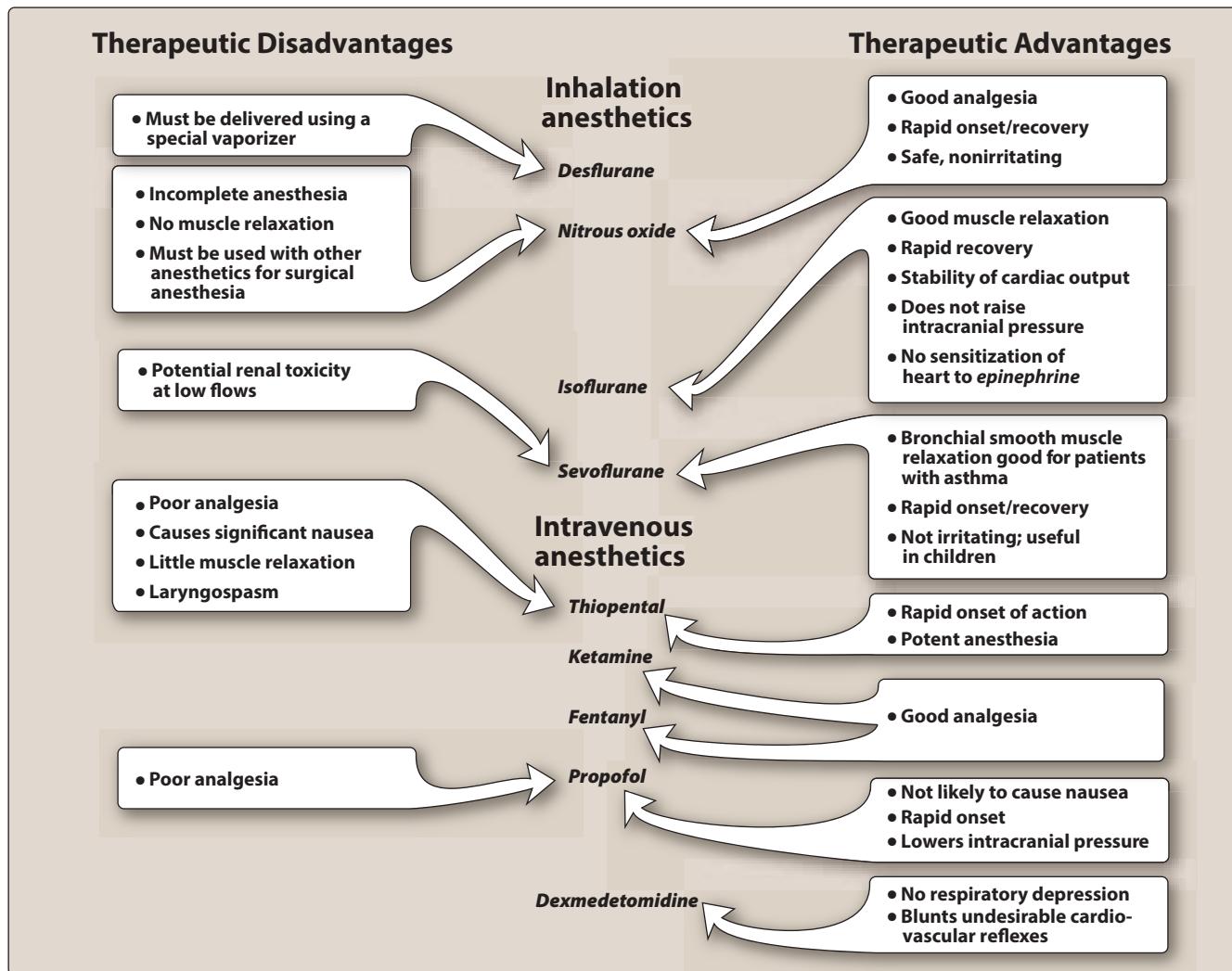
DRUG	INDUCTION/RECOVERY	ADVERSE EFFECTS	SALIENT POINTS
<i>Ether</i>	Slow	Nausea, vomiting, respiratory irritation	Risk of explosion, no longer used
<i>Nitrous oxide</i>	Fast	Anemia with prolonged or repeated use	Good analgesia, safe, nonirritating, and mainly used along with other inhalational agents as it causes incomplete anesthesia and no muscle relaxation
<i>Halothane</i>	Medium	Malignant hyperthermia, hepatotoxicity, arrhythmias, hypotension; sensitizes myocardium to actions of catecholamines; reduces hepatic and renal blood flow	Fair analgesic, skeletal muscle and uterine relaxant properties, and excellent hypnotic properties; use is declining as better newer anesthetics are available
<i>Enflurane</i>	Medium	Increased seizure potential, malignant hyperthermia; pungent may result in breath holding or coughing; contraindicated in patients with renal failure	Good analgesic, skeletal muscle, and excellent hypnotic properties Widely used as less risk of toxicity than <i>halothane</i>
<i>Sevoflurane</i>	Fast	No respiratory irritation and fewer side effects such as nausea and vomiting in some cases; potential renal toxicity at low flow as it produces fluoride ions during its liver metabolism	Nonirritating; mainly used for daycare surgeries and in children Causes bronchodilatation, useful in bronchial asthma patients
<i>Desoflurane</i>	Fast (faster than <i>isoflurane</i> )	Cough, bronchospasm, respiratory tract irritation, salivation; must be delivered using a special vaporizer	Mainly used for daycare surgeries; minimal metabolism, rarely produces organ toxicity
<i>Isoflurane</i>	Medium	Can cause coronary ischemia (coronary steal phenomenon), pungent odor	Widely used as an alternative to <i>halothane</i> ; good analgesic, sedative-hypnotic and muscle relaxation effect, stability of cardiac output; does not raise intracranial pressure, no sensitization of heart to catecholamines; minimal metabolism

#### Intravenous anesthetics:

<i>Thiopentone</i>	Fast	Significant nausea, laryngospasm	Potent anesthetic but poor analgesia; little muscle relaxation; short duration of action; contraindicated in patient with acute intermittent porphyria
<i>Propofol</i>	Fast	Postoperative nausea and vomiting though lesser pain on injection and that it is prepared in a lipid emulsion	Poor analgesia; lowers intracranial pressure; has displaced barbiturates in many anesthesia practices
<i>Fentanyl</i>	Fast	Hypotension, postoperative nausea, and vomiting	Good analgesia; useful drug in patients with renal failure; used as an adjunct to inhalation and IV anesthetic agents; used in high doses to achieve general anesthesia during cardiac surgery when circulatory stability is important
<i>Ketamine</i>	Fast	Pleasant dream-like states to vivid imagery, hallucinations, delirium, confusion, excitement, irrational behavior (less in children), hypertension, tachycardia, severe respiratory depression following rapid intravenous administration, tonic-clonic movements resembling seizures	Produces dissociative anesthesia, an effect in which the patient feels dissociated from the surroundings; produces good analgesia with or without loss of consciousness; used as an induction agent for diagnostic, surgical procedures; used in low doses in infants and children in case of trauma, minor surgical, and diagnostic procedures

**Figure 13.13**

General anesthetics and their characteristics.

**Figure 13.14**

Therapeutic disadvantages and advantages of some anesthetic agents.

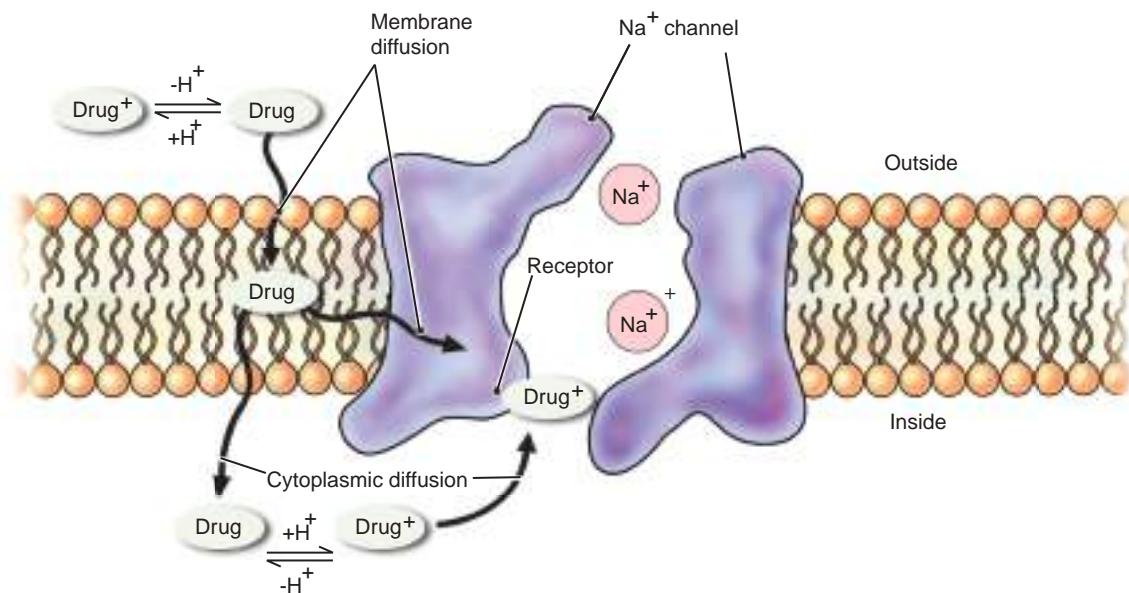
agents include *cisatracurium*, *mivacurium*, *pancuronium*, *rocuronium*, *sucinylcholine*, and *vecuronium* (see Chapter 5).

### A. Sugammadex

*Sugammadex* [soo-GAM-ma-dex] is a selective relaxant-binding agent that terminates the action of both *rocuronium* and *vecuronium*. Its three-dimensional structure traps the neuromuscular blocker in a 1:1 ratio, terminating its action and making it water soluble. It is unique in that it produces rapid and effective reversal of both shallow and profound neuromuscular blockade. *Sugammadex* is eliminated via the kidneys.

## VIII. LOCAL ANESTHETICS

Local anesthetics provide a reversible regional loss of sensation. They reduce pain and thereby facilitate surgical procedures. Local anesthetics block nerve conduction of sensory impulses and in higher concentrations block motor

**Figure 13.15**

Mechanism of local anesthetic action.

impulses from the periphery to the CNS. Sodium ion channels are blocked to prevent the transient increase in permeability of the nerve membrane to  $\text{Na}^+$  that is required for an action potential (Figure 13.15). When propagation of action potentials is prevented, sensation cannot be transmitted from the source of stimulation to the brain. Cocaine is a naturally occurring compound indigenous to the Andes Mountains, West Indies, and Java. It was the first anesthetic to be discovered and is the only naturally occurring local anesthetic; however, it is not used clinically because of its adverse effects and abuse potential. All other anesthetics are synthetically derived. Procaine, the first synthetic derivative of cocaine, was developed in 1904.

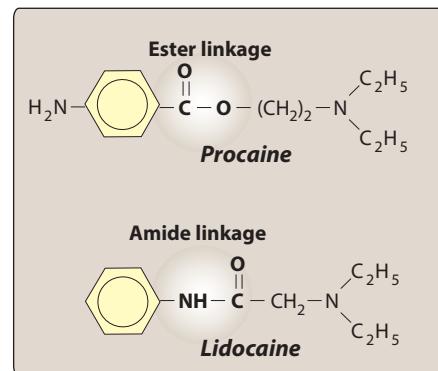
All local anesthetics have a similar chemical structure, which consists of three components: aromatic portion, intermediate chain, and amine group. Structurally, all local anesthetics include a lipophilic group joined by an amide or ester linkage to a carbon chain, which, in turn, is joined to a hydrophilic group (Figure 13.16). The degree of lipid solubility of each anesthetic is an important property because the lipid solubility enables its diffusion through the highly lipophilic nerve membrane. The extent of an anesthetic's lipophilicity is directly related to its potency. All local anesthetics are weak bases that require the addition of hydrochloride salt in order to be water soluble and therefore injectable. Salt equilibrates between an ionized form and a nonionized form in aqueous solution. Equilibration is crucial because, although the ionized form is injectable, it is the nonionized base which has the lipophilic properties and is responsible for their diffusion into the nerve cell membrane. The duration of action of an anesthetic is determined by their protein-binding capacity to anesthetic receptors along the nerve cell membrane. The intermediate chain, which connects the aromatic and amine portions, is composed of either an ester or an amide linkage (Figure 13.16). This intermediate chain can be used in classifying local anesthetics into esters and amides. Ester-type local anesthetics have a very short plasma half-life. They are metabolized by plasma butyrylcholinesterase. In patients with decreased or atypical cholinesterase, the plasma levels of these anesthetics may be higher than usual. Amide-type local

anesthetics are metabolized at varying rates and to a varying extent by hepatic isozymes and are excreted in an unchanged form by the kidney. The rate of metabolism is decreased in case of liver impairment or by drugs interfering with the microsomal enzyme system. The most widely used local anesthetics are *bupivacaine* [byoo-PIV-uh-cane], *lidocaine* [LYE-doe-cane], *mepivacaine* [muh-PIV-uh-cane], *ropivacaine* [roe-PIV-uh-cane], and *tetracaine* [TET-truh-cane].

### A. Delivery techniques of local anesthetics

Various delivery techniques broaden the clinical applicability of local anesthetics. These techniques include topical administration, infiltration, perineural, and neuraxial (spinal, epidural, or caudal) blocks. Small, unmyelinated nerve fibers for pain, temperature, and autonomic activity are most sensitive. These are as follows.

- Regional anesthesia:** It makes a specific part of the body numb to relieve pain or allow surgical procedures to be done. Local anesthetics are safer than general or systemic anesthetics; therefore, they are preferred whenever possible.
- Surface anesthesia:** It is used during ocular tonometry, intubation, and endoscopic procedures. *Tetracaine* 2% and *lidocaine* 2% to 4% are used. The anesthetic effect is superficial and does not last long.
- Infiltration anesthesia:** The local anesthetic is injected directly into the skin or deeper structures to carry out incision, excision, hydrocoele, herniorraphy, incision and drainage of an abscess, etc. *Lignocaine* and *bupivacaine* are generally used for infiltration anesthesia.
- Field block:** The local anesthetic is injected subcutaneously proximal to the site where anesthesia is desired. All nerves distal to the site of injection are blocked. *Lidocaine* (1% to 2%) is used for intermediate duration of anesthesia in dental extraction, operation on forearms, legs, herniorraphy, etc.
- Nerve block:** The local anesthetic is injected around a nerve plexus or a nerve trunk. This results in a large area of anesthesia. Thus even with a small amount of drug, a large area of anesthesia can be produced. *Lidocaine* is most commonly used apart from *bupivacaine*. Intercostal, sciatic, brachial plexus, facial, and phrenic are commonly performed nerve blocks.
- Spinal anesthesia:** A single dose of the local anesthetic is injected into the subarachnoid space in the lower end of the spinal cord (lumbar region). The site of action is nerve roots, resulting in loss of pain sensation and paralysis of the lower abdomen and hind limbs. *Lidocaine*, *bupivacaine*, and *tetracaine* are most commonly used for spinal anesthesia. The duration of anesthesia depends on the concentration and the drug used. Spinal anesthesia is associated with various complications such as respiratory paralysis, hypotension, headache, nausea, vomiting, bradycardia, and septic meningitis. It is used during operations on lower limbs, pelvis, lower abdomen, etc.
- Epidural anesthesia:** The local anesthetic is injected into the epidural space where it acts upon the nerve roots and relieves pain from large areas of the body by stopping pain signals traveling along the nerves in the spine. Epidural anesthesia is similar to but not the same as spinal anesthesia. In epidural anesthesia, local



**Figure 13.16**

Representative structures of ester and amide anesthetics.

anesthetic is administered continuously through an epidural catheter that does not reach the CSF and provides long-term anesthesia and pain relief. The local anesthetics most commonly used for this procedure are *lidocaine* and *bupivacaine*. Epidural anesthesia is used during labor to relieve pain or during a cesarean section. It can also be used to reduce the amount of general anesthesia needed during some operations and can provide pain relief post-operatively. In knee and hip replacement surgery, epidural anesthesia can be used in place of a general anesthetic.

### B. Actions

All local anesthetics cause vasodilation, which leads to a rapid diffusion away from the site of action and short duration when these drugs are administered alone. By adding the vasoconstrictor *epinephrine*, the rate of local anesthetic absorption and diffusion is decreased. This minimizes systemic toxicity and increases the duration of action. However, *epinephrine* should not be coadministered for nerve block in extremities such as fingers and toes as vasoconstriction of end arteries may lead to ischemia and necrosis. It should be used with caution in patients with thyrotoxicosis or cardiovascular disease and in labor. Hepatic function does not affect the duration of action of local anesthesia because that is determined by redistribution rather than biotransformation. Some local anesthetics have other therapeutic uses (for example, *lidocaine* is an IV antiarrhythmic).

### C. Onset, potency, and duration of action

The onset of action of local anesthetics is influenced by several factors including tissue pH, nerve morphology, concentration, pKa, and lipid solubility of the drug. Of these, the pKa is most important. Local anesthetics with a lower pKa have a quicker onset, since more drug exists in the unionized form at physiologic pH, thereby allowing penetration of the nerve cell membrane. Once at the nerve membrane, the ionized form interacts with the protein receptor of the Na<sup>+</sup> channel to inhibit its function and achieve local anesthesia. The pH may drop in infected sites, causing onset to be delayed or even prevented. Potency and duration of these agents depend mainly on lipid solubility, with higher solubility correlating with increased potency and duration of action.

### D. Metabolism

Biotransformation of amides occurs primarily in the liver. *Prilocaine* [PRY-low-cane], a dental anesthetic, is also metabolized in the plasma and kidney, and one of its metabolites may lead to methemoglobinemia. Esters are biotransformed by plasma cholinesterase (pseudo-cholinesterase). Patients with pseudocholinesterase deficiency may metabolize ester local anesthetics more slowly. At normal doses, this has little clinical effect. Reduced hepatic function predisposes patients to toxic effects, but should not significantly increase the duration of action of local anesthetics.

### E. Allergic reactions

Patient reports of allergic reactions to local anesthetics are fairly common, but often times reported “allergies” are actually side effects from the coadministered *epinephrine*. True allergy to an amide local

CHARACTERISTIC	ESTERS • Benzocaine • Chloroprocaine • Cocaine	• Procaine • Tetracaine	AMIDES • Bupivacaine • Lidocaine • Mepivacaine	• Prilocaine • Ropivacaine
Metabolism	Rapid by plasma cholinesterase		Slow, hepatic	
Systemic toxicity	Less likely		More likely	
Allergic reaction	Possible- PABA derivatives form		Very rare	
Stability in solution	Breaks down in ampules (heat, sun)		Very stable chemically	
Onset of action	Slow as a general rule		Moderate to fast	
pKa's	Higher than physiologic pH (8.5–8.9)		Close to physiologic pH (7.6–8.1)	
DRUG	POTENCY	ONSET	DURATION	
Bupivacaine	High	Slow	Long	
Chloroprocaine	Low	Rapid	Short	
Lidocaine	Low	Rapid	Intermediate	
Mepivacaine	Low	Moderate	Intermediate	
Procaine	Low	Rapid	Short	
Ropivacaine	High	Moderate	Long	
Tetracaine	High	Slow	Long (spinal)	

PABA = para-aminobenzoic acid.

**Figure 13.17**

Summary of pharmacologic properties of some local anesthetics.

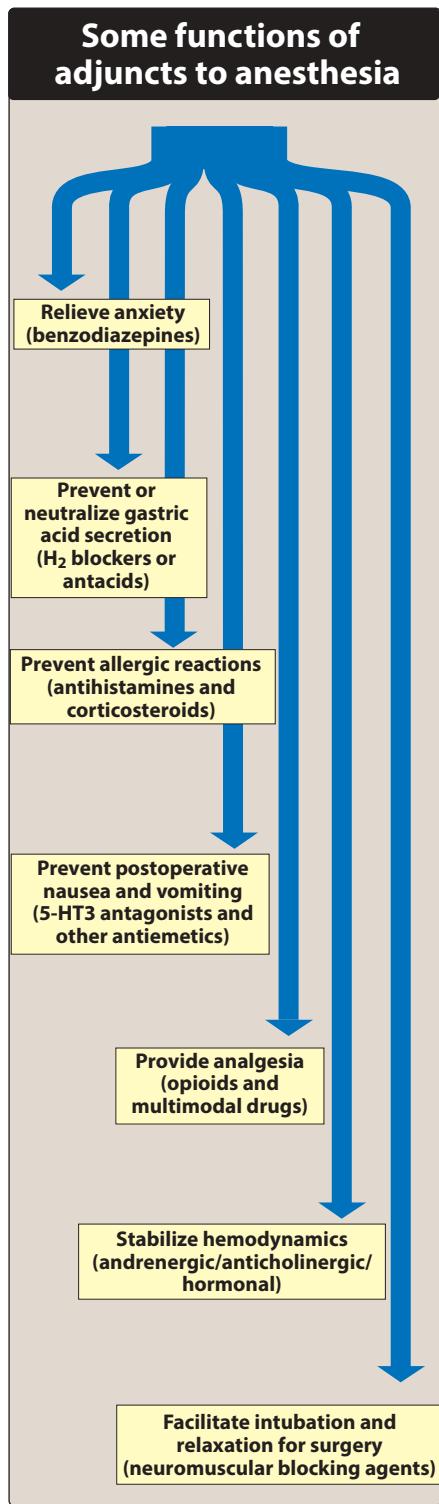
anesthetic is exceedingly rare, while the ester *procaine* is more allergenic and has largely been removed from the market. Allergy to one ester rules out use of another ester, because the allergenic component is the metabolite para-aminobenzoic acid, produced by all esters. By contrast, allergy to one amide does not rule out the use of another amide. A patient may be allergic to other compounds in the local anesthetic, such as preservatives in multidose vials.

## F. Local anesthetic systemic toxicity

Toxic blood levels of a local anesthetic may be due to repeated injections or could result from a single inadvertent IV injection. Each drug has a weight-based toxic threshold that should be calculated. This is especially important in children, the elderly, and women in labor (who are more susceptible to local anesthetics). Aspiration before every injection is imperative. The signs, symptoms, and timing of local anesthetic systemic toxicity (LAST) are unpredictable. One must consider the diagnosis in any patient with altered mental status, seizures, or cardiovascular instability following injection of local anesthetic. Treatment for LAST may include seizure suppression, airway management, and cardiopulmonary support. Administering a 20% lipid emulsion infusion (lipid rescue therapy) is a valuable asset. **Figure 13.17** summarizes pharmacologic properties of some local anesthetics.

## IX. ANESTHETIC ADJUNCTS

Adjuncts are a critical part of the practice of anesthesia and include drugs that affect gastrointestinal (GI) motility, postoperative nausea and vomiting (PONV), anxiety, and analgesia. Adjuncts are used in collaboration to help make the anesthetic experience safe and pleasant.

**Figure 13.18**

Actions of anesthesia adjunct drugs.

### A. Gastrointestinal medications

$H_2$ -receptor antagonists (for example, *ranitidine*; see Chapter 42) and proton-pump inhibitors (for example, *omeprazole*; see Chapter 42) help to reduce gastric acidity in the event of an aspiration. Nonparticulate antacids (*sodium citrate/citric acid*) are given occasionally to quickly increase the pH of stomach contents. These drugs are used in the obstetric population going to surgery, along with other patients with reflux. Finally, a dopamine receptor antagonist (*metoclopramide*) can be used as a prokinetic agent to speed gastric emptying and increase lower esophageal sphincter tone.

### B. Medications for PONV

PONV can be a significant problem during and after surgery for both the clinician and the patient. Risk factors for PONV include female gender, nonsmoker, use of volatile and nitrous anesthetics, duration of surgery, and postoperative narcotic use. 5-HT<sub>3</sub> receptor antagonists (for example, *ondansetron*; see Chapter 42) are commonly used to prevent PONV and are usually administered toward the end of surgery. Caution is advised in patients with long QT intervals on ECG. An anticholinergic and antihistamine (*promethazine*) can also be used; however, sedation, delirium, and confusion can complicate the postoperative period, especially in the elderly. Glucocorticoids such as *dexamethasone* can be used to reduce PONV. The mechanism is unclear, but because of a longer onset, these agents are usually given at the start of surgery. The neuropeptide-1 antagonist *aprepitant* has also been shown to reduce PONV. Lastly, transdermal *scopolamine* is given preoperatively to patients with multiple risk factors or to a patient with a history of PONV. Caution is advised because it can produce central anticholinergic effects.

### C. Anxiety medications

Anxiety is a common part of the surgical experience. Benzodiazepines (*midazolam*, *diazepam*),  $\alpha_2$  agonists (*clonidine*, *dexmedetomidine*), and  $H_1$ -receptor antagonists (*diphenhydramine*) can be used to alleviate anxiety. Benzodiazepines also elicit anterograde amnesia, which can help promote a more pleasant surgical experience.

### D. Analgesia

While opioids are a mainstay in anesthesia for pain control, multimodal analgesia is becoming more common due to the long-term risks of opioid consumption in surgical patients. Nonsteroidal anti-inflammatory drugs (*ketorolac*, *celecoxib*; see Chapter 40) are common adjuncts to opioids. Caution should be used in coagulopathy, GI mucosal and platelet aggregation susceptible patients. *Paracetamol* can be used both PO and IV, but caution is advised in impaired hepatic function. Analogs of GABA (*gabapentin*, *pregabalin*; see Chapter 12) are becoming more common as pretreatment to reduce opioid consumption both during and after surgery. They also have multiple uses in neuropathic pain and addiction medicine. The NMDA antagonist *ketamine* is used to reduce overall opioid consumption both intra- and postoperatively. Actions of anesthesia adjunct drugs are shown in **Figure 13.18**.

## Study Questions

Choose the ONE best answer.

13.1 Regarding levels of sedation, which one applies to loss of perception and sensation to painful stimuli?

- A. Anxiolysis
- B. General anesthesia
- C. Moderate sedation
- D. Deep sedation

Correct answer = B. Anxiolysis is a state of relaxation, but consciousness remains. General anesthesia is a total loss of perception and sensation to stimuli. Moderate sedation maintains mentation with adequate airway and respiratory competency. Deep sedation has some response to stimuli, but respirations may be inadequate.

13.2 Which of the following decreases minimum alveolar concentration (MAC)?

- A. Hyperthermia
- B. Cocaine intoxication
- C. Pregnancy
- D. Chronic ethanol abuse

Correct answer = C. Pregnancy is the only choice that decreases minimum alveolar concentration. All the other options increase MAC.

13.3 Which of the following determines the speed of recovery from intravenous anesthetics used for induction?

- A. Liver metabolism of the drug
- B. Protein binding of the drug
- C. Ionization of the drug
- D. Redistribution of the drug from sites in the CNS

Correct answer = D. Following initial flooding of the CNS with nonionized molecules, the drug diffuses into other tissues. With secondary tissue uptake, the plasma concentration falls, allowing the drug to diffuse out of the CNS. This initial redistribution of drug into other tissues leads to the rapid recovery seen after a single dose of an IV induction drug. Protein binding, ionization, and lipid solubility affect the rate of transfer.

13.4 Which one of the following is a potent intravenous anesthetic and analgesic?

- A. Propofol
- B. Midazolam
- C. Ketamine
- D. Fentanyl

Correct answer = C. Ketamine is unique in its blockade of NMDA receptors, yielding both potent anesthetic and analgesic properties. Propofol is a potent anesthetic but a weak analgesic. Benzodiazepines such as midazolam have little analgesic effect, but can be a potent anesthetic at high doses. Fentanyl is a potent analgesic.

13.5 Which local anesthetic is metabolized by plasma cholinesterase?

- A. Tetracaine
- B. Bupivacaine
- C. Lidocaine
- D. Ropivacaine

Correct answer = A. Tetracaine is the only ester type local anesthetic of the choices. The other choices are amide-type local anesthetics, which are metabolized by biotransformation in the liver.

13.6 A 23-year-old patient with a history of severe postoperative nausea and vomiting is coming in for plastic surgery. Which anesthetic drug would be best to use for maintenance in this situation?

- A. Isoflurane
- B. Sevoflurane
- C. Nitrous oxide
- D. Propofol

Correct answer = D. A propofol infusion (TIVA) anesthetic would be best for this patient with a history of postoperative nausea and vomiting. Propofol is the only anesthetic listed with antiemetic properties. Both fluorinated hydrocarbons (isoflurane and sevoflurane) and nitrous oxide are linked to nausea and vomiting during surgery.

- 13.7 A 61-year-old patient with an acute myocardial infarction has severely reduced cardiac output. He has to undergo emergent coronary artery bypass surgery. Which of the following would you expect in this patient?
- A. Faster induction time with IV anesthetics
  - B. Need for increased dosage of IV anesthetics
  - C. Faster induction time with inhaled anesthetics
  - D. Enhanced removal of inhaled anesthetics to peripheral tissues
- Correct answer = C. For inhaled anesthetics during low CO, a longer period of time permits a larger concentration of gas to dissolve in the slowly moving bloodstream. Furthermore, this large bolus of drug has longer contact time to diffuse into neuronal tissue when it traverses the blood-brain barrier yielding a faster induction time. The dose of an IV drug must be reduced (not increased). In addition, with reduced cardiac output, it takes a longer time for an IV induction drug to reach the brain, resulting in a slower induction time.
- 13.8 A 70-year-old patient in the intensive care unit needs sedation due to prolonged endotracheal intubation. Which of the following medications should be avoided for sedation in this patient?
- A. Fentanyl
  - B. Etomidate
  - C. Propofol
  - D. Dexmedetomidine
- Correct answer = B. Adverse effects of etomidate include decreased plasma cortisol and aldosterone levels by inhibiting the 11- $\beta$  hydroxylase enzyme. Etomidate should not be infused for an extended time, because prolonged suppression of these hormones is dangerous. All of the other choices could be used for sedation in the ICU setting.
- 13.9 A 35-year-old man presents with appendicitis and requires a surgical intervention. He has a family history of malignant hyperthermia. Which anesthetic agent is most appropriate to use in this patient?
- A. Isoflurane
  - B. Propofol
  - C. Succinylcholine
  - D. Sevoflurane
- Correct answer = B. Propofol is the only medication listed that is safe in patients susceptible to malignant hyperthermia. All fluorinated hydrocarbons (isoflurane, sevoflurane, desflurane) as well as succinylcholine are contraindicated and considered triggering agents. Flushing of the anesthesia machine, removal of vaporizers, use of special filters, and availability of dantrolene are highly advised.
- 13.10 A 32-year-old woman presents for a right distal radius fracture. She requests regional anesthesia to help with her pain postoperatively. She reports that as a child she had an allergic reaction to Novocain (procaine) at the dentist's office. Which local anesthetic is appropriate for use in this patient?
- A. Chloroprocaine
  - B. Benzocaine
  - C. Ropivacaine
  - D. Tetracaine
- Correct answer = C. Procaine is an ester local anesthetic. Since this patient has an allergy to procaine, other ester anesthetics (chloroprocaine, tetracaine, benzocaine) should not be used. Benzocaine is mostly used as a topical product for temporary relief of dental or oral pain. Ropivacaine is an amide local anesthetic commonly used in regional anesthesia to facilitate peripheral nerve blockade.

# Opioid Analgesics

Robin Moorman Li

14

## I. OVERVIEW

Management of pain is one of clinical medicine's greatest challenges. Pain is defined as an unpleasant sensation that can be either acute or chronic and is a consequence of complex neurochemical processes in the peripheral and central nervous systems (CNS). It is subjective and the clinician must rely on the patient's perception and description of pain. Alleviation of pain depends on the specific type of pain (nociceptive or neuropathic pain). For example, with mild-to-moderate arthritic pain (nociceptive pain), non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs; see Chapter 40) are often effective. Neuropathic pain responds best to anticonvulsants, tricyclic antidepressants, or serotonin/norepinephrine reuptake inhibitors. However, for severe acute pain or chronic malignant or nonmalignant pain, opioids can be considered as part of the treatment plan in select patients (Figure 14.1). Opioids are natural, semisynthetic, or synthetic compounds that produce *morphine*-like effects (Figure 14.2). These agents are divided into chemical classes based on their chemical structure (Figure 14.3). All opioids act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitters (for example, endorphins, enkephalins, and dynorphins). Although the opioids have a broad range of effects, their primary use is to relieve intense pain that results from surgery, injury, or chronic disease. Unfortunately, widespread availability of opioids has led to abuse of agents with euphoric properties. Antagonists that reverse the actions of opioids are also clinically important for use in cases of overdose (Figure 14.1).

## II. OPIOID RECEPTORS

The major effects of the opioids are mediated by three main receptor families, commonly designated as  $\mu$  (mu, MOR),  $\kappa$  (kappa, KOR), and  $\delta$  (delta, DOR). Each receptor family exhibits a different specificity for the drug(s) it binds. The analgesic properties of the opioids are primarily mediated by the  $\mu$  receptors that modulate responses to thermal, mechanical, and chemical nociception. The  $\kappa$  receptors in the dorsal horn also contribute to analgesia by modulating the response to chemical and thermal nociception. The enkephalins interact more selectively with  $\delta$  receptors in the periphery. All three opioid receptors are members of the G protein-coupled receptor family and inhibit adenylyl cyclase. They are also associated with ion channels, increasing postsynaptic  $K^+$  efflux (hyperpolarization) or reducing pre-synaptic  $Ca^{2+}$  influx, thus impeding neuronal firing and transmitter release in the spinal dorsal horn (Figure 14.4).

### STRONG AGONISTS

*Alfentanil*  
*Fentanyl*  
*Heroin*  
*Morphine*  
*Hydrocodone*  
*Hydromorphone*  
*Levorphanol*  
*Meperidine*  
*Methadone*  
*Oxycodone*  
*Oxymorphone*  
*Remifentanil*  
*Sufentanil*

### MODERATE/LOW AGONISTS

*Codeine*

### MIXED AGONIST-ANTAGONIST AND PARTIAL AGONISTS

*Pentazocine*  
*Buprenorphine*  
*Butorphanol*  
*Nalbuphine*

### ANTAGONISTS

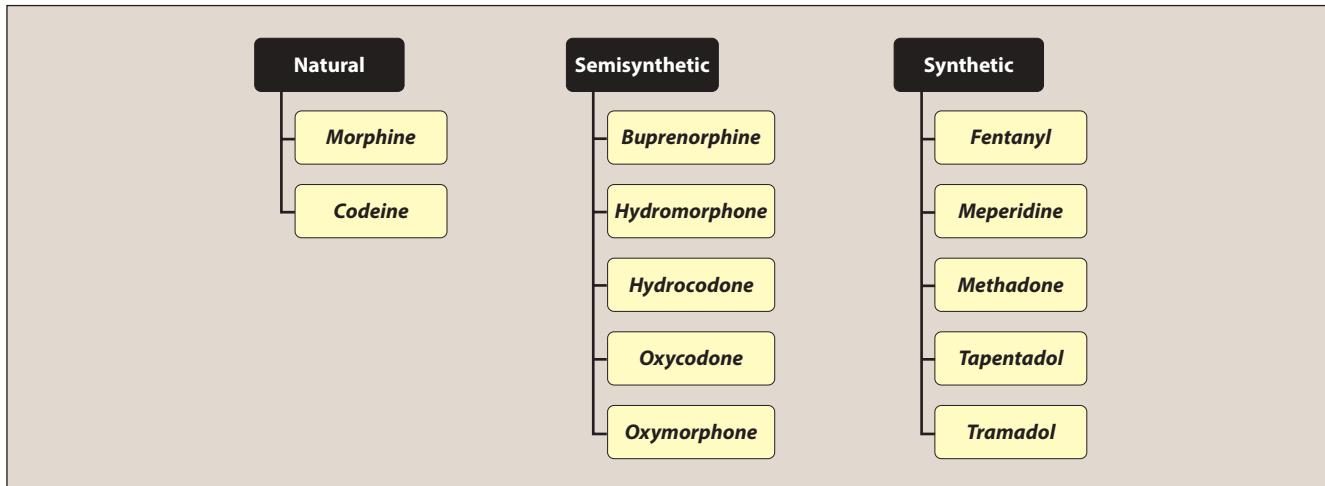
*Naloxone*  
*Naltrexone*

### OTHER ANALGESICS

*Tramadol*  
*Tapentadol*

**Figure 14.1**

Summary of opioid analgesics and antagonists. (For drug dosages, refer to Appendix at the end of the book.)

**Figure 14.2**

Origin of opioids: natural, semisynthetic, or synthetic.

Phenanthrenes	Action on Opioid Receptors
<b>Morphine</b>	Agonist
<b>Codeine</b>	Agonist
<b>Oxycodone</b>	Agonist
<b>Oxymorphone</b>	Agonist
<b>Hydromorphone</b>	Agonist
<b>Hydrocodone</b>	Agonist
<b>Levorphanol</b>	Agonist
<b>Buprenorphine</b>	Partial agonist/Antagonist
<b>Nalbuphine</b>	Mixed agonist/Antagonist
<b>Butorphanol</b>	Mixed agonist/Antagonist
<b>Naloxone</b>	Antagonist
<b>Benzmorphan</b>	
<b>Pentazocine</b>	Mixed agonist/Antagonist
<b>Phenylpiperidines</b>	
<b>Fentanyl</b>	Agonist
<b>Alfentanil</b>	Agonist
<b>Remifentanil</b>	Agonist
<b>Sufentanil</b>	Agonist
<b>Meperidine</b>	Agonist
<b>Diphenylheptane</b>	
<b>Methadone</b>	Agonist
<b>Phenylpropylamines</b>	
<b>Tramadol</b>	Agonist
<b>Tapentadol</b>	Agonist

**Figure 14.3**

Pharmacological classes of opioids and actions on opioid receptors.

### III. OPIOID AGONISTS

**Morphine** [MOR-feen] is the prototypical strong  $\mu$  receptor agonist. **Codeine** [KOE-deen] is inherently less potent and the prototype of the weak  $\mu$  opioid agonists. Currently available opioids have many differences, such as receptor affinity, pharmacokinetic profiles, available routes of administration, and adverse effect profiles. Some opioids are also available in abuse deterrent formulations. Comparing other available opioids to *morphine* is helpful in identifying the unique differences to guide the selection of a safe and effective pain management regimen (Figure 14.5).

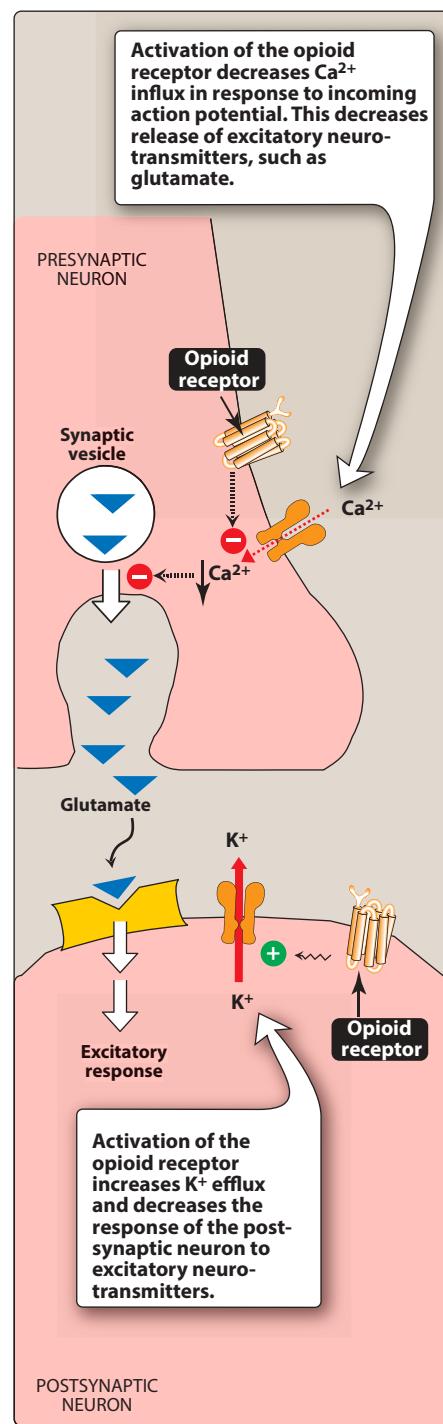
#### A. Morphine

*Morphine* is a plant alkaloid isolated from the latex of opium poppy (*Papaver somiferum*). *Morphine* was isolated from opium and named representing the Greek God of Dreams “*Morpheus*.” The name “opium” was derived from the Greek word “*opos*,” which means *juice*. The compounds derived from *morphine* are generalized as “*opiates*.” The receptor on which *morphine* acts is called opioid receptors. Endorphins are the endogenous peptide ligands found in the brain for opioid receptors. The addictive liability of compounds associated with opioids and other compounds are generally called narcotics. In the legal context, the Greek word “*narkotikos*” which means “*numbing*” or the “state of stupor” refers to substances of abuse or substances with addictive liabilities.

- Mechanism of action:** *Morphine* and other opioids exert analgesic effects by interacting stereospecifically with opioid receptors on the membranes of neuronal cells in the CNS and other anatomic structures, such as the smooth muscles of the gastrointestinal (GI) tract and the urinary bladder. *Morphine* is somewhat selective to the  $\mu$  opioid receptor, but has some affinity for the  $\kappa$  and  $\delta$  receptors. *Morphine* also inhibits the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli. Some therapeutic uses of *morphine* and other opioids are listed in Figure 14.6.

## 2. Actions:

- Analgesia:** Morphine and other opioids relieve pain by raising the pain threshold at the spinal cord level and by altering the brain's perception of pain. The maximum analgesic efficacy for representative opioid agonists is shown in **Figure 14.7**.
- Euphoria:** Morphine produces a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the dopamine-containing neurons of the ventral tegmental area. In normal pain-free individuals, analgesic doses of morphine can cause dysphoria.
- Respiration:** Morphine causes respiratory depression by reduction of the responsiveness of medullary respiratory center neurons to carbon dioxide. This can occur with ordinary doses of morphine in patients who are opioid-naïve and can be accentuated as the dose is increased, until ultimately respiration ceases. Respiratory depression is the most common cause of death in acute opioid overdoses. Tolerance to this effect develops with repeated dosing, which allows for the safer use of morphine for the treatment of pain when the dose is correctly titrated.
- Depression of cough reflex:** Both morphine and codeine have antitussive properties. In general, cough suppression does not correlate closely with analgesic and respiratory depressant properties of opioid drugs. The receptors involved in the antitussive action appear to be different from those involved in analgesia.
- Miosis:** The pinpoint pupil (**Figure 14.8**) characteristic of morphine uses results from stimulation of  $\mu$  and  $\kappa$  receptors at the Edinger-Westphal nucleus. There is little tolerance to this effect. [Note: This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.]
- Emesis:** Morphine directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting.
- GI tract:** Morphine relieves diarrhea by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. Morphine also increases the tone of the anal sphincter. Morphine and other opioids produce constipation, with little tolerance developing. Morphine can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter (sphincter of Oddi). It can aggravate biliary colic pain to multiple folds. This morphine-induced biliary pain is relieved partially by the administration of atropine and completely by opioid antagonists such as naloxone and other smooth muscle relaxants such as papaverine.
- Cardiovascular:** Morphine has no major effects on blood pressure or heart rate at lower dosages, but hypotension and bradycardia may occur at higher doses. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid pressure. Morphine is usually contraindicated in individuals with head trauma or severe brain injury.



**Figure 14.4**

Mechanism of action of  $\mu$  opioid receptor agonists in the spinal cord.

Opioid	Routes of Administration	Comments
<b>Morphine</b>	PO (IR and ER), PR, IM, IV, SC, IA, SL, EA	<ul style="list-style-type: none"> <li>For all drugs listed: opioid class side effects (Figure 14.9). Metabolism through conjugation in liver and P-glycoprotein.</li> <li>Active metabolites are renally eliminated and accumulate in renal impairment.</li> <li>Metabolite M3G has no analgesic action, but can be neuroexcitatory.</li> <li>Metabolite M6G is two to four times more potent than parent drug; accumulation can cause oversedation and respiratory depression.</li> <li>Abuse deterrent formulations available.</li> </ul>
<b>Methadone</b>	PO, IV, IM, SC	<ul style="list-style-type: none"> <li>No active metabolites.</li> <li>Racemic mixture</li> <li><b>Metabolized by many CYP450 isoenzymes:</b> High risk of drug interactions.</li> <li><b>Substrate of P-glycoprotein</b></li> <li>Long and variable half-life increases risks of overdose.</li> <li>Very lipophilic and redistributes to fat stores.</li> <li>Duration of analgesia is much shorter than elimination half-life. Repeated dosing can lead to accumulation.</li> <li>Can prolong QTc interval and cause torsades de pointes.</li> <li>Warning: Conversion to and from <i>methadone</i> and other opioids should be done with great care, since equianalgesic dosing varies dramatically.</li> </ul>
<b>Fentanyl</b>	IV, EA, IA, TD, OTFC, SL, Buccal, Nasal	<ul style="list-style-type: none"> <li>No active metabolites; option for patients with renal dysfunction but should be used with caution.</li> <li>Metabolized by CYP3A4.</li> <li>100 times more potent than <i>morphine</i>.</li> <li>Less histamine release, sedation, and constipation in comparison to <i>morphine</i>.</li> </ul>
<b>Oxycodone</b>	PO (IR and CR)	<ul style="list-style-type: none"> <li>Metabolized by CYP2D6 and CYP3A4.</li> <li>Black box warning: CYP3A4 drug interactions.</li> <li>Less histamine release and nausea in comparison to <i>morphine</i>.</li> <li>Abuse-deterring formulation available.</li> </ul>
<b>Oxymorphone</b>	PO (IR and ER), IV	<ul style="list-style-type: none"> <li>Immediate release has longer duration of action and elimination half-life (8 hours) compared to other immediate-release opioids.</li> <li>Oral bioavailability increases with food.</li> <li>Should be administered 1 to 2 hours after eating.</li> <li>Bioavailability increased with coadministration of alcohol.</li> </ul>
<b>Hydromorphone</b>	PO (IR and ER), PR, IV, SC, EA, IA	<ul style="list-style-type: none"> <li>Metabolized via glucuronidation to H6G and H3G which are renally eliminated and can cause CNS side effects in patients with renal insufficiency.</li> <li>Abuse-deterring formulation available.</li> </ul>
<b>Hydrocodone</b>	PO (IR and ER)	<ul style="list-style-type: none"> <li>Active metabolite is <i>hydromorphone</i>.</li> <li>Metabolized by CYP2D6 and CYP3A4.</li> <li>Abuse-deterring formulations available.</li> </ul>
<b>Tapentadol</b>	PO (IR and ER)	<ul style="list-style-type: none"> <li>Centrally acting analgesic; <math>\mu</math> agonist activity along with inhibition of norepinephrine reuptake.</li> <li>Efficacy in treating nociceptive and neuropathic pain.</li> <li>Metabolized predominantly by glucuronidation; no CYP450 interactions.</li> <li>Seizures and serotonin syndrome can occur in predisposed patients.</li> </ul>
<b>Tramadol</b>	PO (IR, ODT, and ER), Topically	<ul style="list-style-type: none"> <li>Metabolized by Phase 1 and 2. CYP2D6, CYP2B6, and CYP3A4 involved in metabolism; watch drug interactions.</li> <li>Serotonin syndrome can occur due to drug interactions.</li> <li>Cl for treatment of pain in children &lt; 12 y/o.</li> <li>Cl in children &lt; 18 y/o after removal of tonsils/adenoids.</li> <li>Recommended not to use in 12–18 y/o who are obese, have severe lung disease, or sleep apnea.</li> <li>Use is not recommended in breastfeeding mothers due to adverse reactions in breastfed infants.</li> <li>Warning: <ul style="list-style-type: none"> <li>Renal impairment dosing required.</li> <li>Review dosing recommendations in severe hepatic impairment.</li> </ul> </li> </ul>
<b>Codeine</b>	PO, SC	<ul style="list-style-type: none"> <li>Prodrug: Metabolized by CYP2D6 to the active drug <i>morphine</i>.</li> <li>Rapid and poor metabolizers of CYP2D6 can experience toxicity.</li> <li>Inhibitors of CYP2D6 will prevent conversion of <i>codeine</i> to <i>morphine</i>, thereby preventing pain control.</li> <li>Do not use in patients with renal dysfunction.</li> <li>Use only for mild or moderate pain.</li> <li>Cl in treatment of pain or cough in children &lt; 12 years old.</li> <li>Cl in children &lt; 18 years old after removal of tonsils/adenoids.</li> <li>Recommended not to use in 12–18 years old who are obese, have severe lung disease, or have sleep apnea.</li> <li>Use is not recommended in breastfeeding mothers due to adverse reactions in breastfed infants.</li> </ul>
<b>Meperidine</b>	PO, IV, SC, EA, IA	<ul style="list-style-type: none"> <li>Not recommended as first-line opioid choice.</li> <li>Active metabolite normeperidine accumulates with renal dysfunction, leading to toxicity.</li> <li><i>Naloxone</i> does not antagonize the effects of normeperidine; could worsen seizure activity.</li> <li>Do not use in elderly, patients with renal dysfunction, or for chronic pain management.</li> </ul>
<b>Buprenorphine</b>	SL, TD, IM, IV, Buccal (transmucosal), Implant	<ul style="list-style-type: none"> <li>Long duration of action; very lipophilic.</li> <li>Incompletely reversible by <i>naloxone</i>.</li> <li>Drug interactions: contraindicated with <i>atazanavir</i>, <i>convivaptan</i>, MAO inhibitors; metabolized by primarily by CYP3A4.</li> <li>Can prolong QTc interval.</li> <li>Avoid use in patients with hypokalemia, atrial fibrillation, or unstable heart failure, or other predisposing factors increasing QT abnormalities.</li> <li>Transdermal patch is applied every 7 days.</li> <li>Abuse-deterring formulations available.</li> </ul>

Cl = contraindicated; CR = controlled-release; EA = epidural anesthesia; IA = intrathecal anesthesia; IM = intramuscular; IR = immediate release; IV = intravenous; OTFC = oral transmucosal fentanyl citrate; PO = orally; PR = rectally; SC = subcutaneous; SL = sublingual; TD = transdermal; M3G = morphine-3-glucuronide; M6G = morphine-6-glucuronide; NMDA = N-methyl-D-aspartate; H6G = hydromorphone-6-glucuronide; H3G = hydromorphone-3-glucuronide

Note: Many different acronyms may be used to indicate a medication is extended-release. Examples include CR (controlled-release), LA (long-acting), ER (extended-release).

**Figure 14.5**

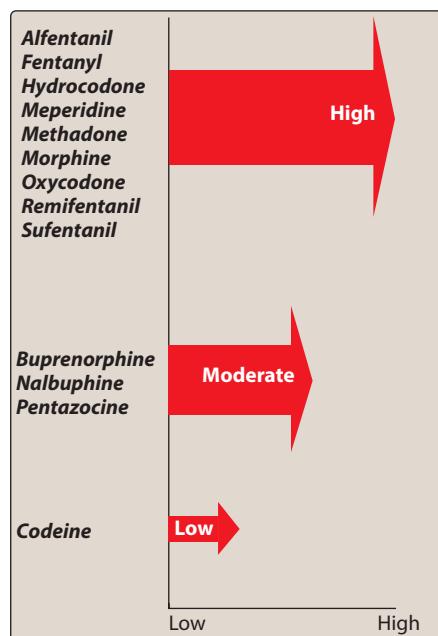
Summary of clinically relevant properties for selected opioids.

- i. **Histamine release:** *Morphine* releases histamine from mast cells causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, *morphine* should be used with caution in patients with asthma.
  - j. **Hormonal actions:** Prolonged use of *morphine* may lead to opioid-induced androgen deficiency due to suppression of the hypothalamic-pituitary-gonadal axis (HPA). This results in decreased production of sex hormones, especially testosterone, resulting in many clinical symptoms (Figure 14.9).
  - k. **Labor:** *Morphine* may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.
  - l. **Thermoregulation:** *Morphine* decreases the body temperature slightly due to its effect on hypothalamus heat-regulating mechanisms. In opioid withdrawal, elevated body temperature has been observed.
  - m. **Immune system:** *Morphine* shows both direct and indirect effects (through centrally mediated neuronal mechanisms) on the immune system. Opioids in general cause moderate immunosuppression which makes the recipient susceptible for infections and tumor metastasis.
3. **Pharmacokinetics:**
- a. **Administration:** *Morphine* has a linear pharmacokinetic profile; however, absorption of morphine after oral administration is slow and erratic. Extended-release oral preparations provide more consistent plasma levels. Because significant first-pass metabolism of *morphine* occurs in the liver, subcutaneous and IV injections produce the most reliable response.
  - b. **Distribution:** *Morphine* rapidly enters all body tissues, including the fetuses of pregnant women. It should not be used for analgesia during labor. Infants born to addicted mothers show physical dependence on opioids and exhibit withdrawal symptoms if opioids are not administered. Only a small percentage of *morphine* crosses the blood-brain barrier, because *morphine* is the least lipophilic of the common opioids. By contrast, the more lipid-soluble opioids, such as *fentanyl* and *methadone*, readily penetrate the CNS.
  - c. **Fate:** *Morphine* is conjugated with glucuronic acid in the liver to two active metabolites (morphine-6-glucuronide [M6G] and morphine-3-glucuronide [M3G]) which are renally excreted. M6G is a very potent analgesic, and morphine glucuronide metabolites undergo enterohepatic circulation. M3G does not have analgesic activity, but is believed to cause neuroexcitatory effects. The duration of action of *morphine* is 4 to 5 hours when administered systemically to opioid-naïve individuals, but considerably longer when injected epidurally because the low lipophilicity prevents redistribution from the epidural space.
4. **Adverse effects:** Many adverse effects are common across the entire opioid class (Figure 14.10). With most  $\mu$  agonists, severe respiratory depression can occur and may result in death from acute opioid overdose. Respiratory drive may be suppressed in patients with respiratory disorders such as obstructive sleep apnea, emphysema, or cor pulmonale, so close monitoring is necessary when using opioids. Opioid-induced constipation (OIC)

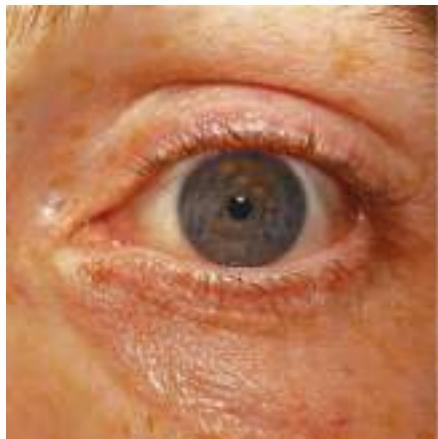
Therapeutic Use	Comments
Analgesia	<i>Morphine</i> is the prototype opioid agonist. Opioids are used for pain in trauma, cancer, and other types of severe pain.
Treatment of diarrhea	Opioids decrease the motility and increase the tone of intestinal circular smooth muscle. [Note: Agents commonly used include diphenoxylate and loperamide (see Chapter 31).]
Relief of cough	<i>Morphine</i> does suppress the cough reflex, but <i>codeine</i> and <i>dextromethorphan</i> are more commonly used.
Treatment of acute pulmonary edema	Intravenous <i>morphine</i> dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure, possibly via the vasodilatory effect. This, in effect, decreases cardiac preload and afterload, as well as anxiety experienced by the patient.
Anesthesia	Opioids are used as pre-anesthetic medications, for systemic and spinal anesthesia, and for postoperative analgesia.

**Figure 14.6**

Selected clinical uses of opioids.

**Figure 14.7**

A comparison of opioid agonist efficacy.



**Figure 14.8**

Characteristic pinpoint pupil associated with *morphine* use.

is a common adverse effect. Initial management includes a non-prescription stimulant laxative such as *senna*. Peripherally acting  $\mu$ -opioid receptor antagonists such as *methylnaltrexone*, *naloxegol*, and *naldemedine* are prescription drugs available for the treatment of OIC. [Note: *Lubiprostone* is a chloride channel activator that is indicated for OIC and irritable bowel syndrome; see Chapter 42.] *Morphine* should be used with caution in patients with liver disease and renal dysfunction.

5. **Tolerance and physical dependence:** Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, emetic, and sedative effects of *morphine*. Tolerance usually does not develop to miosis (constriction of the pupils) or constipation. Physical and psychological dependence can occur with *morphine* and other agonists. Withdrawal produces a series of autonomic, motor, and psychological responses such as goosebumps, muscle spasms, hyperalgesia, lacrimation, rhinorrhea, yawning, sweating, restlessness, dilated pupils, anorexia, irritability, tremors, diarrhea, and flushing that can be severe. The abstinence withdrawal peaks at 48 to 72 hours, though generally it is not life threatening except in neonates and the severely debilitated. Administration of an opioid antagonist may precipitate a severe withdrawal reaction.
6. **Drug interactions:** Drug interactions with *morphine* are possible. The depressant actions of *morphine* are enhanced by coadministration with CNS depressant medications such as phenothiazines, monoamine oxidase inhibitors (MAOIs), and benzodiazepines. Guidelines for opioid prescribing urge clinicians to avoid simultaneous prescribing of opioids and benzodiazepines. A black box warning also has been included on the labeling of both opioids and benzodiazepines to alert prescribers of this dangerous combination.

## B. Codeine

*Codeine* [KOE-deen] is a naturally occurring opioid and a weak analgesic compared to *morphine*. It is used for mild-to-moderate pain. The analgesic actions of *codeine* are derived from its conversion to *morphine* by the CYP2D6 enzyme (see Chapter 1). CYP2D6 activity varies among patients, and ultra-rapid metabolizers may experience higher levels of *morphine*, leading to possible overdose and toxicity. Life-threatening respiratory depression and death have been reported in children who received *codeine*, mostly following tonsillectomy and/or adenoidectomy. *Codeine* is commonly used in combination with *acetaminophen* for management of pain. The drug exhibits good antitussive activity at doses that do not cause analgesia. *Dextromethorphan* [dex-troe-meth-OR-fan] is a synthetic cough depressant that has relatively no analgesic action and much lower potential for abuse in usual antitussive doses. It is preferred over *codeine* in most situations where cough suppression is needed.

## C. Dextromethorphan

*Dextromethorphan* belongs to the morphinan class with sedative, dissociative, and stimulant properties (at lower doses). It is used mainly as a cough suppressant for the temporary relief of cough caused by minor throat and bronchial irritation. It is available in combination with other drugs (such as *paracetamol*, *ibuprofen*, a nasal decongestant, or an antihistamine) in many over-the-counter cold and cough medicines

and is available as in various dosage forms such as syrup, lozenges, tablets, and spray. It should not be used for chronic cough as seen with smoking, asthma, or emphysema or when there is an unusually large amount of mucus or phlegm with the cough. *Dextromethorphan* is also used recreationally. At doses exceeding approved dosages, *dextromethorphan* acts as a dissociative anesthetic. It acts by multiple mechanisms of action, including actions as a sigma-1 receptor agonist and nonselective serotonin reuptake inhibitor. At high doses *dextromethorphan* and its major metabolite, *dextrorphan*, also act as an NMDA receptor antagonist, which produces effects similar to, yet distinct from, the dissociative states created by other dissociative anesthetics such as *ketamine* and *phencyclidine*.

Its use is discouraged as it psychological dependence develops especially in people who use it for recreational purpose though it is considered less addictive than *codeine*. Its use over a long period can cause withdrawal symptoms similar to those of antidepressant discontinuation syndrome due to its action as a serotonin reuptake inhibitor.

*Dextromethorphan* is rapidly absorbed from the gastrointestinal tract and converted into the active metabolite dextrorphan in the liver by the CYP2D6. *Dextromethorphan* DXM has an elimination half-life of 4 hours approximately in individuals with an extensive metabolizer phenotype; this is increased to approximately 13 hours when it is given in combination with *quinidine*.

*Dextromethorphan* should not be administered to children below 4 years and is contraindicated in atopic children. The side effects of *dextromethorphan* at normal therapeutic doses include rash or itching, nausea, vomiting, constipation, diarrhea, drowsiness, dizziness, sedation, and confusion and rarely it may cause respiratory depression.

#### D. Noscapine

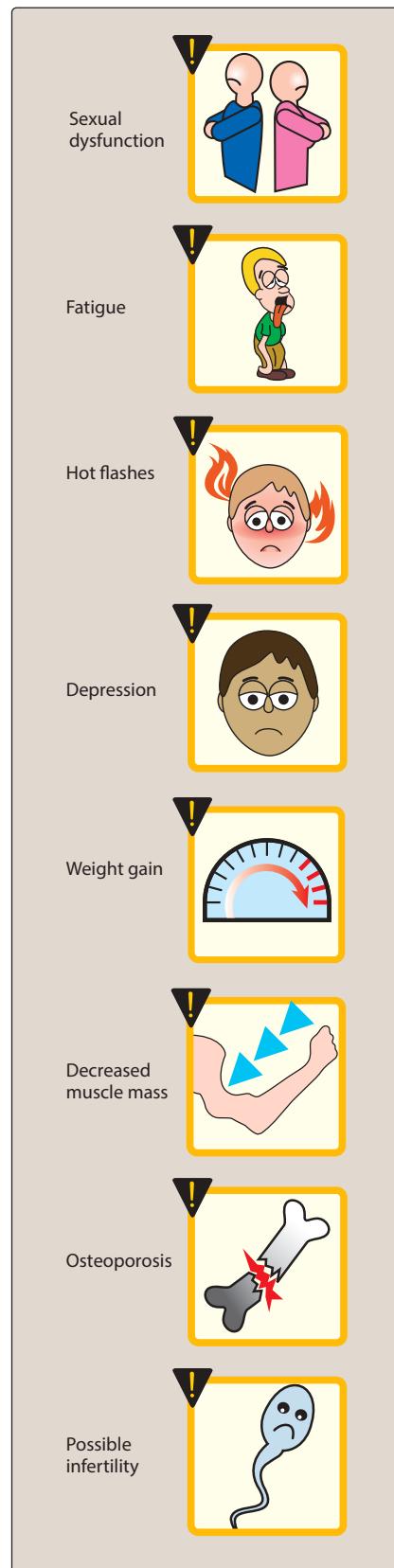
*Noscapine* is an opium alkaloid obtained from the plant *Papaver somniferum* exerts its antitussive effects through the activation of sigma opioid receptors without narcotic, analgesic, or dependence-inducing properties. *Noscapine* is registered for the treatment of a dry nonproductive cough and is available as a syrup and a tablet.

This alkaloid experimentally also appears to exert its antimitotic effect by binding to tubulin that causes cell cycle arrest and potentially promotes apoptosis both in vitro and in vivo in cancer cells.

The side effects of *noscapine* include headache, drowsiness, nausea, bronchoconstriction, and rashes. *Noscapine* can increase the effects of centrally sedating substances such as alcohol and hypnotics. The drug should not be taken with any monoamine oxidase inhibitors (MAOIs), as unknown and potentially fatal effects may occur. Also, *noscapine* should not be taken in conjunction with *warfarin* as the anticoagulant effects of *warfarin* may be increased.

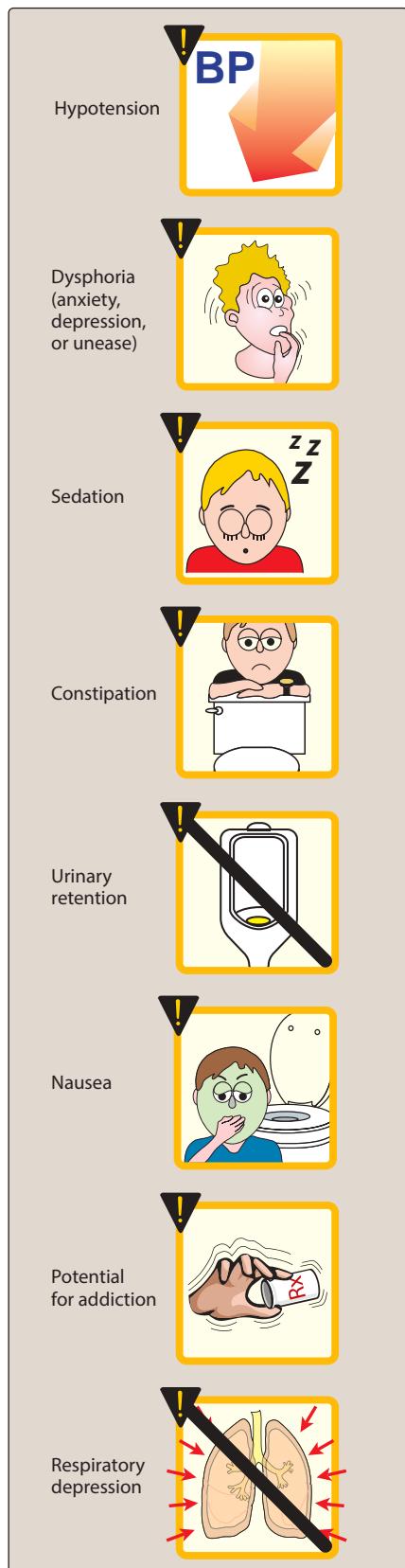
#### E. Oxycodone and oxymorphone

*Oxymorphone* [ox-ee-MOR-fone] and *oxycodone* [ok-see-KOE-done] are orally active, semisynthetic analogs of *morphine* and *codeine*, respectively. *Oxymorphone* given parenterally is approximately 10 times more potent than *morphine*, but when administered orally the potency drops to about three times that of *morphine*. *Oxymorphone* is available in both immediate-release and extended-release oral formulations. This



**Figure 14.9**

Clinical symptoms associated with opioid-induced androgen deficiency (OPIAD).

**Figure 14.10**

Adverse effects commonly observed in individuals treated with opioids.

agent has no clinically relevant drug interactions associated with the CYP450 enzyme system. Oxycodone is approximately two times more potent than *morphine* and is available in an immediate-release formulation, alone or in combination with *acetaminophen*, *aspirin*, or *ibuprofen*. An extended-release formulation is also available. Oxycodone is mainly metabolized via the CYP2D6 and CYP3A4 enzymes.

### F. Hydromorphone and hydrocodone

*Hydromorphone* [hye-droe-MORE-fone] and *hydrocodone* [hye-droe-KOE-done] are orally active, semisynthetic analogs of *morphine* and *codeine*, respectively. Oral *hydromorphone* is approximately four to seven times more potent than oral *morphine*. It is preferred over *morphine* in patients with renal dysfunction due to less accumulation of active metabolites. *Hydrocodone* is the methyl ether derivative of *hydromorphone*, but is a weaker analgesic than *hydromorphone*, with oral analgesic efficacy comparable to that of *morphine*. This agent is often combined with *acetaminophen* or *ibuprofen* to treat moderate-to-severe pain. It is also used as an antitussive. *Hydrocodone* is metabolized in the liver to several metabolites, one of which is *hydromorphone* via the actions of CYP2D6.

### G. Fentanyl

*Fentanyl* [FEN-ta-nil] is a synthetic opioid chemically related to *pethidine*. *Fentanyl* has 100-folds the analgesic potency of *morphine* and is used for anesthesia and acute pain management. The drug is highly lipophilic and has a rapid onset and short duration of action (15 to 30 minutes). It is usually administered IV, epidurally, or intrathecally. *Fentanyl* is combined with local anesthetics to provide epidural analgesia for labor and postoperative pain. IV *fentanyl* is used in anesthesia for its analgesic and sedative effects. Many fast-acting transmucosal and nasal *fentanyl* products are available for cancer-related breakthrough pain in opioid-tolerant patients. The transdermal patch creates a reservoir of the drug in the skin and has a delayed onset of at least 12 hours and a prolonged offset. The patch is used for the management of chronic severe pain. It is contraindicated in opioid-naïve patients and should not be used in management of acute or postoperative pain. *Fentanyl* is metabolized to inactive metabolites by CYP 3A4 and drugs that inhibit this isoenzyme can potentiate the effect of *fentanyl*.

### H. Sufentanil, alfentanil, remifentanil, and carfentanil

*Sufentanil* [soo-FEN-ta-nil], *alfentanil* [al-FEN-ta-nil], *remifentanil* [rem-ih-FEN-ta-nil], and *carfentanil* [car-FEN-ta-nil] are synthetic opioid agonists related to *fentanyl*. These agents differ in potency and metabolic disposition. *Sufentanil* and *carfentanil* are even more potent than *fentanyl*, whereas the other two are less potent and shorter acting. *Sufentanil*, *alfentanil*, and *remifentanil* are mainly used for their analgesic and sedative properties during surgical procedures requiring anesthesia. *Carfentanil* is about 100 times more potent than *fentanyl*. The drug is not used in clinical practice; however, it is of toxicological interest as it is used to lace *heroin* and has contributed to several opioid-related deaths.

## I. Methadone

*Methadone* [METH-a-done] is a synthetic, orally effective opioid that has variable equianalgesic potency compared to that of *morphine*, and the conversion between the two products is not linear. *Methadone* is a  $\mu$  agonist, an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, and a norepinephrine and serotonin reuptake inhibitor. Therefore, it is useful in the treatment of both nociceptive and neuropathic pain. *Methadone* may also be used for opioid withdrawal and maintenance therapy in the setting of prescription opioid and *heroin* abuse. The withdrawal syndrome with *methadone* is milder but more protracted (days to weeks) than that with other opioids. *Methadone* induces less euphoria and has a longer duration of action than *morphine*. Unlike *morphine*, *methadone* is well absorbed after oral administration. *Methadone* is also constipating, but less so than *morphine*.

Understanding the pharmacokinetics of *methadone* is important to ensure proper use. After oral administration, *methadone* is biotransformed in the liver and excreted almost exclusively in the feces. *Methadone* is very lipophilic, rapidly distributed throughout the body, and released slowly during redistribution and elimination. This translates into a long half-life ranging from 12 to 40 hours, although it may extend up to 150 hours. Despite the extended half-life, the actual duration of analgesia ranges from 4 to 8 hours. Attainment of a steady state can vary dramatically, ranging from 35 hours to 2 weeks, so dosage adjustments should occur only every 5 to 7 days. Upon repeated dosing, *methadone* can accumulate due to the long terminal half-life, leading to toxicity. Overdose is possible when prescribers are unaware of the long half-life, the incomplete cross-tolerance between *methadone* and other opioids, and the titration guidelines to avoid toxic accumulation. The metabolism is variable due to involvement of multiple CYP450 isoenzymes, some of which are affected by known genetic polymorphisms. As such, *methadone* is susceptible to many drug-drug interactions.

*Methadone* can produce physical dependence like that of *morphine*, but it has less neurotoxicity than *morphine* due to lack of active metabolites. *Methadone* can prolong the QT<sub>c</sub> interval and cause torsades de pointes, possibly by interacting with cardiac potassium channels. Baseline and routine ECG monitoring is recommended.

## J. Pethidine (meperidine)

*Pethidine* is a lower potency synthetic opioid structurally unrelated to *morphine*. It is used for acute pain and acts primarily as a  $\kappa$  agonist, with some  $\mu$  agonist activity. *Pethidine* is very lipophilic and has anticholinergic effects, resulting in an increased incidence of delirium compared with other opioids. *Pethidine* has an active minor metabolite (norpethidine) which is potentially neurotoxic whereas the major metabolite is meperidinic acid along with glucuronide conjugation metabolites which are excreted via kidney. As they are renally excreted, they can cause accumulation in patients with renal insufficiency. It can cause delirium, hyper-reflexia, myoclonus, and seizures in any patient following overdose, long-term use, especially in patients with renal insufficiency. Due to the short duration of action and the potential for toxicity, *pethidine* should only be used for short-term ( $\leq 48$  hours) management of pain. *Pethidine* should not be used in elderly patients or in those with renal insufficiency, hepatic insufficiency, pre-existing

respiratory compromise, or concomitant or recent administration of MAOIs. Serotonin syndrome has been reported in patients receiving both *pethidine* and selective serotonin reuptake inhibitors (SSRIs). *Pethidine* is primarily used as an analgesic and in preanesthetic medication. It can also be used to control shivering during the postsurgical recovery period. Transdermal *pethidine* is used for the management of cancer pain. On the transdermal route, the onset of pain is delayed up to 12 hours; however, on subsequent administration, the analgesic effect is sustained for prolonged periods in patients.

### K. Propoxyphene

*Propoxyphene* is a congener of *methadone*. However, it has the analgesic activity and side effects similar to those of *codeine* but less antitussive action. It can be combined with NSAIDs such as *paracetamol* and *aspirin*. Its dextro form is found to be analgesic; therefore, it is used as dextropropoxyphene. The levo form is found to have antitussive activity. Primarily, it acts through  $\mu$  receptors for analgesia. It is absorbed well after oral administration reaching higher concentration at 1 to 2 hours. The average half-life is longer than *codeine* and it is metabolized into *norpropoxyphene* which is reported to have a half-life of more than 30 hours. Accumulation of this metabolite is reported to show toxicity. It has low effect on respiration as compared to *codeine*. In moderate toxic doses, *norpropoxyphene* is reported to show respiratory depression, convulsions, delusion, hallucination, confusion, cardiac side effects, etc. Respiratory, convulsion, and cardiac toxicities are reversed with *naloxone*.

## IV. PARTIAL AGONISTS AND MIXED AGONIST-ANTAGONISTS

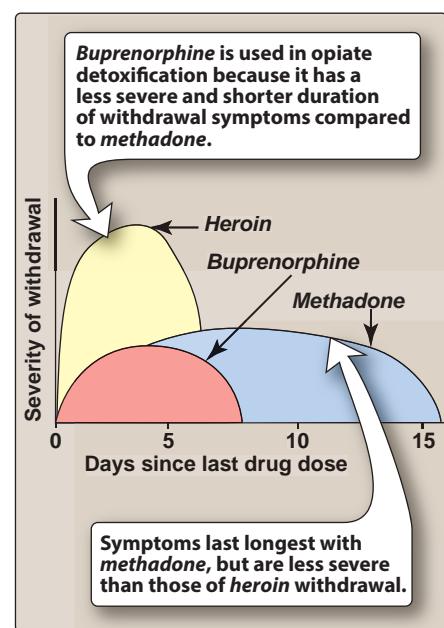
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Partial agonists bind to the opioid receptor, but they have less intrinsic activity than full agonists (see Chapter 1). There is a ceiling to the pharmacologic effects of these agents. Drugs that stimulate one receptor but block another are termed mixed agonist-antagonists. The effects of these drugs depend on previous exposure to opioids. In individuals who are opioid-naïve, mixed agonist-antagonists show agonist activity and are used to relieve pain. In the presence of a full agonist, the agonist-antagonist drugs may precipitate opioid withdrawal symptoms.

### A. Buprenorphine

*Buprenorphine* [byoo-pre-NOR-feen] acts as a potent partial agonist at the  $\mu$  receptor and an antagonist at the  $\kappa$  receptors. *Buprenorphine* is very lipophilic and has a longer duration of action due to its high affinity for the opioid receptors when compared to *morphine*. Due to high affinity for the  $\mu$  receptor, *buprenorphine* can displace full  $\mu$  agonists, leading to withdrawal symptoms in an opioid-dependent patient. Because of the partial  $\mu$  agonist activity, *buprenorphine* provides a “ceiling effect,” causing less euphoric effects and a lower abuse potential than that of full agonists. Additionally, the risk of opioid-induced respiratory depression may be lower when compared with full agonists, except when combined with CNS depressants such as benzodiazepines. *Buprenorphine* is available in sublingual, transmucosal, buccal, parenteral, subdermal, and transdermal formulations.

The drug is approved for moderate-to-severe pain. Certain formulations (for example, sublingual and subdermal) are approved for use in medication-assisted treatment of opioid addiction due to its ability to provide prolonged suppression of opioid withdrawal, the ability to block other  $\mu$  agonists, and less frequent dosing requirements. In contrast to *methadone*, which is available only at specialized clinics when used for opioid detoxification or maintenance, *buprenorphine* is approved for office-based treatment of opioid dependence. It has been shown to have shorter and less severe withdrawal symptoms compared to *methadone* (Figure 14.11). Dosing restrictions are currently in place for many *buprenorphine* products due to the concern of QT<sub>c</sub> prolongation. *Buprenorphine* is metabolized via CYP3A4, and drugs which inhibit CYP3A4 may increase the risk of QT<sub>c</sub> prolongation and other adverse effects. Cardiac histories and concurrent medications should be evaluated to identify potential risk factors for QT<sub>c</sub> prolongation when considering *buprenorphine*. Adverse effects include respiratory depression that cannot easily be reversed by *naloxone* and decreased (or, rarely, increased) blood pressure, nausea, and dizziness.



## B. Pentazocine

*Pentazocine* [pen-TAZ-oh-seen] acts as an agonist on  $\kappa$  receptors and is a weak antagonist or partial agonist at  $\mu$  receptors. It can be administered either orally or parenterally. *Pentazocine* produces less euphoria compared to *morphine*, but in higher doses respiratory depression, increased blood pressure, tachycardia, and hallucinations can occur. For these reasons, *pentazocine* is rarely used for the management of pain. Despite its antagonist action, *pentazocine* does not antagonize the respiratory depression of *morphine*, but it can precipitate withdrawal effects in a *morphine* user. *Pentazocine* should be used with caution in patients with angina or coronary artery disease, since it can increase blood pressure.

## C. Nalbuphine and butorphanol

*Nalbuphine* [NAL-byoo-feen] and *butorphanol* [byoo-TOR-fa-nole] are mixed opioid agonist–antagonists. Like *pentazocine*, they play a limited role in the treatment of chronic pain. *Butorphanol* is available in a nasal spray that has been used for severe headaches, but it has been associated with abuse. Both products are available in an injectable formulation. Their propensity to cause psychotomimetic effects is less than that of *pentazocine*. In contrast to *pentazocine* and *butorphanol*, *nalbuphine* does not affect the heart or increase blood pressure. A benefit of all three medications is that they exhibit a ceiling effect for respiratory depression.

# V. OTHER ANALGESICS

## A. Tapentadol

*Tapentadol* [ta-PEN-ta-dol], a centrally acting analgesic, is an agonist at the  $\mu$  opioid receptor and an inhibitor of norepinephrine reuptake. It is used to manage moderate-to-severe acute and chronic pain, including neuropathic pain associated with diabetic peripheral neuropathy.

*Tapentadol* is mainly metabolized to inactive metabolites via glucuronidation, and it does not inhibit or induce the CYP450 enzyme system. Because *tapentadol* does not produce active metabolites, dosing adjustment is not necessary in mild-to-moderate renal impairment. *Tapentadol* should be avoided in patients who have received MAOIs within the past 14 days. It is available in an immediate-release and extended-release formulation.

### B. Tramadol

*Tramadol* [TRA-ma-dole] is a centrally acting analgesic that binds to the  $\mu$  opioid receptor. It undergoes extensive metabolism via CYP2D6, leading to an active metabolite which has a much higher affinity for the  $\mu$  receptor than the parent compound. In addition, it weakly inhibits reuptake of norepinephrine and serotonin. It is used to manage moderate-to-severe pain. Of note, *tramadol* has less respiratory-depressant activity compared to *morphine*. Administration of *naloxone* can only partially reverse *tramadol* toxicity and has been associated with an increased risk of seizures. Anaphylactoid reactions have been reported. Overdose or drug–drug interactions with SSRIs, MAOIs, and tricyclic antidepressants can lead to toxicity manifested by CNS excitation and seizures. *Tramadol* should be used with caution in patients with a history of seizures. As with other agents that bind the  $\mu$  opioid receptor, *tramadol* has been associated with misuse and abuse.

### C. Diphenoxylate and Loperamide

*Diphenoxylate* and *loperamide* are used for the treatment of diarrhea. At a much higher dose, *diphenoxylate* shows opioid activity including euphoria. Therefore, *diphenoxylate* is combined with *atropine* to reduce the chance of abusing liability. *Definoxin* is a metabolite of *diphenoxylate* which is also being marketed along with *atropine* as a fixed-dose combination. *Loperamide* shows action similar to that of *diphenoxylate*. It exerts its action by interacting with the opioid receptors in the intestine. Abdominal cramps and constipation are the common side effects observed with these agents.

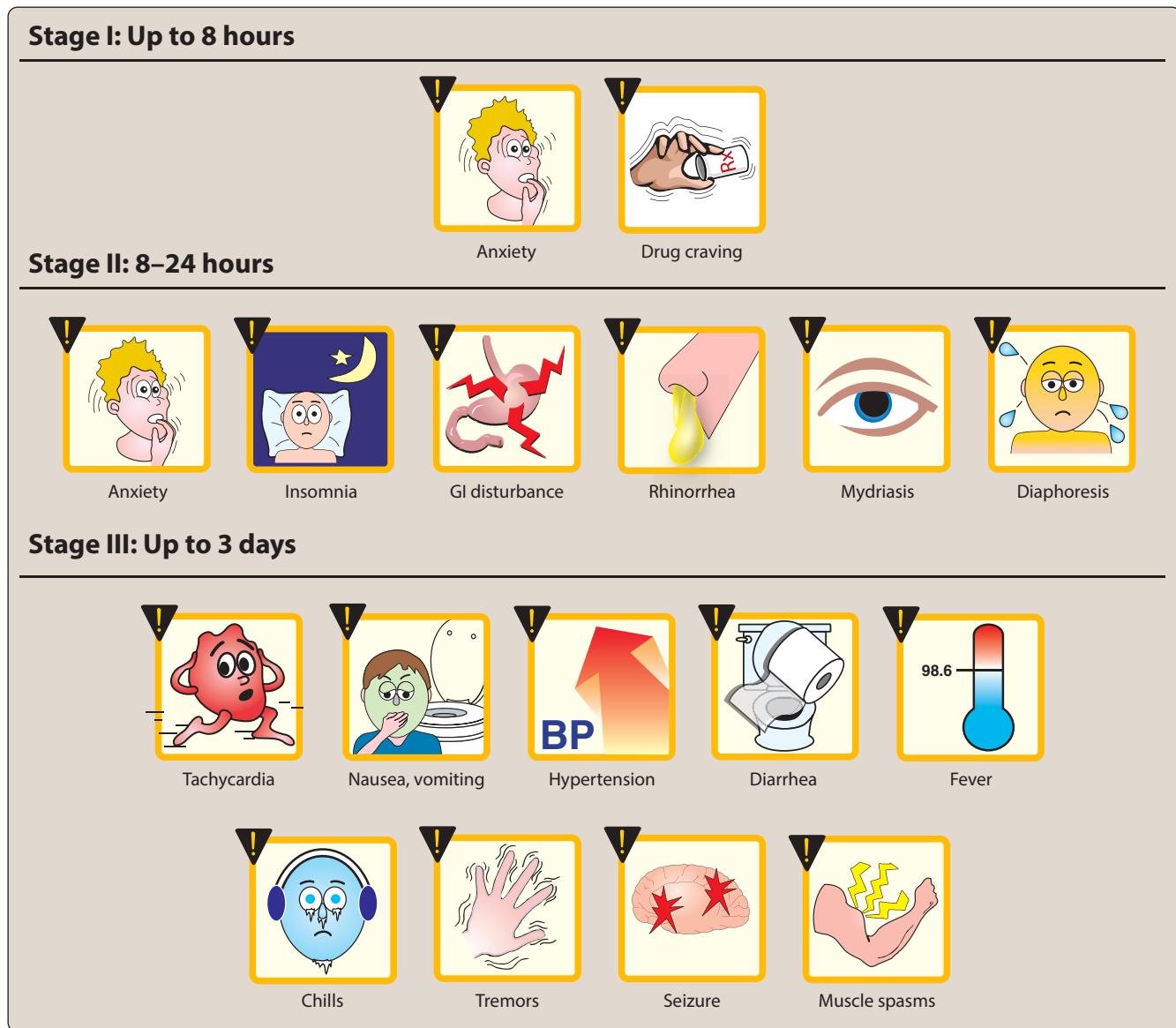
## VI. ANTAGONISTS

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The opioid antagonists bind with high affinity to opioid receptors, but they fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in individuals not taking opioids. In opioid-dependent patients, antagonists rapidly reverse the effect of agonists, such as *morphine* or any full  $\mu$  agonist, and precipitate the symptoms of opioid withdrawal. **Figure 14.12** summarizes some signs and symptoms of opioid withdrawal.

### A. Naloxone

*Naloxone* [nal-OX-own] is a competitive antagonist at  $\mu$ ,  $\kappa$ , and  $\delta$  receptors, with a 10-fold higher affinity for  $\mu$  than for  $\kappa$  receptors. It rapidly displaces all receptor-bound opioid molecules and, therefore, can reverse the effects of *morphine* overdose, such as respiratory depression and coma within 1 to 2 minutes of IV administration. It

**Figure 14.12**

Opiate withdrawal syndrome. GI = gastrointestinal.

is also used to diagnose opioid dependence. *Naloxone* can also be administered intramuscularly, subcutaneously, and intranasally, with a slightly longer onset of 2 to 5 minutes; however, little to no clinical effect is seen with oral *naloxone* due to extensive first-pass metabolism. Since *naloxone* has a half-life of 30 to 81 minutes, a patient who has been treated for an overdose and recovered may lapse back into respiratory depression, depending on the opioid ingested and dosage form of that opioid. Therefore, multiple doses should be administered. [Note: Much higher doses and continuous administration of *naloxone* are needed to reverse the effects of *buprenorphine* due to its high affinity for the  $\mu$  receptor.] The duration of action of *naloxone* lasts for up to 48 hours; it is used to decrease the craving for alcohol.

*Naloxone* is available in an autoinjector and a nasal inhaler for community distribution for treatment of opioid overdose involving *heroin*.

or prescription opioids. It is imperative that prescribers counsel the patient and family members regarding the availability of these products, proper instructions for use, and the importance of calling emergency services in the case of overdose.

### B. Naltrexone

*Naltrexone* [nal-TREX-own] has actions similar to those of *naloxone*, but it has a longer duration of action and can be given orally. For example, a single oral dose of *naltrexone* blocks the effect of injected *heroin* for up to 24 hours, and the intramuscular formulation blocks the effect for 30 days. *Naltrexone* in combination with *clonidine* (and, sometimes, with *buprenorphine*) is used for rapid opioid detoxification. *Naltrexone* has been reported to cause hepatotoxicity, and monitoring of hepatic function is recommended.

## Study Questions

### Choose the ONE best answer.

14.1 Which of the agents listed is a phenanthrene opioid which exhibits a full and immediate response to treatment with naloxone?

- A. Pethidine
- B. Morphine
- C. Buprenorphine
- D. Fentanyl

Correct answer = B. A morphine overdose can be effectively treated with naloxone, and morphine is a phenanthrene. Naloxone antagonizes the opioid by displacing it from the receptor, but there are cases in which naloxone is not effective. Pethidine is a phenylpiperidine, not a phenanthrene, and the active metabolite, norpethidine, is not reversible by naloxone. The effects of buprenorphine are only partially reversible by naloxone. In most cases of buprenorphine overdose, the dose of naloxone needs to be high and continuous due to the higher binding affinity to the  $\mu$  receptor. Naloxone is effective for fentanyl overdoses; however, fentanyl is a phenylpiperidine, and not a phenanthrene.

14.2 A 76-year-old female with renal insufficiency has severe pain secondary to a compression fracture in the lumbar spine. She reports that the pain has been uncontrolled with tramadol and it is decided to start treatment with an opioid. Which is the best opioid for this patient?

- A. Pethidine
- B. Fentanyl transdermal patch
- C. Hydrocodone/acetaminophen
- D. Morphine

Correct answer = C. Hydrocodone/acetaminophen is the best choice. It is very important to use a low dose and monitor closely for proper pain control and adverse effects. Pethidine should not be used for chronic pain, nor should it be used in a patient with renal insufficiency. The transdermal patch is not a good option, since her pain is considered acute and she is opioid naïve. Morphine is not the best choice due to the active metabolites that can accumulate in renal insufficiency.

14.3 Which statement about buprenorphine is correct?

- A. Buprenorphine has a much higher incidence of opioid-induced respiratory depression compared to other  $\mu$  agonists.
- B. Buprenorphine has many dosage formulations and all formulations can be prescribed for the treatment of pain or opioid dependence.
- C. Buprenorphine has a lower number of drug-drug interactions compared to methadone.
- D. Buprenorphine is a full  $\mu$  agonist, an antagonist of the NMDA receptor, and a norepinephrine and serotonin reuptake inhibitor.

Correct answer = C. Buprenorphine is metabolized by the CYP3A4 system, so there are concerns about drug interactions; however, compared to methadone which is metabolized by numerous CYP450 enzymes, the drug interaction concern for buprenorphine is much lower. Buprenorphine has a lower incidence of opioid-induced respiratory depression compared to the  $\mu$  agonists due to the ceiling effect created by the partial  $\mu$  agonist activity. Buprenorphine is available in many different dosage formulations but these formulations are indicated for either pain management or medication-assisted treatment of opioid dependence, not both. Option D describes the mechanism of action for methadone. Buprenorphine is a potent partial  $\mu$  agonist and a  $\kappa$  antagonist.

14.4 A 56-year-old patient has suffered with painful diabetic neuropathy and severe chronic back pain with radiculopathy secondary to spinal stenosis for many years. This patient has failed to receive relief from his neuropathic pain with first-line agents such as tricyclics, SNRIs, or anticonvulsants. Based on the mechanism of action, which opioid could be considered in this patient to treat both nociceptive and neuropathic pain?

- A. Pethidine
- B. Oxymorphone
- C. Morphine
- D. Tapentadol

Correct answer = D. Tapentadol has a unique mechanism of action in comparison to the other choices given. Tapentadol has a dual mechanism of action ( $\mu$  agonist and norepinephrine reuptake inhibition) which has been shown to effectively treat neuropathic pain associated with diabetic peripheral neuropathy. All other  $\mu$  agonists could help manage neuropathic pain, but in some situations, higher doses of opioids are needed to achieve efficacy.

14.5 Which of the following statements regarding methadone is correct?

- A. Methadone is an excellent choice for analgesia in most patients because there are limited drug-drug interactions.
- B. The equianalgesic potency of methadone is similar to that of morphine.
- C. The duration of analgesia for methadone is much shorter than the elimination half-life.
- D. The active metabolites of methadone accumulate in patients with renal dysfunction.

Correct answer = C. The duration of analgesia is much shorter than the elimination half-life, leading to dangers of accumulation and increased potential for respiratory depression and death. The equianalgesic potency of methadone is extremely variable based on many factors, and only providers familiar with methadone should prescribe this agent. The drug interactions associated with methadone are numerous due to the multiple liver enzymes that metabolize the drug. Methadone does not have active metabolites, which makes it a treatment option in patients with renal dysfunction.

14.6 AN is a 57-year-old man who has been treated with oxycodone for chronic nonmalignant pain for over 2 years. He now reports increased pain in the afternoon while at work. Which of the following is a short-acting opioid and is the best choice for this patient's breakthrough pain?

- A. Methadone
- B. Fentanyl
- C. Hydrocodone
- D. Nalbuphine

14.7 A 64-year-old man is preparing for a total knee replacement. He is taking many medications that are metabolized by the CYP450 enzyme system and is worried about drug interactions with the pain medication that will be used following surgery. Which of the following opioids would have the lowest chance of drug interactions in this patient?

- A. Methadone
- B. Tapentadol
- C. Tramadol
- D. Oxycodone

14.8 Which of the following statements regarding adverse effects of opioid therapy is correct?

- A. The risk of respiratory depression is highest during an initial opioid initiation or following a dose increase.
- B. Opioid-induced constipation is only seen with the initiation of opioid therapy.
- C. The incidence of nausea and sedation increases with long-term use of opioid therapy.
- D. Decreased testosterone levels are commonly seen with short-term use of opioid therapy.

14.9 KM is a 64-year-old man who has been hospitalized following a car accident in which he sustained a broken leg and broken arm. He has been converted to oral morphine in anticipation of discharge from the hospital. Upon discharge, which medication should he receive along with the morphine?

- A. Diphenhydramine
- B. Methylphenidate
- C. Senna
- D. Docusate sodium

Correct answer = C. Hydrocodone is a commonly used short-acting agent that is commercially available in combination with either acetaminophen or ibuprofen. Methadone should not routinely be used for breakthrough pain due to the unique pharmacokinetics and should be reserved for practitioners who have experience with this agent and understand the variables associated with this drug. Fentanyl is available in formulations for treatment of breakthrough pain for cancer treatment. It is not appropriate to use fentanyl in this type of chronic pain setting. Nalbuphine is a mixed agonist/antagonist analgesic that could precipitate withdrawal in patients who are currently taking a full  $\mu$  agonist such as oxycodone.

Correct answer = B. Tapentadol is metabolized via glucuronidation and has not been shown to have any clinically relevant drug interactions associated with the CYP450 enzyme family. All other opioids listed are metabolized by one or more CYP450 enzymes and increase the risk of drug interactions.

Correct answer = A. The risk of respiratory depression is highest when the opioid is first initiated or a dosage is raised (or sometimes a drug-drug interaction that leads to higher opioid levels). Opioid-induced constipation can occur at any time during the therapy, and a patient does not develop a tolerance to this side effect. Side effects such as nausea and sedation commonly decrease after repeated dosing due to development of tolerance to these adverse effects. Chronic opioid exposure has been linked to decreased testosterone levels in males.

Correct answer = C. A bowel regimen should be prescribed with the initiation of the opioid since constipation is very common, can occur at any time, and tolerance to this adverse effect does not occur. Senna is a stimulant that is available over-the-counter. Docusate sodium is a stool softener which is ineffective in opioid-induced constipation when used as a single agent. Combination products which include both docusate and senna are commonly used and can be effective, mainly due to the actions of senna. Diphenhydramine can be used for urticaria that might occur with the initiation of an opioid, and methylphenidate has been used for opioid-induced sedation in certain situations, but these issues are not reported in this case.

14.10 AN is a 67-year-old man who has been treated with oxycodone for chronic nonmalignant pain with no changes in the dosing regimen for over 2 years. His pain has been fairly well controlled, and he remains active, reports satisfaction with his pain regimen, and denies any side effects. He has been recently diagnosed with COPD and obstructive sleep apnea (OSA). Which of the following options is the BEST treatment recommendation for him at this time?

- A. Taper off all opioids due to increased risk of opioid-induced respiratory depression.
- B. Prescribe naloxone nasal spray to have at home in case he experiences an opioid overdose.
- C. Prescribe oral naloxone tablets to have at home in case he experiences an opioid overdose.
- D. No action needed at this time. His pain is well controlled, and he is reporting no side effects.

Correct answer = B. Because this patient has just been diagnosed with COPD and OSA, it is clear his risk for opioid-induced respiratory depression is greater. Since the pain is controlled and no side effects are reported, tapering off the opioids at this time is not the best answer. Because of the first-pass effect, naloxone is not clinically effective for management of an overdose when given orally. Therefore, the nasal spray is the best choice. Offering the at-home naloxone nasal spray, along with proper education, might be life-saving if an overdose occurs. Providing proper education to the patient and caregivers on the importance of having the naloxone nasal spray at home and of calling emergency services is critical in case of an overdose situation.



# CNS Stimulants

Jose A. Rey

15

## I. OVERVIEW

Psychomotor stimulants and hallucinogens are two groups of drugs that act primarily to stimulate the central nervous system (CNS). The psychomotor stimulants cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity. The hallucinogens produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord. As a group, the CNS stimulants have diverse clinical uses and are also potential drugs of abuse, as are the CNS depressants (see Chapter 10) and the opioids (see Chapter 14). **Figure 15.1** summarizes the CNS stimulants.

## II. PSYCHOMOTOR STIMULANTS

### A. Methylxanthines

The methylxanthines include *theophylline* [thee-OFF-i-lin], which is found in tea; *theobromine* [thee-oh-BROE-meen], found in cocoa; and *caffeine* [kaf-EEN]. *Caffeine*, the most widely consumed stimulant in the world, is found in highest concentration in certain coffee products (for example, espresso), but it is also in the liver to inert substances present in tea, cola drinks, energy drinks, chocolate candy, and cocoa.

**1. Mechanism of action:** Several mechanisms have been proposed for the actions of methylxanthines, including translocation of extracellular calcium, increase in cyclic adenosine monophosphate and cyclic guanosine monophosphate caused by inhibition of phosphodiesterase, and blockade of adenosine receptors.

#### 2. Actions:

a. **CNS:** The *caffeine* contained in one to two cups of coffee (100 to 200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain. Consumption of 1.5 g of *caffeine* (12 to 15 cups of coffee) produces anxiety and tremors. The spinal cord is stimulated only by very high doses (2 to 5 g) of *caffeine*. Tolerance can rapidly develop to the stimulating properties of *caffeine*, and withdrawal consists of feelings of fatigue and sedation.

b. **Cardiovascular system:** A high dose of *caffeine* has positive inotropic and chronotropic effects on the heart. [Note: Increased contractility can be harmful to patients with angina pectoris. In others, an accelerated heart rate can trigger premature ventricular contractions.]

### PSYCHOMOTOR STIMULANTS

Methylxanthines

*Caffeine*

*Theophylline*

Nicotine

Varenicline

Cocaine

Amphetamine

*Methamphetamine*

*Dextroamphetamine*

*Lisdexamfetamine*

Methylphenidate or mixed amphetamine salts

*Methylphenidate*

*Dexmethylphenidate*

*Modafinil*

*Armodafinil*

Selective norepinephrine (noradrenaline) reuptake inhibitor

Atomoxetine

Hallucinogens

Lysergic acid diethylamide (LSD)

Tetrahydrocannabinol (Marijuana)

### Figure 15.1

Summary of central nervous system (CNS) stimulants. (For drug dosages, refer to Appendix at the end of the book.)

- c. **Diuretic action:** Caffeine has a mild diuretic action that increases urinary output of sodium, chloride, and potassium.
  - d. **Gastric mucosa:** Because methylxanthines stimulate secretion of gastric acid, individuals with peptic ulcers should avoid foods and beverages containing methylxanthines.
3. **Therapeutic uses:** Caffeine and its derivatives relax the smooth muscles of the bronchioles. *Theophylline* has been largely replaced by other agents, such as  $\beta_2$  agonists and corticosteroids for the treatment of asthma (see Chapter 41). Caffeine is also used in combination with the analgesics *acetaminophen* and *aspirin* for the management of headaches in both prescription and over-the-counter products.
  4. **Pharmacokinetics:** The methylxanthines are well absorbed orally. Caffeine distributes throughout the body, including the brain. These drugs cross the placenta to the fetus and are secreted into the breast milk. All methylxanthines are metabolized in the liver, generally by the CYP1A2 pathway, and the metabolites are excreted in the urine.
  5. **Adverse effects:** Moderate doses of *caffeine* cause insomnia, anxiety, and agitation. A high dosage is required for toxicity, which is manifested by emesis and convulsions. The lethal dose is 10 g of *caffeine* (about 100 cups of coffee), which induces cardiac arrhythmias. Lethargy, irritability, and headache occur in users who routinely consume more than 600 mg of *caffeine* per day (roughly six cups of coffee per day) and then suddenly stop.

## B. Nicotine

*Nicotine* [NIK-o-teen] is the active ingredient in tobacco. Although this drug is not currently used therapeutically (except in smoking cessation therapy), *nicotine* remains important because it is second only to *caffeine* as the most widely used CNS stimulant, and it is second only to alcohol as the most abused drug. The composition of tobacco smoke is complex (approximately 500 compounds have been identified) and varies with the type of tobacco and the way it is smoked (cigar, cigarettes, pipe, etc.). The principal components of tobacco smoke are tar and nicotine. In combination with the tars and carbon monoxide found in cigarette smoke, *nicotine* represents a serious risk factor for lung and cardiovascular disease, and other illnesses. *Nicotine* possesses all the characteristics of a drug of dependence and thus a person faces difficulty in quitting smoking. Smoking gives immediate satisfaction due to nicotine and tar which provide flavor. The initial social driver for smoking is psychosocial despite pharmacodynamic effects are unpleasant initially. However, with repeated use the subject learns and adjusts the limit of nicotine intake, tolerance develops to adverse effects, and he/she starts feeling the pleasant effects of nicotine.

The acute effects of smoking tobacco include increased reflex airways resistance, depressed ciliary activity after transient stimulation, and absorption of carbon monoxide, especially in the presence of coronary heart disease.

The adverse effects of chronic smoking include chronic mucus hypersecretion causing persistent cough with sputum and chronic obstructive lung disease, a progressive and largely irreversible condition leading to disability and death.

The risk of smokers developing cancer of lungs is 20-fold higher and that of mouth, throat, and esophagus is 5 to 10 times higher than nonsmokers. The risk of death from lung cancer is related to the number of cigarettes smoked and the period of smoking.

Coronary heart disease (CHD) is a leading cause of death in cigarette smokers. Smoking is particularly dangerous in people with other risk factors (high blood cholesterol and high blood pressure). Smoking cessation reduces the risk of CHD in people below the age of 65 years and after about 4 years of abstinence, the risk approximates to the nonsmokers. Women who smoke are liable to infertility and early menopause than nonsmokers. The risk of complications during pregnancy (spontaneous abortion, stillbirth, and neonatal death) and placental abnormalities is higher, and babies born to women who smoke have lower birth weight and are at an increased risk of perinatal death; however, those who quit smoking in the first 20 weeks of pregnancy have babies with birth weight similar to nonsmokers.

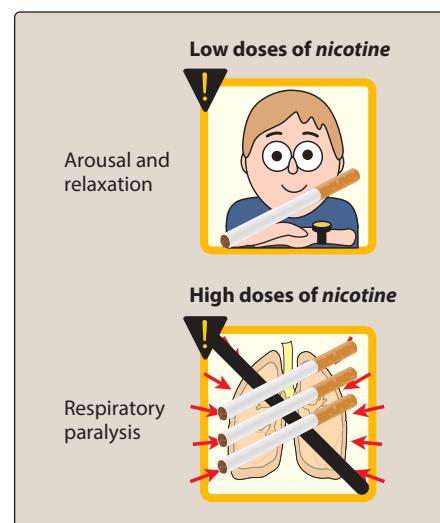
Many nonsmokers are exposed to tobacco smoke and environmental tobacco smoke, referred to as passive (involuntary) smoking. The risk of lung cancer in passive smoking though small still achieves significance considering the large number of people who get affected. The composition of the sidestream smoke is different from that of the mainstream smoke inhaled by the smokers. Many of the substances, such as *nicotine*, carbon monoxide, ammonia, and some carcinogens, are found in greater concentration in undiluted sidestream smoke. Sidestream smoke constitutes around 85% of smoke generated in an average room during cigarette smoking.

**1. Mechanism of action:** In low doses, *nicotine* causes ganglionic stimulation by depolarization. At high doses, *nicotine* causes ganglionic blockade. *Nicotine* receptors exist at a number of sites in the CNS, which participate in the stimulant attributes of the drug including vomiting center, both directly and via chemoreceptors in the carotid body

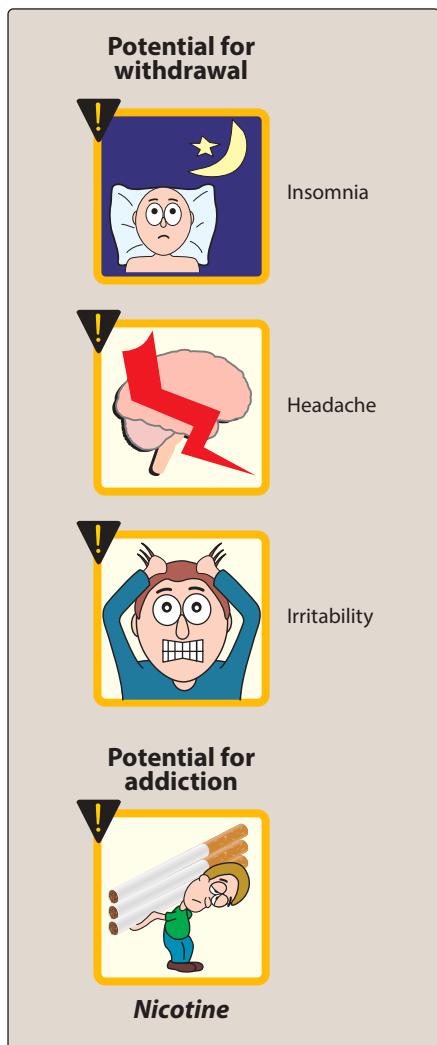
**2. Actions:**

a. **CNS:** *Nicotine* is highly lipid soluble and readily crosses the blood-brain barrier. It causes release of catecholamines and serotonin in the CNS and also antidiuretic hormone, corticotrophin, and growth hormone. Cigarette smoking or administration of low doses of *nicotine* produces some degree of euphoria and arousal, as well as relaxation. It improves attention, learning, problem solving, and reaction time. High doses of *nicotine* result in central respiratory paralysis and severe hypotension caused by medullary paralysis (Figure 15.2). *Nicotine* is also an appetite suppressant.

b. **Peripheral effects:** The peripheral effects of *nicotine* are complex. Stimulation of sympathetic ganglia as well as of the adrenal medulla increases blood pressure and heart rate. Thus, use of tobacco is particularly harmful in hypertensive patients. Many patients with peripheral vascular disease experience an exacerbation of symptoms with smoking. In addition, *nicotine*-induced vasoconstriction can decrease coronary blood flow, adversely affecting a patient with angina. Stimulation of parasympathetic ganglia also increases motor activity of the bowel. At higher doses, blood pressure falls



**Figure 15.2**  
Actions of *nicotine* on the CNS.



**Figure 15.3**

Nicotine has potential for addiction and withdrawal.

and activity ceases in both the gastrointestinal (GI) tract and bladder musculature as a result of a *nicotine*-induced block of parasympathetic ganglia. *Nicotine* increases the metabolic rate due to increase in autonomic sympathetic activity during light exercise such as household tasks or occupational tasks. Weight gain is seen on quitting smoking.

3. **Pharmacokinetics:** Because *nicotine* is highly lipid soluble, absorption readily occurs via the oral mucosa, lungs, GI mucosa, and skin. *Nicotine* crosses the placental membrane and is secreted in the breast milk. By inhaling tobacco smoke, the average smoker takes in 1 to 2 mg of *nicotine* per cigarette although much depends on the amount and depth of inhalation and on the duration of end-inspiratory breath holding by the subject. The acute lethal dose is 60 mg. More than 90% of the *nicotine* inhaled in smoke is absorbed. *Nicotine* is largely metabolized in the lung and the liver to inert substances such as cotinine, however, some is excreted unchanged in the urine. *Nicotine* has a half-life of 2 hours whereas *cotinine* has a half-life of 20 hours. *Cotinine* in urine is used as a marker for *nicotine* intake to indicate if a subject on abstinence program is still actively using tobacco. Tolerance develops rapidly to some of the initial unpleasant effects such as nausea and vomiting of *nicotine* when taken repeatedly over a few hours.
4. **Adverse effects:** The CNS effects of *nicotine* include irritability and tremors. *Nicotine* may also cause intestinal cramps, diarrhea, and increased heart rate and blood pressure. In addition, cigarette smoking increases the rate of metabolism for a number of drugs such as estrogens, *theophylline*, and *warfarin*.
5. **Withdrawal syndrome:** As with the other drugs in this class, *nicotine* is an addictive substance, and physical dependence develops rapidly and can be severe (Figure 15.3). Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia. Appetite is affected, and GI upset often occurs.
6. **Aids to quitting smoking:** The addictive effects of tobacco smoking are mainly due to *nicotine*; therefore, *nicotine* is substituted for tobacco smoke as a pharmacological aid to quitting. The transdermal patch and chewing gum containing *nicotine* have been shown to reduce *nicotine* withdrawal symptoms and to help smokers stop smoking. For example, the blood concentration of *nicotine* obtained from *nicotine* chewing gum is typically about one-half the peak level observed with smoking (Figure 15.4). Other forms of *nicotine* replacement used for smoking cessation include the inhaler, nasal spray, and lozenges. *Bupropion*, an antidepressant (see Chapter 10), can reduce the craving for cigarettes, assist in smoking cessation, and attenuate symptoms of withdrawal.

### C. Varenicline

*Varenicline* [ver-EN-ih-kleen] is a partial agonist at neuronal nicotinic acetylcholine receptors in the CNS. Because *varenicline* is only a partial agonist at these receptors, it produces less euphoric effects than *nicotine* (*nicotine* is a full agonist). Thus, it is useful as an adjunct in the management of smoking cessation in patients with *nicotine* withdrawal symptoms. Patients taking *varenicline* should be monitored for suicidal thoughts, vivid nightmares, and mood changes.

## D. Cocaine

*Cocaine* [koe-KANE] is a widely available and highly addictive drug. Because of its abuse potential, *cocaine* is classified as a Schedule II drug by the U.S. Drug Enforcement Agency. The primary mechanism of action underlying the effects of *cocaine* is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals. This potentiates and prolongs the CNS and peripheral actions of these monoamines. In particular, the prolongation of dopaminergic effects in the brain's pleasure system (limbic system) produces the intense euphoria that *cocaine* initially causes. Chronic intake of *cocaine* depletes dopamine. This depletion triggers craving for *cocaine* (Figure 15.5). A full description of *cocaine* and its effects is provided in Chapter 48.

## E. Amphetamine

*Amphetamine* [am-FET-a-meen] is a sympathetic amine that shows neurologic and clinical effects similar to those of *cocaine*. *Dextroamphetamine* [dex-troe-am-FET-a-meen] is the major member of this class of compounds. *Methamphetamine* [meth-am-FET-a-meen] (also known as "speed") is a derivative of *amphetamine* available for prescription use. *3,4-Methylenedioxymethamphetamine* (also known as MDMA, or ecstasy) is a synthetic derivative of *methamphetamine* with both stimulant and hallucinogenic properties (see Chapter 48).

**1. Mechanism of action:** As with *cocaine*, the effects of *amphetamine* on the CNS and peripheral nervous system are indirect. That is, both depend upon an elevation of the level of catecholamine neurotransmitters in synaptic spaces. *Amphetamine*, however, achieves this effect by releasing intracellular stores of catecholamines (Figure 15.6). Because *amphetamine* also inhibits monoamine oxidase (MAO) and is a weak reuptake transport inhibitor, high levels of catecholamines are present in synaptic spaces. Despite different mechanisms of action, the behavioral effects of *amphetamine* and its derivatives are similar to those of *cocaine*.

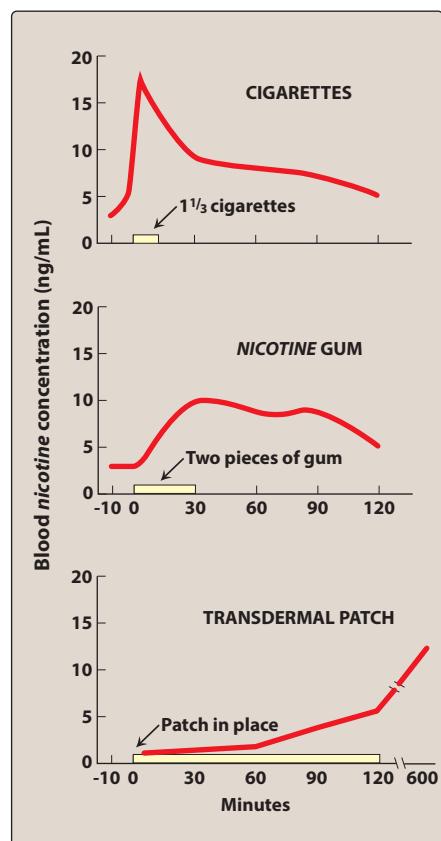
**2. Actions:**

a. **CNS:** The major behavioral effects of *amphetamine* result from a combination of its dopamine and norepinephrine release-enhancing properties. *Amphetamine* stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia. The CNS stimulant effects of *amphetamine* and its derivatives have led to their use in the treatment of hyperactivity in children, narcolepsy, and obesity. At high doses, psychosis and convulsions may occur.

b. **Sympathetic nervous system:** In addition to marked action on the CNS, *amphetamine* acts on the adrenergic system, indirectly stimulating the receptors through norepinephrine release.

3. **Therapeutic uses:** Factors that limit the therapeutic usefulness of *amphetamine* include psychological and physiologic dependence.

a. **Attention deficit hyperactivity disorder (ADHD):** Some children are hyperkinetic and lack the ability to be involved in any activity for longer than a few minutes. *Dextroamphetamine*, *methamphetamine*, the *mixed amphetamine salts*, and



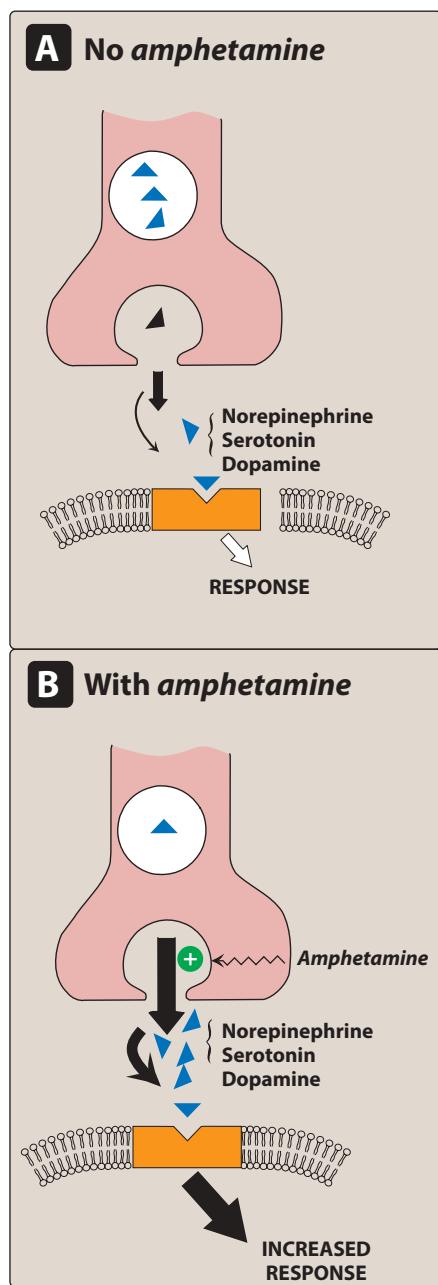
**Figure 15.4**

Blood concentrations of *nicotine* in individuals who smoked cigarettes, chewed *nicotine* gum, or received *nicotine* by transdermal patch. Modified from N. L. Benowitz, Science 319: 1318 (1988).



**Figure 15.5**

*Cocaine* and *amphetamine* have potential for addiction. Modified from B. J. Materson, Drug Therapy 157 (1985).

**Figure 15.6**Mechanism of action of *amphetamine*.

*methylphenidate* [meth-ill-FEN-ih-date] help improve attention span and alleviate many of the behavioral problems associated with this syndrome, in addition to reducing hyperkinesia. *Lisdexamfetamine* [lis-dex-am-FET-a-meen] is a prodrug that is converted to L-lysine and the active component *dextroamphetamine* through the hydrolytic actions of red blood cells. *Atomoxetine* [AT-oh-MOX-ih-teen] is a nonstimulant drug approved for ADHD in children and adults. Unlike *methylphenidate*, which blocks dopamine reuptake more than norepinephrine reuptake, *atomoxetine* is more selective for inhibition of norepinephrine reuptake. Therefore, it is not considered habit forming and is not a controlled substance.

- b. Narcolepsy:** Narcolepsy is a relatively rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day. The sleepiness can be treated with drugs, such as the *mixed amphetamine salts* or *methylphenidate*. *Modafinil* [moe-DA-fi-nil] and its R-enantiomer derivative, *armodafinil* [ar-moe-DA-fi-nil], are considered first-line agents for the treatment of narcolepsy. *Modafinil* promotes wakefulness, but it produces less psychoactive and euphoric effects and fewer alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. The mechanism of action remains unclear, but may involve the adrenergic and dopaminergic systems. *Modafinil* is well distributed throughout the body and undergoes elimination via hepatic metabolism and excretion in the urine. Headaches, nausea, and nervousness are the primary adverse effects. *Modafinil* and *armodafinil* may have some potential for abuse and physical dependence, and both are classified as controlled substances. *Armodafinil* is a congener of *modafinil* approved for the treatment of patients with obstructive sleep apnea. Similar to *modafinil*, it also increases the wakefulness and is useful for the treatment of narcolepsy.
- c. Appetite suppression:** *Phentermine* [FEN-ter-meen] and *diethylpropion* [dye-eth-ill-PROE-pee-on] are sympathomimetic amines that are related structurally to *amphetamine*. These agents are used for appetite suppressant effects in the management of obesity (see Chapter 39).
- 4. Pharmacokinetics:** *Amphetamine* is completely absorbed from the GI tract, metabolized by the liver, and excreted in the urine. [Note: Administration of urinary alkalinizing agents such as *sodium bicarbonate* increases the nonionized species of the drug and enhances the reabsorption of *dextroamphetamine* from the renal tubules into the bloodstream.] *Amphetamine* abusers often administer the drug by IV injection and/or by smoking. The euphoria caused by *amphetamine* lasts 4 to 6 hours, or four- to eight-folds longer than the effects of *cocaine*.
- 5. Adverse effects:** The *amphetamines* may cause addiction, leading to dependence, tolerance, and drug-seeking behavior. In addition, they have the following undesirable effects:
  - a. CNS effects:** Adverse effects of *amphetamine* usage include insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes (Figure 15.7). *Amphetamine* can also

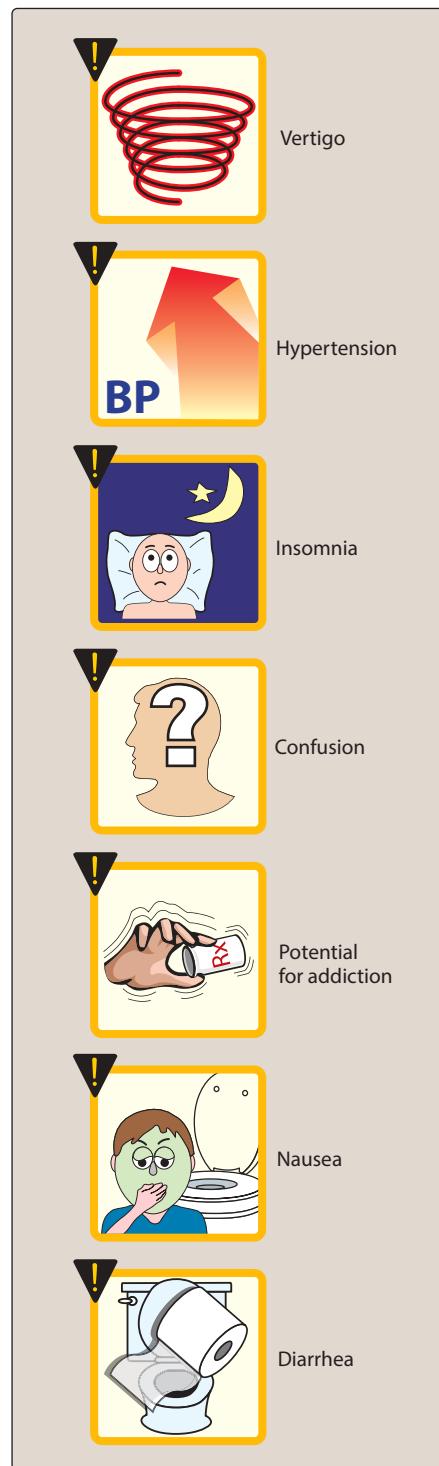
cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients. [Note: Benzodiazepines, such as *lorazepam*, are often used in the management of agitation and CNS stimulation secondary to *amphetamine* overdose.] Chronic *amphetamine* use produces a state of “*amphetamine psychosis*” that resembles the psychotic episodes associated with schizophrenia. Whereas long-term *amphetamine* use is associated with psychological and physical dependence, tolerance to its effects may occur within a few weeks. The anorectic effect of *amphetamine* is due to action in the lateral hypothalamic feeding center.

- b. **Cardiovascular effects:** In addition to CNS effects, *amphetamine* may cause palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse. Headache, chills, and excessive sweating may also occur.
- c. **Gastrointestinal system effects:** *Amphetamine* acts on the GI system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea.
- d. **Contraindications:** Patients with hypertension, cardiovascular disease, hyperthyroidism, glaucoma, or a history of drug abuse or those taking MAO inhibitors should not be treated with *amphetamine*.

## F. Methylphenidate

*Methylphenidate* has CNS stimulant properties similar to those of *amphetamine* and is often used in the treatment of ADHD. *Methylphenidate* has abuse potential and is a Schedule II controlled substance. The pharmacologically active isomer, *dexamethylphenidate*, is also a Schedule II drug used for the treatment of ADHD.

- 1. **Mechanism of action:** Children with ADHD may produce weak dopamine signals, which suggests that once-interesting activities provide fewer rewards to these children. *Methylphenidate* is a dopamine and norepinephrine transport inhibitor and may act by increasing both dopamine and norepinephrine in the synaptic cleft.
- 2. **Therapeutic uses:** *Methylphenidate* is used in the treatment of ADHD. It is also effective in the treatment of narcolepsy. Unlike *methylphenidate*, *dexamethylphenidate* is not indicated in the treatment of narcolepsy.
- 3. **Pharmacokinetics:** Both *methylphenidate* and *dexamethylphenidate* are readily absorbed after oral administration. *Methylphenidate* is available in extended-release oral formulations and as a transdermal patch for once-daily application. The de-esterified product, ritalinic acid, is excreted in urine.
- 4. **Adverse effects:** GI adverse effects are the most common and include abdominal pain and nausea. Other reactions include anorexia, insomnia, nervousness, and fever. In patients with epilepsy, *methylphenidate* may increase seizure frequency. The drug is contraindicated in patients with glaucoma. *Methylphenidate* can inhibit the metabolism of *warfarin*, *phenytoin*, *phenobarbital*, *primidone*, and the tricyclic antidepressants.



**Figure 15.7**

Adverse effects of amphetamines and *methylphenidate*.

### III. HALLUCINOGENS

A few drugs have, as their primary action, the ability to induce altered perceptual states reminiscent of dreams. Many of these altered states are accompanied by visions of bright, colorful changes in the environment and by a plasticity of constantly changing shapes and color. The individual under the influence of these drugs is incapable of normal decision making because the drug interferes with rational thought. These compounds are known as hallucinogens, and *lysergic acid diethylamide (LSD)* and *tetrahydrocannabinol* (from marijuana) are examples of agents in this class. These agents are discussed in detail in Chapter 48.

### Study Questions

Choose the ONE best answer.

15.1 A young male was brought to the emergency room by the police due to severe agitation. Psychiatric examination revealed that he had injected dextroamphetamine several times in the past few days. The last use was 10 hours prior. He was given an intramuscular drug that sedated him, and he fell asleep. Which drug was most likely used to counter this patient's symptoms of dextroamphetamine withdrawal?

- A. Trazodone
- B. Lorazepam
- C. Cocaine
- D. Hydroxyzine

15.2 A 10-year-old boy is sent to a pediatric neurologist for an evaluation due to poor performance and inability to pay attention in school. He has also been fighting with other children. He is given a diagnosis of ADHD with impulsivity and irritability. Which is most appropriate for management of the ADHD?

- A. Clonidine
- B. Mirtazapine
- C. Dextroamphetamine
- D. Haloperidol

15.3 A 10-year-old boy with ADHD has symptoms which are controlled with an oral psychostimulant. However, he and his family wish to avoid having to give a second dose of medication at school. They prefer an alternative treatment that can be administered in the morning and last the entire day. Which treatment option is best?

- A. Mixed amphetamine salts in immediate-release oral tablet formulation
- B. Methylphenidate in a transdermal delivery system
- C. Nicotine in a chewing gum formulation for buccal absorption
- D. Methylphenidate in immediate-release pills

Correct answer = B. The anxiolytic properties of benzodiazepines, such as lorazepam, make them the drugs of choice in treating the anxiety and agitation of amphetamine or cocaine abuse. Lorazepam also has hypnotic properties. Trazodone has hypnotic properties, but its anxiolytic properties are inferior to those of the benzodiazepines. Hydroxyzine, an antihistamine, is effective as a hypnotic, and it is sometimes used to deal with anxiety, especially if emesis is a problem, but rarely used in the emergency situation when rapid anxiolytic and antiseizure treatment is warranted.

Correct answer = C. Dextroamphetamine is the only stimulant medication in the list that is approved for ADHD. Symptoms like fighting may improve with haloperidol, and hyperactivity may improve with clonidine, but these agents would not improve the patient's academic performance and the underlying problems

Correct answer = B. Methylphenidate is also a psychostimulant, and the transdermal (patch) formulation is designed for once-daily use to avoid mid-day dosing. Immediate-release formulations require dosing at least twice daily.

- 15.4 Which of the following agents for ADHD is a controlled substance (Schedule II)?
- A. Clonidine
  - B. Atomoxetine
  - C. Lisdexamfetamine
  - D. Desipramine
- 15.5 Amphetamines may be used in patients with which of the following conditions?
- A. Cardiovascular disease
  - B. Hypertension
  - C. Hyperthyroidism
  - D. Obesity
- 15.6 Which of the following agents is considered a first-line treatment for narcolepsy?
- A. Galantamine
  - B. Atomoxetine
  - C. Temazepam
  - D. Modafinil
- 15.7 Which of the following is a common adverse effect of amphetamines?
- A. Bradycardia
  - B. Somnolence
  - C. Constipation
  - D. Hypertension
- 15.8 Which of the following CNS stimulants occurs naturally and can be found in certain candies?
- A. Amphetamine
  - B. Modafinil
  - C. Caffeine
  - D. Atomoxetine
- 15.9 A 35-year-old man is interested in quitting smoking. In previous quit attempts, he has tried nicotine gum, the nicotine patch, and the “cold turkey” method. He has been unsuccessful in each of these attempts and resumed smoking within 4 to 6 weeks. Which may be useful to assist in his attempt to quit smoking?
- A. Varenicline
  - B. Dextroamphetamine
  - C. Lorazepam
  - D. Methylphenidate
- 15.10 Which of the following agents carries the lowest risk for addiction?
- A. Armodafinil
  - B. Lisdexamfetamine
  - C. Dexmethylphenidate
  - D. Varenicline

Correct answer = C. Lisdexamfetamine is the only controlled substance on the list and is schedule II. The other agents may assist in the management of ADHD but are not controlled substances.

Correct answer= D. The use of amphetamines in the management of obesity should be closely monitored. Amphetamine analogs such as phentermine are approved for obesity. The other conditions are contraindications when considering the use of amphetamines.

Correct answer = D. Modafinil is the only drug listed that is approved for narcolepsy. Temazepam is indicated for insomnia, galantamine for Alzheimer's disease, and atomoxetine for ADHD.

Correct answer = D. Hypertension is a possible adverse effect that warrants caution, especially in individuals with risk factors for increased blood pressure. Amphetamines cause tachycardia (not bradycardia), insomnia (not somnolence), and diarrhea (not constipation).

Correct answer = C. Caffeine is a naturally occurring substance found in cocoa, chocolate, and many forms of tea. Overuse of cola beverages and other caffeine-containing products may cause adverse effects, including anxiety and insomnia, and even increase the risk for seizures.

Correct answer = A. Varenicline is approved as an adjunctive treatment option for the management of nicotine dependence. It is believed to attenuate the withdrawal symptoms of smoking cessation, though monitoring is needed for changes in psychiatric status, including suicidal ideation. The use of dextroamphetamine, lorazepam, and methylphenidate bring the risk of addiction to another substance with abuse potential.

Correct answer = D. Varenicline is the only agent listed that is not a controlled substance. All of the other agents are considered to have a risk for addiction and/or dependence.



## UNIT IV

# Drugs Affecting the Cardiovascular System

# Antihypertensives

Benjamin Gross

# 16

## I. OVERVIEW

Blood pressure is elevated when systolic blood pressure exceeds 120 mm Hg and diastolic blood pressure remains below 80 mm Hg. Hypertension occurs when resting systolic blood pressure exceeds 130 mm Hg or diastolic blood pressure exceeds 80 mm Hg. Hypertension results from increased peripheral vascular arteriolar smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system. In most cases, the cause of the increased vascular tone is unknown. Elevated blood pressure is a common disorder, affecting approximately 30% of adults. Although many patients have no symptoms, chronic hypertension can lead to heart disease and stroke, the top two causes of death in the world. Hypertension is also an important risk factor in the development of chronic kidney disease and heart failure. Before labeling any individual with hypertension, the blood pressure of the patient should be measured on more than two occasions and he/she should have been resting for at least 5 minutes and should not have consumed coffee or smoked during the last 30 minutes. Out-of-office and self-monitoring of BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with lifestyle modification strategies. The risk of organ damage is directly related to the extent of elevation of blood pressure. Even mild hypertension (140/90) has been reported to increase the risk of end-organ damage and it gets double with increment of 20/10 mmHg. Similarly, small reductions in BP result in substantial reductions in the relative risks of complications. The risks involved with the hypertension increase in proportion to the magnitude of elevation of blood pressure. The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed early and is properly treated. The drugs used in the treatment

DRUG CLASS	NAME OF THE DRUG	USUAL DAILY DOSE RANGE (mg)
Diuretics	<i>Hydrochlorothiazide</i> <i>Indapamide</i> <i>Chlorthalidone</i> <i>Metolazone</i> <i>Triamterene</i> <i>Amiloride</i> <i>Furosemide</i> <i>Torsemide</i> <i>Bumetanide</i>	12.5–50 1.25–5 25–50 2.5–5 100–300 5–10 20–400 2.5–5 1–4 (or more)
β-Blockers	<i>Atenolol</i> <i>Metoprolol</i> <i>Bisoprolol</i> <i>Nadolol</i> <i>Pindolol</i> <i>Labetalol</i> <i>Propranolol</i> <sup>1</sup>	25–100 50–200 2.5–10 20–160 15–45 50–200 40–320
α-Blockers	<i>Prazocin</i> <i>Doxazocin</i>	1–16 1–16
Calcium channel blockers	<i>Amlodipine</i> <i>Felodipine</i> <i>Nifedipine</i> <sup>1</sup> <i>Verapamil</i> <sup>1</sup> <i>Diltiazem</i> <sup>1</sup>	2.5–10 2.5–10 20–80 120–480 90–240
ACE inhibitors	<i>Captopril</i> <i>Enalapril</i> <i>Lisinopril</i> <i>Ramipril</i> <i>Perindopril</i>	50–150 2.5–40 10–40 2.5–20 2–8
ARBs	<i>Losartan</i> <i>Telmisartan</i> <i>Valsartan</i> <i>Olmesartan</i>	25–100 20–80 80–320 8–16
Centrally acting	<i>Methyldopa</i> <i>Clonidine</i>	500–2000 0.1–1.2

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

<sup>1</sup>Extended release or long-acting formulations are available.

### Figure 16.1

Summary of antihypertensive drugs.

	Systolic mm Hg		Diastolic mm Hg
Normal	<120	and	<80
Elevated	120–129	or	<80
Stage 1 hypertension	130–139	or	80–89
Stage 2 hypertension	≥140	or	≥90

Figure 16.2

Classification of blood pressure.

of hypertension are shown in Figure 16.1. In recognition of the progressive nature of hypertension, hypertension is classified into four categories (Figure 16.2). The diagnosis of hypertension depends on the measurement of blood pressure and not on symptoms reported by the patients. Hypertension is usually asymptomatic until overt end-organ damage is imminent or has already occurred. The majority of current guidelines recommend treatment decisions based on the goals of the antihypertensive therapy, rather than the category of hypertension.

## II. ETIOLOGY OF HYPERTENSION

More than 90% of patients have essential hypertension (hypertension with no identifiable cause). In 10% to 15% of patients, hypertension may occur secondary to other disease processes (pheochromocytoma, Cushing's

disease, primary aldosteronism, renal artery stenosis, and coarctation of aorta). A family history of hypertension increases the likelihood that an individual will develop hypertension. The prevalence of hypertension increases with age, but decreases with education and income level. Non-Hispanic blacks have a higher incidence of hypertension than do both non-Hispanic whites and Hispanic whites. Persons with diabetes, obesity, or disability status are all more likely to have hypertension than those without these conditions. In addition, environmental factors, such as a stressful lifestyle, high dietary intake of sodium, and smoking, may further predispose an individual to hypertension. For every case, lifestyle modifications should be implemented immediately which remains the cornerstone of the management of hypertension. A healthy lifestyle decreases blood pressure, enhances antihypertensive drug efficacy, and decreases the overall cardiovascular risk. A healthy lifestyle includes weight reduction, increase in physical activity, dietary sodium reduction, limited fat intake, increased fruit and vegetable consumption, restriction on alcohol consumption, and stopping tobacco products. Ideally, these changes should be made within the first 3 months.

### III. MECHANISMS FOR CONTROLLING BLOOD PRESSURE

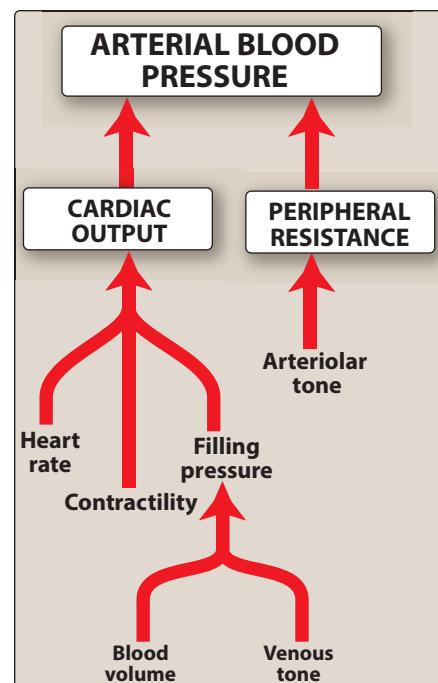
Arterial blood pressure is regulated within a narrow range to provide adequate perfusion of the tissues without causing damage to the vascular system, particularly the arterial intima (endothelium). Arterial blood pressure is directly proportional to cardiac output and peripheral vascular resistance (Figure 16.3). Cardiac output and peripheral resistance, in turn, are controlled mainly by two overlapping mechanisms: the baroreflexes and the renin–angiotensin–aldosterone system (Figure 16.4). Most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral resistance.

#### A. Baroreceptors and the sympathetic nervous system

Baroreflexes act by changing the activity of the sympathetic and parasympathetic nervous system. Therefore, they are responsible for the rapid, moment-to-moment regulation of blood pressure. A fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the aortic arch and carotid sinuses) to send fewer impulses to cardiovascular centers in the spinal cord. This prompts a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output. These changes result in a compensatory rise in blood pressure (Figure 16.4).

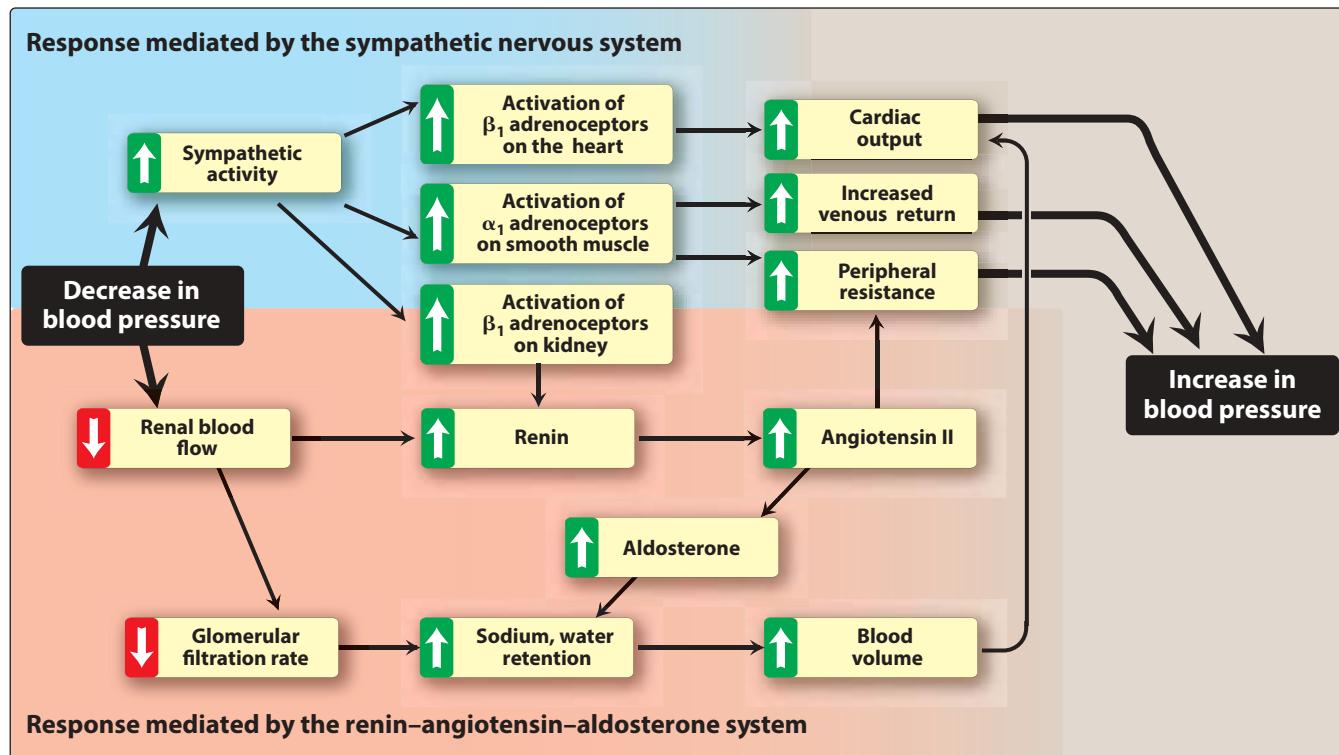
#### B. Renin–angiotensin–aldosterone system

The kidney provides long-term control of blood pressure by altering the blood volume. Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of  $\beta_1$ -adrenoceptors) by releasing the enzyme renin (Figure 16.4). Low sodium intake and greater sodium loss also increase renin release. Renin converts angiotensinogen to angiotensin I, which is converted in turn to angiotensin II, in the presence of angiotensin-converting enzyme (ACE).



**Figure 16.3**

Major factors influencing blood pressure.

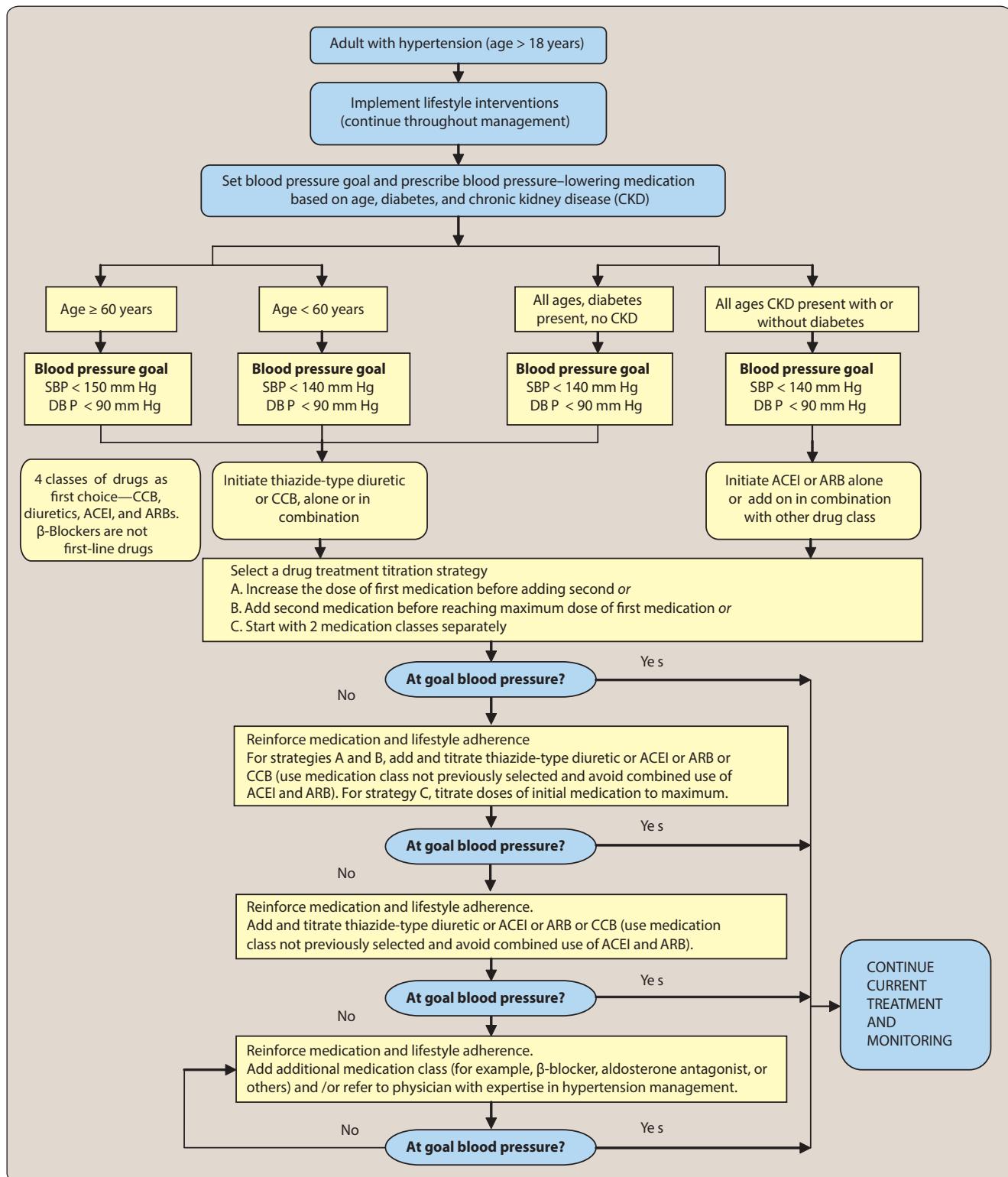
**Figure 16.4**

Response of the autonomic nervous system and the renin-angiotensin-aldosterone system to a decrease in blood pressure.

Angiotensin II is a potent circulating vasoconstrictor, constricting both arterioles and veins, resulting in an increase in blood pressure. Angiotensin II exerts a preferential vasoconstrictor action on the efferent arterioles of the renal glomerulus, increasing glomerular filtration. Furthermore, angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and increased blood volume, which contribute to a further increase in blood pressure. These effects of angiotensin II are mediated by stimulation of angiotensin II type 1 ( $AT_1$ ) receptors.

#### IV. TREATMENT STRATEGIES

The goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. Antihypertensive therapy is indicated in case of systolic blood pressure (SBP) of  $\geq 150$  mm Hg or a diastolic blood pressure (DBP) of  $\geq 90$  mm Hg for the general population at 60 years of age or older. For most patients, the blood pressure goal when treating hypertension is an SBP of less than 140 mm Hg and a DBP of less than 90 mm Hg. Current recommendations are to initiate therapy with a thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker. Each of the antihypertensive agents are roughly equally effective in lowering the BP; however, there is a wide interpatient variability as many patients respond to one drug but not to another, depending in part on patient-specific determinants such as ethnicity, age, and concomitant diseases (Figure 16.5). The amount of



ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; DBP = diastolic blood pressure; SBP = systolic blood pressure.

**Note:** If blood pressure fails to be maintained at goal, re-enter the algorithm where appropriate based on the current individual therapeutic plan.

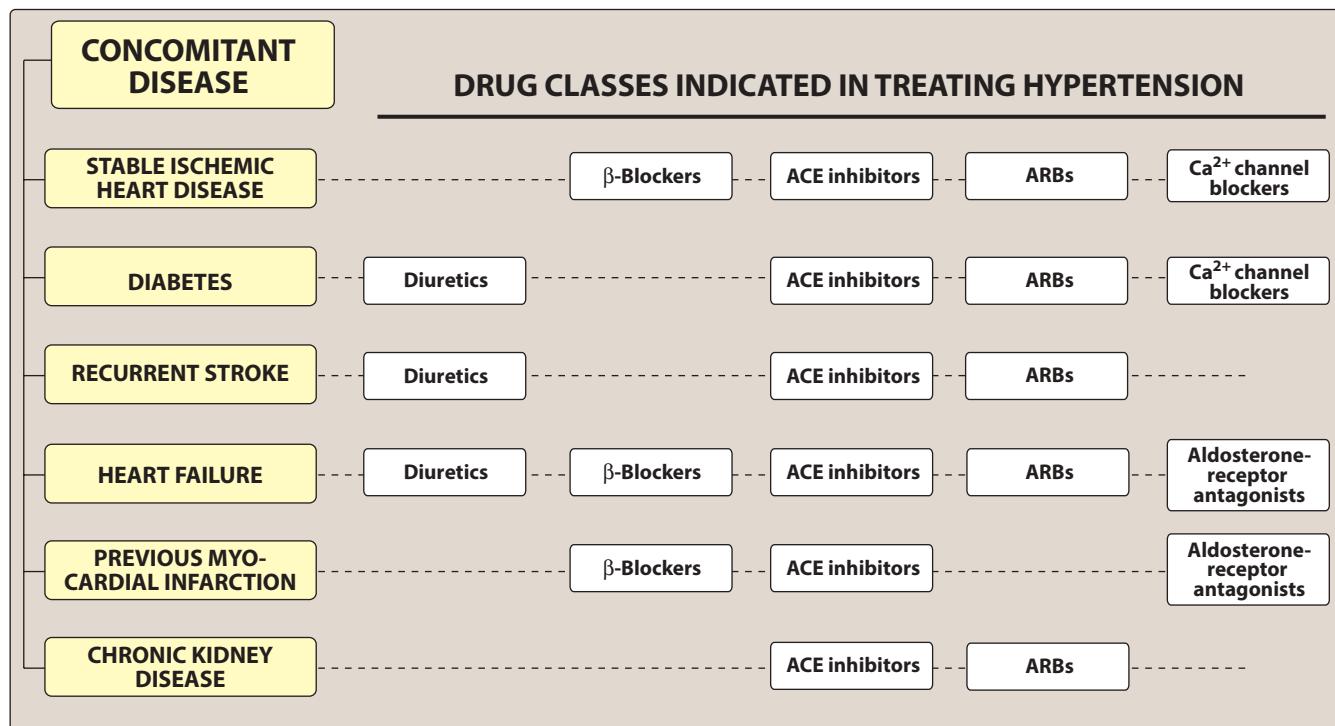
**Figure 16.5**

Algorithm for treatment of hypertension. Adapted from JNC 8 guidelines for treatment of hypertension.

BP reduction, and NOT the choice of therapy, is the major determinant of reduction in cardiovascular risk in patients with hypertension. If blood pressure is inadequately controlled after 1 month of therapy, there are two options—either to increase the dose of the initial drug to the maximum tolerable dose or to add a second drug with the selection based on minimizing the adverse effects of the combined regimen and achieving the goal blood pressure. Patients with SBP greater than 20 mm Hg above goal or DBP more than 10 mm Hg above goal should be started on two antihypertensives simultaneously. A third drug should be added if the goal is not achieved with the two drugs. Combination therapy with separate agents or a fixed-dose combination pill may lower blood pressure more quickly with minimal adverse effects. A variety of combination formulations of the various pharmacologic classes are available to increase ease of patient adherence to treatment regimens that require multiple medications. The initial combination treatment should be used sparingly in frail or very elderly patients; in the presence of orthostatic hypotension, it should be established at baseline and in patients with low baseline DBP ( $\leq 80$  mm Hg), particularly in the presence of coronary artery disease.

### A. Individualized care

Hypertension may coexist with other conditions that can be aggravated by some of the antihypertensive drugs or that may benefit from the use of some antihypertensive drugs independent of blood pressure control. In such cases, it is important to match antihypertensive drugs to the particular patient. Figures 16.5 and 16.6 show preferred therapies



**Figure 16.6**

Treatment of hypertension in patients with concomitant diseases. [Note: Angiotensin receptor blockers (ARBs) are an alternative to angiotensin-converting enzyme (ACE) inhibitors.]

in hypertensive patients with concomitant diseases. In addition to the choice of therapy, blood pressure goals may also be individualized based on concurrent disease states and age. Elderly patients may have less stringent goals (for example, less than 150/90 mm Hg). In general, a gradual reduction in blood pressure is desirable in hypertensive patients, particularly in the elderly patients, but the target control level should be achieved within a few weeks in high-risk patients, such as those with grade III hypertension and multiple risk factors.

## B. Rational drug combinations

A fundamental requirement of any useful combination is evidence that it lowers blood pressure to a greater extent than monotherapy with its individual components. The main objective of drug combinations is to achieve additional blood pressure reduction by using drugs that act by different mechanisms:

- Minimization of the adverse effects
- Block-opposing effects on the homeostatic mechanism
- Block-predictive adverse effects
- Permits the use of lower dose (less adverse effects)

Although the blood pressure-reducing ability of antihypertensive drug classes and individual agents varies by only a few mm Hg, the effect of two agents in combination varies considerably. Thus, combining an ACE inhibitor and a diuretic produces fully additive blood pressure reduction whereas the same ACE inhibitor added to an ARB results in additional blood pressure reduction of only 2–3 mm Hg ([Figure 16.7](#)).

## C. Patient compliance in antihypertensive therapy

Lack of patient compliance is the most common reason for the failure of antihypertensive therapy. The hypertensive patients are usually asymptomatic and are diagnosed by routine screening before the occurrence of overt end-organ damage. Thus, therapy is generally directed at preventing future disease sequelae rather than relieving current discomfort. The adverse effects associated with antihypertensive therapy influence people more than the future benefits.

FULLY ADDITIVE DRUG COMBINATIONS (PREFERRED COMBINATIONS)	QUESTIONABLE DRUG COMBINATIONS	PREFERRED DRUG COMBINATIONS FOR PATIENTS WITH ASSOCIATED CONDITIONS
Diuretic + $\beta$ -blockers Diuretic + ACE inhibitors	Nonadditive: $\beta$ -Blocker + ACE inhibitor ARB + ACE inhibitor	Hypertension with angina— $\beta$ -Blockers + CCB Hypertension with heart failure—Diuretic + ACE inhibitors Hypertension with DM—ACE inhibitors + CCB
CCB + $\beta$ -blockers CCB + ACE inhibitors	Side effects additive: $\beta$ -Blockers + Verapamil/Diltiazem (older CCB) $\alpha$ -Blocker + CCB	Hypertension with COPD—Diuretic + CCB Isolated systolic hypertension (systolic BP $\geq$ 160 mm Hg) Drugs of choice in order of preference are diuretics, $\beta$ -blockers, diuretic + $\beta$ -blockers, diuretic + CCB, and ACE inhibitors + CCB

CCB = calcium channel blocker; DM = diabetes mellitus.

**Note:** Drug combinations include low-dose diuretics, ACE inhibitors and ARBs, and long-acting CCBs.

**Figure 16.7**

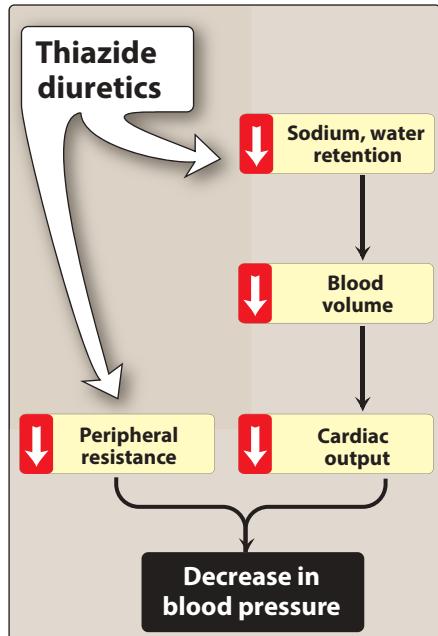
Drug combinations in hypertension.

For example,  $\beta$ -blockers can cause sexual dysfunction in males, which may prompt discontinuation of therapy. Thus, it is important to enhance compliance by selecting a drug regimen that reduces adverse effects and also minimizes the number of doses required daily.

The strategies to improve compliance are given in the following text.

1. **Lifestyle modifications:** Encourage lifestyle modifications at each visit.
2. **Patient education:** Educate patients about the disease and involve their families in the treatment as poor communication with the patient is one of the important reasons for noncompliance. Hypertension is usually asymptomatic and treatment has to continue indefinitely; therefore, emphasize the fact that treatment is lifelong.
3. **Cost factor:** Consider the cost of medications while prescribing. The cost has always been a barrier to an effective treatment. Prescribe less expensive medicines.
4. **Look for adverse effects:** Consider adverse effects at initial prescription and followup visits.
5. **Start with once-daily regimen:** Prescribe simple once-daily regimens. Antihypertensive drugs are administered once a day, in principle; however, the dose may be split into twice a day to control the blood pressure for more than 24 hours. Combining two drug classes in a single pill, at a fixed-dose combination, has been shown to improve patient compliance and improved outcomes in some patients.
6. **Frequent followups:** There should be frequent followup visits (at intervals no more than 3 months apart), during the first year. Allow extra visits for blood pressure measurement at no extra charge to the patient.

## V. DIURETICS



**Figure 16.8**

Actions of thiazide diuretics.

For all classes of diuretics, the initial mechanism of action is based upon decreasing blood volume, which ultimately leads to decreased blood pressure. Routine serum electrolyte monitoring should be done for all patients receiving diuretics. A complete discussion of the actions, therapeutic uses, pharmacokinetics, and adverse effects of diuretics can be found in Chapter 17.

### A. Thiazide diuretics

Thiazide diuretics, such as *hydrochlorothiazide* [hye-droe-klor-oh-THYE-a-zide] and *chlorthalidone* [klor-THAL-ih-done], lower blood pressure initially by increasing sodium and water excretion. This causes a decrease in extracellular volume, resulting in a decrease in cardiac output and renal blood flow (Figure 16.8). With long-term treatment, plasma volume approaches a normal value, but a hypotensive effect persists that is related to a decrease in peripheral resistance. Thiazide diuretics can be used as initial drug therapy for hypertension unless there are compelling reasons to choose another agent. Thiazides are useful in combination therapy with a variety of other antihypertensive agents, including  $\beta$ -blockers, ACE inhibitors, ARBs, and potassium-sparing diuretics. With the exception of *metolazone* [me-TOL-ah-zone], thiazide diuretics are not effective in patients with inadequate kidney function (estimated glomerular filtration rate

less than 30 mL/min/m<sup>2</sup>). Loop diuretics may be required in these patients. Thiazide diuretics can induce hypokalemia, hyperuricemia and, to a lesser extent, hyperglycemia in some patients.

Thiazide diuretics should be used with caution in patients with diabetes, gout, or history of hyponatremia. **Figure 16.9** summarizes commonly used antihypertensives, conditions favoring their use and contraindications, and associated adverse effects.  $\beta$ -Blockers should be avoided in patients with bronchial asthma (however, a selective

ANTIHYPERTENSIVE AGENTS	CONDITIONS FAVORING USE	ADVANTAGES	CONTRAINDICATIONS	POSSIBLE CONTRAINDICATIONS	ADVERSE EFFECTS
<b>Diuretic antihypertensive agents:</b>					
Thiazide and thiazide-related agents: <i>Chlorthiazide, hydrochlorothiazide, chlorthalidone, metolazone, indapamide</i>	Heart failure Elderly hypertensives Isolated systolic hypertension Black hypertensives	Documented reduction in cardiovascular morbidity and mortality Least expensive Best drug for treatment of systolic hypertension and for hypertension in the elderly. Can be combined with all other antihypertensive drugs to produce synergistic effect	Gout Hypokalemia	Pregnancy $\beta$ -blockers (especially <i>atenolol</i> ), impaired glucose tolerance	Hypotension, increased cholesterol and glucose levels, biochemical abnormalities; decreased sodium, potassium, and magnesium levels; increased uric acid and calcium levels
Loop diuretics: <i>Furosemide, bumetanide, ethacrynic acid</i>	Renal insufficiency Heart failure		Anuria, hypersensitivity	Hepatic cirrhosis	
Potassium-sparing agents: <i>Triamterene, spironolactone, amiloride</i>	Heart failure Postmyocardial infarction Resistant hypertension		Renal failure, Hyperkalemia		Hyperkalemia Gynecomastia
<b>Adrenergic receptor blockers:</b>					
$\beta$ -Blockers nonselective ( $\beta_1$ and $\beta_2$ ): <i>Propranolol, nadolol, pindolol</i> $\beta_1$ selective: <i>Acebutalol, atenolol, metoprolol</i>	Angina pectoris Postmyocardial infarction Heart failure (only some $\beta$ -blockers) Tachyarrhythmias	Reduction in cardiovascular morbidity and mortality Provides cardioprotection—primary and secondary prevention against coronary artery events (that is, ischemia, infarction, arrhythmias, death) Relatively nonexpensive	Asthma Chronic obstructive pulmonary disease Marked bradycardia, atrioventricular block (grade 2 or 3)	Peripheral vascular disease Bradycardia Glucose intolerance Metabolic syndrome Athletes and physically active patients Nondihydropyridine CCBs ( <i>verapamil</i> and <i>diltiazem</i> ) Pregnancy	Bronchospasm, bradycardia, heart failure, can mask insulin-induced hypoglycemia. Less serious: impaired peripheral circulation, insomnia, fatigue, decreased exercise tolerance, hypertriglyceridemia (except agents with intrinsic sympathomimetic activity), reduced HDL cholesterol and impaired glycemic control Angioedema (very rare), hyperkalemia; <i>Do not discontinue abruptly</i>

**Figure 16.9**

Commonly used antihypertensives, conditions favoring their use and contraindications, and associated adverse effects. (Figure continues on next page)

ANTIHYPERTENSIVE AGENTS	CONDITIONS FAVORING USE	ADVANTAGES	CONTRAINdicATIONS	POSSIBLE CONTRAINDICATIONS	ADVERSE EFFECTS
<b><math>\alpha</math>-Blockers: Prazosin, terazosin, doxazosin</b>	Mild-to-moderate hypertension Urination disorders associated with prostatic hypertrophy prior to pheochromocytoma surgery Administered before sleep for treatment of morning hypertension	Improve lipid profile and insulin sensitivity			First-dose syncope, postural hypotension, dizziness, headache, somnolence; start at a low dose with gradual increases; administer dose at bedtime
<b><math>\alpha + \beta</math>-Blockers: Labetalol, carvedilol</b>	Hypertension in Pregnancy, Secondary hypertension to pheochromocytoma				Similar to propranolol; more likely to cause orthostatic hypotension, sexual dysfunction

#### Renin-angiotensin-aldosterone system (RAAS) inhibitors:

<b>Angiotensin-converting enzyme inhibitors (ACE inhibitors): Captopril, enalapril, lisinopril, ramipril, quinapril</b>	Heart failure	Reduction of cardiovascular morbidity and mortality in patients with atherosclerotic vascular disease, diabetes, and heart failure	Pregnancy	Monitor carefully renal function, and potassium if high serum creatinine (>3 mg/dl)	Cough (common), hypotension angioedema, hyperkalemia, rash, loss of taste, and leucopenia (rare)
	Left ventricular dysfunction		Hyperkalemia		
	Postmyocardial infarction		Bilateral renal artery stenosis		
	Nondiabetic nephropathy		Known allergy		
	Type 1 diabetic nephropathy				
	Type 2 diabetes mellitus	Favorable metabolic profile. Improvement in glucose tolerance and insulin resistance			
<b>Angiotensin II receptor antagonists (ARBs): Losartan potassium, telmisartan, velsartan, olmesartan</b>	Proteinuria	Renal protection effect, especially in diabetes mellitus. Do not adversely affect the quality of life			
	Type 1 diabetic nephropathy		Pregnancy		
	Type 2 diabetic microalbuminuria	Similar metabolic profile to that of ACE inhibitors	Hyperkalemia		
	Proteinuria	Renal protection	Bilateral renal artery stenosis		
	Left ventricular hypertrophy	Do not produce cough			
	Patients with a compelling indication for ACE inhibitors but do not tolerate them due to ACE inhibitor-induced cough or intolerance				

**Figure 16.9 (Continued)**

Commonly used antihypertensives, conditions favoring their use and contraindications, and associated adverse effects. (Figure continues on next page)

ANTIHYPERTENSIVE AGENTS	CONDITIONS FAVORING USE	ADVANTAGES	CONTRAINDICATIONS	POSSIBLE CONTRAINDICATIONS	ADVERSE EFFECTS
<b>Ca<sup>2+</sup> channel blockers:</b> <b>Dihydropyridine:</b> <i>Amlodipine, felodipine (long acting only), nifedipine (short acting)</i>	Elderly patients Isolated systolic HTN Angina pectoris Peripheral vascular disease (Raynaud's phenomenon) Carotid atherosclerosis Pregnancy Black hypertensives	No metabolic disturbances; no change in blood glucose, potassium, uric acid, and lipids No metabolic disturbance May improve renal function Maintain optimal physical, mental, and sexual activities		Tachyarrhythmias Heart failure Antiretroviral therapy	Edema of the ankles, flushing, headache, gingival hypertrophy, constipation. Tolerance develops to headache. For edema, a diuretic may be needed
<b>Ca<sup>2+</sup> channel blockers:</b> <b>Nondihydropyridine (verapamil and diltiazem)</b>	Angina pectoris, carotid atherosclerosis, supraventricular tachycardia (short-acting drug should be combined with β blockers in CAD and should be avoided in stroke and hypertensive crisis)		Atrioventricular block (grade 2 or 3) Heart failure	Constipation (verapamil) Antiretroviral therapy	Constipation (verapamil) Cardiac conduction defects, worsening of systolic function, gingival hyperplasia
<b>Vasodilators:</b> <i>Hydralazine, minoxidil, sodium nitroprusside, diazoxide</i>	Refractory hypertension (minoxidil) Hypertensive emergency (nitroprusside, diazoxide) Preeclampsia (hydralazine)	Quick action			Headaches, fluid retention, tachycardia, lupus-like syndrome on continuous use (hydralazine), hirsutism (minoxidil)
<b>Central nervous system and sympathetic inhibitors: Methylldopa, clonidine</b>	Hypertension in pregnancy Mild-to-moderate hypertension Can be combined with a diuretic	Increases renal blood flow Drug of choice during pregnancy			Sedation, dry mouth, bradycardia, withdrawal hypertension on abrupt withdrawal

**Figure 16.9 (Continued)**

Commonly used antihypertensives, conditions favoring their use and contraindications, and associated adverse effects.

β-blocker such as carvedilol can be used), reactive airways disease, or second- or third-degree heart block. ACE inhibitors should not be used in patients with a history of angioedema. Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia and should generally be avoided in patients who have serum potassium values of more than 5.0 mEq/L when not taking medications. Measure serum potassium levels 2 weeks after starting ACE/ARBs.

## B. Loop diuretics

The loop diuretics (*furosemide, torsemide, bumetanide*, and *ethacrynic acid*; see Chapter 18) act promptly by blocking sodium and chloride

reabsorption in the kidneys, even in patients with poor renal function or those who have not responded to thiazide diuretics. Loop diuretics cause decreased renal vascular resistance and increased renal blood flow. Like thiazides, they can cause hypokalemia. However, unlike thiazides, loop diuretics increase the calcium content of urine, whereas thiazide diuretics decrease it. These agents are rarely used alone to treat hypertension, but they are commonly used to manage symptoms of heart failure and edema.

### C. Potassium-sparing diuretics

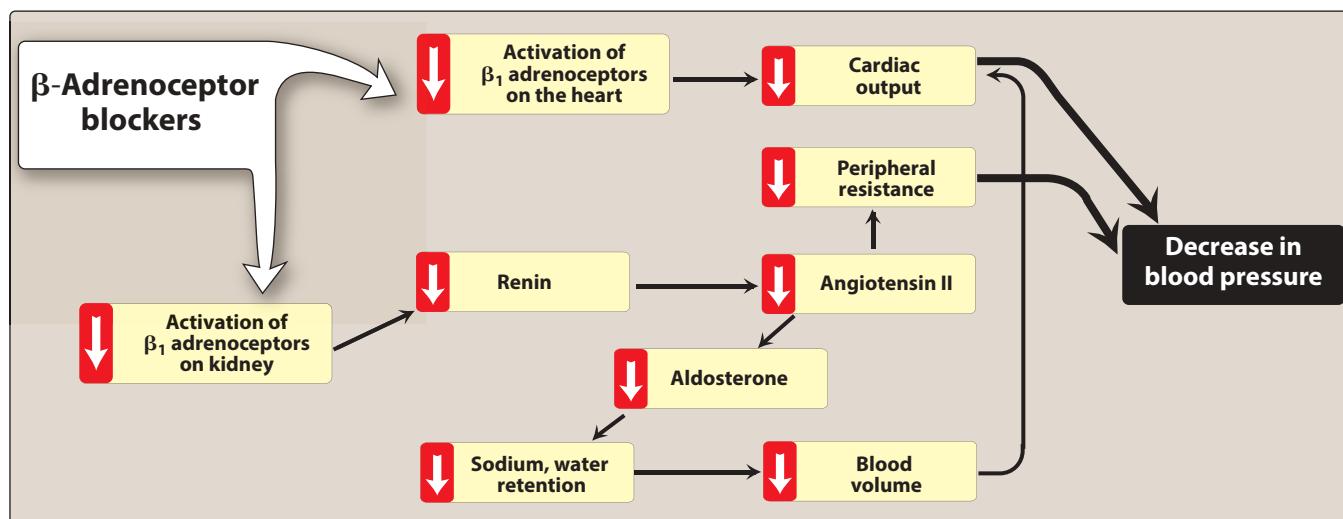
*Amiloride* [uh-MIL-oh-ride] and *triamterene* [tri-AM-ter-een] are inhibitors of epithelial sodium transport at the late distal and collecting ducts, and *spironolactone* [speer-on-oh-LAK-tone] and *epiplerenone* [eh-PLEH-reh-none] are aldosterone receptor antagonists. All of these agents reduce potassium loss in the urine. Aldosterone antagonists have the additional benefit of diminishing the cardiac remodeling that occurs in heart failure (see Chapter 18). Potassium-sparing diuretics are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.

## VI. $\beta$ -ADRENOCEPTOR-BLOCKING AGENTS

$\beta$ -Blockers are a treatment option for hypertensive patients with concomitant heart disease or heart failure (Figures 16.6 and 16.9).

### A. Actions

The  $\beta$ -blockers reduce blood pressure primarily by decreasing cardiac output (Figure 16.10). They may also decrease sympathetic outflow from the central nervous system (CNS) and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and



**Figure 16.10**

Actions of  $\beta$ -adrenoceptor-blocking agents.

the secretion of aldosterone. The prototype  $\beta$ -blocker is *propranolol* [proe PRAN-oh-lo], which acts at both  $\beta_1$  and  $\beta_2$  receptors. Selective blockers of  $\beta_1$  receptors, such as *metoprolol* [met-OH-pro-lo] and *atenolol* [ah-TEN-oh-lo], are among the most commonly prescribed  $\beta$ -blockers. *Nebivolol* [ne-BIV-oh-lole] is a selective blocker of  $\beta_1$  receptors, which also increases the production of nitric oxide, leading to vasodilation. The selective  $\beta$ -blockers may be administered cautiously to hypertensive patients who also have asthma. The nonselective  $\beta$ -blockers are contraindicated in patients with asthma due to their blockade of  $\beta_2$ -mediated bronchodilation. (See Chapter 7 for an in-depth discussion of  $\beta$ -blockers.)  $\beta$ -Blockers should be used cautiously in the treatment of patients with acute heart failure or peripheral vascular disease.

### B. Therapeutic uses

The primary therapeutic benefits of  $\beta$ -blockers are seen in hypertensive patients with concomitant heart disease, such as supraventricular tachyarrhythmia (for example, atrial fibrillation), previous myocardial infarction, stable ischemic heart disease, and chronic heart failure. Conditions that discourage the use of  $\beta$ -blockers include reversible bronchospastic disease such as asthma, second- and third-degree heart block, and severe peripheral vascular disease.

### C. Pharmacokinetics

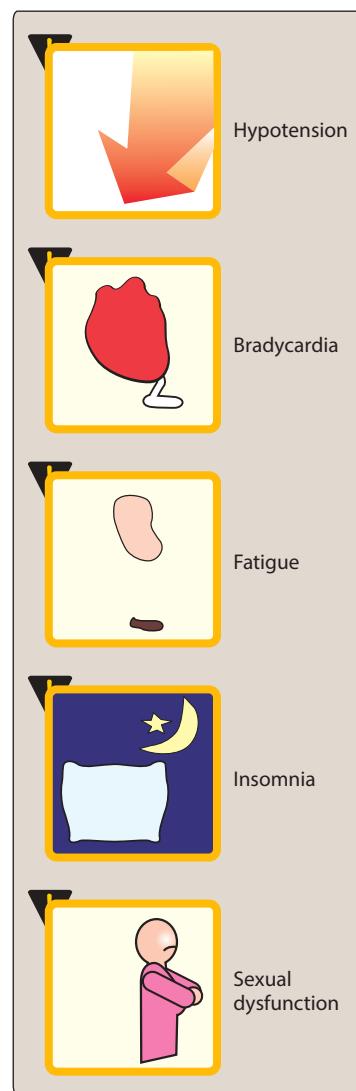
The  $\beta$ -blockers are orally active for the treatment of hypertension. *Propranolol* undergoes extensive and highly variable first-pass metabolism. Oral  $\beta$ -blockers may take several weeks to develop their full effects. *Esmolol*, *metoprolol*, and *propranolol* are available in intravenous formulations.

### D. Adverse effects

- Common effects:** Figure 16.11 describes some of the adverse effects of  $\beta$ -blockers. The  $\beta$ -blockers may decrease libido and cause erectile dysfunction, which can severely reduce patient compliance.
- Alterations in serum lipid patterns:** Noncardioselective  $\beta$ -blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing triglycerides.
- Drug withdrawal:** Abrupt withdrawal may induce severe hypertension, angina, myocardial infarction, and even sudden death in patients with ischemic heart disease. Therefore, these drugs must be tapered over a few weeks in patients with hypertension and ischemic heart disease.

## VII. ACE INHIBITORS

ACE inhibitors such as *captopril* [KAP-toe-pril], *enalapril* [e-NAL-ah-pril], *Lisinopril* [lye-SIN-oh-pril] are recommended as first-line treatment of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease (Figures 16.6 and 16.9).



**Figure 16.11**

Some adverse effects of  $\beta$ -blockers.

### A. Actions

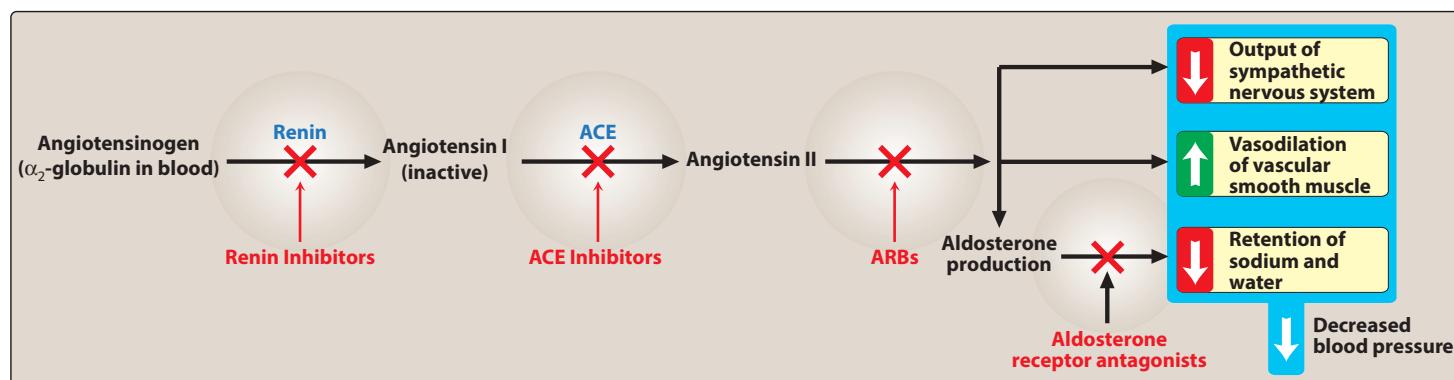
The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, heart rate, or contractility. These drugs block the enzyme ACE which cleaves angiotensin I to form the potent vasoconstrictor angiotensin II (Figure 16.12). ACE is also responsible for the breakdown of bradykinin, a peptide that increases the production of nitric oxide and prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators. Vasodilation of both arterioles and veins occurs as a result of decreased vasoconstriction (from diminished levels of angiotensin II) and enhanced vasodilation (from increased bradykinin). By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention. ACE inhibitors reduce both cardiac preload and afterload, thereby decreasing workload on the heart.

### B. Therapeutic uses

ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria and, thus, have a compelling indication for use in patients with diabetic nephropathy. Beneficial effects on renal function may result from decreasing intraglomerular pressures, due to efferent arteriolar vasodilation. ACE inhibitors are a standard in the care of a patient following a myocardial infarction and first-line agents in the treatment of patients with systolic dysfunction. Chronic treatment with ACE inhibitors achieves sustained blood pressure reduction, regression of left ventricular hypertrophy, and prevention of ventricular remodeling after a myocardial infarction. ACE inhibitors are first-line drugs for treating heart failure, hypertensive patients with chronic kidney disease, and patients at increased risk of coronary artery disease. All of the ACE inhibitors are equally effective in the treatment of hypertension at equivalent doses.

### C. Pharmacokinetics

All of the ACE inhibitors are orally bioavailable as a drug or prodrug. All but *captopril* and *lisinopril* undergo hepatic conversion to



**Figure 16.12**

Effects of various drug classes on the renin–angiotensin–aldosterone system. Blue = drug target enzymes; red = drug class.

active metabolites, so these agents may be preferred in patients with severe hepatic impairment. *Fosinopril* [foe-SIN-oh-pril] is the only ACE inhibitor that is not eliminated primarily by the kidneys. Therefore, it does not require dose adjustment in patients with renal impairment. *Enalaprilat* [en-AL-a-pril-AT] is the only drug in this class available intravenously.

#### D. Adverse effects

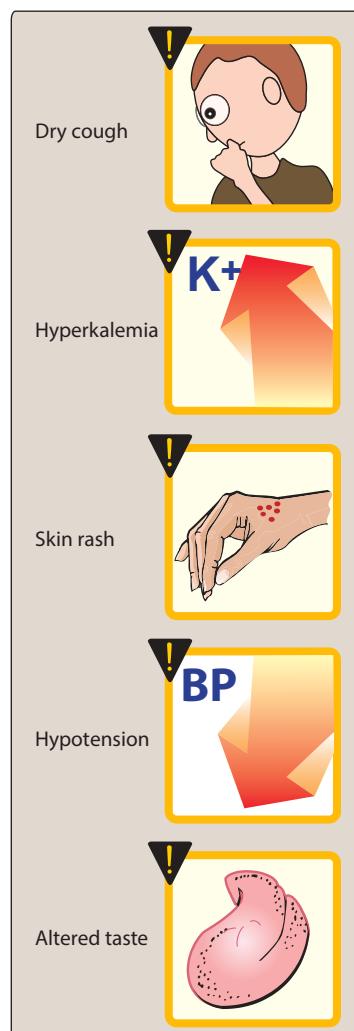
**Figure 16.13** describes some of the common adverse effects of ACE inhibitors. The dry cough, which occurs in up to 10% of patients, is thought to be due to increased levels of bradykinin and substance P in the pulmonary tree, and it occurs more frequently in women. The cough resolves within a few days of discontinuation. Angioedema is a rare but potentially life-threatening reaction that may also be due to increased levels of bradykinin. Potassium levels must be monitored while on ACE inhibitors, and potassium supplements and potassium-sparing diuretics should be used with caution due to the risk of hyperkalemia. Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease. However, an increase in serum creatinine of up to 30% above baseline is acceptable and by itself does not warrant discontinuation of treatment. ACE inhibitors can induce fetal malformations and should not be used by pregnant women.

### VIII. ANGIOTENSIN II RECEPTOR BLOCKERS

The ARBs, such as *losartan* [LOW-sar-tan] and *irbesartan* [ir-be-SAR-tan], block the AT<sub>1</sub> receptors, decreasing the activation of AT<sub>1</sub> receptors by angiotensin II. Their pharmacologic effects are similar to those of ACE inhibitors in that they produce arteriolar and venous dilation and block aldosterone secretion, thus lowering blood pressure and decreasing salt and water retention (**Figure 16.12**). ARBs do not increase bradykinin levels. They may be used as first-line agents for the treatment of hypertension, especially in patients with a compelling indication of diabetes, heart failure, or chronic kidney disease (**Figures 16.5** and **16.6**). Adverse effects are similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased. ARBs should not be combined with an ACE inhibitor for the treatment of hypertension due to similar mechanisms and adverse effects. These agents are also teratogenic and should not be used by pregnant women. [Note: The ARBs are discussed more fully in Chapter 18.]

### IX. RENIN INHIBITOR

A selective renin inhibitor, *aliskiren* [a-LIS-ke-rin], is available for the treatment of hypertension. *Aliskiren* directly inhibits renin and, thus, acts earlier in the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs (**Figure 16.12**). *Aliskiren* should not be combined with an ACE inhibitor or ARB in the treatment of hypertension. *Aliskiren* can cause diarrhea, especially at higher doses. It also causes cough and angioedema, but less often than ACE inhibitors. As with ACE inhibitors and ARBs, *aliskiren* is contraindicated during pregnancy. *Aliskiren* is metabolized by CYP3A4 and is subject to many drug interactions.



**Figure 16.13**

Some common adverse effects of the ACE inhibitors.

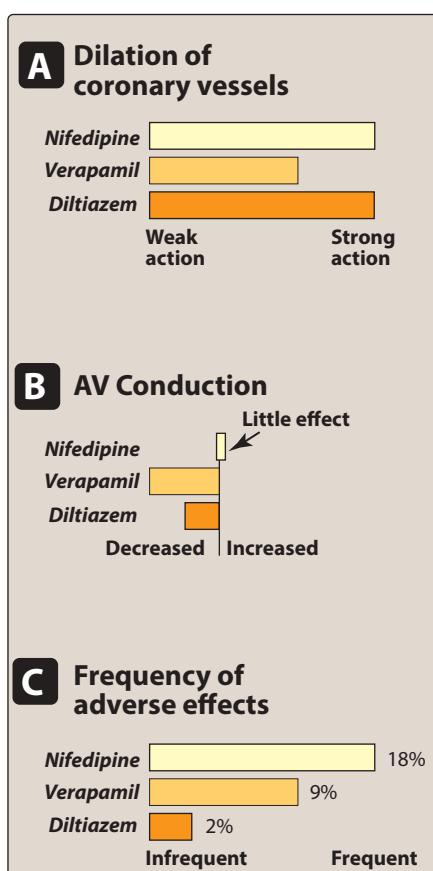
## X. CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are a recommended first-line treatment option in black patients. They may also be useful in hypertensive patients with diabetes or stable ischemic heart disease. High doses of short-acting calcium channel blockers should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation.

### A. Classes of calcium channel blockers

The calcium channel blockers are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications (Figure 16.14).

- Diphenylalkylamines:** *Verapamil* [ver-AP-a-mil] is the only member of this class that is available in the United States. *Verapamil* has significant effects on both cardiac and vascular smooth muscle cells. It is also used to treat angina and supraventricular tachyarrhythmias and to prevent migraine and cluster headaches.
- Benzothiazepines:** *Diltiazem* [dil-TYE-a-zem] is the only member of this class that is currently approved in the United States. Like *verapamil*, *diltiazem* affects both cardiac and vascular smooth muscle cells, but it has a less pronounced negative inotropic effect on the heart compared to that of *verapamil*. *Diltiazem* has a favorable side effect profile.
- Dihydropyridines:** This class of calcium channel blockers includes *nifedipine* [nye-FED-i-peen] (the prototype), *amlodipine* [am-LOE-di-peen], *felodipine* [fe-LOE-di-peen], *isradipine* [is-RAD-i-peen], *nicardipine* [nye-KAR-di-peen], and *nisoldipine* [nye-ZOL-di-peen]. These agents differ in pharmacokinetics, approved uses, and drug interactions. All dihydropyridines have a much greater affinity for vascular calcium channels than for calcium channels in the heart. They are, therefore, particularly beneficial in treating hypertension. The dihydropyridines have the advantage in that they show little interaction with other cardiovascular drugs, such as *digoxin* or *warfarin*, which are often used concomitantly with calcium channel blockers.



**Figure 16.14**

Actions of calcium channel blockers.  
AV = atrioventricular.

### B. Actions

The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium. Calcium channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles. Calcium channel blockers do not dilate veins.

### C. Therapeutic uses

In the management of hypertension, CCBs may be used as an initial therapy or as an add-on therapy. They are useful in the treatment of hypertensive patients who also have asthma, diabetes, and/or peripheral vascular disease, because unlike  $\beta$ -blockers, they do not have the potential to adversely affect these conditions. All CCBs are useful

in the treatment of angina. In addition, *diltiazem* and *verapamil* are used in the treatment of atrial fibrillation.

#### D. Pharmacokinetics

Most of these agents have short half-lives (3 to 8 hours) following an oral dose. Sustained-release preparations are available and permit once-daily dosing. *Amlodipine* has a very long half-life and does not require a sustained-release formulation.

#### E. Adverse effects

First-degree atrioventricular block and constipation are common dose-dependent side effects of *verapamil*. *Verapamil* and *diltiazem* should be avoided in patients with heart failure or with atrioventricular block due to their negative inotropic (force of cardiac muscle contraction) and dromotropic (velocity of conduction) effects. Dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure are more frequent with dihydropyridines (Figure 16.15). Peripheral edema is another commonly reported side effect of this class. *Nifedipine* and other dihydropyridines may cause gingival hyperplasia.

### XI. $\alpha$ -ADRENOCEPTOR-BLOCKING AGENTS

$\alpha$ -Adrenergic blockers used in the treatment of hypertension include *prazosin* [PRA-zoe-sin], *doxazosin* [dox-AH-zoe-sin], and *terazosin* [ter-AH-zoe-sin]. These agents produce a competitive block of  $\alpha_1$ -adrenoceptors. They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle. These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate. Therefore, long-term tachycardia does not occur, but salt and water retention does. Reflex tachycardia and postural hypotension often occur at the onset of treatment and with dose increases, requiring slow titration of the drug in divided doses. Due to weaker outcome data and their side effect profile,  $\alpha$ -blockers are no longer recommended as initial treatment for hypertension, but may be used for refractory cases. Other  $\alpha_1$ -blockers with greater selectivity for the prostate are used in the treatment of benign prostatic hyperplasia (see Chapter 43).

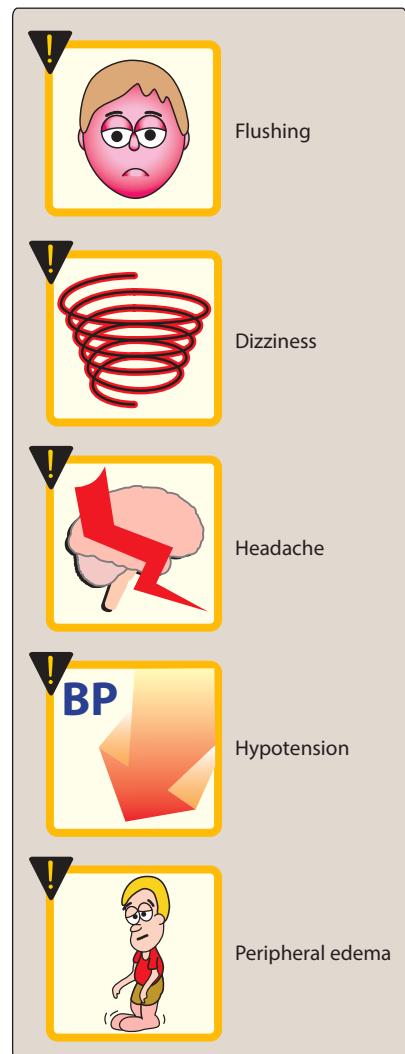
### XII. $\alpha$ -/ $\beta$ -ADRENOCEPTOR-BLOCKING AGENTS

*Labetalol* [la-BAY-ta-lo] and *carvedilol* [kar-VE-di-lo] block  $\alpha_1$ ,  $\beta_1$ , and  $\beta_2$  receptors. *Carvedilol* is indicated in the treatment of heart failure and hypertension. It has been shown to reduce morbidity and mortality associated with heart failure. *Labetalol* is used in the management of gestational hypertension and hypertensive emergencies.

### XIII. CENTRALLY ACTING ADRENERGIC DRUGS

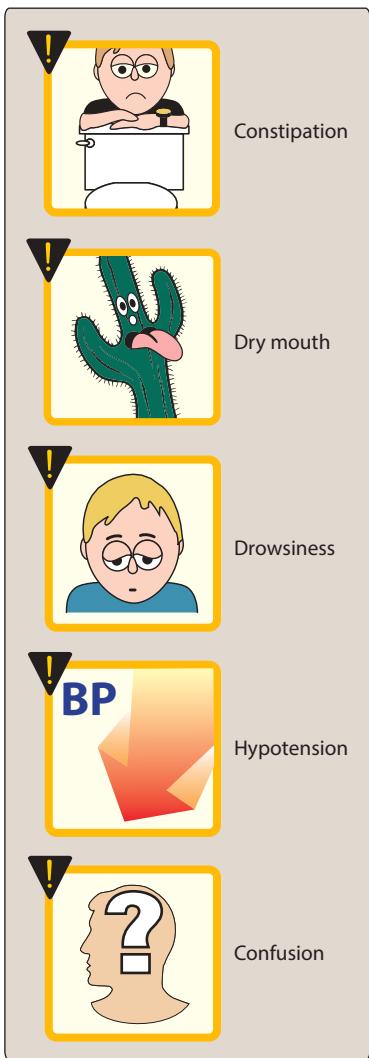
#### A. Clonidine

*Clonidine* [KLON-i-deen] acts centrally as an  $\alpha_2$  agonist to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. This leads to reduced total peripheral resistance and decreased blood pressure. *Clonidine* is used



**Figure 16.15**

Some common adverse effects of the calcium channel blockers.

**Figure 16.16**

Some adverse effects of *clonidine*.

primarily for the treatment of hypertension that has not responded adequately to treatment with two or more drugs. *Clonidine* does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease. *Clonidine* is well absorbed after oral administration and is excreted by the kidney. It is also available in a transdermal patch. Adverse effects include sedation, dry mouth, and constipation (Figure 16.16). Rebound hypertension occurs following abrupt withdrawal of *clonidine*. The drug should, therefore, be withdrawn slowly if discontinuation is required.

### B. Methyldopa

*Methyldopa* [meth-ill-DOE-pa] is an  $\alpha_2$  agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS. The most common side effects of *methyl*dopa are sedation and drowsiness. Its use is limited due to adverse effects and the need for multiple daily doses. It is mainly used for management of hypertension in pregnancy, where it has a record of safety.

## XIV. VASODILATORS

The direct-acting smooth muscle relaxants, such as *hydralazine* [hye-DRAL-a-zeen] and *minoxidil* [min-OX-i-dill], are not used as primary drugs to treat hypertension. These vasodilators act by producing relaxation of vascular smooth muscle, primarily in arteries and arterioles. This results in decreased peripheral resistance and, therefore, blood pressure. Both agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals. Vasodilators also increase plasma renin concentration, resulting in sodium and water retention. These undesirable side effects can be blocked by concomitant use of a diuretic (to decrease sodium retention) and a  $\beta$ -blocker (to balance the reflex tachycardia). Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resistance. *Hydralazine* is an accepted medication for controlling blood pressure in pregnancy-induced hypertension. Adverse effects of *hydralazine* include headache, tachycardia, nausea, sweating, arrhythmia, and precipitation of angina (Figure 16.17). A lupus-like syndrome can occur with high dosages, but it is reversible upon discontinuation of the drug. *Minoxidil* treatment causes hypertrichosis (the growth of body hair). This drug is used topically to treat male pattern baldness.

## XV. HYPERTENSIVE EMERGENCY

Hypertensive emergency is a rare but life-threatening situation characterized by severe elevations in blood pressure (systolic greater than 180 mm Hg or diastolic greater than 120 mm Hg) with evidence of impending or progressive target organ damage (for example, stroke and myocardial infarction). [Note: A severe elevation in blood pressure without evidence of target organ damage is considered a hypertensive urgency.] Hypertensive emergencies require timely blood pressure reduction with

treatment administered intravenously to prevent or limit target organ damage. A variety of medications are used, including calcium channel blockers (*nicardipine* and *clevidipine*), nitric oxide vasodilators (*nitroprusside* and *nitroglycerin*), adrenergic receptor antagonists (*phentolamine*, *esmolol*, and *labetalol*), the vasodilator *hydralazine*, and the dopamine agonist *fenoferolamine*. Treatment is directed by the type of target organ damage and/or comorbidities present.

## XVI. RESISTANT HYPERTENSION

Resistant hypertension is defined as blood pressure that remains elevated (above goal) despite administration of an optimal three-drug regimen that includes a diuretic. The most common causes of resistant hypertension are poor compliance, excessive ethanol intake, concomitant conditions (diabetes, obesity, sleep apnea, hyperaldosteronism, high salt intake, and/or metabolic syndrome), concomitant medications (sympathomimetics, nonsteroidal anti-inflammatory drugs, or corticosteroids), insufficient dose and/or drugs, and use of drugs with similar mechanisms of action.

## XVII. HYPERTENSION IN PREGNANCY

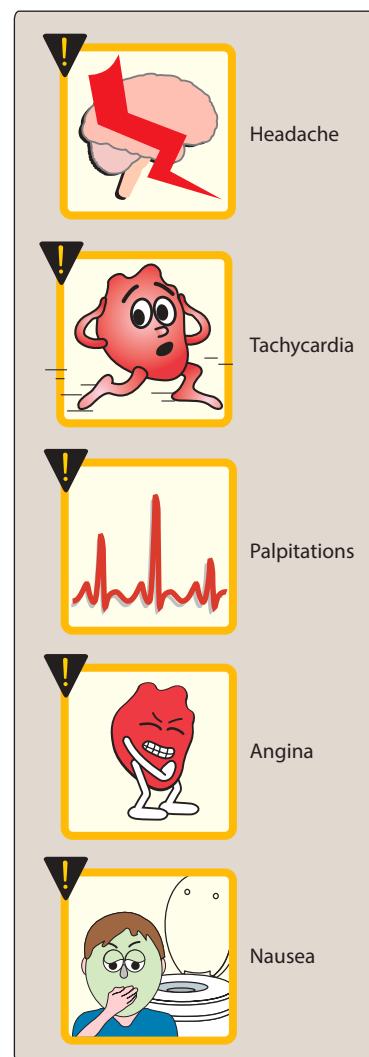
$\alpha$ -Methyldopa,  $\beta$ -blockers, and vasodilators are preferred medications for safety of the fetus. However, caution should be exercised when using  $\beta$ -blockers over a long period as they cause growth retardation in the fetus. ACE inhibitors and ARB blockers are strongly contraindicated in such cases.

## XVIII. HYPERTENSION IN CHILDREN AND ADOLESCENTS

In children and adolescents, hypertension is defined as blood pressure that is, on repeated measurement, at the 95th percentile or greater adjusted for age, height, and gender. The fifth Korotkoff sound is used to define diastolic BP. Rule out the secondary causes of hypertension such as Cushing's diseases, pheochromocytoma, kidney disease, and coarctation of aorta. Lifestyle interventions are strongly recommended, with pharmacological therapy instituted for a higher level of BP or if there is insufficient response to lifestyle modification. The choices of antihypertensive drugs are similar in children and adults, but effective doses for children are often smaller and should be adjusted carefully.

## XIX. DRUG INTERACTIONS

Interactions between antihypertensive drugs may enhance the hypotensive effect or offset adverse effects in some combinations, but may aggravate adverse effects in others. Combination of a  $\beta$ -blocker and a non-dihydropyridine (non-DHP)  $\text{Ca}^{2+}$  channel blocker enhances cardioinhibitory effect. Combination of an RA system inhibitor and an aldosterone antagonist aggravates hyperkalemia and increase in the frequency of withdrawal syndrome is observed with a combination of a central sympatholytic drug and a  $\beta$ -blocker.



**Figure 16.17**

Some adverse effects of *hydralazine*.

Non-steroidal anti-inflammatory drugs (NSAIDs) attenuate the hypotensive effects of diuretics,  $\beta$ -blockers, and ACE inhibitors as they increase fluid retention. Enhancement of the hypotensive effects of  $\text{Ca}^{2+}$  channel blockers and  $\beta$ -blockers is observed with histamine  $\text{H}_2$ -receptor blockers and rise in blood digoxin concentration if combined with a non-DHP  $\text{Ca}^{2+}$  channel blocker. The concomitant use of an ACE inhibitor or ARB with an NSAID or a diuretic may cause acute renal insufficiency or an excessive fall in blood pressure, particularly in elderly patients, with dehydration or under restriction of salt intake. Grapefruit or grapefruit juice increases the blood concentration of DHP  $\text{Ca}^{2+}$  channel blockers (particularly *felodipine* and *nisoldipine*).

## Study Questions

Choose the ONE best answer.

- 16.1. A 55-year-old Non-Hispanic black male has hypertension. His past medical history also includes diabetes and hyperlipidemia. According to the ACC/AHA guidelines, which represents the most appropriate blood pressure goal for the patient?

- A. <140/85
- B. <135/85
- C. <130/80
- D. <140/80

- 16.2. A 59-year-old Non-Hispanic white patient presents for treatment of hypertension. His past medical history also includes diabetes and hyperlipidemia hypertension. The patient's blood pressure is 150/93 (both today and at the last visit). Which is a recommended initial therapy to treat hypertension in this patient?

- A. Enalapril
- B. Hydralazine
- C. Verapamil
- D. Metoprolol

- 16.3. A 45-year-old male complains of constipation. He was recently started on two antihypertensives due to elevated systolic blood pressure (greater than 20 mmHg above goal). His current medications include lisinopril, chlorthalidone, verapamil, rosuvastatin, and aspirin. Which is most likely contributing to his constipation?

- A. Chlorthalidone
- B. Verapamil
- C. Aspirin
- D. Lisinopril

Correct answer = C. Goals of therapy differ depending on which guidelines the clinician uses in practice. According to the ACC/AHA guidelines, the goal blood pressure for a diabetic patient is <130/80.

Correct answer = A. Enalapril is an ACE inhibitor and is recommended for first-line therapy in various patient populations, including those who have a compelling indication such as diabetes. The other therapies are not considered first-line therapy.

Correct answer = B. Common side effects specific for verapamil include constipation and first-degree atrioventricular block which typically are dose-dependent. Electrolyte disturbances are often associated with both diuretics (chlorthalidone) and ACE inhibitors (lisinopril).

- 16.4. Which antihypertensive medication can cause the rare side effect of angioedema?
- A. Amlodipine
  - B. Fosinopril
  - C. Prazosin
  - D. Propranolol
- 16.5. A 52-year-old female has uncontrolled hypertension (blood pressure 154/82 mm Hg) on treatment with lisinopril. She recently had a myocardial infarction and her past medical history includes diabetes, hypertension, hyperlipidemia, and osteoarthritis. Considering her compelling indications, which agent may be appropriate to add to her anti-hypertensive therapy?
- A. Clonidine
  - B. Olmesartan
  - C. Furosemide
  - D. Metoprolol
- 16.6. The blood pressure of a patient with essential hypertension is at goal on treatment with enalapril. Since initiation of enalapril, the serum creatinine has increased 25% above baseline. What is the appropriate next step for the enalapril therapy?
- A. Discontinue enalapril.
  - B. Reduce dose of enalapril.
  - C. Continue current dose of enalapril.
  - D. Increase dose of enalapril.
- 16.7. Which of the following correctly outlines a major difference in electrolyte disturbances associated with thiazide and loop diuretics?
- A. Thiazide diuretics decrease potassium and loop diuretics increase potassium.
  - B. Thiazide diuretics increase potassium and loop diuretics decrease potassium.
  - C. Thiazide diuretics decrease calcium and loop diuretics increase calcium.
  - D. Thiazide diuretics increase calcium and loop diuretics decrease calcium.
- 16.8. Which can precipitate a hypertensive crisis following abrupt cessation of therapy?
- A. Clonidine
  - B. Diltiazem
  - C. Valsartan
  - D. Hydrochlorothiazide

Correct answer = B. ACE inhibitors (fosinopril), ARBs (for example, losartan), and renin inhibitors (aliskiren) can cause angioedema. The occurrence of angioedema is more common with ACE inhibitors. Amlodipine can cause dizziness, headache, and peripheral edema. Prazosin can cause reflex tachycardia and postural hypotension. Propranolol can cause insomnia, decreased libido, fatigue, and bradycardia.

Correct answer = D. Individual patient care is warranted particularly in the case of a compelling indication for certain medication. Considering her recent myocardial infarction, the best choice is a  $\beta_1$  blocker (metoprolol). It is not appropriate to combine an ACE inhibitor (lisinopril) and ARB (olmesartan). The other agents are not considered first-line therapy and do not have a compelling indication for addition to the regimen.

Correct answer = C. The blood pressure is at goal. Electrolytes (such as potassium) and serum creatinine should be monitored in patients who initiate ACE inhibitors. Increases in serum creatinine up to 30% above baseline are acceptable and do not warrant discontinuation or reduction in treatment. Since the blood pressure is at goal, increasing the enalapril is not necessary.

Correct answer = D. Thiazide and loop diuretics decrease potassium, sodium, and magnesium. However, thiazide diuretics increase calcium (through reduced urinary excretion), while loop diuretics reduce calcium (through enhanced urinary excretion).

Correct answer = A. Increased sympathetic nervous system activity occurs if clonidine therapy is abruptly stopped after prolonged administration. Uncontrolled elevation in blood pressure can occur. Patients should be slowly weaned from clonidine while other antihypertensive medications are initiated. The other drugs on the list do not produce this phenomenon.

- 16.9. Which of the following is a dihydropyridine calcium channel blocker?

- A. Amlodipine
- B. Metoprolol
- C. Verapamil
- D. Lisinopril

- 16.10. A 45-year-old man was started on therapy for hypertension and developed a persistent, dry cough. Which is most likely responsible for this side effect?

- A. Lisinopril
- B. Losartan
- C. Nifedipine
- D. Atenolol

Correct answer = A. There are three classes of calcium channel blockers: nondihydropyridines (benzothiazepines, diphenylalkylamines) and dihydropyridines. Amlodipine is a member of the dihydropyridine class of calcium channel blockers which also includes nifedipine and felodipine. Verapamil is a benzothiazepine calcium channel blocker, metoprolol is a  $\beta$  blocker, and lisinopril is an ACE inhibitor.

Correct answer = A. The cough is most likely an adverse effect of the ACE inhibitor lisinopril. Losartan is an ARB that has the same beneficial effects as an ACE inhibitor but is less likely to produce a cough. Nifedipine and atenolol do not cause this side effect.

# Diuretics

Zachary L. Cox

17

## I. OVERVIEW

Diuretics are drugs that increase the volume of urine excreted. Most diuretic agents are inhibitors of renal ion transporters that decrease the reabsorption of  $\text{Na}^+$  at different sites in the nephron. As a result,  $\text{Na}^+$  and other ions enter the urine in greater than normal amounts along with water, which is carried passively to maintain osmotic equilibrium. Diuretics, thus, increase the volume of urine and often change its pH, as well as the ionic composition of the urine and blood. The diuretic effect of the different classes of diuretics varies considerably with the site of action. In addition to the ion transport inhibitors, other types of diuretics include osmotic diuretics, aldosterone antagonists, and carbonic anhydrase inhibitors. While diuretics are most commonly used for management of excessive fluid retention (edema), many agents within this class are prescribed for nondiuretic indications or for systemic effects in addition to their actions on the kidney. Examples, which are discussed below, include use of thiazides in hypertension, use of carbonic anhydrase inhibitors in glaucoma, and use of aldosterone antagonists in heart failure. In this chapter, the diuretic drugs (Figure 17.1) are discussed according to the frequency of their use.

## II. NORMAL REGULATION OF FLUID AND ELECTROLYTES BY THE KIDNEYS

Approximately 16% to 20% of the blood plasma entering the kidneys is filtered from the glomerular capillaries into Bowman's capsule. The filtrate, although normally free of proteins and blood cells, contains most of the low molecular weight plasma components in concentrations similar to that in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes, as well as electrolytes, such as  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$ . The kidney regulates the ionic composition and volume of urine by active reabsorption or secretion of ions and/or passive reabsorption of water at five functional zones along the nephron: 1) the proximal convoluted tubule, 2) the descending loop of Henle, 3) the ascending loop of Henle, 4) the distal convoluted tubule, and 5) the collecting tubule and duct (Figure 17.2).

### A. Proximal convoluted tubule

In the proximal convoluted tubule located in the cortex of the kidney, almost all the glucose, bicarbonate, amino acids, and other metabolites are reabsorbed (Figure 17.3). Approximately 65% of the filtered  $\text{Na}^+$  (and water) is reabsorbed. Given the high water permeability, about

### THIAZIDE DIURETICS

*Chlorothiazide*  
*Hydrochlorothiazide*  
*Chlorthalidone*  
*Indapamide*  
*Metolazone*

### LOOP DIURETICS

*Ethacrynic acid*  
*Furosemide*  
*Bumetanide*  
*Torsemide*

### POTASSIUM-SPARING DIURETICS

*Spironolactone*  
*Triamterene*  
*Amiloride*  
*Eplerenone*

### CARBONIC ANHYDRASE INHIBITORS

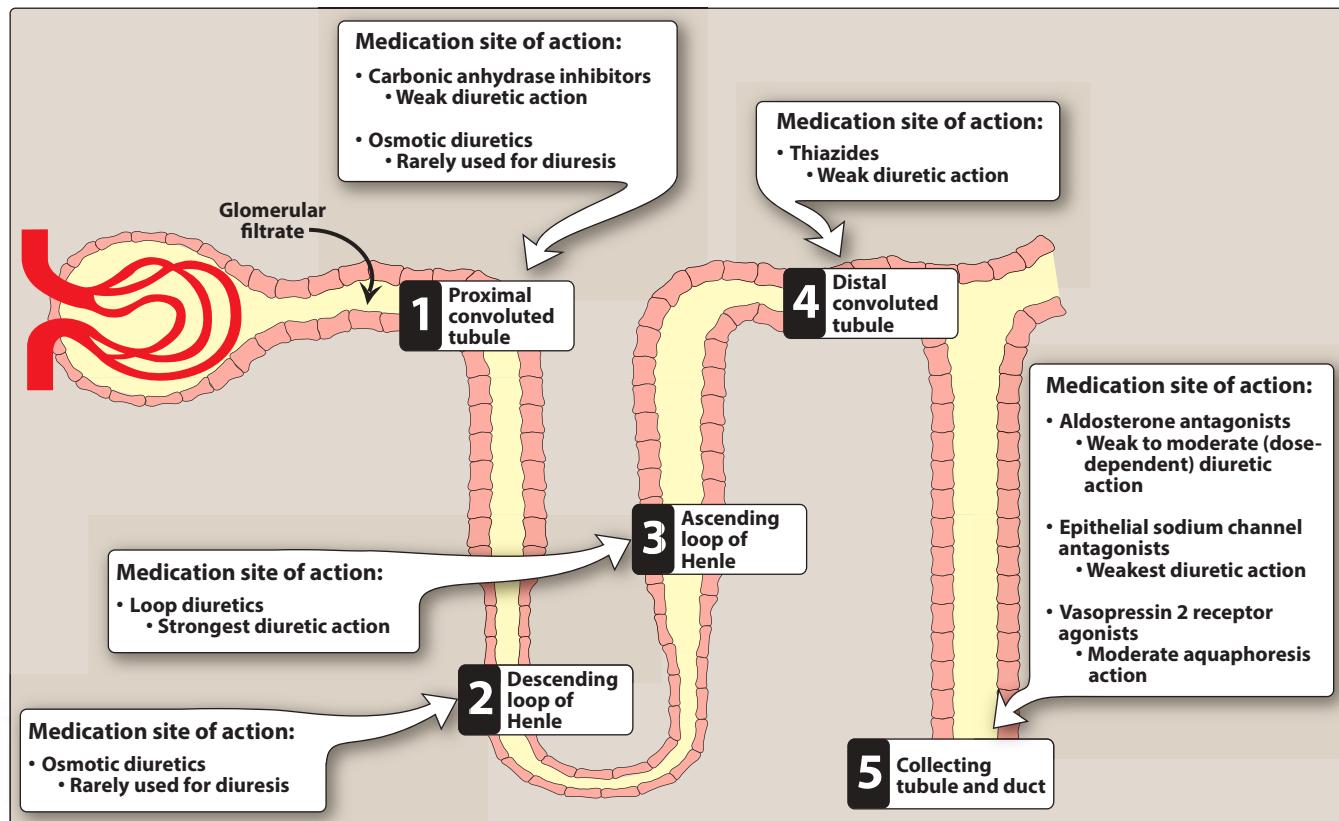
*Acetazolamide*

### OSMOTIC DIURETICS

*Mannitol*

### Figure 17.1

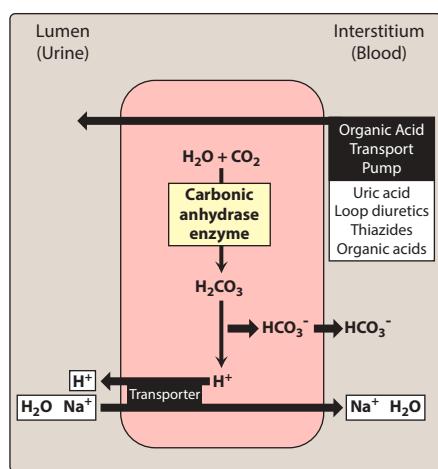
Summary of diuretic drugs.

**Figure 17.2**

Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

60% of water is reabsorbed from the lumen to the blood to maintain osmolar equality. Chloride enters the lumen of the tubule in exchange for an anion, such as oxalate, as well as paracellularly through the lumen. The  $\text{Na}^+$  that is reabsorbed is pumped into the interstitium by the  $\text{Na}^+/\text{K}^+$ -adenosine triphosphatase (ATPase) pump. Carbonic anhydrase in the luminal membrane and cytoplasm of the proximal tubular cells modulate the reabsorption of bicarbonate. Despite having the highest percentage of filtered  $\text{Na}^+$  that is reabsorbed, diuretics working in the proximal convoluted tubule display weak diuretic properties. The presence of a high capacity  $\text{Na}^+$  and water reabsorption area (loop of Henle) distal to the proximal convoluted tubule allows reabsorption of  $\text{Na}^+$  and water kept in the lumen by diuretics acting in the proximal convoluted tubule, and limits effective diuresis.

The proximal tubule is the site of the organic acid and base secretory systems. The organic acid secretory system, located in the middle-third of the proximal tubule, secretes a variety of organic acids, such as uric acid, some antibiotics, and diuretics, from the bloodstream into the proximal tubular lumen. The organic acid secretory system is saturable, and diuretic drugs in the bloodstream compete for transfer with endogenous organic acids such as uric acid. A number of other interactions can also occur. For example, *probenecid* interferes with *penicillin* secretion. The organic base secretory system, located in the upper and middle segments of the proximal tubule, is responsible for the secretion of creatinine and choline.

**Figure 17.3**

Proximal convoluted tubule cell.

## B. Descending loop of Henle

The remaining filtrate, which is isotonic, next enters the descending limb of the loop of Henle and passes into the medulla of the kidney. The osmolarity increases along the descending portion of the loop of Henle because of the countercurrent mechanism that is responsible for water reabsorption. This results in a tubular fluid with a three-fold increase in  $\text{Na}^+$  and  $\text{Cl}^-$  concentration. Osmotic diuretics exert part of their action in this region.

## C. Ascending loop of Henle

The cells of the ascending tubular epithelium are unique in being impermeable to water. Active reabsorption of  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  is mediated by a  $\text{Na}^+/\text{K}^+/2\text{Cl}^-$  cotransporter (Figure 17.4). Both  $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$  are reabsorbed via the paracellular pathway. Thus, the ascending loop dilutes the tubular fluid and raises the osmolarity of the medullary interstitium. Approximately 25% to 30% of the filtered sodium chloride is absorbed here. Because the ascending loop of Henle is a major site for salt reabsorption and no segments distally are capable of significant  $\text{Na}^+$  and water reabsorption, drugs affecting this site, such as loop diuretics, have the greatest diuretic effect.

## D. Distal convoluted tubule

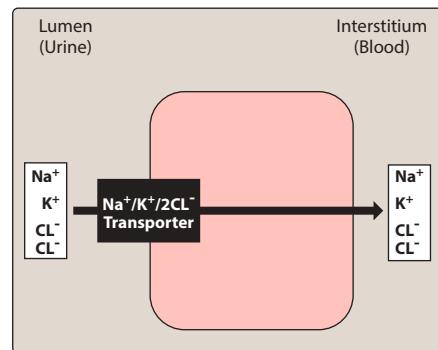
The cells of the distal convoluted tubule are also impermeable to water. About 5% to 10% of the filtered sodium chloride is reabsorbed via a  $\text{Na}^+/\text{Cl}^-$  transporter, the target of thiazide diuretics. Calcium reabsorption, under the regulation of parathyroid hormone, is mediated by an apical channel and then transported by a  $\text{Na}^+/\text{Ca}^{2+}$ -exchanger into the interstitial fluid (Figure 17.5).

## E. Collecting tubule and duct

The principal cells of the collecting tubule and duct are responsible for  $\text{Na}^+$ ,  $\text{K}^+$ , and water transport, whereas the intercalated cells affect  $\text{H}^+$  secretion (Figure 17.6). Approximately 1% to 2% of the filtered sodium enters the principal cells through epithelial sodium channels that are inhibited by *amiloride* and *triamterene*. Once inside the cell,  $\text{Na}^+$  reabsorption relies on a  $\text{Na}^+/\text{K}^+$ -ATPase pump to be transported into the blood. Aldosterone receptors in the principal cells influence  $\text{Na}^+$  reabsorption and  $\text{K}^+$  secretion. Aldosterone increases the synthesis of epithelial sodium channels and of the  $\text{Na}^+/\text{K}^+$ -ATPase pump to increase  $\text{Na}^+$  reabsorption and  $\text{K}^+$  excretion. Antidiuretic hormone (ADH; vasopressin) binds to V2 receptors to promote the reabsorption of water through aquaporin channels.

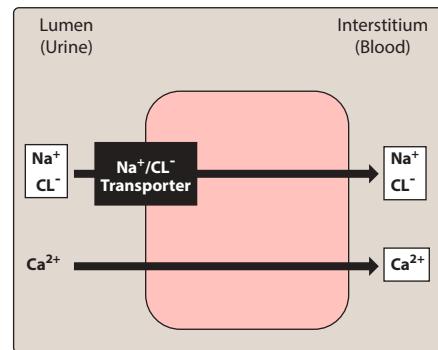
## III. THIAZIDES

The thiazides are the most widely used diuretics because of their anti-hypertensive effects. However, the efficacy of thiazides for hypertension is not entirely dependent on their diuretic actions. These agents also reduce peripheral vascular resistance with long-term therapy. Despite being sulfonamide derivatives, thiazides do not generally cause hypersensitivity



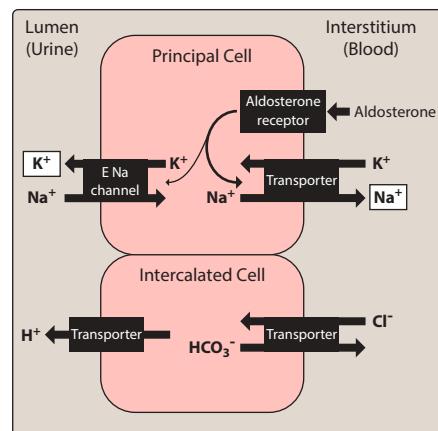
**Figure 17.4**

Ascending loop of Henle cell.



**Figure 17.5**

Distal convoluted tubule cell.



**Figure 17.6**

Collecting tubule and duct cells. E Na channel = Epithelial sodium channel.

reactions in patients with allergies to sulfonamide antimicrobials such as *sulfamethoxazole*. All thiazides affect the distal convoluted tubule ([Figure 17.2](#)), and all have equal maximum diuretic effects, differing only in potency. Thiazides are sometimes called “low ceiling diuretics,” because increasing the dose above normal therapeutic doses does not promote further diuretic response.

### A. Thiazides

*Chlorothiazide* [klor-oh-THYE-ah-zide] was the first orally active thiazide, although *hydrochlorothiazide* [hi-dro-klor-oh-THYE-ah-zide] and *chlorthalidone* [klor-THAL-i-done] are now used more commonly due to better bioavailability. *Hydrochlorothiazide* is more potent, so the required dose is considerably lower than that of *chlorothiazide*, but the efficacy is comparable to that of the parent drug. *Chlorthalidone* is approximately twice as potent as *hydrochlorothiazide*. In all other aspects, *hydrochlorothiazide* resembles *chlorothiazide*. *Chlorthalidone*, *indapamide* [in-DAP-a-mide], and *metolazone* [me-TOL-ah-zone] are referred to as thiazide-like diuretics because they lack the characteristic benzothiadiazine chemical structure; however, their mechanism of action, indications, and adverse effects are similar to those of *hydrochlorothiazide*.

**1. Mechanism of action:** The thiazide and thiazide-like diuretics act mainly in the distal convoluted tubule to decrease the reabsorption of  $\text{Na}^+$  by inhibition of a  $\text{Na}^+/\text{Cl}^-$  cotransporter ([Figure 17.5](#)). As a result, these drugs increase the concentration of  $\text{Na}^+$  and  $\text{Cl}^-$  in the tubular fluid. Thiazides must be excreted into the tubular lumen at the proximal convoluted tubule to be effective ([Figure 17.3](#)). Thiazides must be excreted into the tubular lumen at the proximal convoluted tubule to be effective ([Figure 17.3](#)). Therefore, decreasing renal function reduces the diuretic effects. The antihypertensive effects of thiazides may persist even when the glomerular filtration rate is below 30 mL/min/1.73  $\text{m}^2$ . However, hypertension at this level of renal dysfunction is often exacerbated by hypervolemia, requiring a change to loop diuretics for volume status and, therefore, blood pressure control. The efficacy of thiazides may be diminished with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as *indomethacin*, which inhibit production of renal prostaglandins, thereby reducing renal blood flow.

**2. Actions:**

- Increased excretion of  $\text{Na}^+$  and  $\text{Cl}^-$ :** Thiazide and thiazide-like diuretics cause diuresis with increased  $\text{Na}^+$  and  $\text{Cl}^-$  excretion, which can result in the excretion of very hyperosmolar (concentrated) urine. This latter effect is unique, as the other diuretic classes are unlikely to produce a hyperosmolar urine. [Figure 17.7](#) outlines relative changes in the ionic composition of the urine with thiazide and thiazide-like diuretics.
- Decreased urinary calcium excretion:** Thiazide and thiazide-like diuretics decrease the  $\text{Ca}^{2+}$  content of urine by promoting the reabsorption of  $\text{Ca}^{2+}$  in the distal convoluted tubule where parathyroid hormone regulates reabsorption.
- Reduced peripheral vascular resistance:** An initial reduction in blood pressure results from a decrease in blood volume

DIURETIC CLASS	URINE VOLUME	URINARY EXCRETION OF:						
		Na <sup>+</sup>	K <sup>+</sup>	Mg <sup>2+</sup>	Ca <sup>2+</sup>	Cl <sup>-</sup>	HCO <sub>3</sub> <sup>-</sup>	Uric acid
Thiazide	Initial: 	↑	↑	↑	↓	↑	↓	↓
	Chronic: 							
Loop		↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↓↓↓	↓↓↓
Potassium sparing								
Aldosterone antagonists		↔	↓	↔	↔	↔	↔	↔
Epithelium sodium channel antagonists		↔	↓	↔	↔	↔	↔	↔
Carbonic anhydrase inhibitor		↔	↑	↔	↔	↔	↑	↔

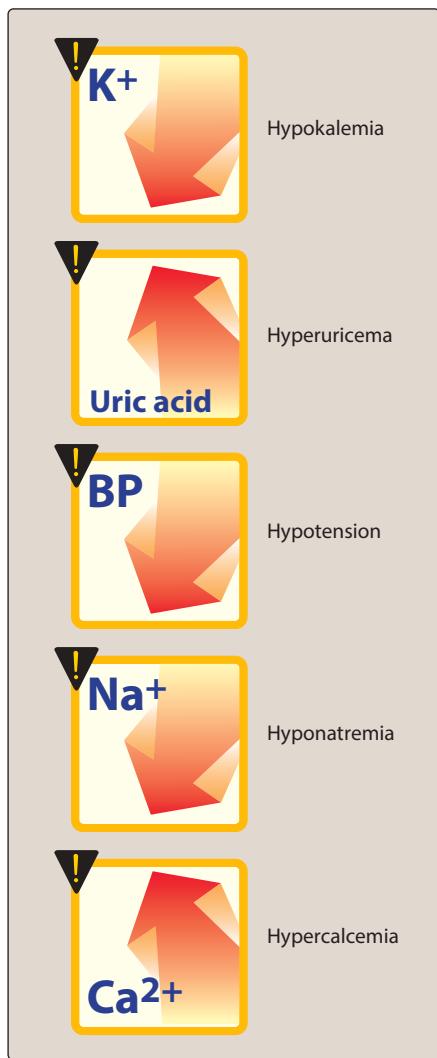
**Figure 17.7**

Urinary excretion from diuretic therapy.

and, therefore, a decrease in cardiac output. With continued therapy, blood volume returns to baseline. However, antihypertensive effects continue, resulting from reduced peripheral vascular resistance caused by relaxation of arteriolar smooth muscle.

### 3. Therapeutic uses:

- Hypertension:** Clinically, thiazides are a mainstay of antihypertensive treatment, because they are inexpensive, convenient to administer, and well tolerated. Blood pressure can be lowered with a daily dose of thiazide. At doses equipotent to *hydrochlorothiazide*, *chlorthalidone* is considered a preferred option by some clinicians because of its longer half-life (50 to 60 hours) and improved control of blood pressure over the entire day. However, current treatment guidelines for hypertension do not recommend any thiazide preferentially.
- Heart failure:** Loop diuretics (not thiazides) are the diuretics of choice in reducing extracellular volume in heart failure. However, thiazide diuretics may be added in patients resistant to loop diuretics, with careful monitoring for hypokalemia. *Metolazone* is most frequently utilized as an addition to loop diuretics, although there is a lack of evidence that it is more effective than other thiazides for this indication when administered at equipotent doses. Historically, thiazides were prescribed to be administered 30 minutes prior to loop diuretics to allow the thiazide time to reach the site of action when combined to augment diuresis in diuretic resistance. This practice is unnecessary and not supported by current evidence.

**Figure 17.8**

Summary of adverse effects commonly observed with thiazide and thiazide-like medications.

- c. **Hypercalciuria:** The thiazides can be useful in treating idiopathic hypercalciuria and calcium oxalate stones in the urinary tract, because they inhibit urinary  $\text{Ca}^{2+}$  excretion.
- d. **Diabetes insipidus:** Thiazides have the unique ability to produce a hyperosmolar urine. Thiazides can be utilized as a treatment for nephrogenic diabetes insipidus. The urine volume of such individuals may drop from 11 L/d to about 3 L/d when treated with thiazides.
- 4. **Pharmacokinetics:** As a class, thiazides are effective orally, with a bioavailability of 60% to 70%. *Chlorothiazide* has a much lower bioavailability (15% to 30%) and is the only thiazide with an intravenous dosage form. Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure and exhibit a prolonged half-life (approximately 10 to 15 hours). *Indapamide* differs from the class because it undergoes hepatic metabolism and is excreted in both the urine and bile. Most thiazides are primarily excreted unchanged in the urine.
- 5. **Adverse effects:** These mainly involve problems in fluid and electrolyte balance (Figure 17.8).
  - a. **Hypokalemia:** Hypokalemia is the most frequent problem with the thiazide diuretics. Because thiazides increase  $\text{Na}^+$  in the filtrate arriving at the distal tubule, more  $\text{K}^+$  is also exchanged for  $\text{Na}^+$ , resulting in a continual loss of  $\text{K}^+$  from the body with prolonged use of these drugs. Thus, serum  $\text{K}^+$  should be measured periodically (more frequently at the beginning of therapy) to monitor for the development of hypokalemia. Potassium supplementation or combination with a potassium-sparing diuretic may be required. Low-sodium diets blunt the potassium depletion caused by thiazide diuretics.
  - b. **Hypomagnesemia:** Urinary loss of magnesium can lead to hypomagnesemia.
  - c. **Hyponatremia:** Hyponatremia may develop due to elevation of ADH, as well as diminished diluting capacity of the kidney and increased thirst.
  - d. **Hyperuricemia:** Thiazides increase serum uric acid by decreasing the amount of acid excreted through competition in the organic acid secretory system. Being insoluble, uric acid deposits in the joints and may precipitate a gouty attack in predisposed individuals. Therefore, thiazides should be used with caution in patients with gout or high levels of uric acid.
  - e. **Hypovolemia:** This can cause orthostatic hypotension or light-headedness.
  - f. **Hypercalcemia:** Thiazides inhibit the secretion of  $\text{Ca}^{2+}$ , sometimes leading to hypercalcemia (elevated levels of  $\text{Ca}^{2+}$  in the blood).
  - g. **Hyperglycemia:** Therapy with thiazides can lead to mild elevations in serum glucose, possibly due to impaired release of insulin related to hypokalemia. Patients with diabetes still benefit from thiazide therapy, but should monitor glucose to assess the need for an adjustment in diabetes therapy if thiazides are initiated.

## IV. LOOP DIURETICS

*Bumetanide* [byoo-MET-ah-nide], *furosemide* [fur-OH-se-mide], *torsemide* [TOR-se-mide], and *ethacrynic acid* have their major diuretic action on the ascending limb of the loop of Henle (Figure 17.2). Of all the diuretics, these drugs have the highest efficacy in mobilizing  $\text{Na}^+$  and  $\text{Cl}^-$  from the body, producing copious amounts of urine. Similar to thiazides, loop diuretics do not generally cause hypersensitivity reactions in patients with allergies to sulfonamide antimicrobials such as *sulfamethoxazole* because of structural differences in their sulfonamide derivative. *Furosemide* is the most commonly used of these drugs. The use of *bumetanide* and *torsemide* is increasing, as these agents have better bioavailability and are more potent compared to *furosemide*. *Ethacrynic acid* is used infrequently due to its adverse effect profile.

### A. Bumetanide, furosemide, torsemide, and ethacrynic acid

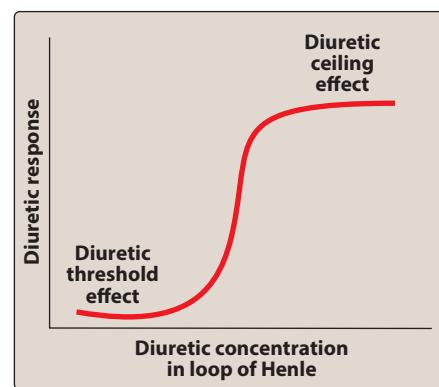
- Mechanism of action:** Loop diuretics inhibit the cotransport of  $\text{Na}^+/\text{K}^+/2\text{Cl}^-$  in the luminal membrane in the ascending limb of the loop of Henle (Figure 17.4). Therefore, reabsorption of these ions into the renal medulla is decreased. By lowering the osmotic pressure in the medulla, less water is reabsorbed from water permeable segments, like the descending loop of Henle, causing diuresis. These agents have the greatest diuretic effect of all the diuretics because the ascending limb accounts for reabsorption of 25% to 30% of filtered  $\text{NaCl}$ , and downstream sites are unable to compensate for the increased  $\text{Na}^+$  load. Loop diuretics must be excreted into the tubular lumen at the proximal convoluted tubule to be effective (Figure 17.3). NSAIDs inhibit renal prostaglandin synthesis and can reduce the diuretic action of loop diuretics.

- Actions:**

- Diuresis:** Loop diuretics cause diuresis, even in patients with poor renal function or lack of response to other diuretics. Changes in the composition of the urine induced by loop diuretics are shown in Figure 17.7.

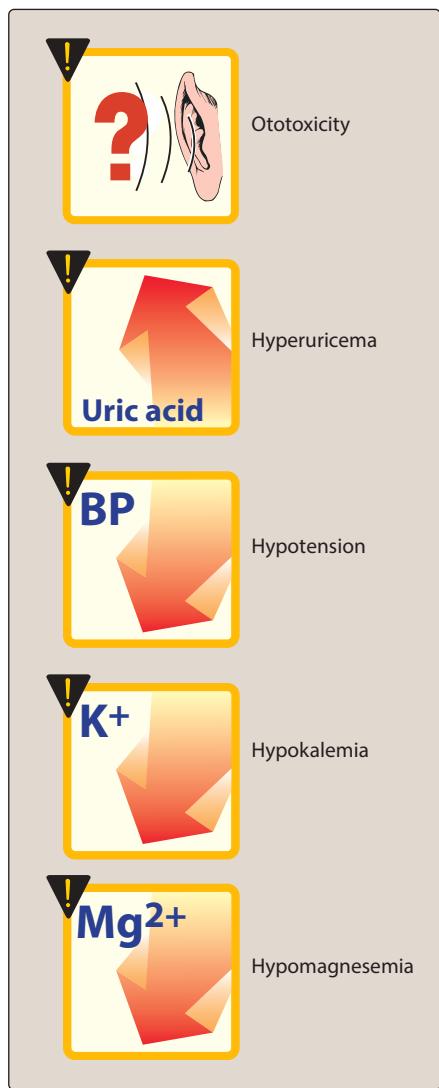
Loop diuretics display a sigmoidal ("S"-shaped) dose-response curve with three parts: a threshold effect, a rapid increase in diuresis with small changes in drug concentration, and a ceiling effect (Figure 17.9). A dose must be selected to cross the response threshold, which is patient-specific. Reducing the effective dose with the intent of a reduction in diuresis can result in no diuresis, if the concentration of loop diuretic drops below the response threshold. Likewise, increasing the effective dose may not cause more diuresis because of the ceiling effect. Thus, after determination of an effective diuretic dose, the clinician should modify the frequency of administration to increase or decrease the daily diuresis.

- Increased urinary calcium excretion:** Unlike thiazides, loop diuretics increase the  $\text{Ca}^{2+}$  content of urine. In patients with



**Figure 17.9**

Loop diuretic dose-response curve.



**Figure 17.10**

Summary of adverse effects commonly observed with loop diuretics.

normal serum  $\text{Ca}^{2+}$  concentrations, hypocalcemia does not result, because  $\text{Ca}^{2+}$  is reabsorbed in the distal convoluted tubule.

- c. **Venodilation:** Prior to their diuretic actions, loop diuretics cause acute venodilation and reduce left ventricular filling pressures via enhanced prostaglandin synthesis.

### 3. Therapeutic uses:

- a. **Edema:** Loop diuretics are the drugs of choice for treatment of pulmonary edema and acute/chronic peripheral edema caused from heart failure or renal impairment. Because of their rapid onset of action, particularly when given intravenously, the drugs are useful in emergency situations such as acute pulmonary edema.
- b. **Hypercalcemia:** Loop diuretics (along with hydration) are also useful in treating hypercalcemia, because they stimulate tubular  $\text{Ca}^{2+}$  excretion.
- c. **Hyperkalemia:** Loop diuretics can be used with or without replacement intravenous fluid for the treatment of hyperkalemia.

- 4. **Pharmacokinetics:** Loop diuretics are administered orally or parenterally. *Furosemide* has unpredictable bioavailability of 10% to 90% after oral administration. *Bumetanide* and *tosemide* have reliable bioavailability of 80% to 100%, which make these agents preferred for oral therapy. The duration of action is approximately 6 hours for *furosemide* and *bumetanide*, and moderately longer for *tosemide*, allowing patients to predict the window of diuresis.

- 5. **Adverse effects:** Fluid and electrolyte issues are the predominant adverse effects (Figure 17.10).

- a. **Acute hypovolemia:** Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias.
- b. **Hypokalemia:** The heavy load of  $\text{Na}^+$  presented to the collecting tubule results in increased exchange of tubular  $\text{Na}^+$  for  $\text{K}^+$ , leading to hypokalemia, the most common adverse effect of the loop diuretics. The loss of  $\text{K}^+$  from cells in exchange for  $\text{H}^+$  leads to hypokalemic alkalosis. Use of potassium-sparing diuretics or supplementation with  $\text{K}^+$  can prevent the development of hypokalemia.
- c. **Hypomagnesemia:** Urinary loss of magnesium can lead to hypomagnesemia.
- d. **Ototoxicity:** Reversible or permanent hearing loss may occur with loop diuretics, particularly when infused intravenously at fast rates, at high doses, or when used in conjunction with other ototoxic drugs (for example, aminoglycoside antibiotics). With current dosing and appropriate infusion rates, ototoxicity is a rare occurrence. *Ethacrynic acid* is the most likely to cause ototoxicity. Although less common, vestibular function may also be affected, inducing vertigo.
- e. **Hyperuricemia:** Loop diuretics compete with uric acid for the renal secretory systems, thus blocking its secretion and, in turn, may cause or exacerbate gouty attacks.

## V. POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics act in the collecting tubule to inhibit  $\text{Na}^+$  reabsorption and  $\text{K}^+$  excretion (Figure 17.6). Potassium levels must be monitored in patients treated with potassium-sparing diuretics. These drugs should be used cautiously in moderate renal dysfunction and avoided in patients with severe renal dysfunction because of the increased risk of hyperkalemia. Within this class, there are drugs with two distinct mechanisms of action with different indications for use: aldosterone antagonists and epithelial sodium channel blockers. Changes in the composition of the urine induced by potassium-sparing diuretics are shown in Figure 17.7.

### A. Aldosterone antagonists: spironolactone and eplerenone

1. **Mechanism of action:** *Spironolactone* [spear-oh-no-LAK-tone] and *eplerenone* [eh-PLEH-reh-none] are synthetic steroids that antagonize aldosterone receptors. This prevents translocation of the receptor complex into the nucleus of the target cell, ultimately resulting in a lack of intracellular proteins that stimulate the  $\text{Na}^+/\text{K}^+$ -exchange sites of the collecting tubule. Thus, aldosterone antagonists prevent  $\text{Na}^+$  reabsorption and, therefore,  $\text{K}^+$  and  $\text{H}^+$  secretion. *Eplerenone* is more selective for aldosterone receptors and causes less endocrine effects (gynecomastia) than *spironolactone*, which also binds to progesterone and androgen receptors.
2. **Actions:** *Spironolactone* and *eplerenone* antagonize aldosterone receptors at renal sites which causes diuresis, and nonrenal sites which causes other effects. In most edematous states, blood levels of aldosterone are high, causing retention of  $\text{Na}^+$ . *Spironolactone* antagonizes the activity of aldosterone, resulting in retention of  $\text{K}^+$  and excretion of  $\text{Na}^+$ .
3. **Therapeutic uses:**
  - a. **Edema:** Aldosterone antagonists are particularly effective diuretics when used in high doses for edema associated with secondary hyperaldosteronism, such as hepatic cirrhosis and nephrotic syndrome. *Spironolactone* is the diuretic of choice in patients with hepatic cirrhosis with fluid in the peritoneal cavity (ascites). By contrast, in patients who have no significant circulating levels of aldosterone, there is minimal diuretic effect with use of this drug.
  - b. **Hypokalemia:** Although the aldosterone antagonists have a low efficacy in mobilizing  $\text{Na}^+$  from the body in comparison with the other diuretics, they have the useful property of causing the retention of  $\text{K}^+$ . These agents are often given in conjunction with thiazide or loop diuretics to prevent  $\text{K}^+$  excretion that occurs with those diuretics.
  - c. **Heart failure:** Aldosterone antagonists are employed at lower doses to prevent myocardial remodeling mediated by aldosterone. Use of these agents has been shown to decrease mortality associated with heart failure, particularly in those with reduced ejection fraction.

- d. **Resistant hypertension:** Resistant hypertension, defined by the use of three or more medications without reaching the blood pressure goal, often responds well to aldosterone antagonists. This effect can be seen in those with or without elevated aldosterone levels.
  - e. **Polycystic ovary syndrome:** *Spironolactone* is often used off-label for the treatment of polycystic ovary syndrome. It blocks androgen receptors and inhibits steroid synthesis at high doses, thereby helping to offset increased androgen levels seen in this disorder.
4. **Pharmacokinetics:** Both *spironolactone* and *eplerenone* are well absorbed after oral administration. *Spironolactone* is extensively metabolized and converted to several active metabolites, which contribute to the therapeutic effects. *Eplerenone* is metabolized by cytochrome P450 3A4.
5. **Adverse effects:**
- a. **Hyperkalemia:** The most common side effect, hyperkalemia, is dose-dependent and increases with renal dysfunction or other potassium-sparing agents such as angiotensin-converting enzyme inhibitors and potassium supplements.
  - b. **Gynecomastia:** *Spironolactone*, but not *eplerenone*, may induce gynecomastia in approximately 10% of male patients and menstrual irregularities in female patients.

## B. Triamterene and amiloride

*Triamterene* [trye-AM-ter-een] and *amiloride* [a-MIL-oh-ride] block epithelial sodium channels, resulting in a decrease in  $\text{Na}^+/\text{K}^+$  exchange. Although they have a  $\text{K}^+$ -sparing diuretic action similar to that of the aldosterone antagonists, their ability to block the  $\text{Na}^+/\text{K}^+$ -exchange site in the collecting tubule does not depend on the presence of aldosterone. Like the aldosterone antagonists, these agents are not very efficacious diuretics. Both *triamterene* and *amiloride* are commonly used in combination with other diuretics, almost solely for their potassium-sparing properties.

## VI. CARBONIC ANHYDRASE INHIBITOR

*Acetazolamide* [ah-set-a-ZOLE-a-mide] and other carbonic anhydrase inhibitors are more often used for their other pharmacologic actions than for their diuretic effect, because they are much less efficacious than the thiazide or loop diuretics.

### A. Acetazolamide

1. **Mechanism of action:** *Acetazolamide* inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium (Figure 17.3). [Note: Carbonic anhydrase catalyzes the reaction of  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , leading to  $\text{H}_2\text{CO}_3$ , which spontaneously ionizes to  $\text{H}^+$  and  $\text{HCO}_3^-$  (bicarbonate).]

The decreased ability to exchange  $\text{Na}^+$  for  $\text{H}^+$  in the presence of *acetazolamide* results in a mild diuresis. Additionally,  $\text{HCO}_3^-$  is retained in the lumen, with marked elevation in urinary pH. The loss of  $\text{HCO}_3^-$  causes a hyperchloremic metabolic acidosis. Changes in the composition of urinary electrolytes induced by *acetazolamide* are summarized in [Figure 17.7](#).

2. **Therapeutic uses:**
  - a. **Glaucoma:** Oral *acetazolamide* decreases the production of aqueous humor and reduces intraocular pressure in patients with chronic open-angle glaucoma, probably by blocking carbonic anhydrase in the ciliary body of the eye. Topical carbonic anhydrase inhibitors, such as *dorzolamide* and *brinzolamide*, have the advantage of not causing systemic effects.
  - b. **Altitude sickness:** *Acetazolamide* can be used in the prophylaxis of symptoms of altitude sickness. *Acetazolamide* prevents weakness, breathlessness, dizziness, nausea, and cerebral as well as pulmonary edema characteristic of the syndrome.
3. **Pharmacokinetics:** *Acetazolamide* can be administered orally or intravenously. It is approximately 90% protein bound and eliminated renally by both active tubular secretion and passive reabsorption.
4. **Adverse effects:** Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur. The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of  $\text{NH}_4^+$ .

## VII. OSMOTIC DIURETICS

A number of simple, hydrophilic chemical substances that are filtered through the glomerulus, such as *mannitol* [MAN-i-tol], result in diuresis ([Figure 17.2](#)). Filtered substances that undergo little or no reabsorption result in a higher osmolarity of the tubular fluid. This prevents further water reabsorption at the descending loop of Henle and proximal convoluted tubule, resulting in osmotic diuresis with little additional  $\text{Na}^+$  excretion (aquaresis). Therefore, these agents are not useful for treating conditions in which  $\text{Na}^+$  retention occurs. They are used to maintain urine flow following acute toxic ingestion of substances capable of producing acute renal failure. Osmotic diuretics are a mainstay of treatment for patients with increased intracranial pressure. [Note: *Mannitol* is not absorbed when given orally and should be given intravenously.] Adverse effects include dehydration and extracellular water expansion from the osmotic effects in the systemic circulation. The expansion of extracellular water occurs because the presence of *mannitol* in the extracellular fluid extracts water from the cells and causes hyponatremia until diuresis occurs.

[Figure 17.11](#) summarizes the major classes of diuretics, their dosage, primary indication, common adverse effects, therapeutic considerations, and drug interactions.

DRUG	DOSE	PRIMARY INDICATION	COMMON ADVERSE EFFECTS	THERAPEUTIC CONSIDERATIONS	DRUG INTERACTIONS
<b>Thiazides:</b>					
<i>Chlorthalidone (oral)</i>	Initial: 12.5 mg daily Usual: 12.5–25 mg daily	Hypertension	Hypotension, muscle cramps, weakness, erectile dysfunction, hypokalemia, hyponatremia, hyperglycemia (in diabetic or prediabetes), hyperlipidemia, hyperuricemia (at low doses)	Low dietary intake of potassium predisposes to hypokalemia, especially in the elderly; therefore, moderate salt restriction is the key for effective antihypertensive effect and for protection from diuretic-induced hypokalemia	Hypokalemia aggravated by other drugs—β-agonists, theophylline, corticosteroids amphotericin; hypokalemia potentiates digitalis toxicity; decrease in the efficacy of a variety of drugs including anticoagulants and uricosurics;
<i>Hydrochlorothiazide (oral)</i>	Initial: 12.5 mg daily Usual (as monotherapy): 12.5–50 mg once daily Usual (as adjunctive therapy): 12.5–25 mg once daily Maximum: 50 mg daily (some sources recommend maximum 25 mg daily) Thiazides can be given once daily or every other day		Less common Allergic reactions (cross-sensitivity to other sulfonamide derivatives), photosensitivity, fatigue, blood dyscrasias, azotemia (in renal disease patients)	Thiazides are not effective in patients with renal failure (serum creatinine > 2mg /dl) because of reduced GFR. Monitor SCr and potassium Monitor and use cautiously in patients at risk or history of gout and in diabetic or prediabetes patients (may change glycemic control) and in arrhythmia	NSAIDs: Reduced diuretic efficacy β-blockers: Potentiate hyperglycemia, hyperlipidemias Thiazides can increase the blood levels of lithium Combination with ARB and ACE inhibitors effectively lowers BP as they have different target for lowering BP while eliminating risk of hypokalaemia with diuretics or hyperkalaemia with ACE inhibitors
<i>Indapamide (oral)</i>	Initial: 1.25 mg once daily Usual (as monotherapy): 2.5 mg once daily Usual (as adjunctive therapy): 1.25–2.5 mg once daily Maximum: 5 mg daily <i>Dose preferred to be taken early morning to avoid sleep disturbance due to nocturia</i>				
<i>Xipamide</i>	Duration of action: 20–40 mg daily for hypertension				
<i>Clopamide</i>	40–80 mg for edema (duration of action is 12 hours) 10–60 mg daily (duration of action is 12–18 hours)				
<i>Frusemide (oral, intravenous)</i>	20–80 mg orally once daily; may be increased by 20–40 mg every 6–8 hours; Not to exceed 400 mg/day <i>Dose preferred to be taken early morning to avoid sleep disturbance due to nocturia</i>	Hypertension; rapid reduction of edematous fluid as seen in congestive heart failure, nephritic syndrome Pulmonary edema, liver and renal failure; acute hypercalcemia (due to increase in $\text{Ca}^{2+}$ excretion effect)	Dehydration, hypotension, electrolyte imbalance, metabolic effects—hyperuricemia, hyperglycemia, hypomagnesemia, increased triglyceride and cholesterol levels, increased dLDL cholesterol and decreased HDL cholesterol; dose-related ototoxicity (more with ethacrynic acid); in pregnancy Category C drug GI adverse effects with ethacrynic acid; hypersensitivity	Strict observation is necessary during the period of diuresis as excessive diuresis is seen particularly in the elderly patients Best initiated in the hospital In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved Use cautiously in patients with hepatic encephalopathy (as hypokalemia may worsen coma) Supplemental potassium chloride and/or an aldosterone antagonist added to prevent hypokalemia and metabolic alkalosis Discontinue, if increasing azotemia and oliguria occur during the treatment of severe progressive renal disease	Increase ototoxicity and nephrotoxicity in patients taking aminoglycosides and cisplatin Increase in lithium levels due to reduced renal elimination Increase risk of arrhythmia with drugs causing hypokalemia; combined with $\text{K}^+$ -sparing diuretics to counter hypokalemia, especially with concomitant digitalis therapy or left ventricular hypertrophy NSAIDS reduce efficacy
<i>Torsemide</i>					
<i>Bumetanide</i>					

**Figure 17.11**

Major classes of diuretics, their dosage, primary indication, common adverse effects, therapeutic indications, and drug interactions. (Figure continues on next page)

DRUG	DOSE	PRIMARY INDICATION	COMMON ADVERSE EFFECTS	THERAPEUTIC CONSIDERATIONS	DRUG INTERACTIONS
<b>K<sup>+</sup> sparing:</b>					
<i>Amiloride</i> <i>Triamterene</i> <i>Spironolac-tone</i> <i>Epleronone (oral)</i>		Used in combination with thiazide diuretics to treat heart failure, hypertension, and refractory edema; hyperaldosteronism as in adrenal hyperplasia and aldosterone-producing adenomas	Hyperkalemia, metabolic acidosis, Gynecomastia, decreased libido and impotence in men as well as menstrual irregularities and hair growth in women (aldosterone antagonists), gastric problems including peptic ulcer	Contraindicated in renal insufficiency, especially in diabetic; should be used with extreme caution in patients taking ACE inhibitors Dietary potassium intake should be reduced	ACE inhibitors: Potentiate hyperkalemia NSIADs: Reduced diuretic efficacy
<i>Acetazolamide (tab)</i> <i>Dorzolamide and Brizolamide (topical eye drops)</i>	<i>Acetazolamide</i> 125–250 mg twice daily	High intraocular pressure (short-term use only), high altitude (mountain sickness); periodic paralysis; occasionally as a second-line drug in epilepsy	Drowsiness and hyperesthesia (in high dose), rashes, hypokalaemia, metabolic acidosis, renal calculi	Contraindicated in hepatic cirrhosis	
<b>Osmotic diuretics:</b>					
<i>Glycerin</i> <i>Iosorbide</i> <i>Mannitol</i> <i>Urea</i>	Glycerin is administered orally; topical anhydrous glycerin for corneal edema; mannitol and urea are administered intravenously	Raised intraocular pressure in glaucoma and raised intracranial pressure to reduce cerebral edema	Headache, nausea, and serious adverse effects include increase in the excretion of all electrolytes; exacerbation of congestive heart failure or pulmonary congestion		

**Figure 17.11** (Continued)

Major classes of diuretics, their dosage, primary indication, common adverse effects, therapeutic indications, and drug interactions.

## Study Questions

Choose the ONE best answer.

- 17.1 An elderly patient with a history of heart disease has difficulty breathing and is diagnosed with acute pulmonary edema. Which treatment is indicated?
- A. Acetazolamide
  - B. Chlorthalidone
  - C. Furosemide
  - D. Spironolactone
- 17.2 A group of college students is planning a mountain climbing trip to the Andes. Which is most appropriate for them to take to prevent altitude sickness?
- A. A thiazide diuretic such as hydrochlorothiazide
  - B. An anticholinergic such as atropine
  - C. A carbonic anhydrase inhibitor such as acetazolamide
  - D. A loop diuretic such as furosemide
- 17.3 An alcoholic male has developed hepatic cirrhosis. To control the ascites and edema, which should be prescribed?
- A. Acetazolamide
  - B. Chlorthalidone
  - C. Furosemide
  - D. Spironolactone
- 17.4 A 55-year-old male with kidney stones needs a medication to decrease urinary calcium excretion. Which diuretic is best for this indication?
- A. Torsemide
  - B. Hydrochlorothiazide
  - C. Spironolactone
  - D. Triamterene
- 17.5 A 75-year-old woman with hypertension and glaucoma is being treated with a chlorthalidone, amlodipine, lisinopril, and acetazolamide. In clinic today, she complains of acute joint pain and redness in her great toe which is diagnosed as gout. Which medication is most likely to have caused the gout attack?
- A. Amlodipine
  - B. Acetazolamide
  - C. Chlorthalidone
  - D. Lisinopril

Correct answer = C. This is a potentially fatal situation. It is important to administer a diuretic that reduces fluid accumulation in the lungs and improves oxygenation and heart function. The loop diuretics are most effective in removing large fluid volumes from the body and are the treatment of choice in this situation. In this situation, furosemide should be administered intravenously. The other choices are inappropriate.

Correct answer = C. Acetazolamide is used prophylactically for several days before an ascent above 10,000 feet. This treatment prevents the cerebral and pulmonary problems associated with altitude sickness as well as other difficulties, such as nausea.

Correct answer = D. Spironolactone is very effective in the treatment of hepatic edema. These patients are frequently resistant to the diuretic action of loop diuretics, although a combination with spironolactone may be beneficial. The other agents are not indicated.

Correct answer = B. Hydrochlorothiazide is effective in increasing calcium reabsorption, thus decreasing the amount of calcium excreted, and decreasing the formation of kidney stones that contain calcium phosphate or calcium oxalate. Furosemide increases the excretion of calcium, whereas the K<sup>+</sup>-sparing diuretics, spironolactone, and triamterene do not have an effect.

Correct answer = C. Thiazides such as chlorthalidone compete with uric acid for secretion into the lumen of the nephron at the proximal convoluted tubule. This competition decreases uric acid secretion, raising the serum concentration and increasing the risk of a gout attack. Loop diuretics have the same risk.

- 17.6 Which is contraindicated in a patient with hyperkalemia?
- Acetazolamide
  - Chlorothiazide
  - Ethacrynic acid
  - Eplerenone
- 17.7 A 59-year-old male patient in the intensive care unit has a metabolic alkalosis. Which therapy will treat this condition?
- Amiloride
  - Hydrochlorothiazide
  - Mannitol
  - Acetazolamide
- 17.8 A male patient is placed on a new medication and notes that his breasts have become enlarged and tender to the touch. Which medication is he most likely taking?
- Furosemide
  - Hydrochlorothiazide
  - Spironolactone
  - Triamterene
- 17.9 A patient with heart failure with reduced ejection fraction researched his medications on the Internet and found he was taking two “diuretics,” bumetanide and spironolactone. He asks if this is a mistake with his therapy. What is the best response?
- Spironolactone is used to prevent hyponatremia.
  - Spironolactone is used to reduce heart structure changes and decrease the risk of death.
  - Bumetanide is used to decrease the potassium lost from spironolactone therapy.
  - This is a duplication error and one diuretic should be stopped.
- 17.10 Which diuretic has been shown to improve blood pressure in resistant hypertension or those already treated with three blood pressure medications including a thiazide or thiazide-like medication?
- Indapamide
  - Furosemide
  - Mannitol
  - Spironolactone

Correct answer = D. Eplerenone acts in the collecting tubule via aldosterone antagonism to inhibit  $\text{Na}^+$  reabsorption and  $\text{K}^+$  excretion. It is extremely important that patients who are treated with any potassium-sparing diuretic be closely monitored for potassium levels. Exogenous potassium supplementation is usually discontinued when potassium-sparing diuretic therapy is initiated. The other drugs promote the excretion of potassium.

Correct answer = D. Acetazolamide causes an increase in the urinary excretion of bicarbonate, lowering the pH of the blood.

Correct answer = C. An adverse drug reaction to spironolactone is gynecomastia due to its effects on androgens and progesterone in the body. Eplerenone may be a suitable alternative if the patient is in need of an aldosterone antagonist but has a history of gynecomastia.

Correct answer = B. Aldosterone antagonists are used at nondiuretic doses in heart failure to prevent myocardial remodeling and decrease mortality. Bumetanide is used as a diuretic to treat edema from heart failure. Both are appropriate to use together because of the unique indications. Spironolactone reduces the potassium lost from diuresis with bumetanide.

Correct answer = D. Resistant hypertension, defined by the use of three or more medications without reaching the blood pressure goal, often responds well to aldosterone antagonists. This effect can be seen in those with or without elevated aldosterone levels.



# Drugs for Heart Failure

Shawn Anderson

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# 18

## I. OVERVIEW

Heart failure (HF) is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body. Its cardinal symptoms are dyspnea, fatigue, and fluid retention. Heart failure is due to an impaired ability of the heart to adequately fill with and/or eject blood. It is often accompanied by abnormal increases in blood volume and interstitial fluid. The underlying causes of HF include, but are not limited to, atherosclerotic heart disease, hypertensive heart disease, valvular heart disease, and congenital heart disease.

### A. Role of physiologic compensatory mechanisms in the progression of HF

Chronic activation of the sympathetic nervous system and the renin-angiotensin–aldosterone system is associated with remodeling of cardiac tissue, loss of myocytes, hypertrophy, and fibrosis. This prompts additional neurohormonal activation, creating a vicious cycle that, if left untreated, leads to death.

### B. Goals of pharmacologic intervention in HF

Goals of treatment are to alleviate symptoms, slow disease progression, and improve survival. Therapeutic agents act by:

- increasing cardiac contractility,
- reducing preload, and
- normalizing heart rate and rhythm.

Accordingly, nine classes of drugs have been shown to be effective: 1) angiotensin-converting enzyme inhibitors, 2) angiotensin-receptor blockers, 3) aldosterone antagonists, 4)  $\beta$ -blockers, 5) diuretics, 6) direct vaso- and venodilators, 7) HCN channel blockers, 8) inotropic agents, and 9) B type natriuretic peptide (Figure 18.1). Depending on the severity of HF and individual patient factors, one or more of these classes of drugs are administered. Pharmacologic intervention provides the following benefits in HF: reduced myocardial work load, decreased extracellular fluid volume, improved cardiac contractility, and a reduced rate of cardiac remodeling. Knowledge of the physiology of cardiac muscle contraction is essential for understanding the compensatory responses evoked by the failing heart, as well as the actions of drugs used to treat HF.

#### ACE INHIBITORS

*Captopril*  
*Enalapril*  
*Ramipril*  
*Lisinopril*  
*Quinapril*  
*Fosinopril*

#### ANGIOTENSIN RECEPTOR BLOCKERS

*Losartan*  
*Telmisartan*  
*Valsartan*  
*Candesartan*

#### ANRI

*Sacubitril/valsartan*

#### ALDOSTERONE ANTAGONISTS

*Spironolactone*  
*Eplerenone*

#### $\beta$ -ADRENORECEPTOR BLOCKERS

*Bisoprolol*  
*Carvedilol*  
*Metoprolol succinate*  
*Metoprolol tartrate*

#### DIURETICS

*Metolazone*  
*Furosemide*  
*Bumetanide*  
*Torsemide*

#### DIRECT VASO- AND VENODILATORS

*Hydralazine*  
*Isosorbide dinitrate*  
*FDC Hydralazine/Isosorbide dinitrate*

#### HCN CHANNEL BLOCKER

*Ivabradine*

#### INOTROPIC AGENTS

*Digoxin*  
*Dobutamine*  
*Milrinone*

#### B-TYPE NATRIURETIC PEPTIDE

*Nesiritide*

#### Figure 18.1

Summary of drugs used to treat HF. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ANRI = angiotensin receptor neprilysin inhibitor; FDC = fixed dose combination. (For drug dosages, refer to Appendix at the end of the book.)

## II. PHYSIOLOGY OF MUSCLE CONTRACTION

The myocardium, like smooth and skeletal muscle, responds to stimulation by depolarization of the membrane, which is followed by shortening of the contractile proteins and ends with relaxation and return to the resting state (repolarization). Cardiac myocytes are interconnected in groups that respond to stimuli as a unit, contracting together whenever a single cell is stimulated.

### A. Action potential

Cardiac myocytes are electrically excitable and have a spontaneous, intrinsic rhythm generated by specialized “pacemaker” cells located in the sinoatrial (SA) and atrioventricular (AV) nodes. Cardiac myocytes also have an unusually long action potential, which can be divided into five phases (0 to 4). [Figure 18.2](#) illustrates the major ions contributing to depolarization and repolarization of cardiac myocytes.

### B. Cardiac contraction

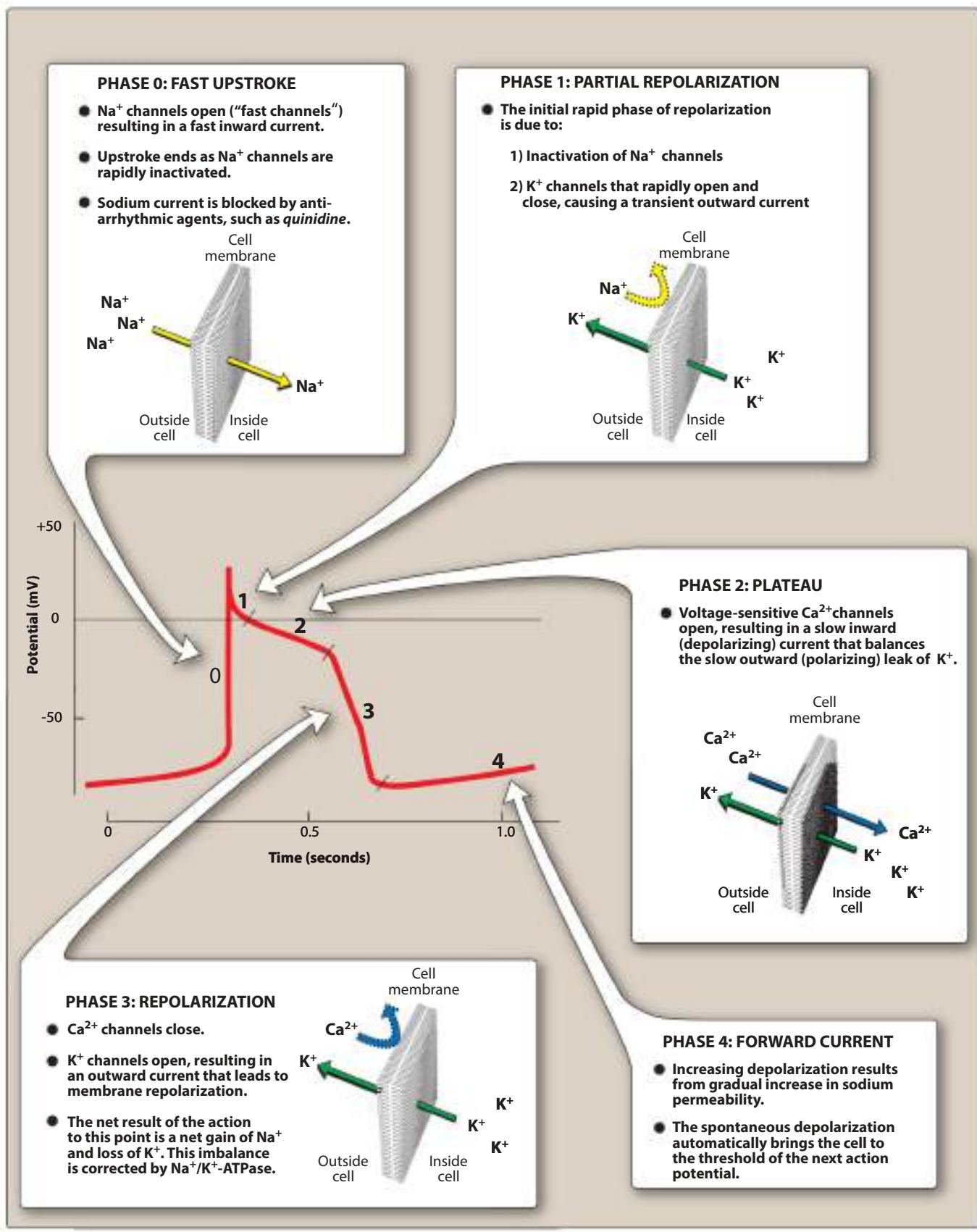
The force of contraction of the cardiac muscle is directly related to the concentration of free (unbound) cytosolic calcium. Therefore, agents that increase intracellular calcium levels (or that increase the sensitivity of the contractile machinery to calcium) increase the force of contraction (inotropic effect). Calcium handling by cardiac myocytes is illustrated in [Figure 18.3](#).

### C. Compensatory physiological responses in HF

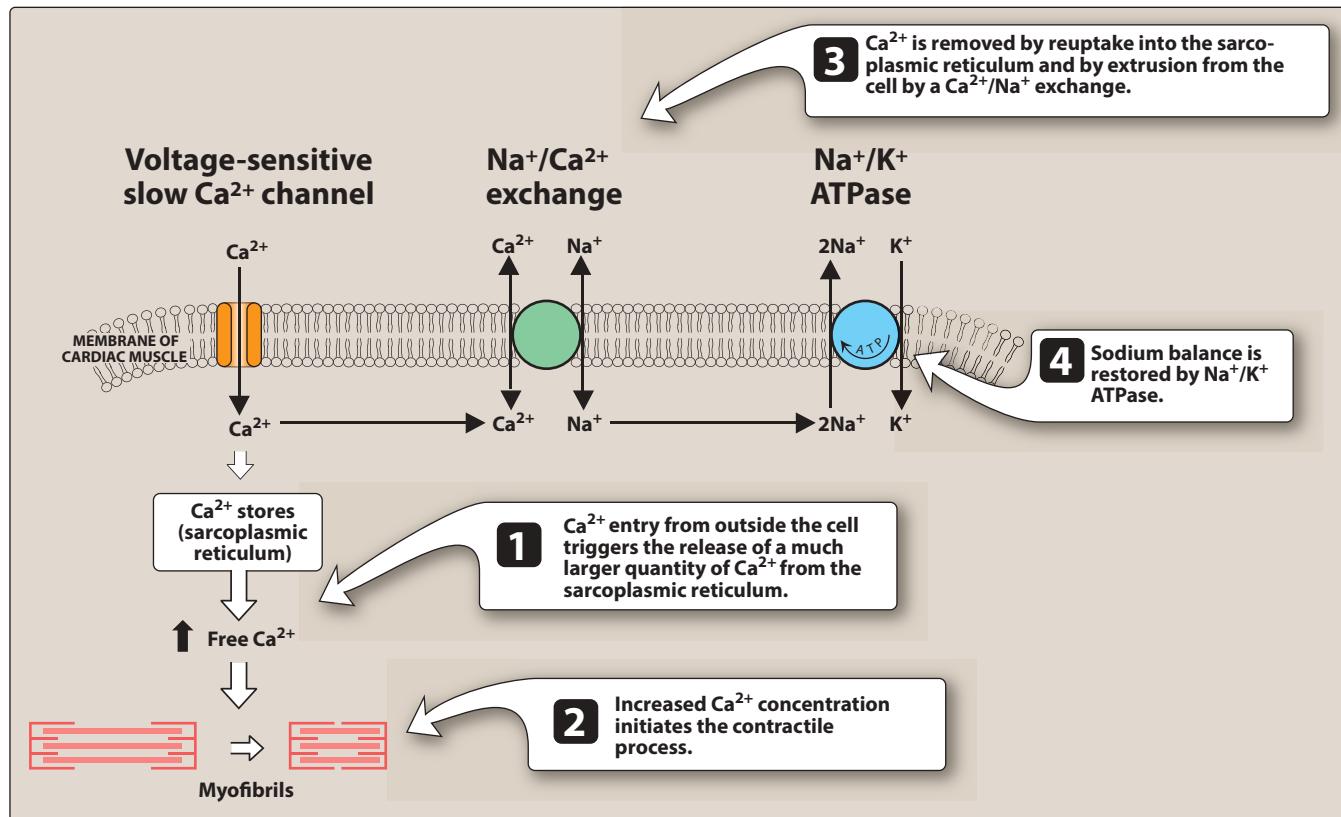
The failing heart evokes four major compensatory mechanisms to enhance cardiac output ([Figure 18.4](#)).

**1. Increased sympathetic activity:** Baroreceptors sense a decrease in blood pressure and activate the sympathetic nervous system. In an attempt to sustain tissue perfusion, this stimulation of  $\beta$ -adrenergic receptors results in an increased heart rate and a greater force of contraction of the heart muscle. In addition, vasoconstriction enhances venous return and increases cardiac preload. An increase in preload (stretch on the heart) increases stroke volume, which, in turn, increases cardiac output. These compensatory responses increase the workload of the heart, which, in the long term, contributes to further decline in cardiac function.

**2. Activation of the renin–angiotensin–aldosterone system (RAAS):** A fall in cardiac output decreases blood flow to the kidney, prompting the release of renin. Renin release is also stimulated by increased sympathetic activity resulting in increased formation of angiotensin II and release of aldosterone. This results in increased peripheral resistance (afterload) and retention of sodium and water. Blood volume increases and more blood is returned to the heart. If the heart is unable to pump this extra volume, venous pressure increases and peripheral and pulmonary edema occur. In addition, high levels of angiotensin II and aldosterone have direct detrimental effects on cardiac muscle, favoring remodeling, fibrosis, and inflammatory changes. Again, these compensatory responses increase the workload of the heart, contributing to further decline in cardiac function.

**Figure 18.2**

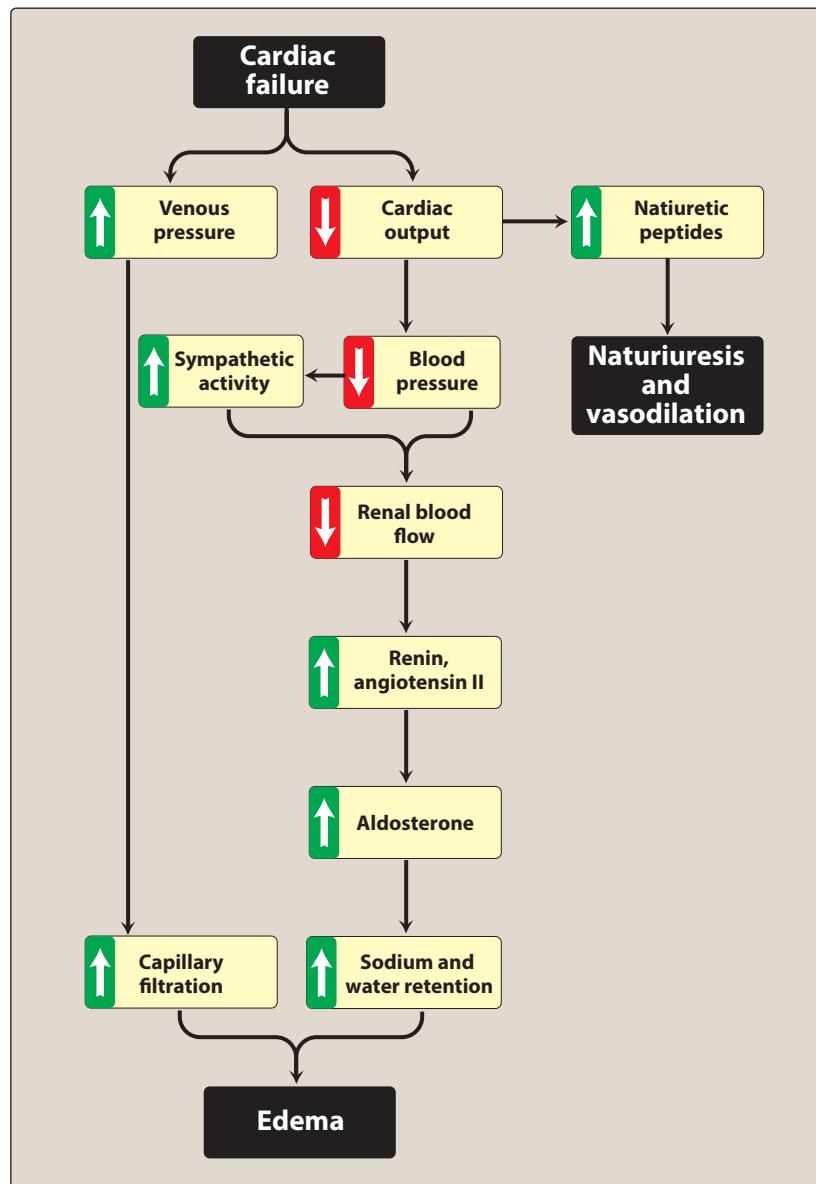
Action potential of a cardiac myocyte. ATPase = adenosine triphosphatase.



**Figure 18.3**

Ion movements during the contraction of cardiac muscle. ATPase = adenosine triphosphatase.

- 3. Activation of natriuretic peptides:** An increase in preload also increases the release of natriuretic peptides. Natriuretic peptides, which include atrial, B-type, and C-type, have differing roles in HF; atrial and B-type natriuretic peptides are the most important. Activation of the natriuretic peptides ultimately results in vasodilation, natriuresis, inhibition of renin and aldosterone release, and a reduction in myocardial fibrosis. This beneficial response may improve cardiac function and HF symptoms.
- 4. Myocardial dysfunction:** Initially, stretching of the heart muscle leads to a stronger contraction of the heart. However, excessive elongation of the fibers results in weaker contractions and a diminished ability to eject blood. This type of failure is termed “systolic failure” or HF with reduced ejection fraction (HFrEF) and is the result of the ventricle being unable to pump effectively. Patients with HF may have “diastolic dysfunction,” a term applied when the ability of the ventricles to relax and accept blood is impaired by structural changes such as hypertrophy. The thickening of the ventricular wall and subsequent decrease in ventricular volume decrease the ability of the heart muscle to relax. In this case, the ventricle does not fill adequately, and the inadequacy of cardiac output is termed “diastolic HF” or HF with preserved ejection fraction (HFpEF). Diastolic dysfunction, in its pure form, is characterized by signs

**Figure 18.4**

Cardiovascular consequences of HF.

and symptoms of HF in the presence of a normal functioning left ventricle. However, both systolic and diastolic dysfunction commonly coexist in HF.

#### D. Acute (decompensated) HF

If the adaptive mechanisms adequately restore cardiac output, HF is said to be compensated. If the adaptive mechanisms fail to maintain cardiac output, HF is decompensated and the patient develops worsening HF signs and symptoms. Typical HF signs and symptoms include dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and peripheral edema.

### E. Therapeutic strategies in HF

Chronic HF is typically managed by fluid limitations (less than 1.5 to 2 L daily); low dietary intake of sodium (less than 2000 mg/d); treatment of comorbid conditions; and judicious use of diuretics. Specifically for HFrEF, inhibitors of the RAAS, inhibitors of the sympathetic nervous system, and drugs that enhance the activity of natriuretic peptides have been shown to improve survival and reduce symptoms. Inotropic agents are reserved for acute signs and symptoms of HF and are used mostly in the inpatient setting. Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, nondihydropyridine calcium channel blockers, and some antiarrhythmic drugs, should be avoided if possible.

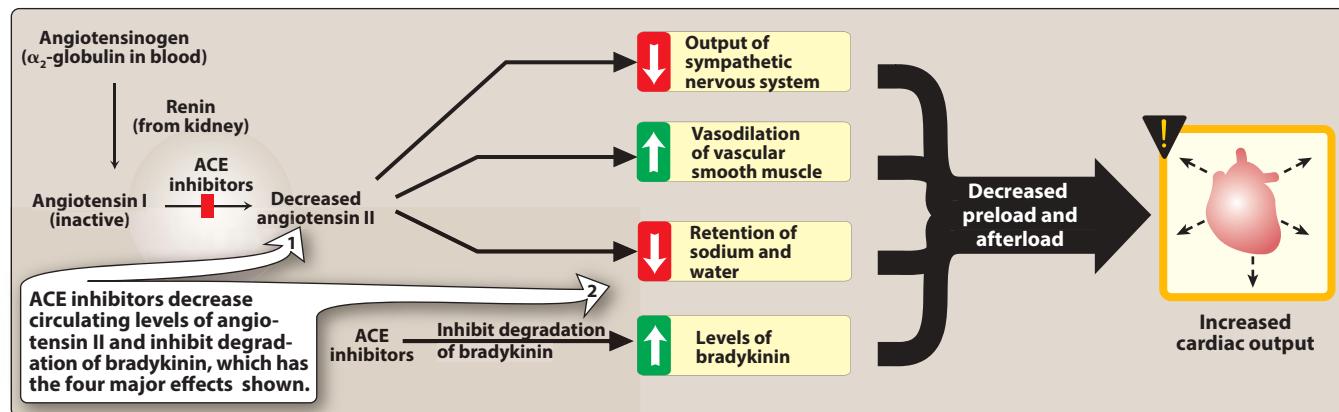
## III. INHIBITORS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The compensatory activation of the RAAS in heart failure leads to increased workload on the heart and a resultant decline in cardiac function. Therefore, inhibition of the RAAS is an important pharmacological target in the management of HF.

### A. Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are a part of standard pharmacotherapy in HFrEF. These drugs block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. They also diminish the inactivation of bradykinin (Figure 18.5).

- Actions:** ACE inhibitors decrease vascular resistance (afterload) and venous tone (preload), resulting in increased cardiac output. ACE inhibitors also blunt the usual angiotensin II-mediated increase in epinephrine and aldosterone seen in HF. ACE inhibitors improve clinical signs and symptoms of HF and have been shown to significantly improve patient survival in HF.



**Figure 18.5**

Effects of ACE inhibitors. [Note: The reduced retention of sodium and water results from two causes: decreased production of angiotensin II and aldosterone.]

2. **Therapeutic use:** ACE inhibitors may be considered for patients with asymptomatic and symptomatic HFrEF. Importantly, ACE inhibitors are indicated for patients with all stages of left ventricular failure. These agents should be started at low doses and titrated to target or maximally tolerated doses in the management of HFrEF. ACE inhibitors are also used in the treatment of hypertension (see Chapter 16). Patients who have had a recent myocardial infarction or are at a high risk for a cardiovascular event also benefit from long-term ACE inhibitor therapy.
3. **Pharmacokinetics:** ACE inhibitors are adequately absorbed following oral administration. Food may decrease the absorption of *captopril* [CAP-toe-pril], so it should be taken on an empty stomach. Except for *captopril* and injectable *enalaprilat* [en-AL-a-pril-at], ACE inhibitors are prodrugs that require activation by hydrolysis via hepatic enzymes. Renal elimination of the active moiety is important for most ACE inhibitors except *fosinopril* [foe-SIH-no-pril], which also undergoes excretion in the feces. Plasma half-lives of active compounds vary from 2 to 12 hours, although the inhibition of ACE may be much longer.
4. **Adverse effects:** These include postural hypotension, renal insufficiency, hyperkalemia, a persistent dry cough, and angioedema (rare). Because of the risk of hyperkalemia, potassium levels must be monitored, particularly with concurrent use of potassium supplements, potassium-sparing diuretics, or aldosterone antagonists. Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease. The potential for symptomatic hypotension with ACE inhibitors is much more common if used concomitantly with a diuretic. ACE inhibitors are teratogenic and should not be used in pregnant women. Please see Chapter 16 for a full discussion of ACE inhibitors.

## B. Angiotensin receptor blockers

Angiotensin receptor blockers (ARBs) are orally active compounds that are competitive antagonists of the angiotensin II type 1 receptor. Because ACE inhibitors inhibit only one enzyme responsible for the production of angiotensin II, ARBs have the advantage of more complete blockade of the actions of angiotensin II. However, ARBs do not affect bradykinin levels. Although ARBs have actions similar to those of ACE inhibitors, they are not therapeutically identical. Even so, ARBs are a substitute for patients who cannot tolerate ACE inhibitors.

1. **Actions:** Although ARBs have a different mechanism of action than ACE inhibitors, their actions on preload and afterload are similar. Their use in HF is mainly as a substitute in patients who cannot tolerate ACE inhibitors due to cough or angioedema, which are thought to be mediated by elevated bradykinin levels. ARBs are also used in the treatment of hypertension (see Chapter 16).
2. **Pharmacokinetics:** ARBs are orally active and are dosed once daily, with the exception of *valsartan* [val-SAR-tan] which is dosed twice daily. They are highly plasma protein bound. *Losartan*

[Ioe-SAR-tan] differs in that it undergoes extensive first-pass hepatic metabolism, including conversion to an active metabolite. The other drugs have inactive metabolites. Elimination of metabolites and parent compounds occurs in urine and feces.

3. **Adverse effects:** ARBs have an adverse effect and drug interaction profile similar to that of ACE inhibitors. However, the ARBs have a lower incidence of cough and angioedema. Like ACE inhibitors, ARBs are contraindicated in pregnancy.

### C. Aldosterone receptor antagonists

Patients with HF have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone. *Spironolactone* [spy-ro-no-LAC-tone] and *epiorenone* [eh-PLEH-reh-none] are antagonists of aldosterone at the mineralocorticoid receptor, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia. Spironolactone also has affinity for androgen and progesterone receptors, and is associated with endocrine-related adverse effects such as gynecomastia and dysmenorrhea. Aldosterone antagonists are indicated in patients with symptomatic HFrEF or HFrEF and recent myocardial infarction. Please see Chapter 17 for a full discussion of aldosterone receptor antagonists.

## IV. $\beta$ -BLOCKERS

Although it may seem counterintuitive to administer drugs with negative inotropic activity in HF, evidence clearly demonstrates improved systolic function and reverse cardiac remodeling in patients receiving  $\beta$ -blockers. These benefits arise in spite of an occasional, initial exacerbation of symptoms. The benefit of  $\beta$ -blockers is attributed, in part, to their ability to prevent the changes that occur because of chronic activation of the sympathetic nervous system. These agents decrease heart rate and inhibit release of renin in the kidneys. In addition,  $\beta$ -blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death. Three  $\beta$ -blockers have shown benefit in HFrEF: *bisoprolol* [bis-oh-PROE-lol], *carvedilol* [KAR-ve-dil-ol], and long-acting *metoprolol succinate* [me-TOE-proe-lol SUK-si-nate]. *Carvedilol* is a nonselective  $\beta$ -adrenoreceptor antagonist that also blocks  $\alpha$ -adrenoreceptors, whereas *bisoprolol* and *metoprolol succinate* are  $\beta_1$ -selective antagonists. [Note: The pharmacology of  $\beta$ -blockers is described in detail in Chapter 7.]  $\beta$ -Blockade is recommended for all patients with chronic, stable HFrEF. *Bisoprolol*, *carvedilol*, and *metoprolol succinate* reduce morbidity and mortality associated with HFrEF. Treatment should be started at low doses and gradually titrated to target doses based on patient tolerance and vital signs. Both *carvedilol* and *metoprolol* are metabolized by the cytochrome P450 2D6 isoenzyme, and inhibitors of this metabolic pathway may increase levels of these drugs and increase the risk of adverse effects. In addition, *carvedilol* is a substrate of P-glycoprotein (P-gp). Increased effects of *carvedilol* may occur if it is coadministered with P-gp inhibitors.  $\beta$ -Blockers should also be used with caution with other drugs that slow AV conduction, such as *amiodarone*, *verapamil*, and *diltiazem*.

## V. DIURETICS

Diuretics reduce signs and symptoms of volume overload, such as dyspnea on exertion, orthopnea, and peripheral edema. Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases cardiac workload and oxygen demand. Diuretics may also decrease afterload by reducing plasma volume, thereby decreasing blood pressure. Loop diuretics are the most commonly used diuretics in HF. These agents are used for patients who require extensive diuresis and those with renal insufficiency. Since diuretics have not been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess. Please see Chapter 17 for a full discussion of diuretics.

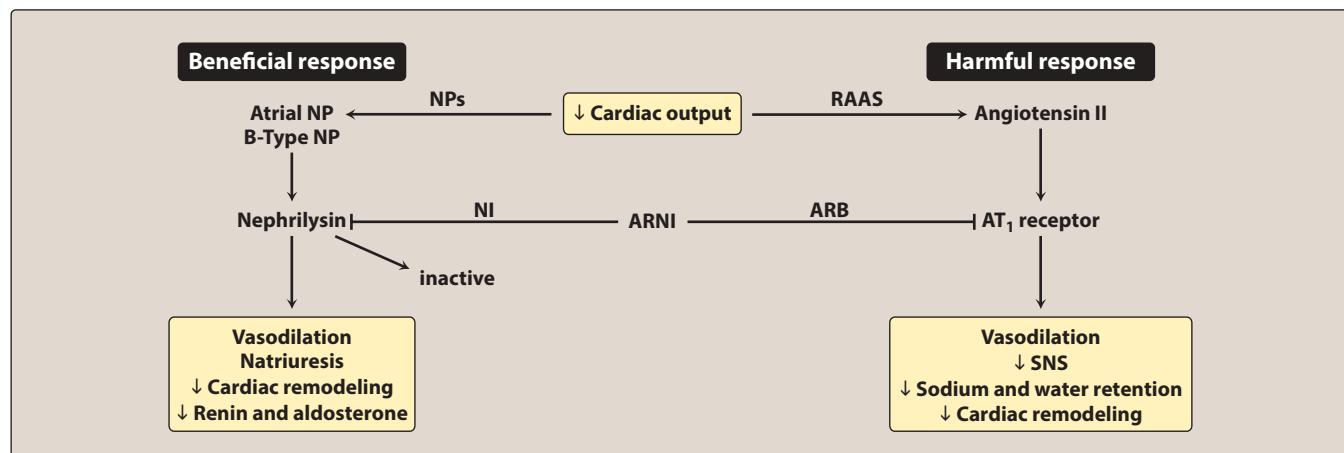
## VI. ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR

Neprilysin is the enzyme responsible for breaking down vasoactive peptides, such as angiotensin I and II, bradykinin, and natriuretic peptides. Inhibition of neprilysin augments the activity of the vasoactive peptides. To maximize the effect of natriuretic peptides, stimulation of the RAAS must be offset without further increase in bradykinin. Therefore an ARB, instead of an ACE inhibitor, is combined with a neprilysin inhibitor to reduce the incidence of angioedema (Figure 18.6).

### A. Sacubitril/valsartan

*Sacubitril* [sak-UE-bi-tril]/*valsartan* is the first available angiotensin receptor-neprilysin inhibitor (ARNI).

1. **Actions:** *Sacubitril/valsartan* combines the actions of an ARB with neprilysin inhibition. Inhibition of neprilysin results in increased concentration of vasoactive peptides, leading to natriuresis,



**Figure 18.6**

Effects of angiotensin-receptor blocker-neprilysin inhibitors. ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; AT1 = angiotensin type 1; NI, neprilysin inhibitor; NP = natriuretic peptide; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system. Modified from King JB, Bress AP, Reese AD, Munger MA. Neprilysin inhibition in heart failure with reduced ejection fraction: a clinical review. *Pharmacotherapy*. 35:823 (2015).

diuresis, vasodilation, and inhibition of fibrosis. Together, the combination decreases afterload, preload, and myocardial fibrosis. An ARNI improves survival and clinical signs and symptoms of HF, as compared to therapy with an ACE inhibitor.

2. **Therapeutic use:** An ARNI should replace an ACE inhibitor or ARB in patients with HFrEF who remain symptomatic on optimal doses of a  $\beta$ -blocker and an ACE inhibitor or ARB.
3. **Pharmacokinetics:** *Sacubitril/valsartan* is orally active, administered with or without food, and quickly breaks down into the separate components. *Sacubitril* is transformed to active drug by plasma esterases. Both drugs have a high volume of distribution and are highly bound to plasma proteins. *Sacubitril* is mainly excreted in the urine. The half-life of approximately 10 hours for both components allows for twice-daily dosing.
4. **Adverse effects:** The adverse effect profile is similar to that of an ACE inhibitor or ARB. Because of the added reduction of afterload, hypotension is more common with an ARNI. Due to inhibition of neprilysin with *sacubitril*, bradykinin levels may increase and angioedema may occur. Therefore, the combination is contraindicated in patients with a history of hereditary angioedema or angioedema associated with an ACE inhibitor or ARB. To minimize risk of angioedema, an ACE inhibitor must be stopped at least 36 hours prior to starting *sacubitril/valsartan*.

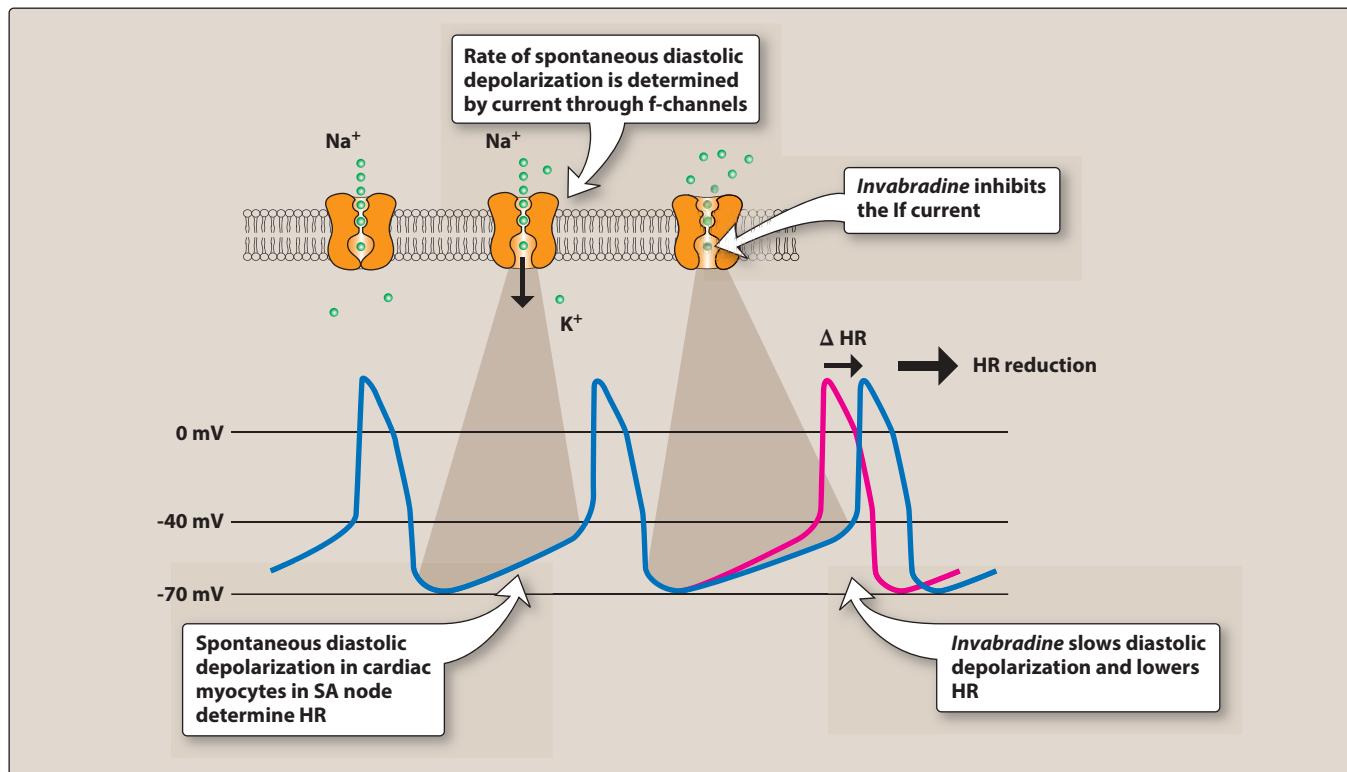
## VII. HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED CHANNEL BLOCKER

The hyperpolarization-activated cyclic nucleotide-gated (HCN) channel is responsible for the  $I_f$  current and setting the pace within the SA node. Inhibition of the HCN channel results in slowing of depolarization and a lower heart rate ([Figure 18.7](#)). Reduction in heart rate is use- and dose-dependent.

### A. Ivabradine

*Ivabradine* [eye-VAB-ra-deen] is the only approved drug in the class of hyperpolarization-activated cyclic nucleotide-gated channel blockers.

1. **Actions:** By selectively slowing the  $I_f$  current in the SA node, reduction of heart rate occurs without a reduction in contractility, AV conduction, ventricular repolarization, or blood pressure. In patients with HFrEF, a slower heart rate increases stroke volume and improves symptoms of HF.
2. **Therapeutic use:** *Ivabradine* is utilized in HFrEF to improve symptoms in patients who are in sinus rhythm with a heart rate above 70 beats per minute and are on optimized HF pharmacotherapy. Specifically, patients should be on an optimal dose of  $\beta$ -blocker or have a contraindication to  $\beta$ -blockers.
3. **Pharmacokinetics:** *Ivabradine* should be administered with meals to increase absorption. It undergoes extensive first-pass metabolism by cytochrome P450 3A4 to an active metabolite, which is also a 3A4 substrate. *Ivabradine* has a high volume of distribution and is 70% protein bound. The half-life is 6 hours which allows for twice-daily dosing.

**Figure 18.7**

Effects of inhibition of  $I_f$  current with *ivabradine*. HR = heart rate;  $K^+$  = potassium;  $Na^+$  = sodium; SA = sinoatrial. Modified from Deedwania P. Selective and specific inhibition of  $I_f$  with ivabradine for the treatment of coronary artery disease or heart failure. Drugs. 73: 1569 (2013).

4. **Adverse effects:** Bradycardia may occur with *ivabradine* which may improve with dose reduction. Because *ivabradine* is mostly selective for the SA node, it is not effective for rate control in atrial fibrillation and has been shown to increase the risk of atrial fibrillation. *Ivabradine* inhibits similar channels in the eye, and luminous phenomena may occur early in therapy. This enhanced brightness may be ameliorated by dose reduction. *Ivabradine* should not be used in pregnancy or breast-feeding, with more advanced heart block, or with potent 3A4 inhibitors.

## VIII. VASO- AND VENODILATORS

Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance. Nitrates are commonly used venous dilators to reduce preload for patients with chronic HF. Arterial dilators, such as *hydralazine* [hye-DRAL-a-zeen], reduce systemic arteriolar resistance and decrease afterload. If the patient is intolerant of ACE inhibitors or ARB, or if additional vasodilator response is required, a combination of *hydralazine* and *isosorbide dinitrate* [eye-soe-SOR-bide dye-NYE-trate] may be used. A fixed-dose combination of these agents has been shown to improve symptoms and survival in black patients with HFrEF on standard HF treatment ( $\beta$ -blocker plus ACE inhibitor or ARB). Headache,

dizziness, and hypotension are common adverse effects with this combination. Rarely, *hydralazine* has been associated with drug-induced lupus.

## IX. INOTROPIC DRUGS

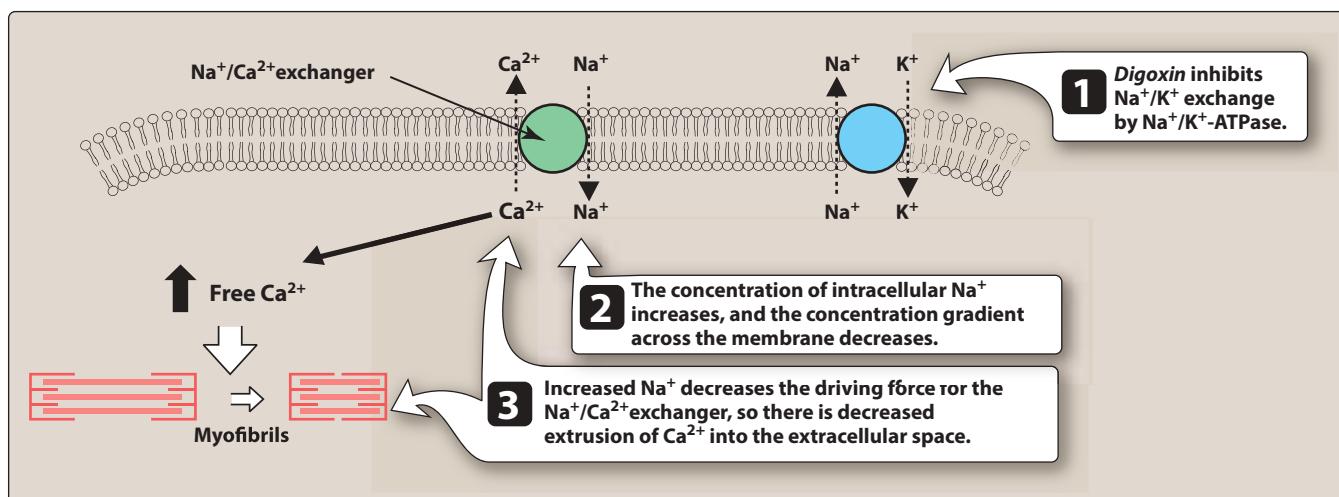
Positive inotropic agents enhance cardiac contractility and, thus, increase cardiac output. Although these drugs act by different mechanisms, the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle. All positive inotropes in HFrEF that increase intracellular calcium concentration have been associated with reduced survival, especially in patients with HFrEF. For this reason, these agents, with the exception of *digoxin*, are only used for a short period mainly in the inpatient setting.

### A. Digitalis glycosides

The cardiac glycosides are often called digitalis or digitalis glycosides, because most of the drugs come from the digitalis (foxglove) plant. They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are used in treating HF. The digitalis glycosides have a low therapeutic index, with only a small difference between a therapeutic dose and doses that are toxic or even fatal. The only available agent is *digoxin* [di-JOX-in].

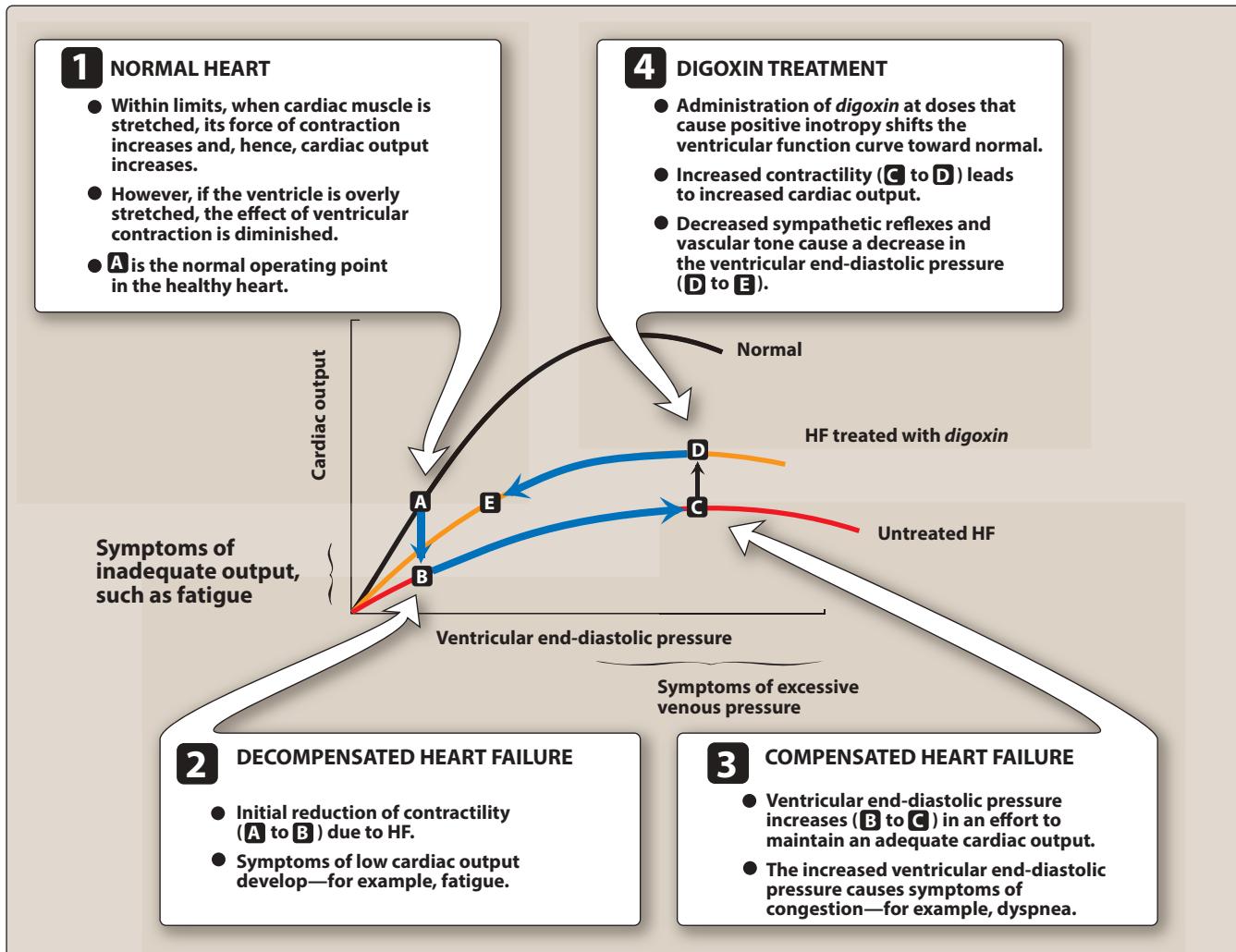
#### 1. Mechanism of action:

- Regulation of cytosolic calcium concentration:** By inhibiting the  $\text{Na}^+/\text{K}^+$ -adenosine triphosphatase (ATPase) enzyme, *digoxin* reduces the ability of the myocyte to actively pump  $\text{Na}^+$  from the cell (Figure 18.8). This ultimately results in a small but physiologically important increase in free  $\text{Ca}^{2+}$ , thereby leading to increased cardiac contractility.
- Increased contractility of the cardiac muscle:** *Digoxin* increases the force of cardiac contraction, causing cardiac output to more closely resemble that of the normal heart (Figure 18.9). Vagal tone is also enhanced, so both heart rate



**Figure 18.8**

Mechanism of action of *digoxin*. ATPase = adenosine triphosphatase.

**Figure 18.9**

Ventricular function curves in the normal heart, in heart failure (HF), and in HF treated with *digoxin*.

and myocardial oxygen demand decrease. *Digoxin* slows conduction velocity through the AV node, making it useful for atrial fibrillation.

- Neurohormonal inhibition:** Although the exact mechanism of this effect has not been elucidated, low-dose *digoxin* inhibits sympathetic activation with minimal effects on contractility. This effect is the reason a lower serum drug concentration is targeted in HFrEF.
- Therapeutic use:** *Digoxin* therapy is indicated in patients with HFrEF who are symptomatic on optimal HF pharmacotherapy. A low serum drug concentration of *digoxin* (0.5 to 0.8 ng/mL) is beneficial in HFrEF.
- Pharmacokinetics:** *Digoxin* is available in oral and injectable formulations. It has a large volume of distribution, because it accumulates in muscle. The dosage is based on lean body weight. In acute situations, such as symptomatic atrial fibrillation, a loading dose regimen is used. *Digoxin* has a long half-life of 30 to 40 hours.

It is mainly eliminated intact by the kidney, requiring dose adjustment in renal dysfunction.

4. **Adverse effects:** At low serum drug concentrations, *digoxin* is well tolerated. However, it has a very narrow therapeutic index. Anorexia, nausea, vomiting, blurred vision, or yellowish vision may be initial indicators of toxicity. When  $\text{Na}^+/\text{K}^+$ -ATPase is markedly inhibited by *digoxin*, the resting membrane potential may increase, which makes the membrane more excitable, increasing the risk of arrhythmias. Decreased levels of serum potassium (hypokalemia) predispose a patient to *digoxin* toxicity, because *digoxin* normally competes with potassium for the same binding site on the  $\text{Na}^+/\text{K}^+$ -ATPase pump. With the use of a lower serum drug concentration in HFrEF, toxic levels are infrequent. *Digoxin* is a substrate of P-gp, and inhibitors of P-gp, such as *clarithromycin*, *verapamil*, and *amiodarone*, can significantly increase *digoxin* levels, necessitating a reduced dose of *digoxin*. *Digoxin* should also be used with caution with other drugs that slow AV conduction, such as  $\beta$ -blockers, *verapamil*, and *diltiazem*.

## B. $\beta$ -Adrenergic agonists

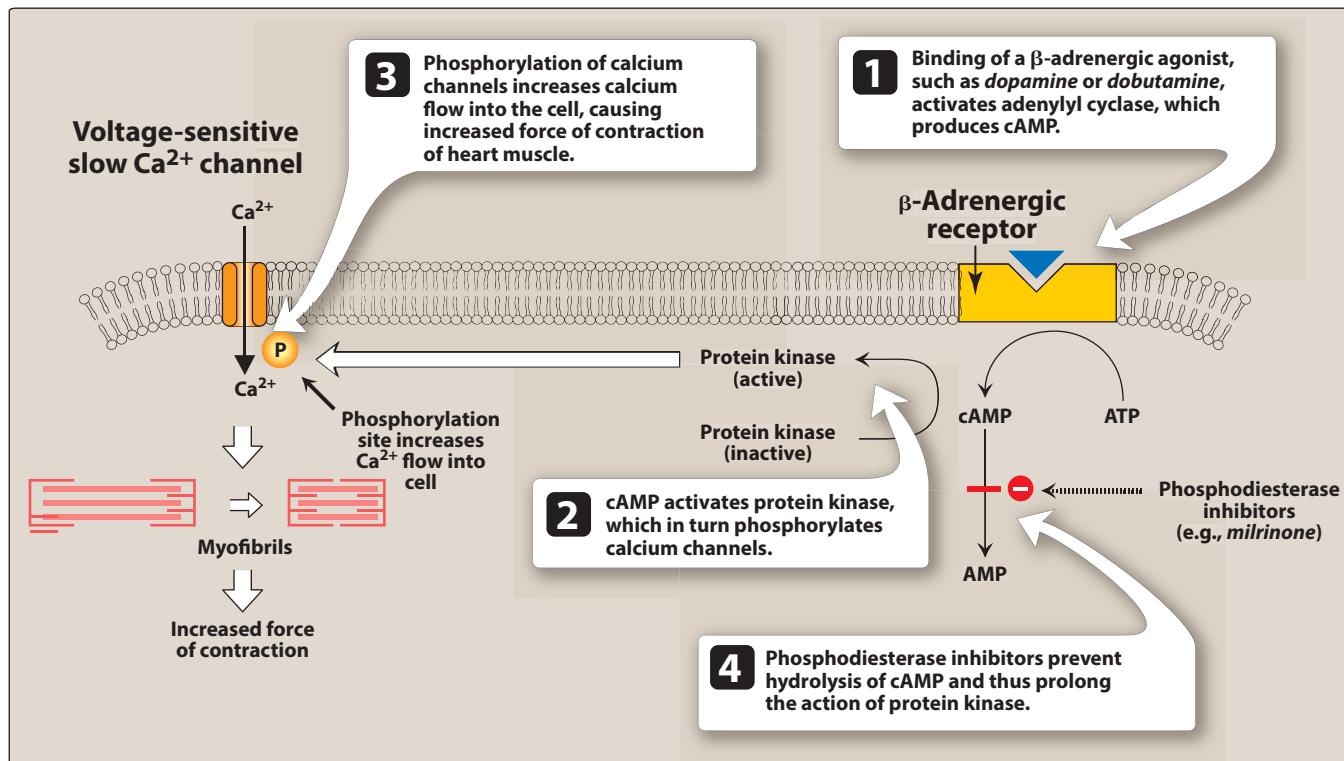
$\beta$ -Adrenergic agonists, such as *dobutamine* [doe-BYOO-ta-meen] and *dopamine* [DOH-puh-meen], improve cardiac performance by causing positive inotropic effects and vasodilation.  $\beta$ -Adrenergic agonists ultimately lead to increased entry of calcium ions into myocardial cells and enhanced contraction (Figure 18.10). Both drugs must be given by intravenous infusion and are primarily used in the short-term treatment of acute HF in the hospital setting.

## C. Phosphodiesterase inhibitors

*Milrinone* [MIL-rih-nohn] is a phosphodiesterase inhibitor that increases the intracellular concentration of cAMP (Figure 18.10). Like  $\beta$ -adrenergic agonists, this results in an increase of intracellular calcium and, therefore, cardiac contractility. *Milrinone* is usually given by intravenous infusion for short-term treatment of acute HF. However, *dobutamine* and *milrinone* may also be considered for intermediate-term treatment in the outpatient setting for palliative care.

## X. RECOMBINANT B-TYPE NATRIURETIC PEPTIDE

In acute decompensated congestive HF, drugs that reduce preload result in improvement in HF symptoms such as dyspnea. Most often, IV diuretics are utilized in the acute setting to reduce preload. When IV diuretics are minimally effective, a recombinant B-type natriuretic peptide (BNP) or *nesiritide* [ni-SIR-i-tide] can be used as an alternative. Through binding to natriuretic peptide receptors, *nesiritide* stimulates natriuresis and diuresis and reduces preload and afterload. *Nesiritide* is administered intravenously as a bolus (most often) and continuous infusion. Like endogenous BNP, *nesiritide* has a short half-life of 20 minutes and is cleared by renal filtration, cleavage by endopeptidases and through internalization after binding to natriuretic peptide receptors. The most common adverse effects are hypotension and dizziness, and like diuretics, *nesiritide* can worsen renal function.

**Figure 18.10**

Sites of action by  $\beta$ -adrenergic agonists on heart muscle. AMP = adenosine monophosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; P = phosphate. Modified from M Jessup, and S Brozena, N. Engl. J. Med. 348: 2007 (2003).

## XI. GOALS OF TREATMENT AND ORDER OF THERAPY

The major goals of treatment in HF are to alleviate symptoms and reduce morbidity by reversing or slowing the cardiac and peripheral dysfunction and to improve prognosis and reduce mortality. For in-hospital patients, in addition to the above goals, other goals of therapy are to reduce the hospital stay and subsequent readmission, to prevent end-organ damage, and to appropriately manage the comorbidities that may contribute to poor prognosis.

Heart failure can be classified according to either symptoms or evolution of the disease. The New York Heart Association (NYHA) functional classification assigns patients to one of the four classes based on the effort needed to elicit clinical symptoms whereas the disease stage emphasizes the progressive development of HF and recognizes risk factors and predisposition to the disease. Figure 18.11 depicts the NYHA functional classification of HF and Figure 18.12 shows a treatment strategy using this classification and the drugs described in this chapter. Note that as the disease progresses, polytherapy is initiated. In patients with overt HF, loop diuretics are often introduced first for relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema. ACE inhibitors or ARBs (if ACE inhibitors are not tolerated) are added after the optimization of diuretic therapy. The dosage is gradually titrated to that which is maximally tolerated and/or produces optimal cardiac output. Historically,  $\beta$ -blockers were added after optimization of ACE inhibitor or ARB therapy; however,

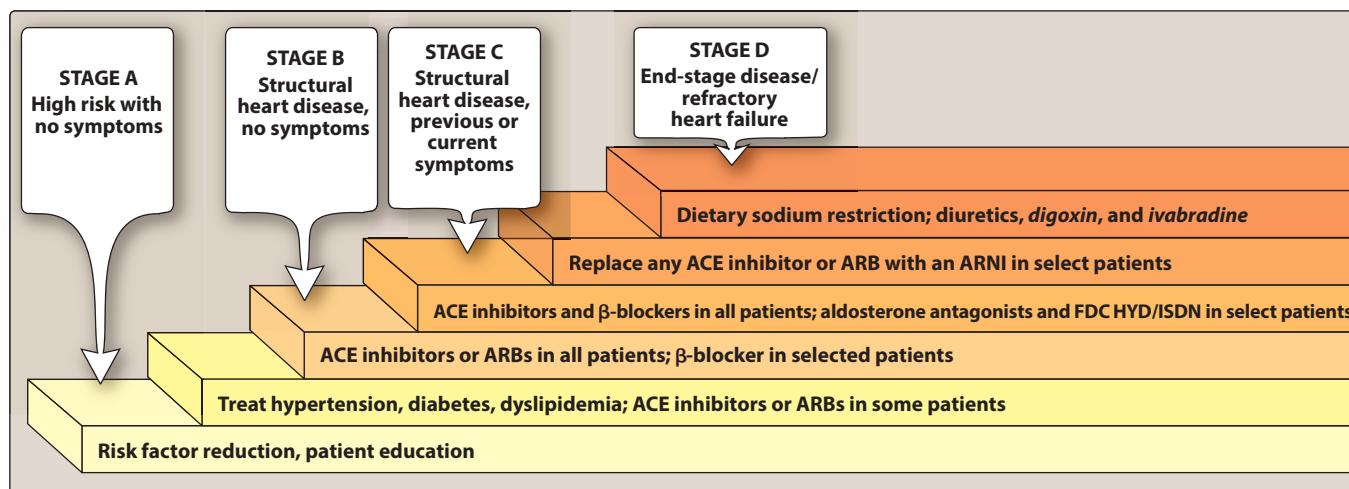
<b>Class I</b>	Symptoms of heart failure only at levels that would limit normal individuals—that is, ordinary physical activity does not cause symptoms.
<b>Class II</b>	The patients are comfortable at rest; symptoms of heart failure appear on ordinary exertion.
<b>Class III</b>	Symptoms of heart failure on less-than-ordinary exertion; marked limitations of physical activity
<b>Class IV</b>	Symptoms of heart failure at rest; unable to carry on any physical activity without HF symptom

**Figure 18.11**

New York Heart Association (NYHA) functional classification of heart failure (HF).

most patients newly diagnosed with HFrEF are initiated on both low doses of an ACE inhibitor and  $\beta$ -blocker after initial stabilization. These agents are slowly titrated to optimal levels to increase tolerability. Aldosterone antagonists and fixed-dose *hydralazine* and *isosorbide dinitrate* are initiated in patients who continue to have HF symptoms despite optimal doses of an ACE inhibitor and  $\beta$ -blocker. Once at an optimal ACE inhibitor or ARB dose and if patient remains symptomatic, either can be replaced by *sacubitril/valsartan*. Lastly, *digoxin* and *ivabradine* are added for symptomatic benefit only in patients on optimal HF pharmacotherapy.

Patients with acute HF require in-patient management in ICU with supportive management (oxygen and respiratory support, in case of respiratory distress). Pharmacotherapy consists of a judicious mix of vasodilators, diuretics, and ionotropic agents depending on the precipitating factors and symptoms/signs for congestion. Anticoagulants are added to decrease the risk of thromboembolism, if required, in bedridden patients.

**Figure 18.12**

Treatment options for various stages of HF. ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; FDC = fixed dose combination; HYD = hydralazine; ISDN = isosorbide dinitrate. Stage D (refractory symptoms requiring special interventions) is not shown. Modified from Yancy CW, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 136:1 (2017).

## Study Questions

Choose the ONE best answer.

- 18.1 A patient is newly diagnosed with HFrEF and is asymptomatic. Which is the most appropriate drug to initiate for symptomatic and survival benefits?
- A. Dobutamine
  - B. Furosemide
  - C. Lisinopril
  - D. SacubitriI/valsartan
- 18.2 Which of the following statements best describes the action of ACE inhibitors on the failing heart?
- A. ACE inhibitors increase vascular resistance.
  - B. ACE inhibitors decrease cardiac output.
  - C. ACE inhibitors reduce preload.
  - D. ACE inhibitors increase aldosterone.
- 18.3 A Hispanic man with HFrEF is currently takes maximally tolerated doses of metoprolol succinate and enalapril, along with moderate dose furosemide. He is euolemic, but continues to have HF symptoms. The systolic blood pressure is low, but the patient does not have signs or symptoms of hypotension. Which is the best recommendation to improve HF symptoms and survival in this patient?
- A. Stop enalapril, wait 36 hours, and start sacubitriI/valsartan.
  - B. Start digoxin.
  - C. Start fixed-dose hydralazine and isosorbide dinitrate.
  - D. Start spironolactone.
- 18.4  $\beta$ -Blockers improve cardiac function in HF by
- A. decreasing cardiac remodeling.
  - B. increasing heart rate.
  - C. increasing renin release.
  - D. activating norepinephrine.
- 18.5 A 70-year-old woman has HFrEF, hypertension, and atrial fibrillation. She takes hydrochlorothiazide, lisinopril, metoprolol tartrate, and warfarin. She feels well and has no cough, shortness of breath, or edema. Which of the following changes is most appropriate for her drug therapy?
- A. Discontinue hydrochlorothiazide.
  - B. Change lisinopril to losartan.
  - C. Decrease warfarin dose.
  - D. Change metoprolol tartrate to metoprolol succinate.

Correct answer = C. ACE inhibitors should be initiated in all patients, unless contraindicated, if they have HFrEF and are asymptomatic. This is known as stage B HF. Dobutamine and furosemide improve symptoms only. SacubitriI/valsartan will replace an ACE inhibitor if the patient remains symptomatic on optimal HF pharmacotherapy.

Correct answer = C. ACE inhibitors decrease vascular resistance, decrease preload, decrease afterload, and increase cardiac output. In addition, ACE inhibitors blunt aldosterone release.

Correct answer = D. Because the patient is on optimal pharmacotherapy and continues to have symptoms, another agent is warranted. Adding low-dose spironolactone will not likely decrease the blood pressure and will confer a survival and symptomatic benefit. Changing to sacubitriI/valsartan will likely worsen the low blood pressure. Digoxin will only improve symptoms and not improve survival. Fixed-dose hydralazine and isosorbide dinitrate would be appropriate if the patient were African-American.

Correct answer = A. Although it seems counterintuitive to decrease heart rate in HF,  $\beta$ -blockers improve cardiac function by slowing heart rate, decreasing renin release, and preventing the direct effects of norepinephrine on cardiac muscle to decrease remodeling.

Correct answer = D. Metoprolol succinate should be used in HF, given that there is mortality benefit shown with metoprolol succinate in landmark HF trials. Hydrochlorothiazide and warfarin are appropriate based on the information given; there is no reason to change to an ARB since the patient has no cough or history of angioedema.

- 18.6 A 75-year-old white man has HFrEF and reports stable HF symptoms. His current drug therapy includes optimal dose enalapril, carvedilol, and spironolactone. Which is the best recommendation to improve HF symptoms and survival?
- A. Start fixed-dose hydralazine/isosorbide dinitrate.
  - B. Start ivabradine.
  - C. Replace enalapril with sacubitril/valsartan.
  - D. Start digoxin.
- 18.7 How is spironolactone beneficial in HF?
- A. Promotes potassium secretion
  - B. Acts as aldosterone agonist
  - C. Prevents cardiac hypertrophy
  - D. Decreases blood glucose
- 18.8 Which of the following is important to monitor in patients taking digoxin?
- A. Chloride
  - B. Potassium
  - C. Sodium
  - D. Zinc
- 18.9 Which of the following describes the mechanism of action of milrinone in HF?
- A. Decreases intracellular calcium
  - B. Increases cardiac contractility
  - C. Decreases cAMP
  - D. Activates phosphodiesterase
- 18.10 BH is a 52 year-old African American woman who has HFrEF. She is seen in clinic today reporting stable HF symptoms, but is having occasional peripheral brightness. Otherwise vision is unchanged. Current medication regimen includes sacubitril/valsartan, carvedilol, fixed-dose hydralazine and isosorbide dinitrate, ivabradine, and bumetanide. Which is the best recommendation to minimize the adverse effect of peripheral brightness?
- A. Stop all HF medications immediately.
  - B. Discontinue sacubitril/valsartan only.
  - C. Do nothing; this adverse effect will slowly improve over time.
  - D. Reduce the dose of ivabradine.

Correct answer = C. Since patient is on optimal doses of HF medications and he continues to have symptoms, replacing enalapril with sacubitril/valsartan is the only option that improves both symptoms and survival in a white patient.

Correct answer = C. Spironolactone antagonizes aldosterone, which in turn prevents salt/water retention, cardiac hypertrophy, and hypokalemia. Spironolactone has endocrine effects on hormones, but not on glucose.

Correct answer = B. Hypokalemia can lead to life-threatening arrhythmias and increases the potential of cardiac toxicity with digoxin.

Correct answer = B. Milrinone is a phosphodiesterase inhibitor that leads to increased cAMP, increased intracellular calcium, and therefore increased contractility.

Correct answer = D. Luminous phenomena can occur with ivabradine. This adverse effect can be minimized with dose reduction or discontinuation.

# Antiarrhythmics

Shawn Anderson and Michelle Chung

19

## I. OVERVIEW

In contrast to skeletal muscle, which contracts only when it receives a stimulus, the heart contains specialized cells that exhibit automaticity. That is, they intrinsically generate rhythmic action potentials in the absence of external stimuli. These “pacemaker” cells differ from other myocardial cells in showing a slow, spontaneous depolarization during diastole (phase 4), caused by an inward positive current carried by sodium and calcium ions. This depolarization is fastest in the sinoatrial (SA) node (the initiation site of the action potential), and it decreases throughout the normal conduction pathway through the atrioventricular (AV) node to the bundle of His and the Purkinje system. Dysfunction of impulse generation or conduction at any of a number of sites in the heart can cause an abnormality in cardiac rhythm. [Figure 19.1](#) summarizes the drugs used to treat cardiac arrhythmias.

## II. INTRODUCTION TO THE ARRHYTHMIAS

Arrhythmias are caused by abnormalities in impulse formation and conduction in the myocardium. Arrhythmias present as a complex family of disorders with a variety of symptoms. To make sense of this large group of disorders, it is useful to organize arrhythmias into groups according to the anatomic site of the abnormality: the atria, the AV node, or the ventricles. [Figure 19.2](#) summarizes several common arrhythmias.

### A. Causes of arrhythmias

Most arrhythmias arise either from aberrations in impulse generation (abnormal automaticity) or from a defect in impulse conduction.

- 1. Abnormal automaticity:** The SA node shows a faster rate of discharge than other pacemaker cells and thus, it normally sets the pace of contraction for the myocardium. If cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli, and arrhythmias may arise. Most of the antiarrhythmic agents suppress automaticity by blocking either sodium ( $\text{Na}^+$ ) or calcium ( $\text{Ca}^{2+}$ ) channels to reduce the ratio of these ions to potassium ( $\text{K}^+$ ). This decreases the slope of phase 4 (diastolic) depolarization and/or raises the threshold of discharge to a less negative voltage, leading to an overall decrease in frequency of discharge. This effect is more pronounced in cells with ectopic pacemaker activity than in normal cells.

### CLASS I ( $\text{Na}^+$ channel blockers)

*Disopyramide (IA)  
Procainamide (IA)  
Quinidine (IA)  
Lidocaine (IB)  
Mexiletine (IB)  
Propafenone (IC)  
Flecainide (IC)*

### CLASS II ( $\beta$ -adrenoreceptor blockers)

*Atenolol  
Metoprolol  
Esmolol*

### CLASS III ( $\text{K}^+$ channel blockers)

*Sotalol  
Amiodarone  
Dofetilide  
Dronedarone  
Ibutilide*

### CLASS IV ( $\text{Ca}^{2+}$ channel blockers)

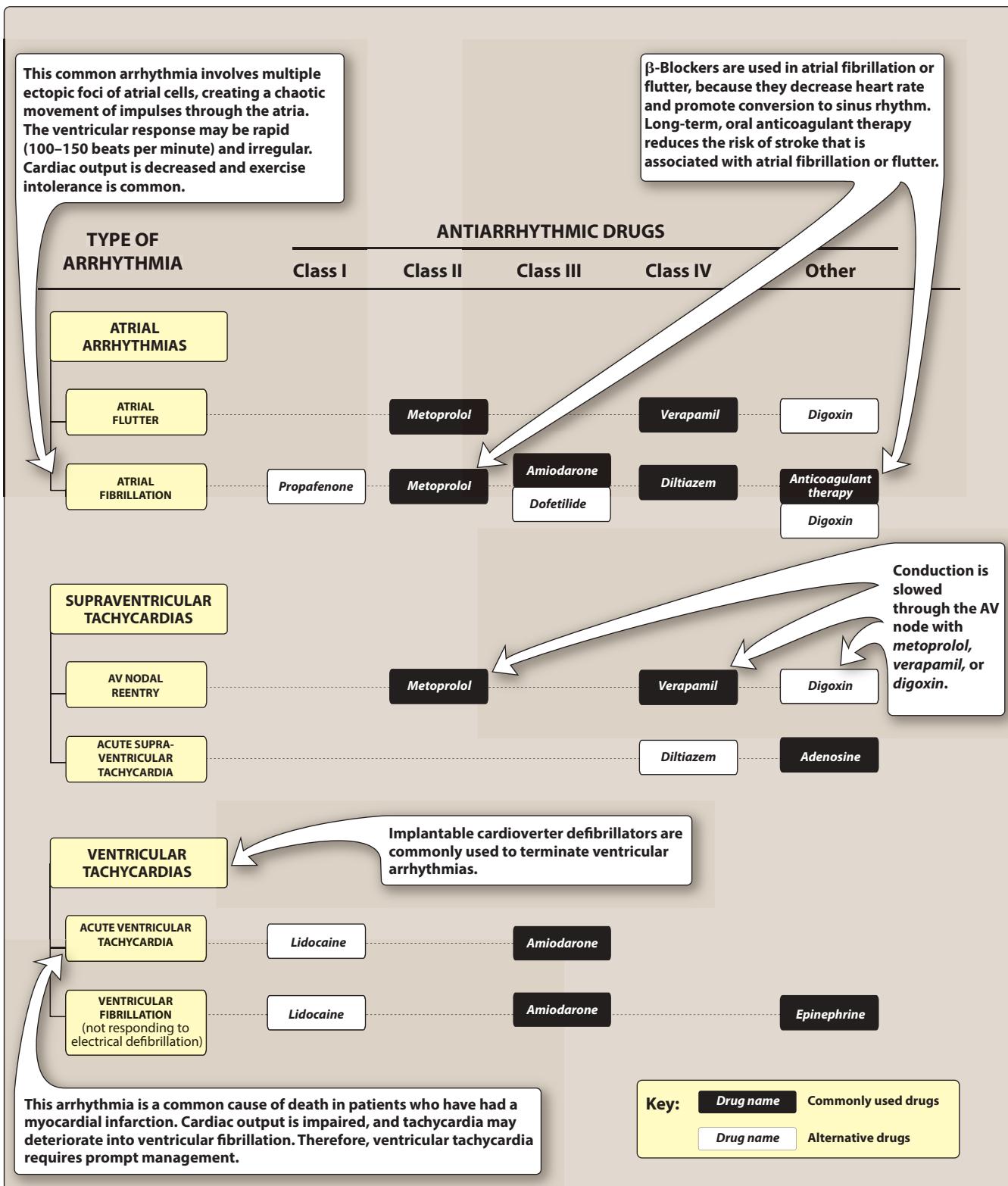
*Diltiazem  
Verapamil*

### OTHER ANTIARRHYTHMIC DRUGS

*Adenosine  
Digoxin  
Magnesium sulfate  
Ranolazine*

**Figure 19.1**

Summary of antiarrhythmic drugs.

**Figure 19.2**

Therapeutic indications for some commonly encountered arrhythmias. AV = atrioventricular.

**2. Abnormalities in impulse conduction:** Impulses from higher pacemaker centers are normally conducted down pathways that bifurcate to activate the entire ventricular surface (Figure 19.3). A phenomenon called reentry can occur if a unidirectional block caused by myocardial injury or a prolonged refractory period results in an abnormal conduction pathway. Reentry is the most common cause of arrhythmias, and it can occur at any level of the cardiac conduction system. This short-circuit pathway results in re-excitation of cardiac muscle, causing premature contraction or a sustained arrhythmia. Antiarrhythmic agents prevent reentry by slowing conduction (class I drugs) and/or increasing the refractory period (class III drugs), thereby converting a unidirectional block into a bidirectional block.

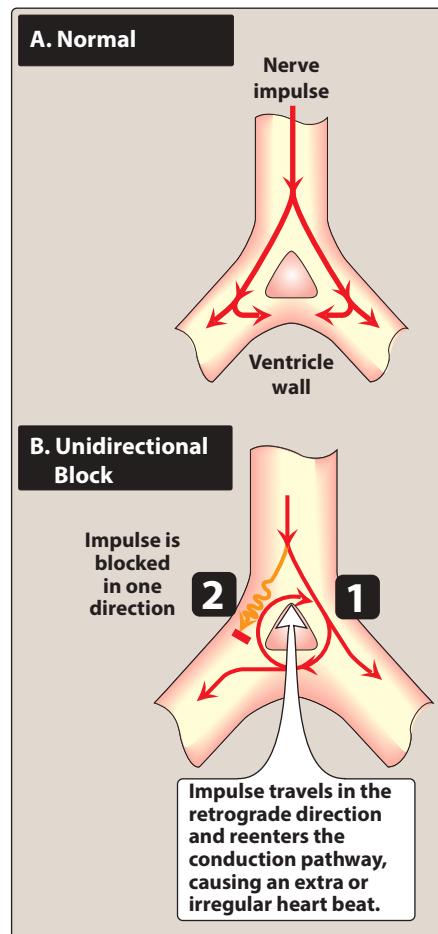
### B. Antiarrhythmic drugs

The ultimate goal of antiarrhythmic drug therapy is to restore normal rhythm and conduction to prevent arrhythmias or to reduce symptoms associated with arrhythmias. When it is not possible to revert to normal sinus rhythm, drugs may be used to prevent more serious and possibly lethal arrhythmias from occurring. Antiarrhythmic drugs are used to

- decrease or increase conduction velocity,
- alter the excitability of cardiac cells by changing the duration of the effective refractory period, and
- suppress abnormal automaticity.

All antiarrhythmic drugs have important efficacy and safety limitations. Unfortunately, many of the antiarrhythmic agents are known to have dangerous proarrhythmic actions—that is, to cause arrhythmias due to narrow therapeutic window. There is a small plasma concentration interval between the lowest effective dose and the first toxic dose—that is, between undertreatment and the toxic or proarrhythmic effect. Multiple factors interfere with drug effects, for example, race, gender, genetics, triggering factors, neurohormonal changes, disease state and severity, and drug–drug interaction. Inhibition of K<sup>+</sup> channels widens the action potential and can, thus, prolong the QT interval. If prolongation is excessive, these drugs increase the risk of developing life-threatening ventricular tachyarrhythmias (*torsades de pointes*). The most common cause of QT prolongation is drug-induced, although other conditions (for example, ischemia and hypokalemia) and genetic abnormalities may contribute. In addition to antiarrhythmics, many other drugs are known to prolong the QT interval, such as macrolide antibiotics and antipsychotics. Caution should be employed when combining drugs with additive effects on the QT interval or when giving QT-prolonging antiarrhythmic agents drugs known to inhibit their metabolism.

Antiarrhythmic drugs can be classified (Vaughan–Williams Classification) according to their predominant effects on the action potential (Figure 19.4). Although this classification is convenient, it has some limitations. Antiarrhythmic drugs have multiple electrophysiological and pharmacological effects where their action relate to more than one class. This action depends on the route of administration, plasma levels, and their active metabolites which may have a different class of action or may have an action that does not meet any formal classification. Examples of prodrugs are *propafenone*, *quinidine*, and *amiodarone*.



**Figure 19.3**

Schematic representation of reentry. Modified from J. A. Beven, and J. H. Thompson, *Essentials of Pharmacology*, Philadelphia, PA, Harper and Row (1983).

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na <sup>+</sup> channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na <sup>+</sup> channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na <sup>+</sup> channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K <sup>+</sup> channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca <sup>2+</sup> channel blocker	Inhibits action potential in SA and AV nodes

AV = atrioventricular; SA = sinoatrial.

**Figure 19.4**

Actions of antiarrhythmic drugs.

### III. CLASS I ANTIARRHYTHMIC DRUGS

Class I antiarrhythmic drugs act by blocking voltage-sensitive Na<sup>+</sup> channels. They bind more rapidly to open or inactivated Na<sup>+</sup> channels than to channels that are fully repolarized. Therefore, these drugs show a greater degree of blockade in tissues that are frequently depolarizing. This property is called use dependence (or state dependence), and it enables these drugs to block cells that are discharging at an abnormally high frequency, without interfering with the normal beating of the heart.

The use of Na<sup>+</sup> channel blockers has declined due to their proarrhythmic effects, particularly in patients with reduced left ventricular function and atherosclerotic heart disease. Class I drugs are further subdivided into three groups according to their effect on the duration of the cardiac action potential: 1) intermediate (IA), 2) fast (IB), and 3) slow (IC) blockers of the Na<sup>+</sup> channel (Figure 19.4).

#### A. Class IA antiarrhythmic drugs: Quinidine, procainamide, and disopyramide

*Quinidine* [KWIN-i-deen] is the prototype class IA drug. Other agents in this class include *procainamide* [proe-KANE-a-mide] and *disopyramide* [dye-soe-PEER-a-mide]. Because of their concomitant class III activity, they can precipitate arrhythmias that can progress to ventricular fibrillation.

**1. Mechanism of action:** *Quinidine* binds to open and inactivated Na<sup>+</sup> channels and prevents Na<sup>+</sup> influx, thus slowing the rapid upstroke during phase 0 (Figure 19.5). It decreases the slope of phase 4 spontaneous depolarization, inhibits K<sup>+</sup> channels, and blocks Ca<sup>2+</sup> channels. Because of these actions, it slows conduction velocity and increases refractoriness. *Quinidine* also has mild α-adrenergic blocking and anticholinergic actions. Although *procainamide* and *disopyramide* have actions similar to those of *quinidine*, there is less anticholinergic activity with *procainamide* and

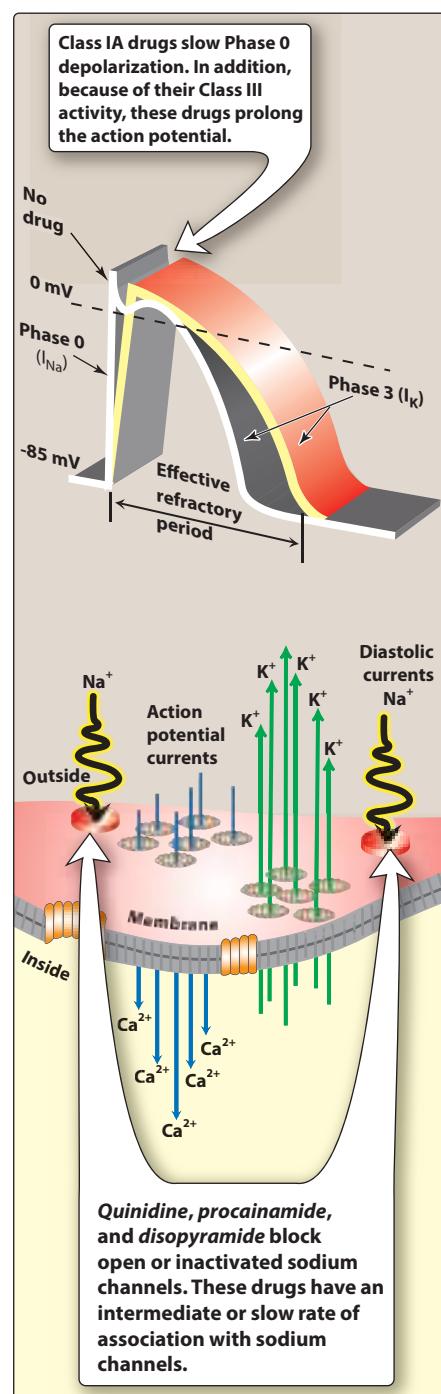
more with *disopyramide*. Neither *procainamide* nor *disopyramide* has  $\alpha$ -blocking activity. *Disopyramide* produces a greater negative inotropic effect, and unlike the other drugs, it causes peripheral vasoconstriction.

2. **Therapeutic uses:** *Quinidine* though effective in the treatment of a wide variety of arrhythmias, including atrial, AV junctional, and ventricular tachyarrhythmias, is used rarely due to its adverse effects. *Procainamide* is only available in an intravenous formulation and may be used to treat acute atrial and ventricular arrhythmias. However, electrical cardioversion or defibrillation and *amiodarone* have mostly replaced *procainamide* in clinical practice. *Disopyramide* is used in vagally mediated atrial fibrillation and in hypertrophic obstructive cardiomyopathy. It can be used as an alternative treatment of ventricular arrhythmias. *Amiodarone* toxicity is a concern. *Amiodarone* has more of class III properties than of class I and is used primarily for atrial fibrillation and ventricular tachycardia.
3. **Pharmacokinetics:** *Quinidine sulfate* or *gluconate* is rapidly and well absorbed after oral administration. It undergoes extensive metabolism primarily by the hepatic cytochrome P450 3A4 (CYP3A4) isoenzyme, forming active metabolites. A portion of *procainamide* is acetylated in the liver to *N*-acetylprocainamide (NAPA), which has the properties and adverse effects of a class III drug. NAPA is eliminated via the kidney; therefore, dosages of *procainamide* should be adjusted in patients with renal dysfunction. *Disopyramide* is well absorbed after oral administration and is metabolized in the liver by CYP3A4 to a less active metabolite and several inactive metabolites. About half of the drug is excreted unchanged by the kidneys.
4. **Adverse effects:** Though class IA drugs are effective to treat atrial fibrillation, but due to enhanced proarrhythmic effects and ability to worsen heart failure symptoms, they should not be used in patients with atherosclerotic heart disease or systolic heart failure. Large doses of *quinidine* may induce the symptoms of cinchonism (for example, blurred vision, tinnitus, headache, disorientation, and psychosis). Drug interactions are common with *quinidine* since it is an inhibitor of both CYP2D6 and P-glycoprotein. Intravenous administration of *procainamide* may cause hypotension and can cause drug-induced lupus erythematosus. *Disopyramide* has the most anticholinergic adverse effects of the class IA drugs (for example, dry mouth, urinary retention, blurred vision, and constipation). Both *quinidine* and *disopyramide* should be used with caution with potent inhibitors of CYP3A4.

## B. Class IB antiarrhythmic drugs: Lidocaine and mexiletine

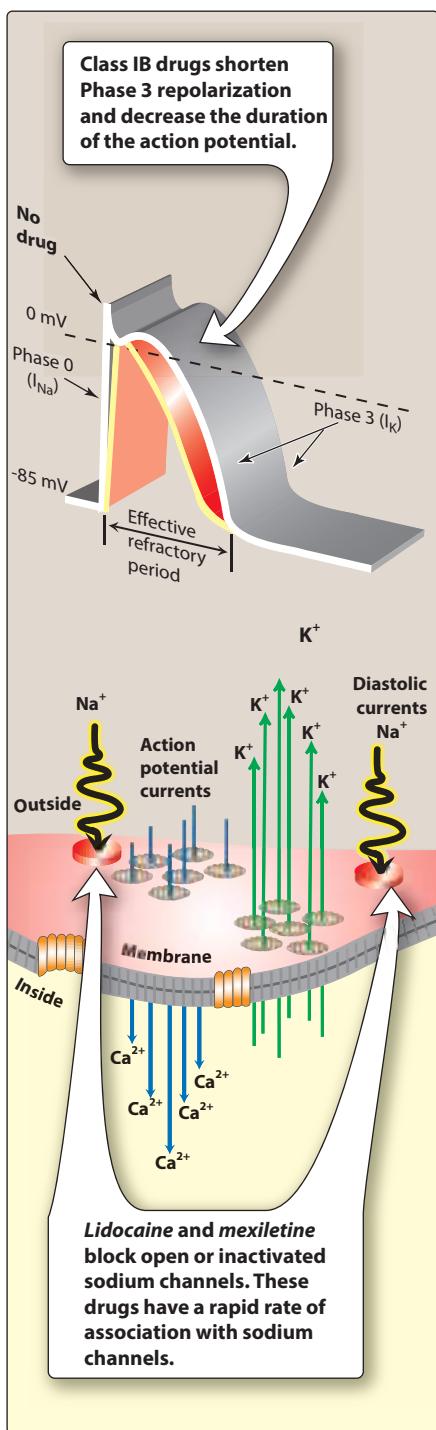
The class IB agents rapidly associate and dissociate from  $\text{Na}^+$  channels. Thus, the actions are greater when the cardiac cell is depolarized or firing rapidly. The class IB drugs *lidocaine* [LYE-doe-kane] and *mexiletine* [MEX-i-le-teen] are useful in treating ventricular arrhythmias.

1. **Mechanism of action:** In addition to  $\text{Na}^+$  channel blockade, *lidocaine* and *mexiletine* shorten phase 3 repolarization and decrease the duration of the action potential (Figure 19.6). Neither drug contributes to negative inotropy.



**Figure 19.5**

Schematic diagram of the effects of class IA agents.  $I_{\text{Na}}$  and  $I_K$  are transmembrane currents due to the movement of  $\text{Na}^+$  and  $\text{K}^+$ , respectively.



**Figure 19.6**

Schematic diagram of the effects of class IB agents.  $I_{Na}$  and  $I_K$  are transmembrane currents due to the movement of  $Na^+$  and  $K^+$ , respectively.

**2. Therapeutic uses:** Although *amiodarone* is the drug of choice for ventricular fibrillation or ventricular tachycardia (VT), intravenous *lidocaine* may be used as an alternative. *Lidocaine* may also be used in combination with *amiodarone* for VT storm. The drug does not markedly slow conduction and thus has little effect on atrial or AV junction arrhythmias. *Mexiletine* is used orally for chronic treatment of ventricular arrhythmias, often in combination with *amiodarone*.

**3. Pharmacokinetics:** *Lidocaine* is given intravenously because of extensive first-pass transformation by the liver. The drug is dealkylated to two active metabolites, primarily by CYP1A2 with a minor role by CYP3A4. *Lidocaine* should be monitored closely when given in combination with drugs affecting these CYP isoenzymes. *Mexiletine* is well absorbed after oral administration. It is metabolized in the liver primarily by CYP2D6 to inactive metabolites and excreted mainly via the biliary route.

**4. Adverse effects:** *Lidocaine* has a fairly wide therapeutic index. Central nervous system (CNS) effects include nystagmus (early indicator of toxicity), drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions, which often limit the duration of continuous infusions. *Mexiletine* has a narrow therapeutic index and caution should be used when administering the drug with inhibitors of CYP2D6. Nausea, vomiting, and dyspepsia are the most common adverse effects.

### C. Class IC antiarrhythmic drugs: Flecainide and propafenone

These drugs slowly dissociate from resting  $Na^+$  channels and show prominent effects even at normal heart rates. Due to their negative inotropic and proarrhythmic effects, use of these agents is avoided in patients with structural heart disease (left ventricular hypertrophy, heart failure, atherosclerotic heart disease).

**1. Mechanism of action:** *Flecainide* [FLEK-a-nide] suppresses phase 0 upstroke in Purkinje and myocardial fibers (Figure 19.7). This causes marked slowing of conduction in all cardiac tissue, with a minor effect on the duration of the action potential and refractoriness. Automaticity is reduced by an increase in the threshold potential, rather than a decrease in the slope of phase 4 depolarization. *Flecainide* also blocks  $K^+$  channels, leading to increased duration of the action potential. *Propafenone* [proe-PA-fen-one], like *flecainide*, slows conduction in all cardiac tissues but does not block  $K^+$  channels. It possesses weak  $\beta$ -blocking properties.

**2. Therapeutic uses:** The class IC drug *flecainide* is commonly used to maintain sinus rhythm in atrial fibrillation patients. It is useful in the maintenance of sinus rhythm in atrial flutter or fibrillation in patients without structural heart disease and in treating refractory ventricular arrhythmias. Significant coronary artery disease is a contraindication to the use of *flecainide* and *propafenone* as it increases the risk of proarrhythmia and sudden cardiac death. These agents must be used in combination with an AV blocking agent in order to prevent rapid atrial fibrillation or atrial flutter conduction (1:1 conduction) through the AV node resulting in very fast

ventricular rates if a breakthrough episode occurs since class IC drugs also act to increase AV nodal conduction. *Flecainide* can be used on an as-needed basis in the outpatient setting. Use of *Propafenone* is restricted mostly to atrial arrhythmias: rhythm control of atrial fibrillation or flutter and paroxysmal supraventricular tachycardia prophylaxis in patients with AV reentrant tachycardias.

3. **Pharmacokinetics:** *Flecainide* is well absorbed after oral administration and is metabolized by CYP2D6 to multiple metabolites. The parent drug and metabolites are mostly eliminated renally. *Propafenone* is metabolized to active metabolites primarily via CYP2D6 and also by CYP1A2 and CYP3A4. The metabolites are excreted in the urine and the feces.
4. **Adverse effects:** *Flecainide* is generally well tolerated, with blurred vision, dizziness, and nausea occurring most frequently. *Propafenone* has a similar side effect profile, but may cause bronchospasm and should be avoided in patients with asthma. *Propafenone* is also an inhibitor of P-glycoprotein. Both drugs should be used with caution with potent inhibitors of CYP2D6.

## IV. CLASS II ANTIARRHYTHMIC DRUGS

Class II agents are  $\beta$ -adrenergic antagonists or  $\beta$ -blockers. These drugs diminish phase 4 depolarization and, thus, depress automaticity, prolong AV conduction, and decrease heart rate and contractility. Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity. They are also used for atrial flutter and fibrillation and for AV nodal reentrant tachycardia. In addition,  $\beta$ -blockers prevent life-threatening ventricular arrhythmias following a myocardial infarction.

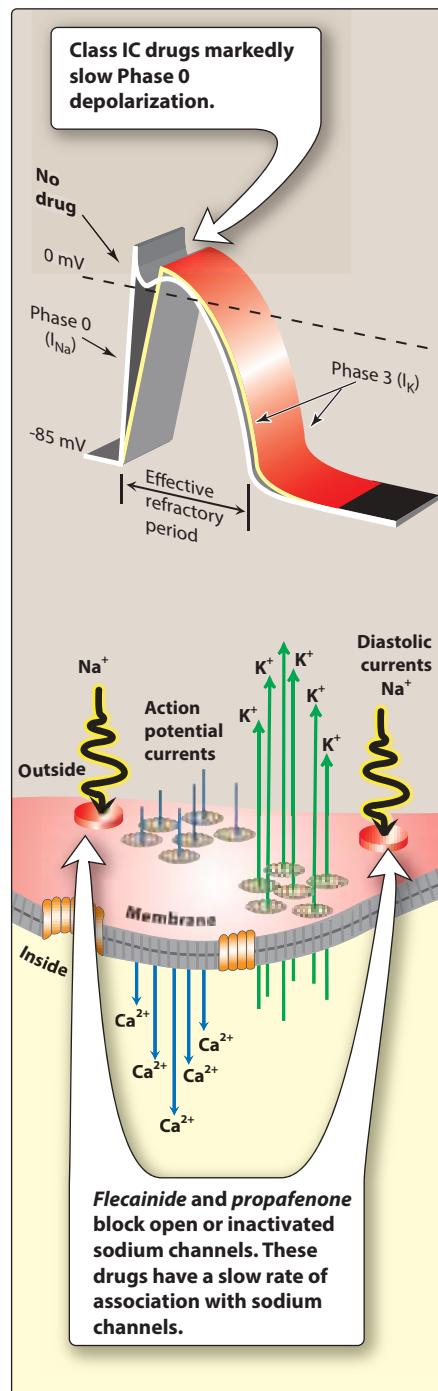
*Metoprolol* [me-TOE-pro-lo] is the most widely used  $\beta$ -blocker for the treatment of cardiac arrhythmias. Compared to nonselective  $\beta$ -blockers, such as *propranolol* [pro-PRAN-oh-lo], it reduces the risk of bronchospasm. It is extensively metabolized by CYP2D6 and has CNS penetration (less than *propranolol*, but more than *atenolol* [a-TEN-oh-lo]). *Esmolol* [ESS-moe-lo] is a very short and fast-acting  $\beta$ -blocker used for intravenous administration in acute arrhythmias that occur during surgery or emergency situations. *Esmolol* is rapidly metabolized by esterases in red blood cells. As such, there are no pharmacokinetic drug interactions. Common adverse effects with  $\beta$ -blockers include bradycardia, hypotension, and fatigue (see Chapter 7).

## V. CLASS III ANTIARRHYTHMIC DRUGS

Class III agents block  $K^+$  channels and, thus, diminish the outward  $K^+$  current during repolarization of cardiac cells. These agents prolong the duration of the action potential without altering phase 0 of depolarization or the resting membrane potential (Figure 19.8). Instead, they prolong the effective refractory period, increasing refractoriness. All class III drugs have the potential to induce arrhythmias.

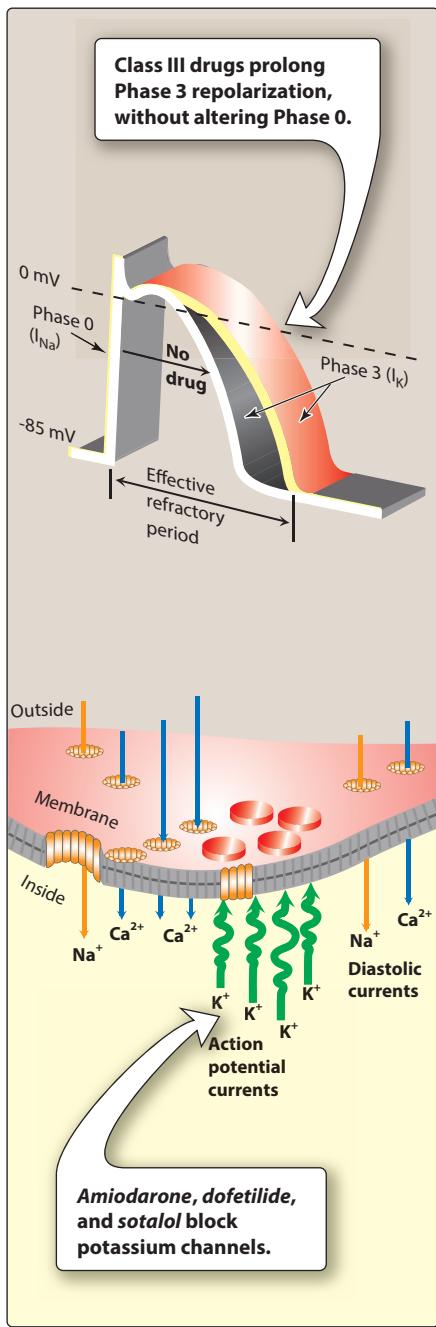
### A. Amiodarone

1. **Mechanism of action:** *Amiodarone* [a-MEE-oh-da-rone] contains iodine and is related structurally to thyroxine. It has complex effects, showing class I, II, III, and IV actions, as well as  $\alpha$ -blocking



**Figure 19.7**

Schematic diagram of the effects of class IC agents.  $I_{Na}$  and  $I_K$  are transmembrane currents due to the movement of  $Na^+$  and  $K^+$ , respectively.

**Figure 19.8**

Schematic diagram of the effects of class III agents.  $I_{Na}$  and  $I_K$  are transmembrane currents due to the movement of  $Na^+$  and  $K^+$ , respectively.

activity. Its dominant effect is prolongation of the action potential duration and the refractory period by blocking  $K^+$  channels.

- Therapeutic uses:** Amiodarone has been a mainstay of therapy for the rhythm management of atrial fibrillation or flutter. Despite its adverse effect profile, amiodarone is thought to be the least proarrhythmic of the class I and III antiarrhythmic drugs. Amiodarone is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias.
- Pharmacokinetics:** Amiodarone is incompletely absorbed after oral administration. The drug is unusual in having a prolonged half-life of several weeks, and it distributes extensively in tissues. Full clinical effects may not be achieved until months after initiation of treatment, unless loading doses are employed.
- Adverse effects:** Amiodarone shows a variety of toxic effects, including pulmonary fibrosis, neuropathy, hepatotoxicity, corneal deposits, optic neuritis, blue-gray skin discoloration, and hypo- or hyperthyroidism. However, use of low doses and close monitoring reduce toxicity, while retaining clinical efficacy. Amiodarone is subject to numerous drug interactions, since it is metabolized by CYP3A4 and serves as an inhibitor of CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein.

### B. Dronedarone

Dronedarone [droe-NE-da-rone] is a benzofuran amiodarone derivative, which is less lipophilic and has a shorter half-life than amiodarone. It does not have the iodine moieties that are responsible for thyroid dysfunction associated with amiodarone. Like amiodarone, it has class I, II, III, and IV actions. Dronedarone has a better adverse effect profile than amiodarone but may still cause liver failure. The drug is contraindicated in those with symptomatic heart failure or permanent atrial fibrillation due to an increased risk of death. Currently, dronedarone is used to maintain sinus rhythm in atrial fibrillation or flutter, but it is less effective than amiodarone.

### C. Sotalol

Sotalol [SOE-ta-lo], although a class III antiarrhythmic agent, also has nonselective  $\beta$ -blocker activity. The levorotatory isomer (*l*-sotalol) has  $\beta$ -blocking activity and *d*-sotalol has class III antiarrhythmic action. Sotalol blocks a rapid outward  $K^+$  current, known as the delayed rectifier current. This blockade prolongs both repolarization and duration of the action potential, thus lengthening the effective refractory period. Sotalol is used for maintenance of sinus rhythm in patients with atrial fibrillation, atrial flutter, or refractory paroxysmal supraventricular tachycardia and in the treatment of ventricular arrhythmias. Since sotalol has  $\beta$ -blocking properties, it is commonly used for these indications in patients with left ventricular hypertrophy or atherosclerotic heart disease. This drug can cause the typical adverse effects associated with  $\beta$ -blockers but has a low rate of adverse effects when compared to other antiarrhythmic agents. The dosing interval should be extended in patients with renal disease, since the drug is renally eliminated. To reduce the risk of proarrhythmic effects, sotalol should be initiated in the hospital to monitor QT interval.

### D. Dofetilide

*Dofetilide* [doh-FET-il-ide] is a pure K<sup>+</sup> channel blocker. It can be used as a first-line antiarrhythmic agent in patients with persistent atrial fibrillation and heart failure or in those with coronary artery disease. Because of the risk of proarrhythmia, *dofetilide* initiation is limited to the inpatient setting. The half-life of this oral drug is 10 hours. The drug is mainly excreted unchanged in the urine. Drugs that inhibit active tubular secretion are contraindicated with *dofetilide*.

### E. Ibutilide

*Ibutilide* [eye-BYOO-tih-lide] is a K<sup>+</sup> channel blocker that also activates the inward Na<sup>+</sup> current (mixed class III and IA actions). *Ibutilide* is the drug of choice for chemical conversion of atrial flutter, but electrical cardioversion has supplanted its use. It undergoes extensive first-pass metabolism and is not used orally. Initiation is also limited to the inpatient setting due to the risk of arrhythmia.

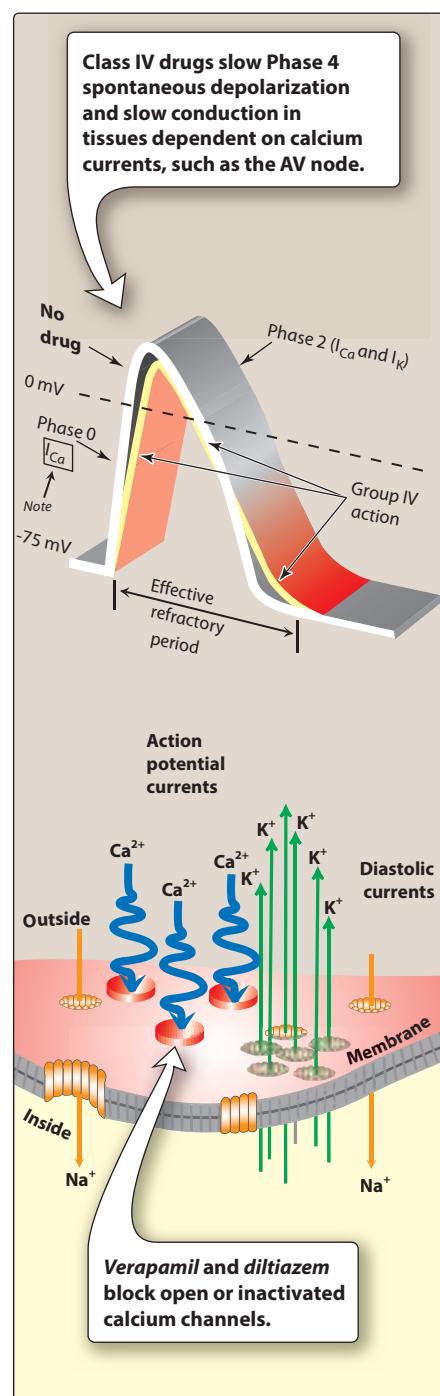
## VI. CLASS IV ANTIARRHYTHMIC DRUGS

Class IV drugs are the nondihydropyridine Ca<sup>2+</sup> channel blockers *verapamil* [ver-AP-a-mil] and *diltiazem* [dil-TYE-a-zem]. Although voltage-sensitive Ca<sup>2+</sup> channels occur in many different tissues, the major effect of Ca<sup>2+</sup> channel blockers is on vascular smooth muscle and the heart. Both drugs show greater action on the heart than on vascular smooth muscle, but more so with *verapamil*. In the heart, *verapamil* and *diltiazem* bind only to open depolarized voltage-sensitive channels, thus decreasing the inward current carried by Ca<sup>2+</sup>. These drugs are use-dependent in that they prevent repolarization until the drug dissociates from the channel, resulting in a decreased rate of phase 4 spontaneous depolarization. They also slow conduction in tissues that are dependent on Ca<sup>2+</sup> currents, such as the AV and SA nodes (Figure 19.9). These agents are more effective against atrial than against ventricular arrhythmias. They are useful in treating reentrant supraventricular tachycardia and in reducing the ventricular rate in atrial flutter and fibrillation. Common adverse effects include bradycardia, hypotension, and peripheral edema. Both drugs are metabolized in the liver by CYP3A4. Dosage adjustments may be needed in patients with hepatic dysfunction. Both agents are subject to many drug interactions as they are CYP3A4 inhibitors, as well as substrates and inhibitors of P-glycoprotein.

## VII. OTHER ANTIARRHYTHMIC DRUGS

### A. Digoxin

*Digoxin* [di-JOX-in] inhibits the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump, ultimately shortening the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing conduction velocity in the AV node. *Digoxin* is used to control ventricular response rate in atrial fibrillation and flutter; however, sympathetic stimulation easily overcomes the inhibitory effects of *digoxin*. At toxic concentrations, *digoxin* causes ectopic ventricular beats that may result in VT and fibrillation. [Note: Serum trough concentrations of 1.0 to 2.0 ng/mL are desirable for atrial fibrillation or flutter, whereas lower



**Figure 19.9**

Schematic diagram of the effects of class IV agents. I<sub>Ca</sub> and I<sub>K</sub> are transmembrane currents due to the movement of Ca<sup>2+</sup> and K<sup>+</sup>, respectively. AV = atrioventricular.

concentrations of 0.5 to 0.8 ng/mL are targeted for systolic heart failure.]

### B. Adenosine

*Adenosine* [ah-DEN-oh-zeen] is a naturally occurring nucleoside, but at high doses, the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node. Intravenous *adenosine* is the drug of choice for converting acute supraventricular tachycardias. It has low toxicity but causes flushing, chest pain, and hypotension. *Adenosine* has an extremely short duration of action (approximately 10 to 15 seconds) due to rapid uptake by erythrocytes and endothelial cells.

### C. Magnesium sulfate

*Magnesium* is necessary for the transport of  $\text{Na}^+$ ,  $\text{Ca}^{2+}$ , and  $\text{K}^+$  across cell membranes. It slows the rate of SA node impulse formation and prolongs conduction time along the myocardial tissue. Intravenous *magnesium sulfate* is the salt used to treat arrhythmias, as oral *magnesium* is not effective in the setting of arrhythmia. Most notably, *magnesium* is the drug of choice for treating the potentially fatal arrhythmia torsades de pointes and *digoxin*-induced arrhythmias.

### D. Ranolazine

*Ranolazine* [ra-NOE-la-zeen] is an antianginal drug with antiarrhythmic properties similar to *amiodarone*. However, its main effect is to shorten repolarization and decrease the action potential duration similar to *mexiletine*. It is used to treat refractory atrial and ventricular arrhythmias, often in combination with other antiarrhythmic drugs. It is well tolerated with dizziness and constipation as the most common adverse effects. *Ranolazine* is extensively metabolized in the liver by CYP3A and CYP2D6 isoenzymes and is mainly excreted by the kidney. Concomitant use with strong CYP3A inducers or inhibitors is contraindicated.

**Figure 19.10** summarizes pharmacokinetics, adverse effects, and drug-drug interaction and dosages of antiarrhythmic drugs.

**Figure 19.11** summarizes the antiarrhythmic drugs that may be used to treat different types of arrhythmias. However, when treating arrhythmias, selection of an antiarrhythmic agent should be individualized for a given condition as a particular drug may not be efficacious and in fact may precipitate other arrhythmias or adverse cardiovascular effects (for example, cardiac depression and hypotension). **Figure 19.12** summarizes the common drug interactions seen with antiarrhythmic agents.

ANTIARRHYTHMIC DRUG	DOSE	PHARMACOKINETICS	NONCARDIOVASCULAR TOXICITY	CARDIOVASCULAR TOXICITY	DRUG INTERACTIONS
<i>Quinidine</i>	Oral as sulfate, 600 mg 3 times a day; gluconate, 324–648 mg every 8 hr; reduced dose for renal failure	Well absorbed orally, 80% protein bound; extensive hepatic metabolism CYP3A4 (70%) to 3-hydroxyquinidine, renal (30%)	Diarrhea, thrombocytopenia, cinchonism, pruritus, rash	QRS prolongation with toxic doses, torsades de pointes (not dose related), hypotension, tachycardia	Inhibits CYP2D6 (may increase concentration of drugs metabolized by this enzyme [for example, ↑ effect of tricyclic antidepressants, <i>haloperidol</i> , some β-blockers, <i>fluoxetine</i> , narcotics])  Increases <i>digoxin</i> and <i>amiodarone</i> levels  Causes cardiac depression with β-blockers; <i>quinidine</i> metabolism is increased by <i>phenobarbital</i> , <i>phenytoin</i> , and <i>rifampicin</i>
<i>Disopyramide</i>	Oral: 100–400 mg every 8–12 hr; maximum dose, 800 mg/24 hr; reduced dose for renal or hepatic dysfunction	Renal/hepatic CYP3A4	Anticholinergic (contraindicated for narrow-angle glaucoma): dry mouth, urinary retention, constipation, blurring of vision	Congestive heart failure exacerbation, torsades de pointes	No significant interactions
<i>Lidocaine</i>	50–100 mg bolus followed by 20–40 mg every 10–20 min intravenously	Inactive orally; IV route, rapid onset, shorter duration of action, high first-pass metabolism, metabolism depends on hepatic blood flow, $t_{1/2}$ 8 min, elimination $t_{1/2}$ 2 hr	CNS: Nystagmus (an early indicator of toxicity), drowsiness, slurred speech, paraesthesia, agitation, confusion, and convulsions	Least cardiotoxic	Propranolol decreases $t_{1/2}$ of <i>lidocaine</i>
<i>Maxiletine</i>	Oral: Analog of <i>lidocaine</i>	No first-pass metabolism	Nausea, vomiting, and dyspepsia; tremors (early sign of toxicity), nystagmus, dizziness	Hypotension, bradycardia, widened QRS	
<i>Flecainide</i> (reserve drug for ventricular arrhythmia)	50–100 mg twice a day, maximum dose 300–400 mg/d	Renal/ variable hepatic metabolism CYP2D6	Dizziness, headache, blurring of visual	Risk of sudden cardiac arrest, atrial flutter with 1:1 conduction; ventricular tachycardia; contraindicated with coronary disease	Use with caution with potent inhibitors of CYP2D6; may decrease the metabolism of <i>warfarin</i> ; increase <i>digoxin</i> levels; <i>flecainide</i> levels are increased by <i>amiodarone</i>
<i>Propafenone</i>	Oral: 150–300 mg every 8 hr or sustained release 225–425 mg twice a day	Hepatic metabolism CYP2D6	Metallic taste, dizziness	Atrial flutter with 1:1 conduction; ventricular tachycardia; contraindicated with coronary disease	May decrease the metabolism of <i>warfarin</i> ; increase <i>digoxin</i> levels  Use with caution with potent inhibitors of CYP2D6
<i>Esmolol</i>	IV (for acute arrhythmia in an emergency situation or during surgery) 500 mcg/kg over 1 min; maintenance 50–200 mcg/kg/min	Very short elimination half-life 9 min; metabolized by RBC esterases	Well tolerated	Generally tolerated well, but it is associated with an increased risk of hypotension that is rapidly reversible	No pharmacokinetic drug interactions; <i>Esmolol</i> should be used with caution in patients on β blocker therapy, bradycardia patients, and patients with decompensated heart failure

**Figure 19.10**

Pharmacokinetics, adverse effects, and drug–drug interaction and dosages of antiarrhythmic drugs. (Figure continues on next page)

ANTIARRHYTHMIC DRUG	DOSE	PHARMACOKINETICS	NONCARDIOVASCULAR TOXICITY	CARDIOVASCULAR TOXICITY	DRUG INTERACTIONS
<i>Metoprolol</i>	IV 2.5–5 mg bolus over 2 min, up to 3 doses Oral: 25–100 mg twice daily May use metoprolol succinate ER 25–200 mg daily	Extensive hepatic metabolism by CYP2D6 and CNS penetration	Dizziness, headache, tiredness, depression, diarrhea, pruritus, rash dyspnea, cold extremities, constipation, dyspepsia	Bradycardia, heart failure, hypotension	CYP2D6 poor metabolizers may have a 5-fold higher risk for developing adverse effects
<i>Atenolol</i>	Oral: 25–100 mg daily	Extensive hepatic metabolism by CYP2D6 and CNS penetration but lesser than metoprolol	Dizziness, headache, tiredness, depression, diarrhea, pruritus, rash dyspnea, cold extremities, constipation, dyspepsia	Bradycardia, heart failure, hypotension	No significant interactions
<i>Amiodarone</i>	Oral load 10 g over 7–10 days, then 400 mg for 3 weeks, then 200 mg/d for atrial fibrillation; maintenance dose of 400 mg/day for ventricular tachycardia; dose-reduced load for bradycardia or QT prolongation; intravenous: 150–300 mg bolus, then 1 mg/min infusion for 6 hr followed by 0.5 mg/min thereafter	Hepatic; half-life of 50 days, distributes extensively in adipose tissues. Full effects take until months; metabolized by CYP3A4 and inhibits CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein	Pulmonary (acute hypersensitivity pneumonitis, chronic interstitial infiltrates); hepatitis; thyroid (hypothyroidism or hyperthyroidism); photosensitivity; blue-gray skin discoloration with chronic high dose; nausea; ataxia; tremor; alopecia	Sinus bradycardia	Numerous drug interactions with drugs with potent activity on CYP3A4 and inhibits CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein; increases concentrations of warfarin, digoxin, cyclosporine, alprazolam, carbamazepine, statins (simvastatin), phenytoin, and quinidine; increases the effect of dabigatran but does not appear to be clinically relevant
<i>Sotalol</i>	80–120 mg twice a day; maximum dose 240 mg twice a day based on renal function	Renal; extend dosing interval in patients with renal disease	Bronchospasm	Bradycardia, torsades de pointes	No significant interactions
<i>Dofetilide</i>	Oral CrCl >60 (500 mcg twice a day), CrCl 40–60 (250 mcg twice a day), CrCl 20–39 (125 mcg twice a day)	Renal/hepatic CYP3A4	None	Torsades de pointes	Contraindicated with verapamil, ketoconazole, cimetidine, megestrol, prochlorperazine, and trimethoprim; hydrochlorothiazide increases dofetilide levels; must discontinue amiodarone at least 3 months before dofetilide initiation
<i>Ibutilide (intravenous)</i>	1 mg intravenous over 10 min; repeat after 10 min, if necessary	Hepatic CYP3A4	Nausea	QT prolongation, torsades de pointes	No significant interactions
<i>Dronedarone</i>	Oral: 400 mg twice a day with meals	Renal, hepatic, gastrointestinal	Anorexia; nausea; hepatotoxicity	Bradycardia	
<i>Verapamil</i>	IV 0.075–0.15 mg/kg over 2 min Second bolus can be given in 15–30 min if needed Oral: Start with a non-sustained release dose 120–480 mg daily Can switch to a slow-release/extended release dose, which is available and preferred	Metabolized by liver CYP3A4; dosage adjustment needed in hepatic dysfunction	Dizziness, slow heart-beat, constipation, nausea, headache, or tiredness. Rarely may cause liver damage	Severe dizziness, fainting, new or worsening symptoms of heart failure	Inhibits CYP3A4; will increase levels of alprazolam, carbamazepine, dihydropyridine, cyclosporine, statins, digoxin; verapamil (but not diltiazem) increases dronedarone levels; contraindicated in the presence of strong CYP3A4 inhibitors such as ketoconazole,

**Figure 19.10** (Continued)

Pharmacokinetics, adverse effects, and drug-drug interaction and dosages of antiarrhythmic drugs. (Figure continues on next page)

ANTIARRHYTHMIC DRUG	DOSE	PHARMACOKINETICS	NONCARDIOVASCULAR TOXICITY	CARDIOVASCULAR TOXICITY	DRUG INTERACTIONS
					<i>itraconazole, cyclosporine, clarithromycin, and ritonavir; increases effects of dabigatran</i> <i>Many drug interactions with potent inhibitors of CYP3A4 and inhibitors of P-glycoprotein; displaces digoxin from binding sites; decreases elimination of digoxin</i>
Diltiazem	IV 0.25 mg/kg over 2 min Second bolus can be given if HR > 100 bpm; maintenance 5–15 mg/hr  Oral: Start with a non-sustained release dose 120–480 mg daily Can switch to a slow-release/extended release dose, which is available and preferred	Metabolized by liver CYP3A4; dosage adjustment needed in hepatic dysfunction	Dizziness, lightheadedness, weakness, tired feeling, nausea, upset stomach, flushing. Serious adverse effects include unexplained or sudden weight gain, mental/mood changes (depression, agitation), or unusual dreams	Fainting, slow/irregular/fast heartbeat, swelling of feet, shortness of breath, unusual tiredness	<i>Many drug interactions with potent inhibitors of CYP3A4 and inhibitors of P-glycoprotein; displaces digoxin from binding sites; decreases elimination of digoxin</i>
Adenosine	IV 6 mg bolus in large peripheral vein followed by 12 mg after 1–2 min with cardiac monitoring, if necessary	Extremely short duration of action of 10–30 sec) due to rapid uptake by erythrocytes and endothelial cells	Nausea, dyspnea, flushing; hypersensitivity	Chest pain, hypotension	
Digoxin	IV 0.25 mg every 4–6 hr up to 1 mg	Serum trough concentration of 1–2 ng/ml for AF/flutter; 0.5–0.8 ng/ml for systolic heart failure	Vomiting, loss of appetite, confusion, blurred vision, changes in color perception	Narrow therapeutic index; causes ectopic ventricular beats resulting in ventricular tachycardia and fibrillation	<i>Macrolides and cardiovascular drugs (especially amiodarone) can cause digoxin overdose through pharmacokinetic interactions. Hypercalcemia- and hypokalemia-inducing drugs, heart-rate lowering drugs, and drugs that prolong the QT interval or slow cardiac conduction potentiate the cardiac adverse effects of digoxin. Plasma concentration of digoxin is reduced by acarbose, cytotoxic agents, and enzyme inducers.</i>

**Figure 19.10** (Continued)

Pharmacokinetics, adverse effects, and drug-drug interaction and dosages of antiarrhythmic drugs.

CONDITION	DRUG CLASS	DRUG OF CHOICE	COMMENTS
Sinus tachycardia	Classes II, IV	<i>Propranolol</i>	Other underlying causes may need treatment
Atrial fibrillation/flutter	Classes IA, IC, II, III, IV Digitalis adenosine	<i>Esmolol, verapamil, digoxin</i>	Ventricular rate control is an important goal; anticoagulation required
Paroxysmal supraventricular tachycardia (PSVT)	Classes IA, IC, II, III, IV adenosine	<i>Adenosine, esmolol</i>	–
AV block	Atropine	<i>Atropine</i>	Acute reversal
Ventricular tachycardia	Classes I, II, III	<i>Lidocaine, procainamide, amiodarone</i>	–
Ventricular fibrillation	Classes II, IV Mg <sup>2+</sup> salts	<i>Lidocaine, amiodarone</i>	–
Digitalis toxicity	Class IB Mg <sup>2+</sup> salts; KCl	–	–

**Figure 19.11**

Antiarrhythmic drugs used to treat different types of arrhythmias.

DRUG NAME	SELECTED DRUG INTERACTIONS
<i>Quinidine</i>	↑ <i>Digoxin</i> and <i>amiodarone</i> concentrations; <i>quinidine</i> inhibits CYP2D6 and may increase drugs metabolized by this enzyme (for example, ↑ effect of tricyclic antidepressants, <i>haloperidol</i> , some β-blockers, <i>fluoxetine</i> , narcotics); <i>quinidine</i> metabolism is inhibited by <i>cimetidine</i> ; <i>quinidine</i> metabolism is increased by <i>phenobarbital</i> , <i>phenytoin</i> , and <i>rifampicin</i>
<i>Propafenone</i>	May decrease the metabolism of <i>warfarin</i> ; increased <i>digoxin</i> levels
<i>Flecainide</i>	May increase <i>digoxin</i> levels; <i>flecainide</i> levels are increased by <i>amiodarone</i> , <i>haloperidol</i> , <i>quinidine</i> , <i>cimetidine</i> , and <i>fluoxetine</i>
<i>Dofetilide</i>	Contraindicated with <i>verapamil</i> , <i>ketoconazole</i> , <i>cimetidine</i> , <i>megestrol</i> , <i>prochlorperazine</i> , and <i>trimethoprim</i> ; <i>hydrochlorothiazide</i> increases <i>dofetilide</i> levels; must discontinue <i>amiodarone</i> at least 3 months before <i>dofetilide</i> initiation
<i>Amiodarone</i>	Inhibits CYP450 enzymes; increases concentrations of <i>warfarin</i> , <i>digoxin</i> , <i>cyclosporine</i> , <i>alprazolam</i> , <i>carbamazepine</i> , <i>statins</i> ( <i>simvastatin</i> ), <i>phenytoin</i> , and <i>quinidine</i> ; increases the effect of <i>dabigatran</i> but does not appear to be clinically relevant
<i>Dronedarone</i>	Inhibits CYP3A4; will increase levels of <i>alprazolam</i> , <i>carbamazepine</i> , <i>dihydropyridine</i> , <i>cyclosporine</i> , <i>statins</i> , <i>digoxin</i> ; <i>verapamil</i> (but not <i>diltiazem</i> ) increases <i>dronedarone</i> levels; contraindicated in the presence of strong CYP3A4 inhibitors such as <i>ketoconazole</i> , <i>itraconazole</i> , <i>cyclosporine</i> , <i>clarithromycin</i> , and <i>ritonavir</i> ; increases effects of <i>dabigatran</i>

**Figure 19.12**

Selected drug interactions.

## Study Questions

Choose the ONE best answer.

- 19.1 A 60-year-old woman had a myocardial infarction. Which agent should be used to prevent life-threatening arrhythmias that can occur post-myocardial infarction in this patient?

- A. Digoxin
- B. Flecainide
- C. Metoprolol
- D. Procainamide

Correct answer = C. β-Blockers such as metoprolol prevent arrhythmias that occur subsequent to a myocardial infarction. None of the other drugs has been shown to be effective in preventing postinfarct arrhythmias. Flecainide should be avoided in patients with structural heart disease.

- 19.2 Suppression of arrhythmias resulting from a reentry focus is most likely to occur if the drug:
- Has vagomimetic effects on the AV node.
  - Is a  $\beta$ -blocker.
  - Converts a unidirectional block to a bidirectional block.
  - Slows conduction through the atria.
- 19.3 A 57-year-old man is being treated for an atrial arrhythmia. He complains of dry mouth, blurred vision, and urinary hesitancy. Which antiarrhythmic drug is he mostly like taking?
- Metoprolol
  - Disopyramide
  - Dronedarone
  - Sotalol
- 19.4 A 58-year-old woman is being treated for chronic suppression of a ventricular arrhythmia. After 1 week of therapy, she complains about feeling severe upset stomach and heartburn. Which antiarrhythmic drug is the likely cause of these symptoms?
- Amiodarone
  - Digoxin
  - Mexiletine
  - Propranolol
- 19.5 A 78-year-old woman has been newly diagnosed with atrial fibrillation. She is not currently having symptoms of palpitations or fatigue. Which is appropriate to initiate for rate control as an outpatient?
- Dronedarone
  - Esmolol
  - Flecainide
  - Metoprolol
- 19.6 Which of the following is correct regarding digoxin when used for atrial fibrillation?
- Digoxin works by blocking voltage-sensitive calcium channels.
  - Digoxin is used for rhythm control in patients with atrial fibrillation.
  - Digoxin increases conduction velocity through the AV node.
  - Digoxin levels of 1 to 2 ng/mL are desirable in the treatment of atrial fibrillation.

Correct answer = C. Current theory holds that a reentrant arrhythmia is caused by damaged heart muscle, so that conduction is slowed through the damaged area in only one direction. A drug that prevents conduction in either direction through the damaged area interrupts the reentrant arrhythmia. Class I antiarrhythmics, such as lidocaine, are capable of producing bidirectional block. The other choices do not have any direct effects on the direction of blockade of conduction through damaged cardiac muscle.

Correct answer = B. The clustered symptoms of dry mouth, blurred vision, and urinary hesitancy are characteristic of anticholinergic adverse effects which are caused by class IA agents (in this case, disopyramide). The other drugs do not cause anticholinergic effects.

Correct answer = C. The patient is exhibiting a classic adverse effect of mexiletine. None of the other agents listed are likely to cause dyspepsia.

Correct answer = D. Only B and D are options to control rate. The other options are used for rhythm control in patients with atrial fibrillation. Since esmolol is IV only, the only option to start as an outpatient is metoprolol.

Correct answer = D. Digoxin works by inhibiting the  $\text{Na}^+/\text{K}^+$ -ATPase pump. It decreases conduction velocity through the AV node and is used for rate control in atrial fibrillation (not rhythm control). Digoxin levels between 1 and 2 ng/mL are more likely to exhibit negative chronotropic effects desired in atrial fibrillation or flutter. A serum drug concentration between 0.5 and 0.8 ng/mL is for symptomatic management of heart failure.

- 19.7 All of the following are adverse effects of amiodarone except:
- A. Cinchonism
  - B. Hypothyroidism
  - C. Pulmonary fibrosis
  - D. Blue skin discoloration
- Correct answer = A. Cinchonism is a constellation of symptoms (blurred vision, tinnitus, headache, psychosis) that is known to occur with quinidine. All other options are adverse effects with amiodarone that require close monitoring.
- 19.8 Which arrhythmia can be treated with lidocaine?
- A. Paroxysmal supraventricular ventricular tachycardia
  - B. Atrial fibrillation
  - C. Atrial flutter
  - D. Ventricular tachycardia
- Correct answer = D. Lidocaine has little effect on atrial or AV nodal tissue; thus, it used for ventricular arrhythmias such as ventricular tachycardia.
- 19.9 A clinician would like to initiate a drug for rhythm control of atrial fibrillation. Which of the following coexisting conditions would allow for initiation of flecainide?
- A. Hypertension
  - B. Left ventricular hypertrophy
  - C. Coronary artery disease
  - D. Heart failure
- Correct answer = A. Since flecainide can increase the risk of sudden cardiac death in those with a history of structural heart disease, only coexisting hypertension will allow for flecainide initiation. Structural heart disease includes left ventricular hypertrophy, heart failure, and atherosclerotic heart disease.
- 19.10 Which statement regarding dronedarone is correct?
- A. Dronedarone is more effective than amiodarone.
  - B. QT interval prolongation is not a risk with dronedarone.
  - C. Dronedarone increases the risk of death in patients with permanent atrial fibrillation or symptomatic heart failure.
  - D. There is no need to monitor liver function with dronedarone.
- Correct answer = C. Dronedarone is not as effective as amiodarone, QT prolongation is a risk with this drug, and liver function should be monitored when taking dronedarone since it increases the risk of liver failure. The drug is contraindicated in those with symptomatic heart failure or permanent atrial fibrillation due to an increased risk of death.

# Antianginal Drugs

Kristyn Pardo

# 20

## I. OVERVIEW

Atherosclerotic disease of the coronary arteries, also known as coronary artery disease (CAD) or ischemic heart disease (IHD), is the most common cause of mortality worldwide. Atherosclerotic lesions in coronary arteries can obstruct blood flow, leading to an imbalance in myocardial oxygen supply and demand that presents as stable angina or an acute coronary syndrome (myocardial infarction [MI] or unstable angina). Spasms of vascular smooth muscle may also impede cardiac blood flow, reducing perfusion and causing ischemia and angina pain. Typical angina pectoris is a characteristic sudden, severe, crushing chest pain that may radiate to the neck, jaw, back, and arms. All patients with IHD and angina should receive guideline-directed medical therapy with emphasis on lifestyle modifications (smoking cessation, physical activity, weight management) and management of modifiable risk factors (hypertension, diabetes, dyslipidemia) to reduce cardiovascular morbidity and mortality. Medications used for the management of stable angina are summarized in [Figure 20.1](#).

## II. TYPES OF ANGINA

Angina pectoris has three patterns: 1) stable, effort-induced, classic, or typical angina; 2) unstable angina; and 3) Prinzmetal, variant, vasospastic, or rest angina. They are caused by varying combinations of increased myocardial demand and decreased myocardial perfusion.

### A. Stable angina, effort-induced angina, classic or typical angina

Classic or typical angina pectoris is the most common form of angina. It is usually characterized by a short-lasting burning, heavy, or squeezing feeling in the chest. Some ischemic episodes may present “atypically”—with extreme fatigue, nausea, or diaphoresis—while others may not be associated with any symptoms (silent angina). Atypical presentations are more common in women, diabetic patients, and the elderly.

Classic angina is caused by the reduction of coronary perfusion due to a fixed obstruction of a coronary artery produced by atherosclerosis. Increased myocardial oxygen demand, such as that produced by physical activity, emotional stress or excitement, or any other cause of increased cardiac workload ([Figure 20.2](#)) may induce ischemia. Typical angina pectoris is promptly relieved by rest or *nitroglycerin*.

#### β-BLOCKERS

*Propranolol*  
*Atenolol*  
*Bisoprolol*  
*Metoprolol*

#### CALCIUM CHANNEL BLOCKERS (DIHYDROPYRIDINES)

*Amlodipine*  
*Nifedipine*  
*Felodipine*

#### CALCIUM CHANNEL BLOCKERS (NONDIHYDROPYRIDINE)

*Diltiazem*  
*Verapamil*

#### NITRATES

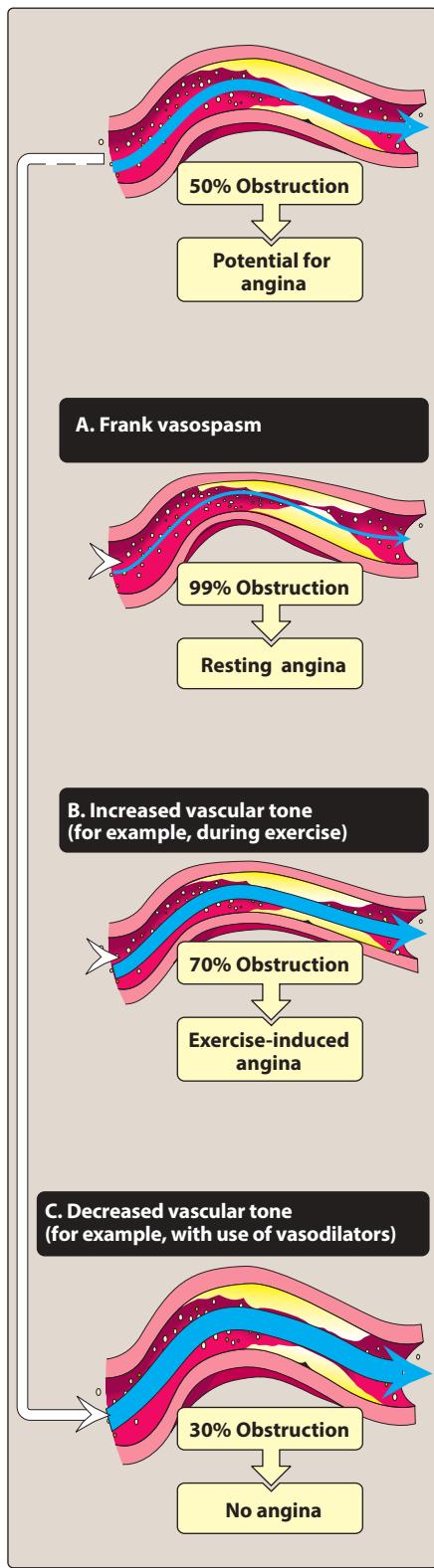
*Nitroglycerin*  
*Isosorbide dinitrate*  
*Isosorbide mononitrate*

#### SODIUM CHANNEL BLOCKER

*Ranolazine*

### Figure 20.1

Summary of antianginal drugs.  
(For drug dosages, refer to Appendix at the end of the book.)

**Figure 20.2**

Blood flow in a coronary artery partially blocked with atherosclerotic plaques.

[nye-troe-GLIS-er-in]. When the pattern of chest pain and the amount of effort needed to trigger the chest pain does not vary over time, the angina is named “stable angina.”

### B. Unstable angina

Unstable angina is chest pain that occurs with increased frequency, duration, and intensity and can be precipitated by progressively less effort. Any episode of rest angina longer than 20 minutes, any new-onset angina, any increasing (crescendo) angina, or even sudden development of shortness of breath is suggestive of unstable angina. The symptoms are not relieved by rest or *nitroglycerin*. Unstable angina is a form of acute coronary syndrome and requires hospital admission and more aggressive therapy to prevent progression to MI and death.

### C. Prinzmetal, variant, vasospastic, or rest angina

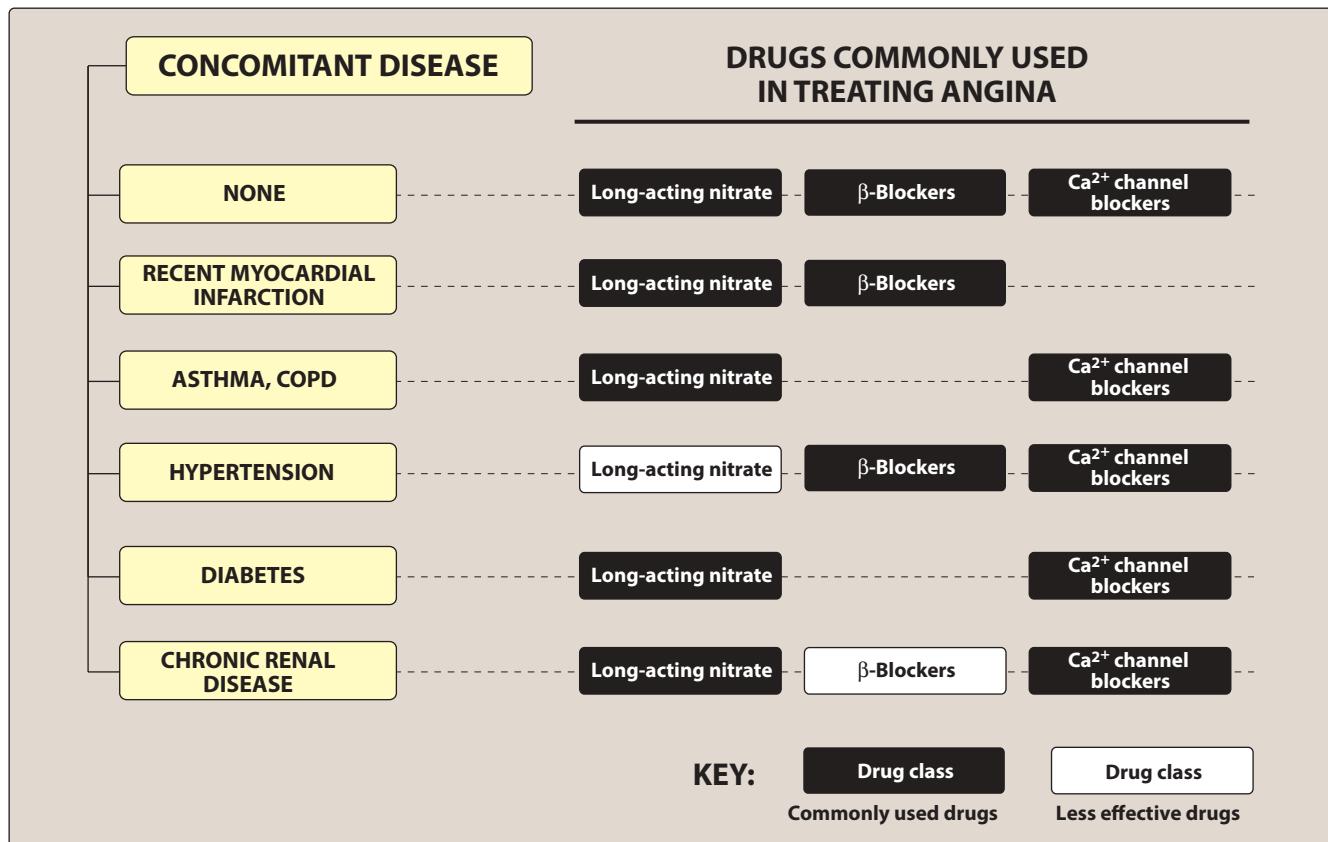
Prinzmetal angina is an uncommon pattern of episodic angina that occurs at rest and is due to decreased blood flow to the heart muscle caused by spasm of the coronary arteries. Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure. Prinzmetal angina generally responds promptly to coronary vasodilators, such as *nitroglycerin* and calcium channel blockers.

### D. Acute coronary syndrome

Acute coronary syndrome is an emergency that commonly results from rupture of an atherosclerotic plaque and partial or complete thrombosis of a coronary artery. If the thrombus occludes most of the blood vessel, and, if the occlusion is untreated, necrosis of the cardiac muscle may ensue. MI (necrosis) is typified by increases in the serum levels of biomarkers such as troponins and creatine kinase. The acute coronary syndrome may present as ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, or as unstable angina. [Note: In unstable angina, increases in biomarkers of myocardial necrosis are not present.]

## III. TREATMENT STRATEGIES

Four types of drugs, used either alone or in combination, are commonly used to manage patients with stable angina:  $\beta$ -blockers, calcium channel blockers, organic nitrates, and the sodium channel-blocking drug, *ranolazine* (Figure 20.1). These agents help to balance the cardiac oxygen supply and demand equation by affecting blood pressure, venous return, heart rate, and contractility. All antianginal drugs have similar efficacy and are equally effective for relief of anginal symptoms. For relief of acute angina and prevention of angina before events that cause acute angina, *nitroglycerin* (sublingual tablets or translingual spray) is usually the primary drug of choice. Sublingual or chewable tablets of *isosorbide dinitrate* may also be used. For long-term prevention or management of recurrent angina, oral or topical nitrates,  $\beta$ -adrenergic blocking agents, or calcium channel blocking agents can be used. Double or triple therapy is often needed to control chronic stable angina since patients with IHD and angina can have several

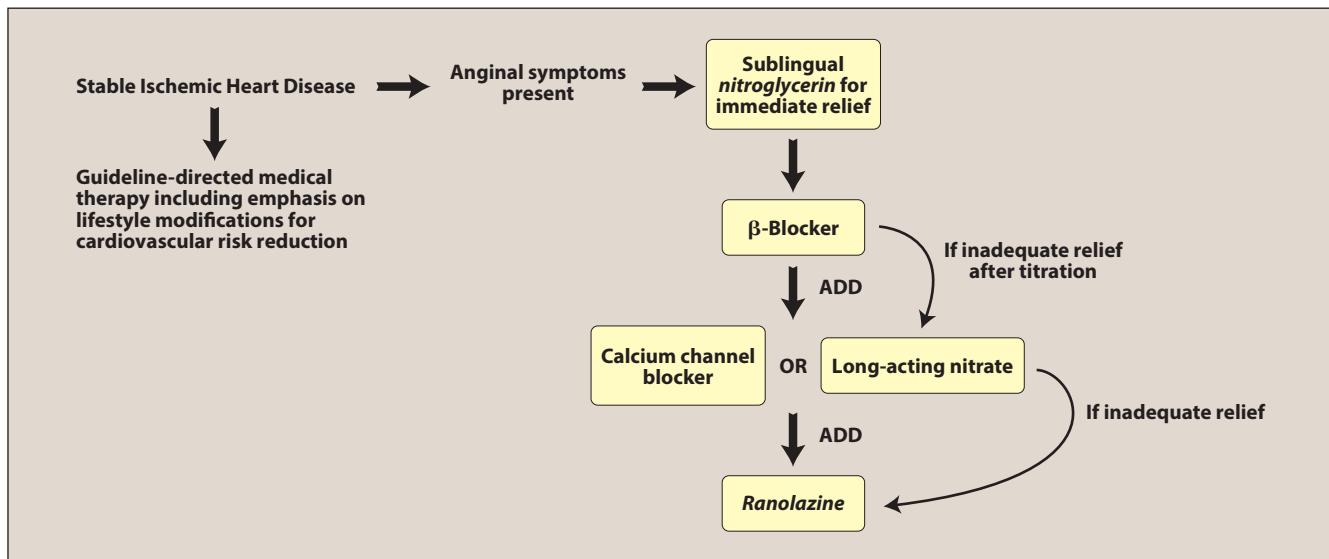
**Figure 20.3**

Treatment of angina in patients with concomitant diseases. COPD = chronic obstructive pulmonary disease.

comorbidities, and cardiac ischemic pain might result from various underlying pathophysiologies. Some antianginal agents have additional properties that could be useful, depending on comorbidities and the mechanisms of the angina. The dosage of all antianginal drugs should be individualized to achieve optimal benefit and minimal adverse effects. This is usually accomplished by starting with relatively small doses and increasing them at appropriate intervals as necessary. Doses may vary widely among individuals. Adverse drug effects, such as hypotension and syncope, are more severe in elderly than in younger adults. Monitor blood pressure and ability to ambulate safely closely, especially when drug therapy is started or dosages are increased. [Figure 20.3](#) summarizes the treatment of angina in patients with concomitant diseases, and [Figure 20.4](#) provides a treatment algorithm for patients with stable angina.

## IV. $\beta$ -ADRENERGIC BLOCKERS

The  $\beta$ -adrenergic blockers decrease the oxygen demands of the myocardium by blocking  $\beta_1$  receptors, resulting in decreased heart rate, contractility, cardiac output, and blood pressure. These agents reduce myocardial oxygen demand during exertion and at rest. As such, they can reduce both the frequency and the severity of angina attacks.  $\beta$ -Blockers can be used to increase exercise duration and tolerance in patients with effort-induced angina.  $\beta$ -Blockers are recommended as initial antianginal therapy

**Figure 20.4**

Treatment algorithm for improving symptoms in patients with stable angina.

in all patients unless contraindicated. [Note: The exception to this rule is vasospastic angina, in which  $\beta$ -blockers are ineffective and may actually worsen symptoms.]  $\beta$ -Blockers reduce the risk of death and MI in patients who have had a prior MI and also improve mortality in patients with heart failure with reduced ejection fraction. Agents with intrinsic sympathomimetic activity (ISA) such as *pindolol* should be avoided in patients with angina and those with a history of MI. *Propranolol* is the prototype for this class of compounds, but it is not cardioselective (see Chapter 7). Thus, other  $\beta$ -blockers, such as *metoprolol* and *atenolol*, are preferred. [Note: All  $\beta$ -blockers are nonselective at high doses and can inhibit  $\beta_2$  receptors.]  $\beta$ -Blockers should be avoided in patients with severe bradycardia; however, they can be used in patients with diabetes, peripheral vascular disease, and chronic obstructive pulmonary disease, as long as they are monitored closely. Nonselective  $\beta$ -blockers should be avoided in patients with asthma. [Note: It is important not to discontinue  $\beta$ -blocker therapy abruptly. The dose should be gradually tapered off over 2 to 3 weeks to avoid rebound angina, MI, and hypertension.]

## V. CALCIUM CHANNEL BLOCKERS

Calcium is essential for muscular contraction. Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces. In turn, this promotes the activity of several ATP-consuming enzymes, thereby depleting energy stores and worsening the ischemia. The calcium channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. All calcium channel blockers are, therefore, arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance. These agents primarily affect the resistance of peripheral and coronary arteriolar smooth muscle. In the treatment of effort-induced angina, calcium channel blockers reduce myocardial oxygen consumption by decreasing vascular resistance, thereby decreasing afterload. Their efficacy in vasospastic

angina is due to relaxation of the coronary arteries. [Note: *Verapamil* mainly affects the myocardium, whereas *amlodipine* exerts a greater effect on smooth muscle in the peripheral vasculature. *Diltiazem* is intermediate in its actions.] All calcium channel blockers lower blood pressure.

### A. Dihydropyridine calcium channel blockers

*Amlodipine* [am-LOE-di-peen], an oral dihydropyridine, has minimal effect on cardiac conduction and functions mainly as an arteriolar vasodilator. The vasodilatory effect of *amlodipine* is useful in the treatment of variant angina caused by spontaneous coronary spasm. *Nifedipine* [ni-FED-i-pine] is another agent in this class; it is usually administered as an extended-release oral formulation. [Note: Short-acting dihydropyridines should be avoided in CAD because of evidence of increased mortality after an MI and an increase in acute MI in hypertensive patients.]

### B. Nondihydropyridine calcium channel blockers

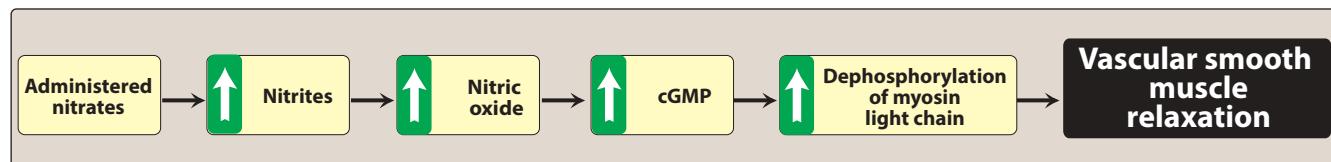
*Verapamil* [ver-AP-a-mil] slows atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand. *Verapamil* has greater negative inotropic effects than *amlodipine*, but it is a weaker vasodilator. *Verapamil* is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities. *Diltiazem* [dil-TYE-a-zem] also slows AV conduction, decreases the rate of firing of the sinus node pacemaker, and is also a coronary artery vasodilator. *Diltiazem* can relieve coronary artery spasm and is particularly useful in patients with variant angina. Nondihydropyridine calcium channel blockers can worsen heart failure due to their negative inotropic effect, and their use should be avoided in this population.

## VI. ORGANIC NITRATES

These compounds cause a reduction in myocardial oxygen demand, followed by relief of symptoms. They are effective in stable, unstable, and variant angina.

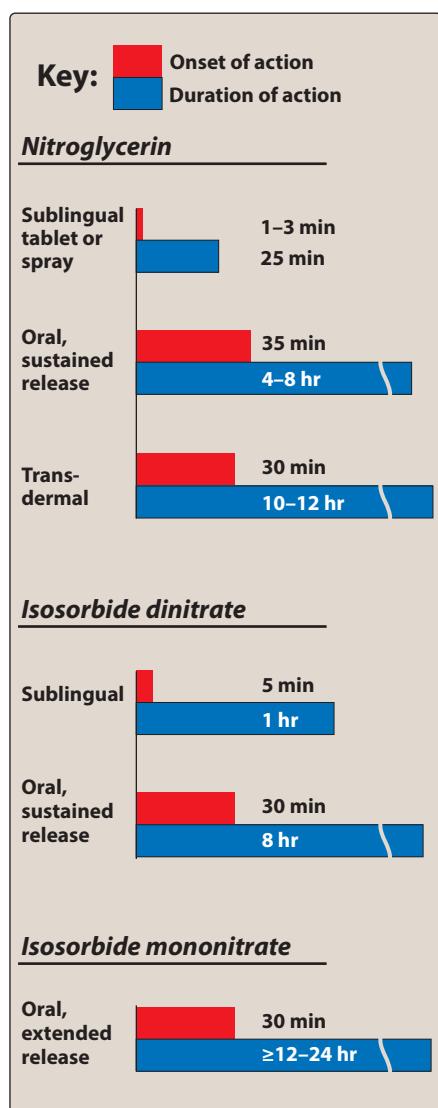
### A. Mechanism of action

Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide, which in turn activates guanylate cyclase and increases synthesis of cyclic guanosine monophosphate (cGMP). Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation (Figure 20.5). Nitrates such as *nitroglycerin* cause



**Figure 20.5**

Effects of nitrates and nitrites on smooth muscle. cGMP = cyclic guanosine 3',5'-monophosphate.

**Figure 20.6**

Time to peak effect and duration of action for some common organic nitrate preparations.

dilation of the large veins, which reduces preload (venous return to the heart) and, therefore, reduces the work of the heart. Nitrates also dilate the coronary vasculature, providing an increased blood supply to the heart muscle.

## B. Pharmacokinetics

Nitrates differ in their onset of action and rate of elimination. The onset of action varies from 1 minute for *nitroglycerin* to 30 minutes for *isosorbide [eye-soe-SOR-bide] mononitrate* (Figure 20.6). Sublingual *nitroglycerin*, available in tablet or spray formulation, is the drug of choice for prompt relief of an angina attack precipitated by exercise or emotional stress. All patients should have *nitroglycerin* on hand to treat acute angina attacks. Significant first-pass metabolism of *nitroglycerin* occurs in the liver. Therefore, it is commonly administered via the sublingual or transdermal route (patch or ointment), thereby avoiding the hepatic first-pass effect. *Isosorbide mononitrate* owes its improved bioavailability and long duration of action to its stability against hepatic breakdown. Oral *isosorbide dinitrate* undergoes denitration to two mononitrates, both of which possess antianginal activity.

## C. Adverse effects

Headache is the most common adverse effect of nitrates. High doses of nitrates can also cause postural hypotension, facial flushing, and tachycardia. Phosphodiesterase type 5 inhibitors such as *sildenafil* potentiate the action of the nitrates. To preclude the dangerous hypotension that may occur, this combination is contraindicated.

Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitized to vasodilation. Tolerance can be overcome by providing a daily “nitrate-free interval” to restore sensitivity to the drug. The nitrate-free interval of 10 to 12 hours is usually taken at night when myocardial oxygen demand is decreased. However, variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. Therefore, the nitrate-free interval in patients with variant angina should occur in the late afternoon. *Nitroglycerin* patches are worn for 12 hours and then removed for 12 hours to provide the nitrate-free interval.

## VII. SODIUM CHANNEL BLOCKER

*Ranolazine* inhibits the late phase of the sodium current (late  $I_{Na}$ ), improving the oxygen supply and demand equation. Inhibition of late  $I_{Na}$  reduces intracellular sodium and calcium overload, thereby improving diastolic function. *Ranolazine* has antianginal as well as antiarrhythmic properties. It is most often used in patients who have failed other antianginal therapies. The antianginal effects of *ranolazine* are considerably less in women than in men. The reason for this difference in effect is unknown. *Ranolazine* is extensively metabolized in the liver, mainly by the CYP3A family and also by CYP2D6. It is also a substrate of P-glycoprotein. As such, *ranolazine* is subject to numerous drug interactions. In addition, *ranolazine* can prolong the QT interval and should be avoided with other drugs that cause QT prolongation.

Figure 20.7 provides a summary of characteristics of the antianginal drugs.

DRUG CLASS	COMMON ADVERSE EFFECTS	DRUG INTERACTIONS	NOTES
β-Blockers  <i>Atenolol</i> <i>Metoprolol</i> <i>Propranolol</i>	Bradycardia, worsening peripheral vascular disease, fatigue, sleep disturbance, depression, blunt hypoglycemia awareness, inhibit β <sub>2</sub> -mediated bronchodilation in asthmatics	β <sub>2</sub> Agonists (blunted effect); non-dihydropyridine calcium channel blockers (additive effects)	β <sub>1</sub> -Selective agents preferred ( <i>atenolol, metoprolol</i> ). Avoid agents with ISA for angina therapy ( <i>pindolol</i> )
Dihydropyridine calcium-channel blockers  <i>Amlodipine</i> <i>Felodipine</i> <i>Nifedipine</i>	Peripheral edema, headache, flushing, rebound tachycardia (immediate-release formulations), hypotension	CYP 3A4 substrates (will increase drug concentrations)	Avoid short-acting agents as they can worsen angina (may use extended-release formulations)
Nondihydropyridine calcium channel blockers  <i>Diltiazem</i> <i>Verapamil</i>	Bradycardia, constipation, heart failure exacerbations, gingival hyperplasia ( <i>verapamil</i> ), edema ( <i>diltiazem</i> )	CYP 3A4 substrates (will increase drug concentrations); increase <i>digoxin</i> levels; β-blockers and other drugs affecting AV node conduction (additive effects)	Avoid in patients with heart failure  Adjust dose of both agents in patients with hepatic dysfunction
Organic nitrates  <i>Isosorbide dinitrate</i> <i>Isosorbide mononitrate</i> <i>Nitroglycerin</i>	Headache, hypotension, flushing, tachycardia	Contraindicated with PDE5 inhibitors ( <i>sildenafil</i> and others)	Ensure nitrate-free interval to prevent tolerance
Sodium-channel inhibitor  <i>Ranolazine</i>	Constipation, headache, edema, dizziness, QT interval prolongation	Avoid use with CYP 3A4 inducers ( <i>phenytoin, carbamazepine, St. John's wort</i> ) and strong inhibitors ( <i>clarithromycin, azole antifungals</i> ) and agents that prolong QT interval ( <i>citalopram, quetiapine, others</i> )	No effect on hemodynamic parameters

CYP = cytochrome P450; ISA = intrinsic sympathomimetic activity; PDE5 = phosphodiesterase type 5.

**Figure 20.7**

Summary of characteristics of antianginal drugs.

## Study Questions

Choose the ONE best answer.

- 20.1 Which of the following best describes stable angina?
- Angina that occurs more frequently or with progressively less exercise or stress than before
  - Angina due to spasm of coronary arteries
  - Angina due to increased myocardial demand which is reproducible and relieved by rest or nitroglycerin
  - Angina pain accompanied by increases in serum biomarkers of myocardial necrosis

Correct answer = C. When the pattern of the chest pain and the amount of effort needed to trigger the chest pain does not vary over time, the angina is named "stable angina."

20.2 Which medication should be prescribed to all angina patients to treat an acute attack?

- A. Isosorbide dinitrate
- B. Nitroglycerin patch
- C. Nitroglycerin sublingual tablet or spray
- D. Ranolazine

Correct answer = C. The other options will not provide prompt relief of angina and should not be used to treat an acute attack.

20.3 Which of the following instructions is important to communicate to a patient receiving a prescription for the nitroglycerin patch?

- A. Apply the patch at onset of angina symptoms for quick relief.
- B. Remove the old patch after 24 hours of use, then immediately apply the next patch to prevent any breakthrough angina pain.
- C. Do not use sublingual nitroglycerin in combination with the patch.
- D. Have a nitrate-free interval of 10 to 12 hours every day to prevent development of nitrate tolerance.

Correct answer = D. Nitrate-free intervals help prevent the development of nitrate tolerance. Sublingual nitroglycerin should be used to treat breakthrough angina due to its quick onset of action; transdermal nitroglycerin has a delayed onset of action.

20.4 A 64-year-old man was prescribed atenolol and sublingual nitroglycerin after his recent hospitalization for unstable angina. Which of his current medications should be discontinued?

- A. Sildenafil
- B. Amlodipine
- C. Metformin
- D. Lisinopril

Correct answer = A. Sildenafil and other PDE-5 inhibitors can potentiate the vasodilator effects of nitrates and cause an unsafe drop in blood pressure. Concomitant use of nitrates and PDE-5 inhibitors should be avoided.

20.5 Which of the following correctly ranks the calcium channel blockers from most active on the myocardium to most peripherally active?

- A. Diltiazem, amlodipine, verapamil
- B. Verapamil, diltiazem, nifedipine
- C. Nifedipine, verapamil, diltiazem
- D. Amlodipine, diltiazem, verapamil

Correct answer = B. Verapamil has the most negative inotropic effects, nifedipine is a peripheral vasodilator, and diltiazem is intermediate with actions on both myocardial and peripheral calcium channels.

20.6 A 76-year-old man with uncontrolled hypertension is experiencing typical angina pain that is relieved with rest and sublingual nitroglycerin. He has a high blood pressure (178/92 mm Hg) and a low heart rate (54 bpm). Which is the most appropriate therapy for his angina at this time?

- A. Ranolazine
- B. Verapamil
- C. Metoprolol
- D. Amlodipine

Correct answer = D. Amlodipine is the best choice because it will improve angina as well as help control blood pressure, without further reducing the heart rate. Adding verapamil or metoprolol may worsen the bradycardia. Ranolazine may help the angina, but it will not improve the hypertension.

- 20.7 A 65-year-old male experiences uncontrolled angina attacks that limit his ability to do household chores. He is adherent to a maximized dose of  $\beta$ -blocker with a low heart rate and low blood pressure. He is unable to tolerate an increase in isosorbide mononitrate due to headache. Which is the most appropriate addition to his antianginal therapy?
- A. Nifedipine
  - B. Aspirin
  - C. Ranolazine
  - D. Verapamil
- 20.8 A 62-year-old man with ischemic heart disease complains of angina pain that has been getting progressively worse over the past 30 minutes despite use of nitroglycerin. Which of the following is the best course of action?
- A. Change nitroglycerin to a long-acting nitrate.
  - B. Initiate metoprolol.
  - C. Initiate ranolazine.
  - D. Refer him to the nearest emergency department for immediate evaluation.
- 20.9 Which is correct regarding antianginal therapy in patients with heart failure with reduced ejection fraction?
- A.  $\beta$ -Blockers have been associated with increased mortality.
  - B. Dihydropyridine calcium channel blockers should be avoided.
  - C.  $\beta$ -Blockers with ISA are preferred over those without ISA.
  - D. Nondihydropyridine calcium channel blockers should be used in patients with heart failure with reduced ejection fraction who cannot tolerate  $\beta$ -blockers.
- 20.10 A 45-year-old woman with type 1 diabetes has been diagnosed with Prinzmetal angina. Which of the following is correct regarding management of angina in this patient?
- A.  $\beta$ -Blockers are the treatment of choice but should be avoided because of her diabetes.
  - B. Nitroglycerin is not beneficial for this type of angina.
  - C. She should be counseled to take nitroglycerin before physical activity to prevent symptoms.
  - D. Felodipine will be more effective than verapamil.

Correct answer = C. Ranolazine is the best answer. The patient's blood pressure is low, so verapamil and nifedipine may drop blood pressure further. Verapamil may also decrease heart rate. Ranolazine can be used when other agents are maximized, especially when blood pressure is well controlled. The patient will need a baseline ECG and lab work to ensure safe use of this medication.

Correct answer = C. Crescendo angina is indicative of unstable angina that requires immediate evaluation.

Correct answer = A.  $\beta$ -Blockers have been shown to improve mortality in heart failure with reduced ejection fraction, but  $\beta$ -blockers with ISA should be avoided in these patients. Dihydropyridine calcium channel blockers can be used in patients with heart failure with reduced ejection fraction, but nondihydropyridine calcium channel blockers should be avoided due to negative inotropic effects.

Correct answer = D. Prinzmetal or vasospastic angina responds well to vasodilators, including the nondihydropyridine calcium channel blocker felodipine. Verapamil is a weak vasodilator.  $\beta$ -Blockers may be used with caution in patients with diabetes, but these drugs are less effective options for Prinzmetal angina. Nitrates are also effective, but Prinzmetal angina is provoked by coronary artery vasospasm rather than physical activity.



# Anticoagulants

Katherine Vogel Anderson and Kaylie Smith

# 21

## I. OVERVIEW

This chapter describes drugs that are useful in the treatment of disorders of hemostasis. Thrombosis, the formation of an unwanted clot within a blood vessel, is the most common abnormality of hemostasis. Thrombotic disorders include acute myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary embolism (PE), and acute ischemic stroke. These conditions are treated with drugs such as anticoagulants and fibrinolytics. Bleeding disorders related to the failure of hemostasis are less common than thromboembolic disorders. Bleeding disorders include hemophilia, which is treated with transfusion of recombinant factor VIII, and vitamin K deficiency, which is treated with vitamin K supplementation. **Figure 21.1** summarizes agents used for the treatment of dysfunctions of hemostasis.

## II. THROMBUS VERSUS EMBOLUS

A clot that adheres to a vessel wall is called a “thrombus,” whereas an intravascular clot that floats in the blood is termed an “embolus.” Thus, a detached thrombus becomes an embolus. Both thrombi and emboli are dangerous, because they may occlude blood vessels and deprive tissues of oxygen and nutrients. Arterial thrombosis most often occurs in medium-sized vessels rendered thrombogenic by atherosclerosis. Arterial thrombosis usually consists of a platelet-rich clot. In contrast, venous thrombosis is triggered by blood stasis or inappropriate activation of the coagulation cascade. Venous thrombosis typically involves a clot that is rich in fibrin, with fewer platelets than are observed with arterial clots.

## III. PLATELET RESPONSE TO VASCULAR INJURY

Physical trauma to the vascular system, such as a puncture or a cut, initiates a complex series of interactions between platelets, endothelial cells, and the coagulation cascade. These interactions lead to hemostasis or the cessation of blood loss from a damaged blood vessel. Platelets are central in this process. Initially, there is vasospasm of the damaged blood vessel to prevent further blood loss. The next step involves the formation of a platelet–fibrin plug at the site of the puncture. The creation of an unwanted thrombus involves many of the same steps as normal clot formation, except that the triggering stimulus is a pathologic condition in the vascular system, rather than external physical trauma.

### PLATELET INHIBITORS

Thromboxane A<sub>2</sub> inhibitor  
*Aspirin (Oral)*  
Vasodilator and inhibitor of *thromboxane A<sub>2</sub> synthesis*  
*Dipyridamole (Oral)*  
ADP receptor inhibitors  
*Clopidogrel (Oral)*  
*Ticlopidine (Oral)*  
*Prasugrel (Oral)*  
*Ticagrelor (Oral)*  
*Cangrelor (IV)*  
Vasodilator and PDE III inhibitor  
*Cilostazol (Oral)*  
GP IIb/IIIa inhibitors  
*Abciximab (IV)*  
*Tirofiban (IV)*  
*Eptifibatide (IV)*

### ANTICOAGULANTS

Heparin (IV, SC)  
Low molecular weight heparins  
*Enoxaparin (SC)*  
*Dalteparin (SC)*  
Synthetic parenteral  
*Argatroban (IV)*  
*Fondaparinux (IV, SC)*  
Analogs of hirudin  
*Bivalirudin (IV)*  
*Desirudin (IV)*  
*Warfarin (Oral)*  
*Dabigatran (Oral)*  
*Apixaban (Oral)*  
*Betrixaban (Oral)*  
*Edoxaban (Oral)*  
*Rivaroxaban (Oral)*

### THROMBOLYTIC AGENTS (IV)

*Streptokinase*  
*Urokinase*  
*Alteplase (tPA)*  
*Reteplase*  
*Tenecteplase*

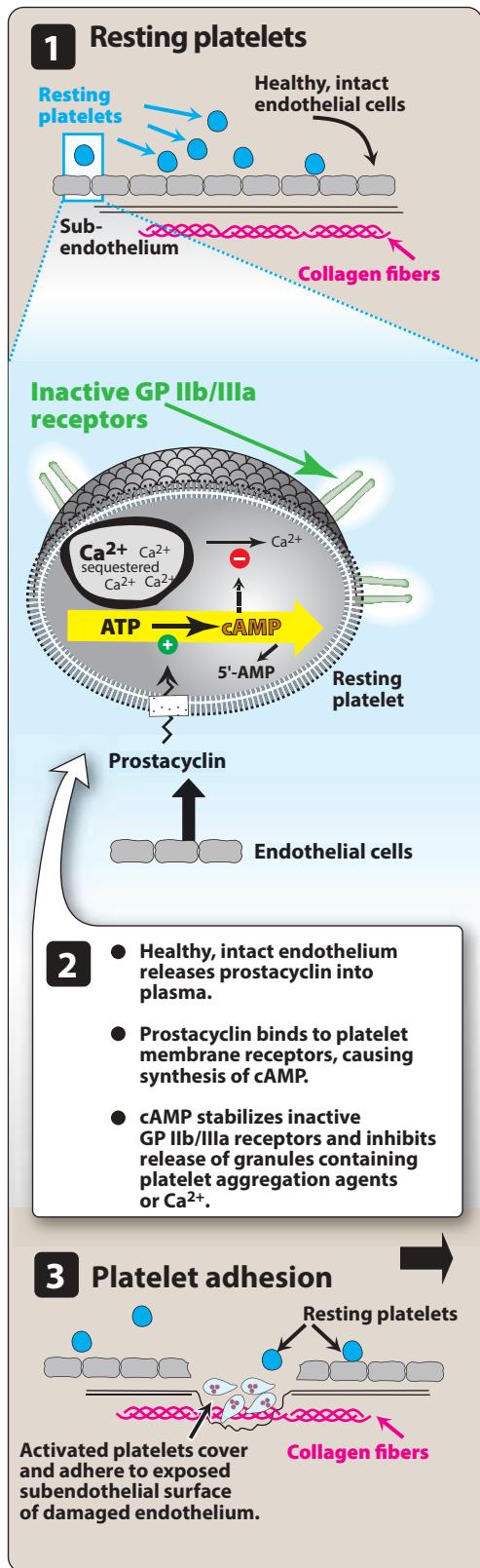
### TREATMENT OF BLEEDING

*Protamine sulfate (IV)*  
*Tranexamic acid (Oral, IV)*  
*Vitamin K<sub>1</sub> (Phytonadione) (SC)*  
*Idarucizumab (IV)*  
*Aminocaproic acid (IV)*

**Figure 21.1**

Summary of drugs used in treating dysfunctions of hemostasis and their route of administration. (For drug dosages, refer to Appendix at the end of the book.)

### A. Resting platelets



**Figure 21.2**

Formation of a hemostatic plug. ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; GP = glycoprotein; (Figure continues on next page)

## B. Platelet adhesion

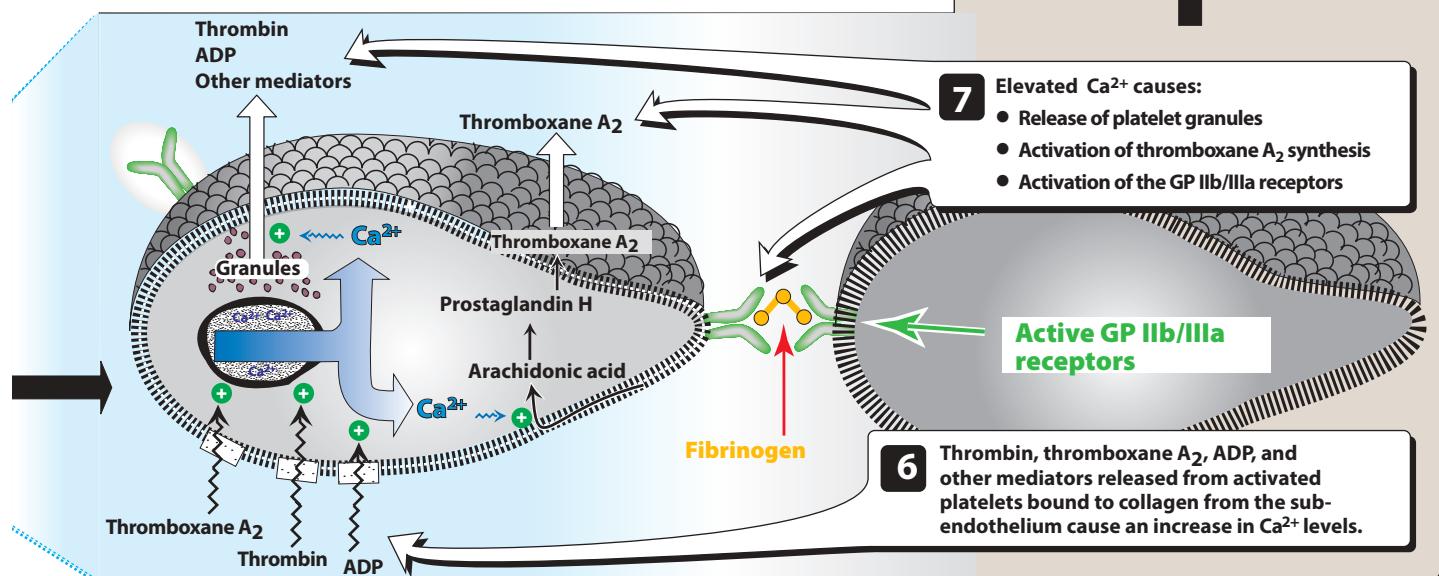
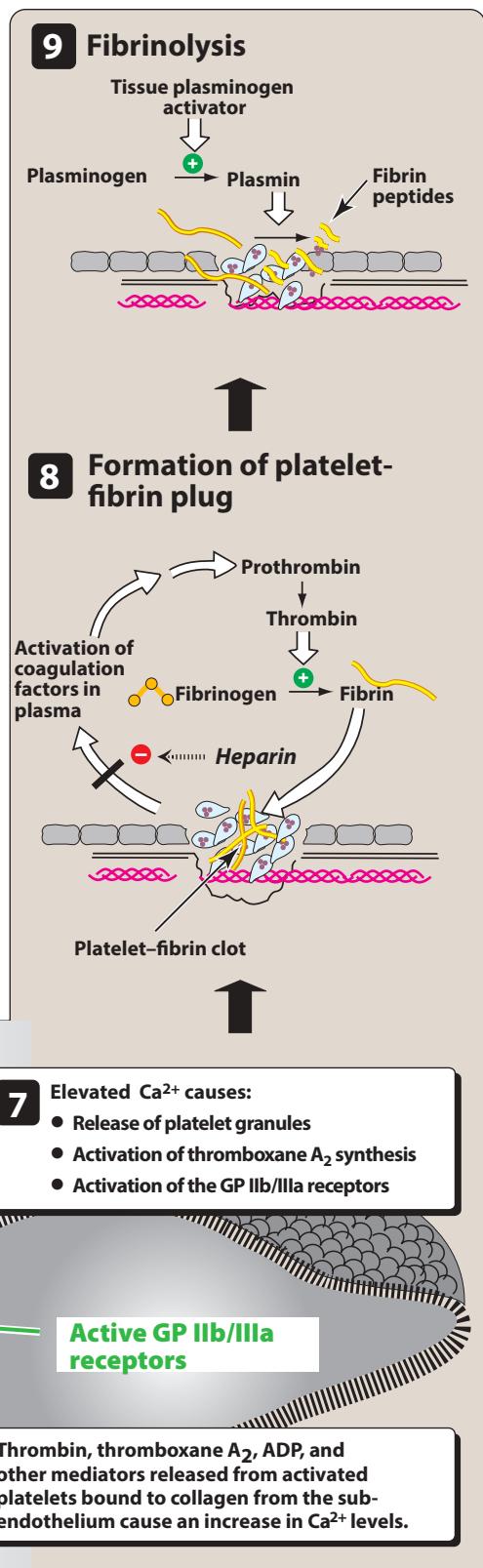
When the endothelium is injured, platelets adhere to and virtually cover the exposed collagen of the subendothelium (Figure 21.2). This triggers a complex series of chemical reactions, resulting in platelet activation.

## C. Platelet activation

Receptors on the surface of the adhering platelets are activated by the collagen of the underlying connective tissue. This causes morphologic changes in platelets (Figure 21.3) and the release of platelet granules containing chemical mediators, such as adenosine diphosphate (ADP), thromboxane A<sub>2</sub>, serotonin, platelet activation factor, and thrombin (Figure 21.2). These signaling molecules bind to receptors in the outer membrane of resting platelets circulating nearby. These receptors function as sensors that are activated by the signals sent from the adhering platelets. The previously dormant platelets become activated and start to aggregate. These actions are mediated by several messenger systems that ultimately result in elevated levels of calcium and a decreased concentration of cAMP within the platelet.

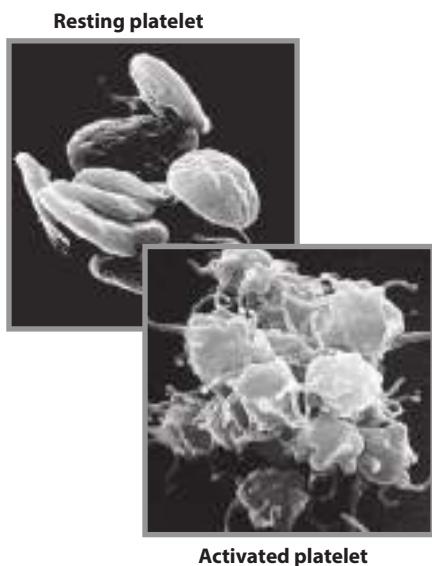
## D. Platelet aggregation

The increase in cytosolic calcium accompanying activation is due to a release of sequestered stores within the platelet (Figure 21.2). This leads to 1) the release of platelet granules containing mediators, such as ADP and serotonin that activate other platelets; 2) activation of thromboxane A<sub>2</sub> synthesis; and 3) activation of glycoprotein (GP) IIb/IIIa receptors that bind fibrinogen and, ultimately, regulate platelet–platelet interaction and thrombus formation. Fibrinogen, a soluble plasma GP, simultaneously binds to GP IIb/IIIa receptors on two separate platelets,



**Figure 21.2 (Continued)**

Formation of a hemostatic plug. ADP = adenosine diphosphate; PAF = platelet activation factor.

**Figure 21.3**

Scanning electron micrograph of platelets.

resulting in platelet cross-linking and platelet aggregation. This leads to an avalanche of platelet aggregation, because each activated platelet can recruit other platelets (Figure 21.4).

### E. Formation of a clot

Local stimulation of the coagulation cascade by tissue factors released from the injured tissue and by mediators on the surface of platelets results in the formation of thrombin (factor IIa). In turn, thrombin, a serine protease, catalyzes the hydrolysis of fibrinogen to fibrin, which is incorporated into the clot. Subsequent cross-linking of the fibrin strands stabilizes the clot and forms a hemostatic platelet–fibrin plug (Figure 21.2).

### F. Fibrinolysis

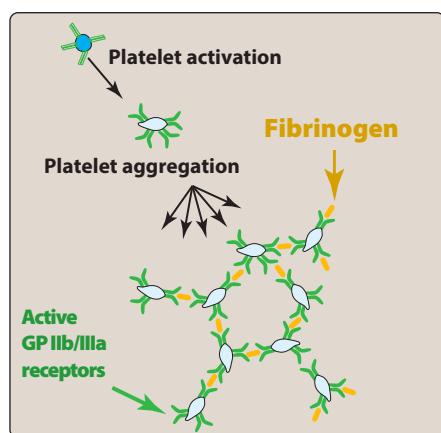
During clot formation, the fibrinolytic pathway is locally activated. Plasminogen is enzymatically processed to plasmin (fibrinolysin) by plasminogen activators in the tissue (Figure 21.2). Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal.

## IV. PLATELET AGGREGATION INHIBITORS

Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation (Figure 21.5). The platelet aggregation inhibitors described below inhibit cyclooxygenase-1 (COX-1), block GP IIb/IIIa, or block ADP receptors, thereby interfering with the signals that promote platelet aggregation. These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases, in the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombin inhibitors or thrombolytic therapy in MI.

### A. Aspirin

- 1. Mechanism of action:** Stimulation of platelets by thrombin, collagen, and ADP results in activation of platelet membrane phospholipases that liberate arachidonic acid from membrane phospholipids. Arachidonic acid is first converted to prostaglandin H<sub>2</sub> by COX-1 (Figure 21.6). Prostaglandin H<sub>2</sub> is further metabolized to thromboxane A<sub>2</sub>, which is released into plasma. Thromboxane A<sub>2</sub> promotes the aggregation process that is essential for the rapid formation of a hemostatic plug. **Aspirin** [AS-pir-in] inhibits thromboxane A<sub>2</sub> synthesis by acetylation of a serine residue on the active site of COX-1, thereby irreversibly inactivating the enzyme (Figure 21.7). This shifts the balance of chemical mediators to favor the antiaggregatory effects of prostacyclin, thereby preventing platelet aggregation. The inhibitory effect is rapid, and **aspirin**-induced suppression of thromboxane A<sub>2</sub> and the resulting suppression of platelet aggregation last for the life of the platelet, which is approximately 7 to 10 days. Repeated administration of **aspirin** has a cumulative effect on the function of platelets. **Aspirin** is the only antiplatelet agent that irreversibly inhibits platelet function.

**Figure 21.4**

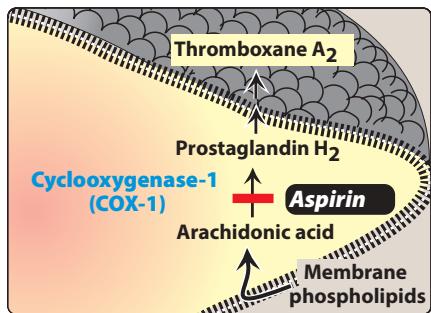
Activation and aggregation of platelets. GP = glycoprotein.

MEDICA-TION	TARGET	HALF-LIFE	TIME FROM LAST DOSE TO OFFSET	USE	ADVERSE EFFECTS	DRUG INTERACTIONS	MONITORING PARAMETERS
<b>Oral agents:</b>							
<i>Aspirin</i> Oral once daily	COX-1 Tx $A_2$		7–10 days	Primary prevention, ACS stable angina, past/recent stroke	Angioedema Bleeding Bronchospasm GI disturbances Reye syndrome SJS	<i>Ketorolac</i> —increased bleeding <i>Cidofovir</i> —nephrotoxicity <i>Probenecid</i> —decreased uricosuric effects Nonselective COX-1 inhibitors decrease <i>aspirin</i> efficacy	CBC LFT
<i>Cilostazol</i> Oral	PDE3	11–13 hr	2 days	Intermittent claudication, PAD, PCI	Bleeding GI disturbances Headache Peripheral edema SJS	Food (administer on empty stomach)	CBC
<i>Clopidogrel</i> Oral once daily	P2Y12 ADP receptor	6–8 hr	7–10 days	NSTEMI, STEMI, PCI, recent stroke or established PDA	Bleeding SJS	Strong CYP2C19 inhibitors reduce antiplatelet effect (for example, <i>omeprazole</i> )	CBC LFT
<i>Dipyridamole</i> Oral	PDE3 and inhibition of adenosine uptake	10 hr	2 days	Transient ischemic attacks	Bleeding Dizziness GI discomfort Rash	Salicylates Thrombolytic agents	None for oral administration
<i>Prasugrel</i> Oral once daily	P2Y12 ADP receptor	8 hr	2–3 days	Patients with ACS undergoing PCI	Angioedema Bleeding Headache Hyperlipidemia Hypertension	Anticoagulants Other antiplatelets No genetic polymorphism influence	CBC
<i>Ticlopidine</i> Oral once daily	P2Y12 ADP receptor	12 hr	7–8 days	Transient ischemic attacks, patients undergoing PCI	Abnormal LFT Bleeding Dizziness GI disturbances SJS	Antacids—decrease levels <i>Cimetidine</i> —reduces clearance	CBC LFT Platelet count
<i>Ticagrelor</i> Oral twice daily	P2Y12 ADP receptor	6–12 hr	5 days	STEMI, ACS, PCI	Bleeding Dyspnea Headache Raised SCr	Strong CYP3A4 inhibitors (for example, <i>ketoconazole, ritonavir, clarithromycin</i> ) Strong CYP3A4 inducers (for example, <i>rifampin, phenytoin, carbamazepine, dexamethasone</i> )	CBC LFT
<b>Injectable agents:</b>							
<i>Abciximab IV</i>	GPIIb/IIIa	<10–30 min	12 hr	NSTEMI, PCI, unstable angina	For all agents: Hypotension Nausea Vomiting	For all agents: Increased bleeding: <i>Ginkgo biloba</i> Antiplatelets Salicylates SSRIs and SNRIs	For all agents: APTT clotting time H/H Platelet count Thrombin time
<i>Eptifibatide IV</i> <i>Tirofiban IV</i>		~2.5 hr 2 hr			Thrombocytopenia		

ACS = acute coronary syndrome; APTT = activated partial thromboplastin time; CBC = complete blood count; COX-1 = cyclo-oxygenase-1; GI = gastrointestinal; H/H = hemoglobin and hematocrit; LFT = liver function test; NSTEMI = non-ST elevation myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SCr = serum creatinine; SJS = Stevens-Johnson syndrome; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; STEMI = ST elevation myocardial infarction; Tx $A_2$  = thrombaxane A<sub>2</sub>.

**Figure 21.5**

Summary of characteristics of platelet aggregation inhibitors.

**Figure 21.6**

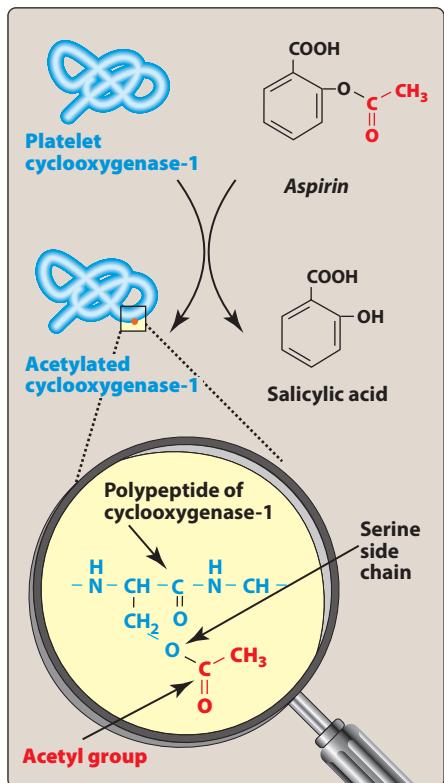
Aspirin irreversibly inhibits platelet cyclooxygenase-1.

- Therapeutic use:** Aspirin is used in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent MI, and to decrease mortality in the setting of primary and secondary prevention of MI. Complete inactivation of platelets occurs with 75 mg of aspirin given daily. The recommended antiplatelet dose of aspirin ranges from 50 to 325 mg daily.
- Pharmacokinetics:** When given orally, aspirin is absorbed by passive diffusion and quickly hydrolyzed to salicylic acid in the liver. Salicylic acid is further metabolized in the liver, and some is excreted unchanged in the urine. The half-life of aspirin ranges from 15 to 20 minutes and for salicylic acid is 3 to 12 hours.
- Adverse effects:** Higher doses of aspirin increase drug-related toxicities as well as the probability that aspirin may also inhibit prostacyclin production. Bleeding time is prolonged by aspirin treatment, causing complications that include an increased incidence of hemorrhagic stroke and gastrointestinal (GI) bleeding, especially at higher doses of the drug. Nonsteroidal anti-inflammatory drugs, such as ibuprofen, inhibit COX-1 by transiently competing at the catalytic site. Ibuprofen, if taken within 2 hours prior to aspirin, can obstruct the access of aspirin to the serine residue and, thereby, antagonize platelet inhibition by aspirin. Therefore, immediate-release aspirin should be taken at least 60 minutes before or at least 8 hours after ibuprofen.

## B. P2Y<sub>12</sub> receptor antagonists

Ticlopidine [ti-KLOE-pi-deen], clopidogrel [kloh-PID-oh-grel], prasugrel [PRA-soo-grel], ticagrelor [tye-KA-grel-or], and cangrelor [KAN-grel-or] are P2Y<sub>12</sub> ADP receptor inhibitors that also block platelet aggregation but by a mechanism different from that of aspirin. All of these agents are administered orally, with the exception of cangrelor which is an injectable formulation.

- Mechanism of action:** These drugs inhibit the binding of ADP to the P2Y<sub>12</sub> receptor on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other (Figure 21.8). Ticagrelor and cangrelor bind to the P2Y<sub>12</sub> ADP receptor in a reversible manner. The other agents bind irreversibly. The maximum inhibition of platelet aggregation is achieved in 2 minutes with intravenous (IV) cangrelor, 1 to 3 hours with ticagrelor, 2 to 4 hours with prasugrel, 3 to 4 days with ticlopidine, and 3 to 5 days with clopidogrel. When treatment is suspended, the platelet system requires time to recover.
- Therapeutic use:** Clopidogrel is approved for prevention of atherosclerotic events in patients with a recent MI or stroke and in those with established peripheral arterial disease. It is also approved for prophylaxis of thrombotic events in acute coronary syndromes (unstable angina or non-ST-elevation MI). Additionally, clopidogrel is used to prevent thrombotic events associated with percutaneous coronary intervention (PCI) with or without coronary stenting. Ticlopidine is similar in structure to clopidogrel. It is indicated for the prevention of transient ischemic attacks (TIA) and strokes in patients with a prior cerebral thrombotic event. However, due to life-threatening hematologic adverse reactions,

**Figure 21.7**

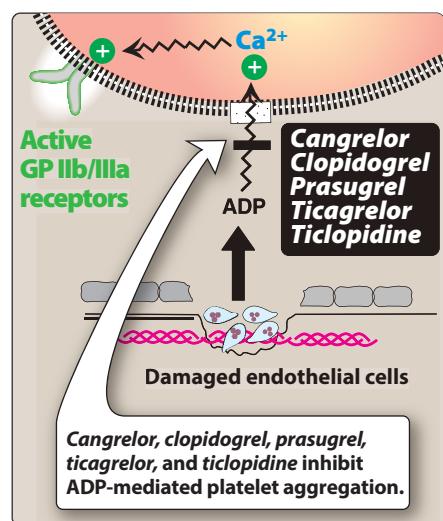
Acetylation of cyclooxygenase-1 by aspirin.

*Ticlopidine* is generally reserved for patients who are intolerant to other therapies. *Prasugrel* is approved to decrease thrombotic cardiovascular events in patients with acute coronary syndromes (unstable angina, non-ST-elevation MI, and ST-elevation MI managed with PCI). *Ticagrelor* is approved for the prevention of arterial thromboembolism in patients with unstable angina and acute MI, including those undergoing PCI. *Cangrelor* is approved as an adjunct during PCI to reduce thrombotic events in select patients.

3. **Pharmacokinetics:** These agents require oral loading doses for quicker antiplatelet effect, except *cangrelor* that has a fast onset of action with intravenous administration. Food interferes with the absorption of *ticlopidine* but not with the other agents. After oral ingestion, the drugs are extensively bound to plasma proteins. They undergo hepatic metabolism by the cytochrome P450 (CYP) system to active metabolites. Elimination of the drugs and metabolites occurs by both the renal and the fecal routes. *Clopidogrel* is a prodrug, and its therapeutic efficacy relies on its active metabolite, which is produced via metabolism by CYP 2C19. Genetic polymorphism of CYP 2C19 leads to a reduced clinical response in patients who are “poor metabolizers” of *clopidogrel*. Tests are currently available to identify poor metabolizers, and it is recommended that other antiplatelet agents (*prasugrel* or *ticagrelor*) be prescribed for these patients. In addition, other drugs that inhibit CYP 2C19, such as *omeprazole* and *esomeprazole*, should be avoided while on *clopidogrel*.
4. **Adverse effects:** These agents can cause prolonged bleeding for which there is no antidote. *Ticlopidine* is associated with severe hematologic reactions that limit its use, such as agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia. *Clopidogrel* causes fewer adverse reactions, and the incidence of neutropenia is lower. However, TTP has been reported as an adverse effect for both *clopidogrel* and *prasugrel* (but not for *ticagrelor*). *Prasugrel* is contraindicated in patients with history of TIA or stroke. *Prasugrel*, *ticagrelor*, and *cangrelor* carry black box warnings for bleeding. Additionally, *ticagrelor* carries a black box warning for diminished effectiveness with concomitant use of aspirin doses above 100 mg.

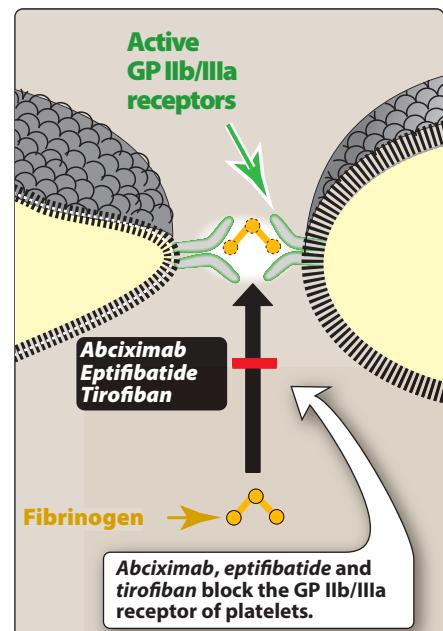
## C. Glycoprotein IIb/IIIa inhibitors

1. **Mechanism of action:** The GP IIb/IIIa receptor plays a key role in stimulating platelet aggregation. A chimeric monoclonal antibody fragment, *abciximab* [ab-SIKS-eh-mab], inhibits the GP IIb/IIIa receptor complex. By binding to GP IIb/IIIa, *abciximab* blocks the binding of fibrinogen and von Willebrand factor and, consequently, aggregation does not occur (Figure 21.9). *Eptifibatide* [ep-ti-FIB-ih-tide] and *tirofiban* [tye-ro-roe-FYE-ban] act similarly to *abciximab*, by blocking the GP IIb/IIIa receptor. *Eptifibatide* is a cyclic peptide that binds to GP IIb/IIIa at the site that interacts with the arginine–glycine–aspartic acid sequence of fibrinogen. *Tirofiban* is not a peptide, but it blocks the same site as *eptifibatide*.



**Figure 21.8**

Mechanism of action of *cangrelor*, *clopidogrel*, *prasugrel*, *ticagrelor*, and *ticlopidine*. ADP = adenine diphosphate; GP = glycoprotein.



**Figure 21.9**

Mechanism of action of glycoprotein (GP) IIb/IIIa receptor blockers.

2. **Therapeutic use:** These agents are given intravenously, along with *heparin* and *aspirin*, as an adjunct to PCI for the prevention of cardiac ischemic complications. *Abciximab* is also approved for patients with unstable angina not responding to conventional medical therapy when PCI is planned within 24 hours.
3. **Pharmacokinetics:** *Abciximab* is given by IV bolus, followed by IV infusion, achieving peak platelet inhibition within 30 minutes. The metabolism of *abciximab* is unknown. After cessation of *abciximab* infusion, platelet function gradually returns to normal, with the antiplatelet effect persisting for 24 to 48 hours. When IV infusion of *eptifibatide* or *tirofiban* is stopped, both agents are rapidly cleared from the plasma. *Eptifibatide* and its metabolites are excreted by the kidney. *Tirofiban* is excreted largely unchanged by the kidney and to a lesser extent in the feces.
4. **Adverse effects:** The major adverse effect of these agents is bleeding, especially if used with anticoagulants.

#### D. *Dipyridamole*

*Dipyridamole* [dye-peer-ID-a-mole], a coronary vasodilator, increases intracellular levels of cAMP by inhibiting phosphodiesterase, thereby resulting in decreased thromboxane A<sub>2</sub> synthesis. The drug may potentiate the effect of prostacyclin and, therefore, decrease platelet adhesion to thrombogenic surfaces (Figure 21.2). *Dipyridamole* is used for stroke prevention and is usually given in combination with *aspirin*. *Dipyridamole* has variable bioavailability following oral administration. It is highly protein bound. The drug undergoes hepatic metabolism, mainly glucuronidation, and is excreted primarily in the feces. Patients with unstable angina should not use *dipyridamole* because of its vasodilating properties, which may worsen ischemia (coronary steal phenomenon). *Dipyridamole* commonly causes headache and dizziness and can lead to orthostatic hypotension (especially if administered IV).

#### E. *Cilostazol*

*Cilostazol* [sill-AH-sta-zole] is an oral antiplatelet agent that also has vasodilating activity. *Cilostazol* and its active metabolites inhibit phosphodiesterase type III, which prevents the degradation of cAMP, thereby increasing levels of cAMP in platelets and vascular tissues. The increase in cAMP prevents platelet aggregation and promotes vasodilation of blood vessels, respectively. *Cilostazol* is approved to reduce the symptoms of intermittent claudication. *Cilostazol* is extensively metabolized in the liver by the CYP 3A4 and 2C19 isoenzymes. As such, this agent has many drug interactions that require dose modification. The primary route of elimination is via the kidney. Headache and GI side effects (diarrhea, abnormal stools, dyspepsia, and abdominal pain) are the most common adverse effects observed with *cilostazol*. Rarely, thrombocytopenia or leukopenia has been reported. Phosphodiesterase type III inhibitors have been shown to increase mortality in patients with advanced heart failure. As such, *cilostazol* is contraindicated in patients with heart failure.

## V. BLOOD COAGULATION

The coagulation process that generates thrombin consists of two inter-related pathways, the extrinsic and the intrinsic systems. The extrinsic system is initiated by the activation of clotting factor VII by tissue factor (also known as thromboplastin). Tissue factor is a membrane protein that is normally separated from the blood by the endothelial cells that line the vasculature. However, in response to vascular injury, tissue factor becomes exposed to blood. There it can bind and activate factor VII, initiating the extrinsic pathway. The intrinsic system is triggered by the activation of clotting factor XII. This occurs when blood comes into contact with the collagen in the damaged wall of a blood vessel.

### A. Formation of fibrin

Both the extrinsic and the intrinsic systems involve a cascade of enzyme reactions that sequentially transform various plasma factors (proenzymes) to their active (enzymatic) forms. [Note: The active form of a clotting factor is denoted by the letter “a.”] Ultimately, factor Xa is produced, which converts prothrombin (factor II) to thrombin (factor IIa; **Figure 21.10**). Thrombin plays a key role in coagulation, because it is responsible for generation of fibrin, which forms the mesh-like matrix of the blood clot. If thrombin is not formed or if its function is impeded (for example, by antithrombin III), coagulation is inhibited.

### B. Inhibitors of coagulation

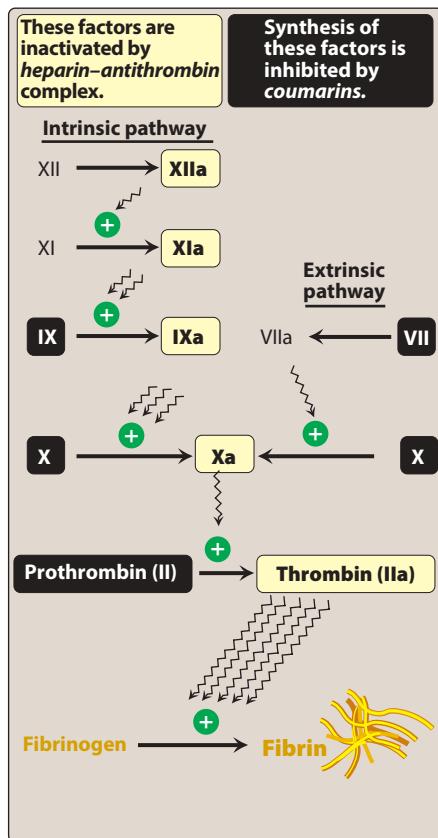
It is important that coagulation is restricted to the local site of vascular injury. Endogenously, protein C, protein S, antithrombin III, and tissue factor pathway inhibitor all inhibit coagulation factors. The mechanism of action of several anticoagulant agents, including *heparin* and *heparin*-related products, involves activation of these endogenous inhibitors (primarily antithrombin III).

## VI. PARENTERAL ANTICOAGULANTS

The anticoagulant drugs inhibit either the action of the coagulation factors (for example, *heparin*) or interfere with the synthesis of the coagulation factors (*warfarin*).

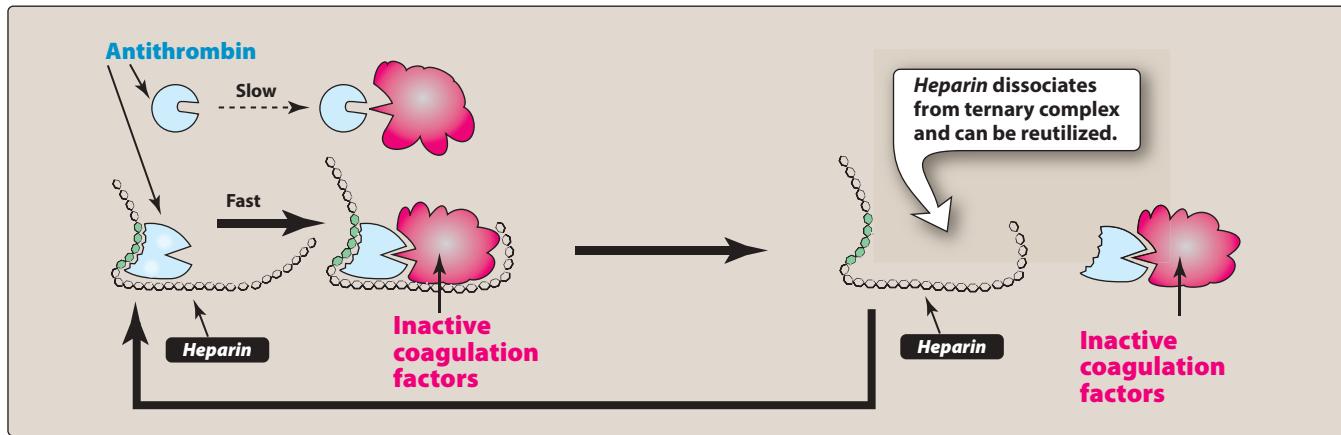
### A. Heparin and low molecular weight heparins

*Heparin* [HEP-a-rin] is an injectable, rapidly acting anticoagulant that is often used acutely to interfere with the formation of thrombi. *Heparin* occurs naturally as a macromolecule complexed with histamine in mast cells, where its physiologic role is unknown. It is extracted for commercial use from porcine intestinal mucosa. Unfractionated *heparin* is a mixture of straight-chain, anionic glycosaminoglycans with a wide range of molecular weights. It is strongly acidic because of the presence of sulfate and carboxylic acid groups. The realization that low molecular weight forms of *heparin* (LMWHs) can also act as anticoagulants led to the isolation of *enoxaparin* [e-NOX-a-par-in] and *dalteparin* [DAL-te-PAR-in], produced by depolymerization of



**Figure 21.10**

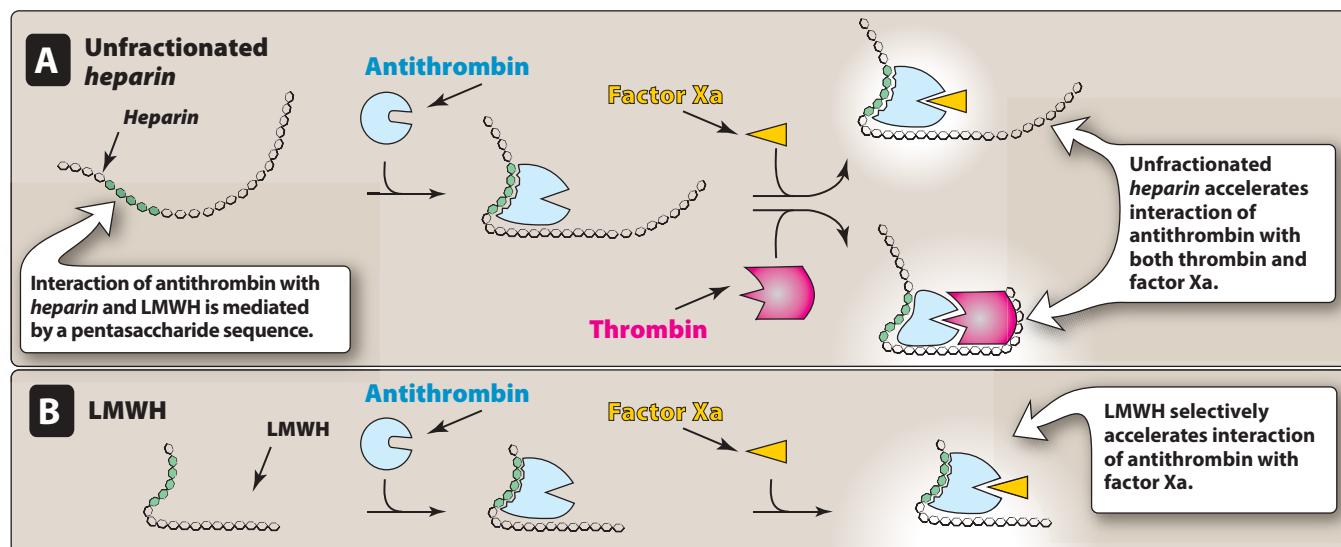
Formation of a fibrin clot.

**Figure 21.11**

Heparin accelerates inactivation of coagulation factors by antithrombin.

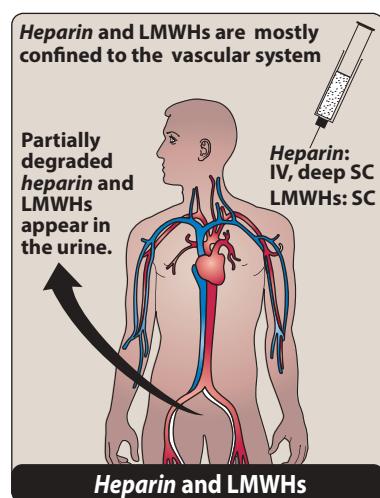
unfractionated *heparin*. The LMWHs are heterogeneous compounds about one-third the size of unfractionated *heparin*.

- Mechanism of action:** *Heparin* acts at a number of molecular targets, but its anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors (Figure 21.11). Antithrombin III is an  $\alpha$  globulin that inhibits serine proteases of thrombin (factor IIa) and factor Xa. In the absence of *heparin*, antithrombin III interacts very slowly with thrombin and factor Xa. When *heparin* molecules bind to antithrombin III, a conformational change occurs that catalyzes the inhibition of thrombin about 1000-fold. LMWHs complex with antithrombin III and inactivate factor Xa (including that located on platelet surfaces) but do not bind as avidly to thrombin. A unique pentasaccharide sequence contained in *heparin* and LMWHs permits their binding to antithrombin III (Figure 21.12).

**Figure 21.12**

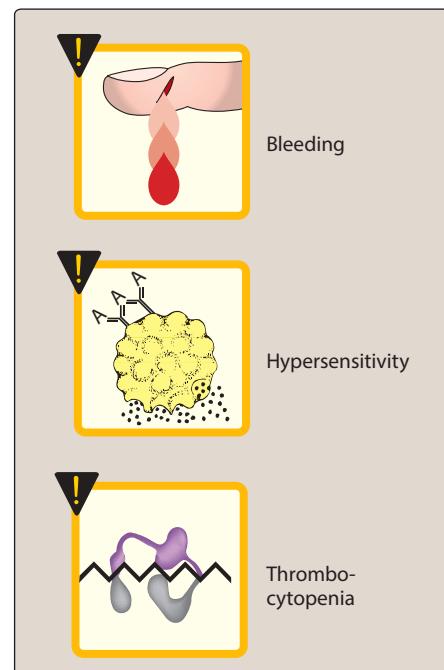
Heparin- and low molecular weight heparin (LMWH)-mediated inactivation of thrombin or factor Xa.

- 2. Therapeutic use:** *Heparin* and the LMWHs limit the expansion of thrombi by preventing fibrin formation. These agents are used for the treatment of acute venous thromboembolism (DVT or PE). *Heparin* and LMWHs are also used for prophylaxis of post-operative venous thrombosis in patients undergoing surgery (for example, hip replacement) and those with acute MI. These drugs are the anticoagulants of choice for treating pregnant women, because they do not cross the placenta, due to their large size and negative charge. LMWHs do not require the same intense monitoring as *heparin*, thereby saving laboratory costs and nursing time. These advantages make LMWHs useful for both inpatient and outpatient therapy.
- 3. Pharmacokinetics:** *Heparin* must be administered subcutaneously or intravenously, because the drug does not readily cross membranes (Figure 21.13). The LMWHs are usually administered subcutaneously. [Note: *Enoxaparin* can be administered intravenously in the treatment of myocardial infarction.] *Heparin* is often initiated as an intravenous bolus to achieve immediate anticoagulation. This is followed by lower doses or continuous infusion of *heparin*, titrated to the desired level of anticoagulation according to the activated partial thromboplastin time (aPTT) or anti-Xa level. Whereas the anticoagulant effect with *heparin* occurs within minutes of IV administration (or 1 to 2 hours after subcutaneous injection), the maximum anti-factor Xa activity of the LMWHs occurs about 4 hours after subcutaneous injection. It is usually not necessary to monitor coagulation values with LMWHs because the plasma levels and pharmacokinetics of these drugs are more predictable. However, in renally impaired, pregnant, and obese patients, monitoring of factor Xa levels is recommended with LMWHs. In the blood, *heparin* binds to many proteins that neutralize its activity, causing unpredictable pharmacokinetics. *Heparin* binding to plasma proteins is variable in patients with thromboembolic diseases. Although generally restricted to the circulation, *heparin* is taken up by the monocyte/macrophage system, and it undergoes depolymerization and desulfation to inactive products. The inactive metabolites as well as some of the parent *heparin* undergo renal excretion. The LMWHs are primarily eliminated in the urine. Therefore, renal insufficiency prolongs the half-life of LMWH, and the dose of LMWH should be reduced in patients with renal impairment. The half-life of *heparin* is approximately 1.5 hours, whereas the half-life of the LMWHs is longer than that of heparin, ranging from 3 to 12 hours.
- 4. Adverse effects:** The chief complication of *heparin* and LMWH therapy is bleeding (Figure 21.14). Careful monitoring of the patient and laboratory parameters is required to minimize bleeding. Excessive bleeding may be managed by discontinuing the drug or by treating with *protamine sulfate*. When infused slowly, the latter combines ionically with *heparin* to form a stable, 1:1 inactive complex. It is important that the dosage of *protamine sulfate* is carefully titrated (1 mg for every 100 units of *heparin* administered), because *protamine sulfate* is a weak anticoagulant, and excess amounts may trigger bleeding episodes or worsen bleeding potential. *Heparin* preparations are obtained from porcine sources and, therefore, may be antigenic. Possible adverse



**Figure 21.13**

Administration and fate of *heparin* and low molecular weight heparins (LMWHs).



**Figure 21.14**

Adverse effects of *heparin*.

reactions include chills, fever, urticaria, and anaphylactic shock. *Heparin*-induced thrombocytopenia (HIT) is a serious condition, in which circulating blood contains an abnormally low number of platelets. This reaction is immune-mediated and carries a risk of venous and arterial embolism. *Heparin* therapy should be discontinued when patients develop HIT or show severe thrombocytopenia. In cases of HIT, *heparin* can be replaced by another anticoagulant, such as *argatroban*. [Note: LMWHs can have cross-sensitivity and are not recommended in patients with HIT.] In addition, osteoporosis has been observed in patients on long-term *heparin* therapy. *Heparin* and LMWHs are contraindicated in patients who have hypersensitivity to *heparin*, bleeding disorders, alcoholism, or who have had recent surgery of the brain, eye, or spinal cord.

### B. Argatroban

*Argatroban* [ar-GA-troh-ban] is a synthetic parenteral anticoagulant that is derived from L-arginine. It is a direct thrombin inhibitor. *Argatroban* is used for the prophylaxis or treatment of venous thromboembolism in patients with HIT, and it is also approved for use during PCI in patients who have or are at risk for developing HIT. Anticoagulant effects are immediate. *Argatroban* is metabolized in the liver and has a half-life of about 39 to 51 minutes. Dose reduction is recommended for patients with hepatic impairment. Monitoring includes aPTT, hemoglobin, and hematocrit. As with other anticoagulants, the major side effect is bleeding.

### C. Bivalirudin and desirudin

*Bivalirudin* [bye-VAL-ih-ruh-din] and *desirudin* [deh-SIHR-uh-din] are parenteral anticoagulants that are analogs of hirudin, a thrombin inhibitor derived from saliva of the medicinal leech. These drugs are selective direct thrombin inhibitors that reversibly inhibit the catalytic site of both free and clot-bound thrombin. *Bivalirudin* is an alternative to *heparin* in patients undergoing PCI who have or are at risk for developing HIT and also in patients with unstable angina undergoing angioplasty. In patients with normal renal function, the half-life of *bivalirudin* is 25 minutes. Dosage adjustments are required in patients with renal impairment. *Desirudin* is indicated for the prevention of DVT in patients undergoing hip replacement surgery. Like the others, bleeding is the major side effect of these agents.

### D. Fondaparinux

*Fondaparinux* [fawn-da-PEAR-eh-nux] is a synthetically derived pentasaccharide anticoagulant that selectively inhibits factor Xa. By selectively binding to antithrombin III, *fondaparinux* potentiates (300- to 1000-fold) the innate neutralization of factor Xa by antithrombin III. *Fondaparinux* is approved for use in the treatment of DVT and PE and for the prophylaxis of venous thromboembolism in the setting of orthopedic and abdominal surgery. The drug is well absorbed from the subcutaneous route with a predictable pharmacokinetic profile and, therefore, requires less monitoring than *heparin*. *Fondaparinux* is

eliminated in the urine mainly as unchanged drug with an elimination half-life of 17 to 21 hours. It is contraindicated in patients with severe renal impairment. Bleeding is the major side effect of *fondaparinux*. There is no available agent for the reversal of bleeding associated with *fondaparinux*. HIT is less likely with *fondaparinux* than with *heparin* but is still a possibility.

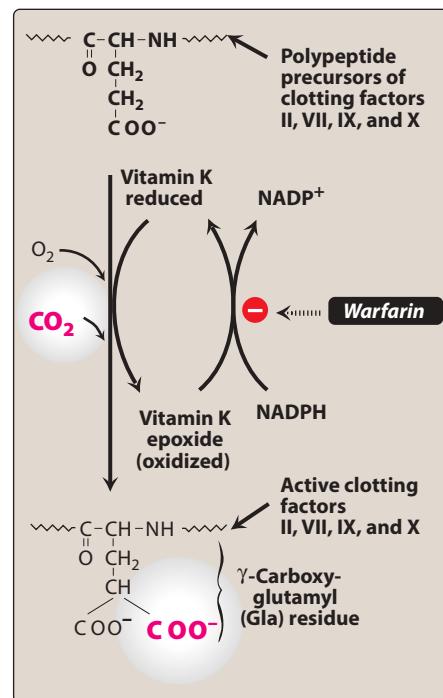
## VII. VITAMIN K ANTAGONISTS

The coumarin anticoagulants owe their action to the ability to antagonize the cofactor functions of vitamin K. The only coumarin anticoagulant available is *warfarin* [WAR-far-in]. The International Normalized Ratio (INR) is the standard by which the anticoagulant activity of *warfarin* therapy is monitored. *Warfarin* has a narrow therapeutic index. Therefore, it is important that the INR is maintained within the optimal range as much as possible, and frequent monitoring may be required.

### A. Warfarin

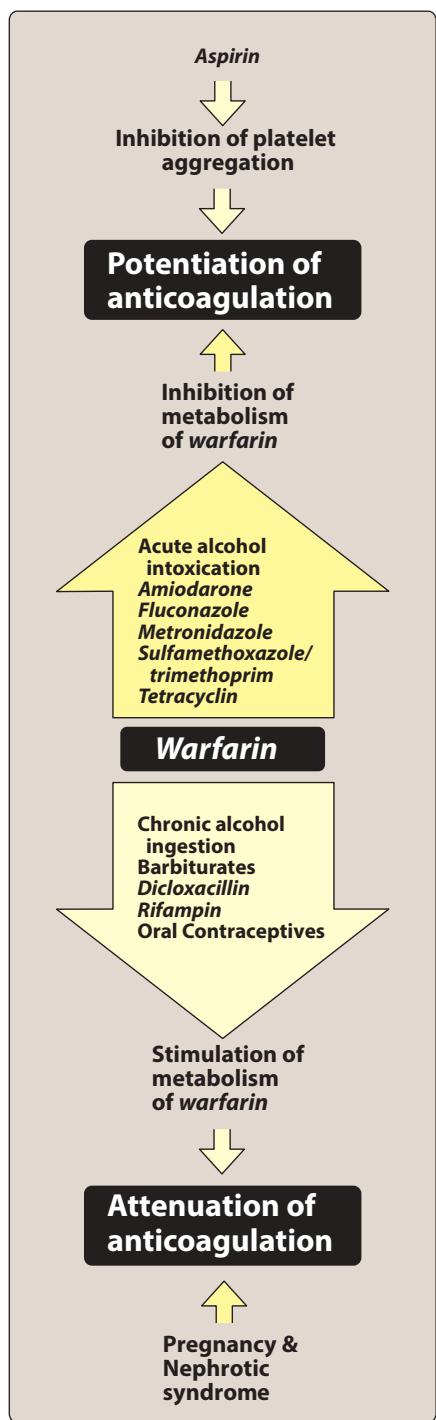
The coumarin anticoagulants owe their action to the ability to antagonize the cofactor functions of vitamin K. The only therapeutically relevant coumarin anticoagulant is *warfarin* [WAR-far-in]. Initially used as a rodenticide, *warfarin* is now widely used clinically as an oral anticoagulant. The INR is the standard by which the anticoagulant activity of *warfarin* therapy is monitored. The INR corrects for variations that occur with different thromboplastin reagents used to perform testing at various institutions. The goal of *warfarin* therapy is an INR of 2 to 3 for most indications, with an INR of 2.5 to 3.5 targeted for some mechanical valves and other indications.

**1. Mechanism of action:** Factors II, VII, IX, and X (Figure 21.10) require vitamin K as a cofactor for their synthesis by the liver. These factors undergo vitamin K-dependent post-translational modification, whereby a number of their glutamic acid residues are carboxylated to form  $\gamma$ -carboxyglutamic acid residues (Figure 21.15). The  $\gamma$ -carboxyglutamyl residues bind calcium ions, which are essential for interaction between the coagulation factors and platelet membranes. In the carboxylation reactions, the vitamin K-dependent carboxylase fixes  $\text{CO}_2$  to form the new COOH group on glutamic acid. The reduced vitamin K cofactor is converted to vitamin K epoxide during the reaction. Vitamin K is regenerated from the epoxide by vitamin K epoxide reductase, the enzyme that is inhibited by *warfarin*. *Warfarin* treatment results in the production of clotting factors with diminished activity (10% to 40% of normal), due to the lack of sufficient  $\gamma$ -carboxyglutamyl side chains. Unlike *heparin*, the anticoagulant effects of *warfarin* are not observed immediately after drug administration. Instead, peak effects may be delayed for 72 to 96 hours, which is the time required to deplete the pool of circulating clotting factors. The anticoagulant effects of *warfarin* can be overcome by the administration of *vitamin K*. However, reversal following administration of *vitamin K* takes approximately 24 hours (the time necessary for degradation of already synthesized clotting factors).



**Figure 21.15**

Mechanism of action of *warfarin*.  
 $\text{NADP}^+$  = oxidized form of nicotinamide adenine dinucleotide phosphate;  $\text{NADPH}$  = reduced form of nicotinamide adenine dinucleotide phosphate.

**Figure 21.16**

Drugs affecting the anticoagulant effect of warfarin.

2. **Therapeutic use:** Warfarin is used in the prevention and treatment of DVT and PE, stroke prevention, stroke prevention in the setting of atrial fibrillation and/or prosthetic heart valves, protein C and S deficiency, and antiphospholipid syndrome. It is also used for prevention of venous thromboembolism following orthopedic surgery.
3. **Pharmacokinetics:** Warfarin is rapidly absorbed after oral administration (100% bioavailability with little individual patient variation). Warfarin is highly bound to plasma albumin, which prevents its diffusion into the cerebrospinal fluid, urine, and breast milk. However, drugs that have a greater affinity for the albumin-binding site, such as sulfonamides, can displace the anticoagulant and lead to a transient, elevated activity. Drugs that affect warfarin binding to plasma proteins can lead to variability in the therapeutic response to warfarin. Warfarin readily crosses the placental barrier. The mean half-life of warfarin is approximately 40 hours, but this value is highly variable among individuals. Warfarin is metabolized by the CYP450 system (mainly CYP2C9) to inactive components. After conjugation to glucuronic acid, the inactive metabolites are excreted in urine and feces. Agents that affect the metabolism of warfarin may alter its therapeutic effects. Warfarin has numerous drug interactions that may potentiate or attenuate its anticoagulant effect. The list of interacting drugs is extensive. A summary of some of the important interactions is shown in Figure 21.16.
4. **Adverse effects:** The principal adverse effect of warfarin is bleeding. Minor bleeding may be treated by withdrawal of the drug or administration of oral vitamin K, but severe bleeding may require greater doses of vitamin K given intravenously. Whole blood, frozen plasma, and plasma concentrates of blood factors may also be used for rapid reversal of warfarin. Skin lesions and necrosis are rare complications of warfarin therapy. Purple toe syndrome, a rare, painful, blue-tinged discoloration of the toe caused by cholesterol emboli from plaques, has also been observed with warfarin therapy. Warfarin is teratogenic and is contraindicated in pregnancy.

## VIII. DIRECT ORAL ANTICOAGULANTS

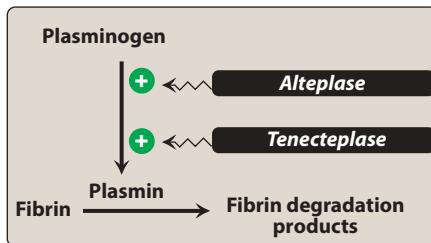
### A. Dabigatran

1. **Mechanism of action:** *Dabigatran etexilate* [da-bi-GAT-ran e-TEX-i-late] is the prodrug of the active moiety *dabigatran*, which is an oral direct thrombin inhibitor. Both clot-bound and free thrombin are inhibited by *dabigatran*.
2. **Therapeutic use:** It is approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It may also be used in the treatment of DVT and PE in patients who have already received parenteral anticoagulants, and as prophylaxis to prevent or reduce the risk of recurrence of DVT and PE. The drug is contraindicated in patients with mechanical prosthetic heart valves and is not recommended in patients with bioprosthetic heart valves.

3. **Pharmacokinetics:** *Dabigatran* is administered orally. It is hydrolyzed to the active drug, *dabigatran*, by various plasma esterases. *Dabigatran* is metabolized by esterases. It is a substrate for P-glycoprotein (P-gp) and is eliminated renally.
4. **Adverse effects:** The major adverse effect, like other anticoagulants, is bleeding. *Dabigatran* should be used with caution in renal impairment or in patients over the age of 75 years, as the risk of bleeding is higher in these groups. *Idarucizumab* may be used to reverse bleeding in severe cases. GI adverse effects are common with *dabigatran* and may include dyspepsia, abdominal pain, esophagitis, and GI bleeding. Abrupt discontinuation should be avoided, as patients may be at increased risk for thrombotic events.

## B. Direct oral factor Xa inhibitors

1. **Mechanism of action:** *Apixaban* [a-PIX-a-ban], *betrixaban* [be-TRIX-a-ban], *edoxaban* [e-DOX-a-ban], and *rivaroxaban* [RIV-a-ROX-a-ban] are oral inhibitors of factor Xa. Inhibition of factor Xa reduces the production of thrombin (IIa) from prothrombin (Figure 21.10).
2. **Therapeutic use:** With the exception of *betrixaban*, these agents are approved for prevention of stroke in nonvalvular atrial fibrillation, as well as the treatment of DVT and PE. *Rivaroxaban* and *apixaban* are also used as prophylaxis to prevent or reduce the risk of recurrence of DVT and PE. *Betrixaban* is indicated for the prophylaxis of DVT and PE in at-risk hospitalized medical patients.
3. **Pharmacokinetics:** These drugs are adequately absorbed after oral administration. *Rivaroxaban* is metabolized by the CYP 3A4/5 and CYP 2J2 isoenzymes to inactive metabolites. About one-third of the drug is excreted unchanged in the urine, and the inactive metabolites are excreted in the urine and feces. *Apixaban* is primarily metabolized by CYP 3A4, with CYP enzymes 1A2, 2C8, 2C9, 2C19, and 2J2 all sharing minor metabolic roles; approximately 27% is excreted renally. *Edoxaban* and *betrixaban* are minimally metabolized and are eliminated primarily unchanged in the urine and feces, respectively. All of these drugs are substrates of P-gp and dosages should be reduced (in some cases, concomitant use should be avoided) with P-gp inhibitors such as *clarithromycin*, *verapamil*, and *amiodarone*. Concomitant administration of *apixaban* and *rivaroxaban* with drugs that are strong P-gp and CYP 3A4 inducers (for example, *phenytoin*, *carbamazepine*, *rifampin*, *St. John's wort*) should be avoided due to the potential for reduced efficacy of the factor Xa inhibitors.
4. **Adverse effects:** Bleeding is the most serious adverse effect for the factor Xa inhibitors. There is no antidote available to reverse bleeding. Declining kidney function can prolong the effect of these drugs and, therefore, increase the risk of bleeding. Renal dosage adjustments are recommended for these agents. Abrupt discontinuation of the factor Xa inhibitors should be avoided.

**Figure 21.17**

Activation of plasminogen by thrombolytic drugs.

## IX. THROMBOLYTIC DRUGS

Acute thromboembolic disease in selected patients may be treated by the administration of drugs that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and, thus, dissolves clots.

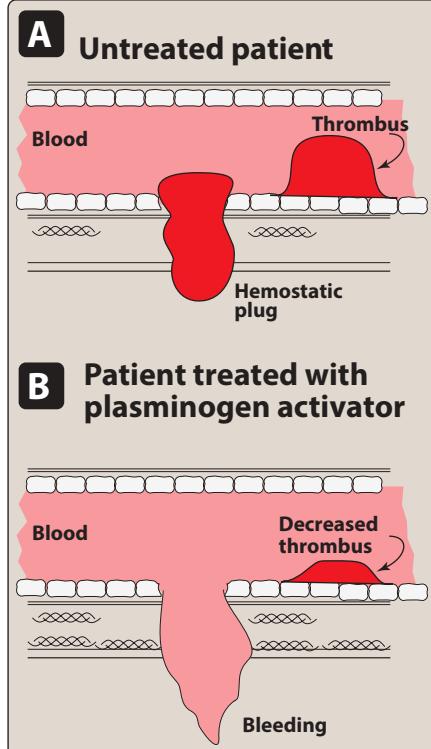
### A. Common characteristics of thrombolytic agents

- Mechanism of action:** The thrombolytic agents act either directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi (Figure 21.17). Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age. Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis. Strategies to prevent this include administration of antiplatelet drugs, such as *aspirin*, or antithrombotics, such as *heparin*.
- Therapeutic use:** Originally used for the treatment of DVT and serious PE, thrombolytic drugs are currently used less frequently because of the tendency to cause serious bleeding. For MI, intracoronary delivery of the drugs is the most reliable in terms of achieving recanalization. However, cardiac catheterization may not be possible in the 2- to 6-hour “therapeutic window,” beyond which significant myocardial salvage becomes less likely. Thus, thrombolytic agents are usually administered intravenously. Thrombolytic agents are helpful in restoring catheter and shunt function, by lysing clots causing occlusions. They are also used to dissolve clots that result in strokes.
- Adverse effects:** Thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. Thus, hemorrhage is a major adverse effect. For example, a previously unsuspected lesion, such as a gastric ulcer, may hemorrhage following injection of a thrombolytic agent (Figure 21.18). These drugs are contraindicated in pregnancy, and in patients with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.

### B. Alteplase, reteplase, and tenecteplase

*Alteplase* [AL-teh-place] (formerly known as *tissue plasminogen activator* or *tPA*) is a serine protease originally derived from cultured human melanoma cells. It is now obtained as a product of recombinant DNA technology. *Reteplase* [RE-teh-place] is a genetically engineered, smaller derivative of recombinant tPA. *Tenecteplase* [ten-EK-te-place] is recombinant tPA with a longer half-life and greater binding affinity for fibrin than *alteplase*. *Alteplase* has a low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug. Thus, *alteplase* is said to be “fibrin selective” at low doses. *Alteplase* is approved for the treatment of MI, massive PE, and acute ischemic stroke. *Tenecteplase* is approved only for use in acute MI.

*Alteplase* has a very short half-life (5 to 30 minutes), and therefore a portion of the total dose is injected intravenously as a bolus and the remaining drug is administered over 1 to 3 hours, depending

**Figure 21.18**

Degradation of an unwanted thrombus and a beneficial hemostatic plug by plasminogen activators.

on the indication. *Tenecteplase* has a longer half-life and, therefore, may be administered as an intravenous bolus. *Alteplase* may cause angioedema, and there may be an increased risk of this effect when combined with angiotensin-converting enzyme (ACE) inhibitors.

### C. Streptokinase

*Streptokinase* [strep-toe-KYE-nase] is an extracellular protein purified from culture broths of group C  $\beta$ -hemolytic streptococci. It forms an active one-to-one complex with plasminogen. This enzymatically active complex converts uncomplexed plasminogen to the active enzyme plasmin (Figure 21.19). In addition to the hydrolysis of fibrin plugs, the complex also catalyzes the degradation of fibrinogen, as well as clotting factors V and VII (Figure 21.20). With the advent of newer agents, *streptokinase* is not preferred. Though nonfibrin selectivity and allergic reaction limit its usage but it is still used for the treatment of acute myocardial infarction, acute pulmonary embolism (PE), deep vein thrombosis (DVT), reperfusion of occluded peripheral arteries, and venous catheters because of its lower cost.

### D. Urokinase

*Urokinase* [URE-oh-KYE-nase] is produced naturally in the body by the kidneys. Therapeutic *urokinase* is isolated from cultures of human kidney cells and has low antigenicity. *Urokinase* directly cleaves the arginine—valine bond of plasminogen to yield active plasmin. It is only approved for lysis of pulmonary emboli. Off-label uses include treatment of acute MI, arterial thromboembolism, coronary artery thrombosis, and DVT. Its use has largely been supplanted by other agents with a more favorable benefit-to-risk-ratio.

## X. DRUGS USED TO TREAT BLEEDING

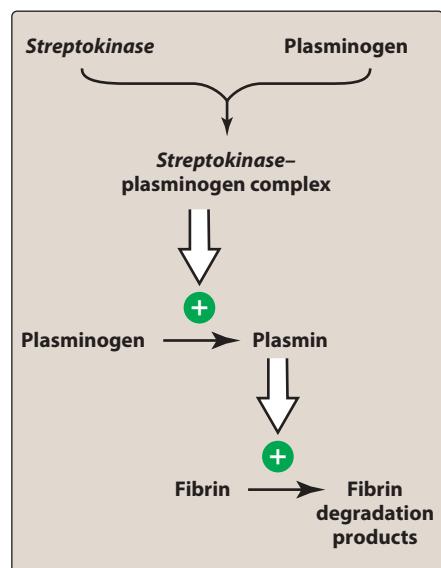
Bleeding problems may have their origin in naturally occurring pathologic conditions, such as hemophilia, or as a result of fibrinolytic states that may arise after surgery. The use of anticoagulants may also give rise to hemorrhage. Certain natural proteins and *vitamin K*, as well as synthetic antagonists, are effective in controlling this bleeding (Figure 21.21). Concentrated preparations of coagulation factors are available from human donors. However, these preparations carry the risk of transferring viral infections. Blood transfusion is also an option for treating severe hemorrhage.

### A. Aminocaproic acid and tranexamic acid

Fibrinolytic states can be controlled by the administration of *aminocaproic acid* or *tranexamic acid*. Both agents are synthetic, orally active, excreted in the urine, and inhibit plasminogen activation. *Tranexamic acid* is 10 times more potent than *aminocaproic acid*. A potential side effect is intravascular thrombosis.

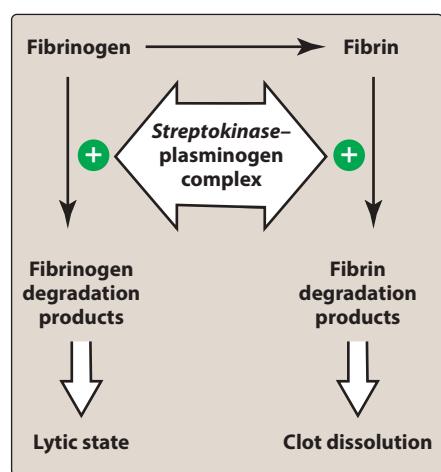
### B. Protamine sulfate

*Protamine sulfate* antagonizes the anticoagulant effects of *heparin*. This protein is derived from fish sperm or testes and is high in arginine content, which explains its basicity. The positively charged *protamine* interacts with the negatively charged *heparin*,



**Figure 21.19**

Mechanism of action of *streptokinase*.



**Figure 21.20**

*Streptokinase* degrades both fibrin and fibrinogen.

PARAMETER	STREPTOKINASE (SK)	UROKINASE (UK)	ALTEPLASE (rt-PA)	RETEPLASE (r-PA)	TENECTEPLASE (TNK t-PA)
Source	Streptococci	Human enzyme found in urine	Recombinant form of human t-PA	Recombinant form (smaller derivative) of human rt-PA	Genetically engineered
Generation	First generation	First generation	Second generation	Second generation	Third generation
Dose	1.5 MU in 30–60 minutes	4400 IU/kg IV at a rate of 90 mL/hr in 10 minutes	Up to 100 mg in 90 min based on weight	10 U two doses (30 min apart) each over 2 minutes	30–50 mg based on weight
Bolus administration	No	No	No	Yes	Yes
Antigenicity	High <sup>1</sup>	Low	Low	Low	Low
Allergic reaction	Yes (dose-related hypotension)	No	No	No	No
Fibrin specificity	Low	Low	High	High	High
PAI-Inhibition	-	+++	+++	++	-
Half-life	30 minutes	20 minutes	4–8 minutes	14–18 minutes	11–20 minutes
Cost per dose	-	+	+++	+++	++++
Uses	AMI, deep vein thrombosis	Acute massive pulmonary emboli, AMI	AMI, stroke	AMI	Stroke, AMI

AMI = acute myocardial infarction; PAI-inhibition = inactivation by endogenous inhibitor (PAI-1).

<sup>1</sup>SK is potentially allergenic and the body produces antistreptococcal antibodies against it, which makes retreatment less effective and unsafe.

**Figure 21.21**

Comparison of thrombolytic enzymes.

forming a stable complex without anticoagulant activity. Adverse effects of drug administration include hypersensitivity as well as dyspnea, flushing, bradycardia, and hypotension when rapidly injected.

### C. Vitamin K

*Vitamin K<sub>1</sub> (phytonadione)* administration can stop bleeding problems due to *warfarin* by increasing the supply of active *vitamin K<sub>1</sub>*, thereby inhibiting the effect of *warfarin*. *Vitamin K<sub>1</sub>* may be administered via the oral, subcutaneous, or intravenous route. [Note: Intravenous *vitamin K* should be administered by slow IV infusion to minimize the risk of hypersensitivity or anaphylactoid reactions.] For the treatment of bleeding, the subcutaneous route of *vitamin K<sub>1</sub>* is not preferred, as it is not as effective as oral or IV administration. The response to *vitamin K<sub>1</sub>* is slow, requiring about 24 hours to reduce INR (time to synthesize new coagulation factors). Thus, if immediate hemostasis is required, fresh frozen plasma should be infused.

### D. Idarucizumab

*Idarucizumab* [EYE-da-roo-KIZ-ue-mab] is a monoclonal antibody fragment used to reverse bleeding caused by dabigatran. By binding to dabigatran and its metabolites, *idarucizumab* neutralizes anticoagulation. *Idarucizumab* is administered intravenously and is rapidly eliminated. *Idarucizumab* is used in emergency situations, in the inpatient setting. Because it reverses the effect of dabigatran, thrombosis is the most serious adverse effect of *idarucizumab*.

## Study Questions

Choose the ONE best answer.

- 21.1 Which of the P2Y<sub>12</sub> ADP receptor antagonists reversibly binds the receptor?

- A. Clopidogrel
- B. Prasugrel
- C. Ticagrelor
- D. Ticlopidine

Correct answer = C. Of the P2Y<sub>12</sub> ADP receptor antagonists listed, ticagrelor is the only one that reversibly binds the receptor. This is important when it comes to compliance. If a patient is not compliant, then the antiplatelet activity of ticagrelor stops when the drug is missed (since the platelets are not irreversibly inhibited as they would be with aspirin, clopidogrel, or prasugrel).

- 21.2 A 70-year-old woman is diagnosed with nonvalvular atrial fibrillation. Her past medical history is significant for chronic kidney disease, and her renal function is moderately diminished. Which anticoagulant for atrial fibrillation avoids the need for renal dose adjustment in this patient?

- A. Apixaban
- B. Dabigatran
- C. Rivaroxaban
- D. Warfarin

Correct answer = D. Warfarin does not require dosage adjustment in renal dysfunction. The INR is monitored and dosage adjustments are made on the basis of this information. All of the other agents are renally cleared to some extent and require dosage adjustments in renal dysfunction.

- 21.3 An 80-year-old man is taking warfarin indefinitely for the prevention of deep venous thrombosis. He is compliant, has a stable INR, and denies bleeding or bruising. He is diagnosed with a urinary tract infection and is prescribed sulfamethoxazole/trimethoprim. What effect will this have on his warfarin therapy?

- A. Sulfamethoxazole/trimethoprim will decrease the anticoagulant effect of warfarin.
- B. Sulfamethoxazole/trimethoprim will increase the anticoagulant effect of warfarin.
- C. Sulfamethoxazole/trimethoprim will activate platelet activity.
- D. Sulfamethoxazole/trimethoprim will not change anticoagulation status.

Correct answer = B. Sulfamethoxazole/trimethoprim has a significant drug interaction with warfarin, such that it inhibits warfarin metabolism. Therefore, sulfamethoxazole/trimethoprim will cause increased anticoagulant effects, and the patient will need to have his warfarin dose decreased and INR checked frequently while he is on this antibiotic.

- 21.4 A 47-year-old woman presents to the emergency room with severe bleeding. Upon evaluation of the medical record, you discover that she takes dabigatran for a history of multiple DVTs. What is the appropriate reversal agent to administer to the patient at this time?

- A. Protamine
- B. Vitamin K
- C. Idarucizumab
- D. A reversal agent does not exist for this medication.

Correct answer = C. Idarucizumab is used to reverse bleeding caused by dabigatran. By binding to dabigatran and its metabolites, idarucizumab neutralizes anticoagulation. It would be important to monitor this patient for any signs of thrombosis due to reversal of her anticoagulation. Vitamin K is the antidote for warfarin, and protamine is the antidote for heparin.

- 21.5 Which must heparin bind to in order to exert its anticoagulant effect?
- A. GP IIb/IIIa receptor
  - B. Thrombin
  - C. Antithrombin III
  - D. von Willebrand factor
- Correct answer = C. Heparin binds to antithrombin III, causing a conformational change. This heparin/antithrombin III complex then inactivates thrombin and factor Xa.
- 21.6 Which is considered “fibrin selective” because it rapidly activates plasminogen that is bound to fibrin?
- A. Alteplase
  - B. Fondaparinux
  - C. Argatroban
  - D. Bivalirudin
- Correct answer = A. Alteplase has a low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug. It has the advantage of lysing only fibrin, without unwanted degradation of other proteins (notably fibrinogen).
- 21.7 A 56-year-old man presents to the emergency room with complaints of swelling, redness, and pain in his right leg. The patient is diagnosed with acute DVT, and the provider wants to start an oral agent. Which drug is most appropriate for treatment of DVT in this patient?
- A. Rivaroxaban
  - B. Betrixaban
  - C. Enoxaparin
  - D. Clopidogrel
- Correct answer = A. Betrixaban is only approved for the prophylaxis of DVT and PE; it is not approved for the treatment of acute DVT. Enoxaparin is used for the treatment of DVT, but it is an injectable medication. Clopidogrel is an antiplatelet medication that is not appropriate for acute treatment of DVT.
- 21.8 Which is most appropriate for reversing the anticoagulant effects of heparin?
- A. Aminocaproic acid
  - B. Protamine sulfate
  - C. Vitamin K<sub>1</sub>
  - D. Tranexamic acid
- Correct answer = B. Excessive bleeding may be managed by ceasing administration of heparin or by treating with protamine sulfate. Infused slowly, protamine sulfate combines ionically with heparin to form a stable, inactive complex. Aminocaproic acid and tranexamic acid are approved for the treatment of hemorrhage but do not specifically reverse the effects of heparin to stop bleeding. Vitamin K<sub>1</sub> is used to help reverse the effects of warfarin-induced bleeding.
- 21.9 A 62-year-old man taking warfarin for stroke prevention in atrial fibrillation presents to his primary care physician with an elevated INR of 10.5 without bleeding. He is instructed to hold his warfarin dose and given oral vitamin K<sub>1</sub>. When would the effects of vitamin K on the INR most likely be noted in this patient?
- A. 1 hour
  - B. 6 hours
  - C. 24 hours
  - D. 72 hours
- Correct answer = C. Vitamin K<sub>1</sub> takes about 24 hours to see a reduction in the INR. This is due to the time required for the body to synthesize new coagulation factors.

21.10 A 58-year-old man receives intravenous alteplase treatment for acute stroke. Five minutes following completion of alteplase infusion, he develops angioedema. Which of the following drugs may have increased the risk of developing angioedema in this patient?

- A. ACE inhibitor
- B. GP IIb/IIIa receptor antagonist
- C. Phosphodiesterase inhibitor
- D. Thiazide diuretic

Correct answer = A. ACE inhibitors, aspirin, and prasugrel all have possible adverse effects including angioedema. In the setting of alteplase administration, ACE inhibitors have been associated with an increased risk of developing angioedema with concomitant use.



# Drugs for Hyperlipidemia

Karen Sando and Kevin Cowart

# 22

## I. OVERVIEW

Hyperlipidemia (elevated cholesterol levels) is a medical condition characterized by an increase in one or more of the plasma lipids including triglycerides (TGs), cholesterol, cholesterol esters, and phospholipids and/or plasma lipoproteins including very-low-density lipoprotein (VLDL-C), low-density lipoprotein (LDL-C), and reduced high-density lipoprotein (HDL-C) levels (Figure 22.1). Hyperlipidemia is considered one of the major risk factors causing cardiovascular diseases (CVDs) and cardiovascular disease is the leading cause of death worldwide. Hyperlipidemia is an increase in one or more of the plasma lipids. Hypercholesterolemia and hypertriglyceridemia are the main causes of atherosclerosis which is strongly related to CVD. Atherosclerosis is a slow, complex process of arteries' hardening due to deposition of plaques of cholesterol in the arterial wall (exact cause is not known), leading to narrowing of the arteries. Atherosclerosis and atherosclerosis-associated disorders (for example, coronary, cerebrovascular, and peripheral vascular diseases) are accelerated by the presence of hyperlipidemia. Plaque initially begins to build up where the arteries are damaged and it hardens over time. As a result, an area of plaque can rupture and initiate clotting cascade. Other risk factors for CVD include cigarette smoking, hypertension, obesity, diabetes, chronic kidney disease, and advanced age. Hyperlipidemia may be due to lifestyle factors (for example, lack of exercise or diet containing excess saturated fats). Hyperlipidemia can also result from an inherited defect in lipoprotein metabolism or, more commonly, from a combination of genetic and lifestyle factors. Appropriate lifestyle changes, along with drug therapy, can lead to a 30% to 40% reduction in CVD mortality. Antihyperlipidemic drugs (Figure 22.2), also called hypolipidemic drugs, are often taken indefinitely to reduce the risk of Atherosclerotic Cardiovascular Disease (ASCVD) in select patients and to control plasma lipid levels. [Note ASCVD includes CHD, stroke, and peripheral arterial disease.] Figure 22.3 illustrates the normal metabolism of serum lipoproteins and the characteristics of the major genetic hyperlipidemias.

	CHOLESTEROL	LDL-C	TRIGLYCERIDE	HDL
Optimal (mg/dL)	150	<100	<100	>60
Normal (mg/dL)	<200	100–129	101–150	60
Borderline (mg/dL)	200–239	130–159	150–199	40–60
High (mg/dL)	>240	160–189	200–499	<50
Very high (mg/dL)		>190	>500	<35

Figure 22.1

Normal lipid profile.

### HMG CoA REDUCTASE INHIBITORS (STATINS)

*Simvastatin  
Atorvastatin  
Fluvastatin  
Lovastatin  
Rosuvastatin  
Pravastatin  
Pitavastatin*

### NIACIN

*Niacin*

### FIBRATES

*Fenofibrate  
Gemfibrozil*

### BILE ACID SEQUESTRANTS

*Cholestyramine  
Colestipol  
Colesevelam*

### CHOLESTEROL ABSORPTION INHIBITOR

*Ezetimibe*

### OMEGA-3 FATTY ACIDS

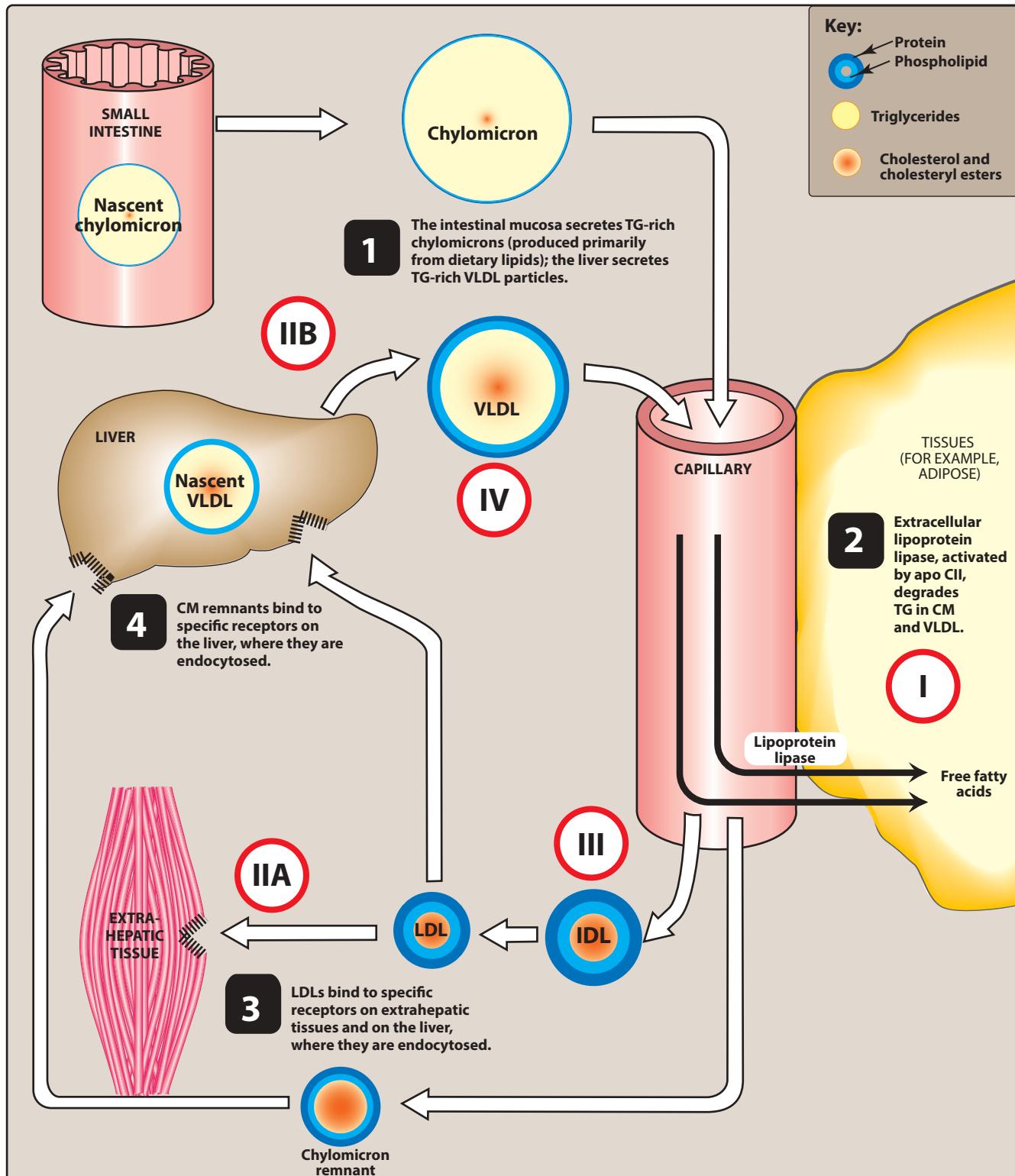
*Docosahexaenoic and eicosapentaenoic acids  
Icosapent ethyl*

### PCSK9 INHIBITORS

*Alirocumab  
Evolucumab*

Figure 22.2

Summary of antihyperlipidemic drugs. HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; OTC = over-the-counter; PCSK9 = proprotein convertase subtilisin kexin type 9.

**Figure 22.3**

Metabolism of plasma lipoproteins and related genetic diseases. Roman numerals in the white circles refer to specific genetic types of hyperlipidemias summarized on the facing page. apo CII = apolipoprotein CII found in chylomicrons and VLDL; CM = chylomicron; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; PCKS9 = proprotein convertase subtilisin kexin type 9; TG = triglyceride; VLDL = very-low-density lipoprotein. (Figure continues on next page)

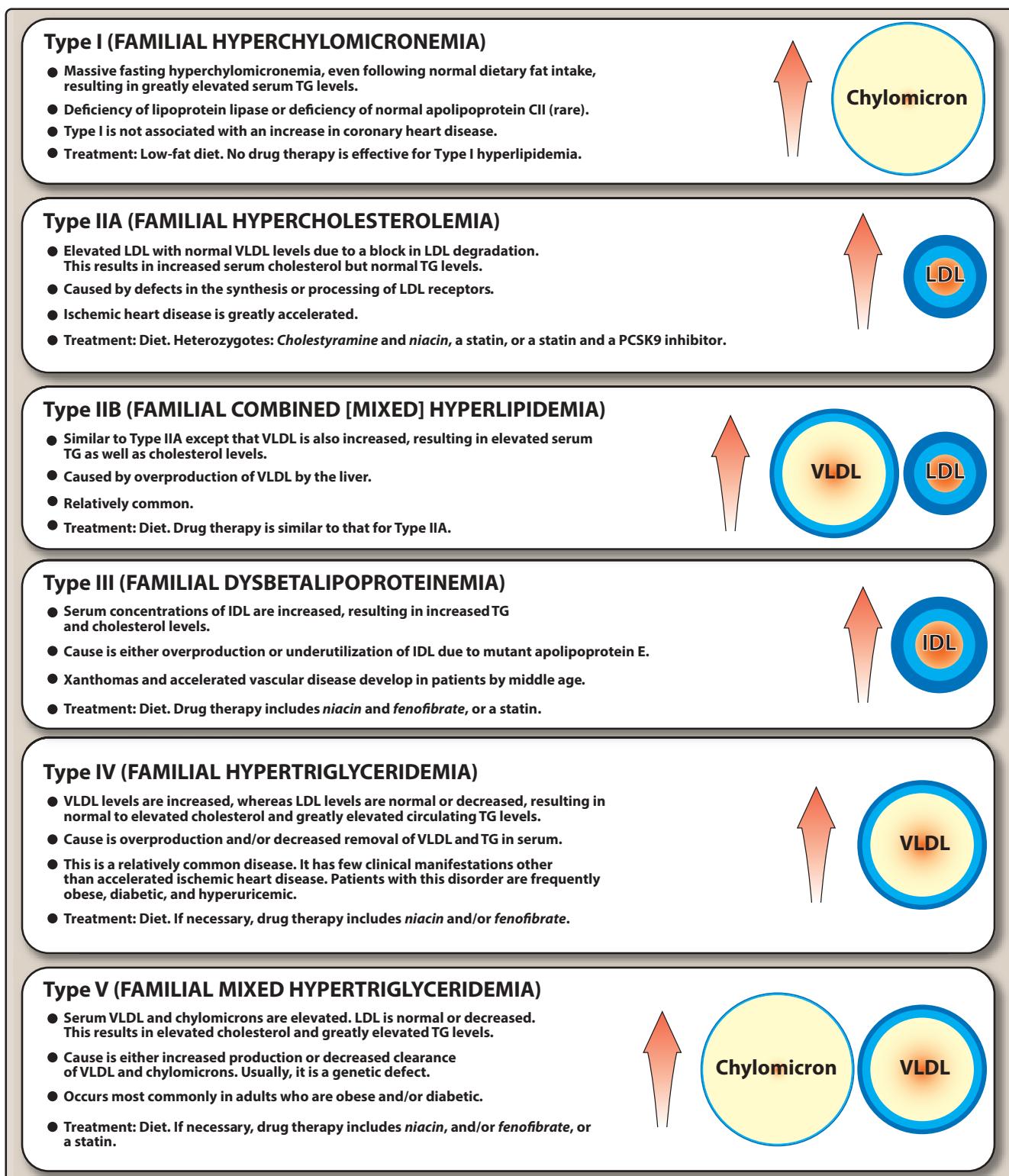
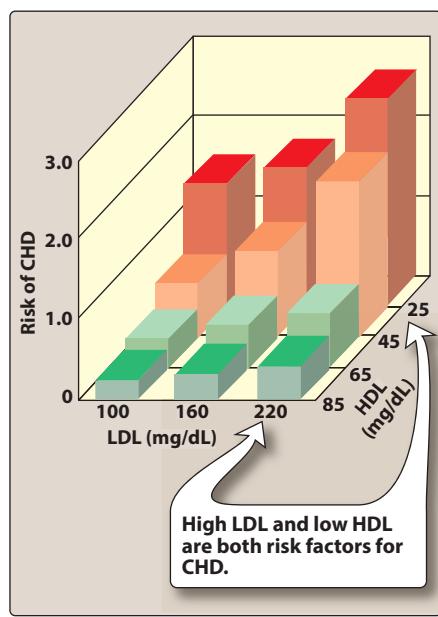


Figure 22.3 (Continued)

**Figure 22.4**

Effect of circulating low-density lipoprotein (LDL) and high-density lipoprotein (HDL) on the risk of coronary heart disease (CVD).

## II. TREATMENT GOALS

Plasma lipids consist mostly of lipoproteins, which are spherical complexes of lipids and specific proteins. The clinically important lipoproteins, listed in a decreasing order of atherogenicity, are LDL, very-low-density lipoprotein (VLDL) and chylomicrons, and HDL. The occurrence of CVD is positively associated with high total cholesterol and has an even stronger correlation with elevated LDL-C. In contrast to LDL-C, high levels of HDL-C have been associated with a decreased risk for CVD (Figure 22.4). Reduction of LDL-C is the primary goal of cholesterol-lowering therapy. According to cholesterol guidelines, the need for antihyperlipidemic drug therapy should be determined based on an assessment of risk for ASCVD, in conjunction with evaluation of lipoprotein levels (for example, LDL-C; Figure 22.5), as hyperlipidemia per se does not have any obvious symptoms but is usually discovered during routine examination or until it reaches the danger stage of a myocardial ischemia or stroke. [Note: Therapeutic lifestyle changes, such as diet, exercise, and weight loss, remain critical of reduction in ASCVD; however, lifestyle modifications do not replace the need for drug therapy in patients who fall into one of the four statin benefit groups (see Figure 22.5).]

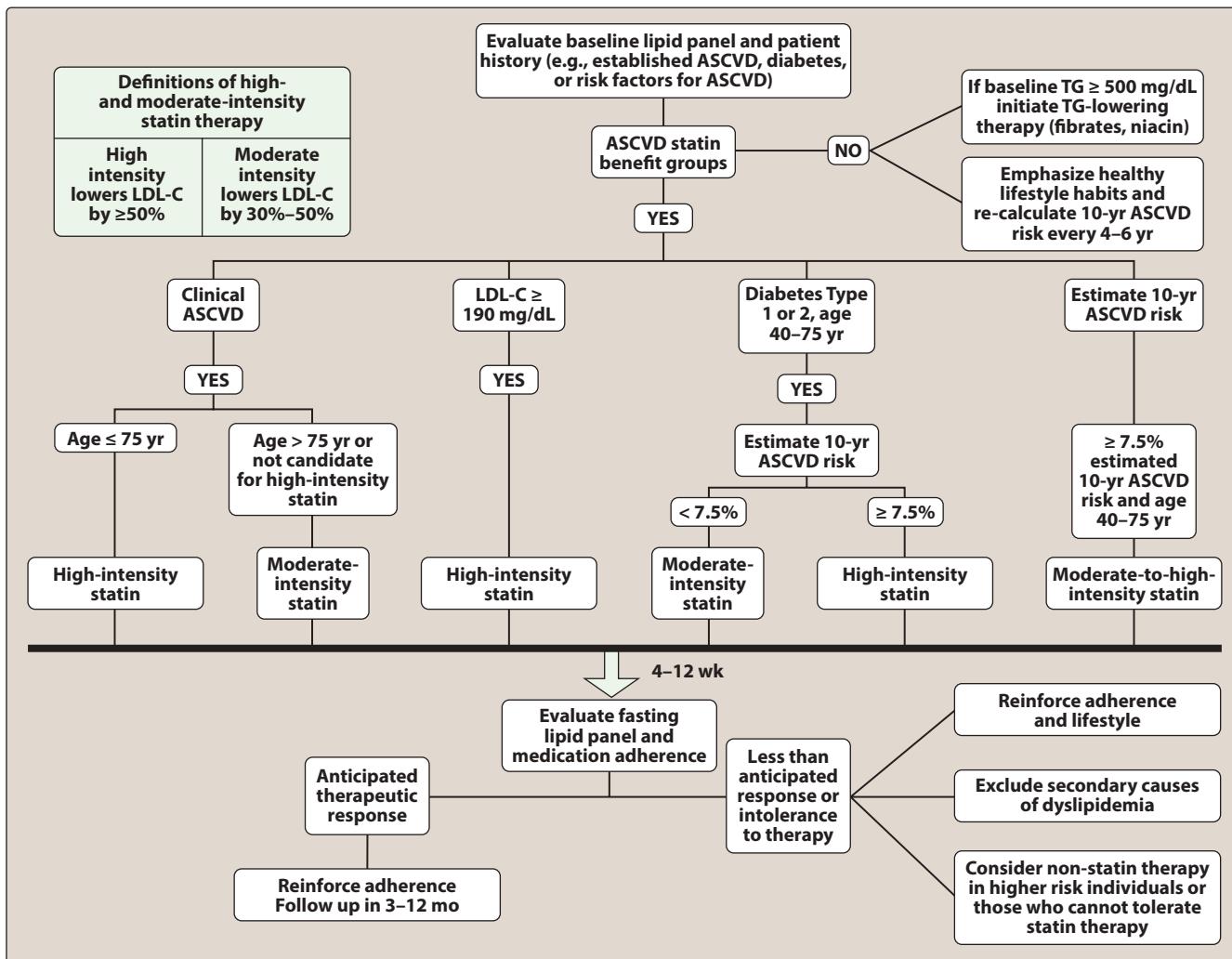
- Patients with any form of clinical ASCVD
- Patients with primary LDL-C levels of  $\geq 190$  mg/dL
- Patients with diabetes mellitus, 40 to 75 years of age, with LDL-C levels of 70 to 189 mg/dL
- Patients without diabetes, 40 to 75 years of age, with an estimated 10-year ASCVD risk  $\geq 7.5\%$

## III. DRUGS FOR HYPERLIPIDEMIA

Antihyperlipidemic drugs include the statins, niacin, fibrates, bile acid sequestrants, a cholesterol absorption inhibitor, proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, and omega-3 fatty acids. These agents may be used alone or in combination. However, drug therapy should always be accompanied by lifestyle modifications, such as exercise and a diet low in saturated fats.

### A. HMG CoA reductase inhibitors

3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (commonly known as statins) lower LDL-C, resulting in a substantial reduction in coronary events and death from CVD. Therapeutic benefits include atherosclerotic plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and vascular anti-inflammatory activity. They are first-line treatment for patients with elevated risk of ASCVD to reduce the occurrence of ASCVD events (Figure 22.5). [Note: The intensity of statin therapy should be guided by the patient's absolute risk for an ASCVD event.] However, the possibility of development of diabetes while on therapy with statins has been reported with intensive doses as compared to moderate doses. Pre-existing conditions such as increased fasting glucose levels more than 100 mg/dL, serum triglycerides  $>150$  mg/dL, and BMI more than 30 kg/m<sup>2</sup> along with a history of hypertension are reported with the higher risk of developing diabetes during statin therapy.



HIGH INTENSITY	MODERATE INTENSITY	LOW INTENSITY
Daily dosage lowers LDL-C by $\geq 50\%$	Daily dosage lowers LDL-C by 30–50%	Daily dosage lowers LDL-C by <30%
Atorvastatin (40–80 mg)	Atorvastatin 10 mg	Simvastatin 10 mg
Rosuvastatin (20 mg)	Rosuvastatin 10 mg	Pravastatin 10–20 mg
	Simvastatin 20–40 mg	Lovastatin 20 mg
	Pravastatin 40 mg	Fluvastatin 20–40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin 40 mg twice daily	
	Pitavastatin 2–4 mg	

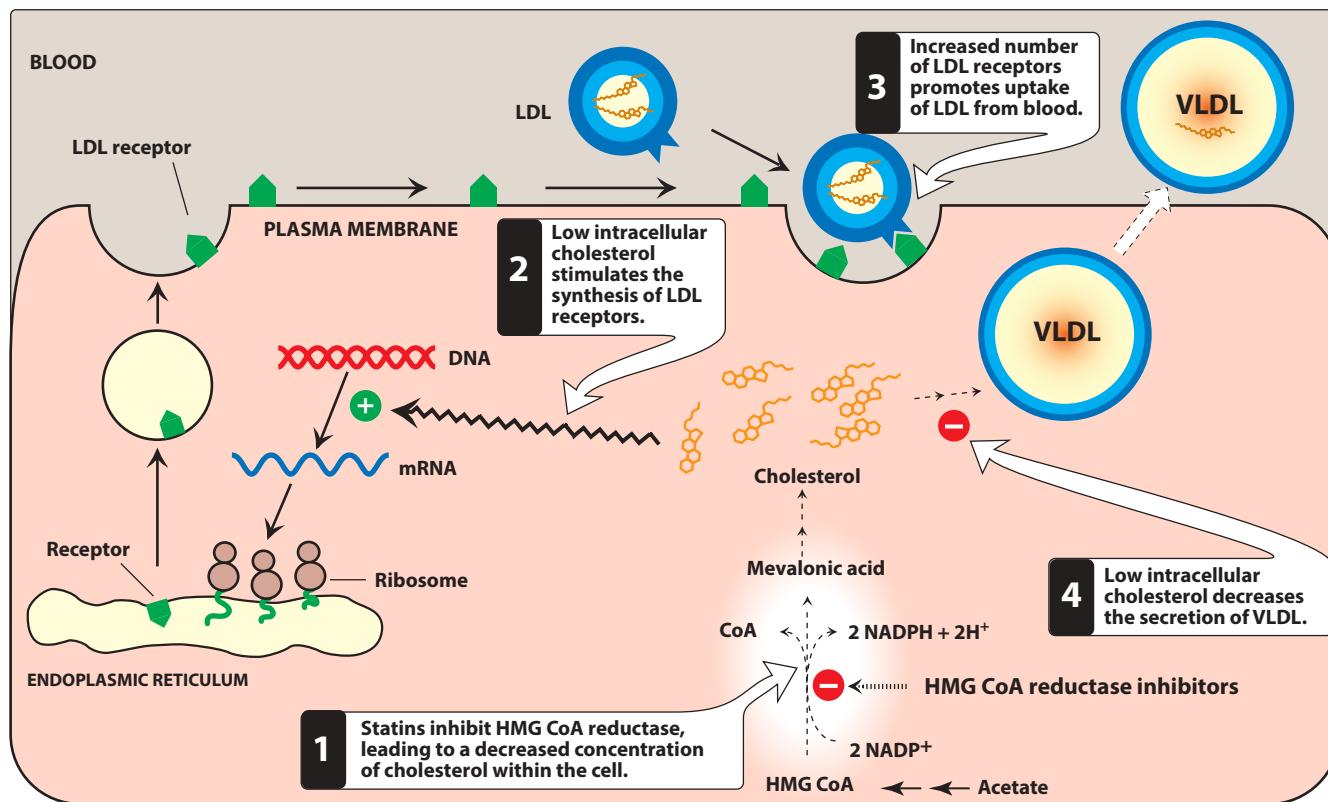
**Figure 22.5**

Treatment guidelines for hyperlipidemia. ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

- Mechanism of action:** Lovastatin [LOE-vah-stat-in], simvastatin [sim-vah-STAT-in], pravastatin [PRAH-vah-stat-in], atorvastatin [a-TOR-vah-stat-in], fluvastatin [FLOO-vah-stat-in], pitavastatin [pit-AV-a-STAT-in], and rosuvastatin [roe-SOO-va-stat-in] are

competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol synthesis. By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol (Figure 22.6). Depletion of intracellular cholesterol causes the cell to increase the number of cell surface LDL receptors that can bind and internalize circulating LDL-C. Thus, plasma cholesterol is reduced, by both decreased cholesterol synthesis and increased LDL-C catabolism. *Rosuvastatin* and *atorvastatin* are the most potent LDL-C lowering statins, followed by *pitavastatin*, *simvastatin*, *lovastatin*, *pravastatin*, and *fluvastatin*. [Note: Because these agents undergo a marked first-pass extraction by the liver, their dominant effect is on that organ.] The HMG CoA reductase inhibitors also decrease triglyceride levels and may increase HDL-C in some patients.

2. **Therapeutic uses:** These drugs are used to lower the risk of ASCVD events for patients in the four statin-benefit groups. Statins are effective in lowering plasma cholesterol levels in all types of hyperlipidemias. However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs.
3. **Pharmacokinetics:** *Lovastatin* and *simvastatin* are lactones that are hydrolyzed to the active drug. The remaining statins are all administered in their active form. Absorption of the statins is



**Figure 22.6**

Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase by the statin drugs. LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein.

CHARACTERISTIC	ATORVASTATIN	FLUVASTATIN	LOVASTATIN	PITAVASTATIN	PRAVASTATIN	ROSUVASTATIN	SIMVASTATIN
Serum LDL cholesterol reduction produced (%)	55	24	34	43	34	60	41
Serum triglyceride reduction produced (%)	29	10	16	18	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	8	12	8	12
Plasma half-life (hr)	14	1–2	2	12	1–2	19	1–2
Penetration of central nervous system	No	No	Yes	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	< 6	10	15	20	10	13

LDL = low-density lipoprotein; HDL = high-density lipoprotein.

**Figure 22.7**

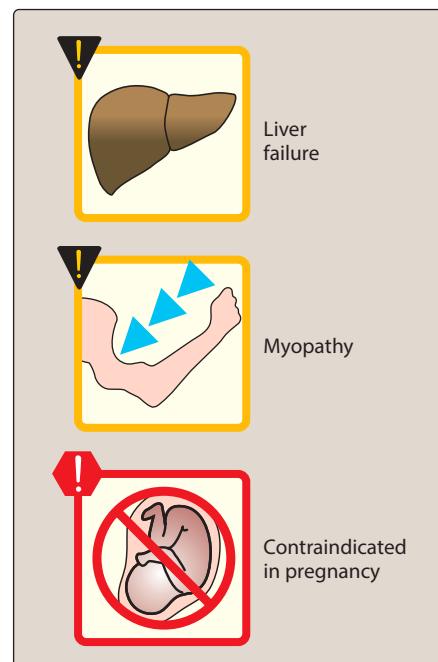
Summary of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors. Modified from M. K. S. Leow, C. L. Addy, and C. S. Mantzoros. Clinical review 159: human immunodeficiency virus/highly active antiretroviral therapy-associated metabolic syndrome: clinical presentation, pathophysiology, and therapeutic strategies. J. Clin. Endocrinol. Metab. 88: 1961 (2003).

variable (30% to 85%) following oral administration. All statins are metabolized by cytochrome P450 (CYP450) isoenzymes in the liver, except *pravastatin*. Excretion takes place principally through bile and feces, but some urinary elimination also occurs. Some characteristics of the statins are summarized in Figure 22.7.

4. **Adverse effects:** Elevated liver enzymes may occur with statin therapy. Therefore, liver function should be evaluated prior to starting therapy or if a patient has symptoms consistent with liver dysfunction. [Note: Hepatic insufficiency can cause drug accumulation.] Myopathy and rhabdomyolysis (disintegration of skeletal muscle; rare) have been reported (Figure 22.8). In most cases of rhabdomyolysis, patients had renal insufficiency, vitamin D deficiency, hypothyroidism, advanced age, were female, or were taking drugs that increase the risk of muscle adverse effects, such as azole antifungals, protease inhibitors, *cyclosporine*, *erythromycin*, *gemfibrozil*, or *niacin*. *Simvastatin* is metabolized by CYP450 3A4, and inhibitors of this enzyme may increase the risk of rhabdomyolysis. Plasma creatine kinase levels should be determined in patients with muscle complaints. The HMG CoA reductase inhibitors may also increase the effect of *warfarin*. Thus, it is important to evaluate the international normalized ratio (INR) when initiating a statin or changing the dosage. These drugs are contraindicated during pregnancy, lactation, and active liver disease.

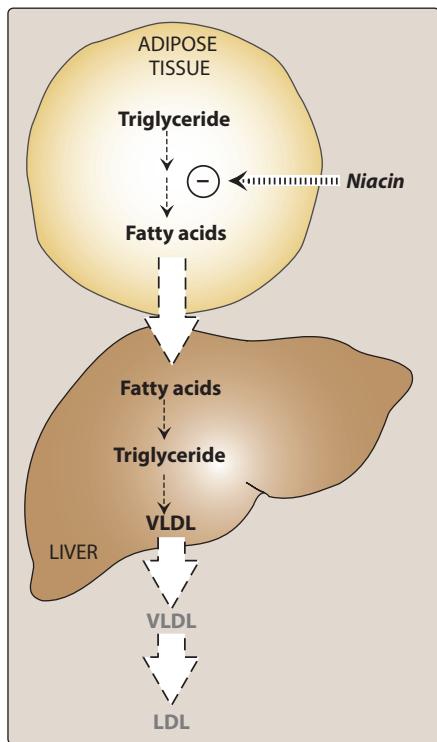
## B. Niacin (nicotinic acid)

*Niacin* [NYE-uh-sin] reduces LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C. It also lowers triglycerides by 20% to 35% at typical doses of 1.5 to 3 g/day. *Niacin* can be used in combination with statins, and fixed-dose combinations of long-acting



**Figure 22.8**

Some adverse effects and precautions associated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors. Modified from D. J. Schneider, P. B. Tracy, and B. E. Sobel, Hosp. Pract. 107 (1998).



**Figure 22.9**

Niacin inhibits lipolysis in adipose tissue, resulting in decreased hepatic very-low-density lipoprotein (VLDL) synthesis and production of low-density lipoprotein (LDL) in the plasma.

niacin with lovastatin and simvastatin are available. [Note: The addition of niacin to statin therapy has not been shown to reduce the risk of ASCVD events.]

- Mechanism of action:** At gram doses, niacin strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids (Figure 22.9). The liver normally uses circulating free fatty acids as a major precursor for triglyceride synthesis. Reduced liver triglyceride levels decrease hepatic VLDL production, which in turn reduces LDL-C plasma concentrations.
- Therapeutic uses:** Because niacin lowers plasma levels of both cholesterol and triglycerides, it is useful in the treatment of familial hyperlipidemias. It is also used to treat other severe hypercholesterolemias, often in combination with other agents.
- Pharmacokinetics:** Niacin is administered orally. It is converted in the body to nicotinamide, which is incorporated into the cofactor nicotinamide adenine dinucleotide ( $\text{NAD}^+$ ). Niacin, its nicotinamide derivative, and other metabolites are excreted in the urine. [Note: Administration of nicotinamide alone does not decrease plasma lipid levels.]
- Adverse effects:** The most common adverse effects of niacin are an intense cutaneous flush accompanied by an uncomfortable feeling of warmth and pruritus. Administration of aspirin prior to taking niacin decreases the flush, which is prostaglandin-mediated. Some patients also experience nausea and abdominal pain. Slow titration of the dosage or use of the sustained-release formulation of niacin reduces bothersome initial adverse effects. Niacin inhibits tubular secretion of uric acid and, thus, predisposes patients to hyperuricemia and gout. Impaired glucose tolerance and hepatotoxicity have also been reported. The drug should be avoided in active hepatic disease or in patients with an active peptic ulcer.

### C. Fibrates

*Fenofibrate* [fen-oh-FIH-brate] and *gemfibrozil* [jem-FI-broh-zill] are derivatives of fibric acid that lower serum triglycerides and increase HDL-C.

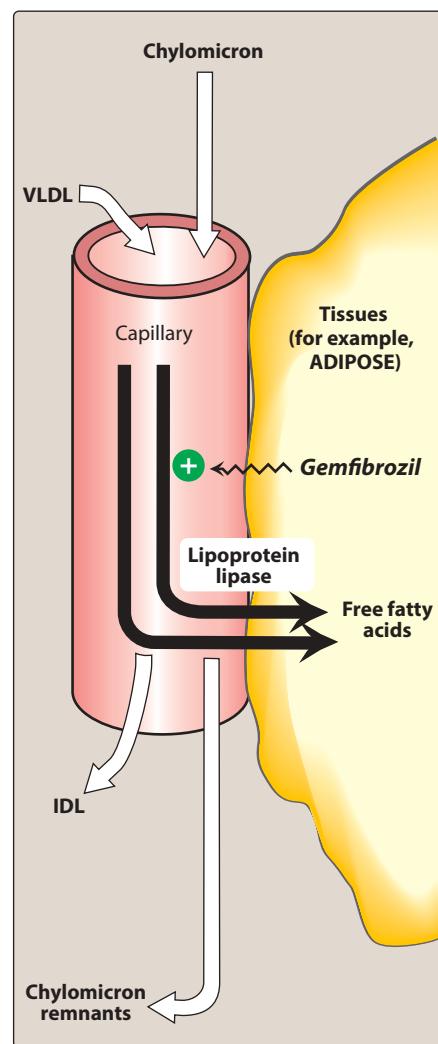
- Mechanism of action:** The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor family that regulate lipid metabolism. PPARs function as ligand-activated transcription factors. Upon binding to their natural ligands (fatty acids or eicosanoids) or antihyperlipidemic drugs, PPARs are activated. They then bind to peroxisome proliferator response elements, which ultimately leads to decreased triglyceride concentrations through increased expression of lipoprotein lipase (Figure 22.10) and decreased apolipoprotein (apo) CII concentration. Fibrates are known to decrease triglyceride levels to the extent of 20% to 50%. *Fenofibrate* is more effective than *gemfibrozil* in lowering triglyceride levels. Fibrates also increase HDL-C by increasing the expression of apo AI and apo AI.
- Therapeutic uses:** The fibrates are used in the treatment of hypertriglyceridemias. They are particularly useful in treating type III hyperlipidemia (dysbeta lipoproteinemia), in which intermediate-density lipoprotein particles accumulate.

3. **Pharmacokinetics:** *Gemfibrozil* and *fenofibrate* are completely absorbed after oral administration and distribute widely, bound to albumin. *Fenofibrate* is a prodrug, which is converted to the active moiety fenofibric acid. Both drugs undergo extensive biotransformation and are excreted in the urine as glucuronide conjugates.
4. **Adverse effects:** The most common adverse effects are mild gastrointestinal (GI) disturbances. These lessen as the therapy progresses. Because these drugs increase biliary cholesterol excretion, there is a predisposition to form gallstones. Myositis (inflammation of a voluntary muscle) can occur, and muscle weakness or tenderness should be evaluated. Patients with renal insufficiency may be at risk. Myopathy and rhabdomyolysis have been reported in patients taking *gemfibrozil* and statins together. The use of *gemfibrozil* is contraindicated with *simvastatin*, and, in general, the use of *gemfibrozil* with any statin should be avoided. Both fibrates may increase the effects of *warfarin*. Therefore, INR should be monitored more frequently when a fibrate is initiated. Fibrates should not be used in patients with severe hepatic or renal dysfunction, in patients with preexisting gallbladder disease or biliary cirrhosis.

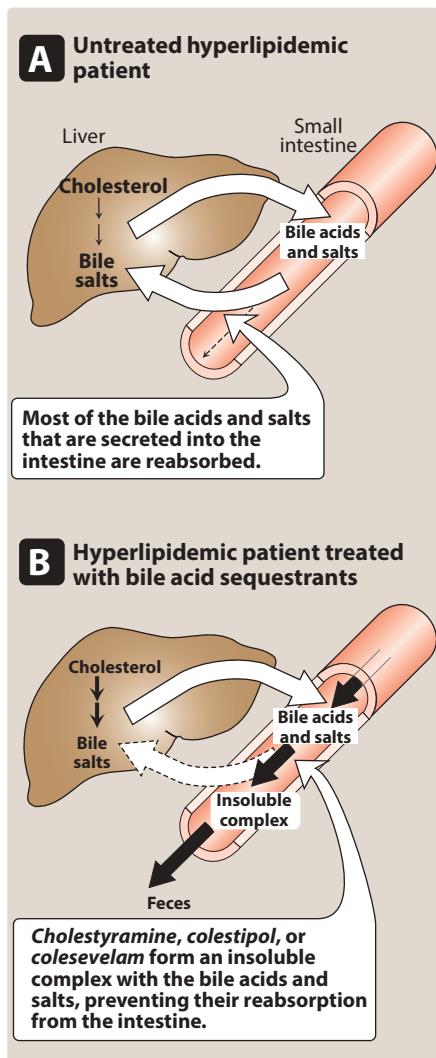
#### D. Bile acid sequestrants

Bile acid sequestrants (resins) have significant LDL-C lowering effects, although the benefits are less than those observed with statins.

1. **Mechanism of action:** *Cholestyramine* [koe-LES-tir-a-meen], *colestipol* [koe-LES-tih-pole], and *colesevelam* [koh-le-SEV-e-lam] are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine (Figure 22.11). The resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration. This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile. Consequently, intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol-containing LDL-C particles, leading to a decrease in plasma LDL-C. [Note: This increased uptake is mediated by an up-regulation of cell surface LDL receptors.]
2. **Therapeutic uses:** The bile acid sequestrants are useful (often in combination with diet or *niacin*) for treating type IIA and type IIB hyperlipidemias. [Note: In those rare individuals who are homozygous for type IIA and functional LDL receptors are totally lacking, these drugs have little effect on plasma LDL levels.] *Cholestyramine* can also relieve pruritus caused by accumulation of bile acids in patients with biliary stasis. *Colesevelam* is also indicated for type 2 diabetes due to its glucose-lowering effects.
3. **Pharmacokinetics:** Bile acid sequestrants are insoluble in water and have large molecular weights. After oral administration, they are neither absorbed nor metabolically altered by the intestine. Instead, they are totally excreted in feces.
4. **Adverse effects:** The most common adverse effects are GI disturbances, such as constipation, nausea, and flatulence. *Colesevelam* has fewer GI side effects than other bile acid sequestrants. These agents may impair the absorption of the fat-soluble



**Figure 22.10**  
Activation of lipoprotein lipase by gemfibrozil. IDL = intermediate-density lipoprotein; VLDL = very-low-density lipoprotein.



**Figure 22.11**

Mechanism of bile acid sequestrants.

vitamins (A, D, E, and K), and they interfere with the absorption of many drugs (for example, *digoxin*, *warfarin*, and thyroid hormone). Therefore, other drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after the bile acid sequestrants. These agents may raise triglyceride levels and are contraindicated in patients with significant hypertriglyceridemia (>400 mg/dL).

### E. Cholesterol absorption inhibitor

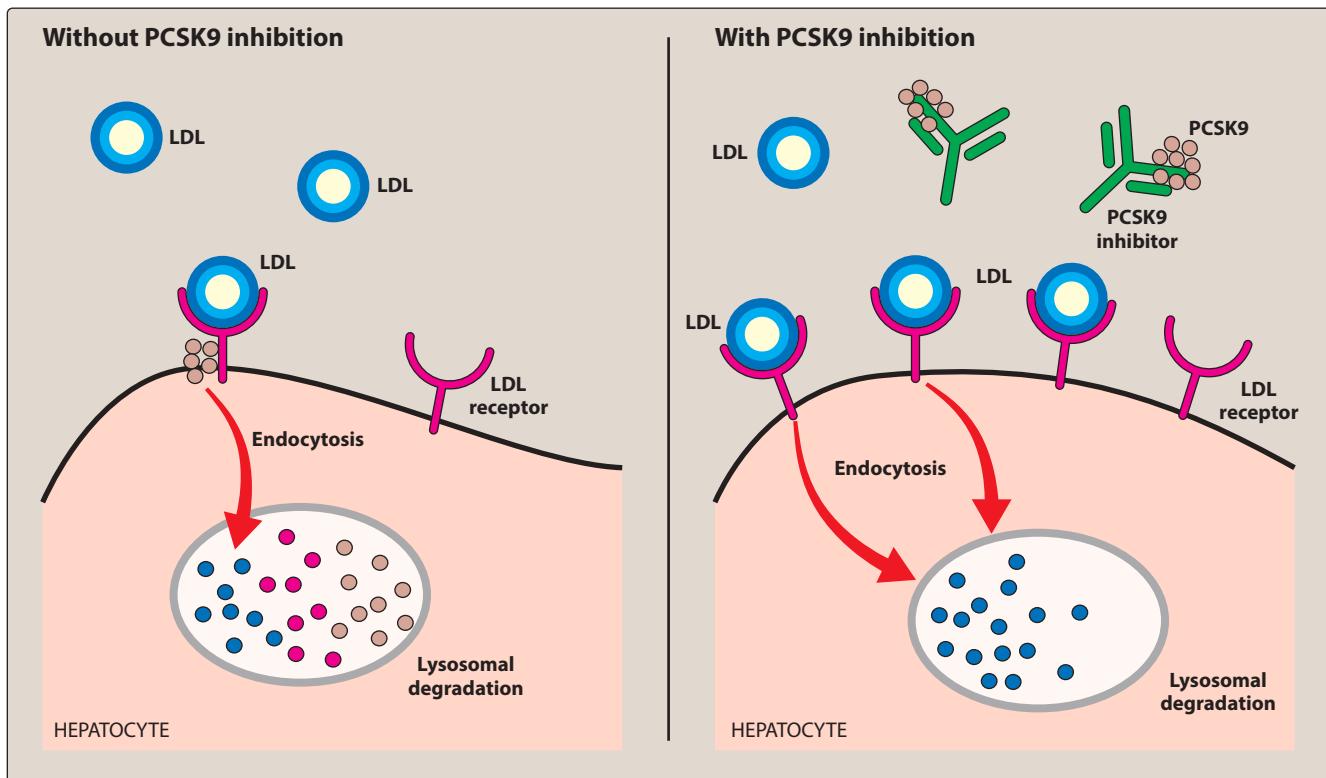
*Ezetimibe* [eh-ZEH-teh-mibe] selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. *Ezetimibe* lowers LDL-C by approximately 18% to 23%. Due to its modest LDL-C lowering, *ezetimibe* is often used as an adjunct to maximally tolerated statin therapy in patients with high ASCVD risk or in statin-intolerant patients. *Ezetimibe* is primarily metabolized in the small intestine and liver via glucuronide conjugation, with subsequent biliary and renal excretion. Patients with moderate-to-severe hepatic insufficiency should not be treated with *ezetimibe*. Adverse effects are uncommon with use of *ezetimibe*.

### F. Proprotein convertase subtilisin kexin type 9 inhibitors

Proprotein convertase subtilisin kexin type 9 (PCSK9) is an enzyme predominately produced in the liver. PCSK9 binds to the LDL receptor on the surface of hepatocytes, leading to the degradation of LDL receptors (Figure 22.12). By inhibiting the PCSK9 enzyme, more LDL receptors are available to clear LDL-C from the serum. *Alirocumab* [al-i-ROK-ue-mab] and *evolocumab* [e-voe-LOK-ue-mab] are PCSK9 inhibitors which are fully humanized monoclonal antibodies. These agents are used in addition to maximally tolerated statin therapy in patients with heterozygous or homozygous familial hypercholesterolemia, or in patients with clinical ASCVD who required additional LDL-C lowering. When combined with statin therapy, PCSK9 inhibitors provide potent LDL-C lowering (50% to 70%). They may also be considered for patients with high ASCVD risk and statin intolerance. PCSK9 inhibitors are only available as subcutaneous injections and are administered every 2 to 4 weeks. Monoclonal antibodies are not eliminated by the kidneys and have been used in dialysis patients or those with severe renal impairment. PCSK9 inhibitors are generally well tolerated. The most common adverse drug reactions are injection site reactions, immunologic or allergic reactions, nasopharyngitis, and upper respiratory tract infections.

### G. Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for triglyceride lowering. Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver. The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna, halibut, and salmon. Approximately 4 g of marine-derived omega-3 PUFAs daily decrease serum triglyceride concentrations by 25% to 30%, with small increases in LDL-C and HDL-C. Over-the-counter or prescription

**Figure 22.12**

Mechanism of action of PCSK9 inhibitors. PCSK9 binds to the LDL receptor on the surface of hepatocytes, leading to degradation of LDL receptors. Inhibition of PCSK9 prevents degradation of LDL receptors and promotes greater clearance of LDL-C from the serum. LDL = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin kexin type 9.

fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources alone. *Icosapent* [eye-KOE-sa-pent] ethyl is a prescription product that contains only EPA and, unlike other fish oil supplements, does not significantly raise LDL-C. Omega-3 PUFAs can be considered an adjunct to other lipid-lowering therapies for individuals with elevated triglycerides ( $\geq 500$  mg/dL). Although effective for triglyceride lowering, omega-3 PUFA supplementation has not been shown to reduce cardiovascular morbidity and mortality. The most common side effects of omega-3 PUFAs include GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste. Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelet agents.

#### H. Combination drug therapy

It is sometimes necessary to use two antihyperlipidemic drugs to achieve treatment goals. Patients with established ASCVD, an elevated 10-year risk of ASCVD, or those that do not achieve intended LDL-C reductions on maximally tolerated statin therapy may be considered for combination therapy. *Ezetimibe* and PCSK9 inhibitors can be considered for add-on therapy, since there is evidence that these combinations further reduce ASCVD events in patients already taking

statin therapy. Combination drug therapy is not without risks. Liver and muscle toxicity occur more frequently with lipid-lowering drug combinations. **Figure 22.13** summarizes some actions of the antihyperlipidemic drugs.

DRUGS	DAILY DOSE	EFFECTS ON LIPIDS	USE	ADVERSE EFFECTS
<b>Statins:</b>				
<i>Lovastatin</i>	10–80 mg	Decrease TG		
<i>Simvastatin</i>	5–40 mg	Decrease LDL		
<i>Atorvastatin</i>	10–80 mg	Increase HDL		
<i>Rosuvastatin</i>	5–20 mg		<ul style="list-style-type: none"> <li>Patients with any form of clinical ASCVD</li> <li>Patients with primary LDL-C levels of <math>\geq 190</math> mg/dL</li> <li>Patients with diabetes mellitus, 40 to 75 years of age, with LDL-C levels of 70 to 189 mg/dL</li> <li>Patients without diabetes, 40 to 75 years of age, with an estimated 10-year ASCVD risk <math>\geq 7.5\%</math></li> </ul>	Usually well tolerated; transient gastrointestinal symptoms, headache, myalgia, and dizziness; myopathy (usually at higher doses), rhabdomyolysis, and an increase in serum transaminase; cardiomyopathy
<b>Bile acid-binding resins:</b>				
<i>Cholestyramine</i> <i>Colestipol</i>	4–16 mg 5–30 mg	TG generally not effected Decrease LDL Increase HDL		Poor patient tolerance due to gastrointestinal disturbances (constipation, nausea, indigestion, bloating, and flatulence); on long-term therapy osteoporosis due to calcium loss, hypertriglyceridemia, and deficiency of vitamins and minerals
<b>Fibric acid derivatives:</b>				
<i>Gemfibrozil</i> <i>Bezafibrate</i> <i>Fenofibrate</i>	1200 mg 600 mg 200 mg	Decrease TG Decrease LDL Increase HDL		Usually well tolerated; gastrointestinal symptoms, myopathy, arrhythmia, skin rashes, and gallstones Avoid in patients with liver and renal dysfunction
<b>Nicotinic acid derivatives:</b>				
<i>Niacin</i>	2–6 g	Decrease TG Decrease LDL Increase HDL		Poor patient tolerance; intense cutaneous flush, itching, headache, nausea and abdominal discomfort; elevation of liver enzymes; glucose in tolerance and hyperuricemia Combination with statins increases the incidence of rhabdomyolysis
<b>Cholesterol absorption inhibitors:</b>				
<i>Ezetimibe</i>	10 mg	Decrease LDL Decrease cholesterol		Usually well tolerated; headache, abdominal pain, and diarrhea; elevations in liver enzymes alanine transaminase and aspartate transaminase

**Figure 22.13**

Various classes of antihyperlipidemic drugs and their effect on lipids.

## Study Questions

Choose the ONE best answer.

- 22.1 Which of the following is the most common adverse effect of antihyperlipidemic drug therapy?
- Elevated blood pressure
  - Gastrointestinal disturbance
  - Neurologic problems
  - Heart palpitations
- 22.2 Which of the following hyperlipidemias is characterized by elevated plasma levels of chylomicrons and has no drug therapy available to lower the plasma lipoprotein levels?
- Type I
  - Type II
  - Type III
  - Type IV
- 22.3 Which of the following drugs decreases cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase?
- Fenofibrate
  - Cholestyramine
  - Lovastatin
  - Gemfibrozil
- 22.4 Which of the following nonstatin drugs lowers LDL-C most effectively?
- Niacin
  - Alirocumab
  - Cholestyramine
  - Ezetimibe
- 22.5 Which of the following drugs binds bile acids in the intestine, thus preventing their return to the liver via the enterohepatic circulation?
- Niacin
  - Fenofibrate
  - Cholestyramine
  - Fluvastatin
- 22.6 A 65-year-old man has type 2 diabetes mellitus and an LDL-C of 165 mg/dL. Which is the best option to lower LDL-C and decrease the risk of ASCVD events in this patient?
- Fenofibrate
  - Colesevelam
  - Rosuvastatin
  - Ezetimibe

Correct answer = B. Gastrointestinal disturbances frequently occur as an adverse effect of antihyperlipidemic drug therapy. The other choices are not seen as often.

Correct answer = A. Type I hyperlipidemia (hyperchylomicronemia) is treated with a low-fat diet. No drug therapy is effective for this disorder.

Correct answer = C. Lovastatin decreases cholesterol synthesis by inhibiting HMG CoA reductase. Fenofibrate and gemfibrozil increase the activity of lipoprotein lipase, thereby increasing the removal of VLDL from plasma. Cholestyramine lowers the amount of bile acids returning to the liver via the enterohepatic circulation.

Correct answer = B. Alirocumab is a PCSK9 inhibitor that can lower LDL-C by up to 70% in patients on statin therapy. Niacin primarily raises HDL-C and decreases triglycerides, with less potent effects on LDL-C lowering. Cholestyramine and ezetimibe both lower LDL-C, although not as potently as PCSK9 inhibitors.

Correct answer = C. Cholestyramine is an anion-exchange resin that binds negatively charged bile acids and bile salts in the small intestine. The resin/bile acid complex is excreted in the feces, thus preventing the bile acids from returning to the liver by the enterohepatic circulation. The other choices do not bind intestinal bile acids.

Correct answer = C. Rosuvastatin, an HMG CoA reductase inhibitor (statin), is the most effective option for lowering LDL-C, achieving reductions of up to 60% from baseline levels. Statins are the primary modality for reducing ASCVD risk when drug therapy is indicated. Fenofibrate is more effective at lowering triglyceride levels or raising HDL-C. Colesevelam can reduce LDL-C, but not as effectively as statins. Ezetimibe lowers LDL-C modestly compared to the LDL-C reduction achieved by statins.

- 22.7 A 62-year-old female with hyperlipidemia and hypothyroidism is prescribed cholestyramine and levothyroxine (thyroid hormone). What advice would you give this patient to avoid a drug interaction between her cholestyramine and levothyroxine?
- Stop taking the levothyroxine as it can interact with cholestyramine.
  - Take levothyroxine 1 hour before cholestyramine on an empty stomach.
  - Switch cholestyramine to colesevelam as this eliminates the interaction.
  - Switch cholestyramine to colestipol as this eliminates the interaction.
- 22.8 A 42-year-old man was started on sustained-release niacin 2 weeks ago. He reports uncomfortable flushing and itchiness that he thinks is related to the niacin. Which of the following can help manage this adverse effect of niacin therapy?
- Administer aspirin 30 minutes prior to taking niacin.
  - Administer aspirin 30 minutes after taking niacin.
  - Increase the dose of niacin.
  - Change the sustained-release niacin to immediate-release niacin.
- 22.9 A 72-year-old man with hyperlipidemia and renal insufficiency has been treated with high-intensity atorvastatin for 6 months. His LDL-C is 131 mg/dL; triglycerides, 710 mg/dL; and HDL-C, 32 mg/dL. His physician wishes to add another agent for hyperlipidemia. Which is the best option to address the hyperlipidemia in this patient?
- Fenofibrate
  - Niacin
  - Colestipol
  - Gemfibrozil
- 22.10 Which patient population is most likely to experience myalgia (muscle pain) or myopathy with use of HMG CoA reductase inhibitors?
- Patients with renal insufficiency
  - Patients with gout
  - Patients with hypertriglyceridemia
  - Patients taking warfarin (blood thinner)

**Correct answer = B.** Cholestyramine and the bile acid sequestrants can bind several medications, causing decreased absorption of medications such as levothyroxine. Administration of levothyroxine 1 hour before or 4 to 6 hours after cholestyramine can help to avoid this interaction. Choices C and D are incorrect, as all bile acid sequestrants cause this interaction. Choice A is incorrect, as this patient should not stop her thyroid medication.

**Correct answer = A.** Flushing associated with niacin is prostaglandin mediated; therefore, use of aspirin (a prostaglandin inhibitor) can help to minimize this adverse effect. It must be administered 30 minutes before the dose of the niacin; therefore, choice B is incorrect. Increasing the dose of niacin is likely to increase these complaints; therefore, choice C is incorrect. The sustained-release formulation of niacin has less incidence of flushing versus that of the immediate release; therefore, choice D is incorrect.

**Correct answer = B.** This patient has significantly elevated triglycerides and low HDL-C. Niacin can lower triglycerides by 35% to 50% and also raise HDL-C. The fibrates (fenofibrate and gemfibrozil) should not be used due to the history of renal insufficiency. In addition, the use of gemfibrozil with statins should be avoided. Colestipol should not be used because triglycerides are greater than 400 mg/dL.

**Correct answer = A.** Patients with a history of renal insufficiency have a higher incidence of developing myalgias, myopathy, and rhabdomyolysis with use of HMG CoA reductase inhibitors (statins), especially with those that are renally eliminated as drug accumulation can occur. The other populations have not been reported to have a higher incidence of this adverse effect with HMG CoA reductase inhibitors.

## UNIT V

# Drugs Affecting the Endocrine System

# Pituitary and Thyroid

Shannon Miller and Karen Whalen

# 23

## I. OVERVIEW

The endocrine system releases hormones into the bloodstream, which carries chemical messengers to target cells throughout the body. Hormones have a much broader range of response time than do nerve impulses, requiring from seconds to days, or longer, to cause a response that may last for weeks or months. [Note: Nerve impulses generally act within milliseconds.] An important function of the hypothalamus is to connect the nervous system with the endocrine system via the pituitary gland. This chapter presents the central role of hypothalamic and pituitary hormones in regulating body functions. In addition, drugs affecting thyroid hormone synthesis and/or secretion are discussed (Figure 23.1). Chapters 24 to 26 focus on drugs that affect the synthesis and/or secretion of specific hormones and their actions.

## II. HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

The hormones secreted by the hypothalamus and the pituitary are peptides or glycoproteins that act by binding to specific receptor sites on target tissues. The hormones of the anterior pituitary are regulated by neuropeptides that are called either “releasing” or “inhibiting” factors or hormones. These are produced in the hypothalamus, and they reach the pituitary by the hypophyseal portal system (Figure 23.2). The interaction of the releasing hormones with receptors results in the activation of genes that promote the synthesis of protein precursors. The protein precursors then undergo post-translational modification to produce hormones, which are released into the circulation. Each hypothalamic regulatory hormone controls the release of a specific hormone from the anterior pituitary. Pituitary hormone preparations are currently used for specific hormonal deficiencies, although most of the agents have limited therapeutic applications. Hormones of the

### HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

Adrenocorticotrophic hormone (corticotropin; ACTH)  
Cosyntropin (synthetic human ACTH or extract of anterior pituitary)  
Growth hormone (somatotropin)  
Growth hormone-inhibiting hormones—somatostatin, octreotide, lanreotide  
Gonadotropin-releasing hormone—histrelin, leuprolide, goserelin, nafarelin  
Gonadotropins—follicle-stimulating hormone, luteinizing hormone, urofollitropin, follitropin alfa, follitropin beta, menotropins (human menopausal gonadotropins or HMG)  
Prolactin

### POSTERIOR PITUITARY HORMONES

Oxytocin  
Vasopressin (ADH)  
Desmopressin

### Figure 23.1

Hormones and drugs affecting the hypothalamus, pituitary, and thyroid. (Figure continues on next page)

THYROID HORMONES
Thyroid hormone synthesis and secretion
Thyrotropin-releasing hormone (TRH)
Thyroid-stimulating hormone (TSH; thyrotropin)
Levothyroxine ( $T_4$ )
Liothyronine ( $T_3$ )
Liotrix ( $T_4/T_3$ combination product)
DRUGS AFFECTING THE THYROID
Iodine and potassium iodide
Methimazole
Propylthiouracil (PTU)

**Figure 23.1** (Continued)

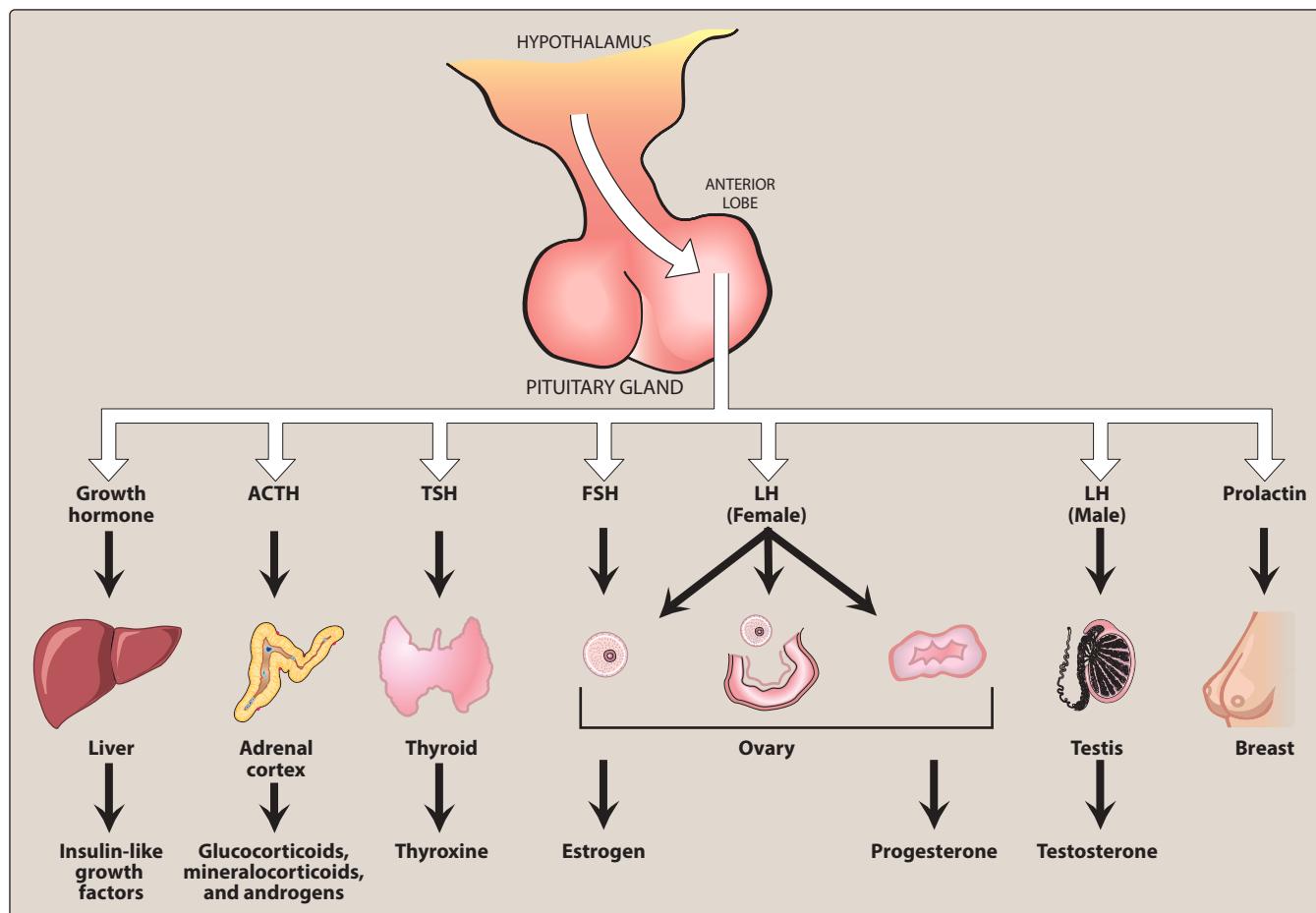
Hormones and drugs affecting the hypothalamus, pituitary, and thyroid.

anterior pituitary are administered intramuscularly (IM), subcutaneously, or intranasally because their peptidyl nature makes them susceptible to destruction by proteolytic enzymes of the digestive tract.

### A. Adrenocorticotrophic hormone (corticotropin)

Corticotropin-releasing hormone (CRH) is responsible for the synthesis and release of the peptide pro-opiomelanocortin by the pituitary (Figure 23.3). Adrenocorticotrophic hormone (ACTH) or *corticotropin* [kor-ti-koe-TROE-pin] is a product of the post-translational processing of this precursor polypeptide. [Note: CRH is used diagnostically to differentiate between Cushing syndrome and ectopic ACTH-producing cells.] Normally, ACTH is released from the pituitary in pulses with an overriding diurnal rhythm, with the highest concentration occurring in early morning and the lowest in late evening. Stress stimulates its secretion whereas cortisol acting via negative feedback suppresses its release.

1. **Mechanism of action:** ACTH binds to receptors on the surface of the adrenal cortex, thereby activating G protein-coupled

**Figure 23.2**

Anterior pituitary hormones. ACTH = adrenocorticotrophic hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; TSH = thyroid-stimulating hormone. Modified from B. G. Katzung, Basic and Clinical Pharmacology, Appleton and Lange (1987).

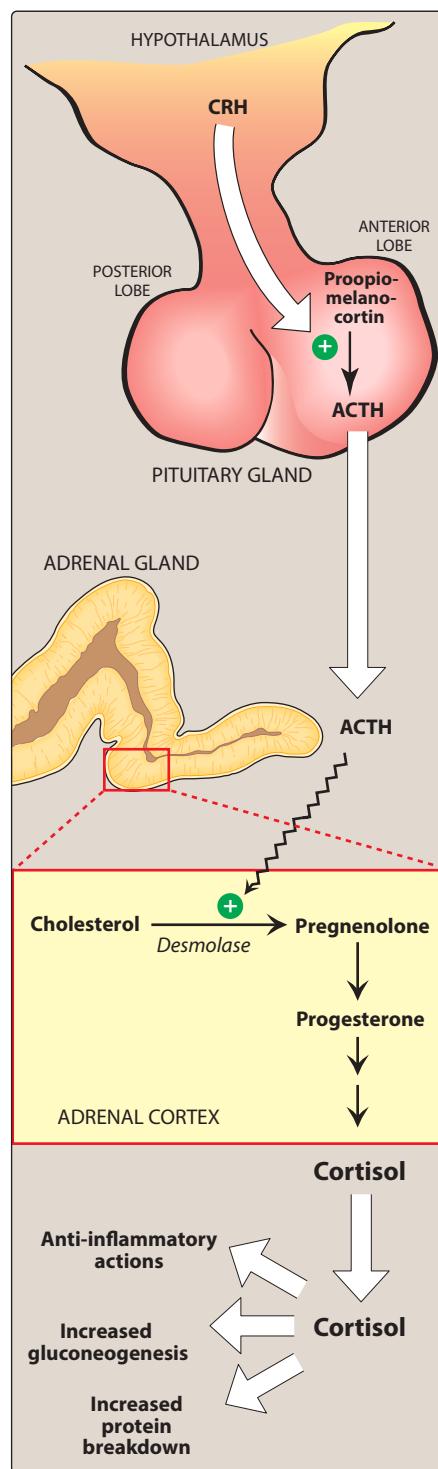
processes that ultimately stimulate the rate-limiting step in the adrenocorticosteroid synthetic pathway (cholesterol to pregnenolone; **Figure 23.3**). This pathway ends with the synthesis and release of adrenocorticosteroids and the adrenal androgens.

2. **Therapeutic uses:** The availability of synthetic adrenocorticosteroids with specific properties has limited the use of *corticotropin* mainly to serving as a diagnostic tool for differentiating between primary adrenal insufficiency (Addison disease, associated with adrenal atrophy) and secondary adrenal insufficiency (caused by inadequate secretion of ACTH by the pituitary). Therapeutic *corticotropin* preparations are extracts from the anterior pituitaries of domestic animals or synthetic human ACTH. The latter, *cosyntropin* [ko-sin-TROE-pin], is preferred for the diagnosis of adrenal insufficiency. ACTH is also used in the treatment of infantile spasms and multiple sclerosis.
3. **Adverse effects:** Short-term use of ACTH for diagnostic purposes is usually well tolerated. With longer use, toxicities are similar to glucocorticoids and include hypertension, peripheral edema, hypokalemia, emotional disturbances, and increased risk of infection.

## B. Growth hormone (somatotropin)

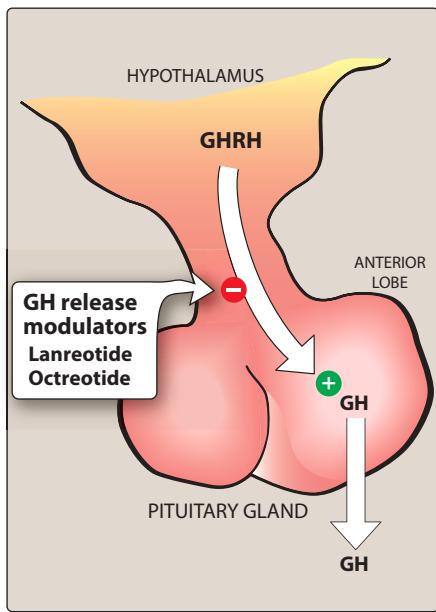
Somatotropin is released by the anterior pituitary in response to growth hormone (GH)-releasing hormone (**Figure 23.4**). Conversely, secretion of GH is inhibited by the hormone somatostatin (see below). GH is released in a pulsatile manner, with the highest levels occurring during sleep. With increasing age, GH secretion decreases, accompanied by a decrease in lean muscle mass. Somatotropin influences a wide variety of biochemical processes (for example, cell proliferation and bone growth). Synthetic human GH (*somatotropin* [soe-mah-TROE-pin]) is produced using recombinant DNA technology.

1. **Mechanism of action:** Although many physiologic effects of GH are exerted directly at its targets, others are mediated through the somatomedins—insulin-like growth factors 1 and 2 (IGF-1 and IGF-2). [Note: In acromegaly (a syndrome of excess GH due to hormone-secreting tumors), IGF-1 levels are consistently high, reflecting elevated GH.]
2. **Therapeutic uses:** *Somatotropin* is used in the treatment of GH deficiency, growth failure in children, treatment of HIV patients with cachexia, and GH replacement in adults with confirmed deficiency. [Note: GH administered to adults increases lean body mass, bone density, and skin thickness and decreases adipose tissue. Many consider GH an “antiaging” hormone. This has led to off-label use of GH by older individuals and by athletes seeking to enhance performance.] *Somatotropin* is administered by subcutaneous or IM injection. Although the half-life of GH is short (approximately 25 minutes), it induces release of IGF-1 from the liver, which is responsible for subsequent GH-like actions.
3. **Adverse effects:** Adverse effects of *somatotropin* include pain at the injection site, edema, arthralgias, myalgias, nausea, and an increased risk of diabetes. *Somatotropin* should not be used in pediatric patients with closed epiphyses, patients with diabetic retinopathy, or obese patients with Prader-Willi syndrome.

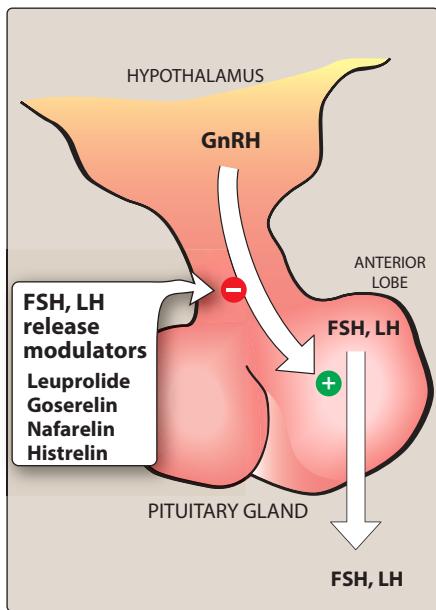


**Figure 23.3**

Secretion and actions of adrenocorticotrophic hormone (ACTH). CRH = corticotropin-releasing hormone.

**Figure 23.4**

Secretion of growth hormone (GH).  
GHRH = growth hormone-releasing hormone.

**Figure 23.5**

Secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). DA = dopamine; GnRH = gonadotropin-releasing hormone; TRH = thyrotropin-releasing hormone.

### C. Somatostatin (growth hormone-inhibiting hormone)

In the pituitary, somatostatin binds to receptors that suppress GH and thyroid-stimulating hormone release. Originally isolated from the hypothalamus, somatostatin is a small polypeptide found in neurons throughout the body as well as in the intestine, stomach, and pancreas. Somatostatin inhibits not only release of GH but also insulin, glucagon, and gastrin. *Octreotide* [ok-TREE-oh-tide] and *Lanreotide* [lan-REE-oh-tide] are synthetic analogs of somatostatin with longer half-lives. Depot formulations of these agents allow for administration every 4 weeks. They have found use in the treatment of acromegaly and in severe diarrhea/flushing episodes associated with carcinoid tumors. An intravenous infusion of *octreotide* is also used for the treatment of bleeding esophageal varices. Adverse effects of *octreotide* include bradycardia, diarrhea, abdominal pain, flatulence, nausea, and steatorrhea. Gallbladder emptying is delayed, and asymptomatic gallstones can occur with long-term treatment.

### D. Gonadotropin-releasing hormone

Pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus is essential for release of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. However, continuous administration of GnRH inhibits gonadotropin release through down-regulation of GnRH receptors on the pituitary.

Continuous administration of synthetic GnRH analogs, such as *Leuprolide* [loo-PROE-lide], is effective in suppressing production of FSH and LH (Figure 23.5).

Suppression of gonadotropins, in turn, leads to reduced production of gonadal steroid hormones (androgens and estrogens). Thus, these agents are effective in the treatment of prostate cancer, endometriosis, and precocious puberty. *Leuprolide* is also used to suppress the LH surge and prevent premature ovulation in women undergoing controlled ovarian stimulation protocols for the treatment of infertility. [Note: GnRH antagonists such as *cetorelix* (set-roE-REL-iks) and *ganirelix* (ga-niREL-iks) can also be used to inhibit LH secretion in infertility protocols]. *Goserelin*, *triptorelin*, and *nafarelin* are the long-acting GnRH agonists available for subcutaneous and intramuscular injection. These are used for the suppression of endogenous gonadotropin before ovulation induction and in endometriosis, carcinoma of prostate, etc. *Goserelin* depot (either 3.6 mg every month or 10.8 mg once in 3 months) along with an androgen antagonist *bicalutamide* is used for the treatment of prostate carcinoma. *Nafarelin* can be administered intranasally at the dose of 200 to 400 µg twice daily for the endogenous FSH and LH suppression for controlled stimulation of ovulation using externally administered FSH and LH. *Nafarelin* intranasal is also used for the reduction of uterine fibroids (leiomyoma) and endometriosis and central precocious puberty.

In women, the GnRH analogs may cause hot flushes and sweating, as well as diminished libido, depression, and ovarian cysts. They are contraindicated in pregnancy and breastfeeding. In men, they initially cause a rise in testosterone that can result in bone pain. Hot flushes, edema, gynecomastia, and diminished libido may also occur.

### E. Gonadotropins

The gonadotropins (FSH and LH) are produced in the anterior pituitary. The regulation of gonadal steroid hormones depends on these

agents. They find use in the treatment of infertility. *Menotropins* [men-oh-TROE-pin] (also known as *human menopausal gonadotropins* or *hMG*) are obtained from the urine of postmenopausal women and contain both FSH and LH. *Urofollitropin* [yoor-oh-fol-ih-TROE-pin] is FSH obtained from postmenopausal women and is devoid of LH. *Follitropin* [fol-ih-TROE-pin] *alfa* and *follitropin beta* are human FSH products manufactured using recombinant DNA technology. *Human chorionic gonadotropin (hCG)* is a placental hormone that is excreted in the urine of pregnant women. The effects of *hCG* and *choriogonadotropin* [kore-ee-oh-goe-NAD-oh-troe-pin] *alfa* (made using recombinant DNA technology) are essentially identical to those of LH. All of these hormones are injected via the IM or subcutaneous route. Injection of *hMG* or FSH products over a period of 5 to 12 days causes ovarian follicular growth and maturation, and with subsequent injection of *hCG*, ovulation occurs. Adverse effects include ovarian enlargement and possible ovarian hyperstimulation syndrome, which may be life threatening. Multiple births can occur. *Menotropin* is a preparation isolated from the urine of menopausal women containing both FSH and LH. It is used at the dose of 75 to 150 IU (each) per day. *Menotropin* or pure FSH is used for the induction of ovulation for 10 days followed by a single dose of HCG. It is used for the treatment of amenorrhea and infertility. *Urofollitropin*, a pure form of FSH, is also available for the induction of ovulation in women with polycystic ovarian syndrome.

## F. Prolactin

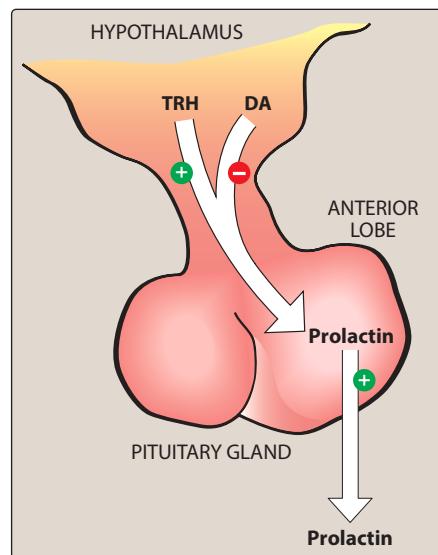
Prolactin is a peptide hormone secreted by the anterior pituitary. Its primary function is to stimulate and maintain lactation. In addition, it decreases sexual drive and reproductive function. Thyrotropin-releasing hormone stimulates the release of prolactin, and secretion is inhibited by dopamine acting at D<sub>2</sub> receptors (Figure 23.6). [Note: Drugs that act as dopamine antagonists (for example, *metoclopramide* and some antipsychotics) can increase the secretion of prolactin.] Hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is treated with D<sub>2</sub> receptor agonists, such as *bromocriptine* and *cabergoline*. Both of these agents also find use in the treatment of pituitary microadenomas. *Bromocriptine* is also indicated for the treatment of type 2 diabetes. Among their adverse effects are nausea, headache and, less frequently, psychosis.

## III. HORMONES OF THE POSTERIOR PITUITARY

In contrast to the hormones of the anterior lobe of the pituitary, those of the posterior lobe, *vasopressin* and *oxytocin*, are not regulated by releasing hormones. Instead, they are synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals, such as high plasma osmolarity or parturition. Both hormones are administered intravenously and have very short half-lives. Their actions are summarized in Figure 23.7.

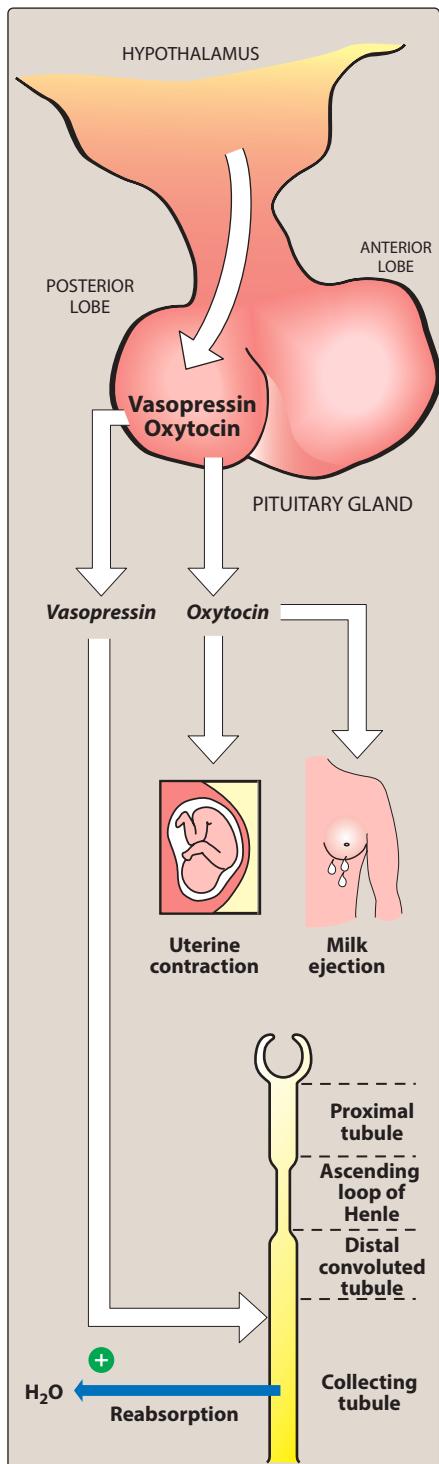
### A. Oxytocin

*Oxytocin* [ok-se-TOE-sin] is used in obstetrics to stimulate uterine contraction and induce labor. *Oxytocin* also causes milk ejection by contracting the myoepithelial cells around the mammary alveoli.



**Figure 23.6**

Secretion and action of prolactin. TRH = Thyrotropin-releasing hormone. From Preston RR, Wilson TE: Lippincott Illustrated Reviews: Physiology. Lippincott Williams and Wilkins (2013).

**Figure 23.7**

Actions of oxytocin and vasopressin.

Although toxicities are uncommon with proper drug use, hypertension, uterine rupture, water retention, and fetal death may occur. Its antidiuretic and pressor activities are much less than those of vasopressin. Desamino-oxytocin has been developed as a buccal tablet formulation for the treatment of postpartum hemorrhage, induction of labor, and breast engorgement. Its action is similar to that of oxytocin. Buccal tablets containing 25 to 50 IU of desamino-oxytocin is available for the above therapy.

### B. Vasopressin

Vasopressin [vas-oh-PRESS-in] (antidiuretic hormone) is structurally related to oxytocin. Vasopressin has both antidiuretic and vasoconstrictive effects (Figure 23.7). In the kidney, it binds to the  $V_2$  receptor to increase water permeability and reabsorption in the collecting tubules. Thus, the major use of vasopressin is to treat diabetes insipidus. It also finds use in septic shock and in controlling bleeding due to esophageal varices. Other effects of vasopressin are mediated by the  $V_1$  receptor, which is found in liver, vascular smooth muscle (where it causes constriction), and other tissues. The major toxicities of vasopressin are water intoxication and hyponatremia. Abdominal pain, tremor, and vertigo can also occur. Desmopressin [des-moe-PRESS-in], an analog of vasopressin, has minimal activity at the  $V_1$  receptor, making it largely free of pressor effects. This analog is longer acting than vasopressin and is preferred for the treatment of diabetes insipidus and nocturnal enuresis. For these indications, desmopressin is administered intranasally or orally. [Note: The nasal spray should not be used for enuresis due to reports of seizures in children using this formulation.] Local irritation may occur with the nasal spray.

## IV. THYROID HORMONES

The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for normal function. The two major thyroid hormones are triiodothyronine ( $T_3$ ; the most active form) and thyroxine ( $T_4$ ). Inadequate secretion of thyroid hormone (hypothyroidism) results in bradycardia, cold intolerance, and mental and physical slowing. In children, this can cause mental retardation and dwarfism. By contrast, excess secretion of thyroid hormones (hyperthyroidism) can cause tachycardia and cardiac arrhythmias, body wasting, nervousness, tremor, and heat intolerance.

### A. Thyroid hormone synthesis and secretion

The thyroid gland is made up of multiple follicles that consist of a single layer of epithelial cells surrounding a lumen filled with thyroglobulin (the storage form of thyroid hormone). Thyroid function is controlled by thyroid-stimulating hormone (TSH; thyrotropin), which is synthesized by the anterior pituitary (Figure 23.8). [Note: The hypothalamic thyrotropin-releasing hormone (TRH) governs the generation of TSH.] TSH action is mediated by cAMP and leads to stimulation of iodide ( $I^-$ ) uptake by the thyroid gland. Oxidation to iodine ( $I_2$ ) by a peroxidase is followed by iodination of tyrosines on thyroglobulin. [Note: Antibodies to thyroid peroxidase are diagnostic for Hashimoto

thyroiditis, a common cause of hypothyroidism.] Condensation of two diiodotyrosine residues gives rise to  $T_4$ , whereas condensation of a monoiodotyrosine residue with a diiodotyrosine residue generates  $T_3$ . The hormones are released following proteolytic cleavage of the thyroglobulin. A summary of the steps in thyroid hormone synthesis and secretion is shown in [Figure 23.9](#).

## B. Mechanism of action

Most circulating  $T_3$  and  $T_4$  is bound to thyroxine-binding globulin in the plasma. The hormones must dissociate from thyroxine-binding globulin prior to entry into cells. In the cell,  $T_4$  is enzymatically deiodinated to  $T_3$ , which enters the nucleus and attaches to specific receptors. The activation of these receptors promotes the formation of RNA and subsequent protein synthesis, which is responsible for the effects of  $T_4$ .

## C. Pharmacokinetics

Both  $T_4$  and  $T_3$  are absorbed after oral administration. Food, calcium preparations, iron salts, and aluminum-containing antacids can decrease the absorption of  $T_4$ . Deiodination is the major route of metabolism of  $T_4$ .  $T_3$  also undergoes sequential deiodination. The hormones are also metabolized via conjugation with glucuronides and sulfates and excreted into bile.

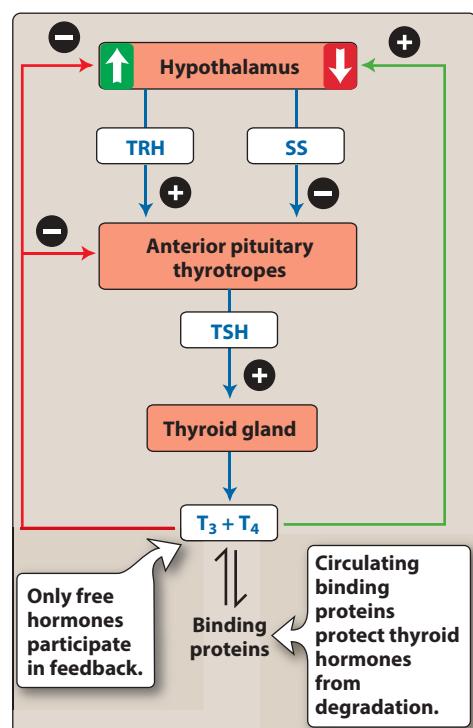
## D. Treatment of hypothyroidism

Hypothyroidism usually results from autoimmune destruction of the gland and is diagnosed by elevated TSH. *Levothyroxine* ( $T_4$ ) [leh-voh-thye-ROK-sin] is preferred over  $T_3$  [*liothyronine* [lye-oh-THYE-ro-neen]] or  $T_3/T_4$  combination products [*liotrix* [LYE-oh-trix]) for the treatment of hypothyroidism. *Levothyroxine* is better tolerated than  $T_3$  preparations and has a longer half-life. It is dosed once daily, and a steady state is achieved in 6 to 8 weeks. Toxicity is directly related to  $T_4$  levels and manifests as nervousness, palpitations and tachycardia, heat intolerance, and unexplained weight loss. Drugs that induce the cytochrome P450 enzymes, such as *phenytoin*, *rifampin*, and *phenobarbital*, accelerate metabolism of thyroid hormones and may decrease the effectiveness ([Figure 23.10](#)).

## E. Treatment of hyperthyroidism (thyrotoxicosis)

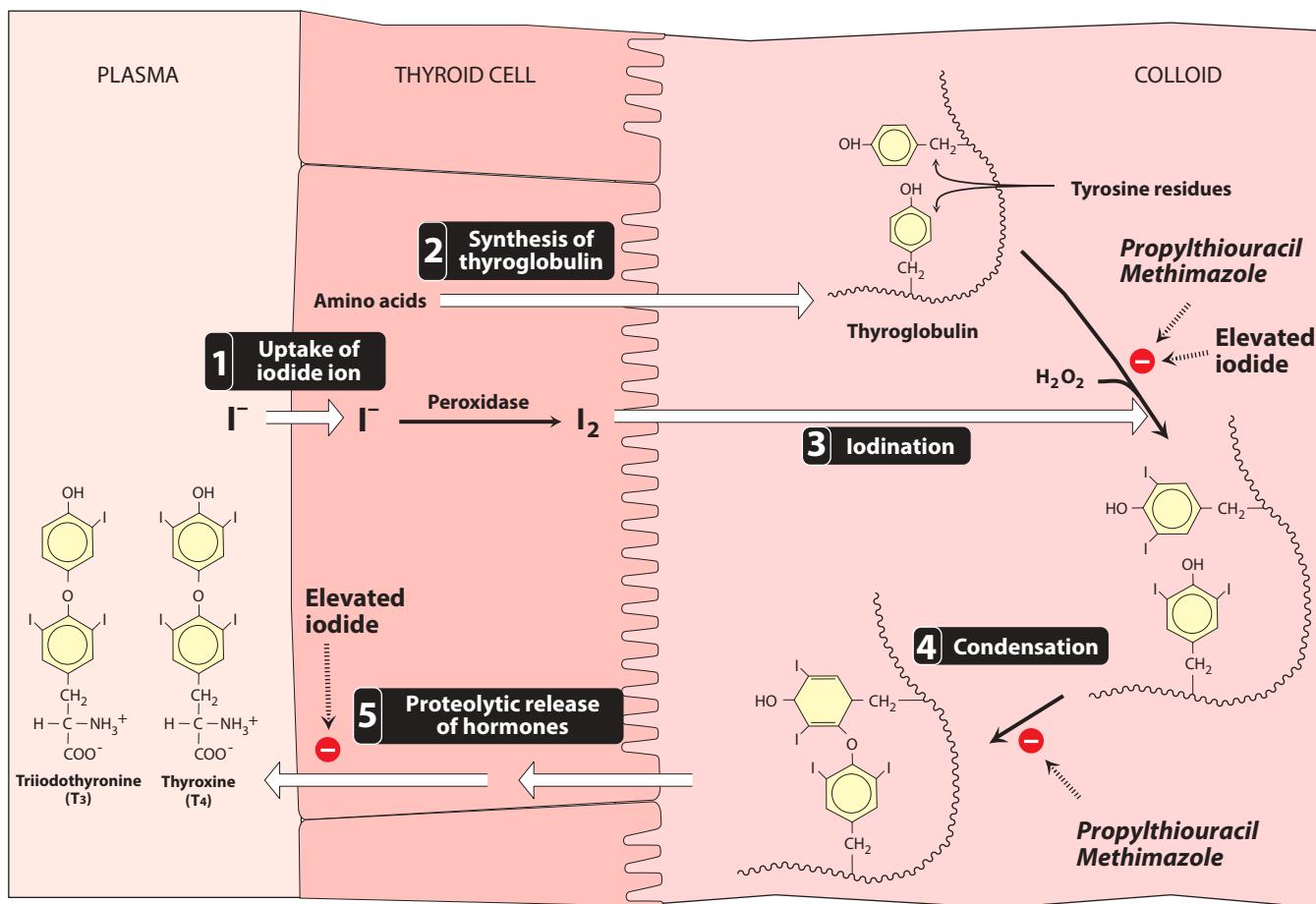
Graves disease, an autoimmune disease that affects the thyroid, is the most common cause of hyperthyroidism. In these situations, TSH levels are low due to negative feedback. [Note: Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone, which, in turn, decreases secretion of TSH.] The goal of therapy is to decrease synthesis and/or release of additional hormone. This can be accomplished by removing part or all of the thyroid gland, by inhibiting synthesis of the hormones, or by blocking release of hormones from the follicle.

- 1. Removal of the thyroid:** This can be accomplished surgically or by destruction of the gland with radioactive iodine ( $^{131}\text{I}$ ), which is

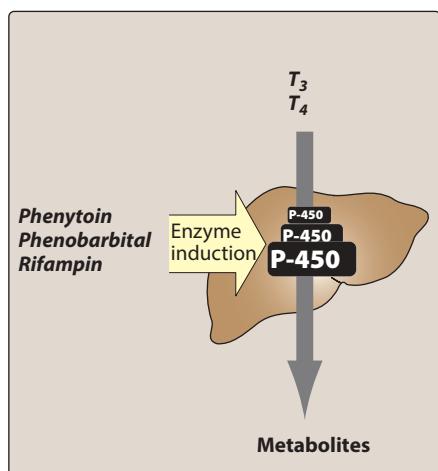


**Figure 23.8**

Feedback regulation of thyroid hormone release. SS = somatostatin;  $T_3$  = triiodothyronine;  $T_4$  = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

**Figure 23.9**

Biosynthesis of thyroid hormones.

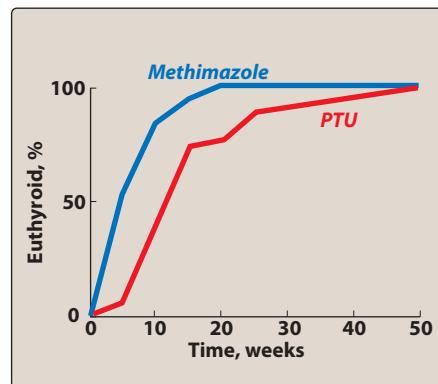
**Figure 23.10**

Enzyme induction can increase the metabolism of the thyroid hormones.  
 $T_3$  = triiodothyronine;  $T_4$  = thyroxine.

selectively taken up by the thyroid follicular cells. Most patients become hypothyroid after radioactive iodine and require treatment with levothyroxine.

- Inhibition of thyroid hormone synthesis:** The thioamides, *propylthiouracil* [proe-pil-thye-oh-YOOR-ah-sil] (*PTU*) and *methimazole* [me-THIM-ah-zole], are concentrated in the thyroid, where they inhibit both the oxidative processes required for iodination of tyrosyl groups and the condensation (coupling) of iodotyrosines to form  $T_3$  and  $T_4$  (Figure 23.9). *PTU* also blocks the peripheral conversion of  $T_4$  to  $T_3$ . [Note: These drugs have no effect on thyroglobulin already stored in the gland. Therefore, clinical effects may be delayed until thyroglobulin stores are depleted (Figure 23.11).] *Methimazole* is preferred over *PTU* because it has a longer half-life, allowing for once-daily dosing, and a lower incidence of adverse effects. However, *PTU* is recommended during the first trimester of pregnancy due to a greater risk of teratogenic effects with *methimazole*. *PTU* has been associated with hepatotoxicity and, rarely, agranulocytosis.

- 3. Blockade of hormone release:** A pharmacologic dose of *iodide* inhibits the iodination of tyrosines ("Wolff–Chaikoff effect"), but this effect lasts only a few days. More importantly, *iodide* inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood. *Iodide* is employed to treat thyroid storm or prior to surgery, because it decreases the vascularity of the thyroid gland. *Iodide*, administered orally, is not useful for long-term therapy; the thyroid ceases to respond to the drug after a few weeks. Adverse effects include sore mouth and throat, swelling of the tongue or larynx, rashes, ulcerations of mucous membranes, and metallic taste.
- 4. Thyroid storm:** Thyroid storm presents with extreme symptoms of hyperthyroidism. The treatment of thyroid storm is the same as for hyperthyroidism, except that the drugs are given in higher doses and more frequently.  $\beta$ -Blockers, such as *metoprolol* or *propranolol*, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism.

**Figure 23.11**

Time required for patients with Graves hyperthyroidism to become euthyroid with normal serum  $T_4$  and  $T_3$  concentrations. Modified from K. Okamura, H. Ikenoue, and A. Shiroozu. Reevaluation of the effects of methylmercaptoimidazole and propylthiouracil in patients with Graves' hyperthyroidism. *J. Clin. Endocrinol. Metab.* 65: 719 (1987).

## Study Questions

Choose the ONE best answer.

- 23.1 Which option is most appropriate for a patient with newly diagnosed hyperthyroidism in the first trimester of pregnancy?
- Methimazole
  - Propylthiouracil (PTU)
  - Radioactive iodine
  - Surgical removal of thyroid
- 23.2 Which drug is beneficial in the treatment of patients with acromegaly?
- Cosyntropin
  - Lanreotide
  - Oxytocin
  - Somatotropin
- 23.3 A 40-year-old female is undergoing infertility treatments. Which drug might be included in her treatment regimen?
- Cabergoline
  - Follitropin
  - Methimazole
  - Vasopressin

Correct answer = B. Methimazole is generally preferred over PTU because it has a longer half-life and lower incidence of adverse effects. However, PTU is recommended in the first trimester of pregnancy due to a greater risk of teratogenic effects with methimazole. Surgery is not ideal in a pregnant patient. Radioactive iodine is contraindicated due to potential effects on the fetus.

Correct answer = B. Lanreotide is a synthetic analog of somatostatin, which inhibits GH. Acromegaly is characterized by an excess of GH. Cosyntropin is used as a diagnostic tool in adrenal insufficiency. Oxytocin is used for induction of labor. Somatotropin is synthetic human GH, so it would not be beneficial.

Correct answer = B. Follitropin is a recombinant version of FSH that causes ovarian follicular growth and maturation. Cabergoline is a dopamine agonist that is used for hyperprolactinemia. Methimazole is the treatment of choice for hyperthyroidism. Vasopressin is an antidiuretic hormone.

- 23.4 A 29-year-old female has a TSH of 13.5 mIU/L (normal 0.5 to 4.7 mIU/L). Which agent is most appropriate to treat the TSH abnormality?
- Levothyroxine
  - Liothyronine
  - Liotrix
  - Propylthiouracil
- 23.5 Which agent is correctly paired with an appropriate clinical use of the drug?
- Desmopressin—treatment of diabetes insipidus
  - Goserelin—growth hormone deficiency
  - hCG—treatment of bleeding esophageal varices
  - Octreotide—treatment of infertility
- 23.6 Which agent is used in infertility treatment to mimic the action of luteinizing hormone and stimulate ovulation?
- Cetrorelix
  - Choriogonadotropin alfa
  - Ganirelix
  - Leuprolide
- 23.7 A patient was recently placed on levothyroxine. Which of her medications may affect the levothyroxine dosage requirements?
- Bromocriptine
  - Calcium carbonate
  - Metoprolol
  - Vitamin D
- 23.8 Which is a common side effect that should be communicated to a patient prescribed octreotide?
- Weight gain
  - Low blood sugar
  - Myalgia
  - Abdominal pain
- 23.9 Which symptom indicates that a patient may need a lower dosage of levothyroxine?
- Bradycardia
  - Cold intolerance
  - Palpitations
  - Weight gain
- 23.10 The adrenocorticosteroid synthetic pathway is responsible for the synthesis and release of cortisol. Which of the following effects is expected after cortisol is released?
- Insulin release
  - Production of inflammation
  - Increased gluconeogenesis
  - Decreased protein breakdown

Correct answer = A. This patient presents with hypothyroidism as evidenced by high TSH. Levothyroxine is preferred due to its long half-life and better tolerability. Liothyronine ( $T_3$ ) and liotrix ( $T_3/T_4$ ) are not as well tolerated. Propylthiouracil is used in the treatment of hyperthyroidism.

Correct answer = A. Goserelin is a GnRH analog that is used for the treatment of prostate cancer or endometriosis. HCG is used in the treatment of infertility. Octreotide is used in the treatment of bleeding esophageal varices.

Correct answer = B. Effects of choriogonadotropin alfa (recombinant hCG) are similar to LH and trigger ovulation. The other agents (leuprolide, a GnRH analog; cetrorelix and ganirelix, GnRH antagonists) are all used to inhibit LH secretion.

Correct answer = B. Calcium carbonate may reduce the absorption of levothyroxine. The other medications should not interact with the levothyroxine.

Correct answer = D. Common side effects of octreotide are gastrointestinal in nature and include diarrhea, abdominal pain, nausea, and steatorrhea.

Correct answer = C. Palpitations are an adverse effect of too much thyroid supplementation. The other symptoms are indicative of untreated or under-treated hypothyroidism and may require an increase in thyroid supplementation.

Correct answer = C. See Figure 23.3. Cortisol has anti-inflammatory actions, increases gluconeogenesis, and increases protein breakdown.

# Drugs for Diabetes

Karen Whalen and Cynthia Moreau

# 24

## I. OVERVIEW

The pancreas produces the peptide hormones insulin, glucagon, and somatostatin. The peptide hormones are secreted from cells in the islets of Langerhans ( $\beta$  cells produce insulin,  $\alpha$  cells produce glucagon, and  $\delta$  cells produce somatostatin). These hormones play an important role in regulating metabolic activities of the body, particularly glucose homeostasis. A relative or absolute lack of insulin, as seen in diabetes mellitus, can cause serious hyperglycemia. Left untreated, retinopathy, nephropathy, neuropathy, and cardiovascular complications may result. Administration of insulin preparations or other glucose-lowering agents (Figure 24.1) can reduce morbidity and mortality associated with diabetes.

## II. DIABETES MELLITUS

The incidence of diabetes is growing rapidly worldwide. An estimated 30.3 million people in the United States and 422 million people worldwide are afflicted with diabetes. In India, more than 62 million individuals are reported to be diabetic and it is predicted to reach 79.4 million in 2030. Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by elevated blood glucose attributed to a relative or absolute deficiency of insulin. The American Diabetes Association (ADA) recognizes four clinical classifications of diabetes: type 1 diabetes, type 2 diabetes, gestational diabetes, and diabetes due to other causes such as genetic defects or medications. Figure 24.2 summarizes the characteristics of type 1 and type 2 diabetes. Gestational diabetes is defined as carbohydrate intolerance with onset or first recognition during pregnancy.

### A. Type 1 diabetes

Type 1 diabetes most commonly afflicts children, adolescents, or young adults, but some latent forms occur later in life. The disease is characterized by an absolute deficiency of insulin due to destruction of  $\beta$  cells. Without functional  $\beta$  cells, the pancreas fails to respond to glucose, and a person with type 1 diabetes shows classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss).

- Cause:** Loss of  $\beta$ -cell function in type 1 diabetes results from autoimmune-mediated processes that may be triggered by viruses or other environmental toxins. In patients without diabetes, constant  $\beta$ -cell secretion maintains low basal levels of circulating insulin. This suppresses lipolysis, proteolysis, and glycogenolysis. A burst of insulin secretion occurs within 2 minutes after ingesting

### ORAL HYPOGLYCEMIC AGENTS

*Sulfonylureas  
Tolbutamide  
Glibenclamide  
Glipizide  
Gliclazide  
Glimepride  
Glyburide*

### BIGUANIDES

*Metformin*

### GLITINIDES

*Repaglinide  
Nateglinide*

### THIOZOLINEDIONES

*Pioglitazone  
Rosiglitazone*

### $\alpha$ -GLUCOSIDASE INHIBITORS

*Acarbose  
Miglitol  
Voglibose*

### DPP-4 INHIBITORS

*Sitagliptin  
Vildagliptin  
Saxagliptin  
Alogliptin  
Linagliptin*

### SODIUM GLUCOSE COTRANSPORTER 2 (SGLT-2) INHIBITORS

*Canagliflozin  
Dapagliflozin  
Empagliflozin  
Ertugliflozin*

**Figure 24.1**

Summary of drugs used in the treatment of diabetes.  
(Figure continues on next page)

<b>GLUCAGON-LIKE PEPTIDE-1 (GLP-1)</b>	
<i>Exenatide</i>	
<i>Liraglutide</i>	
<i>Albiglutide</i>	
<i>Dulaglutide</i>	
<i>Lixisenatide</i>	
<i>Semaglutide</i>	
<b>OTHER AGENTS</b>	
<i>Bromocriptin</i>	
<i>Colesevelam</i>	

**Figure 24.1** (Continued)

Summary of drugs used in the treatment of diabetes.

	<b>Type 1</b>	<b>Type 2</b>
Age at onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence among diagnosed diabetics	5% to 10%	90% to 95%
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β Cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

**Figure 24.2**

Comparison of type 1 and type 2 diabetes.

a meal, in response to transient increases in circulating glucose and amino acids. This lasts for up to 15 minutes, followed by the postprandial secretion of insulin. However, without functional β cells, those with type 1 diabetes can neither maintain basal secretion of insulin nor respond to variations in circulating glucose (Figure 24.3).

2. **Treatment:** A person with type 1 diabetes must rely on exogenous insulin to control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (HbA<sub>1c</sub>). [Note: HbA<sub>1c</sub> is a marker of overall glucose control and is used to monitor diabetes in clinical practice. The rate of formation of HbA<sub>1c</sub> is proportional to the average blood glucose concentration over the previous 3 months. A higher average glucose results in a higher HbA<sub>1c</sub>.] The goal of *insulin* therapy in type 1 diabetes is to maintain blood glucose as close to normal as possible and to avoid wide fluctuations in glucose. The use of home blood glucose monitors facilitates frequent self-monitoring and treatment with *insulin*.

## B. Type 2 diabetes

Type 2 diabetes accounts for greater than 90% of cases. Type 2 diabetes is influenced by genetic factors, aging, obesity, and peripheral insulin resistance, rather than autoimmune processes. The metabolic alterations are generally milder than those observed with type 1 diabetes (for example, patients with type 2 diabetes typically are not ketotic), but the long-term clinical consequences are similar.

1. **Cause:** Type 2 diabetes is characterized by a lack of sensitivity of target organs to insulin (Figure 24.4). In type 2 diabetes, the pancreas retains some β-cell function, but insulin secretion is insufficient to maintain glucose homeostasis (Figure 24.3) in the face of increasing peripheral insulin resistance. The β-cell mass may gradually decline over time in type 2 diabetes. In contrast to patients with type 1 diabetes, those with type 2 diabetes are often obese. Obesity contributes to insulin resistance, which is considered the major underlying defect of type 2 diabetes.
2. **Treatment:** The goal in treating type 2 diabetes is to maintain blood glucose within normal limits and to prevent the development of long-term complications. Weight reduction, exercise, and dietary modification decrease insulin resistance and correct hyperglycemia in some patients with type 2 diabetes. However, most patients require pharmacologic intervention with oral glucose-lowering agents. As the disease progresses, β-cell function declines and insulin therapy is often needed to achieve satisfactory glucose levels (Figure 24.5).

## III. INSULIN AND INSULIN ANALOGS

Insulin [IN-su-lin] is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds. It is synthesized as a precursor (proinsulin) that undergoes proteolytic cleavage to form insulin and C-peptide, both of which are secreted by the β cells of the pancreas. [Note: Because insulin undergoes significant hepatic and renal extraction,

plasma insulin levels may not accurately reflect insulin production. Thus, measurement of C-peptide provides a better index of insulin levels.] Insulin secretion is regulated by blood glucose levels, certain amino acids, other hormones, and autonomic mediators. Secretion is most often triggered by increased blood glucose, which is taken up by the glucose transporter into the  $\beta$  cells of the pancreas. There, it is phosphorylated by glucokinase, which acts as a glucose sensor. The products of glucose metabolism enter the mitochondrial respiratory chain and generate adenosine triphosphate (ATP). The rise in ATP levels causes a blockade of  $K^+$  channels, leading to membrane depolarization and an influx of  $Ca^{2+}$ . The increase in intracellular  $Ca^{2+}$  causes pulsatile insulin exocytosis.

### A. Mechanism of action

Exogenous insulin is administered to replace absent insulin secretion in type 1 diabetes or to supplement insufficient insulin secretion in type 2 diabetes.

### B. Pharmacokinetics

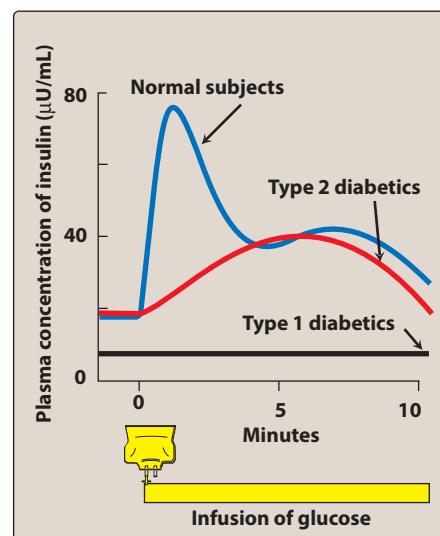
Human insulin is produced by recombinant DNA technology using strains of *Escherichia coli* or yeast that are genetically altered to contain the gene for human *insulin*. Modification of the amino acid sequence of human insulin produces insulins with different pharmacokinetic properties. *Insulin* preparations vary primarily in their onset and duration of activity. Dose, injection site, blood supply, temperature, and physical activity can also affect the onset and duration of various *insulin* preparations. Because *insulin* is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. Therefore, it is generally administered by subcutaneous injection, although an inhaled *insulin* formulation is also available. [Note: In a hyperglycemic emergency, *regular insulin* is administered intravenously (IV).] Continuous subcutaneous *insulin* infusion (also called the *insulin* pump) is another method of insulin delivery. This method of administration may be more convenient for some patients, eliminating multiple daily injections of *insulin*. The pump is programmed to deliver a basal rate of *insulin*. In addition, it allows the patient to deliver a bolus of *insulin* to cover mealtime carbohydrate intake and compensate for high blood glucose.

### C. Adverse effects

Hypoglycemia is the most serious and common adverse reaction to *insulin* (Figure 24.6). Other adverse effects include weight gain, local injection site reactions, and lipodystrophy. Lipodystrophy can be minimized by rotation of injection sites. Diabetics with renal insufficiency may require a decrease in *insulin* dose. Due to the potential for bronchospasm with inhaled *insulin*, patients with asthma, chronic obstructive pulmonary disease, and smokers should not use this formulation.

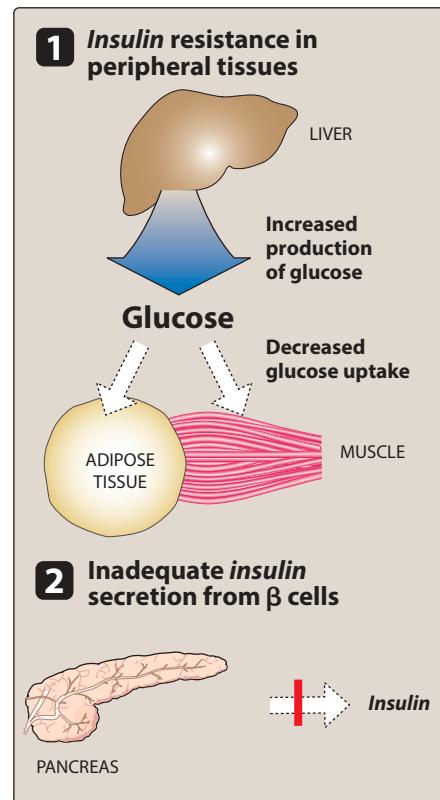
## IV. INSULIN PREPARATIONS AND TREATMENT

*Insulin* preparations are classified as rapid-, short-, intermediate-, or long-acting. Figures 24.7 and 24.8 summarize onset of action, timing of peak level, and duration of action for the various types of *insulin*. It is



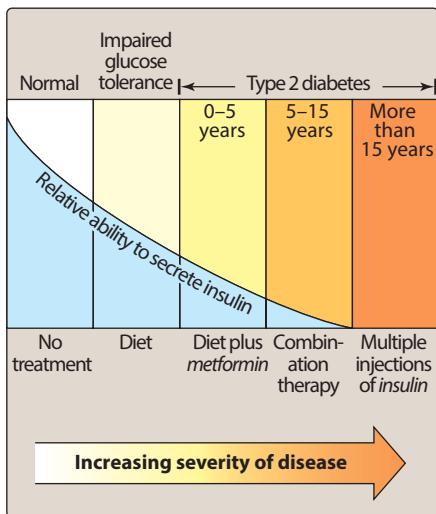
**Figure 24.3**

Release of insulin that occurs in response to an IV glucose load in normal subjects and diabetic patients.



**Figure 24.4**

Major factors contributing to hyperglycemia observed in type 2 diabetes.



**Figure 24.5**

Duration of type 2 diabetes mellitus, sufficiency of endogenous *insulin*, and recommended sequence of therapy. Modified from M. C. Riddle, Postgrad. Med. 92: 89 (1992).

important that clinicians exercise caution when adjusting *insulin* treatment, paying strict attention to the dose and type of *insulin*.

### A. Rapid-acting and short-acting insulin preparations

Five preparations fall into this category: regular *insulin*, *insulin lispro* [LIS-proe], *insulin aspart* [AS-part], *insulin glulisine* [gloo-LYSE-een], and *inhaled insulin*. *Regular insulin* is a short-acting, soluble, crystalline zinc *insulin*. *Insulin lispro*, *aspart*, and *glulisine* are classified as rapid-acting insulins. Modification of the amino acid sequence of *regular insulin* produces analogs that are rapid-acting insulins. This modification results in more rapid absorption, a quicker onset, and a shorter duration of action after subcutaneous injection. Peak levels of *insulin lispro* are seen at 30 to 90 minutes, compared with 50 to 120 minutes for *regular insulin*. *Insulin aspart* and *insulin glulisine* have pharmacokinetic and pharmacodynamic properties similar to those of *insulin lispro*. *Inhaled insulin* is also considered rapid-acting. This dry powder formulation is inhaled and absorbed through pulmonary tissue, with peak levels achieved within 45 to 60 minutes. Rapid- or short-acting insulins are administered to mimic the prandial (mealtime) release of *insulin* and to control postprandial glucose. They may also be used in cases where swift correction of elevated glucose is needed. Rapid- and short-acting insulins are usually used in conjunction with a long-acting basal *insulin* that provides control of fasting glucose. *Regular insulin* should be injected subcutaneously 30 minutes before a meal, whereas rapid-acting insulins are administered in the 15 minutes proceeding a meal or within 15 to 20 minutes after starting a meal. Rapid-acting *insulin* suspensions are commonly used in external *insulin* pumps, and they are suitable for IV administration, although *regular insulin* is most commonly used when the IV route is needed.

### B. Intermediate-acting insulin

*Neutral protamine hagedorn (NPH) insulin* is an intermediate-acting *insulin* formed by the addition of zinc and protamine to *regular insulin*. [Note: Another name for this preparation is *insulin isophane*.] The combination with protamine forms a complex that is less soluble, resulting in delayed absorption and a longer duration of action. *NPH insulin* is used for basal (fasting) control in type 1 or 2 diabetes and is usually given along with rapid- or short-acting *insulin* for mealtime control. *NPH insulin* should be given only subcutaneously (**never IV**), and it should not be used when rapid glucose lowering is needed (for example, diabetic ketoacidosis). Figure 24.9 shows common regimens that use combinations of insulins.

### C. Long-acting insulin preparations

The isoelectric point of *insulin glargine* [GLAR-geen] is lower than that of human *insulin*, leading to formation of a precipitate at the injection site that releases *insulin* over an extended period. It has a slower onset than *NPH insulin* and a flat, prolonged hypoglycemic effect with no peak (Figure 24.8). *Insulin detemir* [deh-TEE-meer] has a fatty acid side chain that enhances association with albumin. Slow dissociation from albumin results in long-acting properties similar to those of

*insulin glargine*. *Insulin degludec* [de-GLOO-dek] remains in solution at physiologic pH, with a slow release over an extended period. It has the longest half-life of the long-acting insulins. As with *NPH insulin*, *insulin glargine*, *insulin detemir*, and *insulin degludec* are used for basal control and should only be administered subcutaneously. Long-acting *insulins* should not be mixed in the same syringe with other insulins, because doing so may alter the pharmacodynamic profile.

#### D. Insulin combinations

Various premixed combinations of human insulins, such as 70% *NPH insulin* plus 30% regular insulin (Figure 24.9), or 50% of each of these are also available. Use of premixed combinations decreases the number of daily injections but makes it more difficult to adjust individual components of the *insulin* regimen.

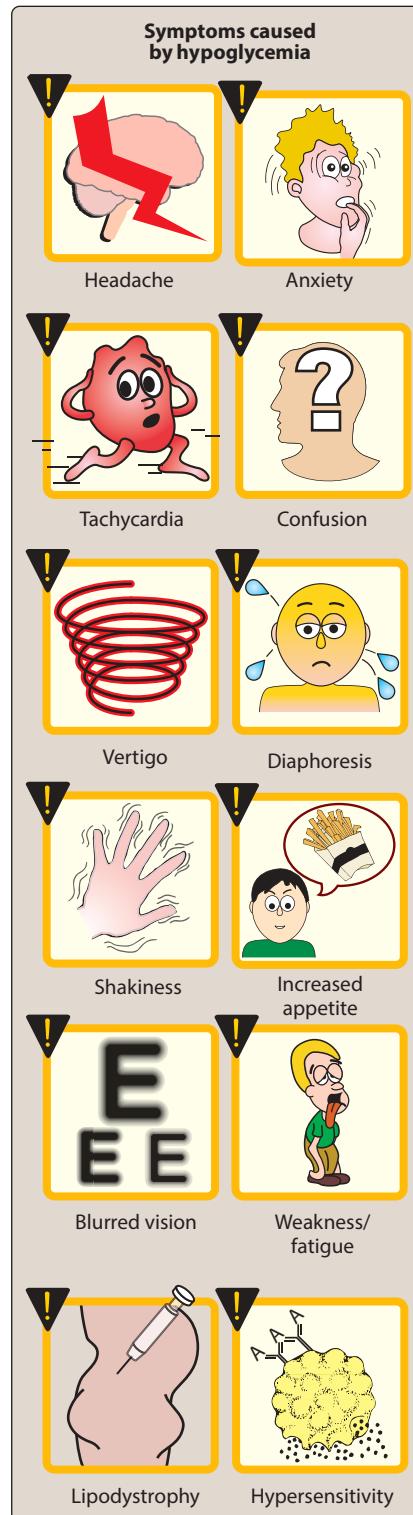
#### E. Insulin delivery devices

Many different types of *insulin* delivery devices are available which include syringes, pens, pumps, jet injectors, and oral insulin.

- Syringes:** Direct subcutaneous *insulin* injection remains the most common form of delivery, using an appropriate needle and syringe. Syringes come in a variety of sizes, with different-sized barrels, different needle gauges (thicknesses), and different needle lengths. The higher the gauge, the finer (thinner) the needle.
- Pens:** Prefilled, plastic, disposable *insulin* pens have a self-contained *insulin* cartridge. Several different types of *insulin* are sold in prefilled pens. *Insulin* pen is a highly improvised system which is patient friendly and reduces the requirement of a trained professional for the injection of *insulin*.
- Durable pens.** *Insulin* pens that use replaceable cartridges of *insulin* are also available. Needles and other “sharps” (such as lancets) should be disposed off in a way that reduces the risk of accidental needle sticks.
- Pumps:** *Insulin* pumps are programmable devices which are connected to a subcutaneously placed cannula to enable continuous delivery of *insulin* (fast-acting insulin) based on requirements. External pumps have benefits over multiple injections and conventional *insulin* therapy only in specific subgroups of patients, for example, those with recurrent severe hypoglycemia. These pumps are implanted and have the option of refilling the reservoir percutaneously.
- Jet injectors:** They are a type of injecting syringe that uses a high-pressure narrow jet of the injection liquid to penetrate the epidermis instead of a hypodermic needle.
- Other routes:** Intranasal and oral routes were attempted; however, they have been withdrawn from the market.

#### F. Storage, injection sites, and administration

*Insulin* should be stored correctly to maintain its efficacy and the patient should be educated about its correct storage, handling, and sharp's disposal as part of his/her education about *insulin* therapy.



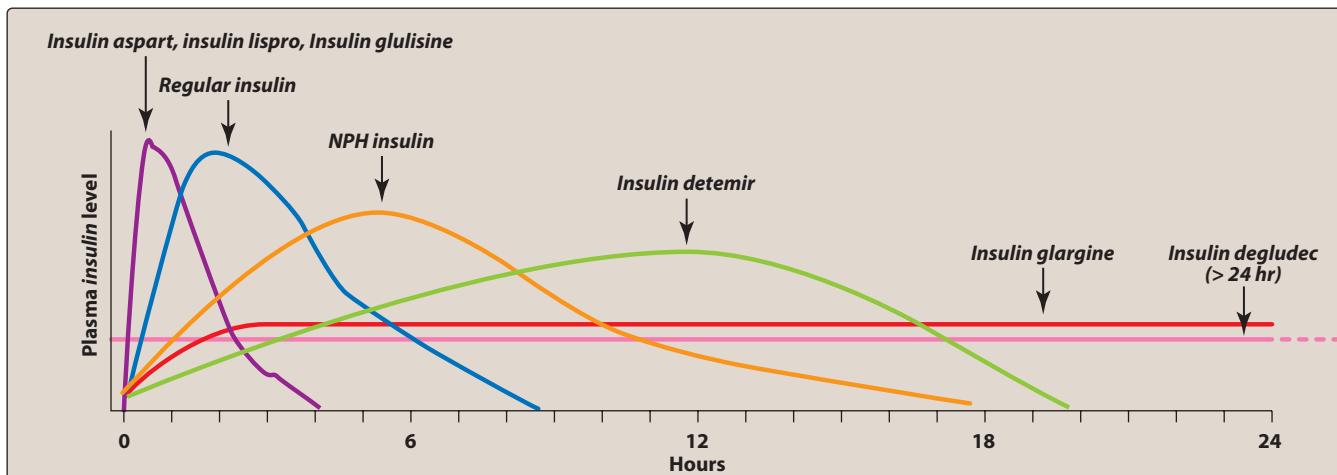
**Figure 24.6**

Adverse effects observed with *insulin*. [Note: Lipodystrophy is a local atrophy or hypertrophy of subcutaneous fatty tissue at the site of injections.]

TYPE OF INSULIN	ONSET	PEAK	DURATION	APPEARANCE	USE
<b>Fast-acting:</b>					
Regular insulin	½–1 hours	2–4 hours	6–8 hours	Clear	Usually taken subcutaneously about 30 minutes before a meal to cover blood glucose elevation during meals and snacks and to correct high blood sugars  The larger the dose, the faster the onset of action, but the longer the time to peak effect and the longer the duration of the effect  Used with long-acting insulin
Ultra short acting—Lispro/Aspart/Glulisine	<15 minutes	1–2 hours	4–6 hours	Clear	Usually taken subcutaneously immediately before a meal or after a meal to cover the blood glucose elevation during meals and snacks and to correct high blood sugars  With all doses, large and small, the onset of action and the time to peak effect are similar  Used with long-acting insulin
Inhaled insulin (not used clinically)	1 minute	12 minutes	1.5–4 hours	Oral inhaled powder; available as cartridge	Inhaled at the beginning of the meal to reduce blood sugar levels caused by eating  Contraindications—lung problems (COPD, asthma, and smokers)
<b>Intermediate-acting:</b>					
Neutral Protamine Hagedoer (NPH) insulin	1–2 hours	6–10 hours	12+ hours	Cloudy	Used to control the blood sugar overnight, while fasting and between meals  Often combined with rapid- or short-acting insulin and usually taken subcutaneously twice a day
Biphasic Insulin 30/70, insulin 50/50, etc.  Fixed mixtures of soluble and isophane insulin	30 minutes	2–12 hours  Biphasic onset and duration of action	12–16 hours	Cloudy	Used to control the blood sugar overnight, while fasting and between meals  Covers the blood glucose elevations when rapid-acting insulins stop working  Usually taken twice a day  Injected subcutaneously immediately before eating or after food
<b>Long-acting:</b>					
Detemir	1 hour	No defined peak  Max effect in 5 hours	12–24 hours	Clear	Used to control the blood sugar overnight, while fasting and between meals
Glargine	1.5 hours	No defined peak  Max effect in 5 hours	24 hours	Clear	Taken subcutaneously once or twice a day at the same time every day, for example, before breakfast and before bed  Often combined, when needed, with rapid- or short-acting insulin  Lowers blood glucose levels when rapid-acting insulins stop working

**Figure 24.7**

Insulin and insulin analogs available.



**Figure 24.8**

Onset and duration of action of human *insulin* and *insulin* analogs. NPH = neutral protamine Hagedorn. Modified from I. R. Hirsch. Insulin analogues. *N. Engl. J. Med.* 352: 174 (2005).

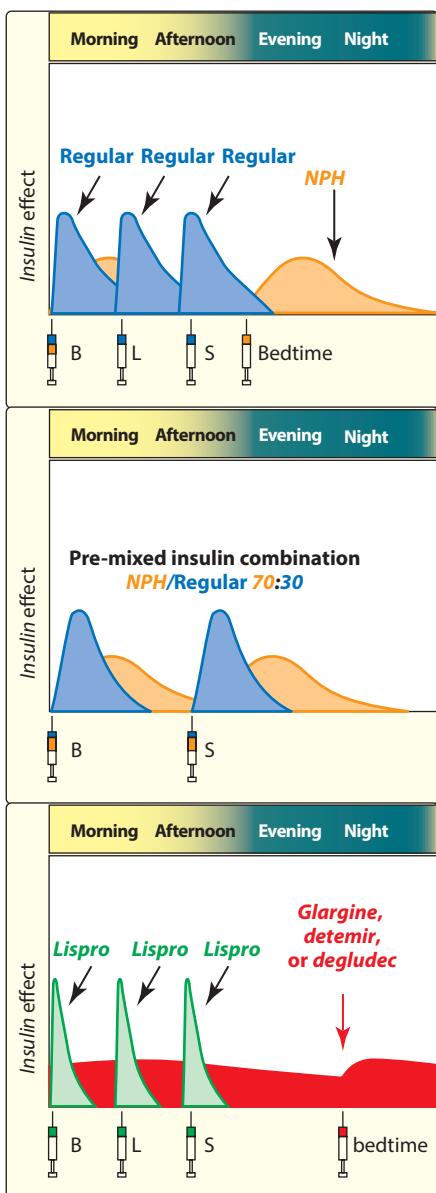
Unopened *insulin* vials should be stored in the refrigerator at 2°C to 8°C. *Insulin* vials in use can be stored out of the refrigerator away from a source of heat or light, namely, in the patient's medication drawer/purse. Hyperglycemia can occur on using incorrectly stored *insulin* and expired *insulin*.

**Insulin is a high-alert medication.** Any error in dosage or mixing of the wrong type of *insulin* can lead to devastating effects on the patients. Do not mix long-acting analogs with other *insulins* and inject at the same site. To avoid errors before injecting, be clear about the color and ensure that they are not mistaken for rapid- or short-acting insulins. Look-alike medicine alert policies should be initiated. For example, consider storing them in a different part of the refrigerator and clearly flagging them with a “look-alike” medication alert label. Carefully check the dose of *NovoMix 30* and *Humalog Mix 25 or 50* to be administered and do not mistake the numbers in the name of the *insulin* for the *insulin* dose.

**Injection site.** The abdominal wall is the common injection site. The back of arm, the outer side of the thigh, and the upper buttocks are also used for injection. Injection sites should be rotated frequently and the same general location should be followed at the same time each day. The injection site should be clean.

## G. Standard treatment versus intensive treatment

Standard *insulin* therapy involves twice-daily injections. In contrast, intensive treatment utilizes three or more injections daily with frequent monitoring of blood glucose levels. The ADA recommends a target mean blood glucose level of 154 mg/dL or less ( $\text{HbA}_{1\text{c}} \leq 7\%$ ) for most patients, and intensive treatment is more likely to achieve this goal. The frequency of hypoglycemic episodes, coma, and seizures is higher with intensive *insulin* regimens (Figure 24.10A). However, patients on intensive therapy show a significant reduction in microvascular complications of diabetes such as retinopathy,

**Figure 24.9**

Examples of three regimens that provide both prandial and basal *insulin* replacement. B = breakfast; L = lunch; S = supper. NPH = neutral protamine Hagedorn.

nephropathy, and neuropathy compared to patients receiving standard care (Figure 24.10B). Intensive therapy should not be recommended for patients with long-standing diabetes, significant microvascular complications, advanced age, and hypoglycemic unawareness.

## V. SYNTHETIC AMYLIN ANALOG

Amylin is a hormone that is cosecreted with *insulin* from  $\beta$  cells following food intake. It delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety. *Pramlintide* [PRAM-lin-tide] is a synthetic amylin analog that is indicated as an adjunct to mealtime *insulin* therapy in patients with type 1 and type 2 diabetes. *Pramlintide* is administered by subcutaneous injection immediately before meals. When *pramlintide* is initiated, the dose of mealtime *insulin* should be decreased by 50% to avoid a risk of severe hypoglycemia. Other adverse effects include nausea, anorexia, and vomiting. *Pramlintide* may not be mixed in the same syringe with *insulin*, and it should be avoided in patients with diabetic gastroparesis (delayed stomach emptying), cresol hypersensitivity, or hypoglycemic unawareness.

## VI. GLUCAGON-LIKE PEPTIDE RECEPTOR AGONISTS

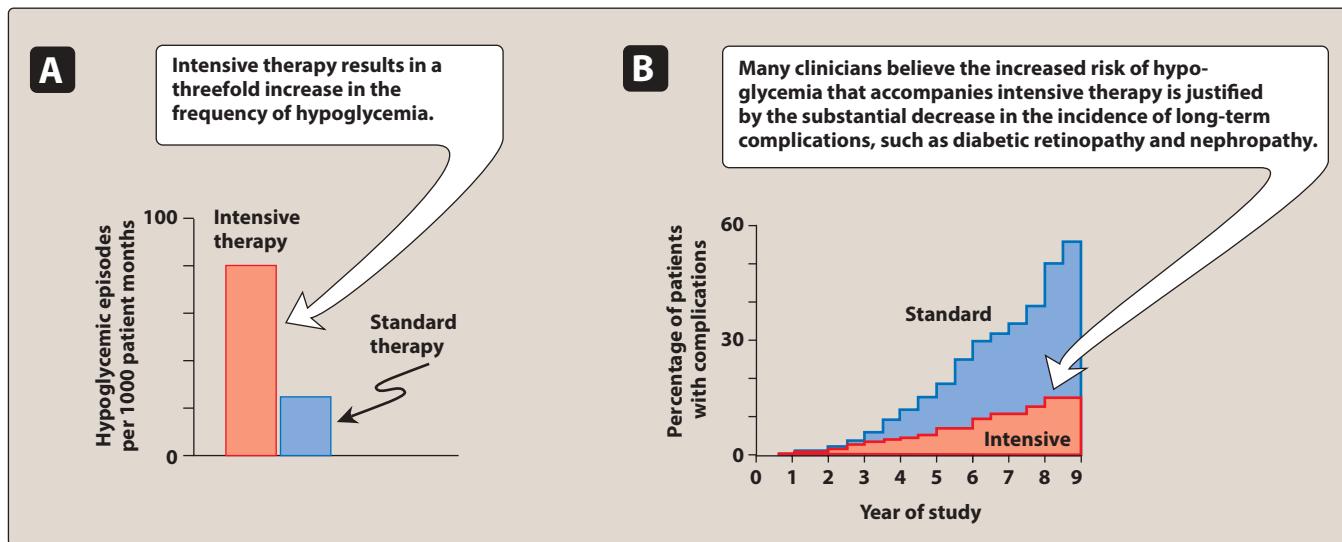
Oral intake of glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given IV. This effect is referred to as the “incretin effect” and is markedly reduced in type 2 diabetes. The incretin effect occurs because the gut releases incretin hormones, notably glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, in response to a meal. Incretin hormones are responsible for 60% to 70% of postprandial insulin secretion. *Albiglutide* [al-bi-GLOO-tide], *dulaglutide* [doo-la-GLOO-tide], *exenatide* [EX-e-nah-tide], *liraglutide* [LIR-a-GLOO-tide], *lixisenatide* [lix-i-SEN-a-tide], and *semaglutide* [sem-a-GLOO-tide] are injectable GLP-1 receptor agonists used for the treatment of type 2 diabetes. *Liraglutide* is also approved to reduce the risk of cardiovascular events and cardiovascular mortality in patients with type 2 diabetes and cardiovascular disease. Two premixed preparations of long-acting insulins and GLP-1 receptor agonists are available: *insulin glargine* plus *lixisenatide* and *insulin degludec* plus *liraglutide*. Use of these combinations may decrease daily insulin requirements and the number of daily injections.

### A. Mechanism of action

These agents are analogs of GLP-1 that exert their activity by improving glucose-dependent insulin secretion, slowing gastric emptying time, reducing food intake by enhancing satiety (a feeling of fullness), decreasing postprandial glucagon secretion, and promoting  $\beta$ -cell proliferation. Consequently, postprandial hyperglycemia is reduced,  $\text{HbA}_{1\text{c}}$  levels decline, and weight loss may occur.

### B. Pharmacokinetics

GLP-1 receptor agonists are administered subcutaneously, since they are polypeptides. *Albiglutide*, *dulaglutide*, *liraglutide*, and *semaglutide*

**Figure 24.10**

**A.** Effect of tight glucose control on hypoglycemic episodes in a population of patients with type 1 diabetes receiving intensive or standard therapy. **B.** Effect of standard and intensive care on the long-term complications of diabetes. Modified from O. B. Crofford. Diabetes control and complications. Annu. Rev. Med. 46: 267 (1995).

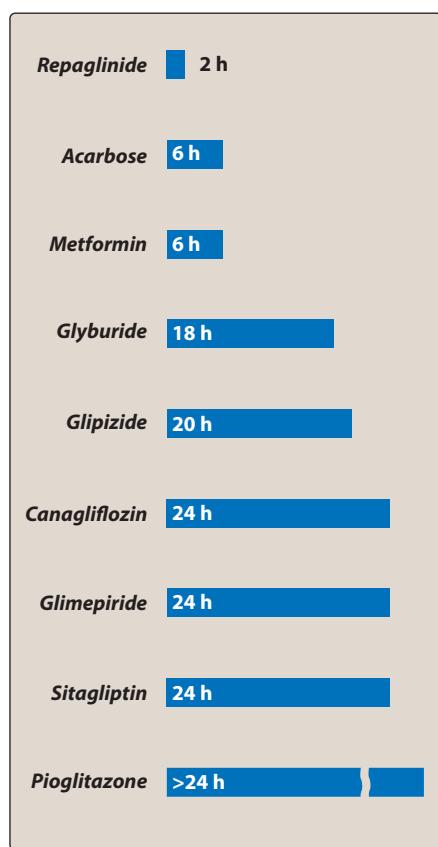
are considered long-acting GLP-1 receptor agonists. *Albiglutide*, *dulaglutide*, and *semaglutide* are dosed once weekly, while *liraglutide* is available as a once-daily injection. *Lixisenatide* is a short-acting GLP-1 receptor agonist that is dosed once daily. *Exenatide* is available as both a short-acting (dosed twice daily) and an extended-release preparation (dosed once weekly). *Exenatide* should be avoided in patients with severe renal impairment.

### C. Adverse effects

The main adverse effects of the incretin mimetics consist of nausea, vomiting, diarrhea, and constipation. GLP-1 receptor agonists have been associated with pancreatitis and should be avoided in patients with chronic pancreatitis. Long-acting agents have been associated with thyroid C-cell tumors in rodents. It is unknown if GLP-1 receptor agonists cause these tumors or thyroid carcinoma in humans, although they are contraindicated in patients with a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.

## VII. ORAL HYPOGLYCEMIC AGENTS (OHA)

Oral agents are useful in the treatment of patients who have type 2 diabetes that is not controlled with diet. Patients who developed diabetes after age 40 and have had diabetes less than 5 years are most likely to respond well to oral glucose-lowering agents. Patients with long-standing disease may require a combination of oral agents with or without *insulin* to control hyperglycemia. Figure 24.11 summarizes the duration of action of some of the oral glucose-lowering drugs, and Figure 24.12 illustrates some of the common adverse effects.

**Figure 24.11**

Duration of action of some oral hypoglycemic agents.

## A. Sulfonylureas

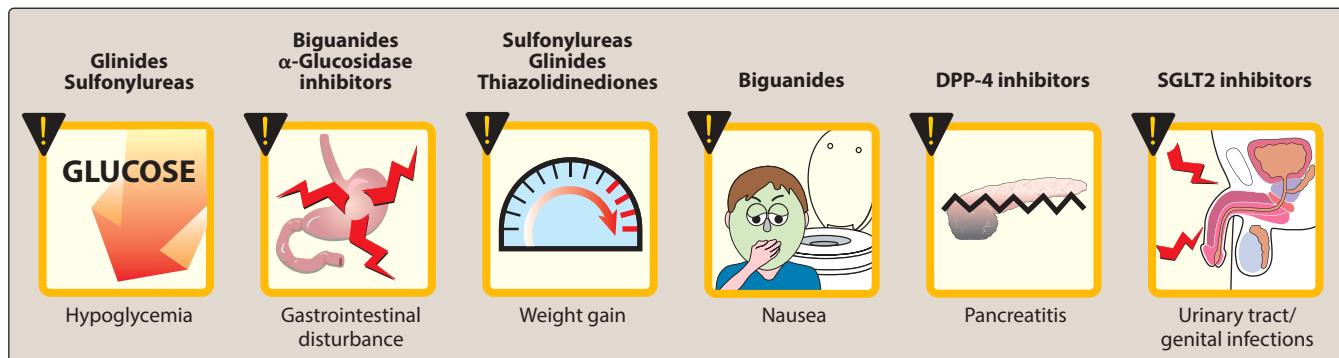
These agents are classified as insulin secretagogues, because they promote insulin release from the  $\beta$  cells of the pancreas. The sulfonylureas most used in clinical practice are the second-generation drugs *glybenclamide* [GLYB-encla-mide], *glyburide* [GLYE-byoor-ide], *glipizide* [GLIP-ih-zide], and *glimepiride* [GLYE-me-pih-ride].

- Mechanism of action:** These agents stimulate insulin release from the  $\beta$  cells of the pancreas. Sulfonylureas block ATP-sensitive  $K^+$  channels, resulting in depolarization,  $Ca^{2+}$  influx, and insulin exocytosis. In addition, sulfonylureas may reduce hepatic glucose production and increase peripheral insulin sensitivity.
- Pharmacokinetics:** Given orally, these drugs bind to serum proteins, are metabolized by the liver, and are excreted in the urine and feces. The duration of action ranges from 12 to 24 hours.
- Adverse effects:** Adverse effects of the sulfonylureas include hypoglycemia, hyperinsulinemia, and weight gain. They should be used with caution in hepatic or renal insufficiency, since accumulation of sulfonylureas may cause hypoglycemia. Renal impairment is a particular problem for *glybenclamide*, as it may increase the duration of action and increase the risk of hypoglycemia significantly. *Glipizide* or *glimepiride* are safer options in renal dysfunction and in elderly patients. [Figure 24.13](#) summarizes some drug interactions with sulfonylureas.

## B. Glinides

This class of agents includes *repaglinide* [re-PAG-lin-ide] and *nateglinide* [nuh-TAY-gli-nide]. Glinides are also considered insulin secretagogues.

- Mechanism of action:** Like the sulfonylureas, the glinides stimulate insulin secretion. In contrast to the sulfonylureas, the glinides have a rapid onset and a short duration of action. They are particularly effective in the early release of insulin that occurs after a meal and are categorized as postprandial glucose regulators. Glinides should not be used in combination with sulfonylureas due to overlapping mechanisms of action and increased risk of serious hypoglycemia.

**Figure 24.12**

Some adverse effects observed with oral hypoglycemic agents.

2. **Pharmacokinetics:** Glinides should be taken prior to a meal and are well absorbed after oral administration. Both glinides are metabolized to inactive products by cytochrome P450 3A4 (CYP3A4; see Chapter 1) in the liver and are excreted through the bile.
3. **Adverse effects:** Although glinides cause hypoglycemia and weight gain, the incidence is lower than that with sulfonylureas. By inhibiting hepatic metabolism, the lipid-lowering drug *gemfibrozil* may significantly increase the effects of *repaglinide*, and concurrent use is contraindicated. These agents should be used with caution in patients with hepatic impairment.

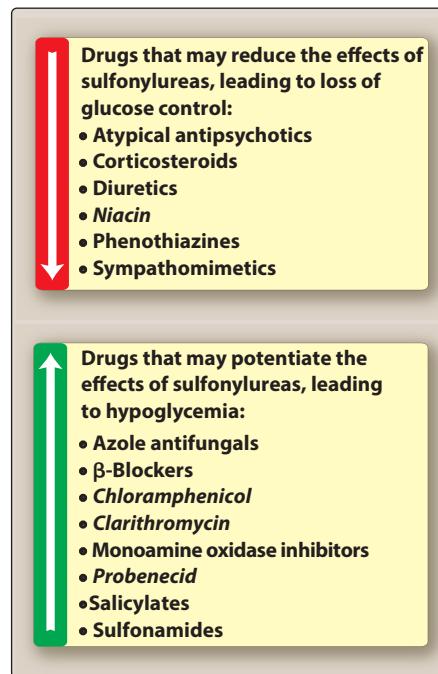
### C. Biguanides

*Metformin* [met-FOR-min], the only biguanide, is classified as an insulin sensitizer. It increases glucose uptake and use by target tissues, thereby decreasing insulin resistance. Unlike sulfonylureas, *metformin* does not promote insulin secretion. Therefore, the risk of hypoglycemia is far less than that with sulfonylureas. *Metformin* is also useful in the treatment of polycystic ovary syndrome, as it reduces insulin resistance seen in this disorder.

1. **Mechanism of action:** The main mechanism of action of *metformin* is reduction of hepatic gluconeogenesis. [Note: Excess glucose produced by the liver is a major source of high blood glucose in type 2 diabetes, accounting for high fasting blood glucose.] *Metformin* also slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization. Weight loss may occur because *metformin* causes loss of appetite. The ADA recommends *metformin* as the initial drug of choice for type 2 diabetes. *Metformin* may be used alone or in combination with other oral agents or *insulin*. Hypoglycemia may occur when *metformin* is taken in combination with *insulin* or insulin secretagogues, so adjustment in dosage may be required.
2. **Pharmacokinetics:** *Metformin* is well absorbed after oral administration, is not bound to serum proteins, and is not metabolized. Excretion is via the urine.
3. **Adverse effects:** These are largely gastrointestinal, including diarrhea, nausea, and vomiting. These effects can be alleviated by titrating the dose of *metformin* slowly and administering doses with meals. *Metformin* is contraindicated in renal dysfunction due to the risk of lactic acidosis. It should be discontinued in cases of acute myocardial infarction, exacerbation of heart failure, sepsis, or other disorders that can cause acute renal failure. *Metformin* should be used with caution in patients older than 80 years and in those with heart failure or alcohol abuse. It should be temporarily discontinued in patients undergoing procedures requiring IV radiographic contrast. Rarely, potentially fatal lactic acidosis has occurred. Long-term use may be associated with vitamin B<sub>12</sub> deficiency and periodic measurement of vitamin B<sub>12</sub> levels is recommended, especially in patients with anemia or peripheral neuropathy.

### D. Thiazolidinediones

The thiazolidinediones (TZDs) are also insulin sensitizers. The two agents in this class are *pioglitazone* [pye-oh-GLI-ta-zone] and



**Figure 24.13**

Drugs interacting with sulfonylureas.

*rosiglitazone* [roe-si-GLIH-ta-zone]. Although insulin is required for their action, the TZDs do not promote its release from the  $\beta$  cells, so hyperinsulinemia is not a risk.

1. **Mechanism of action:** The TZDs lower insulin resistance by acting as agonists for the peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ), a nuclear hormone receptor. Activation of PPAR $\gamma$  regulates the transcription of several insulin-responsive genes, resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle. The TZDs can be used as monotherapy or in combination with other glucose-lowering agents or *insulin*. The dose of *insulin* may have to be lowered when used in combination with these agents. The ADA recommends *pioglitazone* as a second- or third-line agent for type 2 diabetes. *Rosiglitazone* is less utilized due to concerns regarding cardiovascular adverse effects.
2. **Pharmacokinetics:** *Pioglitazone* and *rosiglitazone* are well absorbed after oral administration and are extensively bound to serum albumin. Both undergo extensive metabolism by different CYP450 isozymes (see Chapter 1). Some metabolites of *pioglitazone* have activity. Renal elimination of *pioglitazone* is negligible, with the majority of active drug and metabolites excreted in the bile and eliminated in the feces. Metabolites of *rosiglitazone* are primarily excreted in the urine. No dosage adjustment is required in renal impairment.
3. **Adverse effects:** Liver toxicity has occasionally been reported with these drugs, and baseline and periodic monitoring of liver function is recommended. Weight gain can occur because TZDs may increase subcutaneous fat and cause fluid retention. [Note: Fluid retention can worsen heart failure. These drugs should be avoided in patients with severe heart failure.] TZDs have been associated with osteopenia and increased fracture risk in women. Pioglitazone may also increase the risk of bladder cancer. Additionally, *rosiglitazone* carries a boxed warning about the potential increased risk of myocardial infarction and angina with use of this agent.

## E. $\alpha$ -Glucosidase inhibitors

*Acarbose* [AY-car-bose] and *miglitol* [MIG-li-tol] are oral agents used for the treatment of type 2 diabetes.

1. **Mechanism of action:** Located in the intestinal brush border,  $\alpha$ -glucosidase enzymes break down carbohydrates into glucose and other simple sugars that can be absorbed. *Acarbose* and *miglitol* reversibly inhibit  $\alpha$ -glucosidase enzymes. When taken at the start of a meal, these drugs delay the digestion of carbohydrates, resulting in lower postprandial glucose levels. Since they do not stimulate insulin release or increase insulin sensitivity, these agents do not cause hypoglycemia when used as monotherapy. However, when used with insulin secretagogues or *insulin*, hypoglycemia may develop. [Note: It is important that hypoglycemia in this context be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs.]
2. **Pharmacokinetics:** *Acarbose* is poorly absorbed. It is metabolized primarily by intestinal bacteria, and some of the metabolites are absorbed and excreted into the urine. *Miglitol* is very well

absorbed but has no systemic effects. It is excreted unchanged by the kidney.

3. **Adverse effects:** The most common adverse effects are flatulence, diarrhea, and abdominal cramping. Adverse effects limit the use of these agents in clinical practice. Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

## F. Dipeptidyl peptidase-4 inhibitors

*Alogliptin* [al-oh-GLIP-tin], *linagliptin* [lin-a-GLIP-tin], *saxagliptin* [sax-a-GLIP-tin], and *sitagliptin* [si-ta-GLIP-tin] are oral dipeptidyl peptidase-4 (DPP-4) inhibitors used for the treatment of type 2 diabetes.

1. **Mechanism of action:** These drugs inhibit the enzyme DPP-4, which is responsible for the inactivation of incretin hormones such as GLP-1. Prolonging the activity of incretin hormones increases release of insulin in response to meals and reduces inappropriate secretion of glucagon. DPP-4 inhibitors may be used as monotherapy or in combination with sulfonylureas, *metformin*, TZDs, or *insulin*. Treatment guidelines do not recommend the combination of DPP-4 inhibitors with GLP-1 receptor agonists for management of diabetes due to overlapping mechanisms and toxicity. Unlike GLP-1 receptor agonists, these drugs do not cause satiety or fullness, and are weight neutral.
2. **Pharmacokinetics:** The DPP-4 inhibitors are well absorbed after oral administration. Food does not affect the extent of absorption. *Alogliptin* and *sitagliptin* are mostly excreted unchanged in the urine. *Saxagliptin* is metabolized via CYP450 3A4/5 to an active metabolite. The primary route of elimination for *saxagliptin* and the metabolite is renal. *Linagliptin* is primarily eliminated via the enterohepatic system. All DPP-4 inhibitors except *linagliptin* require dosage adjustments in renal dysfunction.
3. **Adverse effects:** In general, DPP-4 inhibitors are well tolerated, with the most common adverse effects being nasopharyngitis and headache. Although infrequent, pancreatitis has occurred with use of DPP-4 inhibitors. Agents in this class may also increase the risk of severe, disabling joint pain. *Alogliptin* and *saxagliptin* have also been shown to increase the risk of heart failure hospitalizations and should be used with caution in patients with or at risk for heart failure.

## G. Sodium–glucose cotransporter 2 inhibitors

*Canagliflozin* [kan-a-gli-FLOE-zin], *dapagliflozin* [dap-a-gli-FLOE-zin], *empagliflozin* [em-pa-gli-FLOE-zin], and *ertugliflozin* [er-too-gli-FLOE-zin] are oral agents for the treatment of type 2 diabetes. *Empagliflozin* is also indicated to reduce the risk of cardiovascular death in patients with type 2 diabetes and cardiovascular disease.

1. **Mechanism of action:** The sodium–glucose cotransporter 2 (SGLT2) is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney. By inhibiting SGLT2, these agents decrease reabsorption of glucose, increase urinary glucose excretion, and lower blood glucose. Inhibition of SGLT2 also decreases

reabsorption of sodium and causes osmotic diuresis. Therefore, SGLT2 inhibitors may reduce systolic blood pressure. However, they are not indicated for the treatment of hypertension.

2. **Pharmacokinetics:** These agents are given once daily in the morning. *Canagliflozin* should be taken before the first meal of the day. All drugs are mainly metabolized by glucuronidation to inactive metabolites. These agents should be avoided in patients with renal dysfunction.
3. **Adverse effects:** The most common adverse effects with SGLT2 inhibitors are female genital mycotic infections (for example, vulvo-vaginal candidiasis), urinary tract infections, and urinary frequency. Hypotension has also occurred, particularly in the elderly or patients on diuretics. Thus, volume status should be evaluated prior to starting these agents. Ketoacidosis has been reported with use of SGLT2 inhibitors, and these agents should be used with caution in patients with risk factors that predispose to ketoacidosis (for example, alcohol abuse and caloric restriction related to surgery or illness).

#### H. Other agents

Both the dopamine agonist *bromocriptine* and the bile acid sequestrant *colesevelam* produce modest reductions in HbA<sub>1c</sub>. *Bromocriptine* is taken in the morning to regulate hypothalamic dopaminergic control of the circadian rhythm of pituitary hormones. This in turn reduces the insulin resistance. *Colesevelam* is a bile sequestrant which reduces cholesterol levels. The mechanism of action of glucose lowering is unknown for both of these drugs. Although *bromocriptine* and *colesevelam* are indicated for the treatment of type 2 diabetes, their modest efficacy, adverse effects, and pill burden limit their use in clinical practice. *Epalrestat* is an aldose reductase inhibitor which blocks the formation of sorbitol which is reported to cause diabetic neuropathy. It is found to increase improvement in nerve conduction and reduction in neuropathic pain.

Figure 24.14 provides a summary of the oral antidiabetic agents.

Figure 24.15 shows treatment guidelines for type 2 diabetes.

## VIII. MANAGEMENT OF DIABETES

### A. Insulin therapy

*Insulin* is a necessary part of the treatment plan for all people with type 1 diabetes and many with type 2 diabetes. Normal requirements of *insulin* are between 0.5 and 1.0 units/kg/day. The time to commence *insulin* in type 2 DM depends on the individual's blood glucose pattern, HbA<sub>1c</sub>, adherence to medicines, and complication status, especially cardiovascular and renal status and willingness to use *insulin*. Figure 24.14 depicts the treatment guidelines for type 2 diabetes. Commencing *insulin* should be a proactive decision and should not be delayed. Indications for *insulin* include the following:

- In patients with primary (markedly symptomatic and/or elevated blood glucose levels or A<sub>1c</sub>) or secondary failure to OHAs or contraindication, for example, *metformin* if creatinine is high; often as a single dose of intermediate-acting *insulin* 0.3 to 0.4 units/kg/day either before breakfast or at bedtime in combination with Tab. *Metformin*.

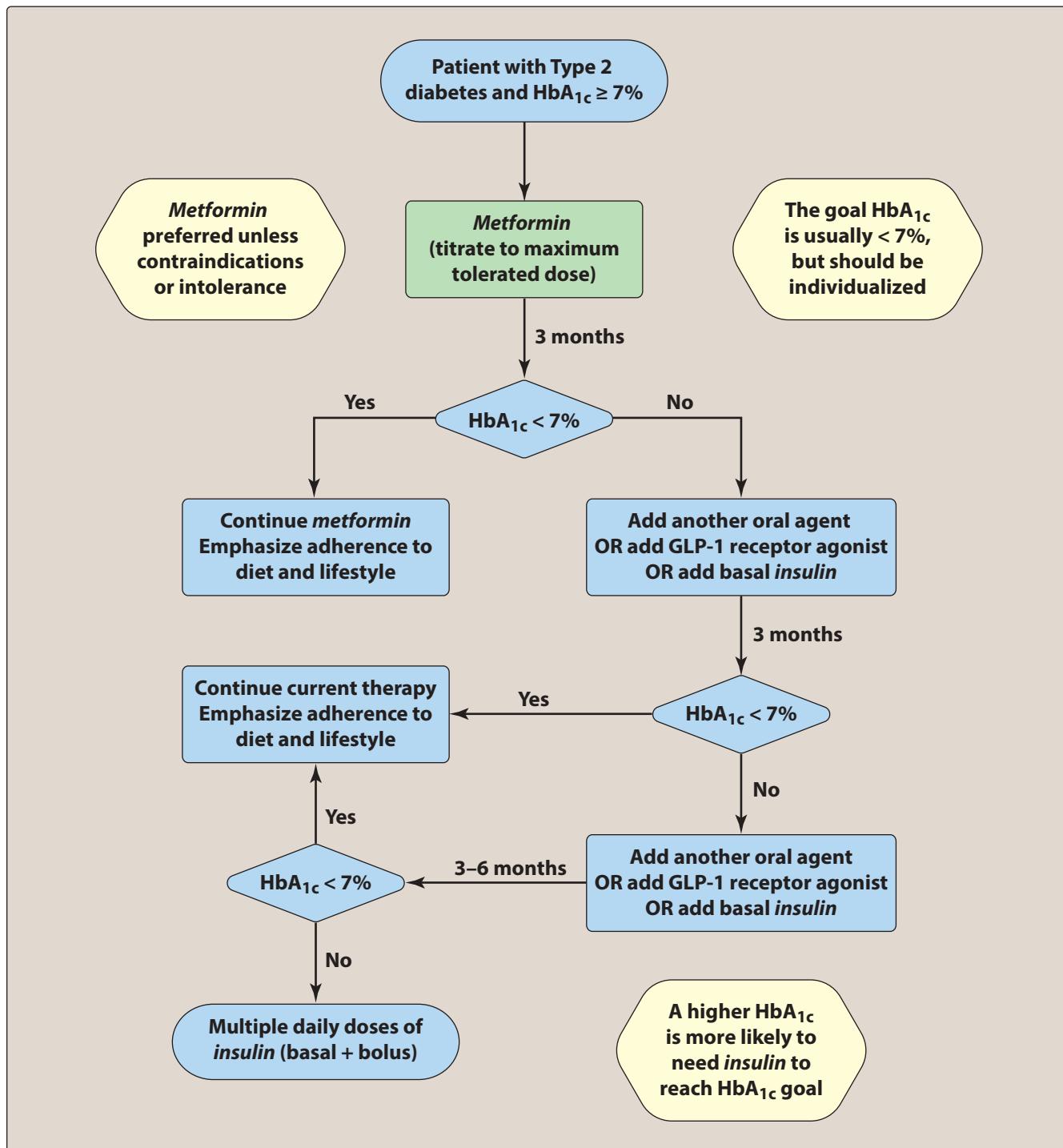
MEDICINE	USUAL DAILY DOSE	FREQUENCY	POSSIBLE SIDE EFFECTS	DURATION OF ACTION (DA)	SITE OF METABOLISM
<b>Sulfonylureas:</b>					
<i>Glibenclamide 5 mg</i>	2.5–20 mg	Up to 10 mg as a single dose >10 mg in divided doses  Taken with or immediately before food	Side effects rarely encountered include nausea, anorexia, skin rashes, severe hypoglycemia, especially in elderly and those with renal dysfunction	DA: 6–12 hours Peak: 6–8 hours	Liver
<i>Glipizide 5 mg</i>	2.6–40 mg	Up to 15 mg as a single dose >15 mg in a twice-daily dosage taken immediately before meals	GIT disturbances Skin reactions Hypoglycemia (uncommon)	DA: Up to 24 hours Peak: 1–3 hours	Liver
<i>Gliclazide 80 mg</i> <i>(Also as sustained release preparation 60 mg)</i>	30–120 mg  Dose increments should be 2 weeks apart  Should not be crushed	Daily	Hypoglycemia	Released over 24 hours	Liver
<i>Glimepiride 1 mg, 2 mg</i>	1–4 mg	2–3 per day	Hypoglycemia	DA: 5–8 hours	Liver
<b>Biguanides:</b>					
<i>Metformin 500 mg, 1 g; SR</i>	0.5–1.5 g	1–3 times/day taken with or immediately after food	GIT disturbances Lactic acidosis Hypoglycemia with other OHAs Decrease B <sub>12</sub> absorption	DA: 5–6 hours	Unchanged in urine
<b>Glitinides:</b>					
<i>Repaglinide 0.5 mg, 1 mg, 2 mg</i>	0.5–16 mg	2–3 per day	Hypoglycemia with other OHAs Weight gain, GIT disturbance	-	Liver
<b>Thiazolidinediones (TZD):</b>					
<i>Pioglitazone 15 mg, 30 mg</i> <i>Rosiglitazone 2 mg, 4 mg</i>	4–8 mg	Daily	Edema, weight gain, heart failure, raised liver enzymes, pregnancy risk in women with polycystic ovarian disease ( <i>rosiglitazone</i> )	DA: 24 hours	Liver
<b>α-Glucosidase inhibitors:</b>					
<i>Acarbose 50 mg, 100 mg</i> <i>Voglibose 0.2 mg, 0.3 mg</i>	50–100 mg 0.2–0.3 mg	TDS with food thrice a day	GIT problems, for example, flatulence, diarrhea Hypoglycemia	-	Feces and urine
<b>DPP-4 inhibitors (incretin mimetics):</b>					
<i>Sitagliptin 50 mg, 100 mg</i> <i>Vildagliptin 50 mg</i>	100 mg per day in BD regimen in combination with <i>metformin</i> , or a sulfonylurea (experience is with <i>glimepiride</i> ) or a TZD (experience is with <i>pioglitazone</i> )  Moderate renal failure 50 mg Severe renal disease 25 mg	With or without food	Hypoglycemia—reduce dose of sulfonylurea if used as a dual therapy to reduce hypoglycemia risk  Safety with insulin has not been established  More research is needed in older people	-	Unchanged in urine

OHAs = oral hypoglycemic agents.

Note: Formulations in each class have similar actions although there are minor differences among them.

**Figure 24.14**

Oral hypoglycemic agents, dose range and dose frequency, possible side effects, duration of action, and main site of metabolism. Adapted from Trisha Dunning, Care of People with DM: A manual of Nursing Practice. 3<sup>rd</sup> edition; Wiley-BlackWell Publishers: Australia (2009).

**Figure 24.15**

Treatment guidelines for type 2 diabetes.

- Patients on two OHAs at maximal doses and not achieving targets where *insulin* may be preferable to adding a third OHA. *Insulin* might be preferable if the HbA<sub>1c</sub> is >8.5% or the person is very symptomatic. In these cases, it might be appropriate to consider latent autoimmune DM of adults (LADA), especially if the individual is thin.
- *Insulin* is also required in situations such as surgery and infection.

Consider *insulin* as the initial therapy in case of:

- fasting plasma glucose >250 to 300 mg/dl since more rapid glycemic control will reduce glucose toxicity to islet cells, improve insulin secretion, and possibly make oral hypoglycemic agents more effective;
- lean patients or those with severe weight loss;
- underlying renal or hepatic disease, or acutely ill or hospitalized; and
- women with type 2 DM who become pregnant and gestational DM.

The goals are to achieve optimal control without causing hypoglycemia or excessive weight gain with minimal impact on lifestyle. The dose is titrated according to the fasting blood glucose pattern including self-adjustment by the patient to achieve targets with minimal hypoglycemia according to a simple algorithm ([Figure 24.15](#)).

## B. Basal–bolus insulin regimen

A basal–bolus regimen involves a person with diabetes taking both basal and bolus *insulin* throughout the day—that is, taking a long-acting form of *insulin* to keep blood glucose levels stable through periods of fasting and separate injections of short-acting *insulin* to prevent rises in blood glucose levels resulting from meals. Bolus *insulin* is often taken before meals but some people may be advised to take their *insulin* during or just after a meal if hypoglycemia needs to be prevented. The advantages of this regimen are flexibility it offers with regard to meal time and control of blood sugar levels overnight. However, the disadvantages of a basal–bolus regimen requirement of multiple injections a day and adapting to this routine can be challenging for some patients. Long-acting basal *insulin* for people with diabetes include:

- Basal *insulin* (long-acting *insulin* glargine and detemir), usually taken once or twice a day to maintain constant blood sugar levels
- Bolus *insulin* (short-acting or rapid-acting), taken at meal times

A stepwise approach to initiating and titrating *insulin* in type 2 DM should be used. Usually, OHAs are continued with basal *insulin* regimens if there are no contraindications to their use. When bolus *insulin* doses are added, secretagogue doses are usually reduced or the medicines discontinued. The advantage of using basal–bolus *insulin* dose regimens is that they usually achieve better postprandial control but eating after injecting is important. BD Lispro/isophane mix and *metformin* also improve pre- and postprandial blood glucose with few episodes of nocturnal hypoglycemia. In diabetic patients, sometimes morning hyperglycemia may be caused by the dawn phenomenon, or the Somogyi effect, or poor glycemic control. The dawn phenomenon occurs when endogenous insulin secretion decreases or when the effect of the exogenous insulin administered to the patient the day before disappears, together with a physiological increase in insulin-antagonistic hormones. The Somogyi effect is present in the case of excessive amounts of exogenous insulin. The dawn phenomenon is more common than the Somogyi effect. In these patients, measuring plasma glucose levels for several nights between 3 a.m. and 5 a.m. or using a continuous glucose monitoring system can be useful to diagnose this phenomenon. Although their treatment differs, an optimal diabetes control with insulin therapy is the best way of preventing both the dawn phenomenon and the Somogyi effect.

### C. Combining OHAs and insulin

Any combination of the currently available OHAs only lowers HbA<sub>1c</sub> by ~3%; thus, people with HbA<sub>1c</sub> >10% are unlikely to achieve management targets using OHA alone. Therefore, *insulin* is assuming an increasingly important role in type 2 DM. Medication administration times should be planned so that OHAs are administered with, or before, meals to reduce the risk of hypoglycemia. In addition, lifestyle factors, concomitant diseases, and often medicines compound the metabolic abnormalities. Assess medication nonadherence from time to time. Most people with type 2 DM have progressive β-cell dysfunction and a decline in β-cell mass due to interplay among a range of factors that reduce β-cell mass and secretory function such as hyperglycemia, elevated free fatty acids, and inflammatory processes associated with adipocyte-derived cytokines.

## Study Questions

Choose the ONE best answer.

24.1 Which of the following statements is correct regarding insulin glargine?

- A. It is primarily used to control postprandial hyperglycemia.
- B. It is a “peakless” insulin.
- C. The prolonged duration of activity is due to slow dissociation from albumin.
- D. It should not be used in a regimen with insulin lispro or glulisine.

Correct answer = B. Insulin glargine has a relatively flat, prolonged hypoglycemic effect. Because of this it is used for basal glucose control, not postprandial. The prolonged duration is due to its low pH, which leads to precipitation at the injection site and resultant extended action. Insulin glargine is often used for basal control in a regimen where insulin lispro, glulisine, or aspart are used for mealtime glucose control. [Note: Glargin should not be combined with other insulins in the same syringe, as it may alter the pharmacodynamic properties of the medication.]

24.2 MC is a patient with type 2 diabetes currently being treated with insulin detemir. The physician determines that MC needs additional insulin therapy for control of postprandial glucose. Which agent is most appropriate to add at this time?

- A. Insulin degludec
- B. NPH insulin
- C. Insulin lispro
- D. NPH/regular 70/30 insulin

Correct answer = C. Insulin lispro is a rapid-acting insulin that has an onset of action within 15 to 30 minutes. Rapid-acting insulins are administered to mimic the prandial (mealtime) release of insulin and control postprandial glucose levels. Insulin degludec is a long-acting insulin used to control fasting glucose levels. NPH insulin is an intermediate-acting insulin also used for basal (fasting) control. NPH/regular 70/30 insulin is a mixture of NPH (intermediate-acting) and regular (short-acting) insulin. The patient is already on a long-acting insulin (detemir) for basal control, and another insulin for basal control is not warranted.

- 24.3 Which class of oral diabetes drugs is paired most appropriately with its primary mechanism of action?
- A. DPP-4 inhibitor— inhibits breakdown of complex carbohydrates
  - B. SGLT2 inhibitor— increases urinary excretion of glucose
  - C. Sulfonylurea— increases insulin sensitivity
  - D. Thiazolidinedione— decreases hepatic gluconeogenesis
- 24.4 Which of the following statements is characteristic of metformin?
- A. Metformin contains a boxed warning due to the potential for increased risk of myocardial infarction.
  - B. Metformin decreases hepatic glucose production.
  - C. Metformin can be used safely in patients with renal dysfunction.
  - D. Weight gain is a common adverse effect.
- 24.5 Which is the most appropriate initial oral agent for management of type 2 diabetes in patients with no other comorbid conditions?
- A. Glipizide
  - B. Empagliflozin
  - C. Metformin
  - D. Pioglitazone
- 24.6 A 64-year-old woman with a history of type 2 diabetes is diagnosed with heart failure. Which of the following medications would be a poor choice for controlling her diabetes?
- A. Exenatide
  - B. Glybenclamide
  - C. Pioglitazone
  - D. Insulin
- 24.7 KD is a 69-year-old male with type 2 diabetes and chronic pancreatitis. Which of the following diabetes medications is contraindicated in this patient?
- A. Glipizide
  - B. Insulin lispro
  - C. Metformin
  - D. Dulaglutide

Correct answer = B. SGLT2 inhibitors work by inhibiting the sodium-glucose cotransporter 2 (SGLT2), resulting in decreased reabsorption of glucose in the kidney and increased urinary excretion. Sulfonylureas work primarily by increasing insulin secretion through stimulation of the  $\beta$  cells in the pancreas. DPP-4 inhibitors work by inhibiting breakdown of incretins, thereby increasing postprandial insulin secretion, decreasing postprandial glucagon, etc. TZDs work primarily by increasing insulin sensitivity.

Correct answer = B. Metformin works by inhibiting hepatic gluconeogenesis. The primary adverse effects associated with metformin are gastrointestinal and in rare cases, lactic acidosis. Metformin does not carry a warning for increased risk of myocardial infarction (this is the case for rosiglitazone). Metformin is contraindicated in renal dysfunction due to the risk of lactic acidosis. Unlike the sulfonylureas and insulin, weight gain is not an adverse effect, and some patients actually lose weight due to GI side effects.

Correct answer = C. Metformin is the preferred initial agent for management of type 2 diabetes. See Figure 24.15.

Correct answer = C. The TZDs (pioglitazone and rosiglitazone) can cause fluid retention and lead to a worsening of heart failure. They should be used with caution and dose reduction, if at all, in patients with heart failure. Exenatide, glybenclamide, and insulin do not have precautions for use in heart failure patients.

Correct answer = D. Dulaglutide is a GLP-1 receptor agonist. Although infrequent, GLP-1 receptor agonists have been associated with pancreatitis and should be avoided in patients with chronic pancreatitis. Glipizide, insulin lispro, and metformin have not been associated with an increased risk of pancreatitis.

- 24.8 Which of the following drugs for diabetes is LEAST likely to cause weight gain?
- A. Liraglutide
  - B. Pioglitazone
  - C. Repaglinide
  - D. Insulin glulisine
- 24.9 HB is a 55-year-old obese female who has had type 2 diabetes for 10 years. She is currently being treated with metformin but her HbA<sub>1c</sub> is above goal. She has a history of heart failure and chronic obstructive pulmonary disorder. Her physician would like to add a medication that will not cause any weight gain. Which of the following would be most appropriate to control HB's diabetes?
- A. Albiglutide
  - B. Glimepiride
  - C. Pioglitazone
  - D. Inhaled insulin
- 24.10 Which of the following diabetes medications is most appropriately paired with an adverse effect associated with its use?
- A. Canagliflozin—urinary tract infections
  - B. Nateglinide—heart failure
  - C. Glipizide—weight loss
  - D. Liraglutide—lactic acidosis

Correct answer = B. GLP-1 receptor agonists are usually associated with weight loss due to their ability to enhance satiety. All of the other agents are associated with weight gain.

Correct answer = A. Albiglutide is a GLP-1 receptor agonist and this class of medications is effective in lowering HbA<sub>1c</sub> levels without causing weight gain (they are more likely to cause weight loss). Sulfonylureas (glimepiride) are associated with weight gain and should be avoided in this obese patient. TZDs (pioglitazone) should be avoided in patients with heart failure. Because of the potential for bronchospasm associated with inhaled insulin, it should be avoided in patients with a history of chronic obstructive pulmonary disorder and asthma.

Correct answer = A. Adverse effects of canagliflozin are genital mycotic infections, urinary tract infections, and urinary frequency. Nateglinide may cause hypoglycemia but has not been associated with heart failure. Sulfonylureas are associated with weight gain. Lactic acidosis is a rare but serious side effect of metformin (not liraglutide).

# Estrogens and Androgens

25

Karen Whalen

## I. OVERVIEW

Estrogens and androgens are sex hormones produced by the gonads. These hormones are necessary for conception, embryonic maturation, and development of primary and secondary sexual characteristics at puberty. The sex hormones are used therapeutically for contraception, management of menopausal symptoms, and replacement therapy in hormone deficiency. Several antagonists are effective in the treatment or prevention of hormone-responsive cancers. Sex hormones are synthesized from the precursor, cholesterol, in a series of steps that includes shortening of the hydrocarbon side chain and hydroxylation of the steroid nucleus. Aromatization is the last step in estrogen synthesis. **Figure 25.1** lists the sex hormones discussed in this chapter.

ESTROGENS	SELECTIVE ESTROGEN-RECEPTOR MODULATORS (SERMs)	PROGESTOGENS	PROGESTERONE AGONIST/ANTAGONIST
<i>Conjugated estrogen</i> <i>Esterified estrogen</i> <i>Estradiol (oral)</i> <i>Estradiol (topical)</i> <i>Estradiol (transdermal)</i> <i>Estradiol (vaginal)</i> <i>Estropipate</i> <i>Ethinyl estradiol<sup>1</sup></i>	<i>Clomiphene</i> <i>Tamoxifen</i> <i>Ospemifene</i> <i>Raloxifene</i>	<i>Progesterone</i> <i>Levonorgestrel</i> <i>Leovnorgestrel (IUD)</i> <i>Desogestrel<sup>2</sup></i> <i>Medroxyprogesterone</i> <i>Dienogest<sup>2</sup></i> <i>Drospirenone<sup>2</sup></i> <i>Etonogestrel<sup>2</sup> (vaginal ring)</i> <i>Etonogestrel (subdermal)</i> <i>Norelgestromin<sup>2</sup> (transdermal)</i> <i>Norethindrone</i> <i>Norethindrone<sup>2</sup></i> <i>Norethindrone acetate</i> <i>Norethindrone acetate<sup>2</sup></i> <i>Norgestimate<sup>2</sup></i> <i>Norgestrel<sup>2</sup></i>	<i>Ulipristal acetate</i>

IUD = intrauterine device.

<sup>1</sup>Available in many combinations with a progestin.

<sup>2</sup>Available in combination with *ethinyl estradiol*. [Note: Dienogest is available in combination with *estradiol valerate*.]

**Figure 25.1**

Summary of sex hormones.

## II. ESTROGENS

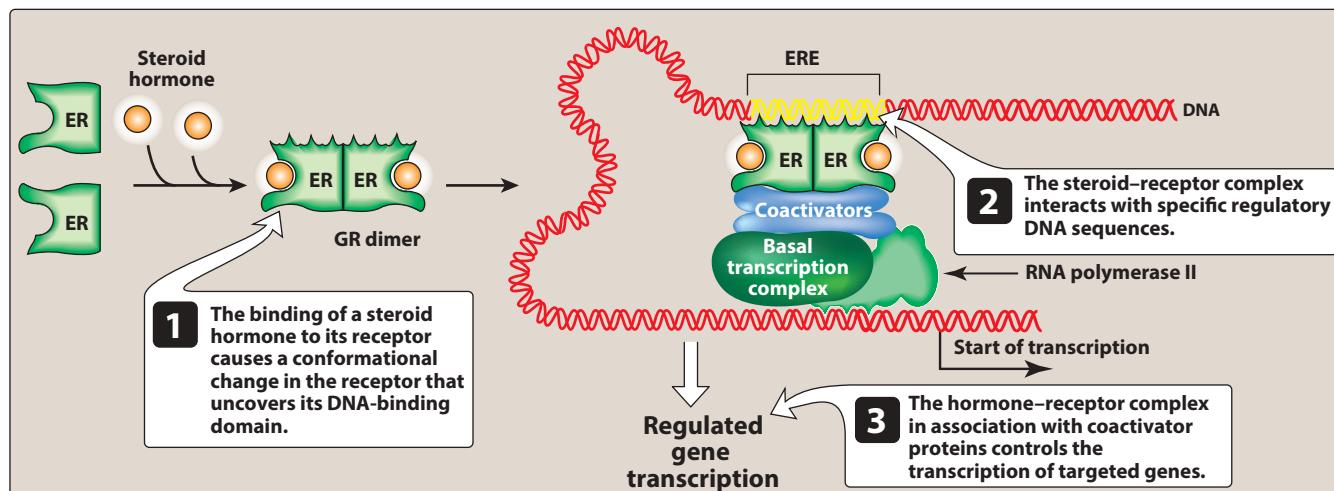
*Estradiol* [ess-tra-DYE-ole] is the most potent estrogen produced and secreted by the ovary. It is the principal estrogen in premenopausal women. *Estrone* [ESS-trone] is a metabolite of *estradiol* that has approximately one-third the estrogenic potency of *estradiol*. *Estrone* is the primary circulating estrogen after menopause, and it is generated mainly from conversion of dehydroepiandrosterone in adipose tissue. *Estriol* [ess-TRI-ole], another metabolite of *estradiol*, is significantly less potent than *estradiol*. It is present in significant amounts during pregnancy, because it is synthesized by the placenta. Synthetic estrogens, such as *ethinyl estradiol* [ETH-i-nil ess-tra-DYE-ole], undergo less first-pass metabolism than do naturally occurring hormones and, thus, are effective when administered orally at lower doses.

### A. Mechanism of action

After dissociation from their binding sites on sex hormone-binding globulin or albumin in the plasma, steroid hormones (for example, *estradiol*) diffuse across the cell membrane and bind with high affinity to specific nuclear receptor proteins (Figure 25.2). The activated steroid-receptor complex interacts with nuclear chromatin to initiate hormone-specific RNA synthesis. This results in the synthesis of specific proteins that mediate a number of physiologic functions. [Note: The steroid hormones may elicit the synthesis of different RNA species in diverse target tissues and, therefore, are both receptor and tissue specific.] Other pathways that require these hormones have been identified that lead to more rapid actions.

### B. Therapeutic uses

Estrogens are most frequently used for contraception and postmenopausal hormone therapy (HT). In the past, estrogens were widely used for prevention of osteoporosis; however, due to risks associated with



**Figure 25.2**

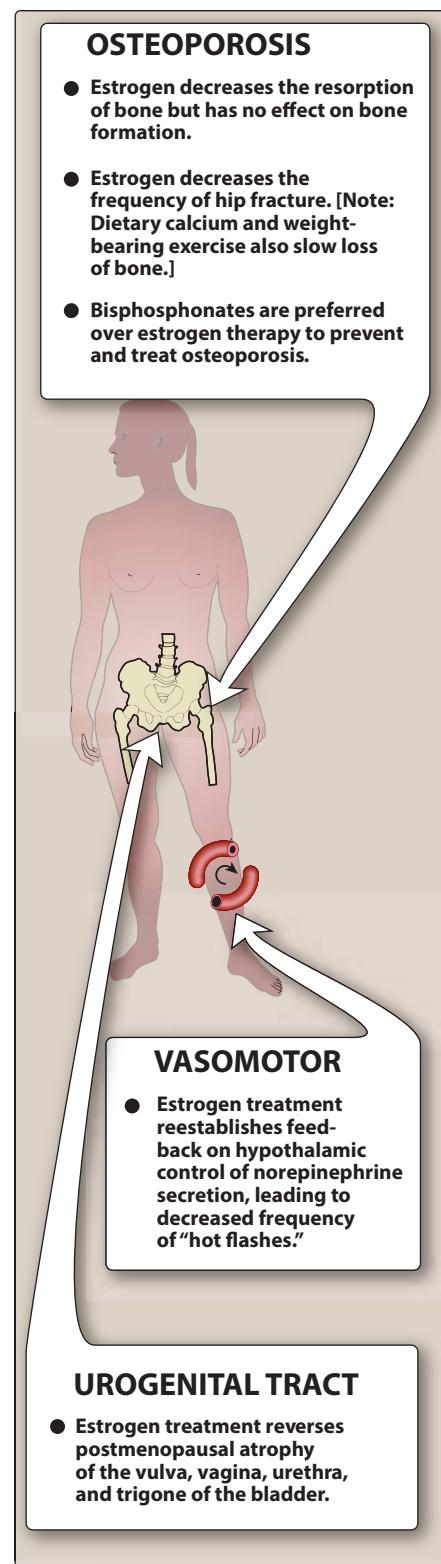
Transcriptional regulation by intracellular steroid hormone receptors. ER = estrogen receptor; ERE = estrogen response element; GR = glucocorticoid receptor.

estrogen therapy, current guidelines recommend use of other therapies, such as bisphosphonates (see Chapter 27).

- Postmenopausal HT:** The primary indication for estrogen therapy in postmenopausal women is menopausal symptoms, such as vasomotor instability (for example, “hot flashes” or “hot flushes”) and vaginal atrophy (Figure 25.3). A common oral preparation used for the treatment of menopausal symptoms is *conjugated equine estrogens* (obtained from urine of pregnant mares), which primarily contains sulfate esters of *estrone* and *equilin*. Other *estrone*-based oral preparations include *esterified estrogens* and *estropipate* [ES-troe-PIP-ate]. Transdermal preparations of *estradiol* are also effective in treating menopausal symptoms. For women with an intact uterus, a progestogen is always included with the estrogen therapy, because the combination reduces the risk of endometrial carcinoma associated with unopposed estrogen. Women who have undergone a hysterectomy may use estrogen alone. [Note: The potency of estrogen used in HT is substantially less than that of estrogens used in contraception. Thus, the adverse effects of estrogen replacement therapy are usually less pronounced than those seen in women taking estrogen for contraceptive purposes.] Use of HT has been associated with an increased risk of cardiovascular events and breast cancer. Thus, HT should be prescribed at the lowest effective dose for the shortest possible time to relieve menopausal symptoms. Women who only have urogenital symptoms, such as vaginal atrophy, should be treated with vaginal rather than systemic estrogen to minimize the risks of use. *Tibolone* is a 19-norsteroid developed for hormone replacement therapy (HRT) and upon administration it is converted to three metabolites having estrogenic, progestogenic, and androgenic properties. A daily single dose of 2.5 mg suppresses menopausal symptoms and lowers raised gonadotropin levels. Side effects’ profile is similar to that of HRT and is also known to increase weight gain along with facial hair growth.
- Contraception:** The combination of an estrogen and progestogen provides effective contraception via the oral, transdermal, or vaginal route.
- Other uses:** Estrogen therapy mimicking the natural cyclic pattern, and usually in combination with a progestogen, is instituted to stimulate development of secondary sex characteristics in young women with primary hypogonadism. Similarly, replacement therapy is used for women who have hormonal deficiencies due to surgical menopause or premature ovarian failure.

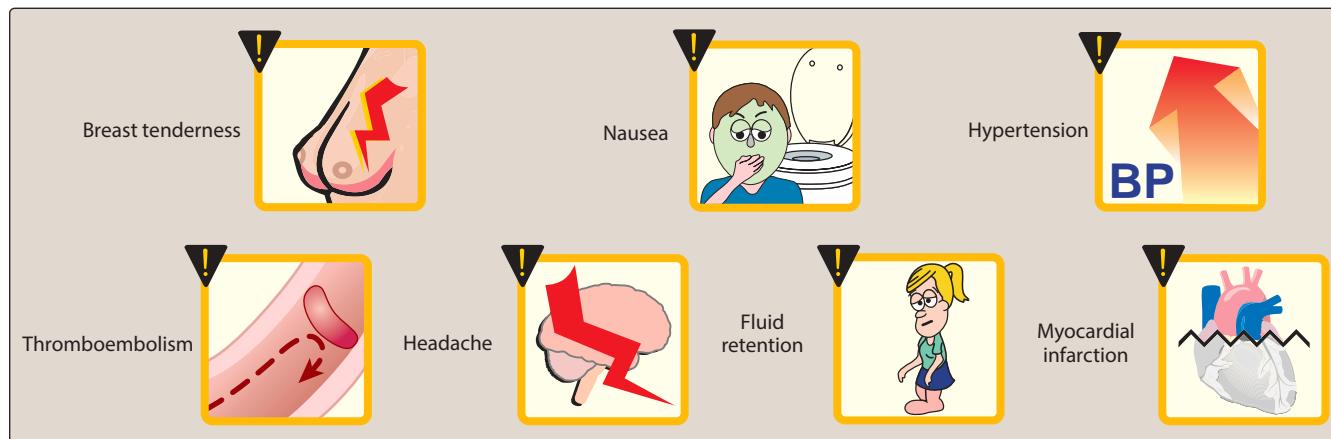
### C. Pharmacokinetics

- Naturally occurring estrogens:** These agents and their esterified or conjugated derivatives are readily absorbed through the gastrointestinal tract, skin, and mucous membranes. Taken orally, *estradiol* is rapidly metabolized (and partially inactivated) by the microsomal enzymes of the liver. Micronized *estradiol* has better bioavailability. Although *estradiol* is subject to first-pass metabolism, it is still effective when taken orally.
- Synthetic estrogens:** These compounds, such as *ethinyl estradiol* and *estradiol valerate*, are well absorbed after oral administration. *Estradiol valerate* is a prodrug of *estradiol* which is rapidly cleaved



**Figure 25.3**

Benefits associated with postmenopausal estrogen replacement.

**Figure 25.4**

Some adverse effects associated with estrogen therapy. BP = blood pressure.

to *estradiol* and *valeric acid*. The synthetic estrogens are fat soluble, stored in adipose tissue, and slowly released. These compounds have a prolonged action and a higher potency compared to the natural estrogens.

3. **Metabolism:** Bioavailability of *estradiol* after oral administration is low due to first-pass metabolism. To reduce first-pass metabolism, *estradiol* may be administered via a transdermal patch, topical formulation (gel or spray), intravaginal preparation (tablet, cream, or ring), or injection. Following oral administration, *estradiol* is metabolized to *estrone* and *estriol*. Estrogens are transported in the blood bound to serum albumin or sex hormone-binding globulin. *Estradiol* and its metabolites subsequently undergo glucuronide and sulfate conjugation. In addition, smaller amounts of *estrone* and *estriol* are metabolized by the hepatic CYP3A4 isoenzyme. Metabolites are mainly excreted in the urine. The glucuronide and sulfate metabolites are also subject to enterohepatic recirculation. These compounds are secreted into the bile, hydrolyzed by gut bacteria, and then reabsorbed.

#### D. Adverse effects

Nausea and breast tenderness are among the most common adverse effects of estrogen therapy. In addition, the risk of thromboembolic events, myocardial infarction, and breast and endometrial cancer is increased with the use of estrogen therapy. [Note: The increased risk of endometrial cancer can be offset by including a progestogen along with the estrogen therapy.] Other effects of estrogen therapy are shown in [Figure 25.4](#).

### III. SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

SERMs are a class of estrogen-related compounds that display selective agonism or antagonism for estrogen receptors depending on the tissue type. This category includes *tamoxifen*, *raloxifene*, *bazedoxifene*, *clomiphene*, and *ospemifene*.

### A. Mechanism of action

*Tamoxifen* [tah-MOKS-ih-fen] and *raloxifene* [rah-LOX-ih-steen] compete with estrogen for binding to the estrogen receptor in breast tissue. [Note: Normal breast growth is stimulated by estrogens. Therefore, some hormone-responsive breast tumors regress following treatment with these agents.] In addition, *raloxifene* acts as an estrogen agonist in bone, leading to decreased bone resorption, increased bone density, and decreased vertebral fractures (Figure 25.5). Unlike estrogen and *tamoxifen*, *raloxifene* does not stimulate growth of the endometrium, and, therefore, does not predispose to endometrial cancer. *Raloxifene* also lowers serum total cholesterol and low-density lipoprotein (LDL). Like *raloxifene*, *bazedoxifene* [BA-ze-DOX-i-steen] antagonizes the action of estrogen on the uterus. The drug reduces the risk of endometrial hyperplasia with estrogen use. *Clomiphene* [KLOE-mi-steen] acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus. This effect increases the secretion of gonadotropin-releasing hormone and gonadotropins, thereby leading to stimulation of ovulation.

### B. Therapeutic uses

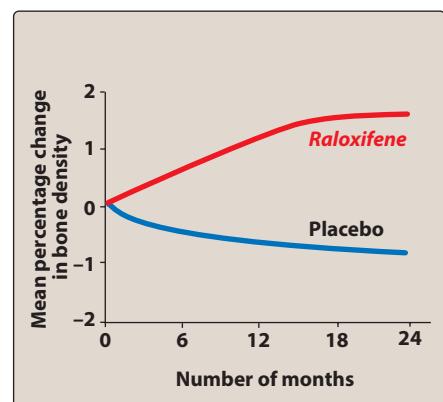
*Tamoxifen* is currently used in the treatment of metastatic breast cancer or as an adjuvant therapy following mastectomy or radiation for breast cancer. Both *tamoxifen* and *raloxifene* can be used as a prophylactic therapy to reduce the risk of breast cancer in high-risk patients. *Raloxifene* is also approved for the prevention and treatment of osteoporosis in postmenopausal women. *Clomiphene* is used in the treatment of infertility. *Ospemifene* is indicated for the treatment of dyspareunia (painful sexual intercourse) related to menopause. *Bazedoxifene* is available in a combination product with *conjugated estrogens*. The combination is indicated for the treatment of menopausal symptoms in women with an intact uterus.

### C. Pharmacokinetics

The SERMs are rapidly absorbed after oral administration. *Tamoxifen* is extensively metabolized by the cytochrome P450 system, including the formation of active metabolites via the CYP3A4/5 and CYP2D6 isoenzymes. [Note: Patients with a genetic polymorphism in CYP2D6 may produce less active metabolite, resulting in diminished activity of *tamoxifen*.] *Raloxifene* is rapidly converted to glucuronide conjugates through first-pass metabolism. These agents undergo enterohepatic cycling, and the primary route of excretion is through the bile into feces.

### D. Adverse effects

The most frequent adverse effects of *tamoxifen* are hot flashes and nausea. Due to its estrogenic activity in the endometrium, endometrial hyperplasia and malignancies have been reported with *tamoxifen* therapy. This has led to recommendations for limiting the length of time on the drug for some indications. Because it is metabolized by various CYP450 isoenzymes, *tamoxifen* is subject to many drug interactions. [Note: *Tamoxifen* is also an inhibitor of CYP3A4 and P-glycoprotein.] Some CYP450 inhibitors may prevent the formation



**Figure 25.5**

Hip bone density increases with *raloxifene* in postmenopausal women.

of active metabolites of *tamoxifen* and possibly reduce the efficacy (for example, *amiodarone*, *haloperidol*, and *risperidone*). Hot flashes and leg cramps are common adverse effects with *raloxifene*. In addition, there is an increased risk of deep vein thrombosis and pulmonary embolism. Women who have a past or active history of venous thromboembolic events should not take the drug. The adverse effects of *clomiphene* are dose-related and include headache, nausea, vaso-motor flushes, visual disturbances, and ovarian enlargement. Use of *clomiphene* increases the risk of multiple gestation, usually twins. *Ospemifene* may stimulate endometrial growth, and addition of a progestogen in women with an intact uterus should be considered.

## IV. PROGESTOGENS

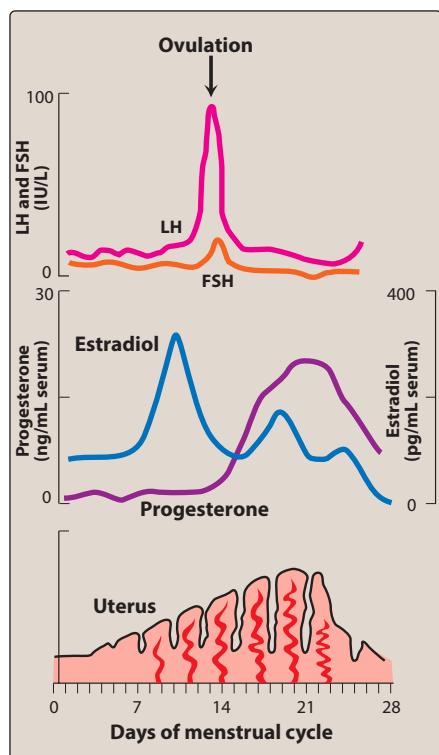
*Progesterone*, the natural progestogen, is produced in response to luteinizing hormone (LH) by both females (secreted by the corpus luteum, primarily during the second half of the menstrual cycle, and by the placenta) and males (secreted by the testes). It is also synthesized by the adrenal cortex in both sexes.

### A. Mechanism of action

Progestogens exert their effects in a manner analogous to that of the other steroid hormones. In females, *progesterone* promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo. The high levels of *progesterone* that are released during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropin and, therefore, prevent further ovulation. If conception takes place, *progesterone* continues to be secreted, maintaining the endometrium in a favorable state for the continuation of the pregnancy and reducing uterine contractions. If conception does not take place, the release of *progesterone* from the corpus luteum ceases abruptly. The decline in *progesterone* stimulates the onset of menstruation. **Figure 25.6** summarizes the hormones produced during the menstrual cycle.

### B. Therapeutic uses of progestogens

The major clinical uses of progestogens are for contraception or hormone replacement therapy. For both contraception and HT, progestogens are often used in combination with estrogens. *Progesterone* is not used as a contraceptive therapy because of its rapid metabolism, resulting in low bioavailability. Synthetic progestogens (that is, progestins) used for contraception are more stable to first-pass metabolism, allowing lower doses when administered orally. These agents include *desogestrel* [des-oh-JES-trel], *dienogest* [dye-EN-oh-jest], *drospirenone* [droe-SPY-re-none], *levonorgestrel* [lee-voe-nor-JES-trel], *norethindrone* [nor-ETH-in-drone], *norethindrone acetate*, *norgestimate* [nor-JES-tih-mate], and *norgestrel* [nor-JES-trel]. *Medroxyprogesterone* [me-DROK-see-proe-JES-ter-one] acetate is an injectable contraceptive, and the oral form is a common progestin component of postmenopausal HT. Progestogens are also used for the control of dysfunctional uterine bleeding, treatment of dysmenorrhea, and management of endometriosis and infertility.



**Figure 25.6**

The menstrual cycle with plasma levels of pituitary and ovarian hormones and a schematic representation of changes in the morphology of the uterine lining. FSH = follicle-stimulating hormone; LH = luteinizing hormone.

### C. Pharmacokinetics

A micronized preparation of *progesterone* is rapidly absorbed after oral administration. It has a short half-life in the plasma and is metabolized by the liver to pregnanediol and glucuronide and sulfate conjugates. The metabolites are excreted primarily in the urine. Synthetic progestins are less rapidly metabolized. Oral *medroxyprogesterone acetate* has a half-life of 30 hours. When injected intramuscularly or subcutaneously, the drug has a half-life of about 40 to 50 days and provides contraception for approximately 3 months. The other progestins have half-lives of 7 to 30 hours, allowing for once-daily dosing.

### D. Adverse effects

The major adverse effects associated with the use of progestins are headache, depression, weight gain, and changes in libido (Figure 25.7). Progestins that are derived from 19-nortestosterone (for example, *norethindrone*, *norethindrone acetate*, *norgestrel*, and *levonorgestrel*) possess some androgenic activity because of their structural similarity to *testosterone* and can cause acne and hirsutism. Less androgenic progestins, such as *norgestimate* and *drosipronone*, may be preferred in women with acne. *Drosipronone* may raise serum potassium due to antimineralcorticoid effects, and concurrent use with other drugs that increase potassium (for example, angiotensin-converting enzyme inhibitors) may increase the risk of hyperkalemia.

### E. Antiprogestin

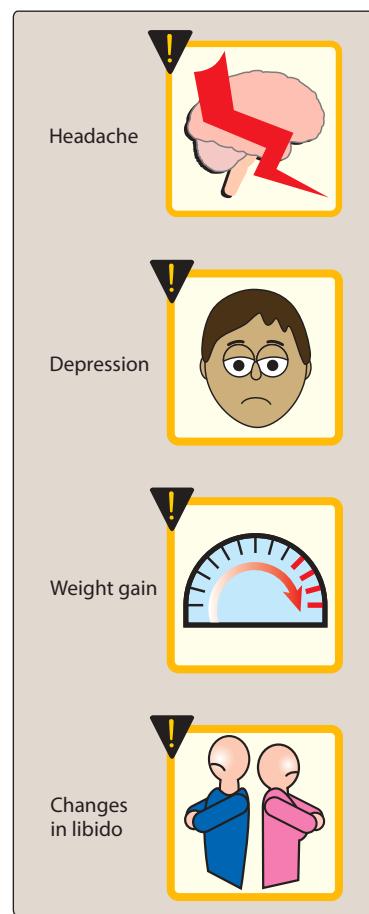
*Mifepristone* [mih-feh-PRIH-stone] (also designated as RU-486) is a progesterone antagonist. Administration of this drug results in termination of pregnancy due to interference with the *progesterone* needed to maintain pregnancy. *Mifepristone* is often combined with the prostaglandin analog *misoprostol* (administered buccally) to induce uterine contractions. The major adverse effects are abdominal pain, uterine bleeding, and the possibility of an incomplete abortion.

## V. CONTRACEPTIVES

Contraceptives may be hormonal or nonhormonal (for example, condom, diaphragm, contraceptive sponge, and copper intrauterine device). Figure 25.8 outlines the frequency of use for various hormonal and nonhormonal methods of contraception. An overview of the hormonal methods of contraception is provided in the following text.

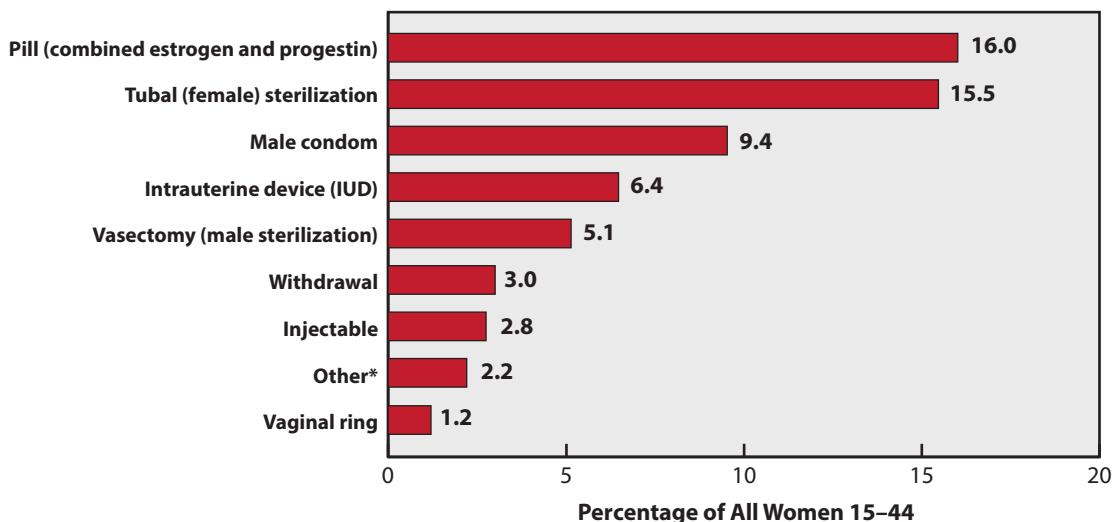
### A. Types of hormonal contraceptives

1. **Combination oral contraceptives:** A combination of estrogen and progestin is the most common type of oral contraceptive. [Note: The most common estrogen in combination pills is *ethynodiol*. The most common progestins are *norethindrone*, *norethindrone acetate*, *levonorgestrel*, *desogestrel*, *norgestimate*, and *drosipronone*.] These preparations are highly effective in achieving contraception (Figures 25.9 and 25.10). Monophasic combination pills contain a constant dose of estrogen and progestin given over

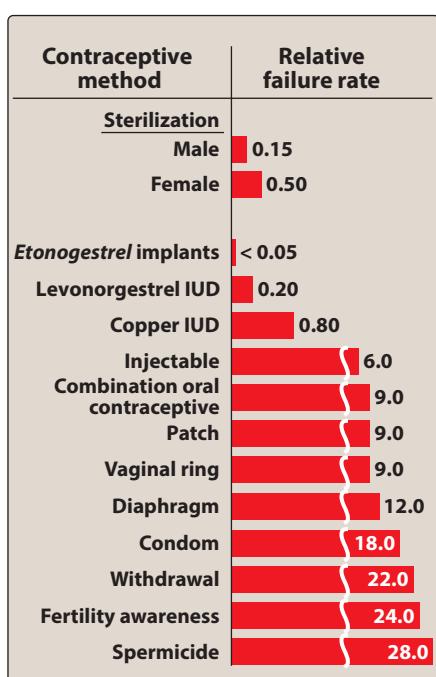


**Figure 25.7**

Some adverse effects associated with progestin therapy.

**Figure 25.8**

Comparison of contraceptive use among U.S. women aged 15 to 44 years. \*Patch, implant, fertility awareness methods, and other barrier methods (for example, diaphragm).

**Figure 25.9**

Comparison of failure rate for various methods of contraception with typical use. Longer bars indicate a higher failure rate—that is, more pregnancies. Adapted from data from the Guttmacher Institute. Contraceptive use in the United States. Available at <https://www.guttmacher.org/fact-sheet/contraceptive-use-united-states>.

21 to 24 days. Triphasic oral contraceptive products attempt to mimic the natural female cycle and usually contain a constant dose of estrogen with increasing doses of progestin given over 21 days. With most oral contraceptives, active pills are taken for 21 to 24 days, followed by 4 to 7 days of placebo, for a total regimen of 28 days. Withdrawal bleeding occurs during the hormone-free (placebo) interval. Use of extended-cycle contraception (84 active pills followed by 7 days of placebo) results in less frequent withdrawal bleeding. A continuous oral contraceptive product (active pills taken every day) is also available.

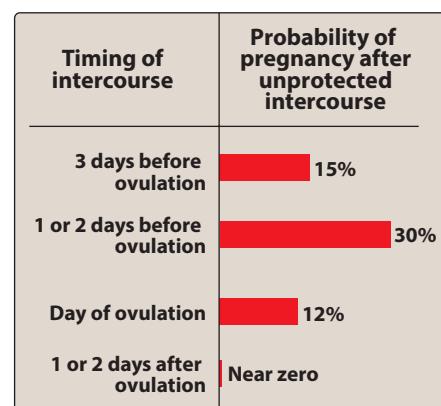
2. **Transdermal patch:** The contraceptive transdermal patch contains *ethinyl estradiol* and the progestin *norelgestromin*. During the 28-day cycle, one patch is applied each week for 3 weeks to the abdomen, upper torso, or buttock. No patch is worn during the fourth week, and withdrawal bleeding occurs. The transdermal patch has efficacy comparable to that of the oral contraceptives, but it is less effective in women weighing greater than 90 kg. Total estrogen exposure with the transdermal patch may be significantly greater than that seen with oral contraceptives.
3. **Vaginal ring:** The contraceptive vaginal ring contains *ethinyl estradiol* and *etonogestrel*. The ring is inserted into the vagina and left in place for 3 weeks. After 3 weeks, the ring is removed, and withdrawal bleeding occurs during the fourth week.
4. **Progestin-only pills:** Progestin-only pills (the “mini-pill”) contain a progestin, usually *norethindrone*, and are administered daily to deliver a low, continuous dosage of drug. These preparations are less effective than combination oral contraceptives (Figure 25.9), and irregular menstrual cycles may be more frequent. Progestin-only pills may be used in patients who are breast-feeding (unlike estrogen, progestins do not have an effect on milk production) or who have intolerance or contraindications to estrogen-containing products.

ESTROGEN	DOSE	PROGESTIN	DOSE	SCHEDULE OF THERAPY
<b>Combined pills:</b>				
Ethinyl estradiol Ethinyl estradiol	30/50 µg 20/30/50 µg	Norgestrel Levonorgestrel	0.3/0.5 mg 0.1/0.15/0.25 mg	21 days 21 days
<b>Phased pills:</b>				
Ethinyl estradiol Ethinyl estradiol	30–40–30 µg 35–35–35 µg	Levonorgestrel Norethindrone	30–75–125 mg 0.5–0.75–1 mg	6+5+10 days 7+7+7 days
<b>Postcoital pill:</b>				
Ethinyl estradiol	50 µg –	Levonorgestrel Levonorgestrel	0.25 mg 1.5 mg	2 tablets 12 hours apart 1 tablet within 72 hours of intercourse
<b>Mini pills:</b>				
	– –	Norethindrone Norgestrel	0.35 mg 75 mg	Daily Daily

**Figure 25.10**

Types and combination of estrogen and progestin used for oral contraception.

5. **Injectable progestin:** *Medroxyprogesterone acetate* is a contraceptive that is administered via intramuscular or subcutaneous injection every 3 months. This product provides high sustained levels of progestin. Many women experience amenorrhea with *medroxyprogesterone acetate*. In addition, return to fertility may be delayed for several months after discontinuation. Weight gain is a common adverse effect. *Medroxyprogesterone acetate* may contribute to bone loss and predispose patients to osteoporosis and/or fractures. Therefore, the drug should not be continued for more than 2 years unless the patient is unable to tolerate other contraceptive options.
6. **Progestin implants:** After subdermal placement in the upper arm, the *etonogestrel* implant offers contraception for up to 3 years. The implant is nearly as reliable as sterilization, and the contraceptive effect is reversible when removed. [Note: Progestin implants and intrauterine devices are known as long-acting reversible contraceptives (LARC).] Adverse effects include irregular menstrual bleeding and headaches. The *etonogestrel* implant has not been studied in women who weigh more than 130% of ideal body weight and may be less effective in this population.
7. **Progestin intrauterine device:** Various *levonorgestrel*-releasing intrauterine devices offer a highly effective method of contraception for 3 to 5 years. This is a suitable method of contraception for women who desire long-term contraception. It should be avoided in patients with pelvic inflammatory disease or a history of ectopic pregnancy. The *levonorgestrel* intrauterine device is a highly effective treatment for heavy menstrual bleeding. [Note: The nonhormonal copper intrauterine device provides contraception for up to 10 years.]
8. **Postcoital contraception:** Postcoital or emergency contraception reduces the probability of pregnancy after intercourse without effective contraception (Figure 25.11) to between 0.2% and 3%. The most common method of emergency contraception uses a

**Figure 25.11**

Risk of pregnancy after unprotected intercourse in young couples in their mid-twenties.

single, high dose of *levonorgestrel*. For maximum effectiveness, emergency contraception should be taken as soon as possible after unprotected intercourse and preferably within 72 hours. The *levonorgestrel* emergency contraceptive regimens are generally better tolerated than the estrogen-progestin combination regimens. An alternative emergency contraceptive is the progesterone agonist/antagonist *ulipristal* [ue-li-PRIS-tal]. It is indicated for emergency contraception within 5 days of unprotected intercourse.

### B. Mechanism of action

Exogenously administered estrogen in contraceptives provides negative feedback which blunts release of follicle-stimulating hormone (FSH) by the pituitary gland and progestin inhibits LH secretion, thus preventing ovulation. Progestin also thickens the cervical mucus, thus hampering the transport of sperm. Withdrawal of the progestin stimulates menstrual bleeding during the placebo week.

### C. Adverse effects

The incidence of adverse effects with contraceptives is determined by the specific compounds and combinations used. The most common adverse effects with estrogens are breast fullness, fluid retention, headache, and nausea. Increased blood pressure may also occur. Progestins may be associated with depression, changes in libido, hirsutism, and acne. Although rare, thromboembolism, thrombophlebitis, myocardial infarction, and stroke may occur with use of estrogen-containing contraceptives. These severe adverse effects are most common among women who are over age 35 and smoke, and estrogen-containing contraceptives should not be avoided in this population. Progestin-only products are preferred in older women who are smokers, due to a lower risk of severe adverse effects. The incidence of cervical cancer may be increased with hormonal contraceptives, because women are less likely to use barrier methods of contraception that reduce exposure to human papillomavirus, the primary risk factor for cervical cancer. [Note: Oral contraceptives are associated with a decreased risk of endometrial and ovarian cancer.] Oral contraceptives are contraindicated in the presence of cerebrovascular and thromboembolic disease, estrogen-dependent neoplasms, liver disease, and pregnancy. Drugs that induce the CYP3A4 isoenzyme (for example, *rifampin* and *bosentan*) significantly reduce the efficacy of oral contraceptives. Concurrent use of these agents with oral contraceptives should be avoided, or an alternate barrier method of contraception should be utilized. Antibiotics that alter normal gastrointestinal flora may reduce enterohepatic recycling of estrogen, thereby diminishing effectiveness of oral contraceptives. Patients should be warned of the possible interaction between antibiotics and oral contraceptives, along with the potential need for an alternate method of contraception during antibiotic therapy.

## VI. ANDROGENS

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The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females. *Testosterone* [tess-TOSS-te-rone], the most important androgen in humans, is synthesized by Leydig cells in

the testes and, in smaller amounts, by thecal cells in the ovaries and by the adrenal gland in both sexes. Other androgens secreted by the testes are 5 $\alpha$ -dihydrotestosterone (DHT), androstenedione, and dehydroepiandrosterone (DHEA) in small amounts. In adult males, testosterone secretion by Leydig cells is controlled by gonadotropin-releasing hormone from the hypothalamus, which stimulates the anterior pituitary gland to secrete FSH and LH. Testosterone or its active metabolite, DHT, inhibits production of these specific trophic hormones through a negative feedback loop and, thus, regulates testosterone production (Figure 25.12). The androgens are required for 1) normal maturation in the male, 2) sperm production, 3) increased synthesis of muscle proteins and hemoglobin, and 4) decreased bone resorption. Synthetic modifications of the androgen structure modify solubility and susceptibility to metabolism (thus prolonging the half-life of the hormone) and separate anabolic and androgenic effects.

### A. Mechanism of action

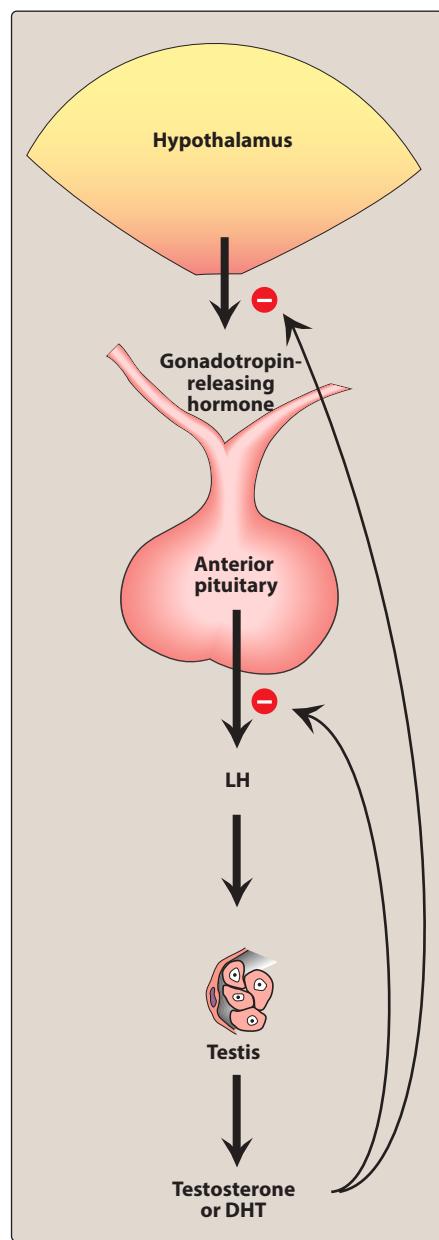
Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell. Although testosterone itself is the active ligand in muscle and liver, in other tissues it must be metabolized to derivatives, such as DHT. For example, after diffusing into the cells of the prostate, seminal vesicles, epididymis, and skin, testosterone is converted by 5 $\alpha$ -reductase to DHT, which binds to the receptor.

### B. Therapeutic uses

Androgenic steroids are used for males with primary hypogonadism (caused by testicular dysfunction) or secondary hypogonadism (due to failure of the hypothalamus or pituitary). [Note: Testosterone replacement should only be used for males with hypogonadism related to medical conditions, and not low testosterone associated with aging.] Anabolic steroids can be used to treat chronic wasting associated with human immunodeficiency virus or cancer. An unapproved use of anabolic steroids is to increase lean body mass, muscle strength, and endurance in athletes and body builders (see the following text). Because of the potential misuse of testosterone and its derivatives, these agents are classified as controlled substances. DHEA (a precursor of testosterone and estrogen) has been touted as an antiaging hormone as well as a “performance enhancer.” There is no definitive evidence that it slows aging, however, or that it improves performance at normal therapeutic doses. Formulations of testosterone or its derivatives (for example, methyltestosterone) may be used in combination with estrogen for women with menopausal symptoms unresponsive to estrogen alone. Danazol [DAH-nah-zole], a weak androgen, is used in the treatment of endometriosis and fibrocystic breast disease. [Note: Danazol also possesses antiestrogenic activity.] Weight gain, acne, decreased breast size, deepening voice, increased libido, and increased hair growth are among the adverse effects.

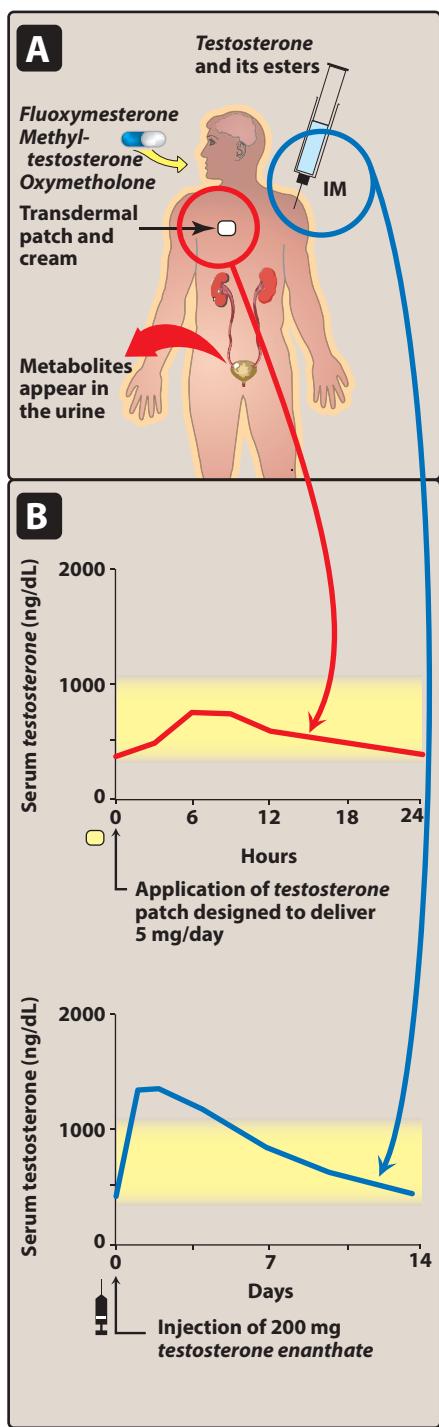
### C. Pharmacokinetics

- Testosterone:** This agent is ineffective orally because of inactivation by first-pass metabolism. Therefore, testosterone is administered via a transdermal patch, topical gel or solution, buccal tablet, or implantable pellet. Esters of testosterone (for example, testosterone cypionate or enanthate) are administered intramuscularly.



**Figure 25.12**

Regulation of secretion of testosterone. DHT = 5- $\alpha$ -dihydrotestosterone; LH = luteinizing hormone.



**Figure 25.13**

**A.** Administration and fate of androgens. IM = intramuscular. **B.** Serum testosterone concentrations after administration by injection or transdermal patch to hypogonadal men. The yellow band indicates the upper and lower limits of normal.

The esterified formulations are more lipid soluble and have an increased duration of action up to several weeks. **Figure 25.13** shows serum levels of testosterone achieved by injection and by a transdermal patch in hypogonadal men. Active metabolites of testosterone include DHT and estradiol, with activity related to the formation of DHT. Inactive metabolites are excreted primarily in the urine. Testosterone and its esters demonstrate a 1:1 relative ratio of androgenic to anabolic activity.

2. **Testosterone derivatives:** Alkylation of the  $17\alpha$  position of testosterone is associated with less hepatic metabolism and allows oral administration of the hormone. *Methyltestosterone* and *fluoxymesterone* [flo-oks-i-MES-te-ron] are examples of orally administered testosterone derivatives. *Oxandrolone* [ox-AN-droe-lone] and *oxymetholone* [OKS-ee-METH-oh-lone] are orally active  $17\alpha$ -alkylated derivatives of DHT. *Oxandrolone* has anabolic activity 3 to 13 times that of *testosterone*.

#### D. Adverse effects

1. **In females:** Androgens can cause masculinization, acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development. Menstrual irregularities may also occur. *Testosterone* should not be used by pregnant women because of possible virilization of the female fetus.
2. **In males:** Excess androgen can cause priapism, impotence, decreased spermatogenesis, gynecomastia, and cosmetic changes such as those described for females. Androgens can also stimulate growth of the prostate.
3. **In children:** Androgens can cause abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates.
4. **General effects:** Androgens can increase serum LDL and lower serum high-density lipoprotein levels. They may also cause fluid retention and peripheral edema. *Testosterone* replacement therapy has been associated with a possible increased risk of myocardial infarction and stroke. Hepatic adverse effects have been associated with the  $17\alpha$ -alkylated androgens. Local skin irritation is a common adverse effect with topical formulations.
5. **In athletes:** Use of anabolic steroids (for example, DHEA) by athletes can cause premature closing of the epiphysis of the long bones, which stunts growth and interrupts development. High doses taken by young athletes may result in reduction of testicular size, hepatic abnormalities, increased aggression ("roid rage"), major mood disorders, and other adverse effects described above.

#### E. Antiandrogens

Antiandrogens counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors. Antiandrogens, such as *flutamide* [FLOO-tah-mide], *bicalutamide* [bye-ka-LOO-ta-mide], *enzalutamide* [enz-a-LOO-ta-mide], and *nilutamide* [nye-LOO-ta-mide], act as competitive inhibitors of androgens at the target cell and are effective orally for the treatment of prostate cancer (see Chapter 43). *Finasteride* [fin-AS-ter-ide] and *dutasteride* [doo-TAS-ter-ide] inhibit

5 $\alpha$ -reductase, resulting in decreased formation of dihydrotestosterone. These agents are used for the treatment of benign prostatic hyperplasia (see Chapter 43).

## Study Questions

**Choose the ONE best answer.**

- 25.1 A 53-year-old woman has severe vasomotor symptoms (hot flushes) associated with menopause. She has no pertinent past medical or surgical history. Which would be most appropriate for her symptoms?
- A. Conjugated estrogens vaginal cream
  - B. Estradiol transdermal patch
  - C. Oral estradiol and medroxyprogesterone acetate
  - D. Injectable medroxyprogesterone acetate
- 25.2 A 70-year-old woman is being treated with raloxifene for osteoporosis. Which is a concern with this therapy?
- A. Breast cancer
  - B. Endometrial cancer
  - C. Venous thrombosis
  - D. Hypercholesterolemia
- 25.3 Which is the most appropriate oral contraceptive for a patient with moderate acne?
- A. Ethinyl estradiol/levonorgestrel
  - B. Ethinyl estradiol/norethindrone acetate
  - C. Ethinyl estradiol/norgestimate
  - D. Ulipristal
- 25.4 A 25-year-old woman is using injectable medroxyprogesterone acetate as a method of contraception. Which adverse effect is a concern if she wishes to use this therapy long-term?
- A. Hyperkalemia
  - B. Male pattern baldness
  - C. Osteoporosis
  - D. Weight loss
- 25.5 Which contraceptive method provides long-acting reversible contraception (LARC)?
- A. Contraceptive vaginal ring
  - B. Intrauterine device
  - C. Extended-cycle oral contraceptives
  - D. Transdermal contraceptive patch

Correct answer = C. Estrogen vaginal cream only treats vaginal symptoms of menopause such as vaginal atrophy and does not treat hot flushes. Since this patient has an intact uterus, a progestin such as medroxyprogesterone needs to be used along with the estrogen to prevent the development of endometrial hyperplasia. Unopposed estrogen (for example, the estradiol transdermal patch) should not be used. Injectable medroxyprogesterone acetate is used for contraception.

Correct answer = C. Raloxifene can increase the risk of venous thromboembolism. Unlike estrogen and tamoxifen, raloxifene does not result in an increased incidence of endometrial cancer. Raloxifene lowers the risk of breast cancer in high-risk women, and it also lowers LDL cholesterol.

Correct answer = C. The progestins levonorgestrel and norethindrone acetate may have androgenic activity and contribute to acne. Norgestimate has less androgenic activity and is preferred for this patient. Ulipristal is an emergency contraceptive and should not be used as a regular method of contraception.

Correct answer = C. Medroxyprogesterone acetate may contribute to bone loss and predispose patients to osteoporosis and/or fractures. Therefore, the drug should not be continued for more than 2 years if possible. The drug often causes weight gain, not weight loss. The other adverse effects are not associated with medroxyprogesterone.

Correct answer = B. The progestin-only intrauterine devices provide contraception for 3 to 5 years, depending on the device. The etonogestrel subdermal implant is another LARC that provides contraception for 3 years. The contraceptive vaginal ring is worn for 3 weeks at a time, and the transdermal patch for 1 week at a time. Extended cycle oral contraceptives must be administered daily.

- 25.6 Which is the most effective form of contraception with typical use?
- Combined oral contraceptives
  - Progestin-only “mini-pill”
  - Depot medroxyprogesterone acetate injection
  - Subdermal progestin implant
- Correct answer = D. See Figure 25.9. The subdermal implant has a very low failure rate, since it does not require adherence of the patient after implantation. Progestin-only pills are less effective than combined oral contraceptives and the depot medroxyprogesterone acetate injection.
- 25.7 A 36-year-old woman requests birth control. She has no medical conditions, and she smokes one pack of cigarettes per day. Which would be the most appropriate to recommend?
- Vaginal contraceptive ring
  - Transdermal contraceptive patch
  - Progestin-only “mini-pill”
  - Combination oral contraceptive pill
- Correct answer = C. Progestin-only products are preferred in older women who are smokers, due to a lower risk of severe adverse effects, such as myocardial infarction and stroke. Estrogen-containing contraceptives are not recommended in women over the age of 35 who are smokers. The vaginal contraceptive ring, transdermal contraceptive patch, and combination oral contraceptive pills all contain estrogen.
- 25.8 A 22-year-old woman requests emergency contraception after unprotected intercourse that occurred 1 day ago. She has no medical conditions. Which agent is most appropriate?
- Ethinyl estradiol/norgestimate
  - Etonogestrel
  - Levonorgestrel
  - Mifepristone
- Correct answer = C. A single dose of levonorgestrel is preferred for emergency contraception and should be administered within 72 hours of unprotected intercourse for best efficacy. Estrogen/progestin regimens are less used for emergency contraception due to a higher incidence of adverse effects such as nausea/vomiting. Etonogestrel is a progestin used in the contraceptive ring and implant. Mifepristone is a progestrone antagonist used to terminate pregnancy once it has occurred.
- 25.9 A 35-year-old woman is experiencing infertility due to anovulation. Which agent is most appropriate for this patient?
- Clomiphene
  - Ospemifene
  - Raloxifene
  - Ulipristal
- Correct answer = A. Clomiphene is a SERM that interferes with negative feedback of estrogens on the hypothalamus, thereby increasing the secretion of gonadotropin-releasing hormone and gonadotropins, and leading to stimulation of ovulation. Ospemifene is an SERM indicated for the treatment of dyspareunia. Raloxifene is an SERM used in the prevention of breast cancer and osteoporosis. Ulipristal is a progestrone agonist/antagonist used as an emergency contraceptive.
- 25.10 Use of testosterone is most appropriate in which patient?
- A 25-year-old competitive athlete
  - A 30-year-old man with hypogonadism due to testicular injury
  - A 50-year-old man with low testosterone related to aging
  - A 65-year-old man with low testosterone and a history of myocardial infarction
- Correct answer = B. Testosterone should only be used only for hypogonadism associated with documented medical conditions, and not low testosterone associated with aging. Testosterone replacement may increase the risk of cardiovascular events and should be used with caution in patients with a history of myocardial infarction and heart disease.

# Adrenal Hormones

Shannon Miller and Karen Whalen

26

## I. OVERVIEW

The adrenal cortex secretes two types of corticosteroids (glucocorticoids and mineralocorticoids; [Figure 26.1](#)) and the adrenal androgens. The adrenal cortex has three zones, and each zone synthesizes a different type of steroid hormone from cholesterol ([Figure 26.2](#)). The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone) that are responsible for regulating salt and water metabolism. The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol) that are involved with metabolism and response to stress. The inner zona reticularis secretes adrenal androgens (see Chapter 25). Secretion by the two inner zones and, to a lesser extent, the outer zone is controlled by pituitary adrenocorticotrophic hormone (ACTH; also called corticotropin), which is released in response to hypothalamic corticotropin-releasing hormone (CRH). Glucocorticoids serve as feedback inhibitors of ACTH and CRH secretion.

## II. CORTICOSTEROIDS

Corticosteroids differ in their metabolic (glucocorticoid) and electrolyte-regulating (mineralocorticoid) activity. The corticosteroids bind to specific intracellular cytoplasmic receptors in target tissues. Glucocorticoid receptors are widely distributed throughout the body, whereas mineralocorticoid receptors are confined mainly to excretory organs, such as the kidney, colon, salivary glands, and sweat glands. Both types of receptors are found in the brain. After dimerizing, the receptor–hormone complex recruits coactivator (or corepressor) proteins and translocates into the nucleus, where it attaches to gene promoter elements. There it acts as a transcription factor to turn genes on (when complexed with coactivators) or off (when complexed with corepressors), depending on the tissue ([Figure 26.3](#)). Because of this mechanism, some effects of corticosteroids take hours to days to occur. This section describes normal actions and therapeutic uses of corticosteroids.

### A. Glucocorticoids

Cortisol is the principal human glucocorticoid. Normally, its production is diurnal, with a peak in early morning followed by a decline and then a secondary, smaller peak in late afternoon. Stress and levels of the circulating steroid influence secretion. The effects of cortisol are many and diverse. In general, all glucocorticoids:

1. **Promote normal intermediary metabolism:** Glucocorticoids stimulate hepatic glucose production by enhancing expression of

### CORTICOSTEROIDS

**Glucocorticoids**  
*Cortisone*  
*Hydrocortisone*  
*Betamethasone*  
*Dexamethasone*  
*Prednisolone*  
*Prednisone*  
*Methylprednisolone*

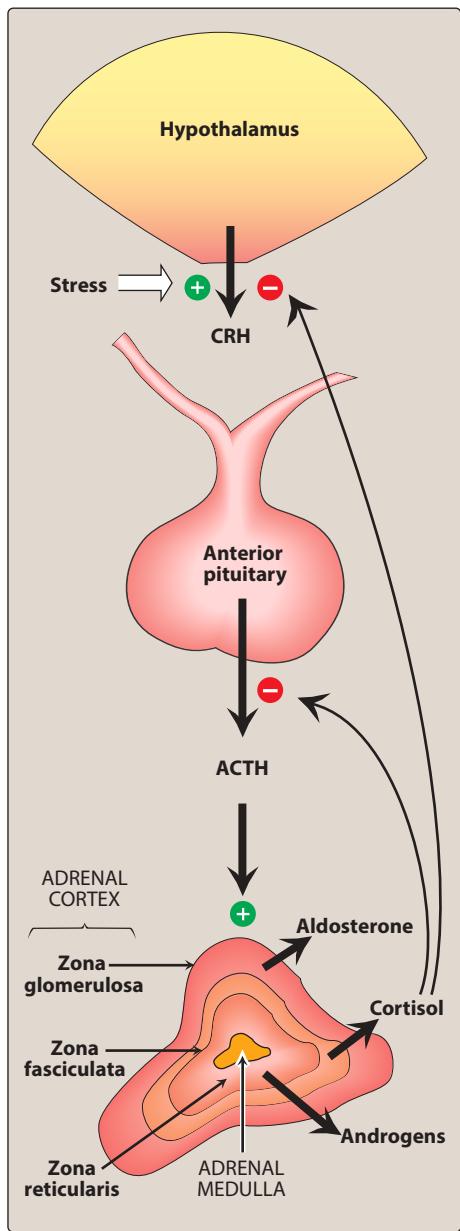
**Mineralocorticoids**  
*Fludrocortisone*  
*Triamcinolone*

### INHIBITORS OF ADRENOCORTICOID BIOSYNTHESIS OR FUNCTION

*Ketoconazole*  
*Spironolactone*  
*Eplerenone*

**Figure 26.1**

Summary of adrenal corticosteroids.



**Figure 26.2**

Regulation of corticosteroid secretion.  
ACTH = adrenocorticotropic hormone;  
CRH = corticotropin-releasing hormone.

enzymes involved in gluconeogenesis. They mobilize amino acids and stimulate lipolysis, thereby providing the building blocks and energy for glucose synthesis.

2. **Increase resistance to stress:** By raising plasma glucose levels, glucocorticoids provide the body with energy to combat stress caused by trauma, fright, infection, bleeding, or debilitating disease. [Note: Glucocorticoid insufficiency may result in hypoglycemia (for example, during stressful periods or fasting).]
3. **Alter blood cell levels in plasma:** Glucocorticoids cause a decrease in eosinophils, basophils, monocytes, and lymphocytes by redistributing them from the circulation to lymphoid tissue. Glucocorticoids also increase hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes.
4. **Possess anti-inflammatory action:** Potent anti-inflammatory and immunosuppressive activities are the most important therapeutic properties of glucocorticoids. Glucocorticoids lower circulating lymphocytes and inhibit the ability of leukocytes and macrophages to respond to mitogens and antigens. Glucocorticoids also decrease the production and release of proinflammatory cytokines. They inhibit phospholipase A<sub>2</sub>, which blocks the release of arachidonic acid (the precursor of the prostaglandins and leukotrienes), resulting in anti-inflammatory actions. Lastly, these agents influence the inflammatory response by stabilizing mast cell and basophil membranes, thereby decreasing histamine release.
5. **Affect other systems:** High levels of glucocorticoids provide negative feedback to reduce ACTH production and affect the endocrine system by suppressing synthesis of glucocorticoids and thyroid-stimulating hormone. In addition, adequate cortisol levels are essential for normal glomerular filtration. Corticosteroids may adversely affect other systems (see Adverse Effects in the following text).

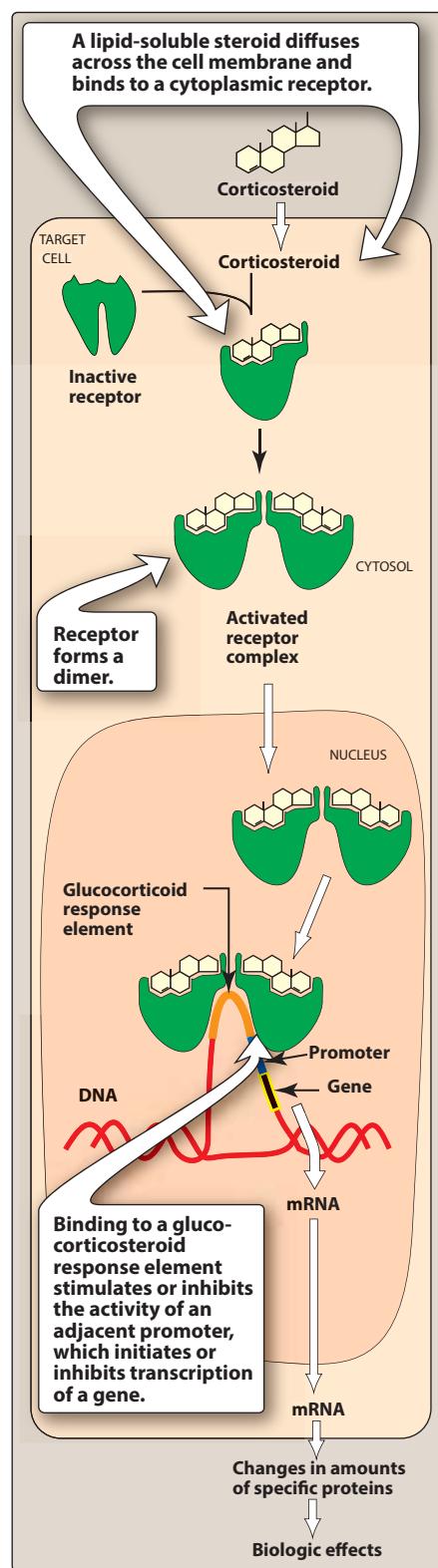
## B. Mineralocorticoids

Mineralocorticoids help to control fluid status and concentration of electrolytes, especially sodium and potassium. Aldosterone acts on mineralocorticoid receptors in the distal tubules and collecting ducts in the kidney, causing reabsorption of sodium, bicarbonate, and water. Conversely, aldosterone decreases reabsorption of potassium, which, with H<sup>+</sup>, is lost in the urine. Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands. [Note: Elevated aldosterone levels may cause alkalo-sis and hypokalemia, retention of sodium and water, and increased blood volume and blood pressure. Hyperaldosteronism is treated with spironolactone.]

## C. Therapeutic uses of the corticosteroids

Semisynthetic derivatives of corticosteroids vary in anti-inflammatory potency, mineralocorticoid activity, and duration of action (Figure 26.4). These agents are used in replacement therapy and in the treatment of severe allergic reactions, asthma, rheumatoid arthritis, other inflammatory disorders, and some cancers.

- 1. Replacement therapy for primary adrenocortical insufficiency (Addison disease):** Addison disease is caused by adrenal cortex dysfunction (diagnosed by lack of response to ACTH administration). *Hydrocortisone* [hye-droe-KOR-tih-sone], which is identical to natural cortisol, is given to correct the deficiency. Failure to do so results in death. Two-thirds of the daily dosage of *hydrocortisone* is administered in the morning and one-third in the afternoon, mimicking the normal diurnal variation in cortisol levels. Administration of *fludrocortisone* [floo-droe-KOR-tih-sone], a potent synthetic mineralocorticoid, may also be necessary to correct mineralocorticoid deficiency.
- 2. Replacement therapy for secondary or tertiary adrenocortical insufficiency:** These disorders are caused by a defect in CRH production by the hypothalamus or in ACTH production by the pituitary. *Hydrocortisone* is used for the treatment of these deficiencies.
- 3. Diagnosis of Cushing syndrome:** Cushing syndrome is caused by hypersecretion of glucocorticoids (hypercortisolism) that results from excessive release of ACTH by the anterior pituitary or an adrenal tumor. [Note: Chronic treatment with high doses of glucocorticoids is a frequent cause of iatrogenic Cushing syndrome.] Cortisol levels (urine, plasma, and saliva) and the *dexamethasone* [dex-a-METH-a-sone] suppression test are used to diagnose Cushing syndrome. The synthetic glucocorticoid *dexamethasone* suppresses cortisol release in normal individuals, but not in those with Cushing syndrome.
- 4. Replacement therapy for congenital adrenal hyperplasia (CAH):** CAH is a group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones. CAH may lead to virilization in females due to overproduction of adrenal androgens. Treatment requires administration of sufficient corticosteroids to suppress release of CRH and ACTH and normalize hormone levels. This decreases production of adrenal androgens. The choice of replacement hormone depends on the specific enzyme defect.
- 5. Relief of inflammatory symptoms:** Corticosteroids significantly reduce inflammation associated with rheumatoid arthritis and inflammatory skin conditions, including redness, swelling, heat, and tenderness. These agents are important for symptom control in persistent asthma, as well as treatment of exacerbations of asthma and inflammatory bowel disease. In osteoarthritis, intra-articular corticosteroids may be used for the treatment of a disease flare. Corticosteroids are not curative in these disorders. Corticosteroids are also used in conditions such as corneal inflammation, ulcerative colitis, Crohn's disease with acute exacerbations, and remissions and in skin diseases like pemphigus vulgaris and exfoliative dermatitis.
- 6. Treatment of allergies:** Corticosteroids are beneficial in the treatment of allergic rhinitis, as well as drug, serum, and transfusion allergic reactions. In the treatment of allergic rhinitis and asthma, *fluticasone* [floo-TIK-a-sone] and others (Figure 26.5) are inhaled into the respiratory tract from a metered dose dispenser. This minimizes systemic effects, reducing or eliminating the use of oral corticosteroids.



**Figure 26.3**  
Gene regulation by glucocorticoids.

GLUCOCORTICOID ACTIVITY	GLUCOCORTICOID (ANTI-INFLAMMATORY) ACTIVITY	MINERALOCORTICOID (SALT-RETAINING) ACTIVITY	EQUIVALENT ANTI-INFLAMMATORY DOSE	DOSE
<b>Short acting (1–12 hr):</b>				
<i>Hydrocortisone (cortisol)</i>	1	1	20 mg	10–400 mg/day (depends on the condition)—injection
<i>Cortisone</i>	0.8	0.8	—	—
<b>Intermediate acting (12–36 hr):</b>				
<i>Prednisolone</i>	4	0.8	5 mg	5–60 mg/day oral 10–40 mg/day injection
<i>Prednisone</i>	4	0.8	5 mg	
<i>Methylprednisolone</i>	5	0.5	4 mg	4–32 mg oral
<i>Triamcinolone</i>	5	0	4 mg	4–32 mg oral 5–40 mg injection
<i>Deflazacort</i>	4	0	6 mg	60–120 mg/day
<b>Long acting (36–55 hr):</b>				
<i>Betamethasone</i>	25	0	0.75 mg	0.5–5 mg/day oral 4–20 mg injection
<i>Dexamethasone</i>	25	0	0.75 mg	0.5–5 mg/day oral 5–20 mg/day injection for severe cases
<b>Mineralocorticoids:</b>				
<i>Fludrocortizone</i>	10	150	0.2 mg	50–200 µg/day
<i>Desoxycoicostefone acetate (DOCA)</i>	0	100	2.5 mg	2–5 mg/day sublingual 10–20 mg injection
<i>Aldosterone</i>	0.3	3000	No clinical use	—
<b>Equivalent salt-retaining dose</b>				

**Figure 26.4**

Pharmacologic effects and duration of action of some commonly used natural and synthetic corticosteroids. Activities are all relative to that of *hydrocortisone*, which is considered to be 1.

7. **Acceleration of lung maturation:** Fetal cortisol is a regulator of lung maturation. Consequently, a regimen of *betamethasone* or *dexamethasone* administered intramuscularly to the mother within 48 hours proceeding premature delivery can accelerate lung maturation in the fetus and prevent respiratory distress syndrome.
8. **Autoimmune disorders:** Immunosuppression and anti-inflammatory activities of steroids are highly helpful in severe immune-related diseases such as rheumatoid arthritis, allergic reactions, hemolytic anemia, idiopathic thrombocytopenic purpura, active chronic hepatitis, Stevens–Johnson’s syndrome, and to avoid allograft rejection.
9. **Corticosteroids in other conditions:** Corticosteroids are used in various conditions such as cerebral edema in the form of intravitreal dexamethasone to suppress inflammation and angiogenesis. It is also used in malignancies; septic shock; thyroid storm; several ocular inflammatory conditions such as retinitis, uveitis, iridocyclitis, keratitis, allergic conjunctivitis, and osteoarthritis; and collagen diseases.

## D. Pharmacokinetics

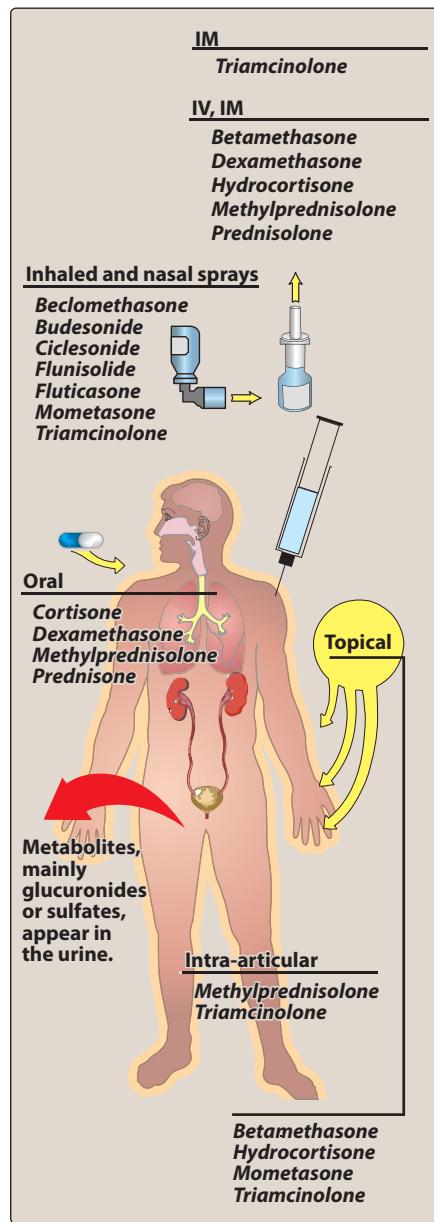
- Absorption and fate:** Corticosteroids are readily absorbed after oral administration. Selected compounds may be administered intravenously, intramuscularly, intra-articularly, topically, or via inhalation or intranasal delivery (Figure 26.5). All topical and inhaled glucocorticoids are absorbed to some extent and, therefore, have the potential to suppress the hypothalamic–pituitary–adrenal (HPA) axis. After absorption, glucocorticoids are greater than 90% bound to plasma proteins, mostly corticosteroid-binding globulin or albumin. Corticosteroids are metabolized by the liver microsomal oxidizing enzymes. The metabolites are conjugated to glucuronic acid or sulfate and excreted by the kidney. [Note: The half-life of corticosteroids may increase substantially in hepatic dysfunction.] *Prednisone* [PRED-nih-sone] is preferred in pregnancy because it minimizes steroid effects on the fetus. It is a prodrug that is not converted to the active compound, *prednisolone* [pred-NIH-so-lone], in the fetal liver. Any *prednisolone* formed in the mother is biotransformed to *prednisone* by placental enzymes.
- Dosage:** Factors that should be considered in determining the dosage of corticosteroids include glucocorticoid versus mineralocorticoid activity, duration of action, type of preparation, and time of day when the drug is administered. When large doses of corticosteroids are required for more than 2 weeks, suppression of the HPA axis occurs. Alternate-day administration of corticosteroids may prevent this adverse effect by allowing the HPA axis to recover/function on days the hormone is not taken.

## E. Adverse effects

Common adverse effects of long-term corticosteroid therapy are often dose-related (Figure 26.6). For example, in rheumatoid arthritis, the daily dose of *prednisone* was the strongest predictor of occurrence of adverse effects (Figure 26.7). Osteoporosis is the most common adverse effect due to the ability of glucocorticoids to suppress intestinal  $\text{Ca}^{2+}$  absorption, inhibit bone formation, and decrease sex hormone synthesis. Patients are advised to take calcium and vitamin D supplements. Bisphosphonates may also be useful in the treatment of glucocorticoid-induced osteoporosis. [Note: Increased appetite is not necessarily an adverse effect. In fact, it is one of the reasons for the use of *prednisone* in cancer chemotherapy.] The classic Cushing-like syndrome (redistribution of body fat, puffy face, hirsutism, and increased appetite) is observed in excess corticosteroid replacement. Cataracts may also occur with long-term corticosteroid therapy. Hyperglycemia may develop and lead to diabetes mellitus. Diabetic patients should monitor blood glucose and adjust medications accordingly if taking corticosteroids. Topical therapy can cause skin atrophy, ecchymosis, and purple striae.

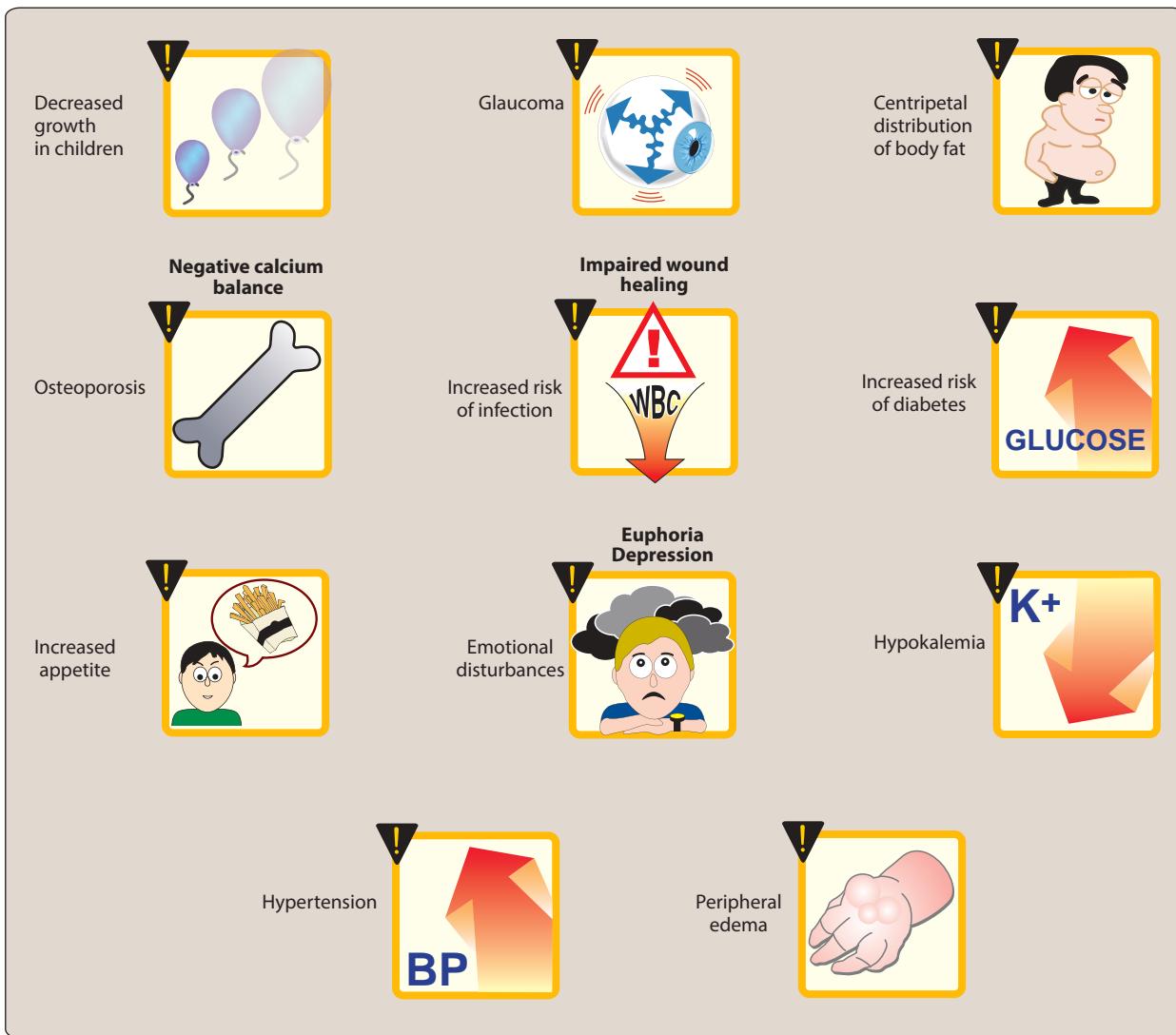
## F. Discontinuation

Sudden discontinuation of these drugs can cause serious consequences if the patient has suppression of the HPA axis. In this case,



**Figure 26.5**

Routes of administration and elimination of corticosteroids.  
IM = intramuscular; IV = intravenous.

**Figure 26.6**

Some commonly observed effects of long-term corticosteroid therapy. BP = blood pressure.

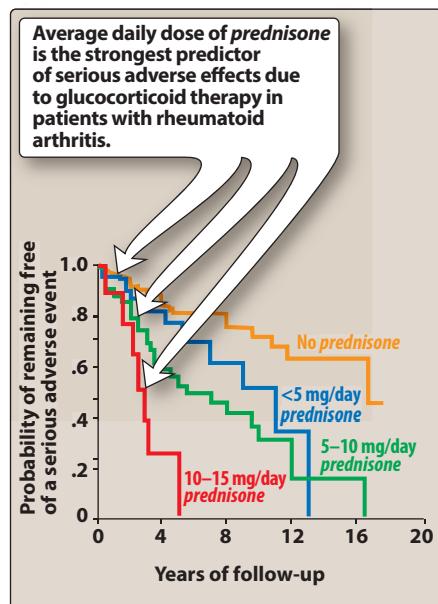
abrupt removal of corticosteroids causes acute adrenal insufficiency that can be fatal. This risk, coupled with the possibility that withdrawal could exacerbate the disease, means that the dose must be tapered slowly according to individual tolerance. The patient must be monitored carefully.

### G. Inhibitors of adrenocorticoid biosynthesis or function

Several substances are therapeutically useful as inhibitors of the synthesis or function of adrenal steroids: *ketoconazole*, *spironolactone*, and *eplerenone*.

1. **Ketoconazole:** *Ketoconazole* [kee-toe-KON-ah-zole] is an anti-fungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. It is used in the treatment of patients with Cushing syndrome.

- 2. Spironolactone:** This antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney. *Spironolactone* [speer-oh-no-LAK-tone] also antagonizes aldosterone and testosterone synthesis. It is effective for hyperaldosteronism and hepatic cirrhosis, and is used with other standard therapies for treatment of heart failure with reduced ejection fraction. It is also useful in the management of hirsutism in women, probably due to antiandrogen activity on the hair follicle. Adverse effects include hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.
- 3. Eplerenone:** *Eplerenone* [e-PLER-ih-none] specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist. This specificity avoids the adverse effect of gynecomastia that is associated with *spironolactone*. It is approved for the treatment of hypertension and for heart failure with reduced ejection fraction.



**Figure 26.7**

Probability of remaining free of a serious adverse event in patients with rheumatoid arthritis treated with no or different doses of *prednisone*. Modified from K. G. Saag, R. Koehnke, and J. R. Caldwell, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am. J. Med. 96: 115 (1994).

## Study Questions

Choose the ONE best answer.

- 26.1 Which part of the adrenal gland is correctly paired with the type of substance it secretes?
- Adrenal medulla—corticotropin
  - Zona fasciculata—cortisol
  - Zona glomerulosa—androgens
  - Zona reticularis—catecholamines
- 26.2 Corticosteroids are useful in the treatment of which of the following disorders?
- Cushing syndrome
  - Diabetes
  - Hypertension
  - Inflammatory bowel disease

Correct answer = B. The adrenal medulla secretes catecholamines. Corticotropin is secreted by the anterior pituitary. The zona glomerulosa secretes aldosterone, and the zona reticularis secretes androgens.

Correct answer = D. Corticosteroids can increase blood pressure and glucose and are not used in the treatment of hypertension or diabetes. Cushing syndrome is an excess secretion of glucocorticoids. Dexamethasone may be used in the diagnosis of Cushing syndrome, but not its treatment. Corticosteroids reduce inflammation and can be used in the management of inflammatory bowel disease.

26.3 Which adverse effect commonly occurs with glucocorticoid therapy?

- A. Glaucoma
- B. Hyperkalemia
- C. Weight loss
- D. Osteoarthritis

26.4 Which contributes to osteoporosis with long-term use of glucocorticoids?

- A. Increased excretion of calcium
- B. Inhibition of calcium absorption
- C. Stimulation of the hypothalamic–pituitary–adrenal axis
- D. Decreased production of prostaglandins

26.5 A child with severe asthma is treated with high-dose inhaled corticosteroids. Which adverse effect is of particular concern?

- A. Hypoglycemia
- B. Hirsutism
- C. Growth suppression
- D. Cushing syndrome

26.6 Which is appropriate for treatment of congenital adrenal hyperplasia in a child?

- A. Adrenocorticotrophic hormone (ACTH)
- B. Ketoconazole
- C. Prednisone
- D. Spironolactone

26.7 A patient with Addison disease treated with hydrocortisone is experiencing dehydration and hyponatremia. Which drug is best to add to the patient's therapy?

- A. Dexamethasone
- B. Fludrocortisone
- C. Prednisone
- D. Triamcinolone

Correct answer = A. Glucocorticoid therapy may cause hypokalemia, not hyperkalemia. Glucocorticoids also cause increased appetite and osteoporosis. Glaucoma is a known potential adverse effect of this class.

Correct answer = B. Glucocorticoid-induced osteoporosis is attributed to inhibition of calcium absorption and bone formation. Increased intake of calcium plus vitamin D and use of bisphosphonates may be indicated. Glucocorticoids suppress rather than stimulate the hypothalamic–pituitary–adrenal axis. The decreased production of prostaglandins does not play a role in bone formation.

Correct answer = C. Corticosteroids may retard bone growth. Chronic use of the medication may lead to growth suppression, so linear growth should be monitored periodically. Hyperglycemia, not hypoglycemia, is a possible adverse effect. Hirsutism and Cushing syndrome are unlikely with the dose that the child receives via inhalation.

Correct answer = C. Congenital adrenal hyperplasia is seen in infancy and childhood. Because cortisol synthesis is decreased, feedback inhibition of adrenocorticotrophic hormone (ACTH) formation and release is also decreased, resulting in enhanced ACTH formation. This in turn leads to increased levels of adrenal androgens and/or mineralocorticoids. The treatment is to administer a glucocorticoid, such as hydrocortisone (in infants) or prednisone, which restores the feedback inhibition. The other options are inappropriate.

Correct answer = B. To combat dehydration and hyponatremia, a corticosteroid with high mineralocorticoid activity is needed. Fludrocortisone has the greatest mineralocorticoid activity of the agents provided. The other drugs have little or no mineralocorticoid activity.

- 26.8 Which strategy is effective to minimize development of HPA axis suppression in a patient with rheumatoid arthritis on long-term high-dose corticosteroid therapy?
- Alternate-day administration
  - Administration via topical or inhalation route when possible
  - Immediate cessation of the corticosteroid
  - Administration of two-thirds of the daily dose in the morning and one-third in the afternoon
- 26.9 Which patient is most likely to have suppression of the HPA axis and require a slow taper of corticosteroid therapy?
- A patient taking 40 mg of prednisone daily for 7 days to treat an asthma exacerbation
  - A patient taking 10 mg of prednisone daily for 3 months for rheumatoid arthritis
  - A patient using mometasone nasal spray daily for 6 months for allergic rhinitis
  - A patient receiving an intra-articular injection of methylprednisolone for osteoarthritis
- 26.10 Which corticosteroid is most appropriate to administer to a woman in preterm labor to accelerate fetal lung maturation?
- Betamethasone
  - Fludrocortisone
  - Hydrocortisone
  - Prednisone

Correct answer = A. Topical or inhaled corticosteroids may minimize HPA axis suppression, but are unlikely to be effective in rheumatoid arthritis. Since the patient has been on long-term therapy, a taper would be necessary. Administration of two-thirds of the dose in the morning and one-third in the afternoon is a strategy to mimic the normal diurnal variation of cortisol secretion, but it does not prevent suppression of the HPA axis. Alternate day administration is beneficial.

Correct answer = B. Suppression of the HPA axis usually occurs with higher doses of corticosteroids when used for a duration of 2 weeks or more. Although the dose of prednisone is higher in the asthma patient, the duration of therapy is short, so the risk of HPA axis suppression is lower. The risk of HPA axis suppression is low with topical therapies such as intranasal mometasone and with one-time joint injections.

Correct answer = A. A corticosteroid with high glucocorticoid activity is needed to speed fetal lung maturation prior to delivery. Betamethasone has high glucocorticoid activity and is one of the recommended drugs in this context. Dexamethasone is the other. Fludrocortisone mainly has mineralocorticoid activity and is not useful in this situation. Hydrocortisone has much lower glucocorticoid activity. Prednisone has a higher glucocorticoid activity than hydrocortisone, but the fetus is not able to convert it to prednisolone, the active form.



# Drugs Affecting Bone Metabolism

Karen Whalen

# 27

## I. OVERVIEW

Osteoporosis, Paget disease, and osteomalacia are disorders of the bone. Osteoporosis is characterized by progressive loss of bone mass and skeletal fragility. Patients with osteoporosis have an increased risk of fractures, which can cause significant morbidity. Osteoporosis occurs most frequently in postmenopausal women and older adults of both sexes. Paget disease is a disorder of bone remodeling that results in disorganized bone formation and enlarged or misshapen bones. Unlike osteoporosis, Paget disease is usually limited to one or a few bones. Patients may experience bone pain, bone deformities, or fractures. Osteomalacia is softening of the bones that is most often attributed to vitamin D deficiency. [Note: Osteomalacia in children is referred to as rickets]. As osteoporosis is more common, drug therapy for osteoporosis is the focus of this chapter (Figure 27.1).

## II. BONE REMODELING

Throughout life, bone undergoes continuous remodeling, with about 10% of the skeleton replaced each year. Bone remodeling serves to remove and replace damaged bone and to maintain calcium homeostasis. Osteoclasts are cells that break down bone, a process known as bone resorption. Following bone resorption, osteoblasts or bone-building cells synthesize new bone. Crystals of calcium phosphate, known as hydroxyapatite, are deposited in the new bone matrix during the process of bone mineralization. Bone mineralization is essential for bone strength. Lastly, bone enters a resting phase until remodeling begins again. Bone loss occurs when bone resorption exceeds bone formation during the remodeling process. Figure 27.2 shows changes in bone morphology seen in osteoporosis.

## III. PREVENTION OF OSTEOPOROSIS

Strategies to reduce bone loss in postmenopausal women include adequate dietary intake of calcium and vitamin D, weight-bearing exercise, smoking cessation, and avoidance of excessive alcohol intake. Patients with inadequate dietary intake of calcium should receive calcium supplementation. *Calcium carbonate* is an inexpensive and commonly used calcium supplement. It contains 40% elemental calcium and should be taken with meals for best absorption. *Calcium citrate* (21% elemental calcium) is

### HORMONAL REGULATION OF CALCIUM AND PHOSPHATE HOMEOSTASIS

*Calcitonin*  
*Parathyroid hormone derivative—teriparatide*  
*Vitamin D*  
*Hormone replacement therapy (HRT)*

### ANTIRESORPTIVE AGENTS

*Bisphosphonates*  
*Abaloparotide*  
*Alendronate*  
*Ibandronate*  
*Risedronate*  
*Zoledronic acid*  
*Biological drug (monoclonal antibody)*  
*Denosumab*

### DRUGS FOR DISORDERS OF BONE REMODELING

*Etidronate*  
*Pamidronate*  
*Tiludronate*

### SELECTIVE ESTROGEN RECEPTOR MODULATOR

*Raloxifene*

#### Figure 27.1

Summary of drugs used in the treatment of osteoporosis and other bone disorders. (For drug dosages, refer to Appendix at the end of the book.)

**Figure 27.2**

Changes in bone morphology seen in osteoporosis.

better tolerated and may be taken with or without food. Adverse effects of calcium supplementation include gas and bloating. Calcium may interfere with absorption of iron preparations, thyroid replacement, and *fluoroquinolone* and *tetracycline* antibiotics, and administration of these drugs should be separated by several hours. Vitamin D is essential for absorption of calcium and bone health, and older patients are often at risk for vitamin D deficiency. Supplementation with vitamin D<sub>2</sub> (*ergocalciferol*) or vitamin D<sub>3</sub> (*cholecalciferol*) is used for treatment. In addition, patients at risk for osteoporosis should avoid drugs that increase bone loss such as glucocorticoids (Figure 27.3). [Note: Use of glucocorticoids (for example, *prednisone* 5 mg/day or equivalent) for 3 months or more is a significant risk factor for osteoporosis.]

#### IV. TREATMENT OF OSTEOPOROSIS

Pharmacologic therapy for osteoporosis is warranted in postmenopausal women and men aged 50 years or over who have a previous osteoporotic fracture, a bone mineral density that is 2.5 standard deviations or more below that of a healthy young adult, or a low bone mass (osteopenia) with a high probability of future fractures.

##### A. Bisphosphonates

Bisphosphonates including *alendronate* [a-LEND-row-nate], *risedronate* [rih-SED-row-nate], and *zoledronic acid* are preferred agents for treatment of postmenopausal osteoporosis. These bisphosphonates, along with *etidronate* [e-TID-row-nate], *ibandronate* [eye-BAN-dro-nate], *pamidronate* [pah-MID-row-nate], and *tiludronate* [till-UH-droe-nate], comprise an important drug group used for the treatment of bone disorders such as osteoporosis and Paget disease, as well as for the treatment of bone metastases and hypercalcemia of malignancy.

- Mechanism of action:** Bisphosphonates bind to hydroxyapatite crystals in the bone and decrease osteoclastic bone resorption, resulting in a small increase in bone mass and a decreased risk of fractures in patients with osteoporosis. The beneficial effects of *alendronate* persist over several years of therapy (Figure 27.4), but discontinuation results in a gradual loss of effects.
- Pharmacokinetics:** The oral bisphosphonates *alendronate*, *risedronate*, and *ibandronate* are dosed on a daily, weekly, or monthly basis depending on the drug (Figure 27.5). Absorption after oral administration is poor, with less than 1% of the dose absorbed. Food and other medications significantly interfere with absorption of oral bisphosphonates, and guidelines for administration should be followed to maximize absorption (Figure 27.5). Bisphosphonates are rapidly cleared from the plasma, primarily because they avidly bind to hydroxyapatite in the bone. Once bound to bone, they are cleared over a period of hours to years. Elimination is predominantly via the kidney, and bisphosphonates should be avoided in severe renal impairment. For patients unable to tolerate oral bisphosphonates, intravenous *ibandronate* and *zoledronic acid* are alternatives.

<b>Aluminum antacids</b>
<b>Anticonvulsants (for example, phenytoin)</b>
<b>Aromatase inhibitors</b>
<b>Furosemide</b>
<b>Glucocorticoids</b>
<b>Heparin</b>
<b>Medroxyprogesterone acetate</b>
<b>Proton-pump inhibitors</b>
<b>Selective serotonin reuptake inhibitors</b>
<b>Thiazolidinediones</b>
<b>Thyroid (excessive replacement)</b>

**Figure 27.3**

Drugs that can contribute to bone loss or increased fracture risk.

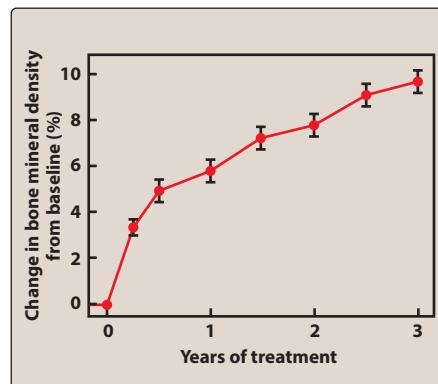
**3. Adverse effects:** These include diarrhea, abdominal pain, and musculoskeletal pain. *Alendronate*, *risedronate*, and *ibandronate* are associated with esophagitis and esophageal ulcers. To minimize esophageal irritation, patients should remain upright after taking oral bisphosphonates. Although uncommon, osteonecrosis of the jaw and atypical femur fractures may occur with use of bisphosphonates. The risk of atypical fractures seems to increase with long-term use of bisphosphonates. Therefore, current guidelines recommend a drug holiday for some patients after 5 years of oral bisphosphonates or 3 years of *zoledronic acid*. Figure 27.6 shows relative potencies of the bisphosphonates.

## B. Denosumab

*Denosumab* [den-OH-sue-mab] is a monoclonal antibody that targets receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibits osteoclast formation and function. *Denosumab* is approved for the treatment of postmenopausal osteoporosis in women at a high risk of fracture. It is administered via subcutaneous injection every 6 months. *Denosumab* is considered a first-line agent for osteoporosis, particularly in patients at a higher risk of fractures. The drug has been associated with an increased risk of infections, dermatological reactions, hypocalcemia, and rarely osteonecrosis of the jaw and atypical fractures.

## C. Parathyroid agents

*Teriparatide* [ter-ih-PAR-a-tide] is a recombinant form of human parathyroid hormone and *abaloparatide* [a-bal-oh-PAR-a-tide] is an analog of parathyroid hormone-related peptide. These drugs act as agonists at the parathyroid hormone receptor, and once-daily subcutaneous administration results in stimulation of osteoblastic activity and increased bone formation and bone strength. By contrast,



**Figure 27.4**

Effect of *alendronate* therapy on the bone mineral density of the lumbar spine.

BISPHOSPHONATE	FORMULATION	DOSING FREQUENCY <sup>1</sup>
<i>Alendronate</i>	Oral tablet Effervescent tablet	Daily or weekly Weekly
<i>Ibandronate</i>	Oral tablet Intravenous	Daily or monthly Every 3 months
<i>Risedronate</i>	Oral tablet Oral delayed-release tablet	Daily, weekly, or monthly Weekly
<i>Zoledronic acid</i>	Intravenous	Yearly

**DOSING INSTRUCTIONS FOR ORAL BISPHOSPHONATES**

- Take with 6 to 8 ounces of plain water only  
[Note: Take *risedronate* delayed-release tablet with at least 4 ounces of plain water]
- Take at least 30 minutes (60 minutes for *ibandronate*) BEFORE other food, drink, or medications  
[Note: Take *risedronate* delayed-release tablet immediately AFTER breakfast]
- Remain upright and do not lie down or recline for at least 30 minutes (60 minutes for *ibandronate*) after taking

<sup>1</sup>Frequency of administration for individual agents varies with dosage, with higher doses administered less frequently.

**Figure 27.5**

Dosage formulations and instructions for administration of bisphosphonates for the treatment of osteoporosis.

Bisphosphonate	Antiresorptive activity
<i>Etidronate</i>	1
<i>Tiludronate</i>	10
<i>Pamidronate</i>	100
<i>Alendronate</i>	1000
<i>Risedronate</i>	5000
<i>Ibandronate</i>	10,000
<i>Zoledronic acid</i>	10,000

**Figure 27.6**

Antiresorptive activity of some bisphosphonates.

other drugs for osteoporosis inhibit bone resorption. These agents should be reserved for patients at a high risk of fractures and those who have failed or cannot tolerate other osteoporosis therapies. Both drugs have been associated with hypercalcemia, orthostatic hypotension, and an increased risk of osteosarcoma in rats. Cumulative lifetime use of either agent for more than 2 years is not recommended.

#### D. Selective estrogen receptor modulators

Lower estrogen levels after menopause promote proliferation and activation of osteoclasts, and bone mass can decline rapidly. Estrogen replacement is effective for the prevention of postmenopausal bone loss. However, since estrogen may increase the risk of endometrial cancer (when used without a progestin in women with an intact uterus), breast cancer, stroke, venous thromboembolism, and coronary events, it is no longer recommended as a preventive therapy for osteoporosis. *Raloxifene* [rah-LOX-ih-feen] is a selective estrogen receptor modulator approved for the prevention and treatment of osteoporosis. It has estrogen-like effects on bone and estrogen antagonist effects on breast and endometrial tissue. Therefore, *raloxifene* increases bone density without increasing the risk of endometrial cancer, and it decreases the risk of invasive breast cancer. Because it has not been shown to reduce nonvertebral or hip fractures, *raloxifene* should be used as an alternative to bisphosphonates or *denu-somab* in the treatment of postmenopausal osteoporosis. Adverse effects include hot flashes, leg cramps, and increased risk of venous thromboembolism.

#### E. Calcitonin

Salmon *calcitonin* [cal-SIH-toe-nin] is indicated for the treatment of osteoporosis in women who are at least 5 years postmenopausal. The drug reduces bone resorption, but it is less effective than other agents and is no longer routinely recommended for the treatment of osteoporosis. A unique property of *calcitonin* is relief of pain associated with osteoporotic fracture. Therefore, *calcitonin* is sometimes prescribed for the short-term treatment of patients with a recent painful vertebral fracture. The intranasal formulation is most commonly used in osteoporosis, and adverse effects include rhinitis and other nasal symptoms. It is available as a synthetic salmon calcitonin 100 IU/ml for subcutaneous injection and 200 IU delivered by nasal spray.

#### F. Parathormone

Parathormone (PTH) is the polypeptide hormone of the parathyroid gland having an 84-amino acid sequence. Its secretion is regulated through the plasma calcium levels by calcium-sensing receptor. Falling plasma levels of calcium induce a raise in PTH levels. Similarly, the active form of vitamin D in plasma is also a key determinant of plasma PTH levels. Elevated serum  $\text{Ca}^{2+}$  levels serve as a negative-feedback loop to signal the parathyroid glands to stop the release of PTH. After secretion, PTH is degraded in liver and

kidney within 2 to 5 minutes. PTH increases bone resorption by activating osteoclasts and enhances bone formation. In kidney, PTH increases calcium reabsorption in the distal tubule and regulates the amount of calcium excretion. Although PTH does not have any direct effect on calcium absorption from the intestine, indirectly it facilitates the synthesis of active vitamin D, calcitriol (1,25-dihydroxyvitamin D), in the kidneys by the activation of  $1\alpha$ -hydroxylase. Calcitriol in turn promotes the absorption of calcium from the intestine. PTH acts through its receptor which is G-protein coupled, and its activation causes an increased intracellular  $\text{Ca}^{2+}$  level in target cells through cAMP.

PTH substitution is not a choice of hypoparathyroidism as the plasma calcium levels can be attained by oral vitamin D therapy. Recombinant PTH *teriparatide* has been introduced to increase bone mineral density in severe osteoporosis. It is administered as 20 µg dose once daily by the subcutaneous route. It stimulates bone formation and it has been found to be more effective than estrogen supplementation in reducing the risk of fractures, especially in women who suffer multiple fractures. Dizziness and leg cramps are the main side effects reported. However, *teriparatide* is contraindicated in Paget's disease and hypercalcemia. It is also used in the differential diagnosis of true hypoparathyroidism from pseudothyroidism by checking the increase in plasma levels of calcium in response to intravenous *teriparatide*.

### G. Calcium and vitamin D supplements

Citrate, carbonate, gluconate, lactate, chloride, and phosphate salts of calcium are used for the substitution of calcium. Among all calcium, gluconate can be safely used for intravenous administration. Oral calcium supplements are generally well tolerated except for a few GI-related side effects such as constipation and bloating. Dietary allowance of calcium supplementation is 0.8 to 1.5 g/day. Absorption of calcium in the intestine is a specialized process such as carrier-mediated active transport and facilitated diffusion. The active form of vitamin D is cholecalciferol (D3) synthesized in the skin by the influence of UV rays of the sun. However, externally supplemented D3 is orally well absorbed and cholecalciferol influences the intestinal absorption of calcium. Therefore, calcium supplementation is accompanied by D3. Prophylactic use of vitamin D is 400 IU/day. For therapeutic supplementation (that is, for correcting the deficiency), the dose varies from 3000 to 4000 IU/day. Further, higher doses are only used for treating hypoparathyroidism. However, caution needs to be exercised to avoid hypervitaminosis-related complications by using higher dose supplementation of vitamin D. Therapeutic vitamin D is used for rickets in children, osteomalacia in adults, Fanconi syndrome and along with calcium for maintaining bone density in postmenopausal women. *Calcipotriol* is the synthetic analog of vitamin D which inhibits cell proliferation and enhances cell differentiation in the skin of patients with psoriasis. As a 0.005% cream, it is approved for the topical treatment of psoriasis.

## Study Questions

Choose the ONE best answer.

27.1 Which is correct regarding the pharmacokinetics of the bisphosphonates?

- A. Bisphosphonates are well absorbed after oral administration.
- B. Food or other medications greatly impair absorption of bisphosphonates.
- C. Bisphosphonates are mainly metabolized via the cytochrome P450 system.
- D. Elimination half-life of bisphosphonates ranges from 4 to 6 hours.

27.2 Which agent is administered once yearly to treat osteoporosis?

- A. Abaloparatide
- B. Denusomab
- C. Risedronate
- D. Zoledronic acid

27.3 Which osteoporosis medication works by preferentially stimulating activity of osteoblasts?

- A. Denosumab
- B. Ibandronate
- C. Raloxifene
- D. Teriparatide

27.4 Which best describes the mechanism of action of denosumab in the treatment of osteoporosis?

- A. Parathyroid hormone analog
- B. RANKL inhibitor
- C. Selective estrogen receptor modulator
- D. Vitamin D analog

27.5 A 52-year-old woman has a history of rheumatoid arthritis, diabetes, hypertension, and heartburn. Her daily medications include methotrexate, prednisone, metformin, hydrochlorothiazide, lisinopril, and calcium carbonate as needed for heartburn symptoms. She is worried about the risk of osteoporosis as she approaches menopause. Which of her medications is most likely to contribute to the risk of developing osteoporosis?

- A. Calcium carbonate
- B. Hydrochlorothiazide
- C. Lisinopril
- D. Prednisone

Correct answer = B. Food and other medications decrease absorption of bisphosphonates, which are already poorly absorbed (less than 1%) after oral administration. Bisphosphonates are cleared from the plasma by binding to bone and being cleared by the kidney (not metabolized by the CYP450 system). The elimination half-life may be years.

Correct answer = D. Zoledronic acid is administered intravenously once per year. Abaloparatide is a daily subcutaneous injection. Denosumab is administered every 6 months, and risedronate is administered daily, weekly, or monthly.

Correct answer = D. Teriparatide is a parathyroid hormone analog that has anabolic effects on bone through stimulation of osteoblast activity. The other medications work primarily by inhibiting osteoclast activity (inhibition of bone resorption).

Correct answer = B. Denosumab is a monoclonal antibody that targets receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibits osteoclast formation and function.

Correct answer = D. Glucocorticoids (for example, prednisone at a dose of  $\geq 5$  mg per day for greater than 3 months) are a significant risk factor for osteoporosis. The other medications have not been shown to increase the risk of osteoporosis, and calcium carbonate and hydrochlorothiazide (diuretic that increases calcium retention) may be beneficial for patients at risk of osteoporosis.

- 27.6 A 65-year-old woman who has been diagnosed with postmenopausal osteoporosis has no history of fractures and no other pertinent medical conditions. Which is most appropriate for management of her osteoporosis?
- A. Alendronate
  - B. Calcitonin
  - C. Denosumab
  - D. Raloxifene
- 27.7 A 55-year-old woman with postmenopausal osteoporosis has a past medical history of ethanol abuse, alcoholic liver disease, erosive esophagitis, and hypothyroidism. Which is the primary reason oral bisphosphonates should be used with caution in this patient?
- A. Age
  - B. Erosive esophagitis
  - C. Liver disease
  - D. Thyroid disease
- 27.8 A 70-year-old woman is being started on ibandronate once monthly for the treatment of osteoporosis. Which is important to communicate to this patient?
- A. Take this medication with orange juice to increase absorption.
  - B. Take this medication after meals to minimize stomach upset.
  - C. Remain upright for at least 60 minutes after taking this medication.
  - D. Adverse effects may include blood clots and leg cramps.
- 27.9 Use of which agent for osteoporosis should be limited to no more than 2 years?
- A. Calcitonin
  - B. Denosumab
  - C. Teriparatide
  - D. Zoledronic acid
- 27.10 A patient has been taking alendronate for postmenopausal osteoporosis for 5 years with a slight increase in bone mineral density and no occurrence of fractures. Risk of which adverse effect might warrant consideration of a drug holiday from alendronate in this patient?
- A. Atypical femur fractures
  - B. Esophagitis
  - C. Osteosarcoma
  - D. Rhinitis

Correct answer = A. Bisphosphonates are first-line therapy for osteoporosis in postmenopausal women without contraindications. Raloxifene is an alternative that may be less efficacious (especially for nonvertebral and hip fractures), and calcitonin is not recommended. Denosumab is best used for patients at high risk of fractures.

Correct answer = B. Bisphosphonates are known to cause esophageal irritation and should be used with caution in a patient with a history of erosive esophagitis. Age is not a factor for consideration in bisphosphonate use. Liver disease is not a contraindication to bisphosphonate use, since bisphosphonates are mainly cleared via the kidney. Thyroid disease is not a contraindication to bisphosphonate use, although overaggressive replacement of thyroid may contribute to osteoporosis.

Correct answer = C. Patients need to remain upright for 60 minutes after ibandronate (30 minutes for other bisphosphonates). Ibandronate should be given on an empty stomach with plain water only. Bisphosphonates, unlike raloxifene, are not associated with blood clots and leg cramps.

Correct answer = C. Use of the recombinant parathyroid hormone teriparatide should be limited to 2 years. Use beyond 2 years has not been studied and is not recommended. The other agents do not have such limitations.

Correct answer = A. Atypical femur fractures are associated with long-term use of bisphosphonates (>5 years). Therefore, a drug holiday might be considered since the patient has had no fractures. Esophagitis, while a side effect of bisphosphonate therapy, can be prevented with appropriate administration. Osteosarcoma is associated with the parathyroid hormone analogs, and rhinitis is associated with intranasal calcitonin.



# UNIT VI

## Chemotherapeutic Drugs

# Principles of Antimicrobial Therapy

28

Jamie Kisgen

### I. OVERVIEW

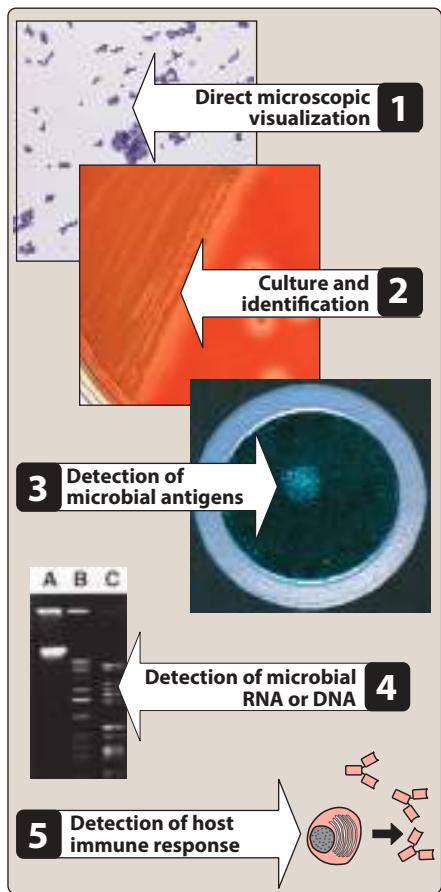
Antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings. Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity—that is, they have the ability to injure or kill an invading microorganism without harming the cells of the host. In most instances, the selective toxicity is relative rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism while still being tolerated by the host. “Antibiotics” refers to the substances which are produced by organisms which are known to selectively retard the growth or kill other microorganisms. In order to cover a wide range of synthetic, semisynthetic, and natural agents, the term “antimicrobial agents” is commonly used.

### II. SELECTION OF ANTIMICROBIAL AGENTS

Selection of the most appropriate antimicrobial agent requires knowledge of 1) the identity of the organism, 2) the susceptibility of the organism to a particular agent, 3) the site of the infection, 4) patient factors, 5) the safety and efficacy of the agent, and 6) the cost of therapy. However, most patients require empiric therapy (immediate administration of drug(s) prior to bacterial identification and susceptibility testing).

#### A. Identification of the infecting organism

Characterizing the organism is central to selection of appropriate therapy. A rapid assessment of the nature of the pathogen can sometimes be made on the basis of the Gram stain, which is particularly useful in identifying the presence and morphologic features of microorganisms in body fluids that are normally sterile (blood, cerebrospinal fluid [CSF], pleural fluid, synovial fluid, peritoneal fluid, and urine). However, it is generally necessary to culture the infective



**Figure 28.1**

Some laboratory techniques that are useful in the diagnosis of microbial diseases.

organism to arrive at a conclusive diagnosis and determine the susceptibility to antimicrobial agents. Thus, it is essential to obtain a sample culture of the organism prior to initiating the first dose of antibiotics. Otherwise, it is impossible to differentiate whether a negative culture is due to the absence of organisms or is a result of antimicrobial effects of administered antibiotic. Definitive identification of the infecting organism may require other laboratory techniques, such as detection of microbial antigens, DNA, or RNA, or an inflammatory or host immune response to the microorganism (Figure 28.1). Newer techniques such as rapid polymerase chain reaction (PCR) and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry offer accurate, rapid, and cost-effective identification of the infecting organism(s).

### B. Empiric antimicrobial therapy

Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its susceptibility to antimicrobial agents established. However, in the critically ill patient, such a delay could prove fatal, and immediate empiric therapy is indicated. Antibiotics used for empirical therapy are usually broad-spectrum antibiotics and should be substituted with narrow-spectrum antibiotics within 48 to 72 hours as per culture and sensitivity report.

1. **Timing:** Acutely ill patients with infections of unknown origin—for example, a neutropenic patient (one who is at risk for infections due to a reduction in neutrophils) or a patient with meningitis (acute inflammation of the membranes covering the brain and spinal cord)—require immediate treatment. If possible, therapy should be initiated after specimens for laboratory analysis have been obtained but before the results of the culture and sensitivity are available.
2. **Selecting a drug:** Drug choice in the absence of susceptibility data is influenced by the site of infection, the patient history (for example, previous infections, age, recent travel history, recent antimicrobial therapy, immune status, whether the infection was hospital- or community-acquired), and local susceptibility data. Broad-spectrum therapy such as third- or fourth-generation cephalosporins, doxycycline, and fluoroquinolones may be indicated initially when the organism is unknown or polymicrobial infections are likely. The choice of agent(s) may also be guided by known association of particular organisms in a given clinical setting. For example, gram-positive cocci in the spinal fluid of a newborn is unlikely to be *Streptococcus pneumoniae* and most likely to be *Streptococcus agalactiae* (group B streptococci), which is sensitive to *penicillin G*. By contrast, gram-positive cocci in the spinal fluid of a 40-year-old patient are most likely to be *S. pneumoniae*. This organism is frequently resistant to *penicillin G* and often requires treatment with a high-dose third-generation cephalosporin (such as *ceftriaxone*) or *vancomycin*.

### C. Determination of antimicrobial susceptibility

After a pathogen is cultured, its susceptibility to specific antibiotics serves as a guide in selection of antimicrobial therapy. Some pathogens, such as *Streptococcus pyogenes* and *Neisseria meningitidis*, usually have predictable susceptibility patterns to certain antibiotics. In contrast, most gram-negative bacilli, enterococci, and staphylococcal species

often show unpredictable susceptibility patterns and require susceptibility testing to determine appropriate antimicrobial therapy. The minimum inhibitory and bactericidal concentrations are used in determining susceptibility of a drug and can be experimentally determined (Figure 28.2).

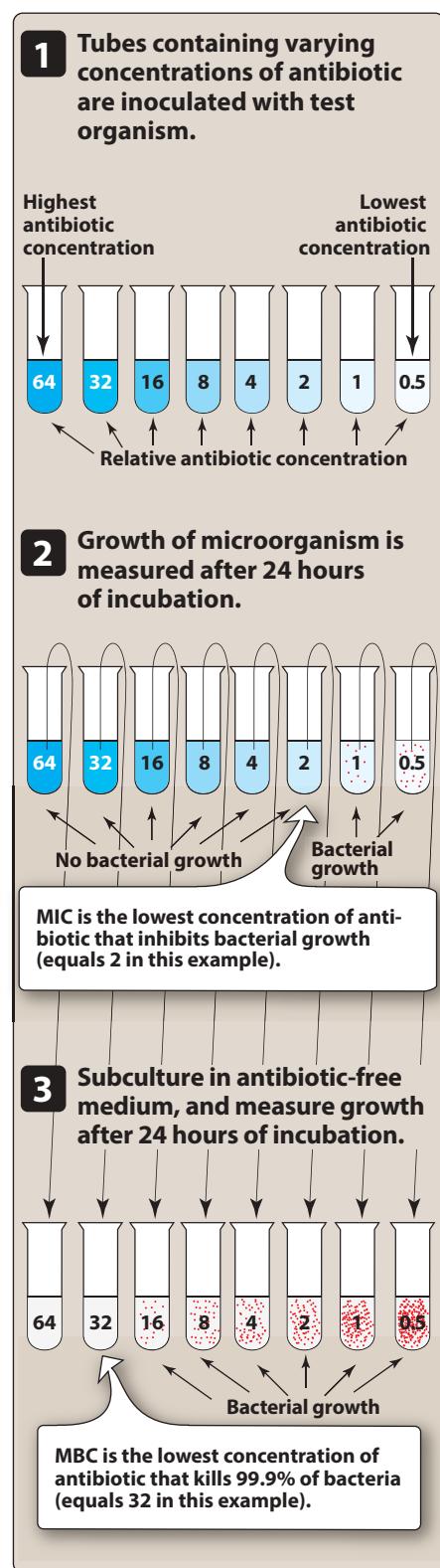
- Bacteriostatic versus bactericidal drugs:** Antimicrobial drugs are commonly classified as either bacteriostatic or bactericidal. Historically, bacteriostatic drugs were thought to only arrest the growth and replication of bacteria at drug serum levels achievable in the patient, whereas bactericidal drugs are able to effectively kill  $\geq 99.9\%$  (3-log reduction) within 18 to 24 hours of incubation under specific laboratory conditions.

Bacteriostatic drugs include *chloramphenicol*, *erythromycins*, *clindamycin*, sulfonamides, and tetracyclines.

Bactericidal drugs include aminoglycosides,  $\beta$ -lactams, *vancomycin*, quinolones, *rifampicin*, and *metronidazole*.

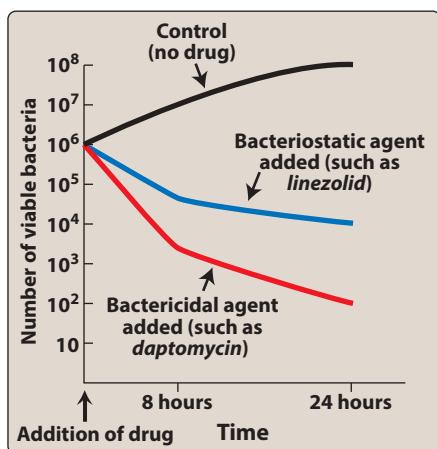
There is a growing consensus that this classification may be too simplistic as most bacteriostatic agents are able to effectively kill organisms; however, they are unable to meet the arbitrary cutoff value in the bactericidal definition. Figure 28.3 shows a laboratory experiment in which a bactericidal agent is compared to a bacteriostatic agent and a control. Note that the rate of in vitro killing is greater with bactericidal agents, but both agents are able to effectively kill the organism. It is also possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another. For example, *linezolid* is bacteriostatic against *Staphylococcus aureus* and enterococci but is bactericidal against most strains of *S. pneumoniae*. Some antimicrobials can be both bacteriostatic and bactericidal depending on dose, duration of exposure, concentration, and state of the invading bacteria. Concentration-dependent killing—that is, rate and extent of killing of microbes—increases with increasing drug concentration (for example *aminoglycosides*, *fluoroquinolones*, and *metronidazole*). However, recent data have demonstrated that bactericidal and bacteriostatic agents have similar efficacy for treating common clinical infections. In the end, other factors may have a greater impact, including the host immune system, drug concentration at the site of infection, and underlying severity of the illness.

- Minimum inhibitory concentration:** The minimum inhibitory concentration (MIC) is the lowest antimicrobial concentration that prevents visible growth of an organism after 24 hours of incubation. This serves as a quantitative measure of in vitro susceptibility and is commonly used in practice to streamline therapy. Computer automation has improved the accuracy and decreased the turnaround time for determining MIC results and is the most common approach used by clinical laboratories.
- Minimum bactericidal concentration:** The minimum bactericidal concentration (MBC) is the lowest concentration of antimicrobial agent that results in a 99.9% decline in colony count after overnight broth dilution incubations (Figure 28.2). [Note: The MBC is rarely determined in clinical practice due to the time and labor requirements.] Time-dependent killing—that is, bactericidal activity—continues as long as the serum concentration is maintained above MIC for the entire interval between doses (for example,  $\beta$ -lactam and *vancomycin*).



**Figure 28.2**

Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.



**Figure 28.3**

Effects of bactericidal and bacteriostatic drugs on the growth of bacteria in vitro.

#### D. Effect of the site of infection on therapy:

##### The blood–brain barrier

Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated. Capillaries with varying degrees of permeability carry drugs to the body tissues. Natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as the prostate, testes, placenta, the vitreous body of the eye, and the central nervous system (CNS). Of particular significance are the capillaries in the brain, which help to create and maintain the blood–brain barrier. This barrier is formed by the single layer of endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules, except those that are small and lipophilic. The penetration and concentration of an antibacterial agent in the CSF are particularly influenced by the following:

- Lipid solubility:** The lipid solubility of a drug is a major determinant of its ability to penetrate the blood–brain barrier. Lipid-soluble drugs, such as *chloramphenicol* and *metronidazole*, have significant penetration into the CNS, whereas  $\beta$ -lactam antibiotics, such as *penicillin*, are ionized at physiologic pH and have low lipid solubility. Therefore, they have limited penetration through the intact blood–brain barrier under normal circumstances. In infections such as meningitis in which the brain becomes inflamed, the barrier does not function as effectively, and local permeability is increased. Some  $\beta$ -lactam antibiotics can enter the CSF in therapeutic amounts when the meninges are inflamed.
- Molecular weight:** A drug with a low molecular weight has an enhanced ability to cross the blood–brain barrier, whereas compounds with a high molecular weight (for example, *vancomycin*) penetrate poorly, even in the presence of meningeal inflammation.
- Protein binding:** A high degree of protein binding of a drug restricts its entry into the CSF. Therefore, the amount of free (unbound) drug in serum, rather than the total amount of drug present, is important for CSF penetration.
- Susceptibility to transporters or efflux pumps:** Antibiotics that have an affinity for transporter mechanisms or do not have an affinity for efflux pumps have better CNS penetration.

#### E. Patient factors

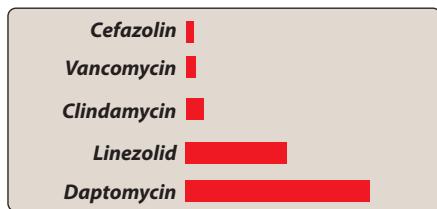
In selecting an antibiotic, attention must be paid to the condition of the patient. For example, the status of the immune system, kidneys, liver, circulation, and age must be considered. In women, pregnancy or breast-feeding also affects selection of the antimicrobial agent.

- Immune system:** Elimination of infecting organisms from the body depends on an intact immune system, and the host defense system must ultimately eliminate the invading organisms. Alcoholism, diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, advanced age, and immunosuppressive drugs can affect immunocompetence. High doses of bactericidal agents or longer courses of treatment may be required to eliminate infective organisms in these individuals.

2. **Renal dysfunction:** Poor kidney function may cause accumulation of certain antibiotics. Dosage adjustment prevents drug accumulation and adverse effects. Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens. However, direct monitoring of serum levels of some antibiotics (for example, *vancomycin* and aminoglycosides) is preferred to identify maximum and/or minimum values and prevent potential toxicities. [Note: The number of functional nephrons decreases with age. Thus, elderly patients are particularly vulnerable to accumulation of drugs eliminated by the kidneys, even with normal serum creatinine levels.]
3. **Hepatic dysfunction:** Antibiotics that are concentrated or eliminated by the liver (for example, *erythromycin* and *doxycycline*) must be used with caution when treating patients with liver dysfunction.
4. **Poor perfusion:** Decreased circulation to an anatomic area, such as the lower limbs of a diabetic patient, reduces the amount of antibiotic that reaches that site of infection, making it more difficult to treat. Decreased perfusion of the gastrointestinal tract may result in reduced absorption, making attainment of therapeutic concentrations more difficult with enteral routes.
5. **Age:** Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of agents such as *chloramphenicol* and sulfonamides. Young children should not be treated with tetracyclines or quinolones, which affect bone growth and joints, respectively. Elderly patients may have decreased renal or liver function, which may alter the pharmacokinetics of certain antibiotics.
6. **Pregnancy and lactation:** Many antibiotics cross the placental barrier or enter the nursing infant via the breast milk. Prescribers should consult the product labeling of an antibiotic to review the risk summary and clinical considerations for use in pregnancy and lactation. Although the concentration of an antibiotic in fetal circulation or in breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects. For example, congenital abnormalities have been reported after administration of tetracyclines to pregnant women, and these agents should generally be avoided in pregnancy due to the risk to the fetus.
7. **Risk factors for multidrug-resistant organisms:** Infections with multidrug-resistant pathogens need broader antibiotic coverage when initiating empiric therapy. Common risk factors for infection with these pathogens include prior antimicrobial therapy in the preceding 90 days, hospitalization for greater than 2 days within the preceding 90 days, current hospitalization exceeding 5 days, high frequency of resistance in the community or local hospital unit (assessed using hospital antibiograms), and immunosuppressive diseases and/or therapies.

#### F. Safety of the agent

Penicillins are among the least toxic of all antimicrobial drugs because they interfere with a site or function unique to the growth of microorganisms. Other antimicrobial agents (for example, *chloramphenicol*)



**Figure 28.4**

Relative cost of some drugs used for the treatment of *Staphylococcus aureus*.

have less specificity and are reserved for life-threatening infections because of the potential for serious toxicity to the patient. [Note: Safety is related not only to the inherent nature of the drug but also to the patient factors described in the preceding text that can predispose to toxicity.]

### G. Cost of therapy

It is common for several drugs to show similar efficacy in treating an infection but vary widely in cost. For example, treatment of *methicillin*-resistant *Staphylococcus aureus* (MRSA) generally includes one of the following: *vancomycin*, *clindamycin*, *daptomycin*, or *linezolid*. Although the choice of therapy usually centers on the site of infection, severity of the illness, and ability to take oral medications, it is also important to consider cost of the medication. [Figure 28.4](#) illustrates the relative cost of commonly used drugs for staphylococcal infections.

## III. ROUTE OF ADMINISTRATION

The oral route of administration is appropriate for mild infections that can be treated on an outpatient basis. Parenteral administration is used for drugs that are poorly absorbed from the GI tract and for treatment of patients with serious infections who require maintenance of higher serum concentrations of antimicrobial agents. In hospitalized patients requiring intravenous (IV) therapy, the switch to oral agents should occur as soon as possible. Switching patients from IV to oral therapy when clinically stable has been shown to decrease healthcare costs, shorten length of stay, and decrease complications from IV catheters. However, some antibiotics, such as *vancomycin* and aminoglycosides, are poorly absorbed from the gastrointestinal (GI) tract and do not achieve adequate serum levels via oral administration.

## IV. DETERMINANTS OF RATIONAL DOSING

Rational dosing of antimicrobial agents is based on pharmacodynamics (the relationship of drug concentrations to antimicrobial effects) and pharmacokinetic properties (the absorption, distribution, metabolism, and elimination of the drug). Three important properties that have a significant influence on the frequency of dosing are concentration-dependent killing, time-dependent (concentration-independent) killing, and postantibiotic effect (PAE). Utilizing these properties to optimize antibiotic dosing regimens can improve clinical outcomes and possibly decrease the development of resistance.

### A. Concentration-dependent killing

Certain antimicrobial agents, including aminoglycosides and *daptomycin*, show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism ([Figure 28.5A](#)). Giving drugs that exhibit this concentration-dependent killing by a once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.

## B. Time-dependent (concentration-independent) killing

In contrast,  $\beta$ -lactams, glycopeptides, macrolides, *clindamycin*, and *linezolid* do not exhibit concentration-dependent killing (Figure 28.5B). The clinical efficacy of these antimicrobials is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC. This effect is sometimes called time-dependent (or concentration-independent) killing. For example, dosing schedules for the penicillins and cephalosporins that ensure blood levels greater than the MIC for 50% and 60% of the time, respectively, provide the most clinical efficacy. Therefore, extended (generally 3 to 4 hours) or continuous (24 hours) infusions can be utilized instead of intermittent dosing (generally 30 minutes) to achieve prolonged time above the MIC and kill more bacteria. Other drugs, such as fluoroquinolones and *vancomycin*, work best by optimizing the ratio of the 24-hour area under the concentration-time curve to MIC ( $AUC_{24}/MIC$ ). The  $AUC_{24}$  is the overall exposure of a drug during the dosing interval and takes into account the concentration as well as the time.

## C. Postantibiotic effect (PAE)

The PAE is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC. Antimicrobial drugs exhibiting a long PAE (for example, aminoglycosides and fluoroquinolones) often require only one dose per day, particularly against gram-negative bacteria.

## V. CHEMOTHERAPEUTIC SPECTRA

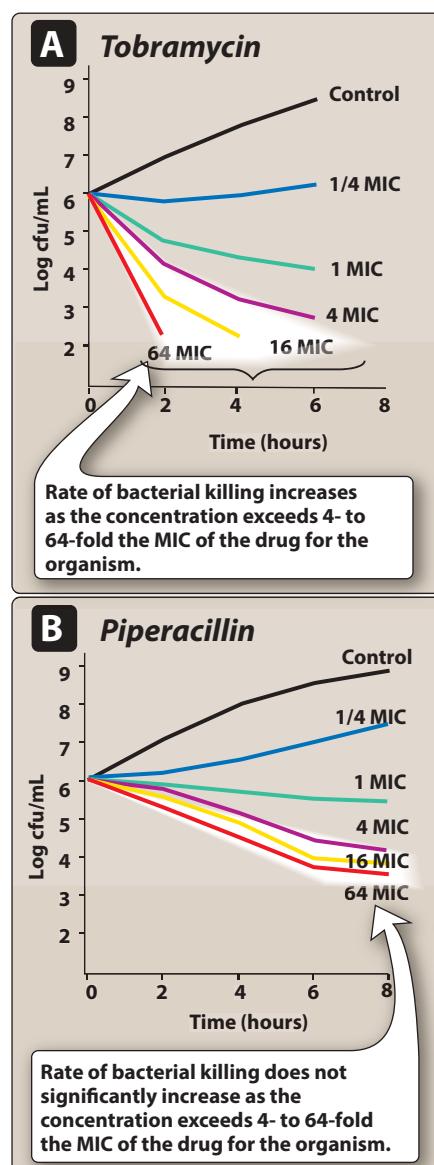
In this book, the clinically important bacteria have been organized into eight groups based on Gram stain, morphology, and biochemical or other characteristics. They are represented as a color-coded list (Figure 28.6A). The ninth section of the list is labeled “Other,” and it is used to represent any organism not included in one of the other eight categories. In Figures 28.6B, C, D, the list is used to illustrate the spectra of bacteria for which a particular class of antibiotics is therapeutically effective.

### A. Narrow-spectrum antibiotics

Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, *isoniazid* is active only against *Mycobacterium tuberculosis* (Figure 28.6B).

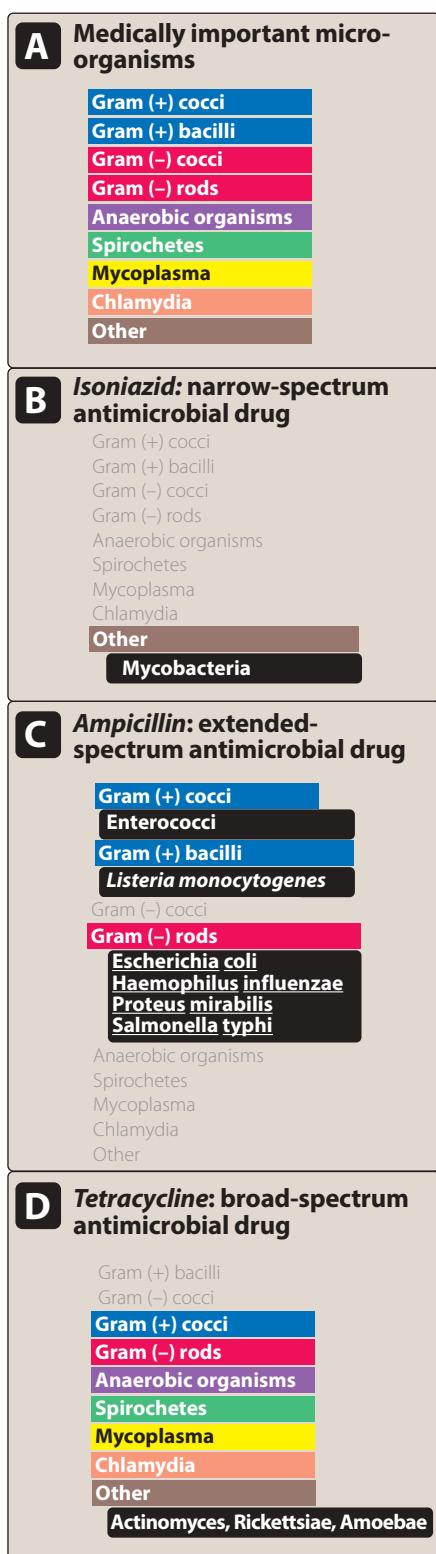
### B. Extended-spectrum antibiotics

Extended spectrum is the term applied to antibiotics that are modified to be effective against gram-positive organisms and also against a significant number of gram-negative bacteria. For example, *ampicillin* is considered to have an extended spectrum because it acts against gram-positive and some gram-negative bacteria (Figure 28.6C).



**Figure 28.5**

- A. Significant dose-dependent killing effect shown by *tobramycin*.
- B. Nonsignificant dose-dependent killing effect shown by *piperacillin*.  
cfu = colony-forming units; MIC = minimum inhibitory concentration.

**Figure 28.6**

- A.** Color-coded representation of medically important microorganisms.  
**B.** *Isoniazid*, a narrow-spectrum antimicrobial agent. **C.** *Ampicillin*, an extended-spectrum antimicrobial agent. **D.** *Tetracycline*, a broad-spectrum antimicrobial agent.

### C. Broad-spectrum antibiotics

Drugs such as fluoroquinolones and carbapenems affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics (Figure 28.6D). Administration of broad-spectrum antibiotics can drastically alter the nature of the normal bacterial flora and precipitate a superinfection due to organisms such as *Clostridium difficile*, the growth of which is normally kept in check by the presence of other colonizing microorganisms.

## VI. COMBINATIONS OF ANTIMICROBIAL DRUGS

It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting organism. This strategy reduces the possibility of superinfections, decreases the emergence of resistant organisms, and minimizes toxicity. However, in some situations, combinations of antimicrobial drugs are advantageous or even required.

### A. Advantages of drug combinations

Certain combinations of antibiotics, such as  $\beta$ -lactams and aminoglycosides, show synergism—that is, the combination is more effective than either of the drugs used separately (for example, *cotrimoxazole*, *amoxicillin*, and *clavulanic acid*). Because such synergism among antimicrobial agents is rare, synergistic combinations are only indicated in special situations (for example, in the treatment of enterococcal endocarditis). Combinations may be used as empirical; treatment until a more specific diagnosis has been made or infective organism has been isolated when an infection is of unknown origin or when there are organisms with variable sensitivity, such as when treating tuberculosis, leprosy, and HIV/AIDS to prevent development of resistance.

### B. Disadvantages of drug combinations

A number of antibiotics act only when organisms are multiplying. Thus, co-administration of an agent that causes bacteriostasis plus a second agent that is bactericidal may result in the first drug interfering with the action of the second. For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effects of penicillins and cephalosporins. Another concern is the risk of selection pressure and the development of antibiotic resistance by giving unnecessary combination therapy. Use of irrational fixed-dose combinations of antibiotics or less-evidenced combinations should be discouraged as many are available in the market. Some of the irrational combinations are (*amoxicillin–tazobactam*; *ofloxacin–ornidazole/tinidazole* *gatifloxacin–ornidazole*; *fluconazole–tinidazole*)

## VII. DRUG RESISTANCE

Bacteria are considered resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt bacterial growth. Some organisms are inherently resistant to an antibiotic. For example, most gram-negative organisms are inherently resistant to *vancomycin*. However, microbial species that are normally responsive to a particular drug may develop more virulent or resistant strains through spontaneous mutation or acquired resistance and selection. Some of these strains may even become resistant to more than one antibiotic.

### A. Genetic alterations leading to drug resistance

Acquired antibiotic resistance requires the temporary or permanent gain or alteration of bacterial genetic information. Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one organism to another (Figure 28.7).

### B. Altered expression of proteins in drug-resistant organisms

Drug resistance is mediated by a variety of mechanisms, such as an alteration in an antibiotic target site, lowered penetrability of the drug due to decreased permeability, increased efflux of the drug, or presence of antibiotic-inactivating enzymes (Figure 28.7).

- Modification of target sites:** Alteration of the target site of an antibiotic through mutation can confer resistance to one or more related antibiotics. For example, *S. pneumoniae* resistance to  $\beta$ -lactam antibiotics involves alterations in one or more of the major bacterial penicillin-binding proteins, resulting in decreased binding of the antibiotic to its target.
- Decreased accumulation:** Decreased uptake or increased efflux of an antibiotic can confer resistance because the drug is unable to attain access to the site of its action in sufficient concentrations to injure or kill the organism. For example, gram-negative organisms can limit the penetration of certain agents, including  $\beta$ -lactam antibiotics, as a result of an alteration in the number and

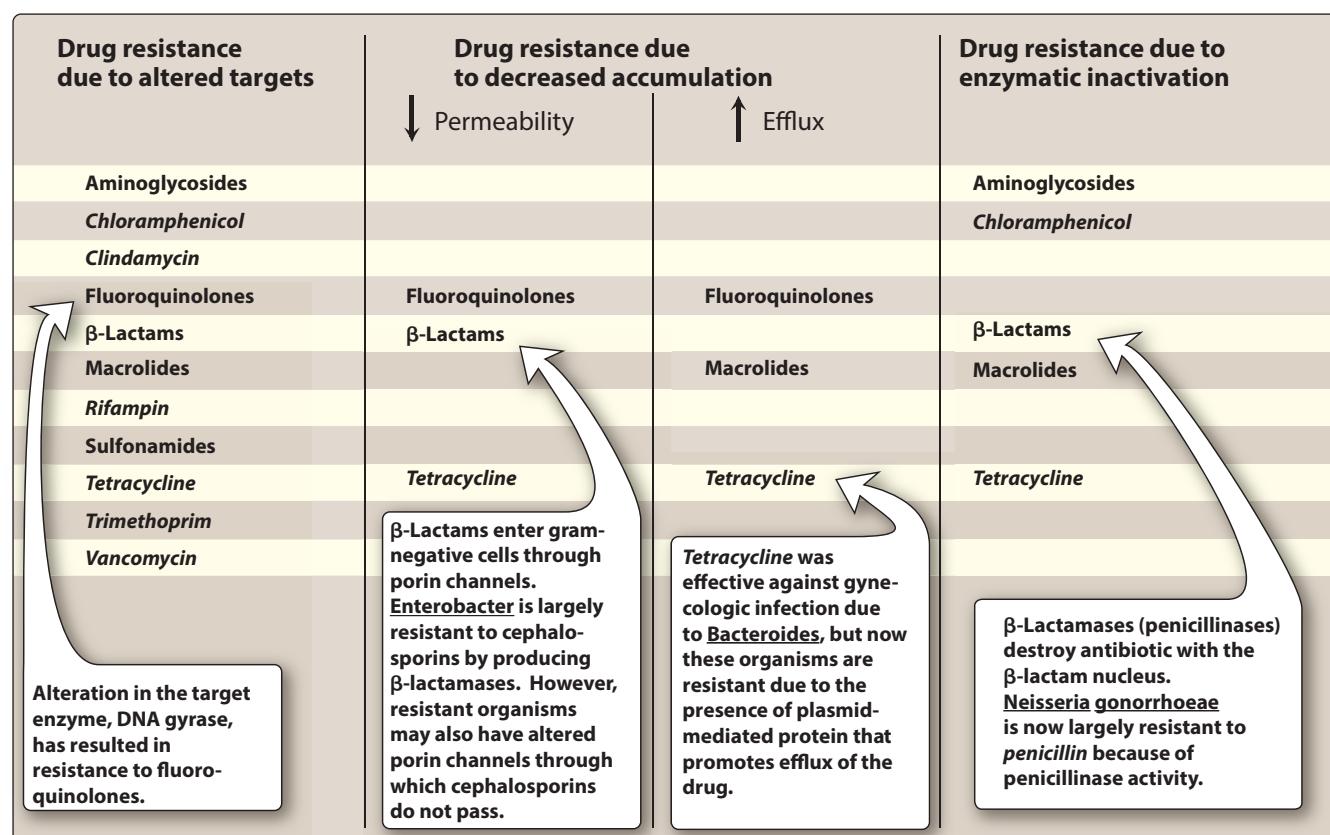


Figure 28.7

Some mechanisms of resistance to antibiotics.

structure of porins (channels) in the outer membrane. Also, the presence of an efflux pump can limit levels of a drug in an organism, as seen with tetracyclines.

3. **Enzymatic inactivation:** The ability to destroy or inactivate the antimicrobial agent can also confer resistance on microorganisms. Examples of antibiotic-inactivating enzymes include 1)  $\beta$ -lactamases ("penicillinases") that hydrolytically inactivate the  $\beta$ -lactam ring of penicillins, cephalosporins, and related drugs; 2) acetyltransferases that transfer an acetyl group to the antibiotic, inactivating *chloramphenicol* or aminoglycosides; and 3) esterases that hydrolyze the lactone ring of macrolides.

### C. Factors leading to increase in antimicrobial resistance (AMR)

The use of antibiotics has saved millions of lives, but its pervasive use to treat any infection, whether serious, minor, or even viral, leads to the increase in antibiotic resistance. Thus, inappropriate use of antimicrobials is leading to increased antimicrobial resistance. Antimicrobial resistance (AMR) is one of the world's most serious public health problems resulting in prolonged illness and hospitalization, which are costly, and the use of drugs other than the first-line drugs may increase costs 100-fold, thus making them unaffordable for many governments and patients, especially in developing countries.

Development and spread of antimicrobial resistance is due to the following reasons.

1. **Overuse, misuse, and irrational use by doctors:** It is often less time consuming and more cost effective to proactively prescribe antibiotics, rather than take precautions and regular followup of patients for development of any secondary bacterial infections.
2. **Noncompliance to prescribed regimen, self-medication, and use of leftover antibiotics by patients:** When antibiotics are not taken for the entire prescribed course, pathogenic bacteria can adapt to the presence of low-dose antibiotics and eventually form a population that is completely resistant to the antibiotic regardless of the dosage.
3. **Use of antibiotics in animal husbandry, aquaculture, and agriculture:** Antibiotic usage is also not exclusive to humans. Antibiotics are used to treat livestock and fish to prevent infections and to increase yield and are mixed in their feed. Thus, uncontrolled use of antibiotics creates a reservoir of bacteria that could become resistant and thus render that antibiotic useless due to cross resistance.
4. **Poor infection control in healthcare settings:** It leads to spread of outbreaks and transmission of resistant organisms among patients.
5. **Poor hygiene and sanitation:** Antimicrobial-drug resistance in hospitals is driven by failures to maintain hospital hygiene and sanitation. Poor hand hygiene is an important cause of spread of infection.
6. **Absence of new antibiotics being discovered:** Without new drugs to combat the ever-increasing number of antibiotic resistance, the society is running out of options in the treatment of infections.

Other factors that promote antibiotic resistance in community and hospital settings are antibiotic-selective pressure, prolonged antibiotic treatment, inadequate doses, prior use of a less-effective drug of the same antibiotic class, protected sites, or foreign bodies.

## VIII. GENERAL ANTIBIOTIC USE GUIDELINES

- All antibiotic initiations should be done after sending appropriate samples for cultures or any changes in antibiotic are done after receiving the culture report.
- Rapid tests (for example, Gram stain should be done to determine therapeutic choices when decision on empiric therapy is required).
- Healthcare facilities (HCF) should categorize usage of antibiotics for restricted use, limited access, and under surveillance based on antibiogram, if available and/or in consultation with Drugs & Therapeutic Committee (DTC) of the HCF.
- A list of antibiotics that should be available for OPD, IPD, emergency, and respective ICUs should be drawn in consultation with DTC of the HCF.
- A list of all available antibiotics is communicated to the prescribers every month or from time to time if there is any change in the list or medicine is not available for some reasons.
- Antimicrobials are chosen as per HCF policy and National Standard Treatment guidelines for infectious diseases. If alternatives are chosen, the reason for the same is documented in the case records.
- An antibiotic should be prescribed only when there is likely to be a clear clinical benefit. The antibiotic should not be prescribed for viral sore throat, simple coughs and colds, and viral diarrhea.
- Empiric therapy should be given where a delay in initiating therapy awaiting microbiological results would be life threatening or risks serious morbidity; antimicrobial therapy based on a clinically defined infection is justified. Necessary specimens should be drawn before commencing therapy. Where empiric therapy is used, the accuracy of the diagnosis is reviewed regularly and treatment altered/stopped when microbiological results become available.
- Once culture/sensitivity report available:
  - Presumptive therapy antibiotic may require to be changed
  - Consult a microbiologist to decide the choice of antibiotic (based on the narrowest spectrum antibiotic which covers the pathogen isolated)
- Following factors affecting antimicrobial choices and the route of administration should be checked, for example, age, type, and site of infection (respiratory, intra-abdominal, pneumonia, blood stream, urinary tract, and skin and soft tissue), renal and hepatic function, interactions, allergy, if any.
- The dose and duration of treatment with antibiotic should be suggested but can be modified by consultants based on clinical scenarios
- Use simple generic antibiotics first whenever possible. Avoid broad-spectrum antibiotics (for example, *amoxicillin + clavulanate*, quinolones, and cephalosporins) when standard and less-expensive antibiotics remain effective, as they increase risk of *Clostridium difficile*, MRSA, and resistant UTIs.
- Avoid widespread use of topical antibiotics (especially those agents also available as systemic preparations).
- Record all allergies prominently in red ink in the allergy box on the patient's case sheet. If no allergy, "No known allergy or allergic to name of the drug ..." is recorded. The box is signed and dated. If allergy history cannot be obtained, then "history not available" is specified. Do not leave the allergy box blank under any circumstances. The allergy box is completed before prescribing a new drug, except in exceptional

circumstances. If patients have a suspected drug allergy, then the drug and suspected reaction is documented in the case sheet and the drug chart.

- Review the need for antimicrobial therapy, especially empirical therapy with antibiotics, on a daily basis for inpatients. For most types of infection, treatment is continued until the clinical signs and symptoms of infection have resolved; exceptions to this are noted. For most infections, 5 to 7 days of antimicrobial therapy are sufficient (simple UTIs can be adequately treated with 3 days of antibiotic).
- Parenteral therapy is normally used in seriously ill patients and those with gastrointestinal upset. All IV antibiotics are initially given for 48 to 72 hours without review, and switching over to oral alternatives is considered after 48 hours. Oral therapy can often be substituted as the patient improves.
- Switch to oral therapy in case of:
  - Oral route is not compromised (that is, no vomiting, nil by mouth, severe diarrhea, swallowing disorder, unconscious).
  - For nasogastric (NG)/PEG feeding, consult the prescriber and pharmacist.
  - Suitable oral antibiotic option available.
  - Fever defervescence for at least 24 hours and marked clinical improvement; BP stable, RR and HR normal for age; white cell count showing a trend toward normal; low CRP.

**High-risk and deep seated infections:** Certain infections may appear to respond promptly but warrant prolonged IV therapy to optimize response and minimize relapse risk. Discuss with microbiology before switching patients with a high risk/deep-seated infection to oral therapy.

**Deep-seated infections** (liver abscess, osteomyelitis, septic arthritis, empyema, cavitating pneumonia): An initial 2 weeks of IV therapy may be needed.

**High-risk infections** need prolonged IV therapy, such as:

- Meningitis
- Intracranial abscesses
- Staphylococcus aureus bacteremia
- Severe or necrotizing soft-tissue infections; severe infections during chemotherapy-related neutropenia
- Infected implants/prosthetics
- Inadequately drained abscesses and empyema
- Intra-abdominal sepsis
- Mediastinitis
- Endocarditis
- Exacerbation of cystic fibrosis
- De-escalate antimicrobials or step down to the narrowest spectrum, most efficacious, and most cost-effective option as per culture reports. If no step-down availed, the reason should be documented and is subjected to clinical audit.
- Seek advice of the microbiologist and/or ID physician where treatment is apparently failing rather than blindly changing to an alternative choice of the antimicrobial agent.
- The indication for all antibiotics should be documented on the drug chart by the prescriber. For all infections, the specific diagnosis should be documented clearly in the medical notes and the indicators for making the diagnosis (increase WBC count, temperature  $>38^{\circ}\text{C}$ , evidence of inflammation, fluid collection, C-reactive protein [CRP], etc.)

## IX. PROPHYLACTIC USE OF ANTIBIOTICS

Certain clinical situations, such as dental procedures and surgeries, require the use of antibiotics for the prevention rather than for the treatment of infection. Usually, a single dose of an antibiotic 60 minutes before incision is required (Figure 28.8). The choice of an antibiotic and duration of therapy depend on the type of surgery. Because the indiscriminate use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks. The duration of prophylaxis should be closely controlled to prevent the unnecessary development of antibiotic resistance. Where prophylaxis is to be continued for longer than 24 hours, it should be clearly documented along with the reasons in the clinical case notes.

## X. COMPLICATIONS OF ANTIBIOTIC THERAPY

Even though antibiotics are selectively toxic to an invading organism, the host may still experience adverse effects. For example, the drug may produce an allergic response or may be toxic in ways unrelated to the antimicrobial activity.

### A. Hypersensitivity

Hypersensitivity or immune reactions to antimicrobial drugs or their metabolic products frequently occur. For example, the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock. Some reactions may be related to the rate of infusion, such as “Red man syndrome” seen with rapid infusion of *vancomycin*. Patients with a documented history of Stevens-Johnson syndrome or toxic epidermal necrolysis reaction (a severe sloughing of skin and mucus membranes) to an antibiotic should never be rechallenged, not even for antibiotic desensitization.

### B. Direct toxicity

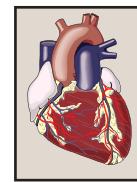
High serum levels of certain antibiotics may cause toxicity by directly affecting cellular processes in the host. For example, aminoglycosides can cause ototoxicity by interfering with membrane function in the auditory hair cells. *Chloramphenicol* can have a direct toxic effect on mitochondria, leading to bone marrow suppression. Fluoroquinolones can have effects on cartilage and tendons, and tetracyclines have direct effects on bones. A number of antibiotics can cause photosensitivity.

### C. Superinfections

Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, oral, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections usually require secondary treatments using specific anti-infective agents.

1

Pretreatment may prevent streptococcal infections in patients with a history of rheumatic heart disease. Patients may require years of treatment.



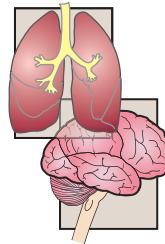
2

Pretreating of patients undergoing dental extractions who have implanted prosthetic devices, such as artificial heart valves, prevents seeding of the prosthesis.



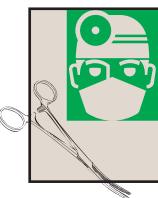
3

Pretreatment may prevent tuberculosis or meningitis among individuals who are in close contact with infected patients.



4

Treatment prior to most surgical procedures can decrease the incidence of infection afterwards. Effective prophylaxis is directed against the most likely organism, not eradication of every potential pathogen.



**Figure 28.8**

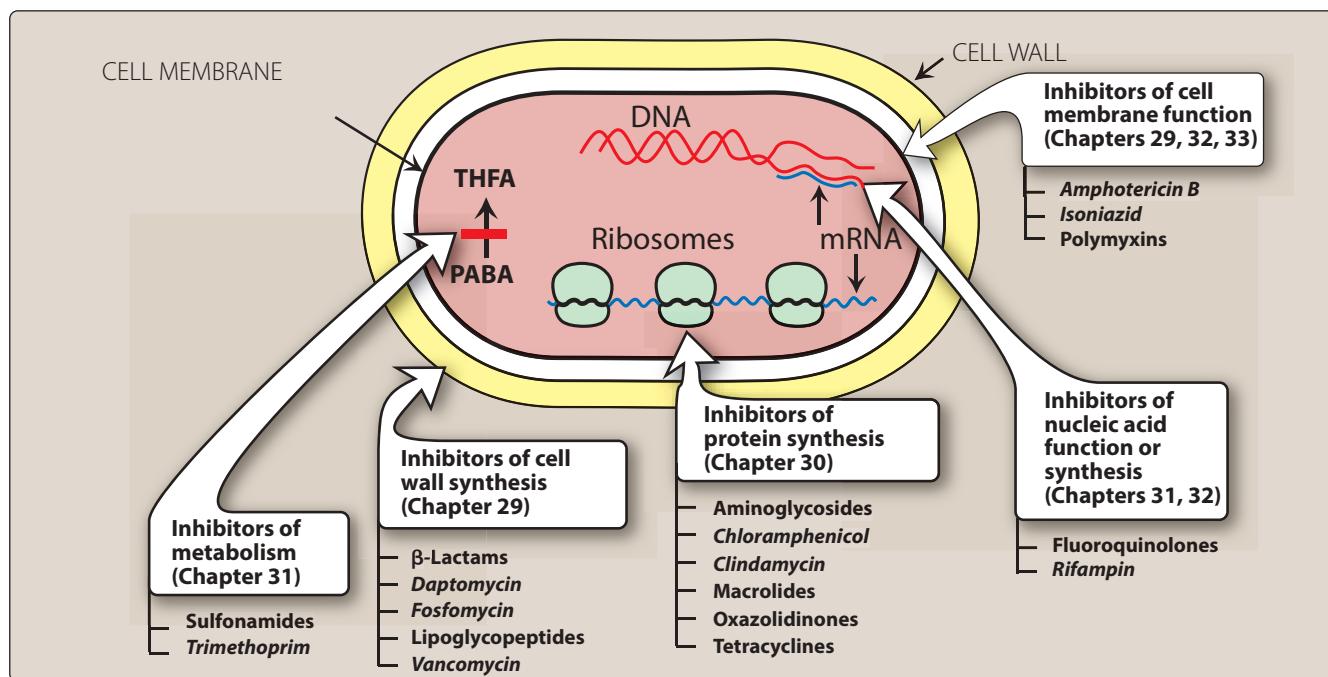
Some clinical situations in which prophylactic antibiotics are indicated.

#### D. Jarisch–Herxheimer Reaction

In 1895 and 1902, European dermatologists described the development of exacerbations of skin lesions in patients undergoing treatment for syphilis with mercurial compounds. This reaction is reported in patients undergoing treatment with antimicrobials for spirochetal infections such as syphilis, Lyme disease, leptospirosis, and relapsing fever. Jarisch–Herxheimer reaction (JHR) is manifested by fever, chills, headache, myalgia, and exacerbation of skin rashes within 24 hours of antimicrobial treatment. However, these symptoms are expected to resolve a few hours later. Therefore, JHR is recognized as a host response due to the extensive destruction of microorganism under the influence of the antimicrobial agent. Antimicrobials such as *penicillins*, *tetracyclines*, *erythromycin*, *cephalosporins*, *meropenem*, *ciprofloxacin*, *levofloxacin*, *clarithromycin*, and *azithromycin* are also reported to provoke the JHR.

### XI. SITES OF ANTIMICROBIAL ACTION

Antimicrobial drugs can be classified in a number of ways: 1) by their chemical structure (for example,  $\beta$ -lactams or aminoglycosides), 2) by their mechanism of action (for example, cell wall synthesis inhibitors), or 3) by their activity against particular types of organisms (for example, bacteria, fungi, or viruses). Chapters 29 through 31 are organized by the mechanisms of action of the drug (Figure 28.9), and Chapters 33 and 34 are organized according to the type of organisms affected by the drug.



**Figure 28.9**

Classification of some antimicrobial agents by their sites of action. THFA = tetrahydrofolic acid; PABA =  $p$ -aminobenzoic acid.

## Study Questions

Choose the ONE best answer.

28.1 A 24-year-old pregnant woman presents to the urgent care clinic with fever and urinary frequency and urgency. She is diagnosed with a urinary tract infection (UTI). Based on potential harm to the fetus, which of the following medications should be avoided in treating her UTI?

- A. Nitrofurantoin
- B. Amoxicillin
- C. Cephalexin
- D. Doxycycline

Correct answer = D. Doxycycline (a tetracycline) should be avoided due to the potential harm to the fetus. Nitrofurantoin, amoxicillin (a penicillin), and cephalexin (a cephalosporin) are generally considered safe.

28.2 Which of the following is the primary method of  $\beta$ -lactam resistance with *Streptococcus pneumoniae*?

- A. Modification of target site
- B. Decreased drug levels due to changes in permeability
- C. Decreased drug levels due to an efflux pump
- D. Enzymatic inactivation

Correct answer = A. *S. pneumoniae* resistance to  $\beta$ -lactam antibiotics involves alteration in one or more of the major penicillin-binding proteins.

28.3 Which of the following agents is considered a narrow-spectrum antibiotic?

- A. Ceftriaxone
- B. Ciprofloxacin
- C. Isoniazid
- D. Imipenem

Correct answer = C. Isoniazid is only active against *Mycobacterium tuberculosis*, while ceftriaxone, ciprofloxacin, and imipenem are considered broad spectrum due to their activity against multiple types of bacteria and increased risk for contributing to the development of a superinfection.

28.4 Which of the following antibiotics exhibits concentration-dependent killing?

- A. Clindamycin
- B. Linezolid
- C. Vancomycin
- D. Daptomycin

Correct answer = D. Clindamycin, linezolid, and vancomycin exhibit time-dependent killing, while daptomycin works best when administered in a fashion that optimizes concentration-dependent killing.

28.5 Which of the following antibiotics exhibits a long postantibiotic effect that permits once-daily dosing?

- A. Gentamicin
- B. Penicillin G
- C. Vancomycin
- D. Aztreonam

Correct answer = A. Aminoglycosides, including gentamicin, possess a long postantibiotic effect, especially when given as a high dose every 24 hours. Penicillin G, clindamycin, and vancomycin have a relatively short postantibiotic effect and require dosing that maintains concentrations above the MIC for a longer portion of the dosing interval.

28.6 A 58-year-old man with a history of hepatitis C, cirrhosis, and ascites presents with spontaneous bacterial peritonitis. Which of the following antibiotics requires close monitoring and dosing adjustment in this patient given his liver disease?

- A. Penicillin G
- B. Tobramycin
- C. Erythromycin
- D. Vancomycin

Correct answer = C. Erythromycin is metabolized by the liver and should be used with caution in patients with hepatic impairment. Penicillin G, tobramycin, and vancomycin are primarily eliminated by the kidneys.

28.7 JS is a 3-day-old neonate, born at 37 weeks' gestation, who presents with new onset fever, lethargy, and decreased desire to feed. Based on JS's age, which of the following antibiotics is considered safe to use in neonates?

- A. Chloramphenicol
- B. Sulfamethoxazole(trimethoprim)
- C. Tetracycline
- D. Ampicillin

28.8 When evaluating drug therapy for meningitis, which of the following factors is expected to have the LEAST influence on the penetration and concentration of an antibacterial agent in the cerebrospinal fluid?

- A. Lipid solubility of the drug
- B. Minimum inhibitory concentration of the drug
- C. Protein binding of the drug
- D. Molecular weight of the drug

28.9 A 72-year-old male presents with fever, cough, malaise, and shortness of breath. His chest x-ray shows bilateral infiltrates consistent with pneumonia. Bronchial wash cultures reveal Pseudomonas aeruginosa sensitive to cefepime. Which of the following is the best dosing scheme for cefepime based on the drug's time-dependent bactericidal activity?

- A. 1 g every 6 hours given over 30 minutes
- B. 2 g every 12 hours given over 3 hours
- C. 4 g every 24 hours given over 30 minutes
- D. 4 g given as continuous infusion over 24 hours

28.10 Which of the following adverse drug reactions precludes a patient from being rechallenged with that drug in the future?

- A. Itching/rash from penicillin
- B. Stevens-Johnson syndrome from sulfamethoxazole(trimethoprim)
- C. Gastrointestinal (GI) upset from clarithromycin
- D. Clostridium difficile superinfection from moxifloxacin

Correct answer = D. Chloramphenicol and sulfonamides (sulfamethoxazole) can cause toxic effects in newborns due to poorly developed renal and hepatic elimination processes. Tetracycline can have effects on bone growth and development and should be avoided in newborns and young children. Ampicillin is safe and effective in this population.

Correct answer = B. Although the minimum inhibitory concentration impacts the effectiveness of the drug against a given bacteria, it does not affect the ability of a drug to penetrate into the brain. Lipid solubility, protein binding, and molecular weight all determine the likelihood of a drug to penetrate the blood-brain barrier and concentrate in the brain.

Correct answer = D. The clinical efficacy of cefepime is based on the percentage of time that the drug concentration remains above the MIC. A continuous infusion would allow for the greatest amount of time above the MIC compared to intermittent (30 minutes) and prolonged infusions (3 to 4 hours).

Correct answer = B. Stevens-Johnson syndrome is a severe idiosyncratic reaction that can be life threatening, and these patients should never be rechallenged with the offending agent. Itching/rash is a commonly reported reaction in patients receiving penicillins but is not life threatening. A patient may be rechallenged if the benefits outweigh the risk (for example, pregnant patient with syphilis) or the patient could be exposed through a desensitization procedure. GI upset is a common side effect of clarithromycin but is not due to an allergic reaction. Moxifloxacin is a broad-spectrum antibiotic that can inhibit the normal flora of the GI tract, increasing the risk for the development of superinfections such as C. difficile. This is not an allergic reaction, and the patient can be rechallenged; however, the patient might be at risk for developing C. difficile infection again.

# Cell Wall Inhibitors

Veena Venugopalan and Kenneth Klinker

# 29

## I. OVERVIEW

Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall—a structure that mammalian cells do not possess. The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links. To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms. **Figure 29.1** shows the classification of agents affecting cell wall synthesis.

## II. PENICILLINS

The basic structure of *penicillins* consists of a core four-membered  $\beta$ -lactam ring which is attached to a thiazolidine ring and an R side chain. Members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue (**Figure 29.2**). The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, cross-hypersensitivity, and susceptibility to bacterial degradative enzymes ( $\beta$ -lactamases).

### A. Mechanism of action

*Penicillins* interfere with the last step of bacterial cell wall synthesis, which is the cross-linking of adjacent peptidoglycan strands by a process known as transpeptidation. Since *penicillins* structurally resemble the terminal portion of the peptidoglycan strand, they compete for and bind to enzymes called *penicillin-binding proteins* (PBPs), which catalyze transpeptidase and facilitate cross-linking of the cell wall (**Figure 29.3**). The result is the formation of a weakened cell wall and ultimately cell death. For this reason, *penicillins* are regarded as bactericidal and work in a time-dependent fashion.

### B. Antibacterial spectrum

The antibacterial spectrum of the various *penicillins* is determined, in part, by their ability to cross the bacterial peptidoglycan cell wall to reach the PBPs in the periplasmic space. Factors determining PBP susceptibility to these antibiotics include size, charge, and hydrophobicity of the particular  $\beta$ -lactam antibiotic. In general, gram-positive microorganisms have cell walls that are easily traversed by *penicillins*, and, therefore, in the absence of resistance, they are susceptible to

### PENICILLINS

Natural penicillins

*Aqueous penicillin G*

(*Benzylpenicillin*)

*Penicillin G benzathine*

*Penicillin G procaine*

*Pencillin V*

$\beta$ -Lactamase resistant

*penicillins* (antistaphylococcal  
penicillins; narrow spectrum)

*Methicillin*

*Cloxacillin*

*Nafcillin*

*Oxacillin*

*Dicloxacillin*

Aminopenicillins (extended  
spectrum)

*Ampicillin*

*Amoxicillin*

*Bacampicillin*

*Cyclacillin*

*Hetacillin*

Extended spectrum penicillins  
(antipseudomonals)

*Carboxypenicillins*

*Carcenicillin*

*Ticarcillin*

*Ureidopenicillins*

*Azlocillin*

*Mezlocillin*

*Piperacillin*

$\beta$ -Lactamase inhibitors

*Clavulanic acid*

*Sulbactam*

*Tazobactam*

Penicillins/inhibitor combination

**Figure 29.1**

Summary of antimicrobial agents affecting cell wall synthesis.  
(Figure continues on next page)

**CEPHALOSPORINS**

**First generation (broad spectrum of activity and low toxicity)**

*Cefadroxil (Oral)*  
*Cefazolin (Parenteral)*  
*Cephalexin (Oral)*  
*Cephradine (Oral)*

**Second generation (intermediate spectrum; extended gram-negative coverage; active against *Enterobacter*, *Proteus vulgaris*, *Klebsiella*, *H. influenzae*)**

*Cefaclor (Oral)*  
*Cefotetan (Parenteral)*  
*Cefoxitin (Parenteral)*  
*Cefprozil (Oral)*  
*Cefuroxime (Parenteral /Oral)*

**Third generation (extended spectrum of activities and extended gram-negative coverage; *Pseudomonas aeruginosa* e; *Serratia*; *Neisseria gonorrhoeae*; activity for *S. aureus*, *Streptococcus pneumoniae*, Enterobacteriaceae)**

*Cefoperazone*  
*Cefotaxime (Parenteral)*  
*Ceftriaxone (Parenteral)*  
*Ceftazidime (Parenteral)*  
*Cefdinir (Oral)*  
*Cefexime (Oral)*  
*Cefpodoxime (Oral)*  
*Cefbuten (Oral)*

**Fourth generation (extended gram-negative coverage; increased activity against Streptococci and MRSA)**

*Cefipime (Parenteral)*

**Fifth generation (extended spectrum against MRSA)**

*Ceftaroline (Parenteral)*  
*Ceftabiprole*

**CARBAPENEMS**

*Doripenem*  
*Ertapenem*  
*Imipenem/cilastatin*  
*Meropenem*

**MONOBACTAMS**

*Aztreonam*

**Figure 29.1** (Continued)

Summary of antimicrobial agents affecting cell wall synthesis. (For drug dosages, refer to Appendix at the end of the book.)

these drugs. Gram-negative microorganisms have an outer lipopolysaccharide membrane surrounding the cell wall that presents a barrier to the water-soluble *penicillins*. However, gram-negative bacteria have proteins inserted in the lipopolysaccharide layer that act as water-filled channels (called porins) to permit transmembrane entry.

- Natural penicillins:** *Penicillin G* and *penicillin V* are obtained from fermentations of the fungus *Penicillium chrysogenum*. *Penicillin [pen-i-SILL-in] G (benzylpenicillin)* has activity against a variety of gram-positive organisms, gram-negative organisms, and spirochetes (Figure 29.4). The potency of *penicillin G* is 5 to 10 times greater than that of *penicillin V* against both *Neisseria* spp. and certain anaerobes. Most streptococci are very sensitive to *penicillin G*, but *penicillin*-resistant viridans streptococci and *Streptococcus pneumoniae* isolates are emerging. The vast majority of *Staphylococcus aureus* (>90%) are now penicillinase-producing and therefore resistant to *penicillin G*. Despite widespread use and increase in resistance to many types of bacteria, *penicillin* remains the drug of choice for the treatment of gas gangrene (*Clostridium perfringens*) and syphilis (*Treponema pallidum*). *Penicillin V*, only available in oral formulation, has a spectrum similar to that of *penicillin G*, but it is not used for treatment of severe infections because of its limited oral absorption. *Penicillin V* is more acid stable than *penicillin G* and is the oral agent employed in the treatment of less severe infections.
- Semisynthetic penicillins:** *Ampicillin [am-pi-SILL-in]* and *amoxicillin [a-mox-i-SILL-in]* (also known as aminopenicillins or extended-spectrum *penicillins*) are created by chemically attaching different R groups to the 6-aminopenicillanic acid nucleus. Addition of R groups extends the gram-negative antimicrobial activity of aminopenicillins to include *Haemophilus influenzae*, *Escherichia coli*, and *Proteus mirabilis* (Figure 29.5A). *Ampicillin* (with or without the addition of *gentamicin*) is the drug of choice for the gram-positive bacillus *Listeria monocytogenes* and susceptible enterococcal species. These extended-spectrum agents are also widely used in the treatment of respiratory infections, and *amoxicillin* is employed prophylactically by dentists in high-risk patients for the prevention of bacterial endocarditis. These drugs are co-formulated with  $\beta$ -lactamase inhibitors, such as *clavulanic acid* or *sulbactam*, to combat infections caused by  $\beta$ -lactamase producing organisms. For example, without the  $\beta$ -lactamase inhibitor, methicillin-sensitive *Staphylococcus aureus* (MSSA) is resistant to *ampicillin* and *amoxicillin*. Resistance in the form of plasmid-mediated penicillinases is a major clinical problem, which limits use of aminopenicillins with some gram-negative organisms.
- Antistaphylococcal penicillins:** *Methicillin [meth-i-SILL-in]*, *nafcillin [naf-SILL-in]*, *oxacillin [ox-a-SILL-in]*, and *dicloxacillin [dye-klox-a-SILL-in]* are  $\beta$ -lactamase (penicillinase)-resistant *penicillins*. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci, including MSSA. [Note: Because of its toxicity (interstitial nephritis), *methicillin* is not used clinically in the United States except in laboratory tests to identify resistant strains of *S. aureus*. *Methicillin*-resistant *Staphylococcus aureus* (MRSA) is currently a source of serious community and

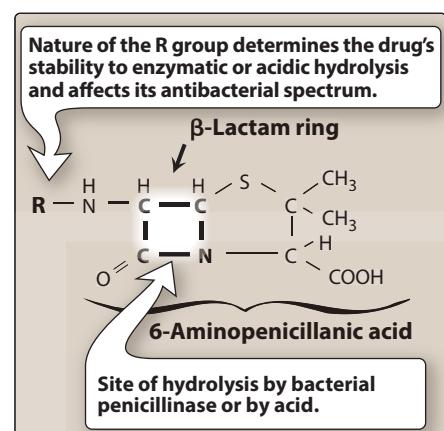
nosocomial (hospital-acquired) infections and is resistant to most commercially available  $\beta$ -lactam antibiotics.] The penicillinase-resistant *penicillins* have minimal to no activity against gram-negative infections

4. **Antipseudomonal penicillin:** *Piperacillin* [pip-er-a-SILL-in] is also referred to as an antipseudomonal *penicillin* because of its activity against *Pseudomonas aeruginosa* (Figure 29.5B). Formulation of *piperacillin* with *tazobactam* extends the antimicrobial spectrum to include penicillinase-producing organisms (for example, most Enterobacteriaceae and *Bacteroides* species). Figure 29.6 summarizes the stability of the *penicillins* to acid or the action of penicillinase.

### C. Resistance

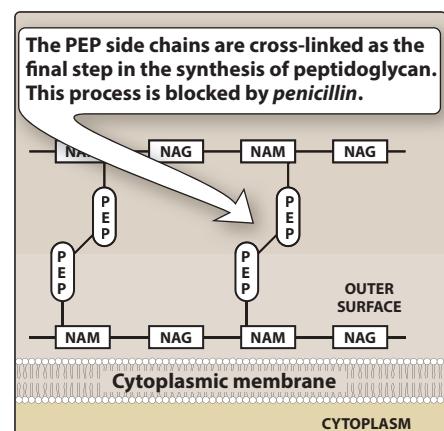
Survival of bacteria in the presence of  $\beta$ -lactam antibiotics occurs due to the following.

1.  **$\beta$ -Lactamase production:** This family of enzymes hydrolyzes the cyclic amide bond of the  $\beta$ -lactam ring, which results in loss of bactericidal activity (Figure 29.2). They are the major cause of resistance to the *penicillins* and are an increasing problem.  $\beta$ -Lactamases either are constitutive, mostly produced by the bacterial chromosome or, more commonly, are acquired by the transfer of plasmids. Some of the  $\beta$ -lactam antibiotics are poor substrates for  $\beta$ -lactamases and resist hydrolysis, thus retaining their activity against  $\beta$ -lactamase-producing organisms. [Note: Certain organisms may have chromosome-associated  $\beta$ -lactamases that are inducible by  $\beta$ -lactam antibiotics (for example, second- and third-generation cephalosporins).] Gram-positive organisms secrete  $\beta$ -lactamases extracellularly, whereas gram-negative bacteria inactivate  $\beta$ -lactam drugs in the periplasmic space.
2. **Decreased permeability to the drug:** Decreased penetration of the antibiotic through the outer cell membrane of the bacteria prevents the drug from reaching the target PBPs. In gram-positive bacteria, the peptidoglycan layer is near the surface of the bacteria and there are few barriers for the drug to reach its target. Reduced penetration of drug into the cell is a greater concern in gram-negative organisms, which have a complex cell wall that includes aqueous channels called porins. An excellent example of a pathogen lacking high permeability porins is *P. aeruginosa*. The presence of an efflux pump which actively removes antibiotics from the site of action, can also reduce the amount of intracellular drug (for example, *Klebsiella pneumoniae*).
3. **Altered PBPs:** These are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of morphologic features of the bacterium. Antibiotic exposure can prevent cell wall synthesis and can lead to morphologic changes or lysis of susceptible bacteria. The number of PBPs varies with the type of organism. Modified PBPs have a lower affinity for  $\beta$ -lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth. This explains MRSA resistance to most commercially available  $\beta$ -lactams.



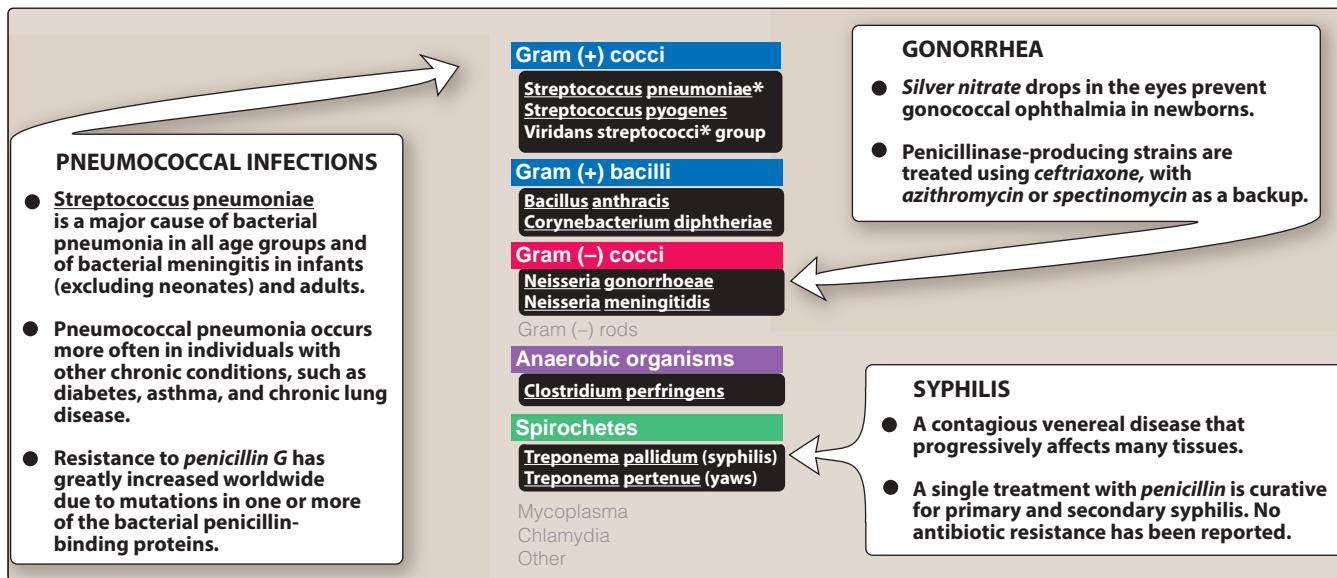
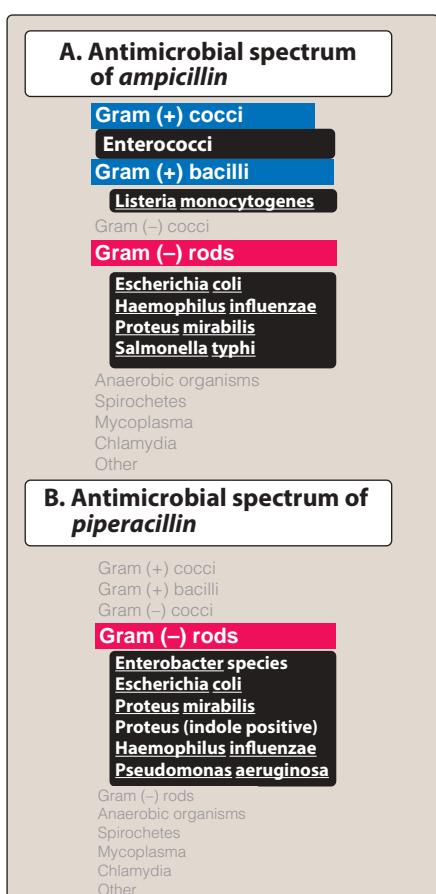
**Figure 29.2**

Structure of  $\beta$ -lactam antibiotics.



**Figure 29.3**

Bacterial cell wall of gram-positive bacteria. NAG = *N*-acetylglucosamine; NAM = *N*-acetylmuramic acid; PEP = cross-linking peptide.

**Figure 29.4**Typical therapeutic applications of *penicillin G*. \*Resistant strains are increasingly seen.**Figure 29.5**Antimicrobial activity of **ampicillin (A)** and the antipseudomonal **piperacillin (B)**.

## D. Pharmacokinetics

1. **Administration:** The route of administration of a  $\beta$ -lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection.
2. **Routes of administration:** The combination of *ampicillin* with *sulbactam*, *piperacillin* with *tazobactam*, and the antistaphylococcal *penicillins nafcillin* and *oxacillin* must be administered intravenously (IV) or intramuscularly (IM). *Penicillin V*, *amoxicillin*, and *dicloxacillin* are available only as oral preparations. Others are effective by the oral, IV, or IM routes (Figure 29.6).
3. **Depot forms:** *Procaine penicillin G* and *benzathine penicillin G* are administered IM and serve as depot forms. They are slowly absorbed into the circulation and persist at low levels over a long time period.
4. **Absorption:** The acidic environment within the intestinal tract is unfavorable for the absorption of *penicillins*. In the case of *penicillin V*, only one-third of an oral dose is absorbed under the best of conditions. Food decreases the absorption of the penicillinase-resistant *penicillin dicloxacillin* because as gastric emptying time increases, the drug is destroyed by stomach acid. Therefore, it should be taken on an empty stomach. Conversely, *amoxicillin* is stable in acid and is readily absorbed from the gastrointestinal (GI) tract.
5. **Distribution:** The  $\beta$ -lactam antibiotics distribute well throughout the body. All the *penicillins* cross the placental barrier, but none have been shown to have teratogenic effects. However, penetration into bone or cerebrospinal fluid (CSF) is insufficient for therapy unless these sites are inflamed (Figures 29.7 and 29.8). [Note: Inflamed meninges are more permeable to the *penicillins*, resulting in an increased ratio of the drug in the CSF compared

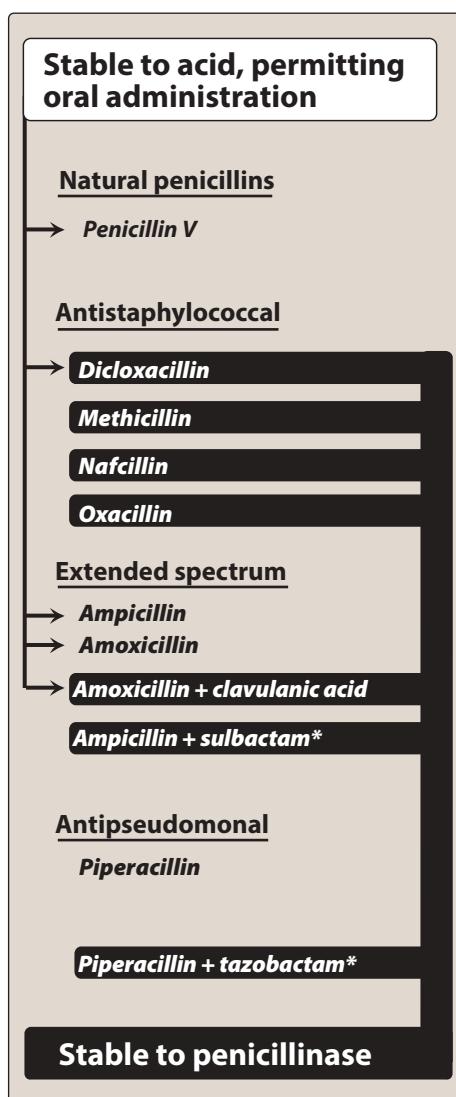
to the serum.] *Penicillin* levels in the prostate are insufficient to be effective against infections.

6. **Metabolism:** Host metabolism of the  $\beta$ -lactam antibiotics is usually insignificant, but some metabolism of *penicillin G* may occur in patients with impaired renal function. *Nafcillin* and *oxacillin* are exceptions to the rule and are primarily metabolized in the liver.
7. **Excretion:** The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Because *nafcillin* and *oxacillin* are primarily metabolized in the liver, they do not require dose adjustment for renal insufficiency. *Probenecid* inhibits the secretion of *penicillins* by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels. The *penicillins* are also excreted in breast milk.

## E. Adverse reactions

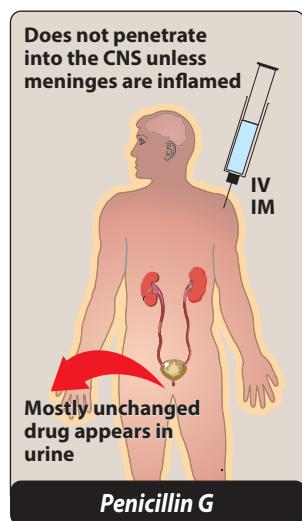
*Penicillins* are among the safest drugs. However, adverse reactions may occur (Figure 29.9).

1. **Hypersensitivity:** Approximately 5% percent of patients have some kind of reaction, ranging from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. Cross-allergic reactions occur among the  $\beta$ -lactam antibiotics. To determine whether treatment with a  $\beta$ -lactam is safe when an allergy is noted, patient history regarding severity of the previous reaction is essential. *Penicillin* allergy in a patient is tested with the intradermal test. It is performed at a low intradermal test dose of 2 to 10 units in the lower arm.
2. **Diarrhea:** Diarrhea is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum. Pseudomembranous colitis from *Clostridium difficile* and other organisms may occur with *penicillin* use.
3. **Nephritis:** *Penicillins*, particularly *methicillin*, have the potential to cause acute interstitial nephritis. [Note: *Methicillin* is therefore no longer used clinically.]
4. **Neurotoxicity:** The *penicillins* are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk due to the ability of *penicillins* to cause GABAergic inhibition.
5. **Hematologic toxicities:** Decreased coagulation may be observed with high doses of *piperacillin* and *nafcillin* (and, to some extent, with *penicillin G*). Cytopenias have been associated with therapy of greater than 2 weeks, and therefore, blood counts should be monitored weekly for such patients.
6. **Jarisch–Herxheimer reaction:** *Penicillin* treatment for syphilis can cause Jarisch–Herxheimer reaction (JHR; see Chapter 28). After initiation of the treatment with *penicillin* for syphilis, JHR is reported to start approximately at 4 hours, peak at 8 hours, and subside by 16 hours.



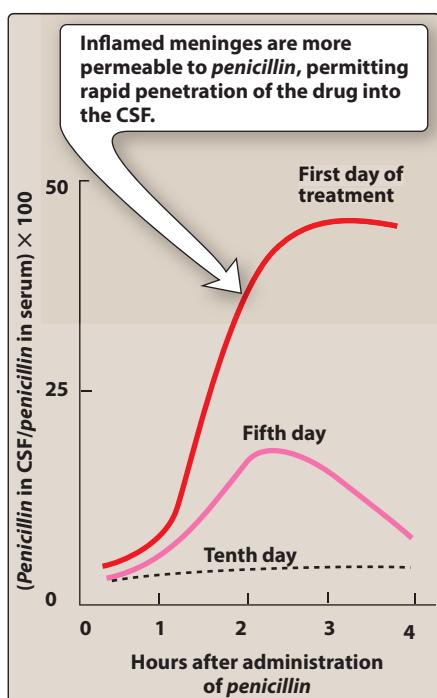
**Figure 29.6**

Stability of the *penicillins* to acid or the action of penicillinase. \*Available only as parenteral preparation.



**Figure 29.7**

Administration and fate of *penicillin*.  
CNS = central nervous system.



**Figure 29.8**

Enhanced penetration of *penicillin* into the cerebral spinal fluid (CSF) during inflammation.

### III. CEPHALOSPORINS

The cephalosporins are  $\beta$ -lactam antibiotics closely related both structurally and functionally to *penicillins*. Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid. Structural changes on the acyl side chain at the 7-position alter antibacterial activity and variations at the 3-position modify the pharmacokinetic profile (Figure 29.10). Cephalosporins have the same mode of action as *penicillins*, and they are affected by the same resistance mechanisms. However, they tend to be more resistant than the *penicillins* to certain  $\beta$ -lactamases.

#### A. Antibacterial spectrum

Cephalosporins have been classified as first, second, third, fourth, and advanced generation, based largely on their bacterial susceptibility patterns and resistance to  $\beta$ -lactamases (Figure 29.11). [Note: Commercially available cephalosporins are ineffective against *L. monocytogenes*, *C. difficile*, and the enterococci.]

- 1. First generation:** The first-generation cephalosporins act as *penicillin G* substitutes. They are resistant to the staphylococcal penicillinase (that is, they cover MSSA). Isolates of *S. pneumoniae* resistant to *penicillin* are also resistant to first-generation cephalosporins. Agents in this generation also have modest activity against *P. mirabilis*, *E. coli*, and *K. pneumoniae*. Most oral cavity anaerobes such as *Peptostreptococcus* are sensitive, but the *Bacteroides fragilis* group is resistant.
- 2. Second generation:** The second-generation cephalosporins display greater activity against gram-negative organisms, such as *H. influenzae*, *Klebsiella* species, *Proteus* species, *Escherichia coli*, and *Moraxella catarrhalis*, whereas activity against gram-positive organisms is weaker. Antimicrobial coverage of the cephemycins (*cefotetan* [sef-oh-TEE-tan] and *cefoxitin* [sef-OX-i-tin]) also includes anaerobes (for example, *B. fragilis*). They are the only cephalosporins commercially available with appreciable activity against gram-negative anaerobic bacteria. However, neither drug is first line because of the increasing prevalence of resistance among *B. fragilis* to both agents.
- 3. Third generation:** These cephalosporins have assumed an important role in the treatment of infectious diseases. Although they are less potent than first-generation cephalosporins against MSSA, the third-generation cephalosporins have enhanced activity against gram-negative bacilli, including  $\beta$ -lactamase producing strains of *H. influenza* and *Neisseria gonorrhoeae*. The spectrum of activity of this class includes enteric organisms, such as *Serratia marcescens* and *Providencia* species. *Ceftriaxone* [sef-trye-AKS-own] and *cefotaxime* [sef-oh-TAKS-eem] have become agents of choice in the treatment of meningitis. *Ceftazidime* [sef-TA-zidime] has activity against *P. aeruginosa*; however, resistance is increasing and use should be evaluated on a case-by-case basis. Third-generation cephalosporins must be used with caution, as they are associated with significant “collateral damage,” including the induction

of antimicrobial resistance and development of *C. difficile* infection. [Note: Fluoroquinolone use is also associated with collateral damage.]

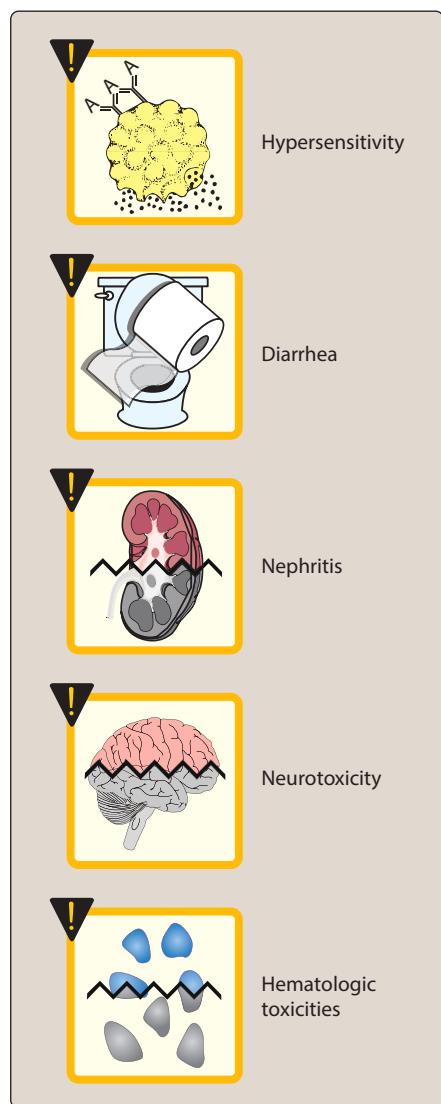
4. **Fourth generation:** *Cefepime* [SEF-eh-peem] is classified as a fourth-generation cephalosporin and must be administered parenterally. *Cefepime* has a wide antibacterial spectrum, with activity against streptococci and staphylococci (but only those that are *methicillin* susceptible). *Cefepime* is also effective against aerobic gram-negative organisms, such as *Enterobacter* species, *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *P. aeruginosa*. When selecting an antibiotic that is active against *P. aeruginosa*, clinicians should refer to their local antibiograms (laboratory testing for the sensitivity of an isolated bacterial strain to different antibiotics) for direction.
5. **Advanced generation:** *Ceftaroline* [sef-TAR-oh-leen] is a broad-spectrum, advanced-generation cephalosporin that is administered IV as a prodrug, *ceftaroline fosamil*. It is the only  $\beta$ -lactam in the United States with activity against MRSA, and it is indicated for the treatment of complicated skin and skin structure infections and community-acquired pneumonia. The unique structure allows *ceftaroline* to bind to PBP2a found with MRSA and PBP2x found with *S. pneumoniae*. In addition to its broad gram-positive activity, it also has similar gram-negative activity to the third-generation cephalosporin *ceftriaxone*. Important gaps in coverage include *P. aeruginosa*, extended-spectrum  $\beta$ -lactamase (ESBL)-producing Enterobacteriaceae, and *Acinetobacter baumannii*. The twice-daily dosing regimen also limits use outside of an institutional setting.

## B. Resistance

Resistance to the cephalosporins is either due to the hydrolysis of the  $\beta$ -lactam ring by  $\beta$ -lactamases or reduced affinity for PBPs.

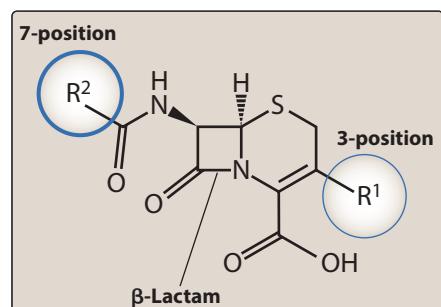
## C. Pharmacokinetics

1. **Administration:** Many of the cephalosporins must be administered IV or IM (Figure 29.12) because of their poor oral absorption. Exceptions are noted in Figure 29.13.
2. **Distribution:** All cephalosporins distribute very well into body fluids. However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved with only a few cephalosporins. For example, *ceftriaxone* and *cefotaxime* are effective in the treatment of neonatal and childhood meningitis caused by *H. influenzae*. *Cefazolin* [se-FA-zo-lin] is commonly used for surgical prophylaxis due to its activity against penicillinase-producing *S. aureus*, along with its good tissue and fluid penetration.
3. **Elimination:** Cephalosporins are eliminated through tubular secretion and/or glomerular filtration (Figure 29.12). Therefore, doses must be adjusted in renal dysfunction to guard against accumulation and toxicity. One exception is *ceftriaxone*, which is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.



**Figure 29.9**

Summary of the adverse effects of penicillins.



**Figure 29.10**

Structural features of cephalosporin antibiotics.

<b>First-generation cephalosporins</b>	
<b>Gram (+) cocci</b>	<i>Staphylococcus aureus*</i> <i>Staphylococcus epidermidis</i> <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i> Anaerobic streptococci
<b>Gram (-) rods</b>	<i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> <i>Proteus mirabilis</i>
<b>Second-generation cephalosporins</b>	
<b>Gram (+) cocci</b>	<i>Staphylococcus aureus*</i> <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i> Anaerobic streptococci
<b>Gram (-) cocci</b>	<i>Neisseria gonorrhoeae</i>
<b>Gram (-) rods</b>	<i>Enterobacter aerogenes</i> <i>Escherichia coli</i> <i>Haemophilus influenzae</i> <i>Klebsiella pneumoniae</i> <i>Proteus mirabilis</i>
Anaerobic organisms**	
<b>Third-generation cephalosporins</b>	
<b>Gram (+) cocci</b>	<i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i> Anaerobic streptococci
<b>Gram (-) cocci</b>	<i>Neisseria gonorrhoeae</i>
<b>Gram (-) rods</b>	<i>Enterobacter aerogenes</i> <i>Escherichia coli</i> <i>Haemophilus influenzae</i> <i>Klebsiella pneumoniae</i> <i>Proteus mirabilis</i> <i>Pseudomonas aeruginosa†</i> <i>Serratia marcescens</i>
<b>Fourth-generation cephalosporins</b>	
Antibacterial coverage comparable to that of the third-generation class; however, demonstrate greater stability against $\beta$ -lactamases	

**Figure 29.11**

Summary of therapeutic applications of cephalosporins. \*Methicillin-resistant staphylococci are resistant. \*\*Cefoxitin and cefotetan have anaerobic coverage. †Ceftazidime only.

## D. Adverse effects

Like the *penicillins*, the cephalosporins are generally well tolerated. However, allergic reactions are a concern. Patients who have had an anaphylactic response, Stevens–Johnson syndrome, or toxic epidermal necrolysis to *penicillins* should not receive cephalosporins. Cephalosporins should be avoided or used with caution in individuals with *penicillin* allergy. Current data suggest that the cross-reactivity between *penicillin* and cephalosporins is around 3% to 5% and is determined by the similarity in the side chain, not the  $\beta$ -lactam structure. The highest rate of allergic cross-sensitivity is between *penicillin* and first-generation cephalosporins.

## IV. OTHER $\beta$ -LACTAM ANTIBIOTICS

### A. Carbapenems

Carbapenems are synthetic  $\beta$ -lactam antibiotics that differ in structure from the *penicillins* in that the sulfur atom of the thiazolidine ring (Figure 29.2) has been externalized and replaced by a carbon atom (Figure 29.14). *Imipenem* [i-mi-PEN-em], *meropenem* [mer-oh-PEN-em], *doripenem* [dore-i-PEN-em], and *ertapenem* [er-ta-PEN-em] are drugs in this group.

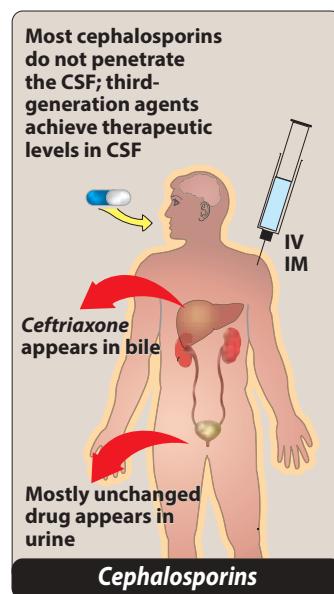
- Antibacterial spectrum:** *Imipenem* resists hydrolysis by most  $\beta$ -lactamases, but not the metallo- $\beta$ -lactamases. This drug plays a role in empiric therapy because it is active against  $\beta$ -lactamase-producing gram-positive and gram-negative organisms, anaerobes, and *P. aeruginosa*. *Meropenem* and *doripenem* have antibacterial activity similar to that of *imipenem*. *Doripenem* may retain activity against resistant isolates of *Pseudomonas* (Figure 29.15). Unlike other carbapenems, *ertapenem* lacks coverage against *P. aeruginosa*, *Enterococcus* species, and *Acinetobacter* species.
- Pharmacokinetics:** *Imipenem*, *meropenem*, and *doripenem* are administered IV and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed. *Meropenem* is known to reach therapeutic levels in bacterial meningitis even without inflammation. These agents are excreted by glomerular filtration. *Imipenem* undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. Compounding *imipenem* with *cilastatin* protects the parent drug from renal dehydropeptidase and, thus, prolongs its activity in the body. The other carbapenems do not require coadministration of *cilastatin*. *Ertapenem* is administered IV once daily. [Note: Doses of these agents must be adjusted in patients with renal insufficiency.]
- Adverse effects:** *Imipenem/cilastatin* can cause nausea, vomiting, and diarrhea. Eosinophilia and neutropenia are less common than with other  $\beta$ -lactams. High levels of *imipenem* may provoke seizures; however, the other carbapenems are less likely to do so. Carbapenems and *penicillin* share a common bicyclic core. Structural similarity may confer cross-reactivity between classes. While those with true *penicillin* allergy should use carbapenems cautiously, the cross-reactivity rate seen in studies is very low (<1%).

## B. Monobactams

The monobactams, which also disrupt bacterial cell wall synthesis, are unique because the  $\beta$ -lactam ring is not fused to another ring (Figure 29.14). *Aztreonam* [az-TREE-oh-nam], which is the only commercially available monobactam, has antimicrobial activity directed primarily against gram-negative pathogens, including the Enterobacteriaceae and *P. aeruginosa*. It lacks activity against gram-positive organisms and anaerobes. *Aztreonam* is administered either IV or IM and can accumulate in patients with renal failure. *Aztreonam* is relatively nontoxic, but it may cause phlebitis, skin rash and, occasionally, abnormal liver function tests. This drug has a low immunogenic potential, and it shows little cross-reactivity with antibodies induced by other  $\beta$ -lactams. Thus, this drug may offer a safe alternative for treating patients who are allergic to other *penicillins*, cephalosporins, or carbapenems.

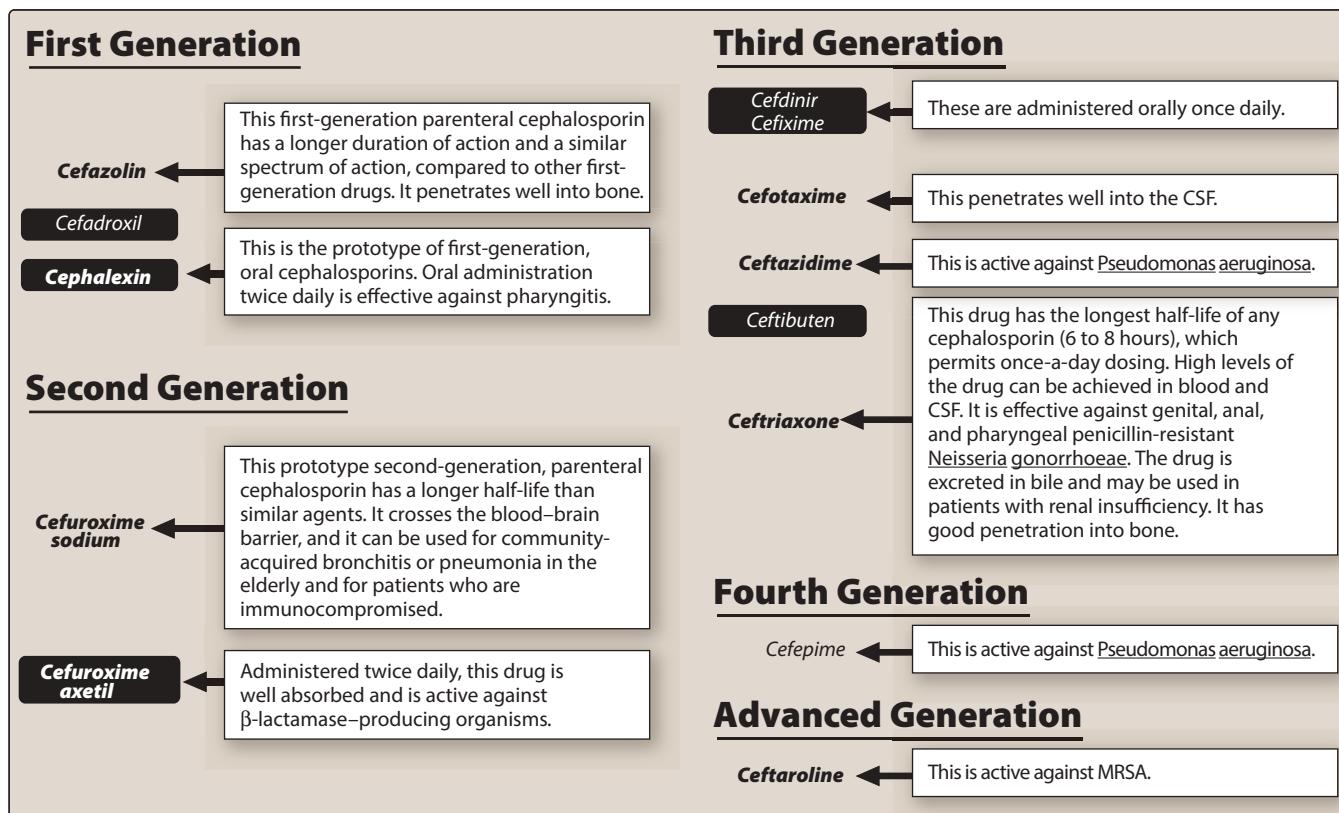
## V. $\beta$ -LACTAMASE INHIBITORS

Hydrolysis of the  $\beta$ -lactam ring, either by enzymatic cleavage with a  $\beta$ -lactamase or by acid, destroys the antimicrobial activity of a  $\beta$ -lactam antibiotic.  $\beta$ -Lactamase inhibitors, such as *clavulanic* [cla-vue-LAN-ick] acid, *sulbactam* [sul-BACK-tam], and *tazobactam* [ta-zoh-BACK-tam], contain a  $\beta$ -lactam ring but, by themselves, do not have significant



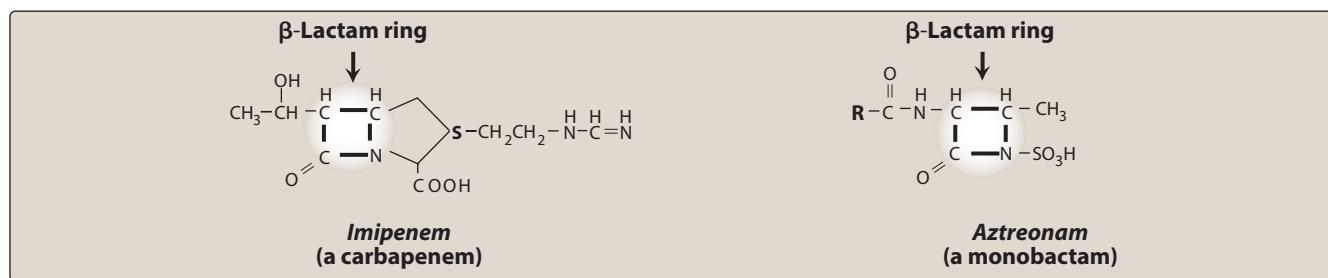
**Figure 29.12**

Administration and fate of the cephalosporins. CSF = cerebrospinal fluid.



**Figure 29.13**

Therapeutic advantages of some clinically useful cephalosporins. [Note: Drugs that can be administered orally are shown in reverse type. More useful drugs shown in **bold**.]. CSF = cerebrospinal fluid; MRSA = *methicillin*-resistant *Staphylococcus aureus*.

**Figure 29.14**Structural features of *imipenem* and *aztreonam*.

Gram (+) cocci
<i>Staphylococcus aureus</i> * <i>Staphylococcus epidermidis</i> <i>Enterococcus faecalis</i> Streptococcus groups A, B, C <i>Streptococcus pneumoniae</i>
Gram (+) bacilli
<i>Listeria monocytogenes</i>
Gram (-) cocci
<i>Neisseria gonorrhoeae</i> ** <i>Neisseria meningitidis</i>
Gram (-) rods
<i>Acinetobacter</i> species <i>Citrobacter</i> species <i>Enterobacter</i> species <i>Escherichia coli</i> <i>Gardnerella vaginalis</i> <i>Haemophilus influenzae</i> <i>Klebsiella</i> species <i>Proteus</i> species <i>Providencia</i> species <i>Pseudomonas aeruginosa</i> <i>Salmonella</i> species <i>Serratia</i> species
Anaerobic organisms
<i>Clostridium</i> species <i>Peptococcus</i> species <i>Peptostreptococcus</i> species <i>Propionibacterium</i> species <i>Bacteroides</i> species <i>Fusobacterium</i> species
Spirochetes Mycoplasma Chlamydia
Other
<i>Actinomyces</i> <i>Nocardia</i> species

**Figure 29.15**Antimicrobial spectrum of *imipenem*.

\**Methicillin*-resistant staphylococci are resistant. \*\*Includes penicillinase-producing strains.

antibacterial activity or cause any significant adverse effects. *Avibactam* [av-ee-BACK-tam] and *vaborbactam* [vay-bor-BACK-tam] are also  $\beta$ -lactamase inhibitors; however, their structures lack the core  $\beta$ -lactam ring.  $\beta$ -Lactamase inhibitors function by inactivating  $\beta$ -lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes. The  $\beta$ -lactamase inhibitors are, therefore, formulated in combination with  $\beta$ -lactamase-sensitive antibiotics (Figure 29.1). For example, Figure 29.16 shows the effect of *clavulanic acid* and *amoxicillin* on the growth of  $\beta$ -lactamase-producing *E. coli*. [Note: *Clavulanic acid* alone is nearly devoid of any antibacterial activity.]

### A. Cephalosporin and $\beta$ -lactamase inhibitor combinations

*Ceftolozane* [sef-TOL-oh-zane] is a third-generation cephalosporin combined with an existing  $\beta$ -lactamase inhibitor, *tazobactam*. *Ceftolozane-tazobactam* is available only in an intravenous formulation. Its niche for use is in the treatment of resistant Enterobacteriaceae and multidrug-resistant *P. aeruginosa*. *Ceftolozane-tazobactam* has activity against some  $\beta$ -lactamase producing bacteria (for example, select strains of ESBLs). This combination has narrow gram-positive and very limited anaerobic activity. *Ceftazidime*, a third-generation cephalosporin is combined with the  $\beta$ -lactamase inhibitor *avibactam* [AV-i-BAK-tam]. *Ceftazidime-avibactam*, available only in intravenous formulation, has broad gram-negative activity including Enterobacteriaceae and *P. aeruginosa*. Addition of *avibactam* allows the drug to resist hydrolysis against broad-spectrum  $\beta$ -lactamases (AmpC, ESBL, carbapenemases) with the exception of metallo- $\beta$ -lactamases. *Ceftazidime-avibactam* has minimal activity against *Acinetobacter* as well as anaerobic and gram-positive organisms. Both of these combinations are indicated for the treatment of intra-abdominal infections (in combination with *metronidazole*) and for the management of complicated urinary tract infections. Given the extensive antimicrobial activity, *ceftolozane-tazobactam* and *ceftazidime-avibactam* are reserved for the treatment of infections due to multidrug-resistant pathogens.

### B. Carbapenem and $\beta$ -lactamase inhibitor combination

*Meropenem* and *vaborbactam* is a combination of a carbapenem and a  $\beta$ -lactamase inhibitor. It is approved for the treatment of complicated urinary tract infections including pyelonephritis. This combination

agent has activity against Enterobacteriaceae producing a broad spectrum of  $\beta$ -lactamases, except metallo- $\beta$ -lactamases.

## VI. VANCOMYCIN

*Vancomycin* [van-koe-MYE-sin] is a tricyclic glycopeptide active against aerobic and anaerobic gram-positive bacteria, including MRSA, *methicillin*-resistant *Staphylococcus epidermidis* (MRSE), *Enterococcus* spp., and *C. difficile* (Figure 29.17). Following cell entry, it binds to peptidoglycan precursors, disrupting polymerization and cross-linking required for maintenance of cell wall integrity. This interaction results in bactericidal activity. Due to an increase in MRSA frequency, *vancomycin* is commonly used in patients with skin and soft-tissue infections, infective endocarditis, and nosocomial pneumonia. Frequency of administration is dependent on renal function. Therefore, monitoring of creatinine clearance is required to optimize exposure and minimize toxicity. Optimal cure rates are observed when trough concentrations are maintained between 10 and 20 mcg/mL. [Note: The area under the curve/minimum inhibitory concentration ratio (AUC/MIC) is the best predictor of *vancomycin* activity against *S. aureus*, with an AUC/MIC of greater than or equal to 400 associated with treatment success.] Initial trough concentrations are attained prior to the fourth or fifth *vancomycin* dose to ensure appropriate dosing. Common adverse events include nephrotoxicity, infusion-related reactions (red-man syndrome and phlebitis), and ototoxicity. Emergence of resistance is uncommon within *Streptococcus* and *Staphylococcus* spp, but frequently observed in *Enterococcus faecium* infections. Resistance is driven by alterations in binding affinity to peptidoglycan precursors. Due to the prevalence of resistance, prudent use of *vancomycin* is warranted. Lastly, *vancomycin* has poor absorption after oral administration, so use of oral formulation is limited to the management of *C. difficile* infection in the colon.

## VII. LIPOGLYCOPEPTIDES

*Telavancin* [tel-a-VAN-sin], *oritavancin* [or-IT-a-VAN-sin], and *dalbavancin* [dal-ba-VAN-sin] are bactericidal concentration-dependent semisynthetic lipoglycopeptide antibiotics with activity against gram-positive bacteria. The lipoglycopeptides maintain a spectrum of activity similar to *vancomycin*, affecting primarily staphylococci, streptococci, and enterococci. Because of structural differences, they are more potent than *vancomycin* and may have activity against *vancomycin*-resistant isolates. Like *vancomycin*, these agents inhibit bacterial cell wall synthesis. The lipid tail is essential in anchoring the drug to the cell walls to improve target site binding. Additionally, *telavancin* and *oritavancin* disrupt membrane potential. In combination, these actions improve activity and minimize selection of resistance. *Telavancin* is considered an alternative to *vancomycin* in treating acute bacterial skin and skin structure infections (ABSSI) and hospital-acquired pneumonia caused by resistant gram-positive organisms, including MRSA. The use of *telavancin* in clinical practice may be limited by its adverse effect profile which includes nephrotoxicity, risk of fetal harm, and interactions with medications known to prolong the QT<sub>c</sub> interval (for example, fluoroquinolones and macrolides). Prior to initiation, assessment of renal function, pregnancy status, and current medications is needed to ensure safe administration.

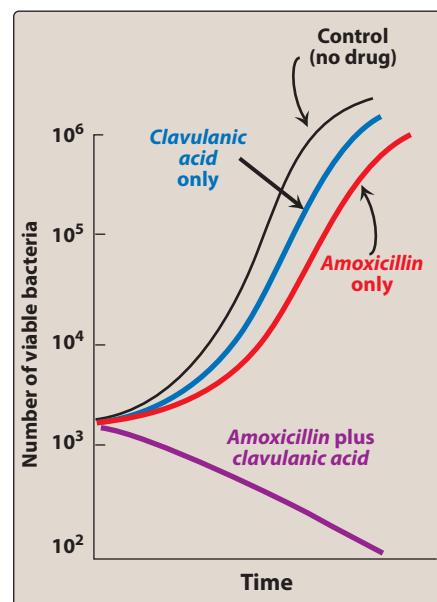


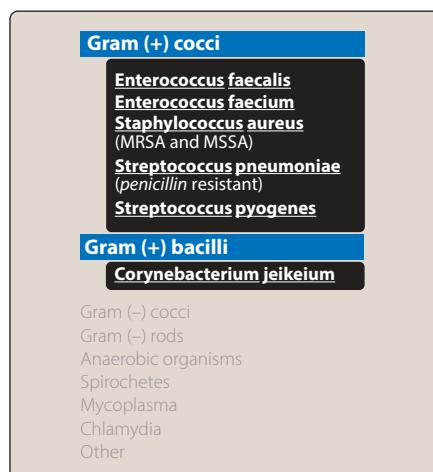
Figure 29.16

The in vitro growth of *Escherichia coli* in the presence of *amoxicillin*, with and without *clavulanic acid*.

<b>Gram (+) cocci</b>
<i>Staphylococcus aureus*</i>
<i>Staphylococcus epidermidis</i>
<i>Streptococcus groups A,B,C</i>
<i>Streptococcus pneumoniae</i>
<i>Enterococcus faecalis</i>
<b>Gram (+) bacilli</b>
<i>Listeria monocytogenes</i>
<i>Corynebacterium jeikeium</i>
Gram (-) cocci
Gram (-) rods
<b>Anaerobic organisms</b>
<i>Clostridium species**</i>
Spirochetes
Mycoplasma
Chlamydia
<b>Other</b>
<i>Actinomyces</i>

Figure 29.17

Antimicrobial spectrum of *vancomycin*. \*Includes *methicillin*-resistant strains. \*\*Oral *vancomycin* only for *C. difficile*.

**Figure 29.18**

Antimicrobial spectrum of *daptomycin*. MRSA = *methicillin*-resistant *S. aureus*; MSSA = *methicillin*-susceptible *S. aureus*.

In contrast to *telavancin*, *oritavancin*, and *dalbavancin* have prolonged half-lives (245 and 187 hours, respectively), allowing for single-dose administration for the management of ABSSSI. Stable patients with ABSSSI may be treated as outpatients, eliminating the need for inpatient admission, central catheter placement, and/or daily outpatient parenteral antibiotic therapy. Consistent with other glycopeptides, infusion-related reactions may occur. *Oritavancin* and *telavancin* are known to interfere with phospholipid reagents used in assessing coagulation. Alternative therapy should be considered with concomitant *heparin* use.

## VIII. DAPTOMYCIN

*Daptomycin* [DAP-toe-mye-sin] is a bactericidal concentration-dependent cyclic lipopeptide antibiotic that is an alternative to other agents, such as *vancomycin* or *linezolid*, for treating infections caused by resistant gram-positive organisms, including MRSA and *vancomycin*-resistant enterococci (VRE) (Figure 29.18). *Daptomycin* is indicated for the treatment of complicated skin and skin structure infections and bacteraemia caused by *S. aureus*, including those with right-sided infective endocarditis. Efficacy of treatment with *daptomycin* in left-sided endocarditis has not been demonstrated. Additionally, *daptomycin* is inactivated by pulmonary surfactants; thus, it should never be used in the treatment of pneumonia. *Daptomycin* is dosed IV once daily. Figure 29.19 provides a comparison of important characteristics of *vancomycin*, *daptomycin*, and lipoglycopeptides.

## IX. FOSFOMYCIN

*Fosfomycin* [fos-foe-MYE-sin] is a bactericidal synthetic derivative of phosphonic acid. It blocks cell wall synthesis by inhibiting the enzyme enolpyruvyl transferase, a key step in peptidoglycan synthesis. It is indicated for urinary tract infections caused by *E. coli* or *E. faecalis* and is considered first-line therapy for acute cystitis. Due to its unique structure and mechanism of action, cross-resistance with other antimicrobial agents is unlikely. *Fosfomycin* is rapidly absorbed after oral administration and distributes well to the kidneys, bladder, and prostate. The drug is excreted in its active form in the urine and maintains high concentrations over several days, allowing for a one-time dose. The most commonly reported adverse effects include diarrhea, vaginitis, nausea, and headache.

## X. POLYMYXINS

The polymyxins are cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria. They have a detergent-like effect that disrupts cell membrane integrity, leading to leakage of cellular components and cell death. Polymyxins are concentration-dependent bactericidal agents with activity against most clinically important gram-negative bacteria, including *P. aeruginosa*, *E. coli*, *K. pneumoniae*, *Acinetobacter* spp, and *Enterobacter* spp. However, alterations in the cell membrane lipid polysaccharides allow many species of *Proteus* and

	<b>VANCOMYCIN</b>	<b>DAPTO MYCIN</b>	<b>TELAVANCIN</b>
<b>Mechanism of action</b>	Inhibits bacterial cell wall synthesis	Causes rapid depolarization of the cell membrane, inhibits intracellular synthesis of DNA, RNA, and protein synthesis	Inhibits bacterial cell wall synthesis; disrupts cell membrane
<b>Pharmacodynamics</b>	Combination of time and concentration dependent Bactericidal	Concentration dependent Bactericidal	Concentration dependent Bactericidal
<b>Common antibacterial spectrum</b>	Activity limited to gram-positive organisms: <i>Staphylococcus aureus</i> (including MRSA), <i>Streptococcus pyogenes</i> , <i>S. agalactiae</i> , penicillin-resistant <i>S. pneumoniae</i> , <i>Corynebacterium jeikeium</i> , vancomycin-susceptible <i>Enterococcus faecalis</i> , and <i>E. faecium</i>		
<b>Unique antibacterial spectrum</b>	<i>Clostridium difficile</i> (oral only)	<i>Vancomycin-resistant E. faecalis</i> and <i>E. faecium</i> (VRE)	Some isolates of <i>vancomycin</i> -resistant enterococci (VRE)
<b>Route</b>	IV/PO	IV	IV
<b>Administration time</b>	60- to 90-minute IV infusion	2-minute IV push 30-minute IV infusion	60-minute IV infusion
<b>Pharmacokinetics</b>	Renal elimination Half-life: 6–10 hours Dose is adjusted based on renal function and serum trough levels	Renal elimination Half-life: 7–8 hours Dose is adjusted based on renal function	Renal elimination Half-life: 7–9 hours Dose is adjusted based on renal function
<b>Unique adverse effects</b>	Infusion related reactions due to histamine release: Fever, chills, phlebitis, flushing (red man syndrome); dose-related ototoxicity and nephrotoxicity	Elevated hepatic transaminases and creatine phosphokinase (check weekly), myalgias and rhabdomyolysis (consider holding HMG-CoA reductase inhibitors [statins] while receiving therapy)	Taste disturbances, foamy urine, QTc prolongation, interferes with coagulation labs (PT/INR, aPTT, ACT), not recommended in pregnancy (box warning recommends pregnancy test prior to initiation)
<b>Key learning points</b>	Drug of choice for severe MRSA infections; oral form only used for <i>C. difficile</i> infection; monitor serum trough concentrations for safety and efficacy	<i>Daptomycin</i> is inactivated by pulmonary surfactants and should never be used in the treatment of pneumonia	Use with caution in patients with baseline renal dysfunction (CrCl < 50 mL/min) due to higher rates of treatment failure and mortality in clinical studies; any necessary coagulation labs should be drawn just prior to the <i>telavancin</i> dose to avoid interaction

**Figure 29.19**

Side-by-side comparison of *vancomycin*, *daptomycin*, and *telavancin*. (For drug dosages, refer to Appendix at the end of the book.)

*Serratia* to be intrinsically resistant. Only two forms of polymyxin are in clinical use today, *polymyxin B* and *colistin* (*polymyxin E*). *Polymyxin B* is available in parenteral, ophthalmic, otic, and topical preparations. *Colistin* is only available as a prodrug, *colistimethate sodium*, which is administered IV or inhaled via a nebulizer. The use of these drugs has been limited due to the increased risk of nephrotoxicity and neurotoxicity (for example, slurred speech and muscle weakness) when used systemically. However, with increasing gram-negative resistance they are now commonly used as salvage therapy for patients with multidrug-resistant infections. Careful dosing and monitoring of adverse effects are important to maximize the safety and efficacy of these agents.

## Study Questions

Choose the ONE best answer.

- 29.1 A 45-year-old man presented to the hospital 3 days ago with severe cellulitis and a large abscess on his left leg. Incision and drainage were performed on the abscess, and cultures revealed methicillin-resistant Staphylococcus aureus. Which is the most appropriate treatment option for once-daily outpatient intravenous therapy in this patient?

- A. Ertapenem
- B. Ceftaroline
- C. Daptomycin
- D. Piperacillin/tazobactam

- 29.2 Which of the following adverse effects is associated with daptomycin?

- A. Ototoxicity
- B. Red man syndrome
- C. QT<sub>c</sub> prolongation
- D. Rhabdomyolysis

- 29.3 A 72-year-old man is admitted to the hospital from a nursing home with severe pneumonia. He was discharged from the hospital 1 week ago after open heart surgery. The patient has no known allergies. Which of the following regimens is most appropriate for empiric coverage of methicillin-resistant Staphylococcus aureus and Pseudomonas aeruginosa in this patient?

- A. Vancomycin + cefepime + ciprofloxacin
- B. Vancomycin + cefazolin + ciprofloxacin
- C. Telavancin + cefepime + ciprofloxacin
- D. Daptomycin + cefepime + ciprofloxacin

- 29.4 A 23-year-old man presents with acute appendicitis that ruptures shortly after admission. He is taken to the operating room for surgery, and postsurgical cultures reveal Escherichia coli and Bacteroides fragilis, susceptibilities pending. Which of the following provides adequate empiric coverage of these two pathogens?

- A. Cefepime
- B. Piperacillin/tazobactam
- C. Aztreonam
- D. Ceftaroline

Correct answer = C. Daptomycin is approved for skin and skin structure infections caused by MRSA and is given once daily. A and D are incorrect because they do not cover MRSA. Ceftaroline covers MRSA, but it must be given twice daily.

Correct answer = D. Ototoxicity and red man syndrome are associated with vancomycin. QTc prolongation is associated with telavancin. Myalgias and rhabdomyolysis have been reported with daptomycin therapy and require patient education and monitoring.

Correct answer = A. Vancomycin provides adequate coverage against MRSA, and cefepime and ciprofloxacin provide adequate empiric coverage of Pseudomonas. B is incorrect because cefazolin does not have activity against Pseudomonas. C is incorrect because telavancin should be avoided if possible with drugs that prolong the QTc interval, in this case ciprofloxacin. Daptomycin is inactivated by pulmonary surfactant and should not be used for pneumonia.

Correct answer = B. While all of these agents cover most strains of E. coli, piperacillin/tazobactam is the only drug on this list that provides coverage against Bacteroides species.

29.5 A 68-year-old man presents from a nursing home with fever, increased urinary frequency and urgency, and mental status changes. He has a penicillin allergy of anaphylaxis. Which of the following  $\beta$ -lactams is the most appropriate choice for gram-negative coverage of this patient's urinary tract infection?

- A. Cefepime
- B. Ertapenem
- C. Aztreonam
- D. Ceftaroline

29.6 A 25-year-old man presents to the urgent care center with a painless sore on his genitals that started 2 weeks ago. He reports unprotected sex with a new partner about a month ago. A blood test confirms the patient has Treponema pallidum. Which is the drug of choice for the treatment of this patient's infection as a single dose?

- A. Benzathine penicillin G
- B. Ceftriaxone
- C. Aztreonam
- D. Vancomycin

29.7 A 20-year-old woman presents to the emergency room with headache, stiff neck, and fever for 2 days and is diagnosed with meningitis. Which is the best agent for the treatment of meningitis in this patient?

- A. Cefazolin
- B. Cefdinir
- C. Cefotaxime
- D. Cefuroxime axetil

29.8 Which of the following cephalosporins has activity against gram-negative anaerobic pathogens like Bacteroides fragilis?

- A. Cefoxitin
- B. Cefepime
- C. Ceftriaxone
- D. Cefazolin

Correct answer = C. Based on the severity of the allergic reaction, aztreonam is the choice of all the  $\beta$ -lactams. Although cross-reactivity with cephalosporins and carbapenems is low, the risk rarely outweighs the benefit in these cases.

Correct answer = A. A single treatment with penicillin is curative for primary and secondary syphilis. No antibiotic resistance has been reported, and it remains the drug of choice unless the patient has a severe allergic reaction.

Correct answer = C. Cefotaxime is the only drug on this list with adequate CSF penetration to treat meningitis. Cefdinir and cefuroxime axetil are only available orally, and cefazolin CSF penetration and spectrum of coverage against S. pneumoniae are likely inadequate to treat meningitis.

Correct answer = A. The cephemycins (cefoxitin and cefotetan) are the only cephalosporins with in vitro activity against anaerobic gram-negative pathogens. Cefepime, ceftriaxone, and cefazolin have no appreciable activity against Bacteroides fragilis.

29.9 In which of the following cases would it be appropriate to use telavancin?

- A. A 29-year-old pregnant woman with ventilator-associated pneumonia.
- B. A 76-year-old man with hospital-acquired pneumonia also receiving amiodarone for atrial fibrillation.
- C. A 36-year-old man with cellulitis and abscess growing MRSA.
- D. A 72-year-old woman with a diabetic foot infection growing MRSA who has moderate renal dysfunction.

29.10 An 18-year-old woman presents to the urgent care clinic with symptoms of a urinary tract infection. Cultures reveal Enterococcus faecalis that is pan sensitive. Which of the following is an appropriate oral option to treat the urinary tract infection in this patient?

- A. Cephalexin
- B. Vancomycin
- C. Cefdinir
- D. Amoxicillin

Correct answer = C. A is not a good option due to the potential of telavancin harming the fetus. Option B is not a good choice because the patient is on amiodarone, and telavancin can cause QT<sub>c</sub> prolongation. Option D is not an appropriate choice because the patient has baseline renal dysfunction and telavancin should be avoided unless benefit outweighs the risk. Option C is the best choice since telavancin is approved for skin and skin structure infections, and the patient has no apparent contraindication.

Correct answer = D. Options A and C are incorrect because enterococci are inherently resistant to all cephalosporins. Option B is incorrect because oral vancomycin is not absorbed and would not reach the urinary tract in sufficient quantities to treat a urinary tract infection. Option D is the best choice, as amoxicillin is well absorbed orally and concentrates in the urine.

# Protein Synthesis Inhibitors

30

Jacqueline Jourjy

## I. OVERVIEW

A number of antibiotics exert their antimicrobial effects by targeting bacterial ribosomes and inhibiting bacterial protein synthesis. Most of these agents exhibit bacteriostatic activity. Bacterial ribosomes differ structurally from mammalian cytoplasmic ribosomes and are composed of 30S and 50S subunits (mammalian ribosomes have 40S and 60S subunits). In general, selectivity for bacterial ribosomes minimizes potential adverse consequences encountered with the disruption of protein synthesis in mammalian host cells. However, high concentrations of drugs such as *chloramphenicol* or the tetracyclines may cause toxic effects as a result of interaction with mitochondrial mammalian ribosomes, because the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes. Figure 30.1 summarizes the antimicrobial protein synthesis inhibitors discussed in this chapter.

## II. TETRACYCLINES

Tetracyclines consist of four fused rings with a system of conjugated double bonds. Substitutions on these rings alter the individual pharmacokinetics and spectrum of antimicrobial activity.

### A. Mechanism of action

Tetracyclines enter susceptible organisms via passive diffusion and by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane. Tetracyclines concentrate intracellularly in susceptible organisms. The drugs bind reversibly to the 30S subunit of the bacterial ribosome. This action prevents binding of tRNA to the mRNA–ribosome complex, thereby inhibiting bacterial protein synthesis (Figure 30.2).

### B. Antibacterial spectrum

The tetracyclines are bacteriostatic antibiotics effective against a wide variety of organisms, including gram-positive and gram-negative bacteria, protozoa, spirochetes, mycobacteria, and atypical species. They are commonly used in the treatment of acne and *Chlamydia* infections (Figure 30.3).

### TETRACYCLINES

**First generation (biosynthesis; broad-spectrum antibiotic)**

*Tetracycline*  
*Demeocycline*  
*Chlortetecycline*  
*Oxytetracycline*

**Second generation (semisynthetic)**

*Doxycycline*  
*Minocycline*  
*Meclocycline*  
*Methacycline*  
*Lymecycline*  
*Rolitetracycline*

**Third generation (synthetic; glycylcyclines)**

*Tigecycline*

### AMINOGLYCOSIDES

*Gentamicin*  
*Amikacin*  
*Neomycin*  
*Streptomycin*  
*Tobramycin*

### MACROLIDES/KETOLIDES

*Erythromycin*  
*Roxithromycin*  
*Azithromycin*  
*Clarithromycin*  
*Telithromycin*

### MACROCYCLIC

*Fidaxomicin*

### LINCOBAMIDES

*Clindamycin*

### OXAZOLIDINONES

*Linezolid*

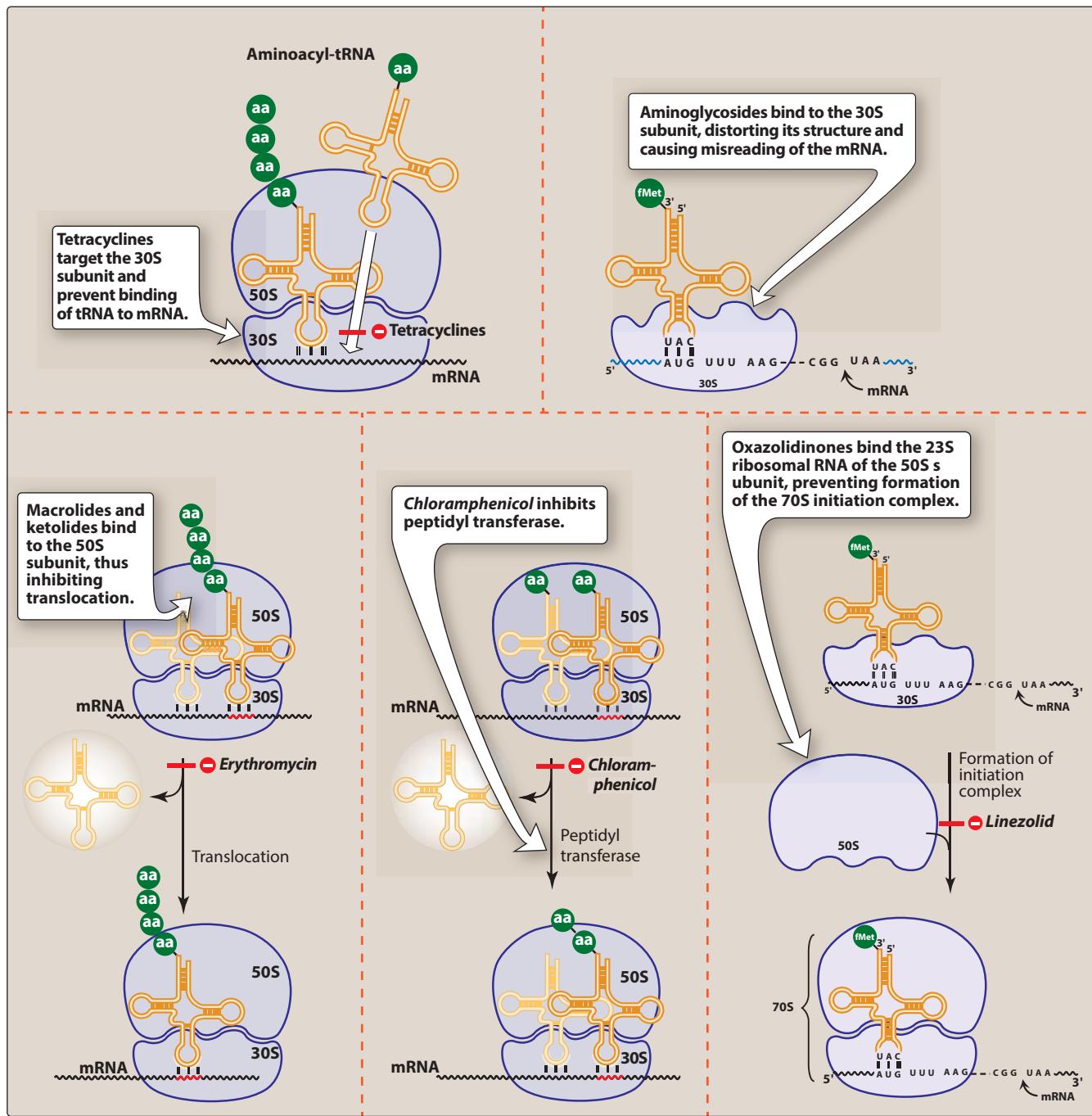
*Tedizolid*

### OTHERS

*Chloramphenicol*  
*Quinupristin/Dalfopristin*

### Figure 30.1

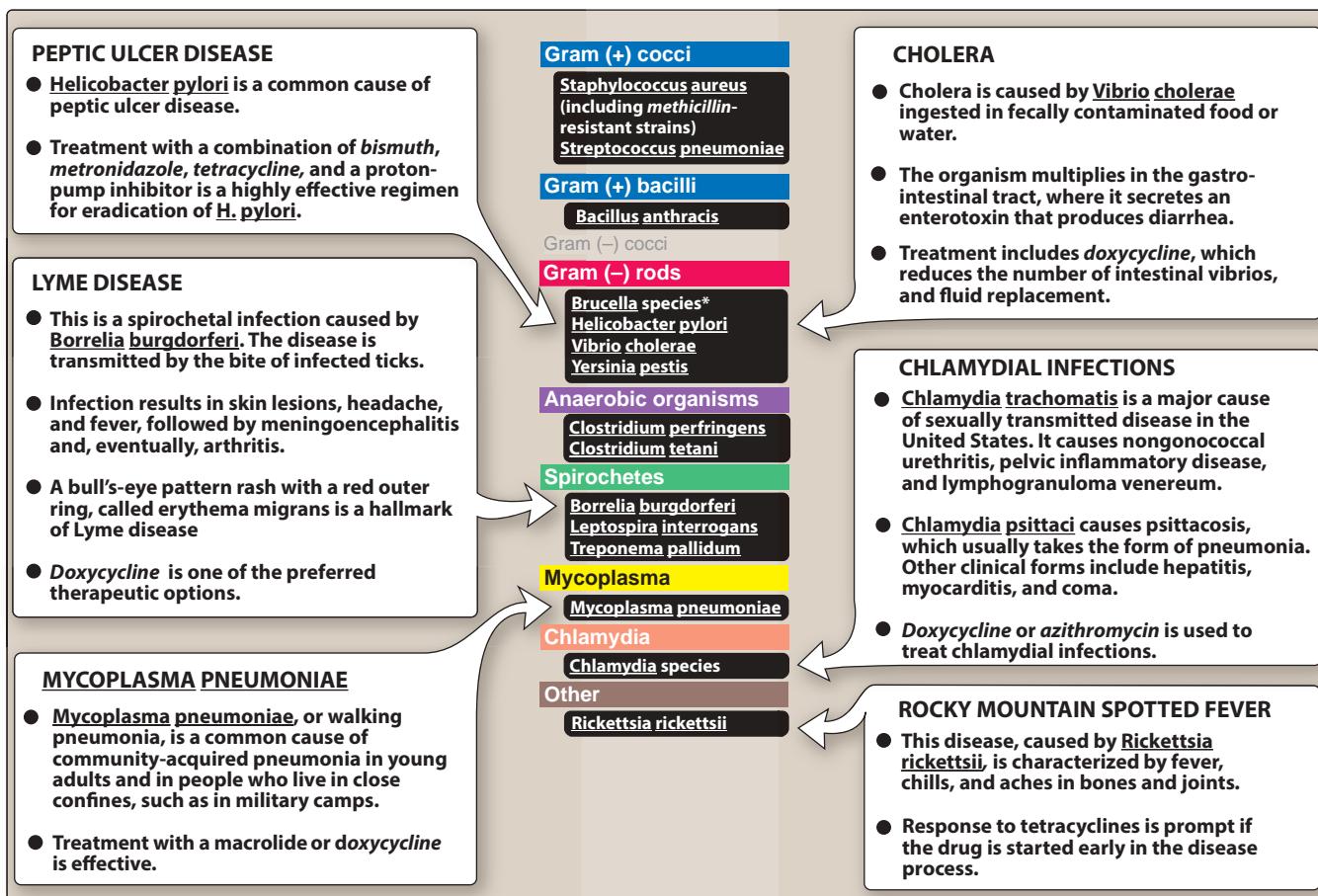
Summary of protein synthesis inhibitors and their routes of administration and dose. (For drug dosages, refer to Appendix at the end of the book.)

**Figure 30.2**

Mechanisms of action of the various protein synthesis inhibitors. aa = amino acid.

### C. Resistance

The most commonly encountered naturally occurring resistance to tetracyclines is an efflux pump that expels drug out of the cell, thus preventing intracellular accumulation. Other mechanisms of bacterial resistance to tetracyclines include enzymatic inactivation of the drug and production of bacterial proteins that prevent tetracyclines from

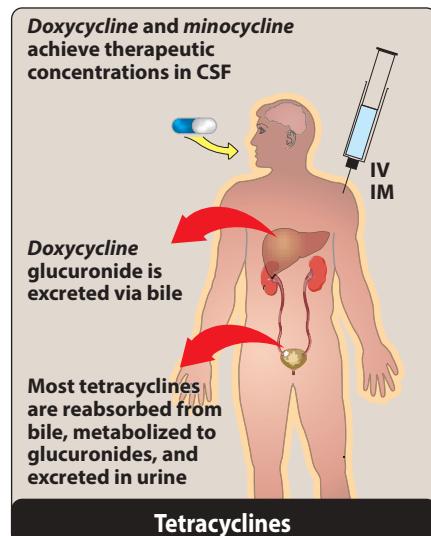
**Figure 30.3**

Typical therapeutic applications of tetracyclines. \*A tetracycline + gentamicin.

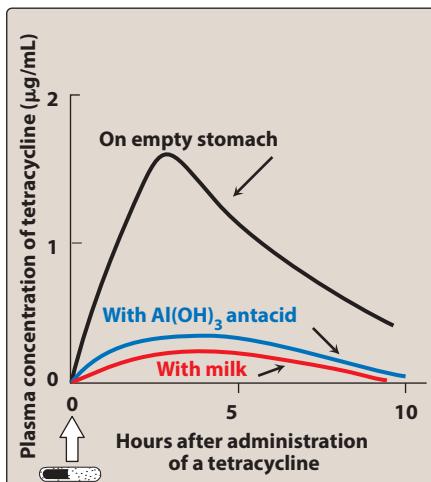
binding to the ribosome. Resistance to one tetracycline does not confer universal resistance to all tetracyclines, and the development of cross-resistance may be dependent on the mechanism of resistance.

#### D. Pharmacokinetics

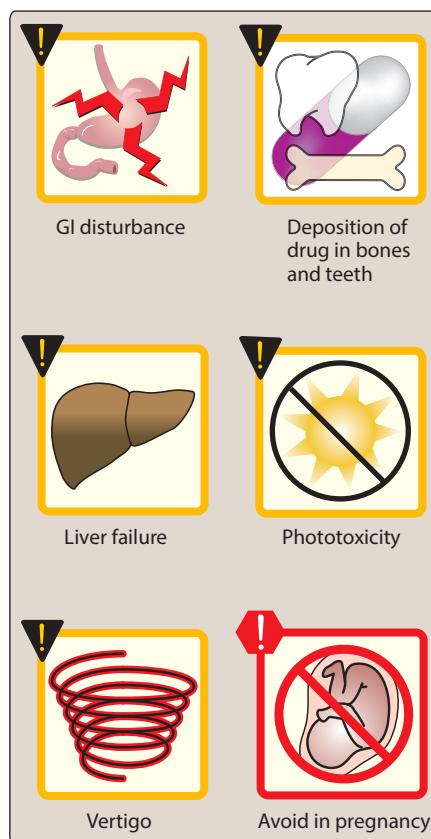
1. **Absorption:** Tetracyclines are adequately absorbed after oral ingestion (Figure 30.4). Administration with dairy products or other substances that contain divalent and trivalent cations (for example, magnesium, calcium, aluminum antacids, or iron supplements) decreases absorption, particularly for *tetracycline* [tet-rah-SYE-kleen], due to the formation of nonabsorbable chelates (Figure 30.5). Both *doxycycline* [dox-i-SYE-kleen] and *minocycline* [min-oh-SYE-kleen] are available as oral and intravenous (IV) preparations.
2. **Distribution:** The tetracyclines concentrate well in the bile, liver, gingival fluid, and skin. Moreover, they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have high calcium content. Penetration into most body fluids is adequate. Only *minocycline* and *doxycycline* achieve therapeutic levels in the cerebrospinal fluid (CSF). *Minocycline*

**Figure 30.4**

Administration and fate of tetracyclines. CSF = cerebrospinal fluid.

**Figure 30.5**

Effect of antacids and milk on the absorption of tetracyclines.

**Figure 30.6**

Some adverse effects of tetracyclines.  
GI = gastrointestinal.

also achieves high concentrations in saliva and tears, rendering it useful in eradicating the meningococcal carrier state. All tetracyclines cross the placental barrier and concentrate in fetal bones and dentition.

3. **Elimination:** *Tetracycline* is primarily eliminated unchanged in the urine, whereas *minocycline* undergoes hepatic metabolism and is eliminated to a lesser extent via the kidney. *Doxycycline* is preferred in patients with renal dysfunction, as it is primarily eliminated via the bile into the feces.

### E. Adverse effects

1. **Gastric discomfort:** Epigastric distress commonly results from irritation of the gastric mucosa (Figure 30.6) and is often responsible for noncompliance with tetracyclines. Esophagitis may be minimized through co-administration with food (other than dairy products) or fluids and the use of capsules rather than tablets. [Note: *Tetracycline* should be taken on an empty stomach.]
2. **Effects on calcified tissues:** Deposition in the bone and primary dentition occurs during the calcification process in growing children. This may cause discoloration and hypoplasia of teeth and a temporary stunting of growth. For this reason, the use of tetracyclines is limited in pediatrics.
3. **Hepatotoxicity:** Rarely hepatotoxicity may occur with high doses, particularly in pregnant women and those with preexisting hepatic dysfunction or renal impairment.
4. **Phototoxicity:** Severe sunburn may occur in patients receiving a tetracycline who are exposed to sun or ultraviolet rays. This toxicity is encountered with any tetracycline, but more frequently with *tetracycline* and *demeclacycline* [dem-e-kloe-SYE-kleen]. Patients should be advised to wear adequate sun protection.
5. **Vestibular dysfunction:** Dizziness, vertigo, and tinnitus may occur particularly with *minocycline*, which concentrates in the endolymph of the ear and affects function.
6. **Pseudotumor cerebri:** Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.
7. **Contraindications:** The tetracyclines should not be used in pregnant or breast-feeding women or in children less than 8 years of age.

## III. GLYCOCYCLINES

*Tigecycline* [tye-ge-SYE-kleen], a derivative of *minocycline*, is the first member of the glycycycline antimicrobial class. It is indicated for the treatment of complicated skin and soft-tissue infections, complicated intra-abdominal infections, and community-acquired pneumonia.

### A. Mechanism of action

*Tigecycline* exhibits bacteriostatic action by reversibly binding to the 30S ribosomal subunit and inhibiting bacterial protein synthesis.

## B. Antibacterial spectrum

*Tigecycline* exhibits broad-spectrum activity that includes *methicillin*-resistant staphylococci (MRSA), multidrug-resistant streptococci, vancomycin-resistant enterococci (VRE), extended-spectrum  $\beta$ -lactamase-producing gram-negative bacteria, *Acinetobacter baumannii*, and many anaerobic organisms. *Tigecycline* is not active against *Morganella*, *Proteus*, *Providencia*, or *Pseudomonas* species.

## C. Resistance

*Tigecycline* was developed to overcome the emergence of tetracycline class-resistant organisms that utilize efflux pumps and ribosomal protection to confer resistance. Resistance to *tigecycline* has been observed and is primarily attributed to overexpression of efflux pumps.

## D. Pharmacokinetics

Following IV infusion, *tigecycline* exhibits a large volume of distribution. It penetrates tissues well but achieves low plasma concentrations. Consequently, *tigecycline* is a poor option for bloodstream infections. The primary route of elimination is biliary/fecal. No dosage adjustments are necessary for patients with renal impairment; however, a dose reduction is recommended in severe hepatic dysfunction.

## E. Adverse effects

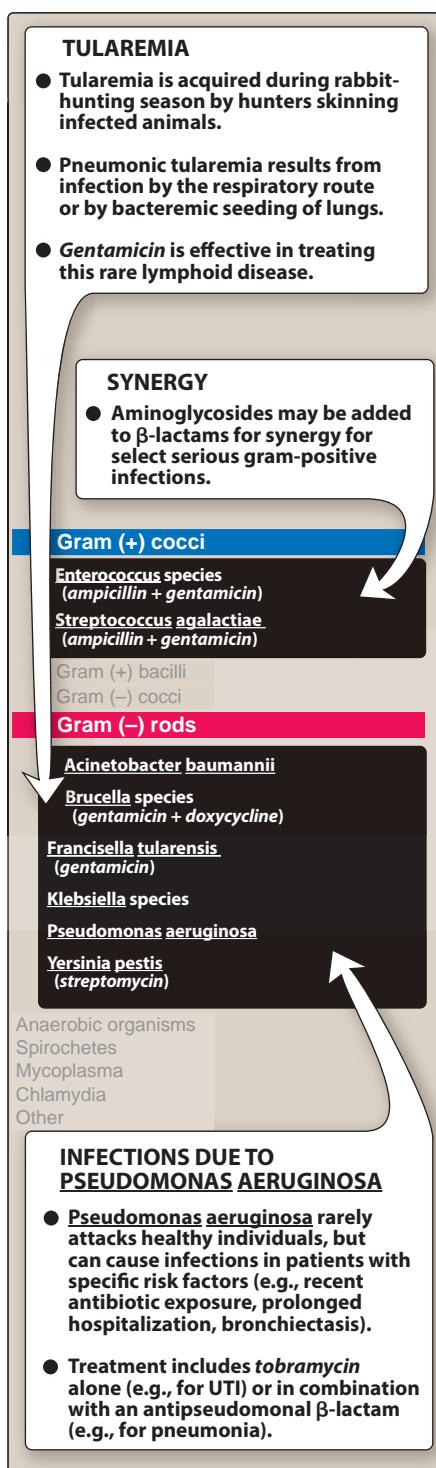
*Tigecycline* is associated with significant nausea and vomiting. Acute pancreatitis, including fatality, has been reported with therapy. Elevations in liver enzymes and serum creatinine may also occur. All-cause mortality in patients treated with *tigecycline* is higher than with other agents. A boxed warning states that *tigecycline* should be reserved for use in situations when alternative treatments are not suitable. Other adverse effects are similar to those of the tetracyclines and include photosensitivity, pseudotumor cerebri, discoloration of permanent teeth when used during tooth development, and fetal harm when administered in pregnancy. *Tigecycline* may decrease the clearance of *warfarin*. Therefore, the international normalized ratio should be monitored closely when *tigecycline* is co-administered with *warfarin*.

# IV. AMINOGLYCOSIDES

Aminoglycosides are highly water-soluble compounds originally isolated from soil actinomycetes and used for the treatment of infections due to aerobic gram-negative bacilli. If the compounds are isolated from *Streptomyces*, they are named with the suffix “mycin” and if they are from *Micromonospora*, the compounds would be having the suffix “micin.”

## A. Mechanism of action

Aminoglycosides diffuse through porin channels in the outer membrane of susceptible organisms. These organisms also have an oxygen-dependent system that transports the drug across the

**Figure 30.7**

Typical therapeutic applications of aminoglycosides. UTI = urinary tract infection.

cytoplasmic membrane. Therefore, in the anaerobic conditions this process is inactivated. Inside the cell, they bind the 30S ribosomal subunit, where they interfere with the assembly of the functional ribosomal apparatus and/or cause the 30S subunit of the completed ribosome to misread the genetic code (Figure 30.2). Aminoglycosides have concentration-dependent bactericidal activity—that is, their efficacy is dependent on the maximum concentration ( $C_{max}$ ) of the drug above the minimum inhibitory concentration (MIC) of the organism. For aminoglycosides, the target  $C_{max}$  is 8 to 10 times the MIC. They also exhibit a postantibiotic effect (PAE), which is continued bacterial suppression after drug concentrations fall below the MIC. The larger the dose, the longer the PAE. Because of these properties, high-dose extended-interval dosing is commonly utilized. This dosing strategy also reduces the risk of nephrotoxicity and increases convenience.

## B. Antibacterial spectrum

The aminoglycosides are effective for the majority of aerobic gram-negative bacilli, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter* sp. Additionally, aminoglycosides are often combined with a  $\beta$ -lactam antibiotic to employ a synergistic effect, particularly in the treatment of *Enterococcus faecalis* and *Enterococcus faecium* infective endocarditis. Some therapeutic applications of four commonly used aminoglycosides—*amikacin* [am-i-KAY-sin], *gentamicin* [jen-ta-MYE-sin], *tobramycin* [toe-bra-MYE-sin], and *streptomycin* [strep-toe-MYE-sin]—are shown in Figure 30.7.

## C. Resistance

Resistance to aminoglycosides occurs via efflux pumps, decreased uptake, and/or modification and inactivation by plasmid-associated synthesis of enzymes. Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance cannot be presumed. [Note: *Amikacin* is less vulnerable to these enzymes than other antibiotics in this group.]

## D. Pharmacokinetics

1. **Absorption:** The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration; therefore, all aminoglycosides (except *neomycin* [nee-oh-MYE-sin]) must be given parenterally to achieve adequate serum concentrations (Figure 30.8). However, absorption from muscles (after the intramuscular injection) is rapid and reaches  $C_{max}$  within 30 to 60 minutes. [Note: *Neomycin* is not given parenterally due to severe nephrotoxicity. It is administered topically for skin infections or orally to decontaminate the gastrointestinal tract prior to colorectal surgery.]
2. **Distribution:** Because of their hydrophilicity, aminoglycoside tissue concentrations may be subtherapeutic and penetration into most body fluids is variable. Their volume of distribution is equivalent to the extracellular volume indicating that they are distributed into extracellular fluid extensively. Concentrations achieved in CSF are inadequate, even in the presence of inflamed

meninges. For central nervous system infections, the intrathecal or intraventricular routes may be utilized. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

3. **Elimination:** More than 90% of the parenteral aminoglycosides are excreted unchanged in the urine (Figure 30.8). Accumulation occurs in patients with renal dysfunction; thus, dose adjustments are required. *Neomycin* is primarily excreted unchanged in the feces.
4. **Protein binding:** Aminoglycosides are reported to have low protein binding; hence, they have lesser clinical significance.

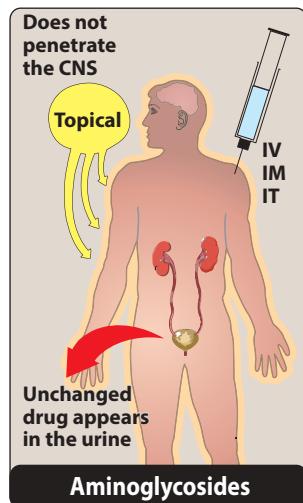
## E. Adverse effects

Therapeutic drug monitoring of *gentamicin*, *tobramycin*, and *amikacin* plasma concentrations is imperative to ensure appropriateness of dosing and to minimize dose-related toxicities (Figure 30.9). The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1. **Ototoxicity:** Ototoxicity (vestibular and auditory) is directly related to high peak plasma concentrations and the duration of treatment. Aminoglycosides accumulate in the endolymph and perilymph of the inner ear. Deafness may be irreversible and has been known to affect developing fetuses. Patients simultaneously receiving concomitant ototoxic drugs, such as *cisplatin* or loop diuretics, are particularly at risk. Vertigo (especially in patients receiving *streptomycin*) may also occur. As aminoglycosides are known to cross the blood placental barrier, they are contraindicated during pregnancy to avoid the risk of fetal ototoxicity.
2. **Nephrotoxicity:** Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes. This results in kidney damage ranging from mild, reversible renal impairment to severe, potentially irreversible acute tubular necrosis.
3. **Neuromuscular paralysis:** This adverse effect is associated with a rapid increase in concentration (for example, high doses infused over a short period) or concurrent administration with neuromuscular blockers. Patients with myasthenia gravis are particularly at risk. Prompt administration of *calcium gluconate* or *neostigmine* can reverse the block that causes neuromuscular paralysis.
4. **Allergic reactions:** Contact dermatitis is a common reaction to topically applied neomycin.

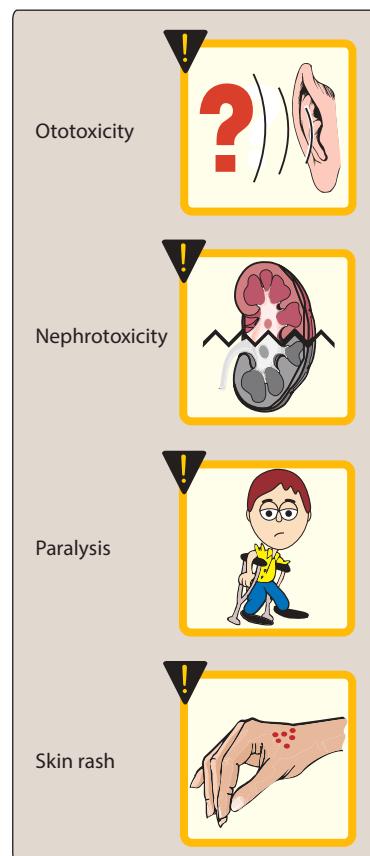
## V. MACROLIDES AND KETOLIDES

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached. *Erythromycin* [er-ith-ro-MYE-sin] was the first of these drugs to have clinical application, both as a drug of first choice and as an alternative to *penicillin* in individuals with an allergy to  $\beta$ -lactam antibiotics. *Clarithromycin* [kla-rith-ro-MYE-sin] (a methylated form of *erythromycin*), *roxithromycin* [ro-xith-ro-MYE-sin], *azithromycin* [a-zith-ro-MYE-sin] (having a larger lactone ring) have some features in common with, and others that improve upon,



**Figure 30.8**

Administration and fate of aminoglycosides. CNS = central nervous system.



**Figure 30.9**

Some adverse effects of aminoglycosides.

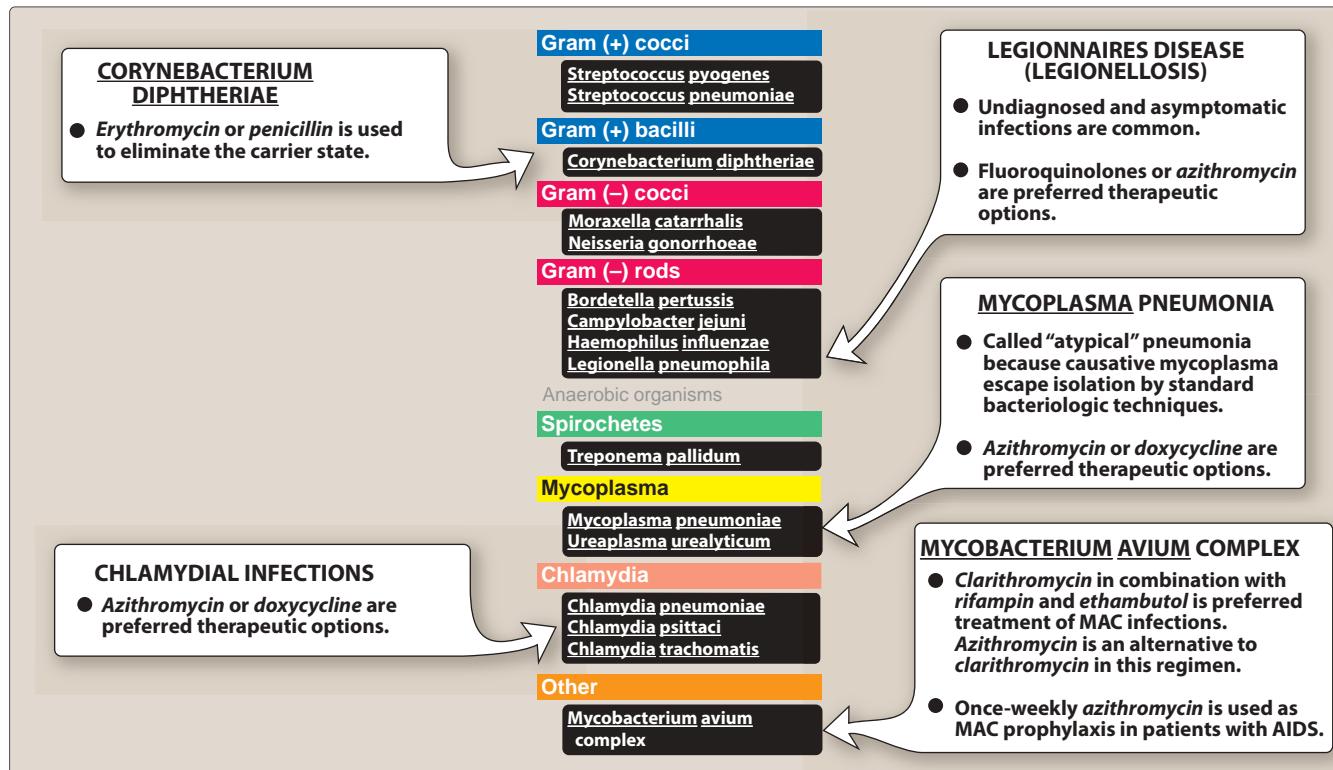
*erythromycin*. *Telithromycin* [tel-ith-roe-MYE-sin], a semisynthetic derivative of *erythromycin*, is the first “ketolide” antimicrobial agent.

### A. Mechanism of action

The macrolides and ketolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting translocation steps of protein synthesis (Figure 30.2). They may also interfere with other steps, such as transpeptidation. Generally considered to be bacteriostatic, they may be bactericidal at higher doses. Their binding site is either identical to or in close proximity to that for *clindamycin* and *chloramphenicol*.

### B. Antibacterial spectrum

1. **Erythromycin:** This drug is effective against many of the same organisms as *penicillin G* (Figure 30.10); therefore, it may be considered as an alternative in patients with *penicillin* allergy.
2. **Clarithromycin:** *Clarithromycin* has activity similar to *erythromycin*, but it is also effective against *Haemophilus influenzae* and has greater activity against intracellular pathogens such as *Chlamydia*, *Legionella*, *Moraxella*, *Ureaplasma* species, and *Helicobacter pylori*.
3. **Roxithromycin:** *Roxithromycin* is a long-acting acid stable semi-synthetic derivative of erythromycin with an N-oxime side chain on the lactone ring having antibacterial and antimalarial activities.



**Figure 30.10**

Typical therapeutic applications of macrolides.

*Roxithromycin* gets highly concentrated in polymorphonuclear leukocytes and macrophages and exhibits intracellular bactericidal activity. It is also reported to enhance the adhesive and chemotactic functions of cells which in the presence of infection produce phagocytosis and bacterial lysis. It shows potent activity against *Gardnerella vaginalis*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Haemophilus ducreyi*, etc.

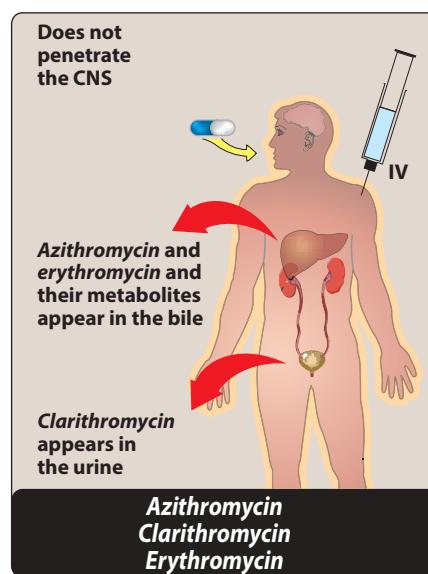
3. **Azithromycin:** Although less active than *erythromycin* against streptococci and staphylococci, *azithromycin* is far more active against respiratory pathogens such as *H. influenzae* and *Moraxella catarrhalis*. Extensive use of *azithromycin* has resulted in growing *Streptococcus pneumoniae* resistance.
4. **Telithromycin:** *Telithromycin* has an antimicrobial spectrum similar to that of *azithromycin*. Moreover, the structural modification within ketolides neutralizes the most common resistance mechanisms that render macrolides ineffective.

### C. Resistance

Resistance to macrolides is associated with: 1) the inability of the organism to take up the antibiotic, 2) the presence of efflux pumps, 3) a decreased affinity of the 50S ribosomal subunit for the antibiotic due to methylation of an adenine in the 23S bacterial ribosomal RNA in gram-positive organisms, and 4) the presence of plasmid-associated *erythromycin* esterases in gram-negative organisms such as the Enterobacteriaceae. *Erythromycin* has limited clinical use due to increasing resistance. Both *clarithromycin* and *azithromycin* share some cross-resistance with *erythromycin*. *Telithromycin* may be effective against macrolide-resistant organisms.

### D. Pharmacokinetics

1. **Absorption:** The *erythromycin* base is destroyed by gastric acid; thus, either enteric-coated tablets or esterified forms of the antibiotic are administered and all have adequate oral absorption (Figure 30.11). *Clarithromycin*, *roxithromycin*, *azithromycin*, and *telithromycin* are stable in stomach acid and are readily absorbed. Food interferes with the absorption of *erythromycin*, *azithromycin*, and *roxithromycin* but can increase that of *clarithromycin*. *Telithromycin* is administered orally without regard to meals. *Erythromycin* and *azithromycin* are available in IV formulations.
2. **Distribution:** *Erythromycin* distributes well to all body fluids except the CSF. It is one of the few antibiotics that diffuse into prostatic fluid, and it also accumulates in macrophages. All four drugs concentrate in the liver. *Clarithromycin*, *roxithromycin*, *azithromycin*, and *telithromycin* are widely distributed in the tissues. *Azithromycin* and *roxithromycin* get concentrated in neutrophils, macrophages, and fibroblasts, and serum concentrations are low. *Azithromycin* has the largest volume of distribution among all macrolides.
3. **Elimination:** Macrolides are extensively metabolized by the liver. Drug interactions are reported with the number of drugs metabolized by the CYP450 system. Interference with the metabolism of drugs such as *theophylline*, statins, and numerous antiepileptics has been reported for *clarithromycin*.



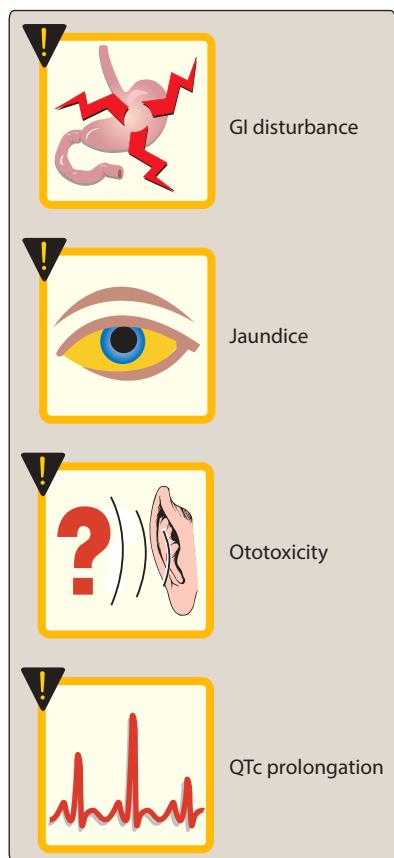
**Figure 30.11**

Administration and fate of the macrolide antibiotics. CNS = central nervous system.

	Erythro-mycin	Clarithro-mycin	Azithro-mycin	Telithro-mycin
Oral absorption	Yes	Yes	Yes	Yes
Half-life (hours)	2	3.5	68	10
Conversion to an active metabolite	No	Yes	No	Yes
Percent excretion in urine	< 15	30–50	< 10	13

**Figure 30.12**

Some properties of the macrolide antibiotics.

**Figure 30.13**

Some adverse effects of macrolide antibiotics.

4. **Excretion:** *Azithromycin* is primarily concentrated and excreted in the bile as active drug. *Erythromycin* and its metabolites are also excreted in the bile (Figure 30.11). Approximately 10% of the dose of *roxithromycin* is excreted in urine. Partial reabsorption occurs through the enterohepatic circulation. In contrast, *clarithromycin* is hepatically metabolized and the active drug and its metabolites are mainly excreted in the urine (Figure 30.12). The dosage of this drug should be adjusted in patients with renal impairment.

## E. Adverse effects

1. **Gastric distress and motility:** Gastrointestinal upset is the most common adverse effect of the macrolides and may lead to poor patient compliance (especially with *erythromycin*). The other macrolides seem to be better tolerated (Figure 30.13). Higher doses of *erythromycin* lead to smooth muscle contractions that result in the movement of gastric contents to the duodenum, an adverse effect sometimes employed for the treatment of gastroparesis or postoperative ileus.
2. **Cholestatic jaundice:** This adverse effect occurs most commonly with the estolate form of *erythromycin*; however, it has been reported with other formulations and other agents in this class.
3. **Ototoxicity:** Transient deafness has been associated with *erythromycin*, especially at high dosages. *Azithromycin* has also been associated with irreversible sensorineural hearing loss.
4. **QT<sub>c</sub> prolongation:** Macrolides and ketolides may prolong the QT<sub>c</sub> interval and should be used with caution in those patients with proarrhythmic conditions or concomitant use of proarrhythmic agents.
5. **Contraindications:** Patients with hepatic dysfunction should be treated cautiously with *erythromycin*, *telithromycin*, or *azithromycin*, because these drugs accumulate in the liver. Severe hepatotoxicity with *telithromycin* has limited its use, given the availability of alternative therapies.
6. **Drug interactions:** *Erythromycin*, *telithromycin*, *roxithromycin*, and *clarithromycin* inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulation of these compounds (Figure 30.14). An interaction with *digoxin* may occur. One theory to explain this interaction is that the antibiotic eliminates a species of intestinal flora that ordinarily inactivates *digoxin*, leading to greater reabsorption of *digoxin* from the enterohepatic circulation.

## VI. FIDAXOMICIN

*Fidaxomicin* [fyeh-DAX-oh-MYE-sin] is a macrocyclic antibiotic with a structure similar to the macrolides; however, it has a unique mechanism of action. *Fidaxomicin* acts on the sigma subunit of RNA polymerase, thereby disrupting bacterial transcription, terminating protein synthesis, and resulting in cell death in susceptible organisms. *Fidaxomicin* has a very narrow spectrum of activity limited to gram-positive aerobes and anaerobes. While it possesses activity against staphylococci and enterococci, it is used primarily for its bactericidal activity against *Clostridium difficile*.

Because of the unique target site, cross-resistance with other antibiotic classes has not been documented. Following oral administration, *fidaxomicin* has minimal systemic absorption and primarily remains within the gastrointestinal tract. This is ideal for the treatment of *C. difficile* infection, which occurs in the gut. The most common adverse effects include nausea, vomiting, and abdominal pain. Anemia and neutropenia have been observed infrequently. Hypersensitivity reactions including angioedema, dyspnea, and pruritus have occurred. *Fidaxomicin* should be used with caution in patients with a macrolide allergy, as they may be at increased risk for hypersensitivity.

## VII. CHLORAMPHENICOL

The use of *chloramphenicol* [klor-am-FEN-i-kole], a broad-spectrum antibiotic, is restricted to life-threatening infections for which no alternatives exist.

### A. Mechanism of action

*Chloramphenicol* binds reversibly to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction (Figure 30.2). Because of some similarity of mammalian mitochondrial ribosomes to those of bacteria, protein and ATP synthesis in these organelles may be inhibited at high circulating *chloramphenicol* concentrations, producing bone marrow toxicity.

### B. Antibacterial spectrum

*Chloramphenicol* is active against many types of microorganisms including chlamydiae, rickettsiae, spirochetes, and anaerobes. The drug is primarily bacteriostatic, but it may exert bactericidal activity depending on the dose and organism.

### C. Resistance

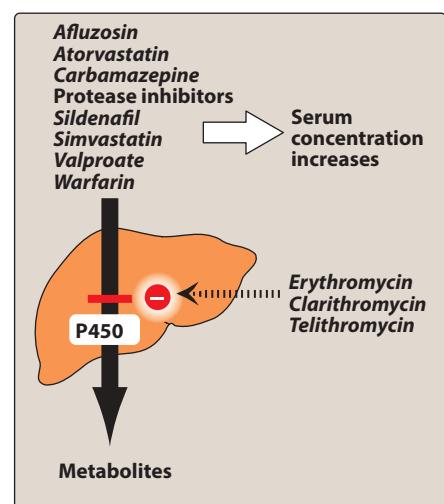
Resistance is conferred by the presence of enzymes that inactivate *chloramphenicol*. Other mechanisms include decreased ability to penetrate the organism and ribosomal binding site alterations.

### D. Pharmacokinetics

*Chloramphenicol* is administered intravenously and is widely distributed throughout the body. It reaches therapeutic concentrations in the CSF. *Chloramphenicol* primarily undergoes hepatic metabolism to an inactive glucuronide, which is secreted by the renal tubule and eliminated in the urine. Dose reductions are necessary in patients with liver dysfunction or cirrhosis. *Chloramphenicol* is also secreted into breast milk and should be avoided in breastfeeding mothers.

### E. Adverse effects

- Anemias:** Patients may experience dose-related anemia, hemolytic anemia (observed in patients with glucose-6-phosphate dehydrogenase deficiency), and aplastic anemia. [Note: Aplastic anemia is independent of dose and may occur after therapy has ceased.]

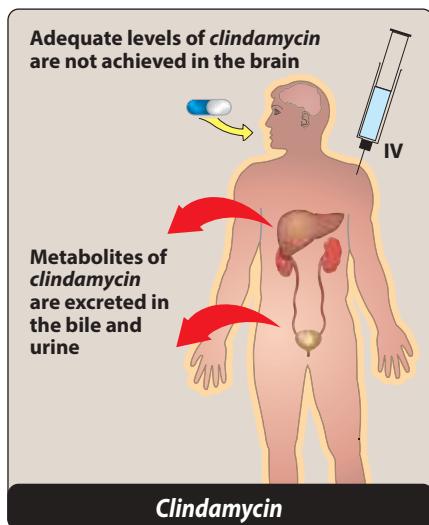


**Figure 30.14**

Inhibition of the cytochrome P450 system by *erythromycin*, *clarithromycin*, and *telithromycin*.

2. **Gray baby syndrome:** Neonates have a low capacity to glucurinate the antibiotic and they have underdeveloped renal function, which decreases their ability to excrete the drug. This leads to drug accumulation to concentrations that interfere with the function of mitochondrial ribosomes, causing poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term “gray baby”), and death. Adults who have received very high doses of *chloramphenicol* may also exhibit this toxicity.
3. **Drug interactions:** *Chloramphenicol* inhibits some of the hepatic mixed-function oxidases, preventing the metabolism of drugs such as *warfarin* and *phenytoin*, which may potentiate their effects.

## VIII. CLINDAMYCIN



**Figure 30.15**

Administration and fate of *clindamycin*.

*Clindamycin* [klin-da-MYE-sin] has a mechanism of action that is similar to that of the macrolides. *Clindamycin* is used primarily in the treatment of infections caused by gram-positive organisms, including MRSA and streptococcus, and anaerobic bacteria. Resistance mechanisms are the same as those for *erythromycin*, and cross-resistance has been described. *C. difficile* is resistant to *clindamycin*, and the utility of *clindamycin* for gram-negative anaerobes (for example, *Bacteroides* sp.) is decreasing due to increasing resistance. *Clindamycin* is available in both IV and oral formulations, but use of oral *clindamycin* is limited by gastrointestinal intolerance. It distributes well into all body fluids, but exhibits poor entry into the CSF. *Clindamycin* undergoes extensive oxidative metabolism to active and inactive products and is excreted into bile and urine. Low urinary excretion of active drug limits its clinical utility for urinary tract infections (Figure 30.15). Accumulation has been reported in patients with either severe renal impairment or hepatic failure. In addition to skin rash, the most common adverse effect is diarrhea, which may represent a serious pseudomembranous colitis caused by overgrowth of *C. difficile*. Oral administration of either *metronidazole* or *vancomycin* is usually effective in the treatment of *C. difficile* infection. Topical *clindamycin* has been used for the treatment to control acne caused by *Propionibacterium* acne.

## IX. QUINUPRISTIN/DALFOPRISTIN

*Quinupristin/dalfopristin* [KWIN-yoo-pris-tin/DAL-foh-pris-tin] is a mixture of two streptogramins in a ratio of 30 to 70, respectively. Due to significant adverse effects, this combination drug is normally reserved for the treatment of severe infections caused by *vancomycin*-resistant *Enterococcus faecium* (VRE) in the absence of other therapeutic options.

### A. Mechanism of action

Each component of this combination drug binds to a separate site on the 50S bacterial ribosome. *Dalfopristin* disrupts elongation by interfering with the addition of new amino acids to the peptide chain. *Quinupristin* prevents elongation similar to the macrolides and causes release of incomplete peptide chains. Thus, they synergistically interrupt protein synthesis. The combination drug has bactericidal activity against most susceptible organisms and has a long PAE.

## B. Antibacterial spectrum

*Quinupristin/dalfopristin* is active primarily against gram-positive cocci, including those resistant to other antibiotics. Its primary use is for the treatment of *E. faecium* infections, including VRE strains, against which it is bacteriostatic. The drug is not effective against *E. faecalis*.

## C. Resistance

Enzymatic processes commonly account for resistance to these agents. For example, the presence of a ribosomal enzyme that methylates the target bacterial 23S ribosomal RNA site can interfere in *quinupristin* binding. In some cases, the enzymatic modification can change the action from bactericidal to bacteriostatic. Plasmid-associated acetyltransferase inactivates *dalfopristin*. An active efflux pump can also decrease levels of the antibiotics in bacteria.

## D. Pharmacokinetics

*Quinupristin/dalfopristin* is available intravenously. It does not achieve therapeutic concentrations in CSF. Both compounds undergo hepatic metabolism, with excretion mainly in the feces.

## E. Adverse effects

Venous irritation commonly occurs when *quinupristin/dalfopristin* is administered through a peripheral rather than a central line. Hyperbilirubinemia occurs in about 25% of patients, resulting from a competition with the antibiotic for excretion. Arthralgia and myalgia have been reported when higher doses are administered. *Quinupristin/dalfopristin* inhibits the cytochrome P450 CYP3A4 isoenzyme, and concomitant administration with drugs that are metabolized by this pathway may lead to toxicities.

# X. OXAZOLIDINONES

*Linezolid* [lih-NEH-zo-lid] and *tedizolid* [ted-eye-ZOE-lid] are synthetic oxazolidinones developed to combat gram-positive organisms, including resistant isolates such as *methicillin*-resistant *Staphylococcus aureus*, VRE, and *penicillin*-resistant streptococci.

## A. Mechanism of action

*Linezolid* and *tedizolid* bind to the bacterial 23S ribosomal RNA of the 50S subunit, thereby inhibiting the formation of the 70S initiation complex (Figure 30.2) and translation of bacterial proteins.

## B. Antibacterial spectrum

The antibacterial action of the oxazolidinones is directed primarily against gram-positive organisms such as staphylococci, streptococci, and enterococci, *Corynebacterium* species and *Listeria monocytogenes*. It is also moderately active against *Mycobacterium tuberculosis* (Figure 30.16). The main clinical use of *linezolid* and *tedizolid*

Gram (+) cocci
<i>Enterococcus faecalis</i> (including <i>vancomycin</i> -resistant strains)
<i>Enterococcus faecium</i> (including <i>vancomycin</i> -resistant strains)
<i>Staphylococcus epidermidis</i> (including <i>methicillin</i> -resistant strains)
<i>Staphylococcus aureus</i> (including <i>methicillin</i> -resistant strains)
<i>Staphylococcus haemolyticus</i>
<i>Streptococcus pneumoniae</i> (including <i>penicillin</i> -resistant strains)
Viridans group streptococci
Gram (+) bacilli
<i>Corynebacterium</i> species
<i>Listeria monocytogenes</i>
Gram (-) cocci
Gram (-) rods
Anaerobic organisms
<i>Clostridium perfringens</i>
Spirochetes
Mycoplasma
Chlamydia
Other
<i>Mycobacterium tuberculosis</i>

**Figure 30.16**

Antimicrobial spectrum of oxazolidinones.

is to treat infections caused by drug-resistant gram-positive organisms. Like other agents that interfere with bacterial protein synthesis, *linezolid* and *tedizolid* are bacteriostatic; however, *linezolid* has bactericidal activity against streptococci. *Linezolid* is an alternative to *daptomycin* for infections caused by VRE. Because they are bacteriostatic, the oxazolidinones are not recommended as first-line treatment for MRSA bacteremia.

### C. Resistance

Resistance primarily occurs via reduced binding at the target site. Reduced susceptibility and resistance have been reported in *S. aureus* and *Enterococcus* sp. Cross-resistance with other protein synthesis inhibitors does not occur.

### D. Pharmacokinetics

*Linezolid* and *tedizolid* are well absorbed after oral administration. IV formulations are also available. These drugs distribute widely throughout the body. Although the metabolic pathway of *linezolid* has not been fully determined, it is known that it is metabolized via oxidation to two inactive metabolites. The drug is excreted by both renal and nonrenal routes. *Tedizolid* is metabolized by sulfation, and the majority of elimination occurs via the liver, and drug is mainly excreted in the feces. No dose adjustments are required for either agent for renal or hepatic dysfunction.

### E. Adverse effects

The most common adverse effects are gastrointestinal upset, nausea, diarrhea, headache, and rash. Thrombocytopenia has been reported, usually in patients taking the drug for longer than 10 days. *Linezolid* and *tedizolid* possess nonselective monoamine oxidase activity and may lead to serotonin syndrome if given concomitantly with large quantities of tyramine-containing foods, selective serotonin reuptake inhibitors, or monoamine oxidase inhibitors. The condition is reversible when the drug is discontinued. Irreversible peripheral neuropathies and optic neuritis causing blindness have been associated with greater than 28 days of use, limiting utility for extended-duration treatments.

## Study Questions

### Choose the ONE best answer.

- 30.1 Which of the following adverse effects is often employed as a therapeutic use for erythromycin?
- QTc prolongation
  - Increased gastrointestinal motility
  - Photosensitivity
  - Deposition in bone

Correct answer = B. Macrolides, but especially erythromycin, cause GI distress and increase motility of the GI tract, which is often used to treat gastroparesis and/or postoperative ileus. QTc prolongation is an adverse effect of erythromycin but not one employed therapeutically. Photosensitivity and deposition in bone are adverse effects of tetracyclines.

30.2 Which of the following describes the mechanism of action of tetracycline antibiotics?

- A. Bind the 30S subunit of the bacterial ribosome, preventing binding of tRNA to the mRNA–ribosome complex.
- B. Bind the 30S ribosomal subunit, interfering with assembly of the functional ribosomal apparatus.
- C. Bind irreversibly to a site on the 50S subunit of the bacterial ribosome, inhibiting translocation steps of protein synthesis.
- D. Bind the bacterial 23S ribosomal RNA of the 50S subunit, inhibiting the formation of the 70S initiation complex.

30.3 Linezolid would be a good choice for antibiotic treatment in which of the following patient scenarios?

- A. Bacteremia caused by Staphylococcus aureus
- B. Urinary tract infection caused by Escherichia coli
- C. Pneumonia caused by drug-resistant Streptococcus pneumoniae
- D. Diabetic foot infection caused by Pseudomonas aeruginosa

30.4 After 5 days of clindamycin treatment for a skin infection, a patient develops diarrhea (10 watery stools/day), severe abdominal pain, and fever. Which of the following organisms would you be concerned about as the causative pathogen of diarrhea?

- A. Escherichia coli
- B. Bacteroides fragilis
- C. Staphylococcus aureus
- D. Clostridium difficile

30.5 Which of the following statements accurately describes the difference in spectrum of activity between erythromycin and azithromycin?

- A. Azithromycin has better activity against respiratory pathogens such as Haemophilus influenzae and Moraxella catarrhalis but less potent activity against staphylococci and streptococci.
- B. Erythromycin has the same activity as azithromycin against gram-positives and gram-negatives.
- C. Azithromycin has better activity against staphylococci and streptococci compared to erythromycin.
- D. Erythromycin has better activity against gram-negatives such as H. influenza.

Correct answer = A. Tetracyclines enter susceptible organisms via passive diffusion and also by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane. The drugs bind reversibly to the 30S subunit of the bacterial ribosome. This action prevents binding of tRNA to the mRNA–ribosome complex, thereby inhibiting bacterial protein synthesis. B is the mechanism for aminoglycosides, C is the mechanism for macrolides, and D is the mechanism for oxazolidinones.

Correct answer = C. Linezolid does have coverage against resistant S. pneumoniae. It is not an optimal choice for treatment of bacteremia. Linezolid also does not have gram-negative coverage against E. coli and P. aeruginosa.

Correct answer = D. Clindamycin use has been associated with Clostridium difficile–associated diarrhea. This infection should be considered in a patient who presents with diarrhea while on clindamycin.

Correct answer = A. Erythromycin has better activity against gram-positive organisms, so B and C are incorrect. D is incorrect as azithromycin has better activity against H. influenza.

30.6 Which of the following antibiotic agents should not be given to children less than 8 years of age due to its deposition in bone and teeth?

- A. Azithromycin
- B. Doxycycline
- C. Linezolid
- D. Quinupristin/dalfopristin

30.7 A 77-year-old woman was started on antibiotics for pneumonia treatment. After 3 days of antibiotic therapy, the serum creatinine doubled. Which of the following antibiotics is most likely responsible for this increase in serum creatinine?

- A. Doxycycline
- B. Clarithromycin
- C. Tobramycin
- D. Linezolid

30.8 A 24-year-old pregnant woman was diagnosed with community-acquired pneumonia and will be managed in the outpatient setting. Which antibiotic is a safe option for this patient to treat her pneumonia?

- A. Azithromycin
- B. Doxycycline
- C. Fidaxomicin
- D. Gentamicin

30.9 Parents of a 1-month-old baby are told their child has developed "gray baby syndrome." Which of the following antibiotics did the baby likely receive?

- A. Tobramycin
- B. Linezolid
- C. Erythromycin
- D. Chloramphenicol

30.10 Aminoglycosides are commonly used for their concentration-dependent bactericidal activity against which group of organisms?

- A. Gram-positive aerobes
- B. Gram-negative aerobes
- C. Gram-positive anaerobes
- D. Gram-negative anaerobes

Correct answer = B. Tetracyclines are contraindicated in this age group because they are deposited in tissues undergoing calcification, such as teeth and bone, and can stunt growth.

Correct answer = C. Aminoglycosides such as tobramycin accumulate in the proximal tubular cells of the kidney and disrupt calcium-mediated transport processes. This results in kidney damage ranging from mild, reversible renal impairment to severe, potentially irreversible acute tubular necrosis. Nephrotoxicity is not commonly associated with tetracyclines, macrolides or oxazolidinones.

Correct answer = A. Azithromycin is available orally and considered safe in pregnancy. Doxycycline should not be used in pregnancy due to its ability to cross the placenta and affect bone and skeletal development in the fetus. Fidaxomicin does not reach therapeutic concentrations in serum or at this site of infection. It concentrates in the gut. Gentamicin crosses the placental barrier and may accumulate in fetal plasma and amniotic fluid. It would also not be used clinically in this outpatient scenario.

Correct answer = D. Gray baby syndrome is an adverse effect caused by chloramphenicol in neonates due to their underdeveloped renal function and low capacity to glucuronidate the antibiotic. The other agents do not undergo this glucuronidation.

Correct answer = B. Although aminoglycosides (such as gentamicin) are sometimes used synergistically against gram-positive aerobes, this is not their most common use. They are typically used for their activity against gram-negative aerobes. Aminoglycosides do not have good anaerobic activity.

# Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

31

Kenneth P. Klinker and Joseph Pardo

## I. FLUOROQUINOLONES

Discovery of quinolone antimicrobials led to the development of numerous compounds utilized in clinical practice. Following synthesis of *nalidixic acid* in the early 1960s, continued modification of the quinolone nucleus expanded the spectrum of activity, improved pharmacokinetics, and stabilized compounds against common mechanisms of resistance. Due to these enhancements, quinolone antimicrobials were rapidly integrated into human and agricultural medicine. Unfortunately, overuse resulted in rising rates of resistance in gram-negative and -positive organisms, increased frequency of *Clostridium difficile* infections, and identification of numerous untoward adverse effects. Consequently, these agents have been relegated to second-line options for various indications. This chapter reviews key characteristics of fluoroquinolones and their role in therapy. The fluoroquinolones and other antibiotics discussed in this chapter are listed in Figure 31.1.

### A. Mechanism of action

Most bacterial species maintain two distinct type II topoisomerases that assist with DNA replication, DNA gyrase and topoisomerase IV. DNA gyrase is responsible for reducing torsional stress ahead of replicating forks by breaking double-strand DNA and introducing negative supercoils. Topoisomerase IV assists in separating daughter chromosomes once replication is completed. Following cell wall entry through porin channels, fluoroquinolones bind to these enzymes and interfere with DNA ligation. This interference increases the number of permanent chromosomal breaks, triggering cell lysis. In general, fluoroquinolones have different targets for gram-negative (DNA gyrase) and gram-positive organisms (topoisomerase IV), resulting in rapid cell death.

### B. Antimicrobial spectrum

Fluoroquinolones are bactericidal and exhibit area-under-the-curve/minimum inhibitory concentration (AUC/MIC)-dependent killing. A major facet of their development centered on improving microbiologic

#### FLUOROQUINOLONES

First generation (active against gram-negative organisms but not *Pseudomonas* species)

*Nalidixic acid*

Second generation (gram-negative organisms [including *Pseudomonas* species] plus some gram-positive organisms [*Staphylococcus aureus* but not *Streptococcus pneumoniae*] and some atypical pathogens)

*Ciprofloxacin*

*Norfloxacin*

*Oflloxacin*

*Levofloxacin*

Third generation (as above plus expanded gram-positive coverage [penicillin-sensitive and penicillin-resistant *S. pneumoniae*] and expanded activity against atypical pathogens)

*Gatifloxacin*

Fourth generation (same as for third-generation agents plus broad anaerobic coverage)

*Moxifloxacin*

*Gemifloxacin*

**Figure 31.1**

Summary of drugs described in this chapter. (Figure continues on next page)

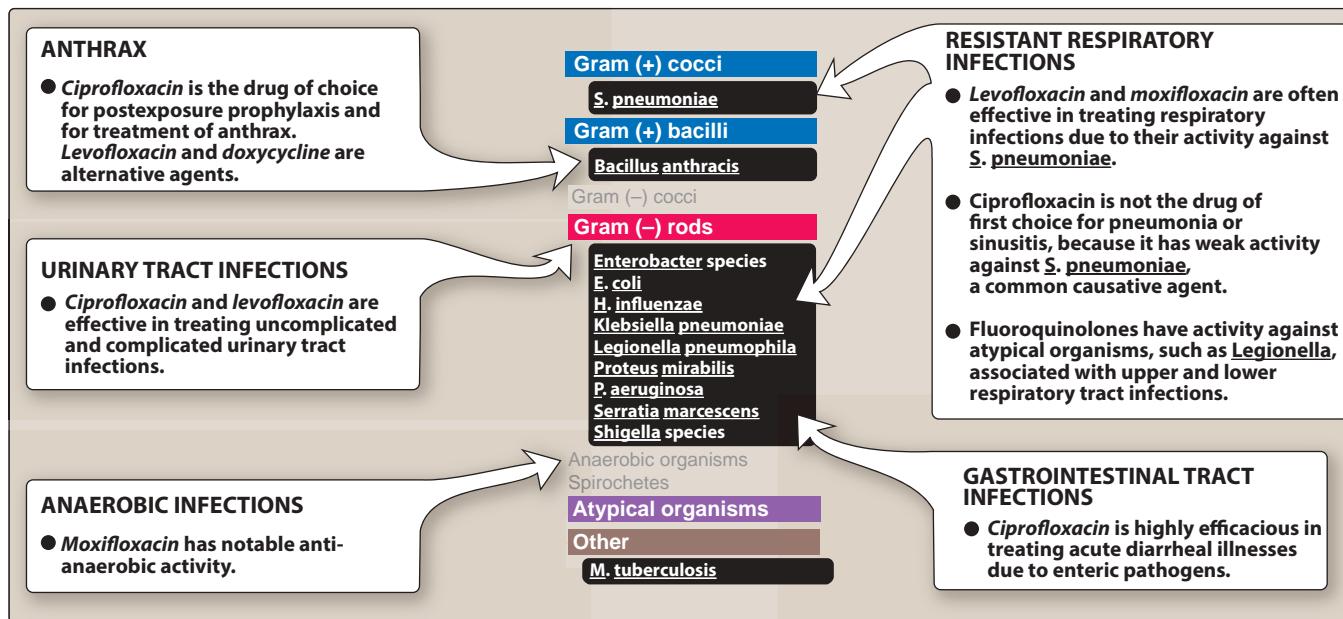
INHIBITORS OF FOLATE SYNTHESIS
Mafenide
Silver sulfadiazine
Sulfadiazine
Sulfasalazine
INHIBITORS OF FOLATE REDUCTION
Pyrimethamine
Trimethoprim
COMBINATION OF INHIBITORS OF FOLATE SYNTHESIS AND REDUCTION
Cotrimoxazole (trimethoprim + sulfamethoxazole)
URINARY TRACT ANTISEPTICS
Methenamine
Nitrofurantoin

**Figure 31.1** (Continued)

Summary of drugs described in this chapter. (For drug dosages, refer to Appendix at the end of the book.)

coverage. Modifications to the quinolone nucleus steadily improved topoisomerase inhibitory activity and facilitated bacterial cell wall penetration. These changes enhanced activity against a variety of pathogens including aerobic gram-negative and gram-positive organisms, atypical organisms (for example, *Chlamydia*, *Legionella*, and *Mycoplasma* spp), and anaerobes. Based on the impact of these structural changes, fluoroquinolones are often classified according to spectrum of activity.

First-generation compounds (for example, *nalidixic acid*) were narrow-spectrum agents with activity against aerobic gram-negative bacilli, mostly Enterobacteriaceae. Second-generation compounds (for example, *ciprofloxacin*) exhibit improved intracellular penetration and broadened coverage which includes Enterobacteriaceae, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Neisseria* spp, *Chlamydia* spp, and *Legionella* spp. Third-generation compounds (for example, *levofloxacin*) maintain the bacterial spectrum of second-generation agents, with improved activity against *Streptococcus* spp, including *S. pneumoniae*, methicillin-susceptible *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, and *Mycobacterium* spp. Fourth-generation compounds (*moxifloxacin*, *gemifloxacin*, and *delafloxacin*) have enhanced gram-positive activity, including *Staphylococcus* and *Streptococcus* spp. *Delafloxacin* has activity against methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis*. Further, *delafloxacin* and *moxifloxacin* have activity against *Bacteroides fragilis* and *Prevotella* spp, while maintaining activity against Enterobacteriaceae and *Haemophilus influenzae*. From this group, only *delafloxacin* has activity against *P. aeruginosa*. Lastly, these agents maintain atypical coverage, with *moxifloxacin* and *delafloxacin* showing activity against *Mycobacteria* spp. Common therapeutic applications of fluoroquinolones are shown in **Figure 31.2**.

**Figure 31.2**

Typical therapeutic applications of fluoroquinolones.

### C. Resistance

Numerous mechanisms of fluoroquinolone resistance exist in clinical pathogens. High-level fluoroquinolone resistance is primarily driven by chromosomal mutations within topoisomerases, although, decreased entry, efflux systems, and modifying enzymes play a role. Mechanisms responsible for resistance include the following:

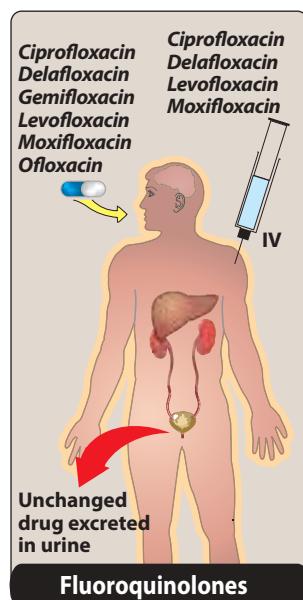
- Altered target binding:** Mutations in bacterial genes encoding DNA gyrase or topoisomerase IV (for example, *gyrA* or *parC*) alter target site structure and reduce binding efficiency of fluoroquinolones.
- Decreased accumulation:** Reduced intracellular concentration is linked to 1) a reduction in membrane permeability or 2) efflux pumps. Alterations in membrane permeability are mediated through a reduction in outer membrane porin proteins, thus, limiting drug access to topoisomerases. Efflux pumps actively remove fluoroquinolones from the cell.
- Fluoroquinolone degradation:** An aminoglycoside acetyltransferase variant can acetylate fluoroquinolones, rendering them inactive.

### D. Pharmacokinetics

- Absorption:** Fluoroquinolones are well absorbed after oral administration, with *levofloxacin* and *moxifloxacin* having a bioavailability that exceeds 90% (Figure 31.3). Ingestion of fluoroquinolones with *sucralfate*, aluminum- or magnesium-containing antacids, or dietary supplements containing iron or zinc can reduce the absorption. Calcium and other divalent cations also interfere with the absorption of these agents (Figure 31.4).
- Distribution:** Binding to plasma proteins ranges from 20 to 84%. Fluoroquinolones distribute well into all tissues and body fluids. Concentrations are high in bone, urine (except *moxifloxacin*), kidney, prostatic tissue (but not prostatic fluid), and lungs as compared to serum. Penetration into cerebrospinal fluid is good, and these agents may be considered in certain central nervous system (CNS) infections. Accumulation in macrophages and polymorphonuclear leukocytes results in activity against intracellular organisms such as *Listeria*, *Chlamydia*, and *Mycobacterium*.
- Elimination:** Most fluoroquinolones are excreted renally. Therefore, dosage adjustments are needed in renal dysfunction. *Moxifloxacin* is metabolized primarily by the liver, and while there is some renal excretion, no dose adjustment is required for renal impairment (Figure 31.3).

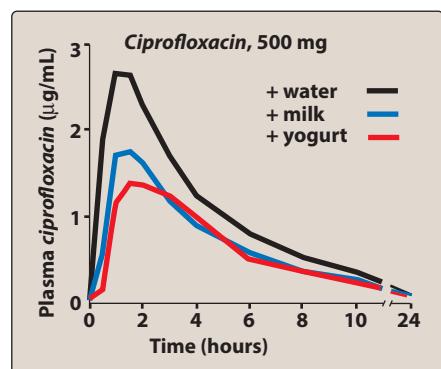
### E. Adverse reactions

In general, fluoroquinolones are well tolerated (Figure 31.5). Common adverse effects leading to discontinuation are nausea, vomiting, headache, and dizziness. These agents carry boxed warnings for tendinitis, tendon rupture, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, insomnia, confusion, and seizures). Patients taking fluoroquinolones are at risk for phototoxicity resulting in exaggerated sunburn reactions. Patients should use sunscreen and avoid excessive exposure to UV light. Arthropathy is



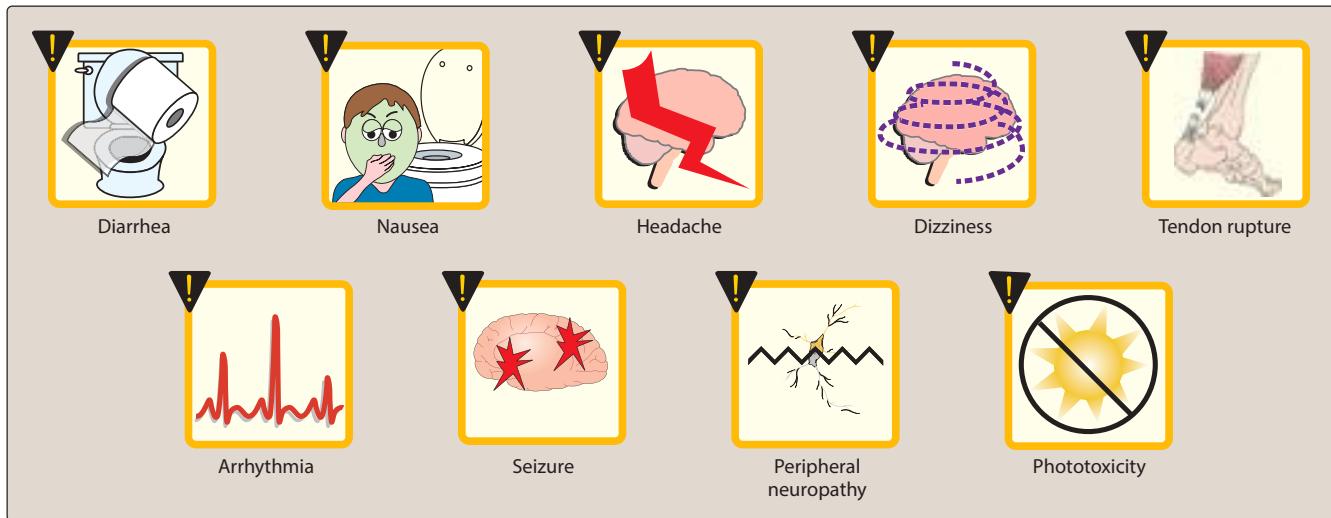
**Figure 31.3**

Administration and fate of the fluoroquinolones.

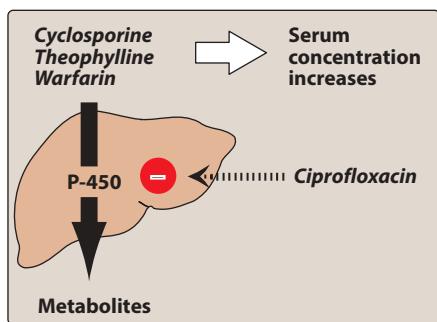


**Figure 31.4**

Effect of dietary calcium on the absorption of *ciprofloxacin*.

**Figure 31.5**

Some adverse reactions to fluoroquinolones.

**Figure 31.6**

Drug interactions with *ciprofloxacin*.

uncommon, but arthralgia and arthritis are reported with fluoroquinolone use in pediatric patients. Use in the pediatric population should be limited to distinct clinical scenarios (for example, cystic fibrosis exacerbation). Hepatotoxicity or blood glucose disturbances (usually in diabetic patients receiving oral hypoglycemic agents or insulin) have been observed. Identification of any of these events should result in prompt removal of the agent. Fluoroquinolones may prolong the QT<sub>c</sub> interval, and these agents should be avoided in patients predisposed to arrhythmias or taking medication associated with QT prolongation. *Ciprofloxacin* inhibits P450 1A2 and 3A4 mediated metabolism. Serum concentrations of medications such as *theophylline*, *tizanidine*, *warfarin*, *ropinirole*, *duloxetine*, *caffeine*, *sildenafil*, and *zolpidem* may be increased (Figure 31.6).

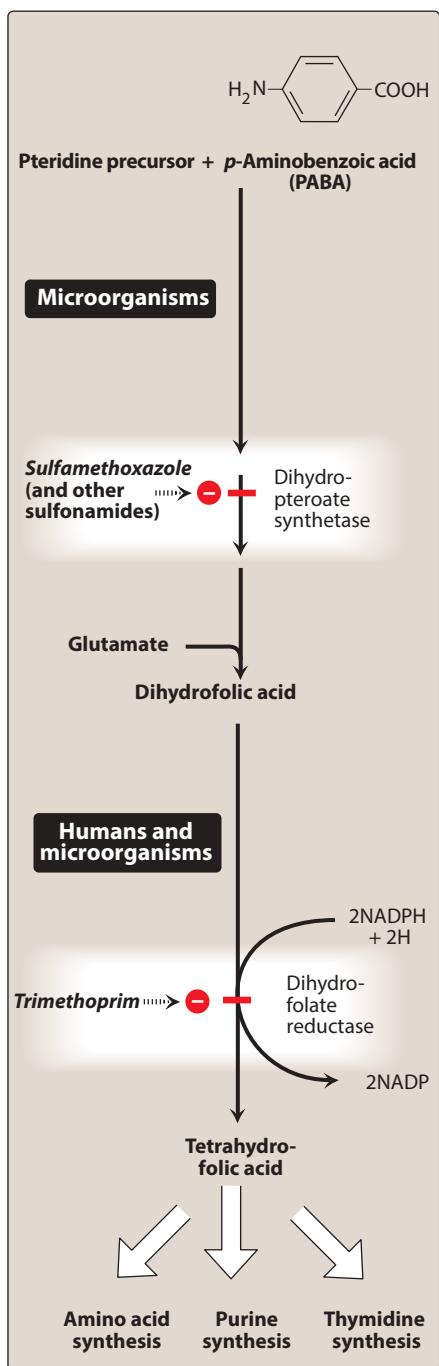
## F. Examples of clinically useful fluoroquinolones

Due to increasing resistance and boxed warnings, fluoroquinolones should be used with caution in select circumstances. They may be considered in patients who do not tolerate other agents (for example, severe  $\beta$ -lactam allergies) or as definitive therapy once susceptibilities are available. Potential indications for these agents are listed in the following text. All of them share a common mechanism of action and similar side effect profiles. Since fluoroquinolones have excellent bactericidal activity against many mycobacteria; achieve effective serum, tissue, and intracellular levels following oral administration; and produce few adverse effects, these properties have led to the increasing use of fluoroquinolones for the treatment of mycobacterial infections and are reserved for multidrug-resistant tuberculosis (MDR-TB). Therefore, routine use of fluoroquinolones (especially respiratory quinolones) should be discouraged in undiagnosed TB patients, as resistance may develop to the quinolones which may compromise the effectiveness of second-line treatment of MDR-TB.

- 1. Ciprofloxacin:** *Ciprofloxacin* [SIP-ro-e-FLOX-a-sin] has good activity against gram-negative bacilli, including *P. aeruginosa*. *Ciprofloxacin* is used in the treatment of traveler's diarrhea, typhoid

fever, and anthrax. It is a second-line agent for infections arising from intra-abdominal, lung, skin, or urine sources. Of note, high-dose therapy should be employed when treating *Pseudomonas* infections. *Ciprofloxacin* is used in the empirical therapy of any infection and prophylaxis for gram-negative rod bacteremia. It is recommended at a dose of 500 mg twice daily in normal cases and 750 mg twice daily in severe cases. It can also be administered as an intravenous infusion.

2. **Norfloxacin:** *Norfloxacin* is another derivative of fluoroquinolone but slightly inferior to *ciprofloxacin* in terms of MIC values of gram-negative bacteria. It is primarily used for urinary tract infections and bacterial diarrhea (due to low bioavailability) causing higher local concentrations in the gut. It is excreted in urine as unchanged after metabolism. A dose of 200 to 800 mg twice daily for adults is recommended. It is available in the form of 200, 400, and 800 mg tablets as well as 100 mg/5ml suspension. Side effect profiles are common to all fluoroquinolones.
3. **Pefloxacin:** *Pefloxacin* is another fluoroquinolone derivative which is having higher lipid solubility. After oral administration, it is absorbed completely and attains higher plasma concentrations. Due to its lipophilicity, its CNS penetration is greater than other fluoroquinolones; therefore it is preferred for meningeal infections. It is metabolized into *norfloxacin* which is also active against the microbes. It is available as 200 and 400 mg tablets and administered twice daily. Intravenous injection needs to be diluted with glucose solution as it is known to precipitate with normal saline. The side effects are same as other fluoroquinolones.
4. **Levofloxacin:** *Levofloxacin* [leev-oh-FLOX-a-sin] has similar activity to *ciprofloxacin* and they are often interchanged when managing gram-negative bacilli, including *P. aeruginosa*. *Levofloxacin* has enhanced activity against *S. pneumoniae* and is first-line therapy for community-acquired pneumonia (CAP). It is a second-line agent for the treatment of *S. maltophilia*. *Ofloxacin* is a racemic mixture from which *levofloxacin* (optical isomer) is separated due to its superior activity as compared to dextroisomer. It is used for urinary tract infections, sinusitis, pyelonephritis, prostatitis, and other skin and soft-tissue infections. It is available as 250, 500, and 750 mg tablets as well as 0.3% eye and ear drops. The dosing of *levofloxacin* ranges from 250 to 750 mg twice daily depending upon the condition.
5. **Moxifloxacin:** *Moxifloxacin* [mox-ee-FLOX-a-sin] has enhanced activity against gram-positive organisms (for example, *S. pneumoniae*), gram-negative anaerobes, and *Mycobacterium* spp. The drug may be used for CAP, but not hospital-acquired pneumonia due to poor coverage of *P. aeruginosa*. It may be considered for mild-to-moderate intra-abdominal infections, but should be avoided if patients have fluoroquinolone exposure within previous 3 months, due to increasing *B. fragilis* resistance. *Moxifloxacin* may be considered a second-line agent for management of drug-susceptible tuberculosis. It has also been approved for topical eye drop for ocular infections as 0.5% eye drops. It is used at a dose of 400 mg once daily. It is also available as an intravenous infusion.

**Figure 31.7**

Inhibition of tetrahydrofolate synthesis by sulfonamides and *trimethoprim*.

**6. Gemifloxacin:** *Gemifloxacin* [gem-ee-FLOX-a-sin] is indicated for the management of community-acquired respiratory infections. Unlike the other compounds, it is only available as an oral formulation. It is used at a dose of 320 mg once daily.

**7. Prulifloxacin:** *Prulifloxacin* is a relatively newer generation lipophilic prodrug of *ulifloxacin*. *Ulifloxacin* has been found to have a broad spectrum of in vitro activity against gram-positive and gram-negative bacteria. It has been considered the most potent fluoroquinolone against *E. coli* and *P. aeruginosa*. It is reported to have good tissue penetration and fluids. It is extracted as unchanged in urine. It has shown good efficacy against bronchitis, UTI, etc. It is found to have no effect on the prolongation of Q-T interval unlike other fluoroquinolones. It has been reported to have an acceptable toxicity profile, as compared to other fluoroquinolones. Trials showed nausea, vomiting, diarrhea, and skin rash of mild-to-moderate severity as the most frequent adverse events. It has a longer half-life, which allows it to be administered as once daily at a dose of 600 mg.

**8. Delafloxacin:** *Delafloxacin* [del-a-FLOX-a-sin] has improved activity against gram-positive cocci, including MRSA and *Enterococcus* spp. Due to its spectrum of activity, it is an option for managing acute bacterial skin and skin structure infections. It is available as an intravenous and oral formulation.

## II. FOLATE ANTAGONISTS

Folic acid is a coenzyme essential in the synthesis of RNA, DNA, and certain amino acids. In the absence of folate, cells cannot grow or divide. Humans use dietary folate to synthesize the critical folate derivative, tetrahydrofolic acid. By contrast, many bacteria are impermeable to folate derivatives and rely on their ability to synthesize folate de novo (Figure 31.7). Sulfonamides (sulfa drugs) are a family of antibiotics that inhibit de novo synthesis of folate. A second type of folate antagonist, *trimethoprim*, prevents microorganisms from converting dihydrofolate acid to tetrahydrofolic acid. Thus, both sulfonamides and *trimethoprim* interfere with the ability of an infecting bacterium to perform DNA synthesis and other essential cellular functions. The combination of the sulfonamide *sulfamethoxazole* with *trimethoprim* (the generic name for the combination is *cotrimoxazole*) provides a synergistic effect.

## III. SULFONAMIDES

Sulfa drugs were among the first antibiotics used in clinical practice. Today, they are seldom prescribed alone except in developing countries, where they are employed because of low cost and efficacy.

### A. Mechanism of action

Microorganisms use the enzyme dihydropteroate synthetase to create dihydrofolate acid from the precursor molecule *p*-aminobenzoic acid (PABA). Sulfonamides are synthetic analogs of PABA. Because of their structural similarity, sulfonamides compete with PABA to inhibit dihydropteroate synthetase and the genesis of bacterial dihydrofolate acid (Figure 31.7). These agents are bacteriostatic.

## B. Antibacterial spectrum

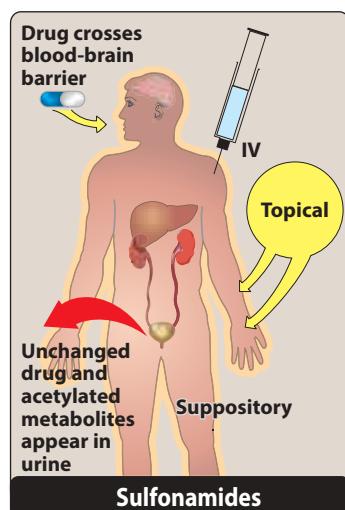
Sulfa drugs have in vitro activity against gram-negative and gram-positive organisms. Common organisms include Enterobacteriaceae, *Haemophilus influenzae*, *Streptococcus* spp, *Staphylococcus* spp, and *Nocardia*. Additionally, *sulfadiazine* [sul-fa-DYE-a-zeen] in combination with the dihydrofolate reductase inhibitor *pyrimethamine* [py-ri-METH-a-meen] is the preferred treatment for toxoplasmosis.

## C. Resistance

Bacteria that obtain folate from their environment are naturally resistant to sulfa drugs. Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations. Resistance may be due to 1) altered dihydropteroate synthetase, 2) decreased cellular permeability to sulfa drugs, or 3) enhanced production of the natural substrate, PABA. [Note: Organisms resistant to one member of this drug family are resistant to all.]

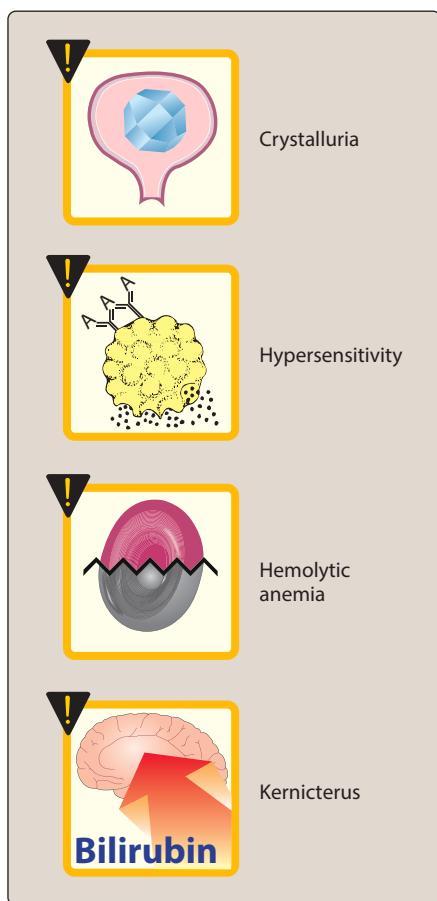
## D. Pharmacokinetics

- Absorption:** Most sulfa drugs are well absorbed following oral administration (Figure 31.8). An exception is *sulfasalazine* [sul-fa-SAL-a-zeen]. It is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of chronic inflammatory bowel diseases. [Note: Intestinal flora split *sulfasalazine* into sulfapyridine and 5-aminosalicylate, with the latter exerting the anti-inflammatory effect. Absorption of sulfapyridine can lead to toxicity in patients who are slow acetylators.] Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations or have severe infections. Because of the risk of sensitization, sulfa drugs are not usually applied topically. However, in burn units, *silver sulfadiazine* [sul-fa-DYE-ah-zeen] or *mafenide* [mah-FEN-ide] acetate ( $\alpha$ -amino-p-toluenesulfonamide) creams have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria. [Note: *Silver sulfadiazine* is preferred because *mafenide* produces pain on application and its absorption may contribute to acid-base disturbances.] *Silver sulfadiazine* is used at a concentration of 1% as topical cream for burns.
- Distribution:** Sulfa drugs are bound to serum albumin in circulation and widely distribute throughout body tissues. Sulfa drugs penetrate well into cerebrospinal fluid (even in the absence of inflammation) and cross the placental barrier to enter fetal tissues.
- Metabolism:** Sulfa drugs are acetylated and conjugated primarily in the liver. The acetylated product is devoid of antimicrobial activity but retains the toxic potential to precipitate at neutral or acidic pH. This causes crystalluria ("stone formation"; see below) and potential damage to the kidney.
- Excretion:** Unchanged sulfa drug and metabolites are eliminated via glomerular filtration and secretion requiring dose adjustments with renal impairment. Sulfonamides may be eliminated in breast milk.



**Figure 31.8**

Administration and fate of the sulfonamides.



**Figure 31.9**

Some adverse reactions to sulfonamides.

## E. Adverse effects

1. **Crystalluria:** Nephrotoxicity may develop as a result of crystalluria (Figure 31.9). Adequate hydration and alkalinization of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.
2. **Hypersensitivity:** Hypersensitivity reactions, such as rashes, angioedema, or Stevens-Johnson syndrome, may occur. When patients report previous sulfa allergies, it is paramount to acquire a description of the reaction to direct appropriate therapy.
3. **Hematopoietic disturbances:** Hemolytic anemia is encountered in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Granulocytopenia and thrombocytopenia can also occur. Fatal reactions have been reported from associated agranulocytosis, aplastic anemia, and other blood dyscrasias.
4. **Kernicterus:** Bilirubin-associated brain damage (kernicterus) may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the blood-brain barrier is not fully developed.
5. **Drug potentiation:** *Sulfamethoxazole* potentiates the anticoagulant effect of *warfarin* due to inhibition of CYP2C9, resulting in reduced clearance of *warfarin*. Sulfonamides may also displace *warfarin* from binding sites on serum albumin. Serum *methotrexate* levels may rise through protein-binding displacement. Other CYP2C9 substrates, such as *phenytoin*, may have increased concentrations when given with sulfonamides.
6. **Contraindications:** Due to the danger of kernicterus, sulfa drugs should be avoided in newborns and infants less than 2 months of age, as well as in pregnant women at term. Sulfonamides should not be given to patients receiving *methenamine*, since they can crystallize in the presence of formaldehyde produced by this agent.

## IV. TRIMETHOPRIM

*Trimethoprim* [try-METH-oh-prim], a potent inhibitor of bacterial dihydrofolate reductase, was initially available in combination with the sulfonamide *sulfamethoxazole* [sul-fa-meth-OX-a-zole] and later approved for use as a single agent. Today, *trimethoprim* is most commonly used in combination with *sulfamethoxazole*.

### A. Mechanism of action

*Trimethoprim* is a potent inhibitor of bacterial dihydrofolate reductase (Figure 31.7). Inhibition of this enzyme prevents the formation of the metabolically active form of folic acid, tetrahydrofolic acid, and thus interferes with normal bacterial cell functions. Trimethoprim binds to bacterial dihydrofolate reductase more readily than it does to human dihydrofolate reductase, which accounts for the selective toxicity of the drug.

## B. Antibacterial spectrum

The antibacterial spectrum of *trimethoprim* is similar to that of *sulfamethoxazole*. However, *trimethoprim* is 20- to 50-fold more potent than the sulfonamides. *Trimethoprim* may be used alone in the treatment of urinary tract infections (UTIs) and in the treatment of bacterial prostatitis (although fluoroquinolones and *cotrimoxazole* are preferred).

## C. Resistance

Resistance in gram-negative bacteria is due to the presence of an altered dihydrofolate reductase that has a lower affinity for *trimethoprim*. Efflux pumps and decreased permeability to the drug may play a role.

## D. Pharmacokinetics

*Trimethoprim* is rapidly absorbed following oral administration. Because the drug is a weak base, higher concentrations of *trimethoprim* are achieved in the relatively acidic prostatic and vaginal fluids. The drug is widely distributed into body tissues and fluids, including penetration into the cerebrospinal fluid. *Trimethoprim* undergoes some O-demethylation, but 60% to 80% is renally excreted unchanged.

## E. Adverse effects

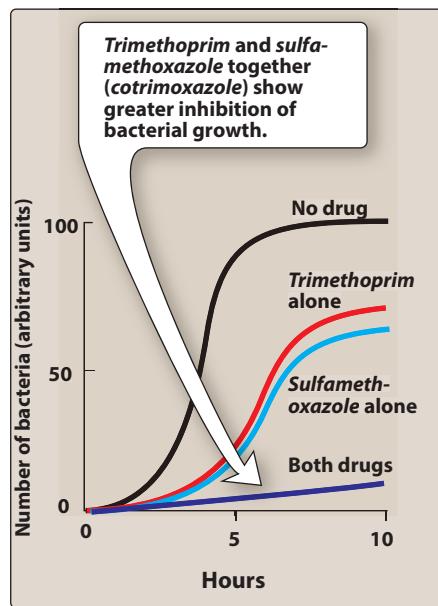
*Trimethoprim* can produce the effects of folic acid deficiency. These effects include megaloblastic anemia, leukopenia, and granulocytopenia, especially in pregnant patients and those with nutrient-poor diets. These blood disorders may be reversed by simultaneous administration of *folic acid* (also known as *leucovorin*), which does not enter bacteria. *Trimethoprim* has a potassium-sparing effect and may cause hyperkalemia, especially at higher doses and when administered with other medication that causes hyperkalemia (for example, angiotensin-converting enzyme inhibitors).

## V. COTRIMOXAZOLE

The combination of *trimethoprim* with *sulfamethoxazole*, called *cotrimoxazole* [co-try-MOX-a-zole], shows greater antimicrobial activity than equivalent quantities of either drug used alone (Figure 31.10). The combination was selected because of the synergistic activity and the similarity in the half-lives of the two drugs. *Trimethoprim* (80 mg) along with *sulfamethoxazole* (400 mg) are used in the ratio of 1:5 in *cotrimoxazole* tablets. Dosage is usually started with 2 tablets twice daily for the duration of therapy. *Trimethoprim* 20 mg with *sulfamethoxazole* 100 mg is used as pediatric dosage. It is also available for intramuscular injection.

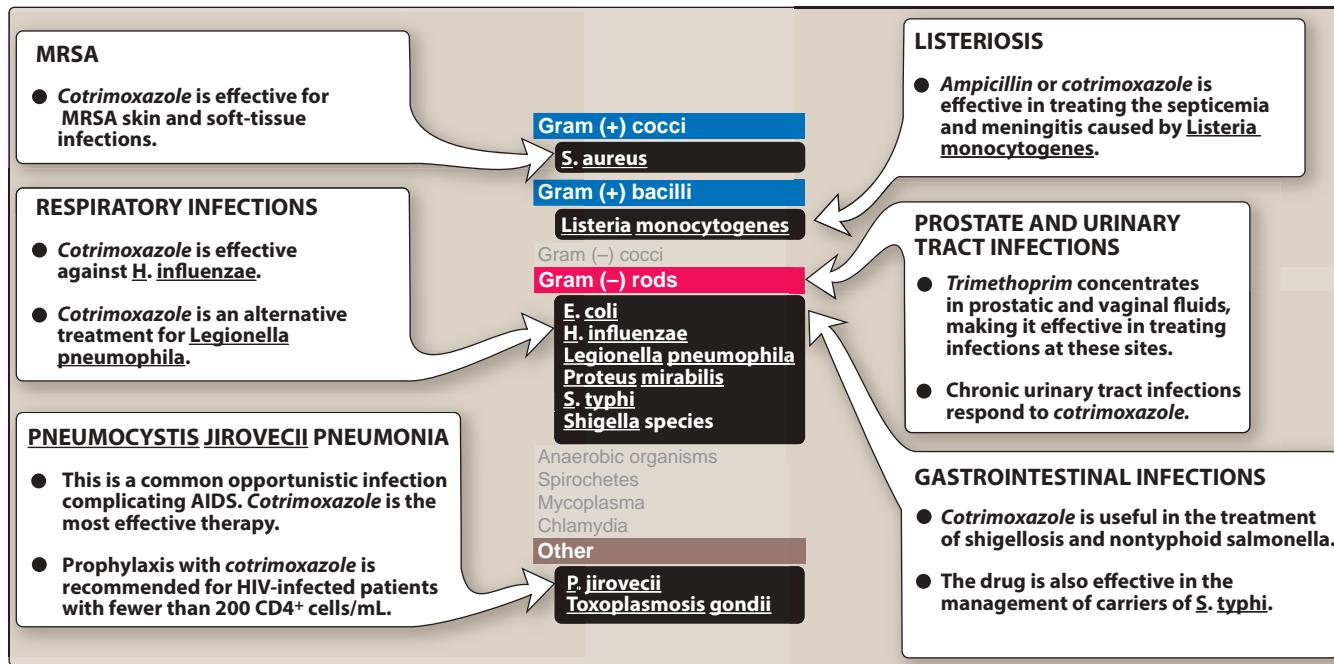
## A. Mechanism of action

The synergistic antimicrobial activity of *cotrimoxazole* results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic



**Figure 31.10**

Synergism between *trimethoprim* and *sulfamethoxazole* inhibits growth of *E. coli*.

**Figure 31.11**

Typical therapeutic applications of cotrimoxazole (sulfamethoxazole plus trimethoprim).

acid. *Sulfamethoxazole* inhibits the incorporation of PABA into dihydrofolic acid precursors, and *trimethoprim* prevents reduction of dihydrofolate to tetrahydrofolate (Figure 31.11).

### B. Antibacterial spectrum

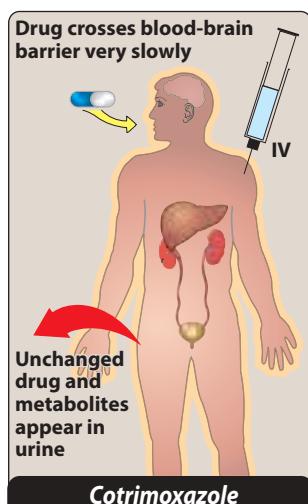
*Cotrimoxazole* has a broader spectrum of antibacterial action than the sulfa drugs alone (Figure 31.11). It is effective in treating UTIs and respiratory tract infections, as well as *Pneumocystis jirovecii*, toxoplasmosis, *Listeria monocytogenes*, and *Salmonella* infections. It has activity against *methicillin*-resistant *S. aureus* and can be particularly useful for skin and soft-tissue infections caused by this organism. It is the drug of choice for infections caused by susceptible *Nocardia* spp and *Stenotrophomonas maltophilia*.

### C. Resistance

Resistance to the *trimethoprim-sulfamethoxazole* combination is encountered less frequently than resistance to either of the drugs alone, because it requires bacterium to maintain simultaneous resistance to both drugs. Significant resistance has been documented in a number of clinically relevant organisms, including *E. coli*.

### D. Pharmacokinetics

*Cotrimoxazole* is generally administered orally (Figure 31.12). Intravenous administration may be utilized in patients with severe pneumonia caused by *Pneumocystis jirovecii*. Both agents distribute throughout the body. *Trimethoprim* concentrates in the relatively acidic

**Figure 31.12**

Administration and fate of cotrimoxazole.

milieu of prostatic fluids, and this accounts for the use of *trimethoprim-sulfamethoxazole* in the treatment of prostatitis. *Cotrimoxazole* readily crosses the blood-brain barrier. Both parent drugs and their metabolites are excreted in the urine.

### E. Adverse effects

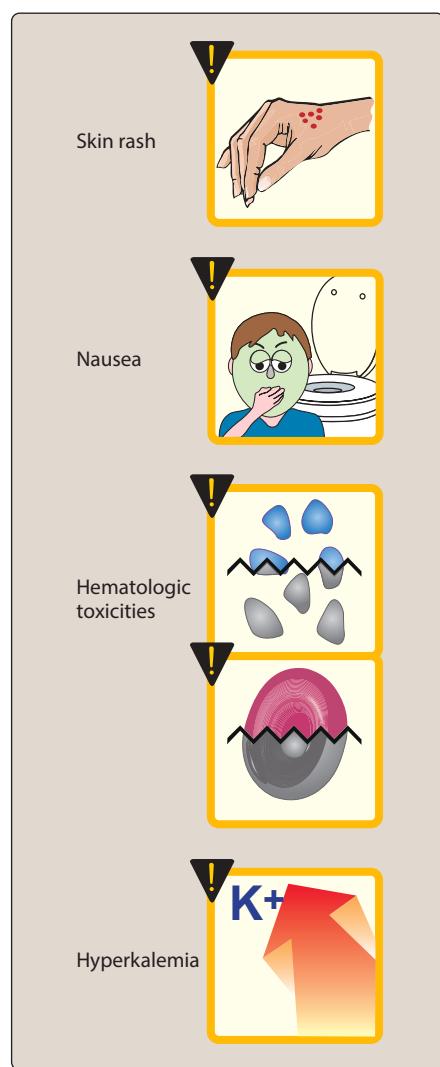
Adverse reactions and drug interactions related to *cotrimoxazole* are similar to those expected with each of the individual components, *sulfamethoxazole* and *trimethoprim*. (Figure 31.13). The most common adverse reactions are nausea and vomiting, skin rash, hematologic toxicity, and hyperkalemia.

## VI. URINARY TRACT ANTISEPTICS/ANTIMICROBIALS

Urinary tract infections are one of the most common bacterial infections in the world, primarily impacting women and the elderly. Historically, fluoroquinolones and *trimethoprim/sulfamethoxazole* have been first-line therapy for the treatment of UTIs. Unfortunately, resistance has increased among common pathogens (for example, *E. coli*). As a result, *methenamine*, *nitrofurantoin*, and *fosfomycin* (see Chapter 29) can be considered for treatment or suppression of recurrence, due to their efficacy against common pathogens and high concentrations in the urine.

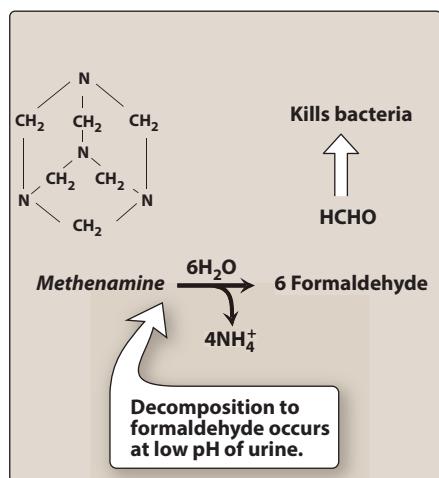
### A. Methenamine

- Mechanism of action:** *Methenamine* [meth-EN-a-meen] salts are hydrolyzed to ammonia and formaldehyde in acidic urine ( $\text{pH} \leq 5.5$ ). Formaldehyde denatures proteins and nucleic acids, resulting in bacterial cell death. *Methenamine* is combined with a weak acid (for example, hippuric acid) to maintain urine acidity and promote production of formaldehyde (Figure 31.14).
- Antibacterial spectrum:** *Methenamine* is primarily used for chronic suppressive therapy to reduce the frequency of urinary tract infections. *Methenamine* is active against *E. coli*, *Enterococcus* spp., and *Staphylococcus* spp. It has some activity against *Proteus* spp. and *Pseudomonas aeruginosa*, but urine pH must be kept acidic to achieve bactericidal activity. The main benefit of *methenamine* is the lack of selection for resistant organisms. It is not used for acute UTI; however, its use is restricted for chronic and resistant urinary infections.
- Pharmacokinetics:** *Methenamine* is orally absorbed, with up to 30% decomposing in gastric juices, unless protected by enteric coating. It reaches the urine through tubular secretion and glomerular filtration. Concentrations are sufficient to treat susceptible organisms. Due to ammonia formation, use should be avoided in hepatic insufficiency. It is used at a dose of 1 g three times a day or four times a day.
- Adverse effects:** The major adverse effect of *methenamine* is gastrointestinal distress, although at higher doses, albuminuria, hematuria, and rashes may develop. *Methenamine mandelate* is contraindicated in patients with renal insufficiency, because mandelic acid may precipitate. The *methenamine hippurate*



**Figure 31.13**

Some adverse reactions to *cotrimoxazole*.

**Figure 31.14**

Formation of formaldehyde from *methenamine* at acid pH.

formulation should be used instead. [Note: Sulfonamides, such as *cotrimoxazole*, react with formaldehyde and must not be used concomitantly with *methenamine*. The combination increases the risk of crystalluria and mutual antagonism.]

## B. Nitrofurantoin

*Nitrofurantoin* was introduced into clinical practice for the management of cystitis in the early 1950s. For decades it was rarely used, but was resurrected due to increasing antibiotic resistance amongst Enterobacteriaceae and is considered first-line therapy for uncomplicated cystitis. *Nitrofurantoin* works by inhibiting DNA and RNA synthesis. Susceptible organisms include *E. coli*, *Klebsiella* spp., *Enterococcus* spp., and *Staphylococcus* spp. Following oral administration, it is rapidly absorbed, with nearly 40% excreted unchanged in the urine. Overall, *nitrofurantoin* is well tolerated. Common adverse events include nausea, vomiting, and diarrhea. Use of the microcrystalline formulation decreases the incidence of gastrointestinal toxicity. Rare complications of therapy include pulmonary fibrosis, neuropathy, and autoimmune hepatitis. These events are observed with prolonged exposure greater than 1 month. Additionally, patients with impaired renal function should not receive *nitrofurantoin* due to an increased risk of adverse events. It is used at a dose of 50 to 100 mg three times a day for adults for 5 to 10 days.

## C. Urinary analgesic

1. **Phenazopyridine:** *Phenazopyridine* is a commonly used urinary analgesic with no antimicrobial activity. It is a dye which exerts action at the urinary tract and renders symptomatic relief for burning sensation, irritation, dysuria, and frequent urgency of urination caused by cystitis of diverse origin. The side effects of this drug include nausea, epigastric pain, orange discoloration of urine, methemoglobinemia, yellowish skin discoloration, hepatitis, and rarely acute renal failure. It is used at a dose of 200 to 400 mg three times a day.

## Study Questions

Choose the ONE best answer.

- 31.1 A 32-year-old man presents to an outpatient clinic with a 5-day history of productive cough, purulent sputum, and shortness of breath. He is diagnosed with community-acquired pneumonia (CAP). It is noted that this patient has a severe ampicillin allergy (anaphylaxis). Which would be an acceptable treatment for this patient?

- A. Levofloxacin
- B. Ciprofloxacin
- C. Penicillin VK
- D. Nitrofurantoin

Correct answer = A. *Streptococcus pneumoniae* is a common cause of CAP, and the respiratory fluoroquinolones levofloxacin and moxifloxacin provide good coverage. Ciprofloxacin does not cover *S. pneumoniae* well and is a poor choice for treatment of CAP. Penicillin would be a poor choice due to allergy. Nitrofurantoin has no clinical utility for respiratory tract infections.

31.2 A 22-year-old woman presents with a 2-day history of dysuria with increased urinary frequency and urgency. A urine culture and urinalysis are done. She is diagnosed with a urinary tract infection caused by *Escherichia coli*. Which agent should be avoided in the treatment of her UTI?

- A. Levofloxacin
- B. Cotrimoxazole
- C. Moxifloxacin
- D. Nitrofurantoin

Correct answer = C. Moxifloxacin does not concentrate in the urine and would be ineffective for treatment of a UTI. All other answers are viable alternatives, and the resistance profile for the *E. coli* can be utilized to direct therapy.

31.3 Which drug is correctly matched with the appropriate adverse effect?

- A. Levofloxacin—hyperkalemia
- B. Nitrofurantoin—pulmonary fibrosis
- C. Cotrimoxazole—hepatic encephalopathy
- D. Methenamine—nystagmus

Correct answer = B. Hyperkalemia may be caused by cotrimoxazole, not fluoroquinolones. Hepatic encephalopathy may be related to therapy with methenamine in patients with hepatic insufficiency. Nystagmus is not associated with methenamine therapy.

31.4 Cotrimoxazole provides activity against which organism?

- A. MRSA
- B. *Pseudomonas aeruginosa*
- C. Anaerobes
- D. *Mycoplasma*

Correct answer = A. Cotrimoxazole is effective against MRSA. It does not have activity against *Pseudomonas*, anaerobes, or *Mycoplasma*.

31.5 A 55-year-old man presents to primary care clinic with an erythematous and tender abscess on his left thigh. He has a history of MRSA skin infections. Which is an appropriate antibiotic for empiric treatment?

- A. Ciprofloxacin
- B. Cotrimoxazole
- C. Pyrimethamine
- D. Cephalexin

Correct answer = B. Cotrimoxazole is the only agent with reliable activity against MRSA. Ciprofloxacin does have some minor activity, but resistance has readily increased and it is no longer a valid recommendation. The other agents do not have activity against MRSA.

31.6 Which is a common adverse effect of cotrimoxazole?

- A. Hyperkalemia
- B. Pulmonary fibrosis
- C. Tendon rupture
- D. Blood glucose disturbances

Correct answer = A. Trimethoprim acts as a potassium-sparing agent, resulting in an increase in serum potassium concentrations. Pulmonary fibrosis is an adverse effect of nitrofurantoin. Tendon rupture and blood glucose disturbances are adverse effects of fluoroquinolones.

31.7 A 21-year-old marathon runner reports to the clinic with acute Achilles tendon rupture. The nurse noted that the patient recently took an antibiotic for community-acquired pneumonia. Which antibiotic may have contributed to tendon rupture?

- A. Amoxicillin/clavulanate
- B. Cefdinir
- C. Levofloxacin
- D. Minocycline

Correct answer = C. Levofloxacin is associated with tendon ruptures and tendinopathy. The other agents are not associated with this adverse effect.

31.8 A 70-year old woman with acute cystitis presents to the Family Medicine clinic for assessment. She has a past medical history of hypertension and chronic kidney disease. The team recommends initiation of nitrofurantoin for cystitis. After reviewing her antimicrobial therapy, which actions should be taken prior to clinic discharge?

- A. Continue current therapy and counsel on gastrointestinal effects of nitrofurantoin.
- B. Change nitrofurantoin to alternative agent due to chronic kidney disease.
- C. Reduce nitrofurantoin dose due to impaired renal function.
- D. Counsel patient regarding neuropathy associated with short-term therapy.

31.9 Which recommendation should be provided to avoid phototoxicity associated with fluoroquinolone therapy?

- A. Use sunscreen and avoid excessive exposure to UV light.
- B. Take the medication at night to avoid high drug concentrations during the day.
- C. Take with food.
- D. Drink with 1 liter of water per day to minimize drug build up in skin tissue.

31.10 What is the main benefit for prescribing methenamine for treatment of a urinary tract infection?

- A. Safe to use in patients with hepatic failure
- B. Available in intravenous and oral formulations
- C. Broad spectrum of activity
- D. Minimal development of resistance

Correct answer = B. The key issue with the antibiotic recommendation is that nitrofurantoin should not be administered in patients with poor kidney function. Adjusting the dose or continuing the current regimen are not acceptable modifications. Neuropathy is more common with therapy greater than 1 month.

Correct answer = A. Patients taking a fluoroquinolone should apply sunscreen and take precautions to minimize risk of phototoxicity. Adjusting the timing of the dose or taking with food or additional water does not change the risk of an event.

Correct answer = D. Methenamine does not select for resistance. Due to its conversion to formaldehyde, this compound is the least likely compound to select for resistant isolates. Methenamine should be avoided in patients with hepatic failure. This agent is only available as an oral formulation, and it has a narrow spectrum of activity.

# Antimycobacterial Drugs

# 32

Charles A. Peloquin and Eric F. Egelund

## I. OVERVIEW

Mycobacteria are rod-shaped aerobic bacilli that multiply slowly, every 18 to 24 hours in vitro. Their cell walls contain mycolic acids, which give the genus its name. Mycolic acids are long-chain,  $\beta$ -hydroxylated fatty acids. Mycobacteria produce highly lipophilic cell walls that stain poorly with Gram stain. Once stained, the bacilli are not decolorized easily by acidified organic solvents. Hence, the organisms are called “acid-fast bacilli.” Mycobacterial infections classically result in the formation of slow-growing, granulomatous lesions that cause tissue destruction anywhere in the body.

*Mycobacterium tuberculosis* can cause latent tuberculosis infection (LTBI) and the disease known as tuberculosis (TB). [Note: In LTBI, the patient is infected with *M. tuberculosis* without signs or symptoms of active TB disease.] TB is the leading infectious cause of death worldwide, and a quarter of the world’s population is infected with TB. Increasing in frequency are diseases caused by nontuberculosis mycobacteria (NTM). These species include *M. avium-intracellulare*, *M. chelonae*, *M. abscessus*, *M. kansasi*, and *M. fortuitum*. Finally, *M. leprae* causes leprosy.

TB treatment generally includes four first-line drugs (Figure 32.1). Second-line drugs are typically less effective, more toxic, and less extensively studied. They are used for patients who cannot tolerate the first-line drugs or who are infected with resistant TB. No drugs are specifically developed for NTM infections. Macrolides, rifamycins, and aminoglycosides are frequently included, but NTM regimens vary widely by organism.

## II. CHEMOTHERAPY FOR TUBERCULOSIS

*M. tuberculosis* is slow growing and requires treatment for months to years. LTBI can be treated for 9 months with *isoniazid* (*INH*) monotherapy or with 12 once-weekly higher doses of *INH* and *rifapentine*. In contrast, active TB disease must be treated with several drugs. Treatment for drug-susceptible TB lasts for at least 6 months, while treatment of multidrug-resistant TB (MDR-TB) typically lasts for about 2 years.

### A. Strategies for addressing drug resistance

Populations of *M. tuberculosis* contain small numbers of organisms that are naturally resistant to a particular drug. Under selective

### DRUGS USED TO TREAT TUBERCULOSIS (1st line)

*Ethambutol*  
*Isoniazid*  
*Pyrazinamide*  
*Rifabutin*  
*Rifampin*  
*Rifapentine*  
*Aminoglycosides*

### DRUGS USED TO TREAT TUBERCULOSIS (2nd line)

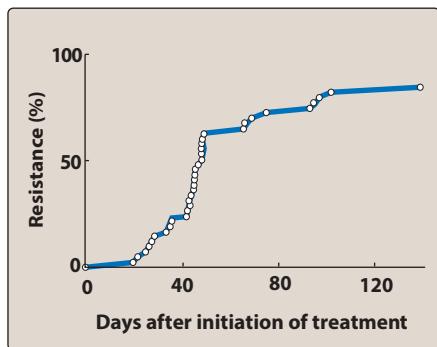
*Aminosalicylic acid*  
*Bedaquiline*  
*Capreomycin*  
*Cycloserine*  
*Ethionamide*  
*Fluoroquinolones*  
*Macrolides*

### DRUGS USED TO TREAT LEPROSY

*Clofazimine*  
*Dapsone*  
*Rifampin (rifampicin)*

### Figure 32.1

Summary of drugs used to treat mycobacterial infections.

**Figure 32.2**

Cumulative percentage of strains of *Mycobacterium tuberculosis* showing resistance to *streptomycin*.

pressure from inadequate treatment, especially from monotherapy, these resistant organisms can emerge as the dominant population.

**Figure 32.2** shows that resistance develops rapidly in TB patients who are given only *streptomycin*. Multidrug therapy is employed to suppress these resistant organisms. The first-line drugs *isoniazid*, *rifampin*, *ethambutol*, and *pyrazinamide* are preferred because of their high efficacy and acceptable incidence of toxicity. *Rifabutin* or *rifapentine* may replace *rifampin* under certain circumstances. Active disease always requires treatment with multidrug regimens, and preferably three or more drugs with proven in vitro activity against the isolate. Although clinical improvement can occur in the first several weeks of treatment, therapy is continued much longer to eradicate persistent organisms and to prevent relapse.

Standard short-course chemotherapy for tuberculosis includes *isoniazid*, *rifampin*, *ethambutol*, and *pyrazinamide* for 2 months (the intensive phase), followed by *isoniazid* and *rifampin* for 4 months (the continuation phase; **Figure 32.3**). Once susceptibility data are available, the drug regimen can be individually tailored. Second-line regimens for MDR-TB (TB resistant to at least *isoniazid* and *rifampin*) normally include an aminoglycoside (*streptomycin*, *kanamycin*, or *amikacin*) or *capreomycin* (all injectable agents), a fluoroquinolone (typically *levofloxacin* or *moxifloxacin*), any first-line drugs that remain active, and one or more of the following: *cycloserine*, *ethionamide*, or *p-aminosalicylic acid*. For extensively drug-resistant TB (XDR-TB), other drugs such as *clofazimine* and *linezolid* may be employed empirically.

Patient adherence can be low when multidrug regimens last for 6 months or longer. One successful strategy for achieving better treatment completion rates is directly observed therapy, (DOT). Patients take the medications under observation of a member of the health-care team. DOT decreases drug resistance and improves cure rates. Most public health departments offer DOT services.

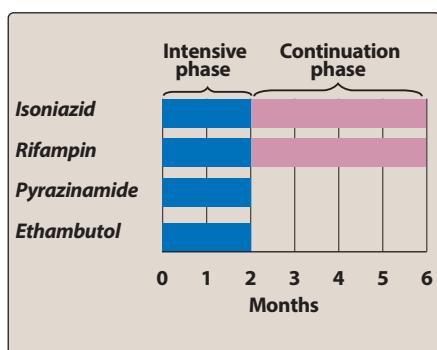
## B. Isoniazid

*Isoniazid* [eye-so-NYE-a-zid], along with *rifampin*, is one of the two most important TB drugs.

**1. Mechanism of action:** *Isoniazid* is a prodrug activated by a mycobacterial catalase-peroxidase (KatG). *Isoniazid* targets the enzymes acyl carrier protein reductase (InhA) and  $\beta$ -ketoacyl-ACP synthase (KasA), which are essential for the synthesis of mycolic acid. Inhibiting mycolic acid leads to a disruption in the bacterial cell wall.

**2. Antibacterial spectrum:** *Isoniazid* is specific for treatment of *M. tuberculosis*, although *M. kansasii* may be susceptible at higher drug concentrations. Most NTM are resistant to INH. The drug is particularly effective against rapidly growing bacilli and is also active against intracellular organisms.

**3. Resistance:** Resistance follows chromosomal mutations, including 1) mutation or deletion of KatG (producing mutants incapable of prodrug activation), 2) varying mutations of the acyl carrier proteins, or 3) overexpression of the target enzyme InhA. Cross-resistance may occur between *isoniazid* and *ethionamide*.

**Figure 32.3**

One of several recommended multi-drug schedules for the treatment of tuberculosis.

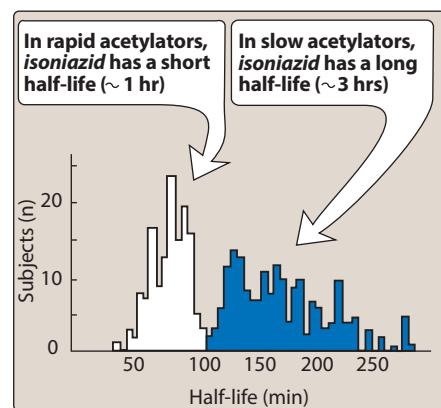
**4. Pharmacokinetics:** *Isoniazid* is readily absorbed after oral administration. Absorption is impaired if *isoniazid* is taken with food, particularly high-fat meals. The drug diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling cheese that is produced in tuberculous lesions). Drug concentrations in the cerebrospinal fluid (CSF) are similar to those in the serum. *Isoniazid* undergoes *N*-acetylation and hydrolysis, resulting in inactive products. *Isoniazid* acetylation is genetically regulated, with fast acetylators exhibiting a 90-minute serum half-life, as compared with 3 to 4 hours for slow acetylators (Figure 32.4). Excretion is through glomerular filtration and secretion, predominantly as metabolites (Figure 32.5). Slow acetylators excrete more of the parent compound.

**5. Adverse effects:** Hepatitis is the most serious adverse effect associated with *isoniazid*. If hepatitis goes unrecognized, and if *isoniazid* is continued, it can be fatal. The incidence increases with age (greater than 35 years old), among patients who also take *rifampin*, or among those who drink alcohol daily. Peripheral neuropathy, manifesting as paresthesia of the hands and feet, appears to be due to a relative pyridoxine deficiency caused by *isoniazid*. This can be avoided by daily supplementation of pyridoxine (vitamin B<sub>6</sub>). Central nervous system (CNS) adverse effects can occur, including convulsions in patients prone to seizures. Hypersensitivity reactions with *isoniazid* include rashes and fever. Because *isoniazid* inhibits the metabolism of *carbamazepine* and *phenytoin* (Figure 32.6), *isoniazid* can potentiate the adverse effects of these drugs (for example, nystagmus and ataxia).

### C. Rifamycins: rifampin, rifabutin, and rifapentine

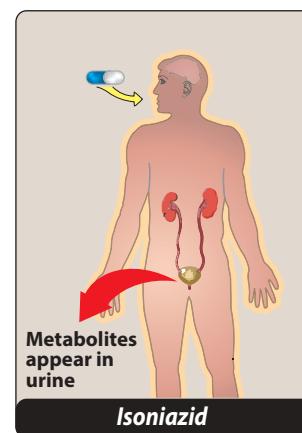
*Rifampin*, *rifabutin*, and *rifapentine* are all considered rifamycins, a group of structurally similar macrocyclic antibiotics, which are first-line oral agents for tuberculosis.

1. **Rifampin:** *Rifampin* [ri-FAM-pin] has broader antimicrobial activity than *isoniazid* and can be used as part of treatment for several different bacterial infections. Because resistant strains rapidly emerge during monotherapy, it is never given as a single agent in the treatment of active tuberculosis.
  - a. **Mechanism of action:** *Rifampin* blocks RNA transcription by interacting with the  $\beta$  subunit of mycobacterial DNA-dependent RNA polymerase.
  - b. **Antimicrobial spectrum:** *Rifampin* is bactericidal for both intracellular and extracellular mycobacteria, including *M. tuberculosis*, and NTM, such as *M. kansasii* and *Mycobacterium avium* complex (MAC). It is effective against many gram-positive and gram-negative organisms and is used prophylactically for individuals exposed to meningitis caused by meningococci or *Haemophilus influenzae*. *Rifampin* also is highly active against *M. leprae*.
  - c. **Resistance:** Resistance to *rifampin* is caused by mutations in the affinity of the bacterial DNA-dependent RNA polymerase gene for the drug.



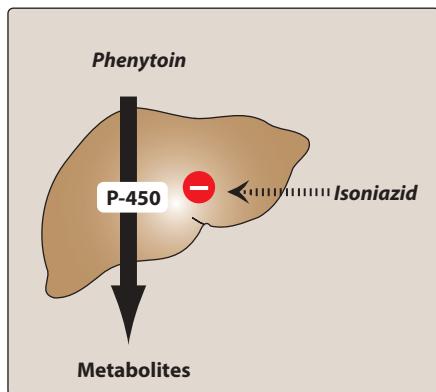
**Figure 32.4**

Bimodal distribution of *isoniazid* half-lives caused by rapid and slow acetylation of the drug. Modified from data of D. A. Evans, K. A. Maley, and V. A. McRusick. Genetic control of *isoniazid* metabolism in man. Br. Med. J. 2: 485 (1960).

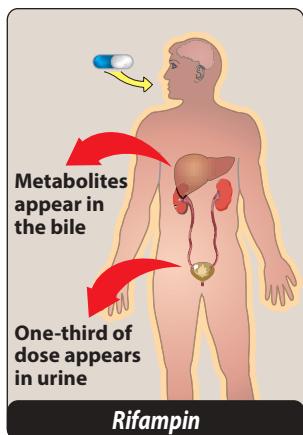


**Figure 32.5**

Administration and fate of *isoniazid*. Modified from data of P. J. Neuvonen, K. T. Kivistö, and P. Lehto, Clin. Pharm. Therapy 50: 499 (1991).

**Figure 32.6**

Isoniazid potentiates the adverse effects of phenytoin.

**Figure 32.7**

Administration and fate of rifampin.  
[Note: Patient should be warned that urine and tears may turn orange-red in color.]

**d. Pharmacokinetics:** Absorption is adequate after oral administration. Distribution of *rifampin* occurs to all body fluids and organs. Concentrations attained in the CSF are variable, often 10% to 20% of blood concentrations. The drug is taken up by the liver and undergoes enterohepatic recycling. *Rifampin* can induce hepatic cytochrome P450 enzymes and transporters (see Chapter 1), leading to numerous drug interactions. Unrelated to its effects on cytochrome P450 enzymes, *rifampin* undergoes autoinduction, leading to a shortened elimination half-life over the first 1 to 2 weeks of dosing. Elimination of *rifampin* and its metabolites is primarily through the bile and into the feces; a small percentage is cleared in the urine (Figure 32.7). [Note: Urine, feces, and other secretions have an orange-red color, so patients should be forewarned. Tears may even stain soft contact lenses orange-red.]

- e. Adverse effects:** *Rifampin* is generally well tolerated. The most common adverse reactions include nausea, vomiting, and rash. Hepatitis and death due to liver failure are rare. However, the drug should be used judiciously in older patients, alcoholics, or those with chronic liver disease. There is a modest increase in the incidence of hepatic dysfunction when *rifampin* is coadministered with *isoniazid* and *pyrazinamide*. When *rifampin* is dosed intermittently, especially with higher doses, a flu-like syndrome can occur, with fever, chills, and myalgia, sometimes extending to acute renal failure, hemolytic anemia, and shock.
- f. Drug interactions:** Because *rifampin* induces a number of phase I cytochrome P450 enzymes and phase II enzymes (see Chapter 1), it can decrease the half-lives of coadministered drugs that are metabolized by these enzymes (Figure 32.8). This may necessitate higher dosages for coadministered drugs, a switch to drugs less affected by *rifampin*, or replacement of *rifampin* with *rifabutin*.

2. **Rifabutin:** *Rifabutin* [rif-a-BYOO-tin], a derivative of *rifampin*, is preferred for TB patients coinfecte with the human immunodeficiency virus (HIV) who are receiving protease inhibitors or several of the non-nucleoside reverse transcriptase inhibitors. *Rifabutin* is a less potent inducer (approximately 40% less) of cytochrome P450 enzymes, thus lessening drug interactions. *Rifabutin* has adverse effects similar to those of *rifampin* but can also cause uveitis, skin hyperpigmentation, and neutropenia.
3. **Rifapentine:** *Rifapentine* [rih-fa-PEN-teen] has a longer half-life than that of *rifampin*. In combination with *isoniazid*, *rifapentine* may be used once weekly in patients with LTBI and in select HIV-negative patients with minimal pulmonary TB.

#### D. Pyrazinamide

*Pyrazinamide* [peer-a-ZIN-a-mide] is a synthetic, orally effective short-course agent used in combination with *isoniazid*, *rifampin*, and *ethambutol*. The precise mechanism of action is unclear. *Pyrazinamide* must be enzymatically hydrolyzed by pyrazinamidase to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack

the pyrazinamidase enzyme. *Pyrazinamide* is active against tuberculosis bacilli in acidic lesions and in macrophages. The drug distributes throughout the body, penetrating the CSF. *Pyrazinamide* may contribute to liver toxicity. Uric acid retention is common, but rarely precipitates a gouty attack. Most of the clinical benefit from *pyrazinamide* occurs early in treatment. Therefore, this drug is usually discontinued after 2 months of a 6-month regimen.

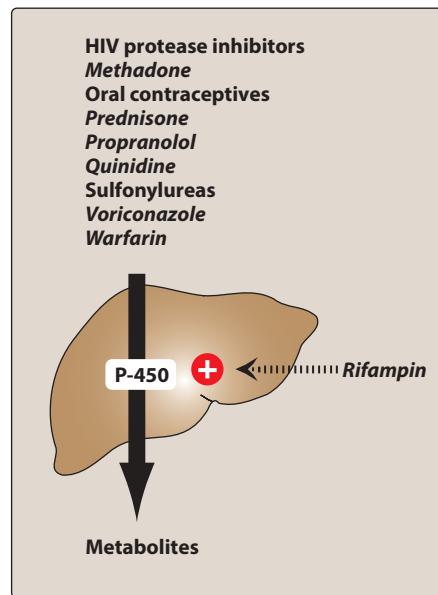
### E. Ethambutol

*Ethambutol* [e-THAM-byoo-tole] is bacteriostatic and specific for mycobacteria. *Ethambutol* inhibits arabinosyl transferase, an enzyme important for the synthesis of the mycobacterial cell wall. *Ethambutol* is used in combination with *pyrazinamide*, *isoniazid*, and *rifampin* pending culture and susceptibility data. [Note: *Ethambutol* may be discontinued if the isolate is determined to be susceptible to *isoniazid*, *rifampin*, and *pyrazinamide*.] *Ethambutol* distributes well throughout the body. Penetration into the CNS is variable, and it is questionably adequate for tuberculous meningitis. Both the parent drug and its hepatic metabolites are primarily excreted in the urine. The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. The risk of optic neuritis increases with higher doses and in patients with renal impairment. Visual acuity and color discrimination should be tested prior to initiating therapy and periodically thereafter. Uric acid excretion is decreased by *ethambutol*, and caution should be exercised in patients with gout.

Figure 32.9 summarizes some of the adverse effects of first-line and second-line drugs and their management.

### F. Alternate second-line drugs

*Streptomycin* [strep-toe-MY-sin], *para-aminosalicylic* [a-mee-noe-sal-i-SIL-ik] *acid*, *capreomycin* [kap-ree-oh-MYE-sin], *cycloserine*



**Figure 32.8**

Induces cytochrome P450, which can decrease the half-lives of coadministered drugs that are metabolized by this system.

DRUG	ADVERSE EFFECTS	COMMENTS
<i>Ethambutol</i>	Optic neuritis with blurred vision, red-green color blindness	Establish baseline visual acuity and color vision; test monthly.
<i>Isoniazid</i>	Hepatic enzyme elevation, hepatitis, peripheral neuropathy	Take baseline hepatic enzyme measurements; repeat if abnormal or patient is at risk or symptomatic. Clinically significant interaction with <i>phenytoin</i> and <i>carbamazepine</i> .
<i>Pyrazinamide</i>	Nausea, hepatitis, hyperuricemia, rash, joint ache, gout (rare)	Take baseline hepatic enzymes and uric acid measurements; repeat if abnormal or patient is at risk or symptomatic.
<i>Rifampin</i>	Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs	Take baseline hepatic enzyme measurements and CBC; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color.

CBC = complete blood count; GI = gastrointestinal.

**Figure 32.9**

Some characteristics of first-line drugs used in treating tuberculosis.

DRUG	ADVERSE EFFECTS	COMMENTS
<i>Fluoroquinolones</i>	GI intolerance, tendonitis, CNS toxicity including caffeine-like effects	Monitor LFTs, serum creatinine / BUN, QT interval prolongation. Avoid concomitant ingestion with antacids, multivitamins or drugs containing di- or trivalent cations.
<i>Aminoglycosides, Capreomycin</i>	Nephrotoxicity, ototoxicity	Not available orally. Monitor for vestibular, auditory and renal toxicity.
<i>Macrolides</i>	GI intolerance, tinnitus	Monitor LFTs, serum creatinine / BUN, QT interval prolongation. Monitor for drug interactions due to CYP inhibition (except <i>azithromycin</i> ).
<i>Ethionamide</i>	GI intolerance, hepatotoxicity, hypothyroidism	Monitor LFTs, TSH. A majority of patients experience GI intolerance. Cross-resistance with <i>isoniazid</i> is possible.
<i>Para-aminosalicylic acid (PAS)</i>	GI intolerance, hepatotoxicity, hypothyroidism	Monitor LFTs, TSH. Patients with G6PD deficiency are at increased risk of hemolytic anemia.
<i>Cycloserine</i>	CNS toxicity	Close monitoring is needed for depression, anxiety, confusion, etc. Seizures may be exacerbated in patients with epilepsy. Monitor serum creatinine.

BUN = blood urea nitrogen; CNS = central nervous system; G6PD = glucose-6 phosphate dehydrogenase; GI = gastrointestinal; LFTs = liver function tests; TSH = thyroid-stimulating hormone.

**Figure 32.10**

Some characteristics of second-line drugs used in treating tuberculosis.

[sye-kloe-SER-een], *ethionamide* [e-thye-ON-am-ide], *bedaquiline* [bed-AK-wi-leen], fluoroquinolones, and macrolides are second-line TB drugs. In general, these agents are less effective and more toxic than the first-line agents. **Figure 32.10** summarizes some of the characteristics of second-line drugs.

- 1. Streptomycin:** *Streptomycin*, an aminoglycoside antibiotic (see Chapter 30), was one of the first effective agents for TB. Its action appears to be greater against extracellular organisms. Infections due to *streptomycin*-resistant organisms may be treated with *kanamycin* or *amikacin*, to which these bacilli usually remain susceptible.
- 2. Para-aminosalicylic acid:** *Para-aminosalicylic acid (PAS)* works via folic acid inhibition. While largely replaced by *ethambutol* for drug-susceptible TB, *PAS* remains an important component of many regimens for MDR-TB.
- 3. Capreomycin:** This is a parenterally administered polypeptide that inhibits protein synthesis similar to aminoglycosides. *Capreomycin* is primarily reserved for the treatment of MDR-TB. Careful monitoring of renal function and hearing is necessary to minimize nephrotoxicity and ototoxicity, respectively.
- 4. Cycloserine:** *Cycloserine* is an orally effective, tuberculostatic drug that disrupts D-alanine incorporation into the bacterial cell wall. It distributes well throughout body fluids, including the CSF. *Cycloserine* is primarily excreted unchanged in urine. Accumulation occurs with renal insufficiency. Adverse effects involve CNS disturbances (for example, lethargy, difficulty concentrating, anxiety, and suicidal tendency), and seizures may occur.

5. **Ethionamide:** *Ethionamide* is a structural analog of *isoniazid* that also disrupts mycolic acid synthesis. The mechanism of action is not identical to *isoniazid*, but there is some overlap in the resistance patterns. *Ethionamide* is widely distributed throughout the body, including the CSF. Metabolism is extensive, most likely in the liver, to active and inactive metabolites. Adverse effects that limit its use include nausea, vomiting, and hepatotoxicity. Hypothyroidism, gynecomastia, alopecia, impotence, and CNS effects also have been reported.
6. **Fluoroquinolones:** The fluoroquinolones (see Chapter 31), specifically *moxifloxacin* and *levofloxacin*, have an important place in the treatment of multidrug-resistant tuberculosis. Some NTM also are susceptible.
7. **Macrolides:** The macrolides (see Chapter 30) *azithromycin* and *clarithromycin* are included in regimens for several NTM infections, including MAC. *Azithromycin* may be preferred for patients at greater risk for drug interactions, since *clarithromycin* is both a substrate and an inhibitor of cytochrome P450 enzymes.
8. **Bedaquiline:** *Bedaquiline*, a diarylquinoline, is an ATP synthase inhibitor. It is approved for the treatment of MDR-TB. *Bedaquiline* is administered orally, and it is active against many types of mycobacteria. *Bedaquiline* has a boxed warning for QT prolongation, and monitoring of the electrocardiogram is recommended. Elevations in liver enzymes have also been reported and liver function should be monitored during therapy. This agent is metabolized via CYP3A4, and administration with strong CYP3A4 inducers (for example, *rifampin*) should be avoided.

#### G. Fixed-dose combinations of drugs

The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB. Patient compliance for the treatment and satisfaction of the treatment are found to increase with FDCs which is very important for the suppression of the development of resistance and for improvement in clinical outcome.

#### H. Drug treatment for tuberculosis as per Revised National Tuberculosis Control Program (RNTCP)

RNTCP guidelines are continuously being updated to enable uniform therapeutic strategies throughout India along with WHO for the eradication of tuberculosis based on the newer evidences. Tuberculosis is a notifiable disease. All cases of tuberculosis should be reported to appropriate health authorities. The treatment classification is based on the status of the organism in terms of resistance.

Figure 32.11 shows drug treatment regimen and duration of TB treatment based on the levels of microbial resistance. The combination of drugs and their duration of treatment is divided into two phases: 1) intensive and 2) continuous phases. Figure 32.12 depicts the dosage of drugs for drug-sensitive tuberculosis for adults and Figure 32.13 shows the dose for pediatric use. For the treatment of other types drug resistances such as mono-drug resistance (MR), poly-drug

ORGANISM STATUS	TYPE OF TB CASE	INTENSIVE PHASE (MONTHS)	CONTINUOUS PHASE (MONTHS)
<b>Sensitive</b>	Newly diagnosed	HRZE (2 mon)	HRE (4 mon)
	Previously treated (recurrence, lost followup during treatment, after failure of recent course)	HRZE (2 mon) + HRZE (1 mon)	HRE (5 mon)
<b>Resistant</b>	RR + HR/or unknown	Kn Lfx, Eto, Cs, Z, E, H (6 to 9 mon)	Lfx, Eto, Cs, E, H (18 mon)
<b>Resistant</b>	MDR	Km, Lfx, Eto, Cs, Z, E (6 to 9 mon)	Lfx, Eto, Cs, E (18 mon)
<b>Resistant</b>	XDR	Cm, PAS, Mfx, High dose H, Cfz, Lzd, Amx/Clv (6 to 12 mon)	PAS, Mfx, high dose-H, Cfz, Lzd, Amx/Clv (18 mon)

H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; Kn = kanamycin; Lfx = levofloxacin; M = moxifloxacin; Cs = cycloserine; Eto = ethionamide; PAS = para-amino salicylic acid; Cfz = clofazimine; Cm = capreomycin; Lzd = linezolid; Amx/Clv = amoxicillin and clavulanic acid.

**Figure 32.11**

Drug treatment for various regimens for TB treatment based on the levels of microbial resistance. Courtesy: RNTCP.

WEIGHT CATEGORY (kg)	NUMBER OF TABLETS (FDCs)		INJ. STREPTOMYCIN <sup>1</sup> (g)	
	Intensive phase			
	HRZE	HRE		
	75/150/400/275	75/150/275		
25–39	2	2	0.5	
40–54	3	3	0.75	
55–69	4	4	1	
≥70	5	5	1	

FDC = fixed-dose combination.

<sup>1</sup>Inj. Streptomycin to be added in IP phase for 2 months in the previously treated regimen of drug-sensitive patients.

In patients above 50 years of age, maximum dose of streptomycin should be 0.75 g. Adults weighing less than 25 kg will be given loose drugs as per body weight.

**Figure 32.12**

Drug dosage of antitubercular drugs for drug-sensitive tuberculosis for adults having various body weight. Courtesy: RNTCP.

WEIGHT CATEGORY (kg)	NUMBER OF TABLETS (DISPERSIBLE FDCs)			INJ. STREPTOMYCIN (mg)
	Intensive phase		Continuation phase	
	HRZ	E	HRE	
	50/75/150	100	50/75/100	
4–7	1	1	1	100
8–11	2	2	2	150
12–15	3	3	3	200
16–24	4	4	4	300
25–29	3 + 1A <sup>1</sup>	3	3 + 1A <sup>1</sup>	400
30–39	2 + 2A <sup>1</sup>	2	2 + 2A <sup>1</sup>	500

<sup>1</sup>A = Adult FDC (HRZE = 75/150/400/275; HRE = 75/150/275)

**Figure 32.13**

Drug dosage for pediatric use according to the body weight and standardized fixed-dose combinations (FDCs) for the treatment of TB. Courtesy: RNTCP.

resistance (PDR), and rifampicin resistance (RR), modified regimens are used for which one need to refer further to RNTCP guidelines.

## I. Multidrug-resistant tuberculosis

Drug resistance in TB patients can be classified into isoniazid resistant, rifampicin resistant (RR-TB), multidrug resistant (MDR-TB), and extensively drug resistant (XDR-TB). As per a study done in 2016, China, India, and the Russian Federation contributed to 47% of the global drug resistance tuberculosis (MDR and RR-TB), out of which 6.2% of them were classified as XDR-TB. WHO recommends a shorter MDR-TB treatment regimen (9 to 12 months) under specific conditions. Longer MDR-TB regimens up to 18 months or more are used for the treatment of RR-TB or MDR-TB. *Clofazimine* and *linezolid* are now recommended as a core second-line therapy for MDR-TB with p-aminosalicylic acid as an add-on agent. They are now recommended for all patients with RR-TB, regardless of confirmation of *isoniazid* resistance. *Clarithromycin* and other macrolides are no longer included among the drugs to be used for the treatment of MDR and RR-TB. Drugs are selected from groups as per WHO guidelines. These groups are given in [Figure 32.14](#). Four to seven drugs are selected from these groups, for which the pathogen is susceptible for a better outcome. This regrouping is intended to guide the design of longer regimens. Drugs of Groups A and C ([Figure 32.14](#)) are shown by a decreasing order of usual preference for use. As per the WHO guidelines, the HIV status must be confirmed to be negative before *thioacetazone* is started.

## J. Shorter MDR-TB treatment regimens

Based on the duration of treatment, it is split into two distinct phases given in the following text.

- Intensive phase:** The duration of the intensive phase is 4 months (extended up to a maximum of 6 months in case of lack of sputum smear conversion) and includes the following drugs: *gatifloxacin* (or *moxifloxacin*), *kanamycin*, *prothionamide*, *clofazimine*, high-dose *isoniazid*, *pyrazinamide*, and *ethambutol*. The continuation phase follows the intensive phase.
- Continuation phase:** The duration of the continuation phase is 5 months and includes the following drugs: *gatifloxacin* (or *moxifloxacin*), *clofazimine*, *pyrazinamide*, and *ethambutol*.

The regimen for the drug treatment for tuberculosis and MDR-TB is a matter of constant debate and the regimen changes from time to time. Therefore, one must follow WHO guidelines to update the current guidelines.

## III. DRUGS FOR LEPROSY

Leprosy (or Hansen's disease) is uncommon in the United States; however, worldwide it is a much larger problem ([Figure 32.15](#)). Leprosy can be treated effectively with *dapsone* and *rifampin* ([Figure 32.16](#)).

<b>Group A. Fluoroquinolones<sup>1</sup></b>	<b><i>Levofloxacin</i> <i>Moxifloxacin</i> <i>Gatifloxacin</i></b>
<b>Group B. Second-line injectable agents</b>	<b><i>Amikacin</i> <i>Capreomycin</i> <i>Kanamycin</i> <i>(Streptomycin)<sup>2</sup></i></b>
<b>Group C. Other core second-line agents<sup>1</sup></b>	<b><i>Ethionamide/</i> <i>prothionamide</i> <i>Cycloserine/terizidone</i> <i>Linezolid</i> <i>Clofazimine</i></b>
<b>Group D. Add-on agents (not part of the core MDF-TB regimen)</b>	<b>D1 <i>Pyrazinamide</i> <i>Ethambutol</i> <i>High-dose</i> <i>isoniazid</i> D2 <i>Bedaquiline</i> <i>Delamanid</i> D3 <i>p-Aminosalicylic</i> <i>acid</i> <i>Imipenem-</i> <i>cilastatin<sup>3</sup></i> <i>Meropenem<sup>3</sup></i> <i>Amoxicillin-</i> <i>clavulanate<sup>3</sup></i> <i>(Thioacetazone)<sup>4</sup></i></b>

<sup>1</sup>Medicines in Groups A and C are shown by a decreasing order of usual preference for use (subject to other considerations; see the text).

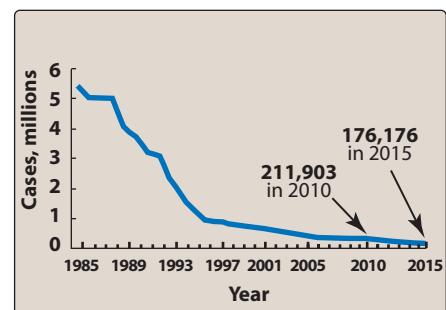
<sup>2</sup>Refer to the text for the conditions under which *streptomycin* may substitute other injectable agents. Resistance to *streptomycin* alone does not qualify for the definition of XDR-TB.

<sup>3</sup>*Carbapenems* and *clavulanate* are meant to be used together; *clavulanate* is only available in formulations combined with *amoxicillin*.

<sup>4</sup>HIV status must be confirmed to be negative before *thioacetazone* is started.

**Figure 32.14**

Drug regimen recommended for the treatment of RR-TB and MDR-TB by WHO (2016).



**Figure 32.15**

Reported prevalence of leprosy worldwide.



### A. Dapsone

*Dapsone* [DAP-sone] is structurally related to the sulfonamides and similarly inhibits dihydropteroate synthase in the folate synthesis pathway. It is bacteriostatic for *M. leprae*, and resistant strains may be encountered. *Dapsone* is also used in the treatment of pneumonia caused by *Pneumocystis jirovecii* in immunosuppressed patients. The drug is well absorbed from the gastrointestinal tract and is distributed throughout the body, with high concentrations in the skin. The parent drug undergoes hepatic acetylation. Both parent drug and metabolites are eliminated in the urine. Adverse reactions include hemolysis (especially in patients with glucose-6-phosphate dehydrogenase deficiency), methemoglobinemia, and peripheral neuropathy.

### B. Clofazimine

*Clofazimine* [kloe-FAZ-i-meen] is a phenazine dye. Its mechanism of action may involve binding to DNA, although alternative mechanisms have been proposed. Its redox properties may lead to the generation of cytotoxic oxygen radicals that are toxic to the bacteria. *Clofazimine* is bactericidal to *M. leprae*, and it has potentially useful activity against *M. tuberculosis* and NTM. The drug is recommended by the World Health Organization as part of a shorter regimen (9 to 12 months) for MDR-TB. Following oral absorption, *clofazimine* accumulates in tissues, allowing intermittent therapy but does not enter the CNS. Patients typically develop a pink to brownish-black discoloration of the skin and should be informed of this in advance. Eosinophilic and other forms of enteritis, sometimes requiring surgery, have been reported. *Clofazimine* has some anti-inflammatory and anti-immune activities. Thus, erythema nodosum leprosum may not develop in patients treated with this drug.

**Figure 32.16**

Patient with leprosy. **A.** Before therapy. **B.** After 6 months of multidrug therapy. Modified from Y. Nivoix, D. Leveque, and R. Herbrecht, et al. The enzymatic basis of drug-drug interactions with systemic triazole antifungals. Clin. Pharmacokinet. 47: 779 (2008).

## Study Questions

Choose the ONE best answer.

32.1 A 22-year-old female intravenous drug user was admitted to the hospital with a 4-week history of cough and fever. A chest radiograph showed left upper lobe cavitary infiltrate. Cultures of sputum yielded *M. tuberculosis* susceptible to all antimycobacterial drugs. The patient received self-administered isoniazid, rifampin, pyrazinamide and ethambutol. Two weeks following initiation of therapy, the patient is concerned that her urine is a “funny-looking reddish color.” Which drug is the most likely cause?

- A. Isoniazid
- B. Rifampin
- C. Pyrazinamide
- D. Ethambutol

32.2 A 32-year-old man has been on standard four-drug therapy for active pulmonary tuberculosis for the past 2 months. He has no other comorbid conditions. At his regular clinic visit, he complains of a “pins and needles” sensation in his feet. Which drug is most likely causing this?

- A. Isoniazid
- B. Rifampin
- C. Pyrazinamide
- D. Ethambutol

32.3 A 32-year-old man who takes standard four-drug therapy for active pulmonary tuberculosis complains about a “pins and needles” feeling in his feet. He is diagnosed with peripheral neuropathy. Which vitamin should have been included in the regimen for this patient to reduce the risk of neuropathy?

- A. Niacin
- B. Pyridoxine
- C. Thiamine
- D. Ascorbic acid

32.4 A 23-year-old man was started on standard four-drug antimycobacterial therapy for treatment of active TB. He has epilepsy which is controlled with carbamazepine. He has had no seizures in 5 years; however, upon return to clinic at 1 month, he reports having two seizures since his last visit. Which drug may be the reason his carbamazepine is less effective?

- A. Isoniazid
- B. Rifampin
- C. Pyrazinamide
- D. Ethambutol

Correct answer = B. Rifampin (as well as rifabutin and rifapentine) and its metabolites may color urine, feces, saliva, sputum, sweat, and tears a bright red-orange. Patients should be counseled that this is an adverse effect which is not harmful, but can stain clothes and contact lenses.

Correct answer = A. Standard four-drug therapy for active pulmonary tuberculosis includes isoniazid. Isoniazid can cause peripheral neuropathy with symptoms including paresthesias, such as “pins and needles” and numbness.

Correct answer = B. Concurrent administration of pyridoxine (vitamin B<sub>6</sub>) prevents the neuropathic actions of isoniazid. The relative deficiency of pyridoxine appears to be due to the interference of isoniazid with its activation and enhancement of the excretion of pyridoxine.

Correct answer = B. Rifampin is a potent inducer of cytochrome P450-dependent drug-metabolizing enzymes and may reduce the concentration of carbamazepine. None of the other drugs listed induce cytochrome P450 enzymes.

32.5 A 26-year-old female HIV patient was recently diagnosed with active tuberculosis. Currently, she is on a stable HIV regimen consisting of two protease inhibitors and two nucleoside reverse transcriptase inhibitors. Which is the most appropriate regimen for treatment of her tuberculosis?

- A. Rifampin + isoniazid + pyrazinamide + ethambutol
- B. Rifabutin + isoniazid + pyrazinamide + ethambutol
- C. Rifapentine + isoniazid + pyrazinamide + ethambutol
- D. Rifampin + moxifloxacin + pyrazinamide + ethambutol

32.6 A 28-year-old man with MDR-TB is receiving the following medications for treatment: pyrazinamide, ethionamide, moxifloxacin, streptomycin, and para-aminosalicylic acid. Which drug in his regimen requires monitoring for QT prolongation?

- A. Pyrazinamide
- B. Ethionamide
- C. Moxifloxacin
- D. Streptomycin

32.7 A 46-year-old male patient with active tuberculosis is to be initiated on the four-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol. The patient reports no other conditions except gout. Which pair of antituberculosis drugs has the potential to worsen his gout?

- A. Rifampin and isoniazid
- B. Ethambutol and pyrazinamide
- C. Rifampin and ethambutol
- D. Isoniazid and ethambutol

32.8 A 24-year-old man returns to the clinic 1 month after starting treatment for tuberculosis. He is receiving isoniazid, rifampin, pyrazinamide, and ethambutol. He states he feels fine, but now is having difficulty reading and feels he may need to get glasses. Which drug may be causing his decline in vision?

- A. Isoniazid
- B. Rifampin
- C. Pyrazinamide
- D. Ethambutol

Correct answer = B. Rifabutin is recommended in place of rifampin in patients co-infected with HIV, since it is a less potent inducer of CYP enzymes than rifampin. However, rifabutin is a CYP3A4 substrate and “bidirectional” interactions may result. That is, other medications, such as the protease inhibitors may affect the concentration of rifabutin, requiring dose adjustment of rifabutin or use of alternative HIV agents.

Correct answer = C. While rare, prolongation of the QT interval is associated with the fluoroquinolones. QT interval prolongation is due to the blocking of voltage-gated potassium channels. Of the available quinolones, moxifloxacin has the greatest risk. The risk may be minimized by avoiding co-administration of other medications which may prolong the QT interval. The other agents are not associated with QT prolongation.

Correct answer = B. Ethambutol and especially pyrazinamide both may increase uric acid concentrations and have the potential to precipitate gouty attacks. Pyrazinamide and ethambutol-induced hyperuricemia may be controlled by use of anti-gout medications, such as xanthine oxidase inhibitors. Symptoms of gout must be monitored closely.

Correct answer = D. Optic neuritis, exhibited as a decrease in visual acuity or loss of color discrimination, is the most important side effect associated with ethambutol. Visual disturbances generally are dose-related and more common in patients with reduced renal function. They are reversible (weeks to months) if ethambutol is discontinued promptly.

32.9 A 36 year-old woman with multidrug-resistant tuberculosis is being treated with the following agents: streptomycin, cycloserine, pyrazinamide, ethionamide, and p-aminosalicylic acid. Her physician recently noticed she appears confused and anxious and has a slight tremor. Which drug is most likely contributing to her current state?

- A. Streptomycin
- B. Cycloserine
- C. Pyrazinamide
- D. Ethionamide

Correct answer = B. Cycloserine easily penetrates the CNS and may cause adverse effects involving the nervous system, including psychoses, drowsiness, tremor, paresthesia, aggression, and suicidal ideation, among others. Patients should be monitored continually for these signs and symptoms.

32.10 Which is correct regarding clofazimine in the treatment of leprosy?

- A. Clofazimine should not be used in patients with a deficiency in glucose-6-phosphate dehydrogenase (G6PD).
- B. Peripheral neuropathy is one of the most common adverse effects seen with the drug.
- C. Clofazimine may cause skin discoloration over time.
- D. The risk of erythema nodosum leprosum is increased in patients given clofazimine.

Correct answer = C. Clofazimine is a phenazine dye and causes bronzing (the skin pigment color will change color, from pink to brownish-black), especially in fair-skinned patients. This occurs in a majority of patients and generally is not considered harmful but may take several months to years to fade after discontinuing the medication.

32.11 MDR-TB is considered to be dangerous because:

- A. Drugs are few for the treatment.
- B. There are chances of spread of MDR-TB to others.
- C. Drugs are expensive.
- D. Drugs are toxic.
- E. All of the above.

Correct answer = E. Multidrug-resistant TB is considered dangerous because second-line drugs for treating MDR are few and are toxic with lot of side effects and are expensive. Moreover, it is a public health concern as chances of spread of MDR-TB to others are increased if not treated properly. Over the years, the number of MDR-TB cases is rising.



# Antifungal Drugs

Lindsey Childs-Kean

# 33

## I. OVERVIEW

Infectious diseases caused by fungi are called mycoses, and they are often chronic in nature. Mycotic infections may involve only the skin (cutaneous mycoses extending into the epidermis), or may cause subcutaneous or systemic infections. Unlike bacteria, fungi are much more complex organisms, are eukaryotic, with rigid cell walls composed largely of chitin rather than peptidoglycan (a characteristic component of most bacterial cell walls), and often grow slowly. Consequently, only a few drugs are aimed at interfering with cell division and have limited use. In addition, the fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes. These structural characteristics are useful targets for chemotherapeutic agents against mycoses. Fungi are generally resistant to antibiotics; conversely, bacteria are resistant to antifungal agents. The incidence of mycoses such as candidemia, though not as frequent as bacterial or viral infections, has been on the rise for the last few decades. This is attributed to an increased number of patients with chronic immunosuppression due to organ transplantation, cancer chemotherapy, or human immunodeficiency virus (HIV) infection. In the past decade, there have been several advances in antifungal therapy. [Figure 33.1](#) summarizes clinically useful agents for cutaneous and systemic mycoses. A new class of antifungal agents (echinocandins) and safer and/or more bioavailable formulations of *itraconazole* and *amphotericin B* have been developed. [Figure 33.2](#) lists the common pathogenic organisms of the Kingdom Fungi, and [Figure 33.3](#) provides an overview of the mechanism of action of the various antifungal agents. Antifungal agents are sufficiently diverse in activity, toxicity, and drug interaction potential. These characteristics allow clinicians to differentiate among agents when tailoring therapy to meet the needs of a particular patient.

## II. DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOTIC INFECTIONS

### A. Amphotericin B

*Amphotericin* [am-foe-TER-i-sin] *B* is a naturally occurring polyene antifungal produced by *Streptomyces nodosus*. In spite of its toxic potential, *amphotericin B* remains the drug of choice for the treatment of several life-threatening mycoses.

- Mechanism of action:** *Amphotericin B* binds to ergosterol in the plasma membranes of fungal cells. There, it forms pores (channels)

### DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOSES

*Amphotericin B*

**Echinocandin derivatives**

*Anidulafungin*

*Caspofungin*

*Micafungin*

**Pyrimidine analog**

*Flucytosine*

**Azole derivatives**

*Ketoconazole*

*Fluconazole*

*Itraconazole*

*Isavuconazole*

*Posaconazole*

*Voriconazole*

### DRUGS FOR CUTANEOUS MYCOSES

**(Topical agents)**

*Nystatin*

*Naftifine*

**Topical azole derivatives**

*Clotrimazole*

*Miconazole*

*Econazole*

*Butoconazole*

*Oxiconazole*

*Efinaconazole*

*Sertaconazole*

*Sulconazole*

*Terconazole*

*Tioconazole*

**Topical allylamine derivatives**

*Terbinafine*

*Butenafine*

*Tolnaftate*

*Naftifine*

### OTHER ANTIFUNGAL AGENTS

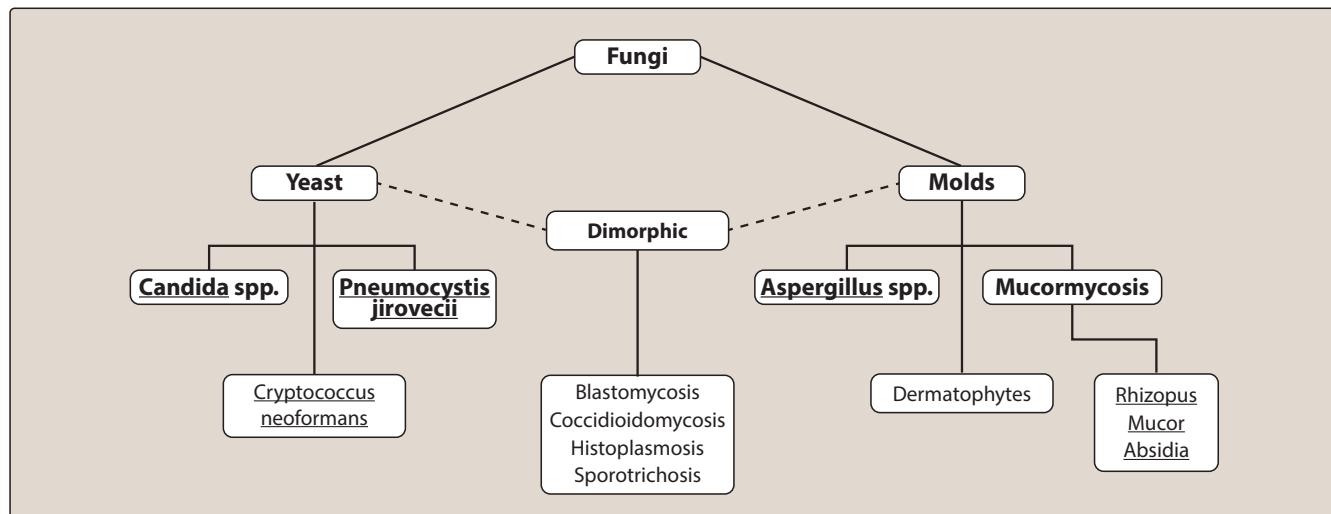
*Ciclopirox*

*Tavaborole*

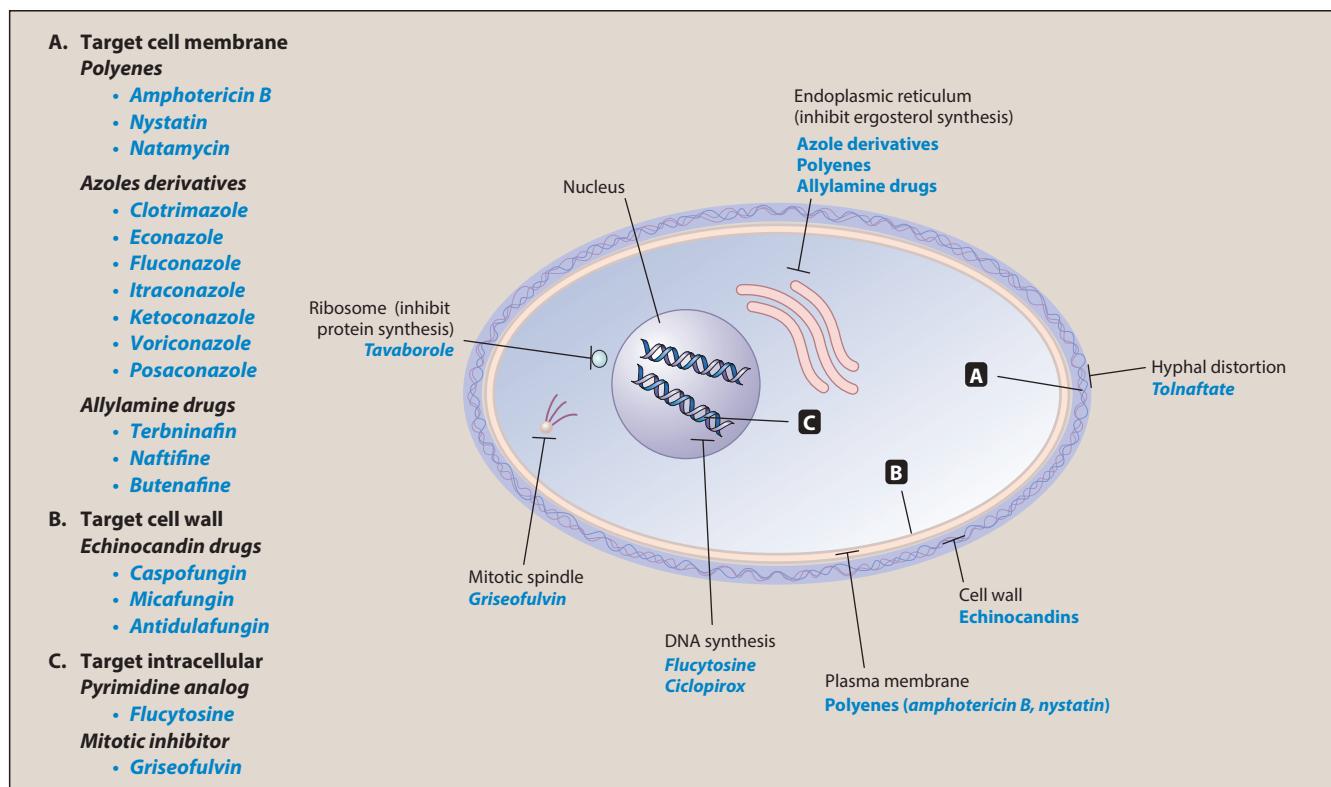
*Griseofulvin*

### Figure 33.1

Summary of antifungal agents, class, route of administration, and therapeutic dosages. (For drug dosages, refer to Appendix at the end of the book.)

**Figure 33.2**

Common pathogenic organisms of Kingdom Fungi.

**Figure 33.3**

Cellular targets of antifungal drugs.

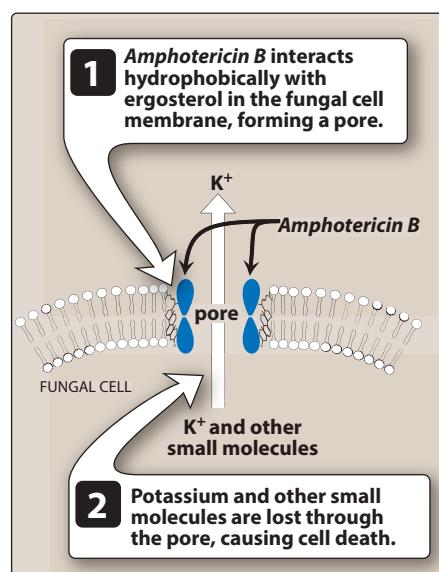
that require hydrophobic interactions between the lipophilic segment of the polyene antifungal and the sterol (Figure 33.4). The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.

2. **Antifungal spectrum:** *Amphotericin B* is either fungicidal or fungistatic, depending on the organism and the concentration of the drug. It is effective against a wide range of fungi, including *Candida albicans*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces dermatitidis*, and many strains of *Aspergillus*. [Note: *Amphotericin B* is also used in the treatment of the protozoal infection leishmaniasis.]
3. **Resistance:** Fungal resistance to *amphotericin B*, although infrequent, is associated with decreased ergosterol content of the fungal membrane.
4. **Pharmacokinetics:** *Amphotericin B* is administered by slow intravenous (IV) infusion (Figure 33.5). *Amphotericin B* is insoluble in water and must be coformulated with sodium deoxycholate (conventional) or artificial lipids to form liposomes. The liposomal preparations are associated with reduced renal and infusion toxicity but are more costly. *Amphotericin B* is extensively bound to plasma proteins and is distributed throughout the body. Inflammation favors penetration into various body fluids, but little of the drug is found in the cerebrospinal fluid (CSF), vitreous humor, peritoneal fluid, or synovial fluid. Low levels of the drug and its metabolites are excreted primarily in the urine over a long period of time.
5. **Adverse effects:** *Amphotericin B* has a low therapeutic index. Toxic manifestations are outlined below (Figure 33.6).
  - a. **Fever and chills:** These occur most commonly 1 to 3 hours after starting the IV administration but usually subside with repeated administration of the drug. Premedication with a corticosteroid or an antipyretic helps to prevent this problem.
  - b. **Renal impairment:** Despite the low levels of the drug excreted in the urine, patients may exhibit a decrease in glomerular filtration rate and renal tubular function. Serum creatinine may increase, creatinine clearance can decrease, and potassium and magnesium are lost. Renal function usually returns with discontinuation of the drug, but residual damage is likely at high doses. Azotemia is exacerbated by other nephrotoxic drugs, such as aminoglycosides, *cyclosporine*, and *vancomycin*, although adequate hydration can decrease its severity. Sodium loading with infusions of normal saline prior to administration of the conventional formulation or use of the liposomal *amphotericin B* products minimizes the risk of nephrotoxicity.
  - c. **Hypotension:** A shock-like fall in blood pressure accompanied by hypokalemia may occur, requiring potassium supplementation. Care must be exercised in patients taking *digoxin* and other drugs that can cause potassium fluctuations.
  - d. **Thrombophlebitis:** Adding *heparin* to the infusion can alleviate this problem.

## B. Antimetabolite antifungals

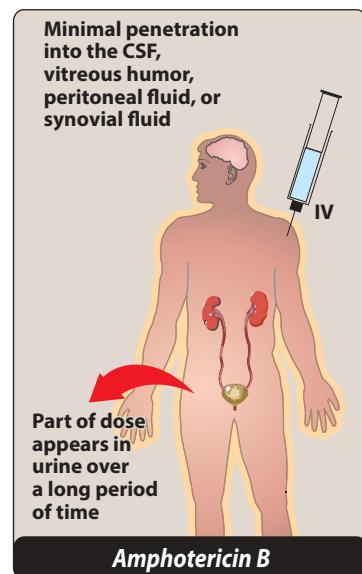
*Flucytosine* [floo-SYE-toe-seen] (5-FC) is a synthetic pyrimidine antimetabolite that is often used in combination with other antifungal agents.

1. **Mechanism of action:** 5-FC enters the fungal cell via a cytosine-specific permease, an enzyme not found in mammalian cells. It is subsequently converted to a series of compounds, including



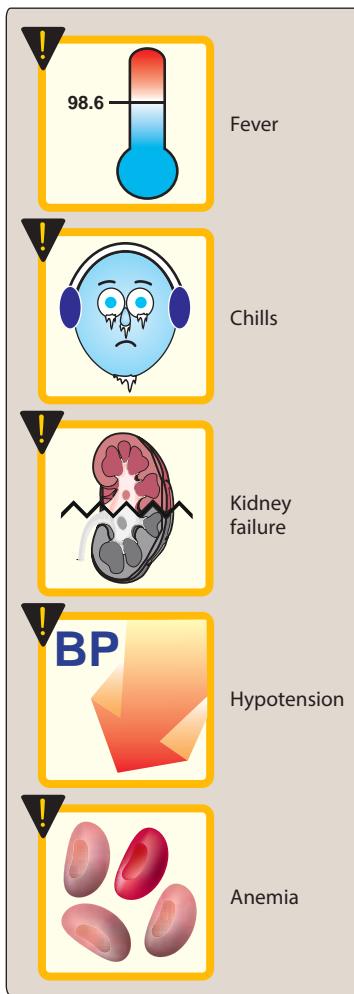
**Figure 33.4**

Model of a pore formed by *amphotericin B* in the lipid bilayer membrane.



**Figure 33.5**

Administration and fate of *amphotericin B*. CSF = cerebrospinal fluid.

**Figure 33.6**

Adverse effects of amphotericin B.

*5-fluorouracil (5-FU)* and *5-fluorodeoxyuridine 5'-monophosphate*, which disrupt nucleic acid and protein synthesis (**Figure 33.7**). [Note: *Amphotericin B* increases cell permeability, allowing more *5-FC* to penetrate the cell leading to synergistic effects.]

2. **Antifungal spectrum:** *5-FC* is fungistatic. It is effective in combination with *itraconazole* for treating chromoblastomycosis. It is also used in combination with *amphotericin B* for the treatment of systemic mycoses and for meningitis caused by *C. neoformans* and *C. albicans*. *Flucytosine* can also be used for *Candida* urinary tract infections when *fluconazole* is not appropriate; however, resistance can occur with repeated use.
3. **Resistance:** Resistance may occur due to decreased levels of any of the enzymes in the conversion of *5-FC* to *5-FU* and other metabolites. The emergence of resistant fungal cells is lower with a combination of *5-FC* plus a second antifungal agent. Thus, *5-FC* is not used as a single antimycotic drug.
4. **Pharmacokinetics:** *5-FC* is well absorbed after oral administration. It distributes throughout the body water and penetrates well into the CSF. *5-FU* is detectable in patients and is probably the result of metabolism of *5-FC* by intestinal bacteria. Excretion of both the parent drug and metabolites is via glomerular filtration, and the dose must be adjusted in patients with compromised renal function.
5. **Adverse effects:** *5-FC* causes reversible neutropenia, thrombocytopenia, and dose-related bone marrow depression. Reversible hepatic dysfunction with elevation of serum transaminases has been observed. Nausea, vomiting, and diarrhea are common, and severe enterocolitis may occur.

### C. Azole antifungals

Azole antifungals are made up of two different classes of drugs—imidazoles and triazoles. Although these drugs have similar mechanisms of action and spectra of activity, their pharmacokinetics and therapeutic uses vary significantly. In general, imidazoles are applied topically for cutaneous infections, whereas triazoles are administered systemically for the treatment or prophylaxis of cutaneous and systemic mycoses. [Note: Imidazole antifungals are discussed in the section on agents for cutaneous mycotic infections.] The systemic triazole antifungals include *fluconazole*, *itraconazole*, *posaconazole*, *voriconazole*, and *isavuconazole*.

1. **Mechanism of action:** Azoles are predominantly fungistatic. They inhibit  $14\text{-}\alpha$  demethylase (a cytochrome P450 [CYP450] enzyme), thereby blocking the demethylation of lanosterol to ergosterol (**Figure 33.8**). The inhibition of ergosterol biosynthesis disrupts fungal membrane structure and function, which, in turn, inhibits fungal cell growth.
2. **Resistance:** Resistance to azole antifungals is becoming a significant clinical problem, particularly with protracted therapy required in immunocompromised patients, such as those who have advanced HIV infection or bone marrow transplant. Mechanisms of resistance include mutations in the  $14\text{-}\alpha$  demethylase gene that lead to decreased azole binding and efficacy. Additionally, some

strains of fungi develop efflux pumps that pump the drug out of the cell or have reduced ergosterol in the cell wall.

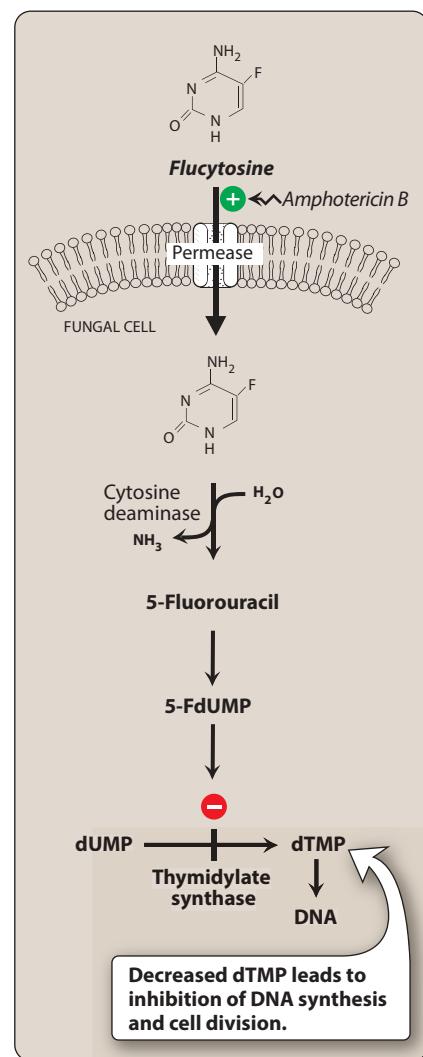
3. **Drug interactions:** All azoles inhibit the hepatic CYP450 3A4 isoenzyme to varying degrees. Several azoles, including *itraconazole* and *voriconazole*, are metabolized by CYP450 3A4 and other CYP450 isoenzymes except *posaconazole* which undergoes minimal CYP metabolism; most of its metabolites are glucuronide conjugates formed by uridine diphosphate glucuronosyltransferase (UGT) pathways, mainly UGT1A4. Patients on concomitant medications that are substrates for this isoenzyme may have increased concentrations and risk for toxicity. However, the clinical relevance of these interactions may vary upon the azole involved and upon the “target” drug including over-the-counter or alternative medicines and herbs. Therefore, concomitant use of potent CYP450 inhibitors (for example, *ritonavir*) and inducers (for example, *rifampin* and *phenytoin*) can lead to increased adverse effects or clinical failure of these azoles, respectively.
4. **Contraindications:** Azoles are considered teratogenic, and they should be avoided in pregnancy unless the potential benefit outweighs the risk to the fetus.

#### D. Fluconazole

*Fluconazole* [floo-KON-a-zole] was the first triazole antifungal agent. It is the least active of all triazoles, with most of its spectrum limited to yeasts and some dimorphic fungi. It has no role in the treatment of aspergillosis or zygomycosis. It is highly active against *Cryptococcus neoformans* and certain species of *Candida*, including *C. albicans* and *C. parapsilosis*. Resistance is a concern, however, with other species, including *C. krusei* and *C. glabrata*. *Fluconazole* is used for prophylaxis against invasive fungal infections in recipients of bone marrow transplants. It is the drug of choice for *Cryptococcus neoformans* after induction therapy with *amphotericin B* and *flucytosine* and is used for the treatment of candidemia and coccidioidomycosis. *Fluconazole* is effective against most forms of mucocutaneous candidiasis. It is commonly used as a single-dose oral treatment for vulvovaginal candidiasis. *Fluconazole* is available in oral and IV dosage formulations. It is well absorbed after oral administration and distributes widely to body fluids and tissues. The majority of the drug is excreted unchanged via the urine, and doses must be reduced in patients with renal dysfunction. The most common adverse effects with *fluconazole* are nausea, vomiting, headache, and skin rashes.

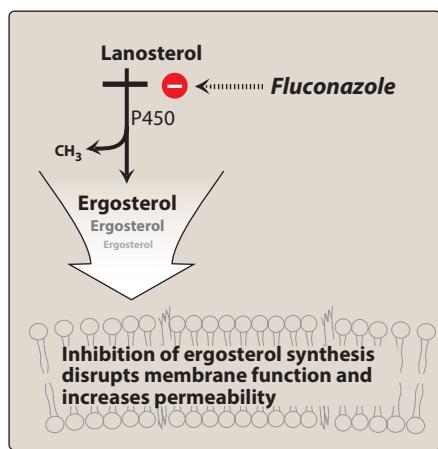
#### E. Itraconazole

*Itraconazole* [it-ra-KON-a-zole] is a synthetic triazole that has a broad antifungal spectrum compared to *fluconazole*. *Itraconazole* is a drug of choice for the treatment of blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis. It is rarely used for treatment of infections due to *Candida* and *Aspergillus* species because of the availability of more effective agents. *Itraconazole* is available as a capsule, tablet, or oral solution. The capsule and tablet should be taken with food, and ideally an acidic beverage,



**Figure 33.7**

Mode of action of *flucytosine*.  
5-FdUMP = 5-fluorodeoxyuridine 5'-monophosphate; dTMP = deoxythymidine 5'-monophosphate.

**Figure 33.8**

Mode of action of azole antifungals.

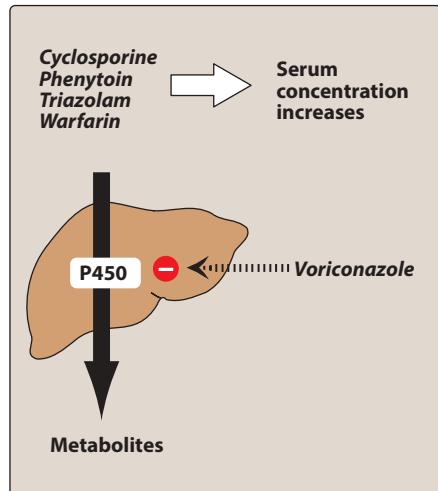
to increase absorption. By contrast, the solution should be taken on an empty stomach, as food decreases the absorption. The drug distributes well in most tissues, including bone and adipose tissues. *Itraconazole* is extensively metabolized by the liver, and the drug and inactive metabolites are excreted in the urine and feces. Adverse effects include nausea, vomiting, rash (especially in immunocompromised patients), hypokalemia, hypertension, edema, and headache. Liver toxicity can also occur, especially when given with other hepatotoxic drugs. *Itraconazole* has a negative inotropic effect and should be avoided in patients with evidence of ventricular dysfunction, such as heart failure.

#### F. Posaconazole

*Posaconazole* [poe-sa-KONE-a-zole], a synthetic triazole, is a broad-spectrum antifungal structurally similar to *itraconazole*. It is available as an oral suspension, oral tablet, or IV formulation. *Posaconazole* is commonly used for the treatment and prophylaxis of invasive *Candida* and *Aspergillus* infections in severely immunocompromised patients. Because of its broad spectrum of activity, *posaconazole* is used in the treatment of invasive fungal infections caused by *Scedosporium* and *Zygomycetes*. The drug has low oral bioavailability and should be given with food. Unlike other azoles, *posaconazole* is not metabolized by CYP450, but is eliminated via glucuronidation. Drugs that increase gastric pH (for example, proton-pump inhibitors) may decrease the absorption of oral *posaconazole* and should be avoided if possible. Due to its potent inhibition of CYP450 3A4, concomitant use of *posaconazole* with a number of agents (for example, ergot alkaloids, *atorvastatin*, *citalopram*, and *risperidone*) is contraindicated.

#### G. Voriconazole

*Voriconazole* [vor-i-KON-a-zole], a synthetic triazole related to *fluconazole*, is a broad-spectrum antifungal agent that is available in both IV and oral dosage forms. *Voriconazole* has replaced *amphotericin B* as the drug of choice for invasive aspergillosis. It is also approved for treatment of invasive candidiasis, as well as serious infections caused by *Scedosporium* and *Fusarium* species. *Voriconazole* has high oral bioavailability and penetrates into tissues well. It is extensively metabolized by CYP450 2C19, 2C9, and 3A4 isoenzymes, and the metabolites are primarily excreted via the urine. *Voriconazole* displays nonlinear kinetics, which can be affected by drug interactions and pharmacogenetic variability, particularly CYP450 2C19 polymorphisms. High trough concentrations have been associated with visual and auditory hallucinations and an increased incidence of hepatotoxicity. *Voriconazole* is also an inhibitor of CYP2C19, 2C9, and 3A4 isoenzymes. Inhibitors and inducers of these isoenzymes may impact levels of *voriconazole*, leading to toxicity or clinical failure, respectively. In addition, drugs that are substrates of these isoenzymes are impacted by *voriconazole* (Figure 33.9). Because of significant interactions, use of *voriconazole* is contraindicated with many drugs (for example, *rifampin*, *rifabutin*, *carbamazepine*, and *St. John's wort*).

**Figure 33.9**

By inhibiting cytochrome P450, voriconazole can potentiate the toxicities of other drugs.

## H. Isavuconazole

*Isavuconazole* [eye-sa-voo-KON-a-zole] is a broad-spectrum antifungal agent which is supplied as the prodrug *isavuconazonium* in IV and oral dosage forms. *Isavuconazonium* is rapidly hydrolyzed by esterases in the blood to *isavuconazole*. *Isavuconazole* has a spectrum of activity similar to *voriconazole* and is approved for invasive aspergillosis and invasive mucormycosis. *Isavuconazonium* has high bioavailability after oral administration and distributes well into tissues. The drug is metabolized by CYP450 3A4/5 and uridine diphosphate-glucuronosyltransferases. Coadministration of *isavuconazole* with potent CYP450 3A4 inhibitors and inducers is contraindicated. *Isavuconazole* is also an inhibitor of the CYP450 3A4 isoenzyme, thereby increasing the concentrations of drugs that are substrates of CYP450 3A4. Nausea, vomiting, diarrhea, and hypokalemia are common adverse effects.

Figures 33.10 and 33.11 summarize the azole antifungal agents.

## I. Echinocandins

Echinocandins interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of  $\beta(1,3)$ -D-glucan, leading to lysis and cell death. *Caspofungin*, *micafungin*, and *anidulafungin* are available for IV administration once daily. *Micafungin* is the only echinocandin that does not require a loading dose. The echinocandins have potent activity against *Aspergillus* and most *Candida* species, including

	FLUCONAZOLE	ITRACONAZOLE	ISAVUCONAZOLE	VORICONAZOLE	POSACONAZOLE
Spectrum of activity	+	++	+++	+++	++++
Route(s) of administration	Oral, IV	Oral	Oral, IV	Oral, IV	Oral, IV
Oral bioavailability (%)	95	55 (solution)	98	96	Variable
Drug levels affected By food or gastric pH	No	Yes	No	No	Yes
Protein binding (%)	10	99	99	58	99
Primary route of elimination	Renal	Hepatic CYP3A4	Hepatic CYP3A4, UGT	Hepatic CYP2C19, 2C9, 3A4	Hepatic glucuronidation
Cytochrome P450 enzymes Inhibited	CYP3A4, 2C9, 2C19	CYP3A4, 2C9	CYP3A4	CYP2C19, 2C9, 3A4	CYP3A4
Half-life ( $t_{1/2}$ )	25 hours	30–40 hours	130 hours	Dose dependent	20–66 hours
CSF penetration	Yes	No	Yes	Yes	Yes
Renal excretion of active drug (%)	> 90	< 2	45	< 2	< 2
TDM recommended (Rationale)	No	Yes (efficacy)	Unknown (therapeutic levels not yet determined)	Yes (efficacy and safety)	Yes (efficacy)

CSF = cerebrospinal fluid; TDM = therapeutic drug monitoring.

**Figure 33.10**

Summary of triazole antifungals.

INTERACTING DRUG	AZOLE DRUG	EFFECT ON DRUG EXPOSURE	MAIN CLINICAL CONSEQUENCE OF INTERACTION
<i>Amiodarone, dronedarone, citalopram, pimozide, quinidine</i>	<i>Isavuconazole, itraconazole, fluconazole, voriconazole, posaconazole<sup>1</sup></i>	↑ Exposure to interacting drugs	QT interval prolongation with risk of torsades de pointes
<i>Carbamazepine</i>	<i>Isavuconazole, voriconazole</i>	↓ Exposure to voriconazole	Treatment failure of voriconazole
<i>Efavirenz</i>	<i>Isavuconazole, voriconazole</i>	↓ Exposure to voriconazole	Treatment failure of voriconazole
		↑ Exposure to efavirenz	Risk of efavirenz toxicity
<i>Ergot alkaloids</i>	<i>Isavuconazole, itraconazole, fluconazole, voriconazole, posaconazole<sup>1</sup></i>	↑ Exposure to ergot alkaloid	Ergotism
<i>Lovastatin, simvastatin</i>	<i>Itraconazole, voriconazole, posaconazole</i>	↑ Exposure to HMG-CoA reductase inhibitor	Risk of rhabdomyolysis
<i>Midazolam, triazolam</i>	<i>Isavuconazole, itraconazole, voriconazole, posaconazole</i>	↑ Exposure to benzodiazepine	Sleepiness
<i>Phenytoin</i>	<i>Isavuconazole, voriconazole, posaconazole</i>	↓ Exposure to voriconazole, posaconazole	Treatment failure
		↑ Exposure to phenytoin	Nystagmus, ataxia
<i>Rifabutin</i>	<i>Isavuconazole, voriconazole, posaconazole</i>	↓ Exposure to voriconazole	Treatment failure of voriconazole
		↑ Exposure to rifabutin	Uveitis
<i>Rifampicin (rifampin)</i>	<i>Isavuconazole, voriconazole, posaconazole</i>	↓ Exposure to voriconazole	Treatment failure of voriconazole
<i>High-dose ritonavir (400 mg twice daily)</i>	<i>Isavuconazole, voriconazole</i>	↓ Exposure to voriconazole	Treatment failure of voriconazole
<i>Vincristine, vinblastine</i>	<i>Isavuconazole, itraconazole, voriconazole, posaconazole</i>	↑ Exposure to vinca alkaloids	Neurotoxicity
<i>Sirolimus</i>	<i>Isavuconazole, voriconazole, posaconazole</i>	↑ Exposure to sirolimus	Risk of sirolimus toxicity

<sup>1</sup>Where an interaction has been reported for one triazole, the contraindication has been extended to all others.

**Figure 33.11**

Major or life-threatening drug interactions of azole drugs. ↑ indicates increased; ↓ indicates decreased.

those species resistant to azoles. However, they have minimal activity against other fungi. The most common adverse effects are fever, rash, nausea, and phlebitis at the infusion site. They should be administered via a slow IV infusion, as they can cause a histamine-like reaction (flushing) when infused rapidly.

- 1. Caspofungin:** *Caspofungin* [kas-poh-FUN-jin] is a first-line option for patients with invasive candidiasis, including candidemia, and a second-line option for invasive aspergillosis in patients who have failed or cannot tolerate *amphotericin B* or an azole. The dose of *caspofungin* should be adjusted with moderate hepatic dysfunction. Concomitant administration of *caspofungin* with CYP450

enzyme inducers (for example, *rifampin*) may require an increase in *caspofungin* dose. *Caspofungin* should not be coadministered with *cyclosporine* due to a high incidence of elevated hepatic transaminases with concurrent use.

- Micafungin and anidulafungin:** *Micafungin* [mi-ka-FUN-jin] and *anidulafungin* [ay-nid-yoo-la-FUN-jin] are first-line options for the treatment of invasive candidiasis, including candidemia. *Micafungin* is also indicated for the prophylaxis of invasive *Candida* infections in patients who are undergoing hematopoietic stem cell transplantation. These agents are not substrates for CYP450 enzymes and do not have any associated drug interactions.

### III. DRUGS FOR CUTANEOUS MYCOTIC INFECTIONS

Mold-like fungi that cause cutaneous infections are called dermatophytes or tinea. Tinea infections are classified by the affected site (for example, *tinea pedis*, which refers to an infection of the feet). Common dermatomycoses, such as tinea infections that appear as rings or round red patches with clear centers, are often referred to as “ringworm.” This is a misnomer because fungi rather than worms cause the disease. The three different fungi that cause the majority of cutaneous infections are *Trichophyton*, *Microsporum*, and *Epidermophyton*. The drugs used in the treatment of cutaneous mycoses are listed in [Figure 33.1](#).

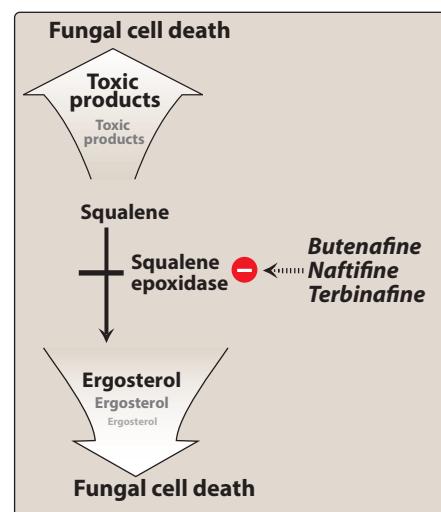
#### A. Squalene epoxidase inhibitors

These agents act by inhibiting squalene epoxidase, thereby blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane ([Figure 33.12](#)). Accumulation of toxic amounts of squalene results in increased membrane permeability and death of the fungal cell.

- Terbinafine:** Oral *terbinafine* [TER-bin-a-feen] is the drug of choice for treating dermatophyte onychomycoses (fungal infections of nails). It is better tolerated, requires a shorter duration of therapy, and is more effective than either *itraconazole* or *griseofulvin* for *Trichophyton*. Therapy is prolonged (usually about 3 months) but considerably shorter than that with *griseofulvin*. Oral *terbinafine* may also be used for *tinea capitis* (infection of the scalp). [Note: Oral antifungal therapy (*griseofulvin*, *terbinafine*, *itraconazole*) is needed for *tinea capitis*. Topical antifungals are ineffective.] Topical *terbinafine* (1% cream, gel or solution) is used to treat *tinea pedis*, *tinea corporis* (ringworm), *tinea cruris* (infection of the groin), and *tinea versicolor* due to *Malessezia furfur*. The duration of treatment is usually 1 week.

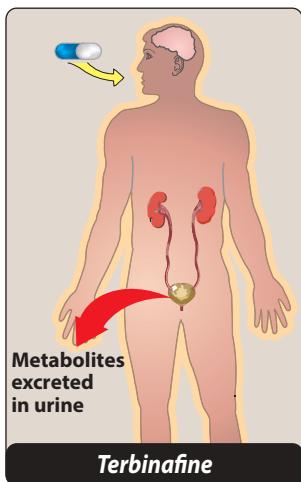
- Antifungal spectrum:** *Terbinafine* is active against *Trichophyton*. It may also be effective against *Candida*, *Epidermophyton*, and *Scopulariopsis*, but the efficacy in treating clinical infections due to these pathogens has not been established.

- Pharmacokinetics:** *Terbinafine* is available for oral and topical administration. The bioavailability after oral administration



**Figure 33.12**

Mode of action of squalene epoxidase inhibitors.



**Figure 33.13**

Administration and fate of *terbinafine*.

is only 40% due to first-pass metabolism. *Terbinafine* is highly protein bound and is deposited in the skin, nails, and adipose tissue. A prolonged terminal half-life of 200 to 400 hours may reflect the slow release from these tissues. Oral *terbinafine* is extensively metabolized by several CYP450 isoenzymes and is excreted mainly via the urine (Figure 33.13). The drug should be avoided in patients with moderate-to-severe renal impairment or hepatic dysfunction. *Terbinafine* is an inhibitor of the CYP450 2D6 isoenzyme, and concomitant use with substrates of CYP450 2D6 may result in an increased risk of adverse effects with those agents.

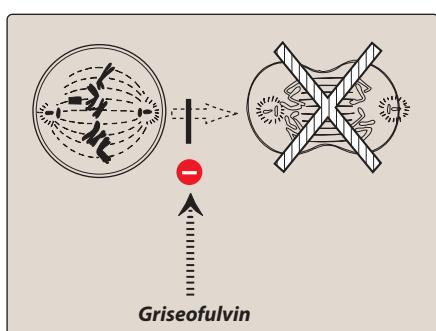
- c. **Adverse effects:** Common adverse effects include diarrhea, dyspepsia, nausea, headache, and rash. Taste and visual disturbances have been reported, as well as elevations in serum hepatic transaminases.
- 2. **Naftifine:** *Naftifine* [NAF-ti-feen] is active against *Trichophyton*, *Microsporum*, and *Epidermophyton*. *Naftifine* cream and gel are used for the topical treatment of tinea corporis, tinea cruris, and tinea pedis. The duration of treatment is usually 2 to 4 weeks.
- 3. **Butenafine:** *Butenafine* [byoo-TEN-a-feen] is active against *Trichophyton rubrum*, *Epidermophyton*, and *Malassezia*. Like *naftifine*, *butenafine* cream is used for topical treatment of tinea infections.

## B. Griseofulvin

*Griseofulvin* [gris-ee-oh-FUL-vin] causes disruption of the mitotic spindle and inhibition of fungal mitosis (Figure 33.14). It has been largely replaced by oral *terbinafine* for the treatment of onychomycosis, although it is still used for dermatophytosis of the scalp and hair. *Griseofulvin* is fungistatic and requires a long duration of treatment (for example, 6 to 12 months for onychomycosis). The duration of therapy is dependent on the rate of replacement of healthy skin and nails. Ultrafine crystalline preparations are absorbed adequately from the gastrointestinal tract, and absorption is enhanced by high-fat meals. The drug concentrates in skin, hair, nails, and adipose tissue. *Griseofulvin* induces hepatic CYP450 activity, which increases the rate of metabolism of a number of drugs, including anticoagulants. The use of *griseofulvin* is contraindicated in pregnancy and patients with porphyria.

## C. Nystatin

*Nystatin* [nye-STAT-in] is a polyene antifungal, and its structure, chemistry, mechanism of action, and resistance profile resemble those of *amphotericin B*. It is used for the treatment of cutaneous and oral *Candida* infections. The drug is negligibly absorbed from the gastrointestinal tract, and it is not used parenterally due to systemic toxicity (acute infusion-related adverse effects and nephrotoxicity). It is administered as an oral agent (“swish and swallow” or “swish and spit”) for the treatment of oropharyngeal candidiasis (thrush), intravaginally for vulvovaginal candidiasis, or topically for cutaneous candidiasis.



**Figure 33.14**

Inhibition of mitosis by *griseofulvin*.

#### D. Imidazoles

Imidazoles are azole derivatives, which currently include *butoconazole* [byoo-toe-KON-a-zole], *clotrimazole* [kloe-TRIM-a-zole], *econazole* [e-KONE-a-zole], *ketoconazole* [kee-toe-KON-a-zole], *miconazole* [my-KON-a-zole], *oxiconazole* [oks-i-KON-a-zole], *sertaconazole* [ser-ta-KOE-na-zole], *sulconazole* [sul-KON-a-zole], *terconazole* [ter-KON-a-zole], and *tioconazole* [tye-oh-KONE-a-zole]. As a class of topical agents, they have a wide range of activity against *Epidermophyton*, *Microsporum*, *Trichophyton*, *Candida*, and *Malassezia*, depending on the agent. The topical imidazoles have a variety of uses, including tinea corporis, tinea cruris, tinea pedis, and oropharyngeal and vulvovaginal candidiasis. Topical use is associated with contact dermatitis, vulvar irritation, and edema. *Clotrimazole* is also available as a troche (lozenge), and *miconazole* is available as a buccal tablet for the treatment of thrush. Oral *ketoconazole* is rarely used today due to the risk of severe liver injury, adrenal insufficiency, and adverse drug interactions.

#### E. Efinaconazole

*Efinaconazole* [eff-in-a-CON-a-zole] is a topical triazole antifungal agent approved for the treatment of toenail onychomycosis caused by *Trichophyton rubrum* and *Trichophyton mentagrophytes*. The duration of treatment is 48 weeks. It has also shown activity against *Candida albicans*.

#### F. Ciclopirox

*Ciclopirox* [sye-kloe-PEER-oks], a pyridine antimycotic, inhibits the transport of essential elements in the fungal cell, disrupting the synthesis of DNA, RNA, and proteins. *Ciclopirox* is active against *Trichophyton*, *Epidermophyton*, *Microsporum*, *Candida*, and *Malassezia*. It is available in a number of formulations. *Ciclopirox* shampoo is used for the treatment of seborrheic dermatitis. Tinea pedis, tinea corporis, tinea cruris, cutaneous candidiasis, and tinea versicolor may be treated with the cream, gel, or suspension. Onychomycosis can be treated with the nail lacquer formulation.

#### G. Tavaborole

*Tavaborole* [tav-a-BOOR-ole] inhibits an aminoacyl-transfer ribonucleic acid synthetase, preventing fungal protein synthesis. *Tavaborole* is active against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Candida albicans*. A topical solution is approved for the topical treatment of toenail onychomycosis, requiring 48 weeks of treatment.

#### H. Tolnaftate

*Tolnaftate* [tole-NAF-tate], a topical thiocarbamate, distorts the hyphae and stunts mycelial growth in susceptible fungi. *Tolnaftate* is active against *Epidermophyton*, *Microsporum*, and *Malassezia furfur*. [Note: *Tolnaftate* is not effective against *Candida*.] *Tolnaftate* is used to treat tinea pedis, tinea cruris, and tinea corporis. It is available as a solution, cream, and powder.

## IV. MISCELLANEOUS AGENTS MEANT FOR TOPICAL USE IN FUNGAL INFECTIONS

### A. Natamycin (pimiricin)

*Natamycin* is a polyene amphoteric macrolide having a mechanism similar to that of amphotericin B with wide-spectrum antifungal properties. It is a poorly water-soluble compound used as a 5% suspension for topical use in eye. Upon ocular instillation, *natamycin* is retained in the conjunctival fornices and reaches effective concentrations in cornea for its antimycotic property.

### B. Hamycin

*Hamyacin* is an antifungal agent similar to nystatin but relatively more water soluble. It is developed for topical application for oral thrush, cutaneous candidiasis, trichomonas vaginitis, etc.

### C. Ciclopirox olamine

*Ciclopirox olamine* is a broad-spectrum antifungal agent which also shows anti-inflammatory and antibacterial activity. It is reported to penetrate the skin to the level of dermis, hair follicles, and sebaceous glands. The lotion and cream formulations of *ciclopirox* are effective in many types of infection, including tinea corporis/cruris, tinea pedis, tinea mentagrophytes, tinea rubrum, cutaneous candidiasis, pityriasis (tinea) versicolor, and seborrheic dermatitis and in infections caused by *Epidermophyton floccosum* and *Microsporum canis*. It is used as a topical formulation (0.77% cream) for the treatment of seborrheic dermatitis of the scalp, interdigital tinea pedis, and tinea corporis. It is used as 8% nail lacquer for onychomycosis. It has been reported to have high cure rates up to 90% for dermatomycoses and candidal infections, and no significant topical toxicity has been reported.

### D. Undecylenic acid

Undecylenic acid is a semisynthetic fatty acid isolated from ricinoleic acid of castor oil by pyrolysis. It is a yellow-colored liquid with a typical rancid odor. It is fungistatic and upon usage for longer duration at higher concentration, it becomes fungicidal. It is used along with zinc for the treatment of dermatomycoses caused due to tinea pedis, tinea cruris, and *Candida*. Some clinical studies show that topical undecylenic acid is equivalent to topical *tolnaftate* in the treatment of cutaneous fungal infections. It has also been reported to be effective against tinea pedis when used as a topical dusting powder. However, its efficacy is lower than that of *imidazole* and *tolnaftate*. Undecylenic acid is commonly used for the treatment of diaper rash, tinea cruris, and other milder forms of fungal infections.

### E. Benzoic acid

Benzoic acid is one of the old remedies for topical antifungal therapy. The combination of benzoic acid with salicylic acid (in the ratio of 2:1) is called Whitfield's ointment. This combination associates fungistatic

activity of benzoic acid with keratolytic activity of salicylic acid that causes the infected stratum corneum to shed. It is used for treating tinea pedis and tinea capitis; a prolonged treatment is required to get the desired result. It causes mild irritation upon application.

#### F. Quiniodochlor

*Quiniodochlor* is an antiamoebic compound used by the oral route. It has also been reported to exhibit antifungal and antibacterial activity on topical application. It has been used for treating dermatophytosis seborrhoeic dermatitis, pityriasis versicolor, mycosis barbae, athlete's foot, impetigo, infected eczema, and furunculosis. It is used as vaginal creams for the treatment of monilial and *trichomonas vaginitis*. Upon topical application (3% to 8%), it can cause itching, redness, peeling, dryness, swelling, and irritation of the skin.

#### G. Sodium thiosulfate

Sodium thiosulfate is used topically as a solution at a concentrations of 20% to 25% for the treatment of pityriasis (tinea) versicolor. It takes 3 to 4 weeks to exhibit its effectiveness but repigmentation of skin will take a longer time. It is a weak fungistatic agent which is also used for treating Malassezia furfur infection. Its application is safe during pregnancy. It is generally well tolerated but occasionally it can cause mild irritation.

### Study Questions

Choose the ONE best answer.

33.1 Which antifungal agent is MOST likely to cause renal insufficiency?

- A. Fluconazole
- B. Amphotericin B
- C. Itraconazole
- D. Posaconazole

Correct answer = B. Amphotericin B is the best choice since nephrotoxicity is commonly associated with this medication. Although the dose of fluconazole must be adjusted for renal insufficiency, it is not associated with causing nephrotoxicity. Itraconazole and posaconazole are metabolized by the liver and are not associated with nephrotoxicity.

33.2 A 55-year-old woman presents to the hospital with shortness of breath, fever, and malaise. She has a history of breast cancer and is receiving chemotherapy. Her chest x-ray shows pneumonia, and respiratory cultures are positive for *Aspergillus fumigatus*. Which is the MOST appropriate choice for treatment?

- A. Voriconazole
- B. Fluconazole
- C. Flucytosine
- D. Ketoconazole

Correct answer = A. Voriconazole is the drug of choice for aspergillosis. Studies have found it to be superior to other regimens including amphotericin B. Fluconazole, flucytosine, and ketoconazole do not have reliable *in vitro* activity and are therefore not recommended.

33.3 Which antifungal agent should be avoided in patients with evidence of ventricular dysfunction?

- A. Micafungin
- B. Itraconazole
- C. Terbinafine
- D. Posaconazole

Correct answer = B. There is a black box warning that warns against the use of itraconazole in patients with evidence of ventricular dysfunction, including patients with heart failure.

33.4 A 56-year-old woman with diabetes complains of thickening of the nail of the right big toe and a change in color (yellow). The podiatrist diagnoses the patient with onychomycosis of the toenails. Which is the most appropriate choice for treating this infection?

- A. Terbinafine
- B. Micafungin
- C. Itraconazole
- D. Griseofulvin

Correct answer = A. Terbinafine is better tolerated, requires a shorter duration of therapy, and is more effective than either itraconazole or griseofulvin. Micafungin is not active for this type of infection.

33.5 A 44-year-old man presents to clinic with fevers and chills, headaches, and shortness of breath. He reports that he was exploring caves about 5 weeks ago. He is diagnosed with mild/moderate acute pulmonary histoplasmosis. Which is the most appropriate choice for treating this infection?

- A. Micafungin
- B. Itraconazole
- C. Terbinafine
- D. Griseofulvin

Correct answer = B. Itraconazole is the treatment of choice in patients with mild/moderate acute pulmonary histoplasmosis who have had symptoms for more than 1 month. Micafungin, terbinafine, and griseofulvin are not active for this type of infection.

33.6 A 32-year-old HIV-positive woman is admitted to the hospital with severe confusion and dizziness. She has been nonadherent with her HIV medications for several months. She is diagnosed with meningitis caused by Cryptococcus neoformans. Which is the most appropriate choice for treating the infection in this patient?

- A. Anidulafungin alone
- B. Amphotericin B plus flucytosine
- C. Flucytosine alone
- D. Isavuconazole plus anidulafungin

Correct answer = B. The treatment of choice for initial therapy for cryptococcal meningitis is the combination of amphotericin B and flucytosine. Flucytosine should not be given alone because of the rapid development of resistance. Anidulafungin is not active against this type of infection. Isavuconazole has not been studied for the treatment of cryptococcal meningitis.

33.7 A 22-year-old woman reports a cottage cheese-like vaginal discharge and slight dysuria for 1 week. The patient is diagnosed with vulvovaginal candidiasis. She requests as short a course of treatment as possible due to her busy schedule. Which antifungal is the best choice?

- A. Oral fluconazole
- B. Topical miconazole
- C. Oral terbinafine
- D. Topical efinaconazole

Correct answer = A. Oral fluconazole can be given as a one-time dose for vulvovaginal candidiasis. Topical miconazole requires multiple days of therapy. Terbinafine and efinaconazole are not used clinically for vulvovaginal candidiasis.

33.8 Which drug is relatively free of drug–drug interactions?

- A. Voriconazole
- B. Itraconazole
- C. Micafungin
- D. Terbinafine

Correct answer = C. The echinocandins (including micafungin) are not metabolized by the CYP450 enzyme system, so they have very few drug–drug interactions. Voriconazole, itraconazole, and terbinafine are all metabolized by the CYP450 enzyme system, so they have significant drug–drug interactions.

33.9 Which drug works by creating pores/channels in the fungal cell membrane?

- A. Fluconazole
- B. Anidulafungin
- C. Amphotericin B
- D. Flucytosine

Correct answer = C. Amphotericin B creates pores/channels in the fungal cell membrane. Fluconazole works by inhibiting the conversion of lanosterol to ergosterol. Anidulafungin inhibits the synthesis of  $\beta$ -d-glucan. Flucytosine disrupts nucleic acid and protein synthesis.

33.10 Which drug requires a loading dose?

- A. Caspofungin
- B. Micafungin
- C. Liposomal amphotericin B
- D. Tavaborole

Correct answer = A. Caspofungin is the only drug listed that requires a loading dose before starting the maintenance dosing.



# Antiviral Drugs

Elizabeth Sherman

# 34

## I. OVERVIEW

Viruses are obligate intracellular parasites. They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes. Viruses use much of the metabolic machinery of the host, and few drugs are selective enough to prevent viral replication without injury to the infected host cells. Therapy for viral diseases is further complicated by the fact that clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated. At this stage of viral infection, administration of drugs that block viral replication has limited effectiveness in many cases. However, a few virus groups respond to available antiviral drugs, and some antiviral agents are useful as prophylactic agents. These agents are discussed in this chapter. To assist in the review of these drugs, they are grouped according to the type of viral infection they target (Figure 34.1).

## II. TREATMENT OF RESPIRATORY VIRAL INFECTIONS

Viral respiratory tract infections for which treatments exist include influenza A and B and respiratory syncytial virus (RSV). [Note: Immunization against influenza is the preferred approach. However, antiviral agents are used when patients are allergic to the vaccine or outbreaks occur.]

### A. Neuraminidase inhibitors

The neuraminidase inhibitors *oseltamivir* [os-el-TAM-i-veer] and *zamivir* [za-NA-mi-veer] are effective against both type A and type B influenza viruses. They do not interfere with the immune response to influenza vaccine. Administered prior to exposure, neuraminidase inhibitors prevent infection and, when administered within 24 to 48 hours after the onset of symptoms, they modestly decrease the intensity and duration of symptoms.

- Mechanism of action:** Influenza viruses employ a specific neuraminidase that is inserted into the host cell membrane for the purpose of releasing newly formed virions. This enzyme is essential for the virus life cycle. *Oseltamivir* and *Zanamivir* selectively inhibit neuraminidase, thereby preventing the release of new virions and their spread from cell to cell.
- Pharmacokinetics:** *Oseltamivir* is an orally active prodrug that is rapidly hydrolyzed by the liver to its active form. *Zanamivir* is not active orally and is administered via inhalation. Both drugs are eliminated unchanged in the urine (Figure 34.2). It is available as

### FOR RESPIRATORY VIRUS INFECTIONS

*Amantadine*  
*Oseltamivir*  
*Ribavirin*  
*Rimantadine*  
*Zanamivir*

### FOR HEPATIC VIRAL INFECTIONS: HEPATITIS B

*Adefovir*  
*Entecavir*  
*Lamivudine*  
*Peginterferon α-2a*  
*Tenofovir alafenamide (TAF)*  
*Tenofovir disoproxil fumarate (TDF)*

### FOR HEPATIC VIRAL INFECTIONS: HEPATITIS C

*Daclatasvir*  
*Elbasvir/grazoprevir*  
*Glecaprevir/pibrentasvir*  
*Ledipasvir/sofosbuvir*  
*Paritaprevir/ritonavir/ombitasvir*  
*Paritaprevir/ritonavir/ombitasvir + dasabuvir*  
*Ribavirin*  
*Simeprevir*  
*Sofosbuvir*  
*Sofosbuvir/velpatasvir*  
*Sofosbuvir/velpatasvir/voxilaprevir*

### FOR HERPESVIRUS AND CYTOMEGALOVIRUS INFECTIONS

*Acyclovir*  
*Valacyclovir*  
*Valganciclovir*  
*Ganciclovir*  
*Penciclovir*  
*Cidofovir*  
*Famciclovir*  
*Foscarnet*  
*Trifluridine*

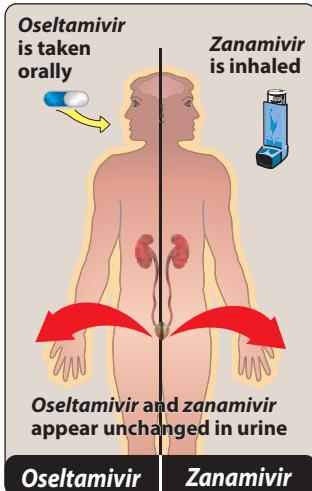
Figure 34.1

Summary of antiviral drugs.  
HIV = human immunodeficiency virus.  
(Figure continues on next page)

FOR HIV: NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS
Zidovudine (AZT, ZDV)
Abacavir (ABC)
Didanosine (DDI)
Stavudine (d4T)
Emtricitabine (FTC)
Lamivudine (3TC)
Tenofovir (TAF and TDF)
Zalcitabine (ddC)
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
Efaviranz (EFV)
Nevirapine (NVP)
Delavirdine (DLV)
PROTEASE INHIBITORS
Atazanavir (ATV)
Fosamprenavir (FPV)
*Ritonavir (RTV)
Lopinavir (LPV)
Sequinavir (SQV)
Tipranavir (TPV)
INTEGRASE STRAND TRANSFER INHIBITOR
Raltegravir (RAL)
FUSION AND ENTRY INHIBITOR
Enfluvirtide (T 20)
Maraviroc (MVC)

**Figure 34.1** (Continued)

Summary of antiviral drugs. HIV = human immunodeficiency virus. \*Part of a fixed-dose combination. (For drug dosages, refer to Appendix at the end of the book.)



**Figure 34.2**

Administration and fate of oseltamivir and zanamivir.

75 mg capsules or 12 mg and 6 mg oral suspension. For adults, 75 mg OD is the prophylactic dose and therapeutic dose is 75 mg twice daily for 5 days.

3. **Adverse effects:** The most common adverse effects of oseltamivir are gastrointestinal (GI) discomfort and nausea, which can be alleviated by taking the drug with food. Irritation of the respiratory tract occurs with zanamivir. It should be used with caution in individuals with asthma or chronic obstructive pulmonary disease, because bronchospasm may occur.
4. **Resistance:** Mutations of the neuraminidase enzyme have been identified in adults treated with either of the neuraminidase inhibitors. These mutants, however, are often less infective and virulent than the wild type.

## B. Adamantane antivirals

1. **Amantadine and rimantadine:** The therapeutic spectrum of the adamantane derivatives, *amantadine* [a-MAN-ta-deen] and *rimantadine* [ri-MAN-ta-deen], is limited to influenza A infections. *Amantadine* is a unique tricyclic amine which is known to inhibit the replication of influenza A viruses. M2 protein of influenza A virus is a proton channel spanning the viral envelope. This proton channel is required for uncoating of viral particles. By binding to the M2 proton channel, *poreamantadine* inhibits the step of uncoating of virus which is an early step in viral replication. *Rimantadine* is an  $\alpha$ -methyl derivative of *amantadine* having 4 to 10 times more activity and a similar mechanism of action. Due to widespread resistance, the adamantanes are not widely recommended in few countries in the world for the treatment or prophylaxis of influenza A. *Amantadine* is administered orally and excreted unchanged in urine over 2 to 3 days. The reported side effects are minor GI related and dose related. Nervousness, lightheadedness, concentration difficulties, insomnia, and loss of appetite are also reported but they are much less reported with *rimantadine*. Seasonal prophylaxis a total dose of 200 mg/day is used as a single or divided dose. For the treatment of influenza, it is used at a dose of 200 mg/day for 5 days. For the prevention in nosocomial influenza, 100 mg/day is administered. *Amantadines* are effective if used within 2 days of H1N1 infection. All H3N3 strains of influenzae around the world are resistant to *amantadines*. Resistance develops in virus by mutation in the RNA sequence encoding M2 protein transmembrane domain, and it happens 2 to 3 days of the initiation of treatment. *Amantadine* has also been used in Parkinson's disease as it shows a mild anti-Parkinson activity.

## C. Ribavirin

*Ribavirin* [rye-ba-VYE-rin], a synthetic guanosine analog, is effective against a broad spectrum of RNA and DNA viruses. For example, *ribavirin* is used in the treatment of immunosuppressed infants and young children with severe RSV infections. *Ribavirin* is also effective in chronic hepatitis C infections when used in combination with other direct-acting antivirals.

- Mechanism of action:** *Ribavirin* inhibits replication of RNA and DNA viruses. The drug is first phosphorylated to the 5'-phosphate derivatives. The major product ribavirin triphosphate exerts its antiviral action by inhibiting guanosine triphosphate formation, preventing viral messenger RNA (mRNA) capping, and blocking RNA-dependent RNA polymerase.
- Pharmacokinetics:** *Ribavirin* is effective orally and by inhalation. An aerosol is used in the treatment of RSV infection. Absorption is increased if the oral drug is taken with a fatty meal. A steady state can be achieved in 4 weeks of treatment. The drug and its metabolites are eliminated in urine (Figure 34.3). In renal insufficiency, *ribavirin* has to be used cautiously. It is used at a dose of 500 mg, or 600 mg (for >75 kg) is given as twice daily over a period of 6 to 12 months depending upon the necessity (based on virology parameters).
- Adverse effects:** Adverse effects of *ribavirin* include dose-dependent transient anemia. Elevated bilirubin has also been reported. The aerosol may be safer, although respiratory function in infants can deteriorate quickly after initiation of aerosol treatment. Therefore, monitoring is essential. *Ribavirin* is contraindicated in pregnancy (Figure 34.4).

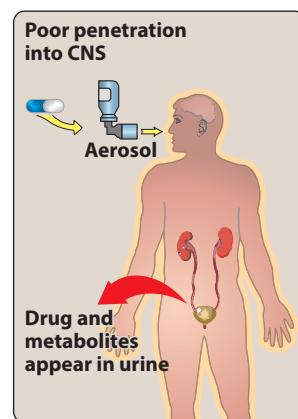
### III. TREATMENT OF HEPATIC VIRAL INFECTIONS

Each of the hepatitis viruses currently identified (A, B, C, D, and E) has a pathogenesis which specifically involves replication in and destruction of hepatocytes. Of this group, hepatitis B (a DNA virus) and hepatitis C (an RNA virus) are the most common causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (Figure 34.5) and are the only hepatic viral infections for which therapy is currently available. [Note: Hepatitis A is a commonly encountered infection caused by oral ingestion of the virus, but it is not a chronic disease.] Chronic hepatitis B may be treated with *peginterferon-α-2a* [peg-in-ter-FEER-on AL-fa], which is injected subcutaneously once weekly. Oral therapy for chronic hepatitis B virus (HBV) includes *lamivudine* [la-MIV-yoo-deen], *adefovir* [a-DEF-o-veer], *entecavir* [en-TEK-a-vir], and *tenofovir* [ten-OH-vir] (see Section VIII for *tenofovir*). The preferred treatment for chronic hepatitis C virus (HCV) is a combination of direct-acting antivirals (DAAs), the selection of which is based on the hepatitis C genotype. In certain cases, *ribavirin* is added to a DAA regimen to enhance virologic response. With the introduction of new DAAs, *pegylated interferon α* is no longer commonly used in HCV, and it is not recommended in current guidelines due to inferior efficacy and poor tolerability.

### IV. TREATMENT OF HEPATITIS B

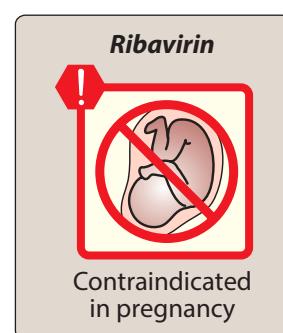
#### A. Interferons

Interferons are a family of naturally occurring, inducible glycoproteins that interfere with the ability of viruses to infect cells. The interferons are synthesized by recombinant DNA technology. At least three types of interferons exist— $\alpha$ ,  $\beta$ , and  $\gamma$  (Figure 34.6). In “pegylated” formulations, bis-monomethoxy polyethylene glycol has been covalently attached to *interferon α* to increase the size of the molecule.



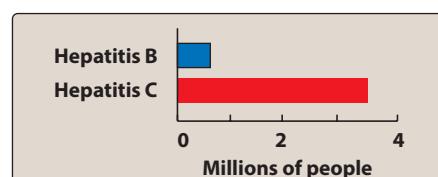
**Figure 34.3**

Administration and fate of *ribavirin*.



**Figure 34.4**

*Ribavirin* causes teratogenic effects.



**Figure 34.5**

The prevalence of chronic hepatitis B and C in the United States. Data from Surveillance for Viral Hepatitis – United States 2015; [https://www.cdc.gov/hepatitis/statistics/2015\\_surveillance/commentary.htm](https://www.cdc.gov/hepatitis/statistics/2015_surveillance/commentary.htm)

<i>Interferon-α</i>	<i>Interferon-β</i>	<i>Interferon-γ</i>
Chronic hepatitis B and C	Relapsing-remitting multiple sclerosis	Chronic granulomatous disease
Genital warts caused by papilloma-virus		
Leukemia, hairy-cell		
Leukemia, chronic myelogenous		
Kaposi sarcoma		

**Figure 34.6**

Some approved indications for *interferon*.

The larger molecular size delays absorption from the injection site, lengthens the duration of action of the drug, and also decreases its clearance.

- Mechanism of action:** The antiviral mechanism is incompletely understood. It appears to involve the induction of host cell enzymes through the activation of JAK-STAT tyrosine protein kinase receptors causing the inhibition of viral RNA translation, ultimately leading to the degradation of viral mRNA and tRNA.
- Therapeutic uses:** *Peginterferon α-2a* is approved for the treatment of chronic HBV infection. It is also indicated for the treatment of HCV in combination with other agents, although its use is uncommon due to availability of more effective agents. For chronic hepatitis B infection, it is *interferon α-2a* that is administered at a dose of 5 to 10 MU (INF 2β = 5 to 10 MU) three times a week for 4 to 6 months depending upon virologic parameters.
- Adverse effects:** These include flu-like symptoms, such as fever, chills, myalgias, arthralgias, and GI disturbances. Fatigue and mental depression are common. The principal dose-limiting toxicities are bone marrow suppression, severe fatigue and weight loss, neurotoxicity characterized by somnolence and behavioral disturbances, autoimmune disorders such as thyroiditis, and, rarely, cardiovascular problems such as heart failure.

## B. Lamivudine

This cytosine analog is an inhibitor of both hepatitis B virus (HBV) and human immunodeficiency virus (HIV) reverse transcriptases (RTs). *Lamivudine* must be phosphorylated by host cellular enzymes to the triphosphate (active) form. This compound competitively inhibits HBV RNA-dependent DNA polymerase. As with many nucleotide analogs, the intracellular half-life of the triphosphate is many hours longer than its plasma half-life. The rate of HBV resistance is high following long-term therapy with *lamivudine* and, therefore, *lamivudine* is no longer recommended in current hepatitis B guidelines. For chronic HBV, it is used at a dose of 100 mg once daily till hepatic and virological parameters improve.

## C. Adefovir

*Adefovir* is a nucleotide analog that is phosphorylated by cellular kinases to adefovir diphosphate, which is then incorporated into viral DNA. This leads to termination of chain elongation and prevents replication of HBV. *Adefovir* is administered once daily and is renally excreted via glomerular filtration and tubular secretion. As with other agents, discontinuation of *adefovir* may result in severe exacerbation of hepatitis. Nephrotoxicity may occur with chronic use, and the drug should be used cautiously in patients with existing renal dysfunction. *Adefovir* is no longer recommended in current hepatitis B guidelines due to lower efficacy compared to other agents. *Adefovir* is used at an oral dose of 10 mg once daily.

#### D. Entecavir

*Entecavir* is a guanosine nucleoside analog for the treatment of HBV infection. Following intracellular phosphorylation to the triphosphate, it competes with the natural substrate, deoxyguanosine triphosphate, for viral RT. *Entecavir* is effective against *lamivudine*-resistant strains of HBV and is dosed once daily. The drug is primarily excreted unchanged in the urine and dosage adjustments are needed in renal dysfunction. Concomitant use of drugs with renal toxicity should be avoided.

### V. TREATMENT OF HEPATITIS C

Hepatitis C virus (HCV) enters the hepatocyte following interaction with cellular entry factors. Once inside the cell, a viral genome is released from the nucleocapsid and an HCV polyprotein is translated using the internal ribosome entry site. The polyprotein is then cleaved by cellular and viral proteases to yield structural and nonstructural proteins. The core NS3 and NS5A proteins form the replication complex on lipid droplets and serve as a scaffold for RNA polymerase to replicate the viral genome, which is then packaged in envelope glycoproteins before noncytolytic secretion of mature virions. Several direct-acting antiviral agents targeting the NS3/NS4A protease, NS5B polymerase, and NS5A involved in HCV replication and assembly are available.

Combination therapy with DAAs is necessary to optimize HCV treatment response rates. Current combinations employ multiple DAAs that target different stages of the HCV life cycle simultaneously (Figure 34.7). With combination therapy, the agents are collectively able to suppress both wild-type and drug-resistant viral populations. Certain combinations may have different efficacy based on the genotype of HCV. It is anticipated that additional agents will be available in the near future. For a summary of current guidelines and regimens recommended in specific scenarios, see [www.hcvguidelines.org](http://www.hcvguidelines.org).

#### A. NS3/NS4A protease inhibitors

The viral NS3/NS4A serine protease is crucial for processing the single polyprotein encoded by HCV RNA into individually active proteins, NS4A, NS4B, NS5A, and NS5B. Without these serine proteins, RNA replication does not occur and the HCV life cycle is effectively

GENERIC NAME(S)	BRAND NAME(S)	APPROVED HCV GENOTYPES
Elbasvir/grazoprevir	Zepatier	1, 4
Glecaprevir/pibrentasvir	Mavyret	1, 2, 3, 4, 5, 6
Paritaprevir/ritonavir/ombitasvir	Technivie	4
Paritaprevir/ritonavir/ombitasvir + dasabuvir	Viekira Pak, Viekira XR	1
Sofosbuvir + daclatasvir	Sovaldi + Daklinza	1, 3
Sofosbuvir/ledipasvir	Harvoni	1, 4, 5, 6
Sofosbuvir + simeprevir	Sovaldi + Olysio	1
Sofosbuvir/velpatasvir	Epclusa	1, 2, 3, 4, 5, 6
Sofosbuvir/velpatasvir/voxilaprevir	Vosevi	1, 2, 3, 4, 5, 6

**Figure 34.7**

Combinations of direct-acting antiviral agents for treatment of hepatitis C virus. HCV = hepatitis C virus.

disrupted. *Simeprevir* [sim-E-pre-vir], *paritaprevir* [PAR-i-TAP-re-vir] (which requires *ritonavir* [rit-OH-na-vir] boosting), *grazoprevir* [graz-OH-pre-vir], *voxilaprevir* [VOX-i-LA-pre-vir], and *glecaprevir* [glec-A-pre-vir] are DAAs that inhibit the NS3/NS4A serine protease as their primary mechanism of action. [Note: HCV protease inhibitors often have the ending “-previr.”] These drugs have a lower barrier to resistance than other agents, such as *sofosbuvir*. Use of HCV protease inhibitors presents significant potential for drug–drug interactions due to their metabolism by CYP3A enzymes. Adverse effects of NS3/NS4A protease inhibitors include rash, pruritus, nausea, fatigue, and anemia.

### B. NS5B polymerase inhibitors

NS5B is the sole RNA polymerase responsible for HCV replication and is processed with other HCV proteins into an individual polypeptide by the viral NS3/NS4A serine protease. There are two types of NS5B RNA polymerase inhibitors: 1) nucleoside/nucleotide analogs that compete for the enzyme active site and 2) non-nucleoside analogs that target allosteric sites. *Sofosbuvir* [soe-FOS-bue-vir] is currently the only NS5B nucleotide polymerase inhibitor for the treatment of HCV infection, and *dasabuvir* [da-SAB-ue-vir] is the only non-nucleoside analog. [Note: NS5B inhibitors often end in “-buvir.”] NS5B polymerase inhibitors are well tolerated with few adverse effects.

### C. NS5A replication complex inhibitors

NS5A is a viral protein that is essential for HCV RNA replication and assembly. Its role in replication appears to be the formation of a membranous web along with viral protein NS4B, and this web provides a platform for replication. The currently available NS5A inhibitors include *ledipasvir* [le-DIP-as-vir], *ombitasvir* [om-BIT-as-vir], *elbasvir* [ELB-as-vir], *velpatasvir* [vel-PAT-as-vir], *pibrentasvir* [pi-BRENT-as-vir], and *daclatasvir* [dak-LAT-as-vir]. [Note: NS5A inhibitors often end in “-asvir.”] With the exception of *daclatasvir*, these agents are all coformulated with other direct-acting antivirals (Figure 34.7). NS5A inhibitors have a number of clinically significant drug interactions due to their metabolism by hepatic CYP450 isoenzymes and inhibition of P-glycoprotein (P-gp). For example, *daclatasvir* is extensively metabolized via hepatic CYP3A4 enzymes, and the drug is contraindicated in combination with strong CYP3A4 inducers because of the potential for reduced efficacy. In addition, the dose of *daclatasvir* should be decreased when coadministered with strong CYP3A4 inhibitors and increased when coadministered with moderate CYP3A4 inducers. Absorption of *ledipasvir* is reduced when gastric pH is increased. Patients receiving proton-pump inhibitors should either stop these agents during HCV therapy with *ledipasvir* or take the proton-pump inhibitor with *ledipasvir*-containing regimens under fasted conditions to ensure that gastric pH is at its lowest point at the time of drug administration.

### D. Ribavirin

*Ribavirin* is approved for the treatment of chronic HCV when used in combination with standard or pegylated *interferon* or with DAAs. *Ribavirin*, a guanosine analog, improves viral clearance, decreases relapse rates, and improves rates of sustained virologic response

when used in combination with other agents. The addition of *ribavirin* to DAA-based regimens is based on HCV genotype/subtype, cirrhosis status, mutational status, and treatment history. Despite its use in patients with HCV for more than 20 years, the precise mechanism(s) by which *ribavirin* improves outcomes is unknown. *Ribavirin* remains an important component of HCV therapy, even in the age of DAA therapy. Whether use of *ribavirin* will be necessary with future DAAs is not known. The dose of *ribavirin* is always weight-based and it is administered in two daily divided doses with food.

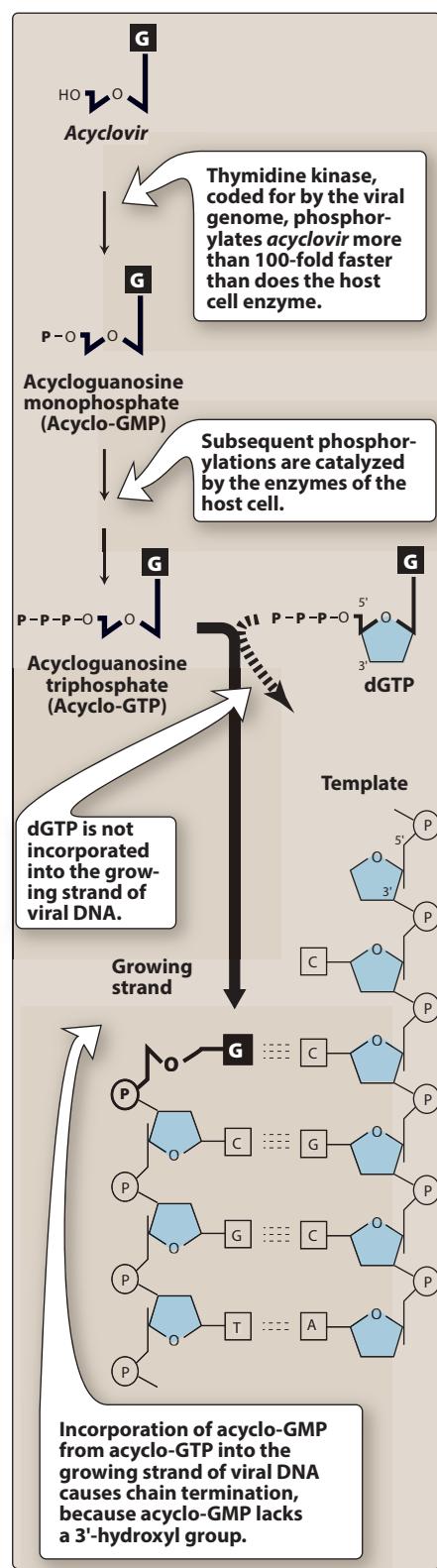
## VI. TREATMENT OF HERPES VIRUS INFECTIONS

Herpes viruses are associated with a broad spectrum of diseases, for example, cold sores, viral encephalitis, and genital infections. The drugs that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect during the latent phase.

### A. Acyclovir

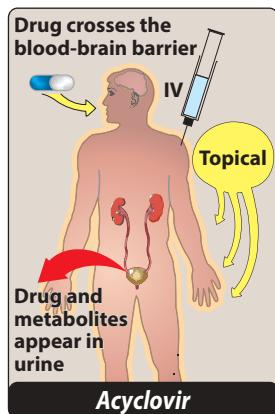
*Acyclovir* [ay-SYE-kloe-veer] is the prototypic antiherpetic therapeutic agent. Herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), and some Epstein-Barr virus-mediated infections are sensitive to *acyclovir*. It is the treatment of choice in HSV encephalitis. The most common use of *acyclovir* is in therapy for genital herpes infections. It is also given prophylactically to seropositive patients before bone marrow transplant and post-heart transplant to protect such individuals from herpetic infections.

- Mechanism of action:** *Acyclovir*, a guanosine analog, is mono-phosphorylated in the cell by the herpesvirus-encoded enzyme thymidine kinase (Figure 34.8). Therefore, virus-infected cells are most susceptible. The monophosphate analog is converted to the di- and triphosphate forms by the host cell kinases. *Acyclovir* triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase and is itself incorporated into the viral DNA, causing premature DNA chain termination.
- Pharmacokinetics:** *Acyclovir* is administered by intravenous (IV), oral, or topical routes. [Note: The efficacy of topical applications is questionable.] The drug distributes well throughout the body, including the cerebrospinal fluid (CSF). *Acyclovir* is partially metabolized to an inactive product. Excretion into the urine occurs by both glomerular filtration and tubular secretion (Figure 34.9). *Acyclovir* accumulates in patients with renal failure. The valyl ester, *valacyclovir* [val-a-SYE-kloe-veer], has greater oral bioavailability than *acyclovir*. This ester is rapidly hydrolyzed to *acyclovir* and achieves levels of the latter comparable to those of *acyclovir* following IV administration (as infusion for 1 hour) at a dose of 5 to 15 mg/kg up to 7 to 10 days. Orally, *acyclovir* is used at a dose of 200 mg five times a day or 400 mg three times a day for 7 to 10 days. For topical application, *acyclovir* is used at a dose of 5% ointment.
- Adverse effects:** Adverse effects of *acyclovir* treatment depend on the route of administration. For example, local irritation may occur from topical application; headache, diarrhea, nausea, and vomiting may result after oral administration. Transient renal

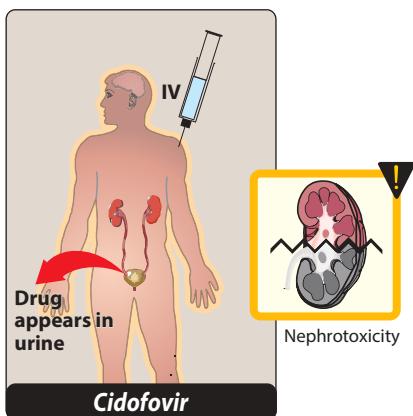


**Figure 34.8**

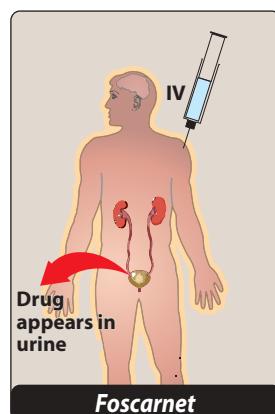
Incorporation of *acyclovir* into replicating viral DNA, causing chain termination. dGTP = deoxyguanosine triphosphate.

**Figure 34.9**

Administration and fate of acyclovir.  
IV = intravenous.

**Figure 34.10**

Administration, fate, and toxicity of cidofovir. IV = intravenous.

**Figure 34.11**

Administration and fate of foscarnet.

dysfunction may occur at high doses or in a dehydrated patient receiving the drug intravenously.

4. **Resistance:** Altered or deficient thymidine kinase and DNA polymerases have been found in some resistant viral strains and are most commonly isolated from immunocompromised patients. Cross-resistance to the other agents in this family occurs.

## B. Cidofovir

*Cidofovir* [si-DOE-foe-veer] is indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. [Note: CMV is a member of the herpesvirus family.] *Cidofovir* is a nucleotide analog of cytosine, the phosphorylation of which is not dependent on viral or cellular enzymes. It inhibits viral DNA synthesis. Slow elimination of the active intracellular metabolite permits prolonged dosage intervals and eliminates the permanent venous access needed for *ganciclovir* therapy. *Cidofovir* is administered intravenously. *Cidofovir* produces significant renal toxicity (Figure 34.10), and it is contraindicated in patients with pre-existing renal impairment and in those taking nephrotoxic drugs. Neutropenia and metabolic acidosis also occur. Oral *probenecid* and IV normal saline are coadministered with *cidofovir* to reduce the risk of nephrotoxicity. Since the introduction of highly active antiretroviral therapy (HAART), the prevalence of CMV infections in immunocompromised hosts has markedly declined, as has the importance of *cidofovir* in the treatment of these patients.

## C. Foscarnet

Unlike most antiviral agents, *foscarnet* [fos-KAR-net] is not a purine or pyrimidine analog. Instead, it is a pyrophosphate derivative and does not require activation by viral (or cellular) kinases. *Foscarnet* is approved for CMV retinitis in immunocompromised hosts and for acyclovir-resistant HSV infections. *Foscarnet* works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis. Mutation of the polymerase structure is responsible for resistant viruses. *Foscarnet* is poorly absorbed orally and must be injected intravenously. It must also be given frequently to avoid relapse when plasma levels fall. It is dispersed throughout the body, and greater than 10% enters the bone matrix, from which it slowly disperses. The parent drug is eliminated by glomerular filtration and tubular secretion (Figure 34.11). Adverse effects include nephrotoxicity, anemia, nausea, and fever. Due to chelation with divalent cations, hypocalcemia and hypomagnesemia are also seen. In addition, hypokalemia, hypo- and hyperphosphatemia, seizures, and arrhythmias have been reported.

## D. Ganciclovir

*Ganciclovir* [gan-SYE-kloe-veer] is an analog of *acyclovir* that has greater activity against CMV. It is used for the treatment of CMV retinitis in immunocompromised patients and for CMV prophylaxis in transplant patients. *Ganciclovir* is used at a dose of 5 mg/kg twice daily for 2 to 3 weeks followed by once a day as injection. It is administered at an oral dose of 1000 mg thrice daily with food or 500 mg six times a day (every 3 hours with food). *Valacyclovir* is used at a dose of 0.5 to 1 g twice daily orally for 5 to 10 days depending upon the type of

herpes infection. Intravenous formulation of *ganciclovir* has also been used for intravitreal injection for CMV retinitis.

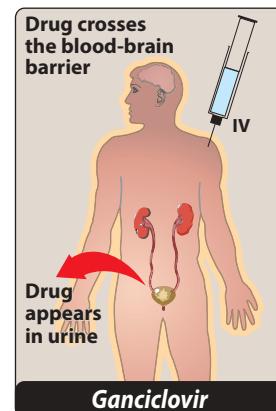
1. **Mechanism of action:** Like *acyclovir*, *ganciclovir* is activated through conversion to the nucleoside triphosphate by viral and cellular enzymes. The nucleotide inhibits viral DNA polymerase and can be incorporated into the DNA resulting in chain termination.
2. **Pharmacokinetics:** *Ganciclovir* is administered IV and distributes throughout the body, including the CSF. Excretion into the urine occurs through glomerular filtration and tubular secretion (Figure 34.12). Like *acyclovir*, *ganciclovir* accumulates in patients with renal failure. *Valganciclovir* [val-gan-SYE-kloe-veer], an oral drug, is the valyl ester of *ganciclovir*. Like *valacyclovir*, *valganciclovir* has high oral bioavailability, because rapid hydrolysis in the intestine and liver after oral administration leads to high levels of *ganciclovir*.
3. **Adverse effects:** Adverse effects include severe, dose-dependent neutropenia. *Ganciclovir* is carcinogenic as well as teratogenic and carries a boxed warning for use in pregnancy.
4. **Resistance:** Resistant CMV strains have been detected that have lower levels of *ganciclovir* triphosphate.

## E. Penciclovir and famciclovir

*Penciclovir* [pen-SYE-kloe-veer] is an acyclic guanosine nucleoside derivative that is active against HSV-1, HSV-2, and VZV. *Penciclovir* is administered topically (Figure 34.13). It is monophosphorylated by viral thymidine kinase, and cellular enzymes form the nucleoside triphosphate, which inhibits HSV DNA polymerase. *Penciclovir* triphosphate has an intracellular half-life much longer than *acyclovir* triphosphate. *Penciclovir* is negligibly absorbed upon topical application and is well tolerated. *Famciclovir* [fam-SYE-kloe-veer], another acyclic analog of 2'-deoxyguanosine, is a prodrug that is metabolized to the active *penciclovir*. The antiviral spectrum is similar to that of *ganciclovir*, and it is approved for treatment of acute herpes zoster, genital HSV infection, and recurrent herpes labialis. The drug is effective orally (Figure 34.13). Adverse effects include headache and nausea. *Famciclovir* is used at a dose of 250 mg thrice a day for 5 to 10 days for the first episode of genital herpes. For recurrent infections, it is used at a dose of 250 mg twice a day for prolonged periods. Higher doses up to 500 mg twice a day are used for herpes in immunocompromised patients to suppress recurrent genital HSV. Topical 1% *penciclovir* is applied every 2 hours in day time for 4 days to enhance the healing.

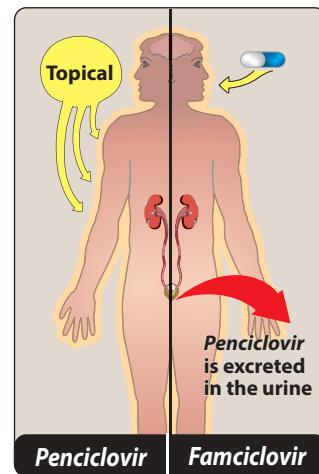
## F. Trifluridine

*Trifluridine* [trye-FLURE-i-deen] is a fluorinated pyrimidine nucleoside analog that is structurally similar to thymidine. Once converted to the triphosphate, the agent is believed to inhibit the incorporation of thymidine triphosphate into viral DNA and, to a lesser extent, lead to the synthesis of defective DNA that renders the virus unable to replicate. *Trifluridine* is active against HSV-1, HSV-2, and vaccinia virus. It is indicated for the treatment of HSV keratoconjunctivitis and recurrent epithelial keratitis. Because the triphosphate form of *trifluridine* can also incorporate to some degree into cellular DNA, the drug is too



**Figure 34.12**

Administration and fate of *ganciclovir*.



**Figure 34.13**

Administration and fate of *penciclovir* and *famciclovir*.

toxic for systemic use. Therefore, the use of *trifluridine* is restricted to a topical ophthalmic preparation (1% solution). A short half-life necessitates that the drug be applied frequently. Adverse effects include a transient irritation of the eye and palpebral (eyelid) edema.

### G. Imiquimod

Imiquimod is an immunomodulatory compound which is used as a topical treatment in the case of Condylomata acuminata (genital wart), Molluscum contagiosum, and other dermatological conditions due to DNA viruses. It does not have any direct effect on the virus and the effect is indirect. It is applied as a topical 5% cream for the treatment of genital warts. Upon application, it induces local cytokines such as INF (*interferon*)  $\alpha$ ,  $\beta$ , and  $\gamma$  along with tumor necrosis factor (TNF)  $\alpha$  which in turn decreases the viral load and the size of the warts in most of the cases. It is applied topically on the warts, three times a week for 10 to 16 weeks. Its application causes localized erythema, itching, burning, and excoriation in patients.

**Figure 34.14** summarizes selected antiviral agents.

ANTIVIRAL DRUG	MECHANISM OF ACTION	VIRUSES OR DISEASES AFFECTED
<i>Acyclovir</i>	Metabolized to acyclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex, varicella-zoster, cytomegalovirus
<i>Amantadine</i>	Blockage of the M2 protein ion channel and its ability to modulate intracellular pH	Influenza A
<i>Cidofovir</i>	Inhibition of viral DNA polymerase	Cytomegalovirus; indicated only for virus-induced retinitis
<i>Famciclovir</i>	Same as <i>penciclovir</i>	Herpes simplex, varicella-zoster
<i>Foscarnet</i>	Inhibition of viral DNA polymerase and reverse transcriptase at the pyrophosphate-binding site	Cytomegalovirus, <i>acyclovir</i> -resistant herpes simplex, <i>acyclovir</i> -resistant varicella-zoster
<i>Ganciclovir</i>	Inhibits viral DNA polymerase	Cytomegalovirus
<i>Interferon-<math>\alpha</math></i>	Induction of cellular enzymes that interfere with viral protein synthesis	Hepatitis B and C, human herpesvirus 8, papilloma virus, Kaposi sarcoma, hairy cell leukemia, chronic myelogenous leukemia
<i>Lamivudine</i>	Inhibition of viral DNA polymerase and reverse transcriptase	Hepatitis B (chronic cases), human immunodeficiency virus type 1
<i>Oseltamivir</i>	Inhibition of viral neuraminidase	Influenza A and B
<i>Penciclovir</i>	Metabolized to penciclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex
<i>Ribavirin</i>	Interference with viral messenger RNA	Lassa fever, hantavirus (hemorrhagic fever renal syndrome), hepatitis C (in combination with direct-acting antiviral agents), RSV in children and infants
<i>Rimantadine</i>	Blockage of the M2 protein ion channel and its ability to modulate intracellular pH	Influenza A
<i>Valacyclovir</i>	Same as <i>acyclovir</i>	Herpes simplex, varicella-zoster, cytomegalovirus
<i>Zanamivir</i>	Inhibition of viral neuraminidase	Influenza A and B

**Figure 34.14**

Summary of selected antiviral agents. RSV = respiratory syncytial virus. Modified from H. H. Balfour. Antiviral drugs. N. Engl. J. Med. 340: 1255 (1999).

## VII. TREATMENT OF HIV INFECTION

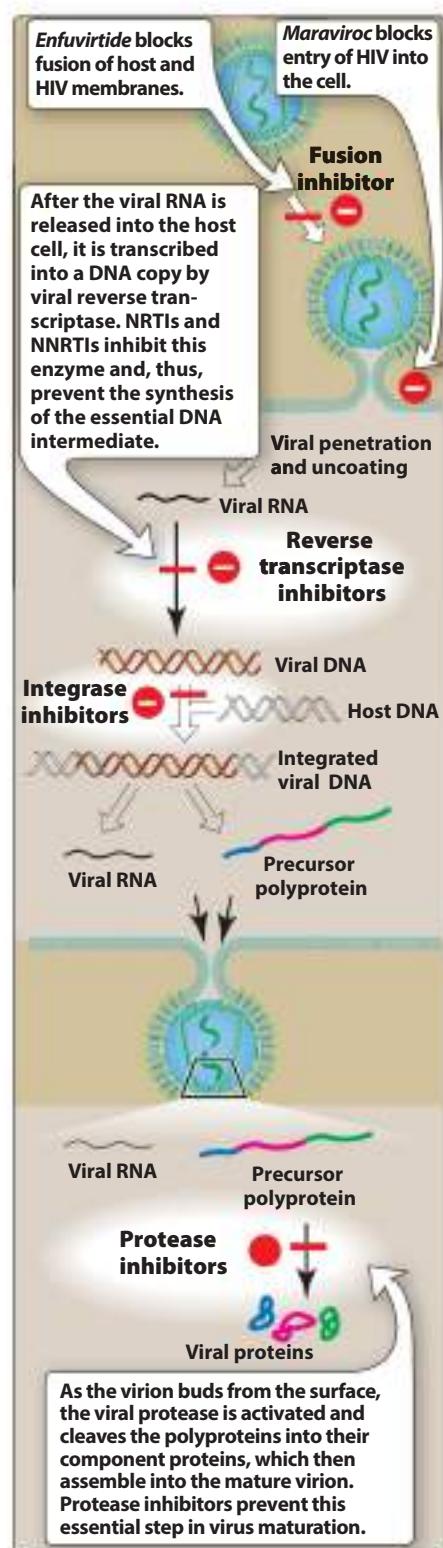
Prior to approval of *zidovudine* [zye-DOE-vyoo-deen] in 1987, the treatment of HIV infections focused on decreasing the occurrence of opportunistic infections that caused a high degree of morbidity and mortality in AIDS patients. Today, the viral life cycle is understood (Figure 34.15), and a combination of drugs is used to suppress replication of HIV and restore the number of CD4 cells and immunocompetence to the host. This multidrug regimen is commonly referred to as antiretroviral therapy, or ART (Figure 34.16). There are five classes of antiretroviral drugs, each of which targets one of the four viral processes. These classes of drugs are nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors, and integrase inhibitors. There are also two pharmacokinetic enhancers, also known as “boosters,” which lack anti-HIV activity themselves, but rather serve to increase drug levels of concomitantly administered antiretroviral agents and allow for less-frequent dosing and less variation in drug levels. The initial therapy for HIV consists of a combination of two NRTIs with an integrase inhibitor, an NNRTI, or a boosted PI. Selection of the appropriate combination is based on 1) avoidance of the use of two agents of the same nucleoside analog; 2) avoidance of overlapping toxicities and genotypic and phenotypic characteristics of the virus; 3) patient factors, such as disease symptoms and concurrent illnesses; 4) impact of drug interactions; and 5) ease of adherence to the regimen. The goals of therapy are to maximally and durably suppress HIV RNA replication, to restore and preserve immunologic function, to reduce HIV-related morbidity and mortality, and to improve quality of life.

## VIII. NRTIs USED TO TREAT HIV INFECTION

### A. Overview of NRTIs

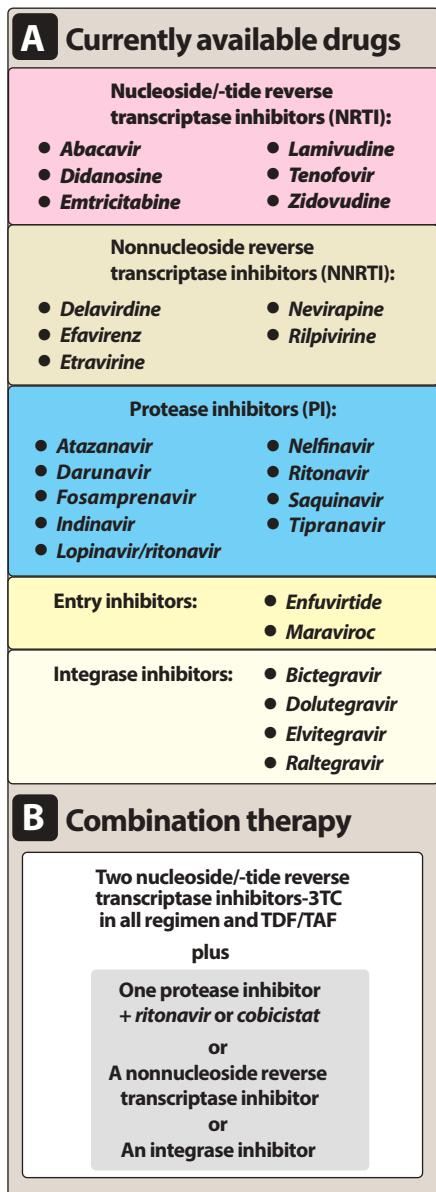
NRTIs were the first agents available to treat HIV infection and currently, the use of two NRTIs is a mainstay of most initial antiretroviral regimens. Available NRTIs include *zidovudine*, *lamivudine*, *emtricitabine* [em-trye-SYE-ta-been], *tenofovir*, *didanosine* [dye-DAN-oh-seen], and *abacavir* [a-BAK-a-veer]. *Stavudin* is no longer recommended because of its life-threatening side effects. The most commonly used NRTIs are *tenofovir*, *abacavir*, *emtricitabine*, and *lamivudine*, and these NRTIs are recommended parts of initial regimens for most patients with HIV. *Tenofovir disoproxil fumarate* in combination with *emtricitabine* can also be used for pre-exposure prophylaxis in individuals at high risk for HIV acquisition.

- Mechanism of action:** These agents are inhibitors of HIV reverse transcriptase. NRTIs are analogs of native ribosides (nucleosides or nucleotides containing ribose), which all lack a 3'-hydroxyl group. Once they enter cells, they are phosphorylated by cellular enzymes to the corresponding triphosphate analog, which is preferentially incorporated into the viral DNA by RT. Because the 3'-hydroxyl group is not present, a 3',5'-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed, and DNA chain elongation is terminated. Affinities of the drugs for many host cell DNA polymerases are lower than they are for HIV RT, although mitochondrial DNA polymerase  $\gamma$  appears to be susceptible at therapeutic concentrations.



**Figure 34.15**

Drugs used to prevent HIV from replicating. NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside and nucleotide reverse transcriptase inhibitor.



**Figure 34.16**

Antiretroviral therapy for treatment of HIV. [Note: *Elvitegravir* is coformulated with *cobicistat*. *Cobicistat* inhibits the metabolism of *elvitegravir*, thereby increasing its concentration in the plasma.]

- Pharmacokinetics:** All of the NRTIs are administered orally. [Note: *Zidovudine* is also available as an intravenous formulation.] *Tenofovir* is available in two different salt forms as *tenofovir disoproxil fumarate* (TDF) and *tenofovir alafenamide* (TAF), both prodrugs of *tenofovir*. The *tenofovir* prodrug is converted by lymphoid cellular enzymes to *tenofovir diphosphate*, which is the active form of the drug and an inhibitor of HIV RT. TAF achieves improved anti-HIV activity at lower doses than TDF, resulting in a 5- to 7-fold increase in intracellular diphosphate in the lymphoid cell and in lower circulating plasma *tenofovir* levels. Because of this, TAF has fewer adverse effects (renal insufficiency and loss of bone mineral density) than TDF. The NRTIs are primarily renally excreted, and all require dosage adjustment in renal insufficiency except *abacavir*, which is metabolized by alcohol dehydrogenase and glucuronyl transferase.
- Adverse effects:** Many toxicities of the NRTIs are believed to be due to inhibition of the mitochondrial DNA polymerase in certain tissues. As a general rule, the dideoxynucleosides, such as *didanosine* and *stavudine*, have a greater affinity for the mitochondrial DNA polymerase, leading to toxicities such as peripheral neuropathy, pancreatitis, and lipoatrophy. Because of these mitochondrial toxicities, *didanosine* and *stavudine* are rarely used in current antiretroviral regimens. When more than one NRTI is given, care is taken to avoid overlapping toxicities. All NRTIs have been associated with potentially fatal liver toxicity characterized by lactic acidosis and hepatomegaly with steatosis. *Abacavir* is associated with a hypersensitivity reaction which affects approximately 5% of patients, which is usually characterized by drug fever, plus a rash, GI symptoms, malaise, or respiratory distress (Figure 34.17). Sensitized individuals should never be rechallenged with *abacavir* because of rapidly appearing, severe reactions that may lead to death. A genetic test (HLA-B\*5701) is available to screen patients for the potential of this reaction. Figure 34.18 shows some adverse reactions commonly seen with nucleoside analogs.
- Drug interactions:** Due to the renal excretion of the NRTIs, there are not many drug interactions encountered with these agents except for *zidovudine* and *tenofovir*.
- Resistance:** NRTI resistance is well characterized, and the most common resistance pattern is a mutation at viral RT codon 184, which confers a high degree of resistance to *lamivudine* and *emtricitabine* but, more importantly, restores sensitivity to *zidovudine* and *tenofovir*. Because cross-resistance and antagonism occur between agents of the same analog class (thymidine, cytosine, guanosine, and adenosine), concomitant use of agents with the same analog target is contraindicated (for example, *zidovudine* and *stavudine* are both analogs of thymidine and should not be used together).

## IX. NNRTIs USED TO TREAT HIV INFECTION

NNRTIs are highly selective, noncompetitive inhibitors of HIV RT. They bind to HIV RT at an allosteric hydrophobic site adjacent to the active site,

inducing a conformational change that results in enzyme inhibition. They do not require activation by cellular enzymes. These drugs have common characteristics that include cross-resistance with other NNRTIs, drug interactions, and a high incidence of hypersensitivity reactions, including rash. The NNRTIs include *nevirapine* [ne-VYE-ra-peen], *delavirdine* [de-LA-vir-deen], *efavirenz* [e-FA-veer-enz], *etravirine* [et-ra-VYE-rine], and *rilpivirine* [ril-pi-VIR-een]. *Efavirenz* (Figure 34.19) or *rilpivirine* are recommended in initial antiretroviral regimens in certain clinical situations. For example, *efavirenz* is safe to use in patients co-infected with tuberculosis because of its lower potential for drug interactions with rifamycins, and *rilpivirine* has the smallest tablet size, making it ideal for patients with difficulty in swallowing. *Etravirine* is a second-generation NNRTI active against many HIV strains that are resistant to the first-generation NNRTIs; its use is limited to HIV treatment-experienced, multidrug-resistant patients who have evidence of ongoing viral replication. *Delavirdine* and *nevirapine* are rarely used due to toxicities and/or inferior antiviral efficacy.

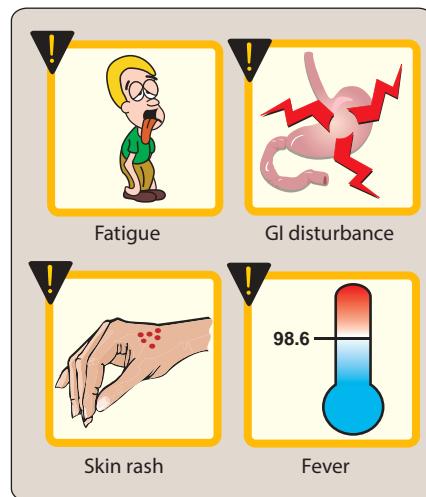
## X. PROTEASE INHIBITORS USED TO TREAT HIV INFECTION

Inhibitors of HIV protease have significantly altered the course of this devastating viral disease. Shortly after their introduction, the number of deaths in the United States due to AIDS decreased, and continues to remain on the decline (Figure 34.20). Available PIs include *atazanavir* (ATV), *darunavir* (DRV) [da-ROON-a-veer], *fosamprenavir* (FPV) [FOS-am PREN-a-veer], *indinavir* (IDV) [in-DIN-a-veer], *lopinavir* (LPV) [loe-PIN-a-vir], *nelfinavir* (NFV) [nel-FIN-a-veer], *saquinavir* (SQV) [sa-KWIN-a-veer], and *tipranavir* (TPV) [tip-RA-na-veer]. However, current HIV guidelines only list a select few (for example, *atazanavir* or *darunavir*) due to improved adverse effect profile, virologic efficacy, and ease of dosing. Due to their high genetic barrier to resistance, protease inhibitors are recommended in initial regimens in certain clinical situations (for example, patients with uncertain adherence or when resistance testing results are not yet available).

### A. Overview

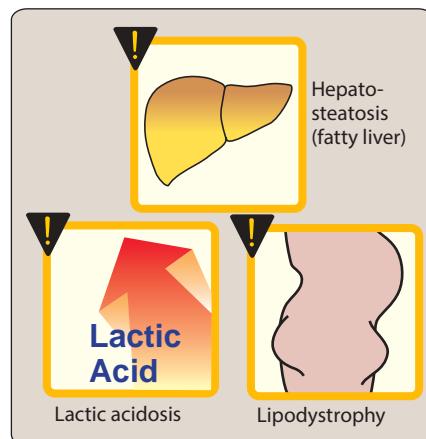
These potent agents have several common features that characterize their pharmacology.

- Mechanism of action:** Drugs in this group are reversible inhibitors of the HIV aspartyl protease (retropepsin), which is the viral enzyme responsible for cleavage of the viral polyprotein into a number of essential enzymes (RT, protease, and integrase) and several structural proteins. The inhibition prevents maturation of the viral particles and results in the production of noninfectious virions.
- Pharmacokinetics:** High-fat meals substantially increase the bioavailability of some PIs, such as *nelfinavir* and *saquinavir*, whereas the bioavailability of *indinavir* is decreased, and others are essentially unaffected. The HIV PIs are all substantially bound to plasma proteins. These agents are substrates for the CYP3A4 isoenzyme, and individual PIs are also metabolized by other CYP450 isoenzymes. Metabolism is extensive, and very little drug is excreted unchanged in urine.



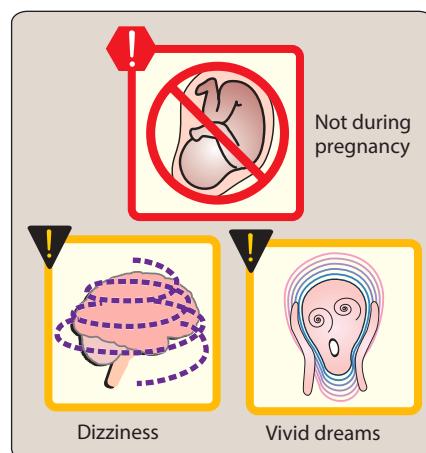
**Figure 34.17**

Hypersensitivity reactions to abacavir.



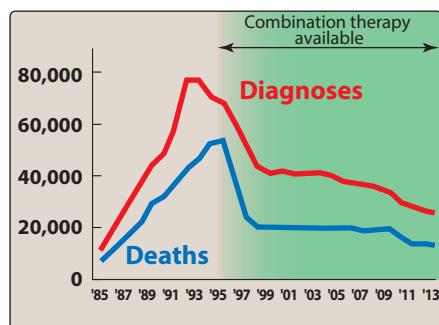
**Figure 34.18**

Some adverse reactions of nucleoside analogs.



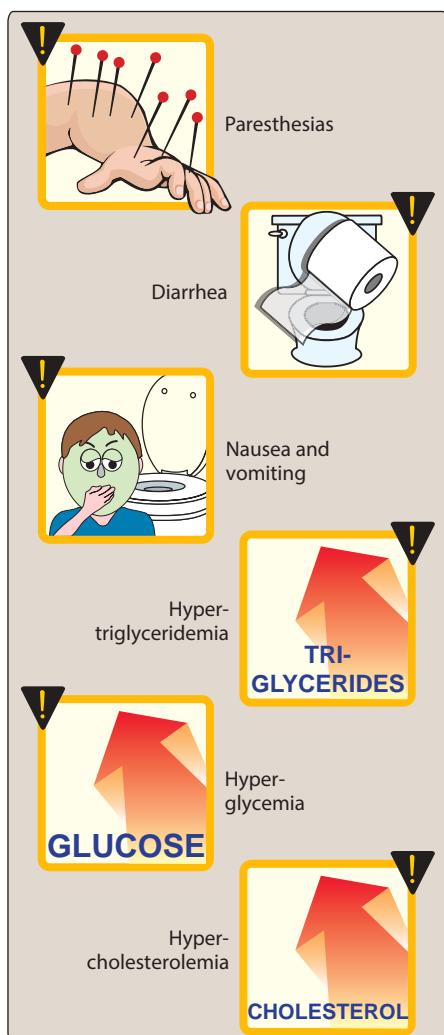
**Figure 34.19**

Adverse reactions of efavirenz.



**Figure 34.20**

Estimated number of AIDS cases and deaths due to AIDS. Green background indicates years in which combination antiretroviral therapy came into common usage.



**Figure 34.21**

Some adverse effects of the HIV protease inhibitors.

**3. Adverse effects:** PIs commonly cause nausea, vomiting, and diarrhea (Figure 34.21). Disturbances in glucose and lipid metabolism also occur, including diabetes, hypertriglyceridemia, and hypercholesterolemia. Chronic administration results in fat redistribution, including loss of fat from the extremities, fat accumulation in the abdomen and the base of the neck ("buffalo hump"; Figure 34.22), and breast enlargement. These physical changes may indicate to others that an individual is HIV infected.

**4. Drug interactions:** Drug interactions are a common problem for PIs, because they are substrates and also potent inhibitors of CYP450 isoenzymes. Drug interactions are, therefore, quite common. Drugs that rely on metabolism for their termination of action may accumulate to toxic levels. Examples of potentially dangerous interactions with PIs include rhabdomyolysis from *simvastatin* or *lovastatin*, excessive sedation from *midazolam* or *triazolam*, and respiratory depression from *fentanyl* (Figure 34.23). Other drug interactions that require dosage modification and cautious use include *warfarin*, *sildenafil*, and *phenytoin* (Figure 34.24). In addition, inducers of CYP450 isoenzymes may decrease PI plasma concentrations to suboptimal levels, contributing to treatment failures. Thus, drugs such as *rifampin* and *St. John's wort* are also contraindicated with PIs.

**5. Resistance:** Resistance occurs as an accumulation of step-wise mutations of the protease gene. Initial mutations result in decreased ability of the virus to replicate, but as the mutations accumulate, virions with high levels of resistance to the protease inhibitors emerge. Suboptimal concentrations of PI result in the more rapid appearance of resistant strains.

## B. Atazanavir

*Atazanavir* is well absorbed after oral administration. It must be taken with food to increase absorption and bioavailability. *Atazanavir* requires an acidic environment for absorption. Thus, unboosted *atazanavir* is contraindicated with concurrent use of proton-pump inhibitors, and administration must be spaced apart from H<sub>2</sub>-blockers and antacids. *Atazanavir* can be boosted by *ritonavir* or *cobicistat*. The drug is highly protein bound and undergoes extensive metabolism by CYP3A4 isoenzymes. It is excreted primarily in bile. It has a half-life of about 7 hours, but it may be administered once daily. *Atazanavir* is a competitive inhibitor of glucuronyl transferase, and benign hyperbilirubinemia and jaundice are known adverse effects. In addition, the drug may prolong the PR interval. *Atazanavir* exhibits a decreased risk of hyperlipidemia compared with other PIs.

## C. Darunavir

*Darunavir* [da-RU-na-veer] is coadministered with *cobicistat* or a low dose of *ritonavir*. *Darunavir* is approved for initial therapy in treatment-naïve HIV-infected patients, as well as for treatment-experienced patients with HIV resistant to other PIs. *Darunavir* must be taken with food to increase absorption. The elimination half-life is 15 hours when combined with *ritonavir*. *Darunavir* is extensively metabolized by the

CYP3A enzymes and is also an inhibitor of the CYP3A4 isoenzyme. Adverse effects are similar to those of the other PIs. In addition, *darunavir* therapy has been associated with a rash.

A summary of PIs is presented in [Figure 34.25](#).

## XI. ENTRY INHIBITORS

### A. Enfuvirtide

*Enfuvirtide* [en-FU-veer-tide] is a fusion inhibitor. For HIV to gain entry into the host cell, it must fuse its membrane with that of the host cell. This is accomplished by changes in the conformation of the viral transmembrane glycoprotein gp41, which occurs when HIV binds to the host cell surface. *Enfuvirtide* is a polypeptide that binds to gp41, preventing the conformational change. *Enfuvirtide*, in combination with other antiretroviral agents, is indicated for therapy of treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral drug therapy. As a peptide, it must be given subcutaneously. Most of the adverse effects are related to the injection, including pain, erythema, induration, and nodules, which occur in almost all patients. *Enfuvirtide* must be reconstituted prior to administration.

### B. Maraviroc

*Maraviroc* [ma-RAV-i-rok] is an entry inhibitor that blocks the CCR5 coreceptor that works with gp41 to facilitate HIV entry through the membrane into the cell. HIV may express preference for either the CCR5 coreceptor or the CXCR4 coreceptor, or both (dual-tropic). Prior to use of *maraviroc*, a test to determine viral tropism is required to distinguish whether the strain of HIV virus uses the CCR5 coreceptor, the CXCR4 coreceptor, or is dual-tropic. Only strains of HIV that use CCR5 to gain access to the cell can be successfully treated with *maraviroc*. The drug is well absorbed after oral administration. *Maraviroc* is metabolized mainly by the hepatic CYP3A isoenzyme, and the dose must be reduced when given with most PIs or strong CYP450 inhibitors. Conversely, it should be increased in patients receiving *efavirenz*, *etravirine*, or strong CYP450 inducers. *Maraviroc* is generally well tolerated. The drug has been associated with severe hepatotoxicity which may be preceded by a fever or rash. Monitoring of liver function is recommended.

## XII. INTEGRASE INHIBITORS

*Raltegravir* [ral-TEG-ra-veer], *elvitegravir* [el-vi-TEG-ra-vir], *dolutegravir* [doe-loo-TEG-ra-vir], and *bictegravir* are integrase strand transfer inhibitors (INSTIs), often called integrase inhibitors. These agents work by inhibiting the insertion of proviral DNA into the host cell genome. The active site of the integrase enzyme binds to the host cell DNA and includes two divalent metal cations that serve as chelation targets for the INSTIs. As a result, when an INSTI is present, the active site of the enzyme is occupied and the integration process is halted. The half-life of *elvitegravir* is 3 hours when administered alone, but increases to approximately 9 hours when



**Figure 34.22**

Accumulation of fat at the base of the neck in a patient receiving a protease inhibitor.

DRUG CLASS	EXAMPLE
ANTIARRHYTHMICS	<i>Amiodarone</i>
ERGOT DERIVATIVES	<i>Ergotamine</i>
ANTIMYCOBACTERIAL DRUGS	<i>Rifampin</i>
BENZODIAZEPINES	<i>Triazolam</i>
INHALED STEROIDS	<i>Fluticasone</i>
HERBAL SUPPLEMENTS	<i>St. John's wort</i>
HMG CoA REDUCTASE INHIBITORS	<i>Lovastatin</i> <i>Simvastatin</i>
NARCOTICS	<i>Fentanyl</i>
β-2 AGONIST	<i>Salmeterol</i>

**Contraindicated**

### PROTEASE INHIBITORS

**Figure 34.23**

Drugs that should not be coadministered with any protease inhibitor.

DRUG CLASS	EXAMPLE
ANTICOAGULANTS	<i>Warfarin</i>
ANTICONVULSANTS	<i>Phenytoin</i>
ANTIFUNGALS	<i>Voriconazole</i>
ANTIMYCOBACTERIALS	<i>Rifabutin</i>
ERECTILE DYSFUNCTION AGENTS	<i>Sildenafil</i> <i>Tadalafil</i> <i>Vardenafil</i>
LIPID-LOWERING AGENTS	<i>Atorvastatin</i>
NARCOTICS	<i>Methadone</i>
	
<b>PROTEASE INHIBITORS</b>	

**Figure 34.24**

Drugs that require dose modifications or cautious use with any protease inhibitor.

boosted by *cobicistat*. Pharmacokinetic boosting of *elvitegravir* allows once-daily dosing with food. The INSTIs are generally well tolerated, with nausea and diarrhea being the most commonly reported adverse effects. Importantly, INSTIs are subject to chelation interactions with antacids, resulting in significant reductions in bioavailability. Therefore, INSTI doses should be separated from antacids and other polyvalent cations by several hours. Resistance to INSTIs occurs with single-point mutations within the integrase gene. Cross-resistance between *raltegravir* and *elvitegravir* can occur, although *dolutegravir* has limited cross-resistance to other INSTIs.

### XIII. PHARMACOKINETIC ENHancers

#### A. Ritonavir

*Ritonavir* [ri-TOE-na-veer] is no longer used as a single PI but, instead, is used as a pharmacokinetic enhancer or “booster” of other PIs. *Ritonavir* is a potent inhibitor of CYP3A, and concomitant *ritonavir* administration at low doses increases the bioavailability of the second PI, often allowing for longer dosing intervals. The resulting higher  $C_{min}$  levels of the “boosted” PI also help to prevent the development of HIV resistance. Therefore, “boosted” PIs are recommended for use in initial HIV regimens in certain clinical situations. Metabolism by CYP3A4 and CYP2D6 and biliary excretion are the primary methods of elimination. *Ritonavir* has a half-life of 3 to 5 hours. Although *ritonavir* is primarily an inhibitor of CYP450 isoenzymes, it may also induce several CYP450 isoenzymes, and numerous drug interactions have been identified.

#### B. Cobicistat

*Cobicistat* [koe-BIK-i-stat] is a pharmacokinetic enhancer or booster drug used in combination treatments for HIV. This agent inhibits CYP3A isoenzymes and is used to enhance the bioavailability of the protease inhibitors *atazanavir* and *darunavir*, and the integrase inhibitor *elvitegravir*. Because *cobicistat* inhibits CYP3A, CYP2D6, and the transporter P-gp, numerous drug interactions exist. *Cobicistat* may also cause elevations in serum creatinine due to inhibition of tubular creatinine secretion.

### XIV. NATIONAL AIDS CONTROL ORGANIZATION (NACO) GUIDELINES

The principles for selecting the first-line regimen as per National AIDS Control Organization guidelines (2013) are as follows:

- Choose *lamivudine* in all regimens.
- Choose one NRTI to combine with *lamivudine* (*zidovudine* or *tenofovir*).
- Choose one NNRTI (*nevirapine* or *efavirenz*).

Monotherapy or dual therapy for the management of HIV infection or unboosted PIs and structured treatment interruptions should **NEVER be used**. Fixed-dose combinations are available under National AIDS Control Programme. As per the guidelines, different regimens are prescribed

depending upon the comorbid conditions. One must update himself/herself with the current guidelines before initiating the treatment for HIV.

- Do not start ART in the presence of an active ongoing opportunistic infection (OI). Diagnose and treat active infection with fever, if any, before commencing antiretroviral therapy (ART).
- If the patient suffers from TB, treat TB first and then start ART.
- OIs should be treated or at least stabilized before ART is started.
- Adherence counseling and monitoring (patient/parent education) are essential in patients initiated on ART at every visit.
- Patients should be monitored for clinical effect, adverse effects, and toxicities (both early and long-term). If a life-threatening toxicity occurs, all ARTs should be stopped until the toxicity has resolved and a revised regimen commenced when the patient has recovered.

DRUGS	MAJOR TOXICITIES AND CONCERNs
<i>Atazanavir</i>	Nausea, abdominal discomfort, skin rash, hyperbilirubinemia
<i>Darunavir</i>	Nausea, abdominal discomfort, headache, skin rash
<i>Fosamprenavir</i>	Nausea, diarrhea, vomiting, oral and perioral paresthesia, and rash
<i>Indinavir</i>	Benign hyperbilirubinemia, nephrolithiasis; take 1 hour before or 2 hours after food; may take with skim milk or a low-fat meal; drink >1.5 L of liquid daily
<i>Lopinavir</i>	Gastrointestinal, hyperlipidemia, insulin resistance
<i>Nelfinavir</i>	Diarrhea, nausea, flatulence, rash
<i>Ritonavir</i>	Diarrhea, nausea, taste perversion, vomiting, anemia, increased hepatic enzymes, increased triglycerides. Capsules require refrigeration, tablets do not. Take with meals; chocolate milk improves the taste
<i>Saquinavir</i>	Diarrhea, nausea, abdominal discomfort, elevated transaminase levels. Take with high-fat meal or within 2 hours of a full meal
<i>Tipranavir</i>	Nausea, vomiting, diarrhea, rash, severe hepatotoxicity, intracranial hemorrhage

**Figure 34.25**

Summary of protease inhibitors. [Note: *Lopinavir* is coformulated with *ritonavir*. *Ritonavir* inhibits the metabolism of *lopinavir*, thereby increasing its level in the plasma.]

## Study Questions

Choose the ONE best answer.

- 34.1 A 30-year-old man with human immunodeficiency virus infection is being treated with an antiretroviral regimen. Four weeks after initiating therapy, he presents to the emergency department complaining of fever, rash, and gastrointestinal upset. His HLA-B\*5701 test is positive. Which drug is most likely the cause of his symptoms?

- A. Zidovudine
- B. Abacavir
- C. Efavirenz
- D. Darunavir

- 34.2 A 75-year-old man with chronic obstructive pulmonary disease is diagnosed with suspected influenza based on complaints of flu-like symptoms that began 24 hours ago. Which agent is most appropriate to initiate for the treatment of influenza?

- A. Oseltamivir
- B. Zanamivir
- C. Rimantadine
- D. Amantadine

- 34.3 A 24-year-old woman is diagnosed with genital herpes simplex virus infection. Which agent is indicated for use in this diagnosis?

- A. Valacyclovir
- B. Cidofovir
- C. Ganciclovir
- D. Zanamivir

- 34.4 A woman who is being treated for chronic hepatitis B develops nephrotoxicity while on treatment. Which medication is most likely to be included in her HBV treatment?

- A. Entecavir
- B. Ribavirin
- C. Lamivudine
- D. Adefovir

- 34.5 Which class of direct-acting antivirals for hepatitis C works by inhibiting formation of the membranous web that provides a platform for viral replication?

- A. NS3/NS4A protease inhibitors
- B. NS5B polymerase inhibitors
- C. NS5A replication complex inhibitors
- D. Interferons

Correct answer = B. The abacavir hypersensitivity reaction is characterized by fever, rash, and gastrointestinal upset. The patient must stop therapy and should not be rechallenged with abacavir.

Correct answer = A. Oseltamivir is the best choice since it is administered orally and not associated with resistance. Zanamivir is administered via inhalation and is not recommended for patients with underlying COPD. High rates of resistance have developed to adamantanes (amantadine, rimantadine), and these drugs are infrequently indicated.

Correct answer = A. Valacyclovir, famciclovir, penciclovir, and acyclovir are all indicated for herpes simplex virus infection. Cidofovir and ganciclovir are used for CMV retinitis. Zanamivir is indicated for influenza.

Correct answer = D. Nephrotoxicity is the most commonly seen with adefovir in the treatment of HBV. This adverse effect is uncommon with lamivudine and entecavir. Ribavirin is used for the treatment of hepatitis C infection (not HBV).

Correct answer = C. NS5A inhibitors work to inhibit the formation of proteins that form a membranous web which serves as a platform for viral replication. NS3/NS4A protease inhibitors prevent processing of the single polyprotein encoded by HCV RNA into individually active proteins. NS5B polymerase inhibitors act on the RNA polymerase responsible for HCV replication. The mechanism of interferons has not been fully defined.

34.6 Which antiretroviral drug class chelates with polyvalent cations and, as such, their administration must be separated from antacids by several hours?

- A. Integrase inhibitors
- B. Non-nucleoside reverse transcriptase inhibitors
- C. Protease inhibitors
- D. Entry inhibitors

34.7 A 62-year-old man with human immunodeficiency virus infection is being treated with an antiretroviral regimen containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate and has achieved a sustained undetectable level of HIV RNA. His prescriber would like to change his therapy to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. Which information should the prescriber provide to the patient that best summarizes the advantage of tenofovir alafenamide over tenofovir disoproxil fumarate?

- A. Removal of food restrictions
- B. Fewer drug interactions
- C. Twice-daily dosing
- D. Improved renal and bone safety profile

34.8 A 37-year old woman with GERD and chronic hepatitis C genotype 1a infection is preparing to begin treatment with ledipasvir/sofosbuvir. Which is the most appropriate information for the patient regarding use of a proton-pump inhibitor during treatment with ledipasvir/sofosbuvir?

- A. Absorption of ledipasvir is increased with increasing pH.
- B. A proton-pump inhibitor can be safely administered with ledipasvir/sofosbuvir without regard to timing of the dose or food intake.
- C. The patient should either stop using the proton-pump inhibitor or take it with ledipasvir/sofosbuvir under fasted conditions.
- D. Absorption of ledipasvir is not affected by gastric pH.

34.9 Which HIV antiretroviral is an orally administered entry inhibitor?

- A. Maraviroc
- B. Enfuvirtide
- C. Rilpivirine
- D. Raltegravir

34.10 Which drug is a pharmacokinetic enhancer used to boost levels of some HIV protease inhibitors and elvitegravir?

- A. Cobicistat
- B. Dolutegravir
- C. Entecavir
- D. Tenofovir

Correct answer = A. Integrase inhibitors bind to other positively charged ions, rendering them ineffective. As such, separation of doses of these agents from aluminum-, magnesium-, and calcium-containing antacids is recommended.

Correct answer = D. Tenofovir alafenamide delivers the same active drug as tenofovir disoproxil fumarate, but with a lower incidence of renal and bone adverse effects. Both tenofovir-containing combinations are dosed once daily and should be taken with food. No change in drug interactions is expected, since tenofovir alafenamide is a prodrug which, like TDF, is metabolized to tenofovir.

Answer = C. Absorption of ledipasvir is reduced when gastric pH is increased. Patients receiving proton-pump inhibitors should stop these agents during HCV therapy with ledipasvir, or take the proton-pump inhibitor with ledipasvir/sofosbuvir under fasted conditions to ensure that gastric pH is at its lowest point of the day at the time of drug administration.

Answer = A. Maraviroc is the only orally administered entry inhibitor for HIV infection. Enfuvirtide is an entry inhibitor (fusion inhibitor), but it is injected. Rilpivirine is an NNRTI, and raltegravir is an INSTI for HIV infection.

Answer = A. Cobicistat is a pharmacokinetic enhancer used to boost serum levels of HIV protease inhibitors atazanavir, darunavir, and the integrase inhibitor elvitegravir. Like elvitegravir, dolutegravir is an INSTI. Entecavir is a guanosine nucleoside analog for the treatment of HBV infection. Tenofovir is a nucleoside reverse transcriptase inhibitor used in the treatment of HIV and HBV.



# Anticancer Drugs

Kourtney LaPlant and Paige May

# 35

## I. OVERVIEW

It is estimated that 10 lakh new cases of cancer are diagnosed every year in a population of 120 crore in India. Cancer is responsible for 60 to 70 lakh deaths every year (as per 2012 calculation). It is estimated that over 25% of the population of the United States will face a diagnosis of cancer during their lifetime, with more than 1.6 million new cancer patients diagnosed each year. Less than a quarter of these patients will be cured solely by surgery and/or local radiation. Most of the remainder will receive systemic chemotherapy at some time during their illness. In a small fraction (approximately 10%) of patients with cancer representing selected neoplasms, the chemotherapy will result in a cure or a prolonged remission. However, in most cases, drug therapy will produce only a regression of the disease, and complications and/or relapse may eventually lead to death. Thus, the overall 5-year survival rate for cancer patients is about 68%, ranking cancer second only to cardiovascular disease as a cause of mortality. **Figure 35.1** provides a list of the anticancer agents discussed in this chapter.

## II. PRINCIPLES OF CANCER CHEMOTHERAPY

Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cells that can arrest the progression of tumor growth. The attack is generally directed toward DNA or against metabolic sites essential to cell replication, for example, the availability of purines and pyrimidines, which are the building blocks for DNA or RNA synthesis (**Figure 35.2**). Ideally, anticancer drugs should interfere only with cellular processes that are unique to malignant cells. Unfortunately, most traditional anticancer drugs do not specifically recognize neoplastic cells but, rather, affect all kinds of proliferating cells, both normal and abnormal. Therefore, almost all antitumor agents have a steep dose-response curve for both therapeutic and toxic effects. Newer agents are being developed that take a different approach to cancer treatment by blocking checkpoints and allowing the patient's own immune system to attack cancer cells. While this strategy is showing great promise, adverse effects are also a concern and present as autoimmune toxicity, as compared to the myelosuppressive profile with traditional chemotherapy agents.

### A. Treatment strategies

- Goals of treatment:** The ultimate goal of chemotherapy is a cure (that is, long-term, disease-free survival). A true cure requires the

### ANTIMETABOLITES

#### Folate antagonists

*Methotrexate*  
*Pemetrexed*  
*Pralatrexate*

#### Purine antagonists

*6-Mercaptopurine*  
*6-Thioguanine*  
*Azathioprine*  
*Fludarabine*  
*Cladribine*

#### Pyrimidine antagonists

*Fluorouracil (5-FU)*  
*Capecitabine*  
*Floxuridine*

#### Cytidine analogs

*Cytarabine*  
*Azacytidine*  
*Gemcitabine*

### ANTIBIOTICS

*Bleomycin*  
*Daunorubicin*  
*Doxorubicin*  
*Epirubicin*  
*Idarubicin*  
*Mitoxantrone*  
*Actinomycin D (dactinomycin)*  
*Mitomycin C*  
*Bleomycin*

### ALKYLATING AGENTS

**Nitrogen mustards**  
*Mechloreththamine*  
*Cyclophosphamide*  
*Ifosfamide*  
*Chlorambucil*  
*Melphalan*  
*Bendamustine*

### Figure 35.1

Summary of chemotherapeutic agents.  
(Figure continues on next page)

<b>Ethyleneimines</b>
<i>Altretamine</i>
<i>Thiotepa</i>
<b>Alkyl sulfonates</b>
<i>Busulfan</i>
<b>Nitrasoureas</b>
<i>Carmustine</i>
<i>Lomustine</i>
<i>Streptozotocin</i>
<b>Triazine</b>
<i>Decarbazine</i>
<i>Temozolomide</i>
<b>Methylhydrazine</b>
<i>Procarbazine</i>
<b>MICROTUBULE INHIBITORS</b>
<b>Taxene derivatives</b>
<i>Paclitaxel</i>
<i>Docetaxel</i>
<b>Vinca alkaloids</b>
<i>Vincristine</i>
<i>Vinblastine</i>
<i>Vinorelbine</i>
<b>TOPOISOMERASE INHIBITORS</b>
<b>Photophyllam derivatives</b>
<b>Topoisomerase-II inhibitors</b>
<i>Etoposide</i>
<i>Tiniposide</i>
<b>Topoisomerase-I inhibitors</b>
<i>Topotecan</i>
<i>Irinotecan</i>
<b>PLATINUM COMPOUNDS</b>
<i>Cisplatin</i>
<i>Carboplatin</i>
<i>Oxaliplatin</i>
<b>DRUGS ACTING THROUGH SPECIFIC TARGETS</b>
<b>Angiogenesis inhibitors</b>
<i>Bevacizumab</i>
<i>Sunitinib</i>
<b>Proteasome inhibitor</b>
<i>Bortezomib</i>
<b>EGF receptor inhibitors</b>
<i>Cefitinib</i>
<i>Erlotinib</i>
<i>Cetuximab</i>

**Figure 35.1** (Continued)

Summary of chemotherapeutic agents.  
(Figure continues on next page)

eradication of every neoplastic cell. If a cure is not attainable, then the goal becomes control of the disease (prevent the cancer from enlarging and spreading) to extend survival and maintain quality of life. Thus, the individual maintains a “near-normal” existence, with the cancer treated as a chronic disease. In all cases, the neoplastic cell burden is initially reduced (debulked), either by surgery and/or by radiation, followed by chemotherapy, immunotherapy, therapy using biological modifiers, or a combination of these treatment modalities (Figure 35.3). In advanced stages of cancer, the likelihood of controlling the cancer is unlikely, and the goal is palliation (alleviation of symptoms and avoidance of life-threatening toxicity). This means that chemotherapeutic drugs may be used to relieve symptoms caused by the cancer and improve the quality of life, even though the drugs may not extend survival. The goal of treatment should always be kept in mind, as it often influences treatment decisions. Figure 35.4 illustrates how treatment goals can be dynamic.

2. **Indications for treatment:** Chemotherapy is sometimes used when neoplasms are disseminated and are not amenable to surgery. Chemotherapy may also be used as a supplemental treatment to attack micrometastasis following surgery and radiation treatment, in which case it is called adjuvant chemotherapy. Chemotherapy given prior to the surgical procedure in an attempt to shrink the cancer is referred to as neoadjuvant chemotherapy, and chemotherapy given in lower doses to assist in prolonging remission is known as maintenance chemotherapy.
3. **Tumor susceptibility and the growth cycle:** The fraction of tumor cells that are in the replicative cycle (“growth fraction”) influences susceptibility to most cancer chemotherapeutic agents. Rapidly dividing cells are generally more sensitive to chemotherapy, whereas slowly proliferating cells are less sensitive to chemotherapy. In general, nondividing cells (those in the G<sub>0</sub> phase; Figure 35.5) usually survive the toxic effects of many chemotherapeutic agents.
  - a. **Cell cycle specificity of drugs:** Both normal cells and tumor cells go through growth cycles (Figure 35.5). However, the number of cells that are in various stages of the cycle may differ in normal and neoplastic tissues. Chemotherapeutic agents that are effective only against replicating cells (that is, those cells that are dividing) are said to be cell cycle–specific (Figure 35.5), whereas other agents are cell cycle–nonspecific. Although the nonspecific drugs generally have greater toxicity in cycling cells, they are also useful against tumors that have a low percentage of replicating cells.
  - b. **Tumor growth rate:** The growth rate of most solid tumors is initially rapid, but growth rate usually decreases as the tumor size increases (Figure 35.3). This is due to a deficiency of nutrients and oxygen caused by inadequate vascularization and lack of blood circulation. Tumor burden can be reduced through surgery, radiation, or use of cell cycle–nonspecific drugs that promote the remaining cells into active proliferation, thus increasing susceptibility to cell cycle–specific chemotherapeutic agents.

## B. Treatment regimens and scheduling

Drug dosages are usually calculated on the basis of the body surface area, in an effort to tailor the dosage to each patient.

1. **Log kill phenomenon:** Destruction of cancer cells by chemotherapeutic agents follows first-order kinetics (that is, a given dose of drug destroys a constant fraction of cells). The term “log kill” is used to describe this phenomenon. For example, a diagnosis of leukemia is generally made when there are about  $10^9$  (total) leukemic cells. Consequently, if treatment leads to a 99.999% kill, then 0.001% of  $10^9$  cells (or  $10^4$  cells) remain. This is defined as a 5-log kill (reduction of  $10^5$  cells). At this point, the patient becomes asymptomatic, and the patient is in remission (Figure 35.3). For most bacterial infections, a 5-log (100,000-fold) reduction in the number of microorganisms results in a cure, because the immune system can destroy the remaining bacterial cells. However, tumor cells are not as readily eliminated, and additional treatment is required to totally eradicate the leukemic cell population.
2. **Pharmacologic sanctuaries:** Leukemic or other tumor cells find sanctuary in tissues such as the central nervous system (CNS), where transport constraints prevent certain chemotherapeutic agents from entrance. Therefore, a patient may require irradiation of the craniospinal axis or intrathecal administration of drugs to eliminate leukemic cells at that site. Similarly, drugs may be unable to penetrate certain areas of solid tumors.
3. **Treatment protocols:** Combination chemotherapy is more successful than single-drug treatment in most cancers for which chemotherapy is effective.
  - a. **Combination chemotherapy:** Cytotoxic agents with different toxicities, and with different molecular sites and mechanisms of action, are usually combined at full doses. This results in higher response rates, due to additive and/or potentiated cytotoxic effects, and nonoverlapping host toxicities.

### Tyrosine protein-kinase inhibitors

*Imatinib*

*Nilotinib*

### Unarmed monoclonal antibody

*Rituximab*

*Trastuzumab*

### ACTIVE THROUGH HORMONAL PATHWAY

#### Estrogen and receptor modulators

*Ethynodiol diacetate*

*Diethylstilbestrol diphosphate (fostesterone)*

#### Selective estrogen receptor modulators (SERMS)

*Tamoxifen*

*Toremifene*

#### Estrogen receptor down-regulators

*Fluvestrant*

#### Aromatase inhibitors

*Letrozole*

*Anastrozole*

*Exemestane*

#### Antiandrogen

*Flutamide*

*Bicalutamide*

*Nilutamide*

#### GnRH analogs

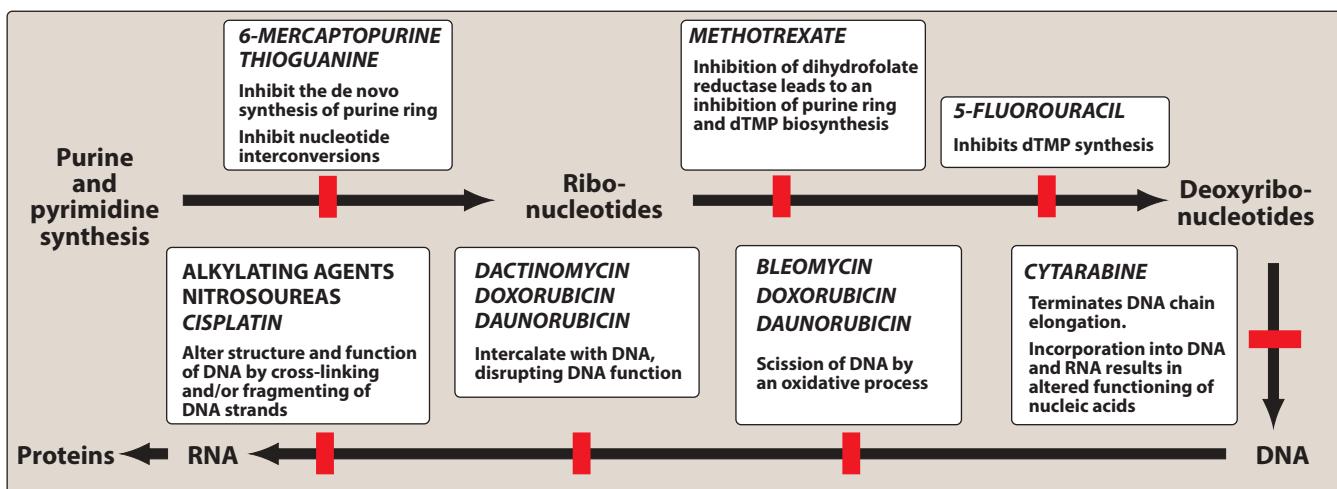
*Leuprolide*

*Nafarelin*

*Goserelin*

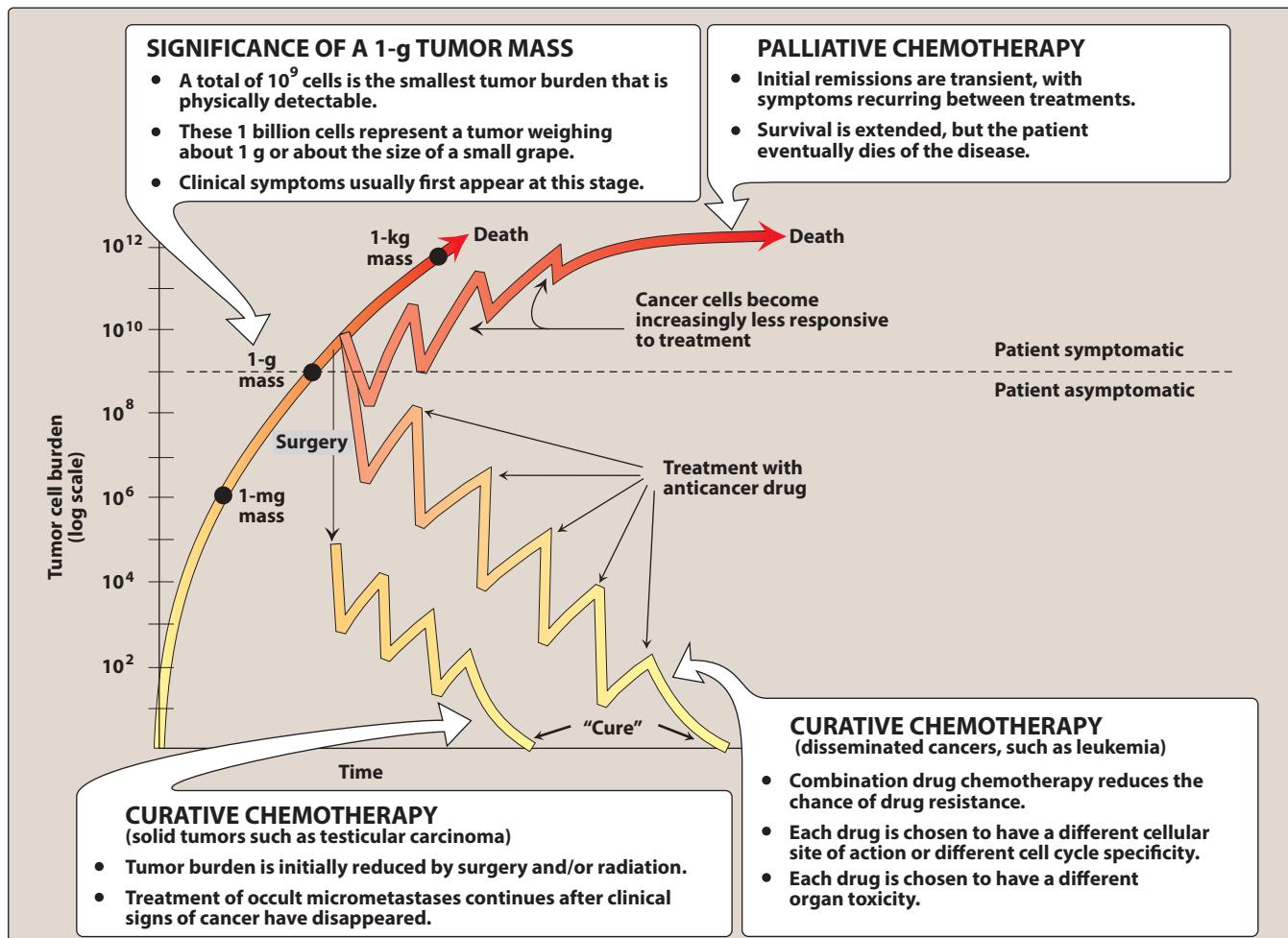
**Figure 35.1** (Continued)

Summary of chemotherapeutic agents.

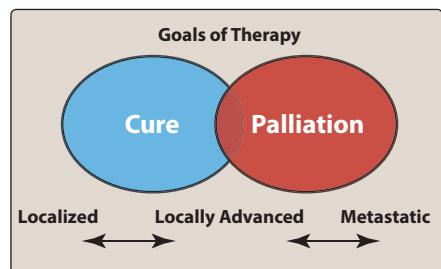


**Figure 35.2**

Examples of chemotherapeutic agents affecting RNA and DNA. dTMP = deoxythymidine monophosphate.

**Figure 35.3**

Effects of various treatments on the cancer cell burden in a hypothetical patient.

**Figure 35.4**

Goals of treatment with chemotherapeutic agents. Reprinted and amended with permission from Dr. Thomas George, MD.

In contrast, agents with similar dose-limiting toxicities, such as myelosuppression, nephrotoxicity, or cardiotoxicity, can be combined safely only by reducing the doses of each.

b. **Advantages of combinations:** The advantages of combination chemotherapy are that it 1) provides maximal cell killing within the range of tolerated toxicity, 2) is effective against a broader range of cell lines in the heterogeneous tumor population, and 3) may delay or prevent the development of resistant cell lines.

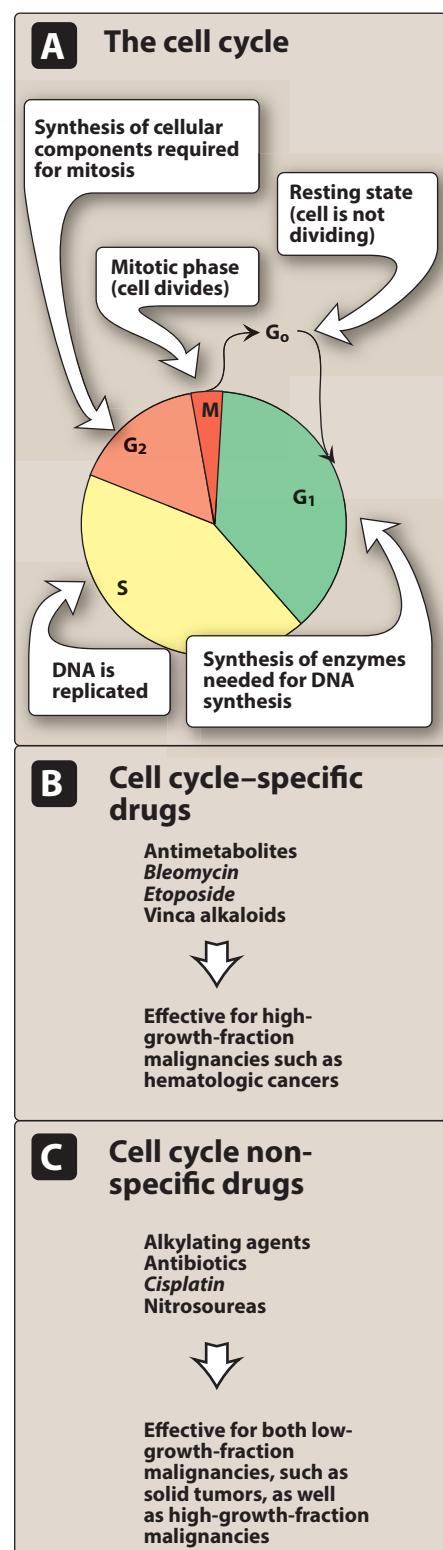
c. **Treatment protocols:** Many cancer treatment protocols have been developed, and each is applicable to a particular neoplastic state. They are usually identified by an acronym. For example, a common regimen called R-CHOP, used for the treatment of non-Hodgkin lymphoma, consists of *rituximab*, *cyclophosphamide*, *hydroxydaunorubicin (doxorubicin)*, *Oncovin (vincristine)*, and *prednisone*. Therapy is scheduled intermittently to allow recovery or rescue of the immune system, which is also affected by the chemotherapeutic agents, thus reducing the risk of serious infection.

### C. Resistance and toxicity with chemotherapy

Cancer drugs are toxins that present a lethal threat to the cells. It is, therefore, not surprising that cells have evolved elaborate defense mechanisms to protect themselves from chemical toxins, including chemotherapeutic agents.

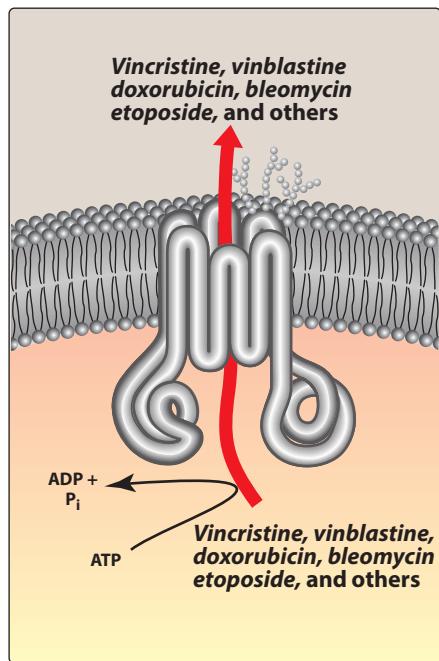
- Resistance:** Some neoplastic cells (for example, melanoma) are inherently resistant to most anticancer drugs. Other tumor types may acquire resistance to the cytotoxic effects of a drug by mutating, particularly after prolonged administration of suboptimal doses. The development of drug resistance is minimized by short-term, intensive, intermittent therapy with combinations of drugs. Drug combinations are also effective against a broader range of resistant cells in the tumor population.
- Multidrug resistance:** Stepwise selection of an amplified gene that codes for a transmembrane protein (P-glycoprotein for “permeability” glycoprotein; Figure 35.6) is responsible for multidrug resistance. This resistance is due to adenosine triphosphate-dependent pumping of drugs out of the cell in the presence of P-glycoprotein. Cross-resistance following the use of structurally unrelated agents also occurs. For example, cells that are resistant to the cytotoxic effects of the Vinca alkaloids are also resistant to *dactinomycin* and to the anthracycline antibiotics, as well as to *colchicine*, and vice versa. These drugs are all naturally occurring substances, each of which has a hydrophobic aromatic ring and a positive charge at neutral pH. [Note: P-glycoprotein is normally expressed at low levels in most cell types, but higher levels are found in the kidney, liver, pancreas, small intestine, colon, and adrenal gland. It has been suggested that the presence of P-glycoprotein may account for the intrinsic resistance to chemotherapy observed with adenocarcinomas.] Certain drugs at high concentrations (for example, *verapamil*) can inhibit the pump and, thus, interfere with the efflux of the anticancer agent. However, these drugs are undesirable because of adverse pharmacologic actions of their own. The third-generation P-gp inhibitor, elacridar, has been found to be an efficient inhibitor of human breast cancer resistance protein (BCRP); however, clinical translation of the promise is yet to be demonstrated not just for elacridar but also for other P-gp inhibitors in this class.
- Toxicity:** Therapy aimed at killing rapidly dividing cancer cells also affects normal cells undergoing rapid proliferation (for example, cells of the buccal mucosa, bone marrow, gastrointestinal [GI] mucosa, and hair follicles), contributing to the toxic manifestations of chemotherapy.

- Common adverse effects:** Most chemotherapeutic agents have a narrow therapeutic index. Severe vomiting, stomatitis, bone marrow suppression, and alopecia occur to a lesser or greater extent during therapy with all antineoplastic agents. Vomiting is often controlled by administration of antiemetic drugs. Some toxicities, such as myelosuppression that predisposes to infection, are common to many chemotherapeutic agents (Figure 35.7), whereas other adverse reactions are confined to specific agents, such as bladder toxicity with *cyclophosphamide*, cardiotoxicity with *doxorubicin*, and pulmonary



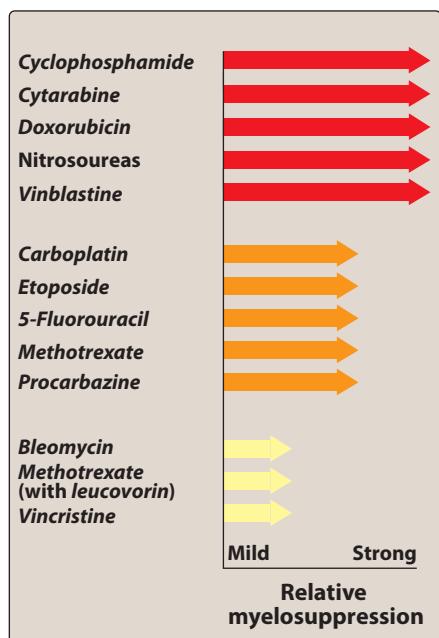
**Figure 35.5**

Effects of chemotherapeutic agents on the growth cycle of mammalian cells.



**Figure 35.6**

The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.  
Modified from N. Kartner, and V. Ling, Sci. Am. (1989).



**Figure 35.7**

Comparison of myelosuppressive potential of chemotherapeutic drugs.

fibrosis with *bleomycin*. The duration of the adverse effects varies widely. For example, alopecia is transient, but the cardiac, pulmonary, and bladder toxicities can be irreversible.

- b. **Minimizing adverse effects:** Some toxic reactions may be ameliorated by interventions, such as the use of cytoprotectant drugs, local perfusion of the tumor (for example, a sarcoma of the arm), removal of some marrow of the patient prior to intensive treatment and then reimplantation afterwards, or intensive hydration and diuresis to prevent bladder toxicities. The megaloblastic anemia that occurs with *methotrexate* can be effectively counteracted by administering *folinic acid (leucovorin)*. With the availability of human granulocyte colony-stimulating factor (*filgrastim*), the neutropenia associated with treatment of cancer by many drugs can be partially reversed.
4. **Treatment-induced tumors:** Because most antineoplastic agents are mutagens, neoplasms (for example, acute nonlymphocytic leukemia) may arise 10 or more years after the original cancer was cured. [Note: Treatment-induced neoplasms are especially a problem after therapy with alkylating agents.] Most tumors that develop from cancer chemotherapeutic agents respond well to treatment strategies.

### III. ANTIMETABOLITES

Antimetabolites are structurally related to normal compounds that exist within the cell (Figure 35.8). They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are in S-phase and are, therefore, cell cycle-specific.

#### A. Methotrexate, pemetrexed, and pralatrexate (folate antagonists)

The vitamin folic acid plays a central role in a variety of metabolic reactions involving the transfer of one-carbon units and is essential for cell replication. Folic acid is obtained mainly from dietary sources and from food sources produced by intestinal flora. *Methotrexate* [meth-oh-TREK-sate] (*MTX*), *pemetrexed* [pem-e-TREX-ed], and *pralatrexate* [pral-a-TREX-ate] are antifolate agents.

1. **Mechanism of action:** *MTX* is structurally related to folic acid and acts as an antagonist of the vitamin by inhibiting mammalian dihydrofolate reductase (DHFR), the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid ( $\text{FH}_4$ ) (Figure 35.9). The inhibition of DHFR can only be reversed by a 1000-fold excess of the natural substrate, dihydrofolate ( $\text{FH}_2$ ), or by administration of *leucovorin*, which bypasses the blocked enzyme and replenishes the folate pool (Figure 35.9). [Note: *Leucovorin*, or *folinic acid*, is the  $\text{N}^5$ -formyl group-carrying form of  $\text{FH}_4$ .] *MTX* is specific for the S-phase of the cell cycle. *Pemetrexed* is an antimetabolite similar in mechanism to *methotrexate*. However, in addition to inhibiting DHFR, it also inhibits thymidylate synthase and other enzymes involved in folate metabolism and DNA synthesis. *Pralatrexate* is an antimetabolite that also inhibits DHFR.

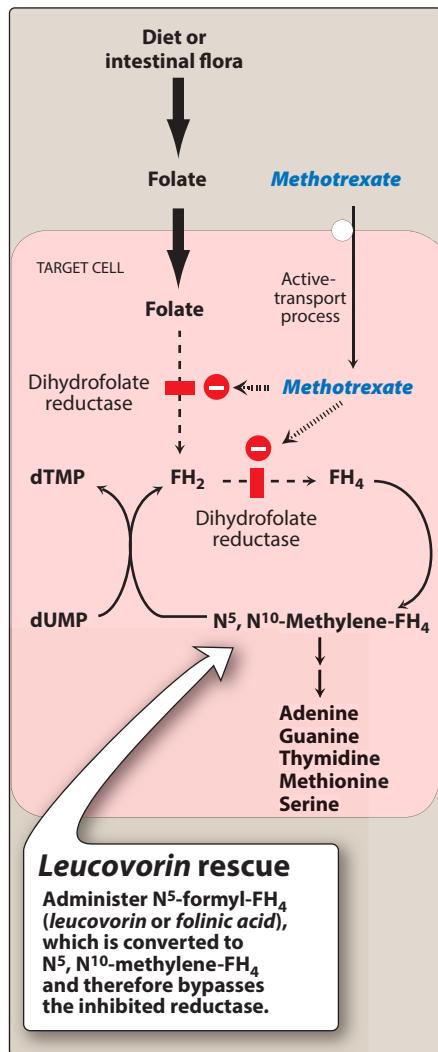
DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
<i>Methotrexate</i>	IV/PO/IM/IT	N/V/D, stomatitis, rash, alopecia, myelosuppression, high-dose: renal damage IT: neurologic toxicities	<i>Omeprazole, folic acid, warfarin, NSAIDs, penicillins, cephalosporins</i>	CBC; renal, hepatic function; <i>methotrexate</i> levels (after high-dose infusion)	Some adverse effects can be prevented or reversed by administering <i>leucovorin</i> . Adjust dose in renal impairment.
<i>6-Mercaptopurine (6-MP)</i>	PO	N/V/D, myelosuppression, anorexia, hepatotoxicity (jaundice)	<i>Warfarin, allopurinol, SMZ/TMP</i>	CBC; renal, hepatic function	Reduce dose of <i>6-MP</i> by 50%–75% when used with <i>allopurinol</i> to prevent toxicity.
<i>Fludarabine</i>	IV	N/V/D, myelosuppression, rash, immunosuppression, fever, edema, neurologic toxicity	<i>Cytarabine, cyclophosphamide, cisplatin, mitoxantrone, pentostatin</i>	CBC; renal, hepatic function; tumor lysis syndrome	Immunosuppression increases risk of opportunistic infections. Adjust dose in renal impairment.
<i>Cladribine</i>	IV/SC	Neutropenia, immunosuppression, fever, N/V, teratogenic, peripheral neuropathy		CBC; renal function; tumor lysis syndrome	Immunosuppression increases risk of opportunistic infections.
<i>5-Fluorouracil (5-FU)</i>	IV	D, alopecia, severe mucositis, myelosuppression (bolus), "hand-foot syndrome" (continuous infusion), coronary vasospasm	<i>Methotrexate</i> (antifolate analogs)	CBC; renal, hepatic function; D	"Hand-foot syndrome"/palmar-plantar erythrodysesthesia is an erythematous desquamation of the palms and soles.
<i>Capecitabine</i>	PO	D, mucositis, myelosuppression, "hand-foot syndrome", chest pain	<i>Warfarin, phenytoin</i>	CBC; renal, hepatic function; D	Should be taken within 30 minutes of a meal; keep skin well moisturized.
<i>Cytarabine</i>	IV/IT	N/V/D, myelosuppression, hepatotoxicity; neurologic toxicity, conjunctivitis (high dose)	<i>Digoxin, alkylating agents, methotrexate</i>	CBC; renal, hepatic function; CNS toxicity	Administer steroid eye drops with high dose to prevent conjunctivitis.
<i>Azacitidine</i>	IV/SC	Myelosuppression (neutropenia, thrombocytopenia), N/V, constipation, hypokalemia, renal toxicity		CBC; renal, hepatic function	Stability of prepared drug (IV) is only 60 minutes.
<i>Gemcitabine</i>	IV	Myelosuppression, (thrombocytopenia), N/V, alopecia, rash, flu-like syndrome	Potent radiosensitizer	CBC; hepatic function, rash	–

CBC = complete blood count; CNS, central nervous system; D = diarrhea; IM = intramuscular; IT = intrathecal; IV = intravenous; N = nausea; NSAID, nonsteroidal anti-inflammatory drug; PO = oral; SC = subcutaneous; SMZ/TMP = sulfamethoxazole/trimethoprim; V = vomiting.

**Figure 35.8**

Summary of antimetabolites. (For drug dosages, refer to Appendix at the end of the book.)

- Therapeutic uses:** *MTX*, usually in combination with other drugs, is effective against acute lymphocytic leukemia, Burkitt lymphoma in children, breast cancer, bladder cancer, and head and neck carcinomas. In addition, low-dose *MTX* is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis, as well as Crohn disease. All patients receiving *MTX* require close monitoring for possible toxic effects. *Pemetrexed* is primarily used in non-small cell lung cancer. *Pralatrexate* is used in relapsed or refractory T-cell lymphoma.
- Pharmacokinetics:** *MTX* is variably absorbed at low doses from the GI tract, but it can also be administered by intramuscular, intravenous (IV), and intrathecal routes (Figure 35.10). Because *MTX* does not easily penetrate the blood-brain barrier, it can be administered intrathecally to destroy neoplastic cells that thrive in the sanctuary of the CNS. High concentrations of the drug are found in the intestinal epithelium, liver, and kidney, as well as in ascites and pleural effusions. *MTX* is also distributed to the skin. Small amounts of *MTX* undergo hydroxylation at the 7 position to form 7-hydroxymethotrexate. This derivative is less water soluble than *MTX* and may lead to crystalluria. Therefore, it is important to keep the urine alkaline

**Figure 35.9**

Mechanism of action of *methotrexate* and the effect of administration of *leucovorin*.  $\text{FH}_2$  = dihydrofolate;  $\text{FH}_4$  = tetrahydrofolate; dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine monophosphate.

and the patient well hydrated to avoid renal toxicity. Excretion of the parent drug and the 7-OH metabolite occurs primarily via urine. It is used at an oral dose of 15 to 30 mg daily and at a dose of 20 to 40 mg/m<sup>2</sup> of the body surface area by intramuscular or intravenous injection in twice-a-week schedule. High-dose *methotrexate* such as 1 to 5.5 g/m<sup>2</sup> is used for long infusion over a period of 24 hours in every 2 to 4 weeks' duration. For cases of acute lymphoblastic leukemia, leucovorin rescue therapy within 24 hours of *methotrexate* infusion is started. Low doses such as 2.5 mg/kg for 5 days followed by 2 days' rest or 10 to 25 mg by the intravenous route once weekly is given for severe psoriasis. Smaller doses are also used for the induction of remission in rheumatoid arthritis.

4. **Adverse effects:** Adverse effects of MTX are outlined in Figure 35.8. *Pemetrexed* and *pralatrexate* should be given with folic acid and vitamin B<sub>12</sub> supplements to reduce hematologic and GI toxicities. Pretreatment with corticosteroids to prevent cutaneous reactions is recommended with *pemetrexed*.

### B. 6-Mercaptopurine (purine antagonists)

6-Mercaptopurine [mer-kap-toe-PYOOR-een] (6-MP), a purine antimetabolite, is the thiol analog of hypoxanthine. 6-MP and 6-thioguanine were the first purine analogs to prove beneficial for treating neoplastic disease. [Note: *Azathioprine*, an immunosuppressant, exerts its cytotoxic effects after conversion to 6-MP.] 6-MP is used principally in the maintenance of remission in acute lymphoblastic leukemia. 6-MP and its analog, *azathioprine*, are also beneficial in the treatment of Crohn disease. Adverse effects are noted in Figure 35.8. *Azathioprine* is used at an oral dose of 3 to 5 mg/kg/day followed by the maintenance dose of 1 to 2 mg/kg/day.

### C. Fludarabine

*Fludarabine* [floo-DARE-a-been] is the 5'-phosphate of 2-fluoroadenine arabinoside, a purine nucleotide analog. It is useful in the treatment of chronic lymphocytic leukemia, hairy cell leukemia, and indolent non-Hodgkin lymphoma. *Fludarabine* is a prodrug, and the phosphate is removed in the plasma to form 2-F-araA, which is taken up into cells and again phosphorylated (initially by deoxycytidine kinase). Although the exact cytotoxic mechanism is uncertain, the triphosphate is incorporated into both DNA and RNA. This decreases their synthesis in the S-phase and affects their function. Resistance is associated with reduced uptake into cells, lack of deoxycytidine kinase, and decreased affinity for DNA polymerase, as well as other mechanisms. *Fludarabine* is administered IV rather than orally, because intestinal bacteria split off the sugar to yield the very toxic metabolite, fluoroadenine. It is used at a dose of 25 mg/m<sup>2</sup> of the body surface area every day for 5 days and every 28 days by intravenous infusion.

### D. 5-Fluorouracil (pyrimidine antagonists)

5-Fluorouracil [flure-oh-YOOR-ah-sil] (5-FU), a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring. The fluorine interferes with the conversion of deoxyuridylic acid to

thymidylic acid, thus depriving the cell of thymidine, one of the essential precursors for DNA synthesis. 5-FU is employed primarily in the treatment of slow-growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas). When applied topically, 5-FU is also effective for the treatment of superficial basal cell carcinomas.

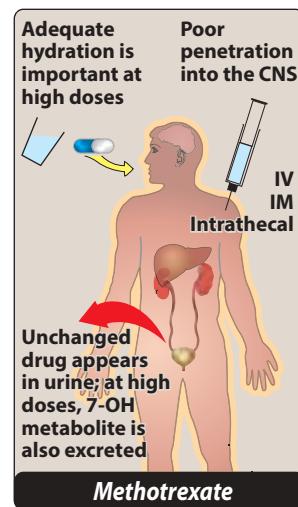
- Mechanism of action:** 5-FU itself is devoid of antineoplastic activity. It enters the cell through a carrier-mediated transport system and is converted to the corresponding deoxynucleotide (5-fluorodeoxyuridine monophosphate [5-FdUMP]; **Figure 35.11**), which competes with deoxyuridine monophosphate for thymidylate synthase, thus inhibiting its action. DNA synthesis decreases due to lack of thymidine, leading to imbalanced cell growth and “thymidine-less death” of rapidly dividing cells. [Note: *Leucovorin* is administered with 5-FU, because the reduced folate coenzyme is required in the thymidylate synthase inhibition. For example, a standard regimen for advanced colorectal cancer is *irinotecan* plus 5-FU/*leucovorin*.] 5-FU is also incorporated into RNA, and low levels have been detected in DNA. In the latter case, a glycosylase excises the 5-FU, damaging the DNA. 5-FU produces the anticancer effect in the S-phase of the cell cycle.
- Pharmacokinetics:** Because of severe toxicity to the GI tract, 5-FU is administered IV or, in the case of skin cancer, topically. The drug penetrates well into all tissues, including the CNS. 5-FU is rapidly metabolized in the liver, lung, and kidney. It is eventually converted to fluoro-β-alanine, which is removed in the urine. Elevated levels of dihydropyrimidine dehydrogenase (DPD) can increase the rate of 5-FU catabolism and decrease its bioavailability. The level of DPD level varies from individual to individual and may differ by as much as 6-fold in the general population. Patients with DPD deficiency may experience severe toxicity manifested by pancytopenia, mucositis, and life-threatening diarrhea. Knowledge of DPD activity in an individual should allow more appropriate dosing of 5-FU. It is infused at a dose of 500 mg/m<sup>2</sup> by the intravenous route over a period of 1 to 3 hours weekly for 6 to 8 weeks, or 12 mg/kg/day intravenously for 4 days followed by 6 mg/kg intravenously on alternate days for three to six cycles.

## E. Capecitabine

*Capecitabine* [cape-SITE-a-been] is a fluoropyrimidine carbamate. It is used in the treatment of colorectal and metastatic breast cancer. *Capecitabine* is well absorbed following oral administration. After being absorbed, *capecitabine*, which is itself nontoxic, undergoes a series of enzymatic reactions, the last of which is hydrolysis to 5-FU.

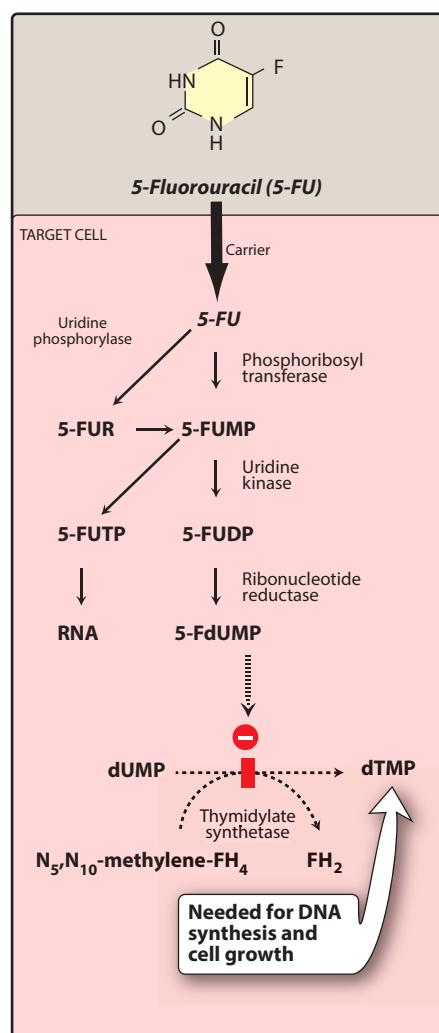
**Figure 35.11**

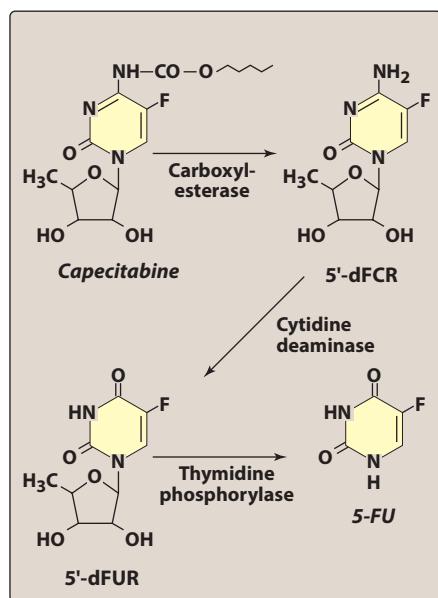
Mechanism of the cytotoxic action of 5-FU. 5-FU is converted to 5-fluorodeoxyuridine monophosphate (5-FdUMP), which competes with deoxyuridine monophosphate (dUMP) for the enzyme thymidylate synthetase. 5-FU = 5-fluorouracil; 5-FUR = 5-fluorouridine; 5-FUMP = 5-fluorouridine monophosphate; 5-FUDP = 5-fluorouridine diphosphate; 5-FUTP = 5-fluorouridine triphosphate; dUMP = deoxyuridine monophosphate; dTMP = deoxythymidine monophosphate.



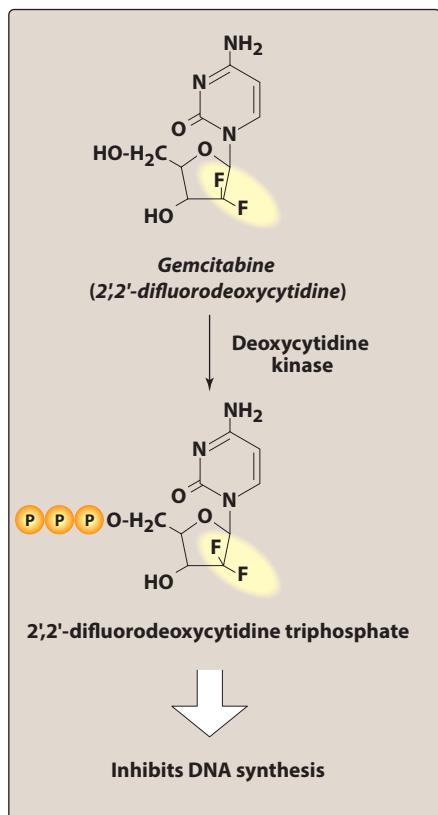
**Figure 35.10**

Administration and fate of *methotrexate*. CNS = central nervous system; IV = intravenous; IM = intramuscular.



**Figure 35.12**

Metabolic pathway of *capecitabine* to 5-fluorouracil (5-FU). 5'-dFCR = 5'-deoxy-5-fluorocytidine; 5'-dFUR = 5'-deoxy-5-fluorouridine.

**Figure 35.13**

Mechanism of action of *gemcitabine*.

This step is catalyzed by thymidine phosphorylase, an enzyme that is concentrated primarily in tumors. (Figure 35.12). Thus, the cytotoxic activity of *capecitabine* is the same as that of 5-FU and is tumor specific. The most important enzyme inhibited by 5-FU (and, thus, *capecitabine*) is thymidylate synthase.

### F. Cytarabine (cytidine analogs)

*Cytarabine* [syeh-TARE-ah-been] (*cytosine arabinoside* or *ara-C*) is an analog of 2'-deoxycytidine in which the natural ribose residue is replaced by D-arabinose. *Cytarabine* acts as a pyrimidine antagonist. The major clinical use of *cytarabine* is in acute nonlymphocytic (myelogenous) leukemia (AML). *Cytarabine* enters the cell by a carrier-mediated process and, like the other purine and pyrimidine antagonists, must be sequentially phosphorylated by deoxycytidine kinase and other nucleotide kinases to the nucleotide form (*cytosine arabinoside triphosphate* or *ara-CTP*) to be cytotoxic. Ara-CTP is an effective inhibitor of DNA polymerase. The nucleotide is also incorporated into nuclear DNA and can terminate chain elongation. It is, therefore, S-phase (and, hence, cell cycle) specific.

1. **Pharmacokinetics:** *Cytarabine* is not effective when given orally, because of deamination to the noncytotoxic ara-U by cytidine deaminase in the intestinal mucosa and liver. Given IV, it distributes throughout the body but does not penetrate the CNS in sufficient amounts. Therefore, it may also be injected intrathecally. *Cytarabine* undergoes extensive oxidative deamination in the body to ara-U, a pharmacologically inactive metabolite. Both *cytarabine* and ara-U are excreted in urine.

### G. Azacitidine

*Azacitidine* [A-zuh-SITE-i-dine] is a pyrimidine nucleoside analog of cytidine. It is used for the treatment of myelodysplastic syndromes and AML. *Azacitidine* undergoes activation to the nucleotide metabolite azacitidine triphosphate and gets incorporated into RNA to inhibit RNA processing and function. It is S-phase cell cycle-specific.

### H. Gemcitabine

*Gemcitabine* [jem-SITE-ah-been] is an analog of the nucleoside deoxycytidine. It is used most commonly for pancreatic cancer and non-small cell lung cancer. *Gemcitabine* is a substrate for deoxycytidine kinase, which phosphorylates the drug to 2',2'-difluorodeoxycytidine triphosphate. (Figure 35.13). *Gemcitabine* is administered by IV infusion. It is deaminated to difluorodeoxyuridine, which is not cytotoxic, and is excreted in urine.

## IV. ANTIBIOTICS

The antitumor antibiotics (Figure 35.14) owe their cytotoxic action primarily to their interactions with DNA, leading to disruption of DNA function. In addition to intercalation, their abilities to inhibit topoisomerases (I and II) and produce free radicals also play a major role in their cytotoxic effect. They are cell cycle-nonspecific, with *bleomycin* as an exception.

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Doxorubicin	IV	Myelosuppression, N/V/D, mucositis, cardiac toxicity, alopecia, red coloration of urine. Strong vesicants	Phenytoin, trastuzumab (cardiotoxicity), digoxin	CBC; renal, hepatic function; cardiac function (ECHO or MUGA); adjust in hepatic dysfunction	Cumulative doses > 450 mg/m <sup>2</sup> increase risk of cardiotoxicity. Vesicant!
Daunorubicin	IV				Cumulative doses > 550 mg/m <sup>2</sup> increase risk of cardiotoxicity. Vesicant!
Liposomal Doxorubicin	IV				Not a substitute for doxorubicin, less cardiotoxicity
Epirubicin	IV		Cimetidine		Cumulative doses > 900 mg/m <sup>2</sup> increase risk of cardiotoxicity. Vesicant! Less N/V
Idarubicin	IV				Cumulative doses > 150 mg/m <sup>2</sup> increase risk of cardiotoxicity. Vesicant!
Bleomycin	IV/SC/IM	Pulmonary fibrosis, alopecia, skin reactions, hyperpigmentation of hands, fever, chills, anaphylaxis	Phenothiazines, cisplatin (renal), radiation (pulmonary)	Pulmonary function tests; adjust in renal dysfunction; anaphylaxis	"Bleomycin lung" pulmonary fibrosis can be fatal. Discontinue if any signs of lung dysfunction.

CBC = complete blood count; D = diarrhea; IM = intramuscular; IV = intravenous; N = nausea; SC = subcutaneous; V = vomiting.

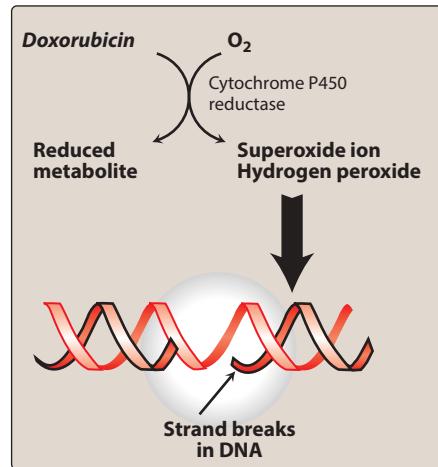
**Figure 35.14**

Summary of antitumor antibiotics. (For drug dosages, refer to Appendix at the end of the book.)

### A. Anthracyclines: Doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone

*Doxorubicin* [dox-oh-ROO-bi-sin] and *daunorubicin* [daw-noe-ROO-bi-sin] are classified as anthracycline antibiotics. *Doxorubicin* is the hydroxylated analog of *daunorubicin*. *Idarubicin* [eye-da-ROO-bi-sin], the 4-demethoxy analog of *daunorubicin*, *epirubicin* [eh-pee-ROO-bih-sin], and *mitoxantrone* [mye-toe-ZAN-trone] are also available. Therapeutic uses for these agents differ despite their structural similarity and apparently similar mechanisms of action. *Doxorubicin* is one of the most important and widely used anticancer drugs. It is used in combination with other agents for treatment of sarcomas and a variety of carcinomas, including breast and lung, as well as for treatment of acute lymphocytic leukemia and lymphomas. *Daunorubicin* and *idarubicin* are used in the treatment of acute leukemias, and *mitoxantrone* is used in prostate cancer.

- Mechanism of action:** *Doxorubicin* and other anthracyclines induce cytotoxicity through several different mechanisms. For example, *doxorubicin*-derived free radicals can induce membrane lipid peroxidation, DNA strand scission, and direct oxidation of purine or pyrimidine bases, thiols, and amines (Figure 35.15).
- Pharmacokinetics:** These agents must be administered intravenously, because they are inactivated in the GI tract. Extravasation is a serious problem that can lead to tissue necrosis. The anthracycline antibiotics bind to plasma proteins as well as to other tissue components, where they are widely distributed. They do not penetrate the blood-brain barrier or the testes. These agents undergo extensive hepatic metabolism, and dosage adjustments



**Figure 35.15**

*Doxorubicin* interacts with molecular oxygen, producing superoxide ions and hydrogen peroxide, which cause single-strand breaks in DNA.

are needed in patients with impaired hepatic function. Biliary excretion is the major route of elimination. Because of the dark red color of the anthracycline drugs, the veins may become visible surrounding the site of infusion, and red discoloration of urine may occur.

3. **Adverse effects:** Irreversible, dose-dependent cardiotoxicity is the most serious adverse reaction and is more common with *daunorubicin* and *doxorubicin* than with *idarubicin* and *epirubicin*. Cardiotoxicity apparently results from the generation of free radicals and lipid peroxidation. Addition of *trastuzumab* to protocols with *doxorubicin* or *epirubicin* increases congestive heart failure. There has been some success with the iron chelator *dexrazoxane* in protecting against the cardiotoxicity of *doxorubicin*. The liposomal-encapsulated *doxorubicin* is reported to be less cardio-toxic than the standard formulation.

## B. Bleomycin

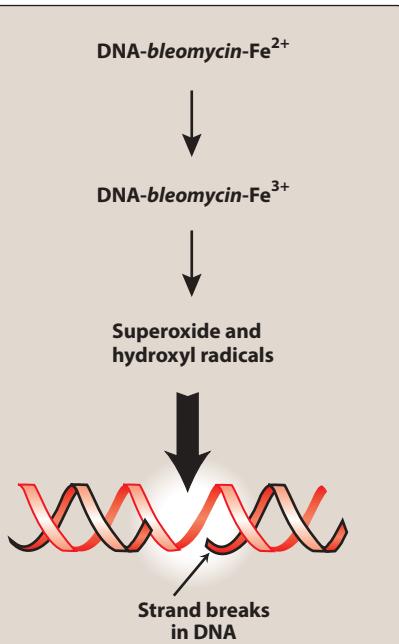
*Bleomycin* [blee-oh-MYE-sin] is a mixture of different copper-chelating glycopeptides that, like the anthracycline antibiotics, cause scission of DNA by an oxidative process. *Bleomycin* is cell cycle-specific and causes cells to accumulate in the G<sub>2</sub> phase. It is primarily used in the treatment of testicular cancers and Hodgkin lymphoma.

1. **Mechanism of action:** A DNA–bleomycin–Fe<sup>2+</sup> complex appears to undergo oxidation to bleomycin–Fe<sup>3+</sup>. The liberated electrons react with oxygen to form superoxide or hydroxyl radicals, which, in turn, attack the phosphodiester bonds of DNA, resulting in strand breakage and chromosomal aberrations (Figure 35.16).
2. **Pharmacokinetics:** *Bleomycin* is administered by a number of routes. The *bleomycin*-inactivating enzyme (a hydrolase) is high in a number of tissues (for example, liver and spleen) but is low in the lung and absent in the skin, accounting for toxicity in those tissues. Most of the parent drug is excreted unchanged in the urine, necessitating dose adjustment in patients with renal failure.
3. **Adverse effects:** Pulmonary toxicity is the most serious adverse effect, progressing from rales, cough, and infiltrate to potentially fatal fibrosis. The pulmonary fibrosis that is caused by *bleomycin* is often referred to as “bleomycin lung.” Hypertrophic skin changes and hyperpigmentation of the hands are prevalent. *Bleomycin* is unusual in that myelosuppression is rare.

## C. Dactinomycin (actimomycin D)

*Dactinomycin* (clear, gold-colored liquid) is a chromopeptide antibiotic first discovered for cancer. Most of the chromopeptides contain planar phenoxazone actinosin which is responsible for the color. *Dactinomycin* is used for the treatment of solid tumors in children and choriocarcinomas in adults. *Dactinomycin* is used alone or in combination with other agents in chemotherapy regimens. It is mostly used for the treatment of rhabdomyosarcoma and Wilm’s tumor in children.

1. **Mechanism of action:** *Dactinomycin* binds to double-helical DNA and makes a complex. This complexation blocks the transcription of DNA by RNA polymerase. *Dactinomycin*, a potent anticancer agent, exhibits cytotoxicity by inhibiting all rapidly proliferating cancer cells.



**Figure 35.16**

*Bleomycin* causes breaks in DNA by an oxidative process.

- 2. Pharmacokinetics:** *Dactinomycin* is administered by the intravenous route which is minimally metabolized. Excreted in urine and bile with a terminal half-life of 36 hours, it does not cross the blood-brain barrier.
- 3. Adverse effects:** *Dactinomycin* causes hematopoietic suppression with pancytopenia in the first week after completion of therapy. It can cause proctitis, diarrhea, glossitis, cheilitis, and ulcerations. Due to its action on multiplying of cells, *dactinomycin* causes alopecia. *Dactinomycin* can cause nausea, anorexia, and vomiting within a few hours of administration. Extravasation during intravenous administration can cause severe local injury.

## V. ALKYLATING AGENTS

Alkylating agents (Figure 35.17) exert their cytotoxic effects by covalently binding to nucleophilic groups on various cell constituents. Alkylation of DNA is probably the crucial cytotoxic reaction that is lethal to the tumor cells. Alkylating agents do not discriminate between cycling and resting cells, even though they are most toxic for rapidly dividing cells. They are

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
<i>Cyclophosphamide</i>	IV/PO	Myelosuppression, hemorrhagic cystitis, N/V/D, alopecia, amenorrhea, secondary malignancies	<i>Phenobarbital, phenytoin</i> (P450); <i>digoxin, anticoagulants</i>	Urinalysis; CBC; renal, hepatic function	Good hydration to prevent bladder toxicity (mesna with high doses)
<i>Ifosfamide</i>	IV	Myelosuppression, hemorrhagic cystitis, N/V, neurotoxicity, alopecia, amenorrhea	<i>Phenobarbital, phenytoin</i> (P450); <i>cimetidine, allopurinol, warfarin</i>	Urinalysis; neurotoxicity	Use mesna and hydration to prevent bladder toxicity
<i>Carmustine (BCNU)</i>	IV	Myelosuppression, N/V, facial flushing, hepatotoxicity, pulmonary toxicity, impotence, infertility	<i>Cimetidine, amphotericin B, digoxin, phenytoin</i>	CBC; PFTs; renal, hepatic function	Also available as an implantable wafer (brain)
<i>Lomustine (CCNU)</i>	PO	Myelosuppression, N/V, pulmonary toxicity, impotence, infertility, neurotoxicity	<i>Cimetidine, alcohol</i>	CBC; PFTs; renal function	Administer on an empty stomach
<i>Dacarbazine</i>	IV	Myelosuppression, N/V, flu-like syndrome, CNS toxicity, hepatotoxicity, photosensitivity	<i>Phenytoin, phenobarbital</i> (P450)	CBC; renal, hepatic function	Vesicant
<i>Temozolomide</i>	PO	N/V, myelosuppression, headache, fatigue, photosensitivity		CBC; renal, hepatic function	Requires <i>Pneumocystis pneumonia</i> prophylaxis
<i>Melphalan</i>	IV/PO	Myelosuppression, N/V/D, mucositis, hypersensitivity (IV)	<i>Cimetidine, steroids, cyclosporine</i>	CBC; renal, hepatic function; adjust in renal dysfunction	Take on an empty stomach
<i>Chlorambucil</i>	PO	Myelosuppression, skin rash, pulmonary fibrosis (rare), hyperuricemia, seizures	<i>Phenobarbital, phenytoin</i> (P450)	CBC; renal, hepatic function; uric acid	Take with food
<i>Busulfan</i>	IV	Myelosuppression, N/V/D, mucositis, skin rash, pulmonary fibrosis, hepatotoxicity	<i>Acetaminophen, itraconazole, phenytoin</i>	CBC; pulmonary symptoms; renal, hepatic function	"Busulfan lung"

CBC = complete blood count; CNS = central nervous system; D = diarrhea; IV = intravenous; N = nausea; PFT = pulmonary function test; PO = by mouth; V = vomiting.

**Figure 35.17**

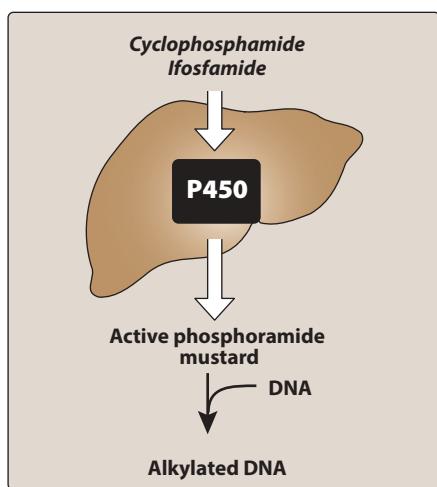
Summary of alkylating agents. (For drug dosages, refer to Appendix at the end of the book.)

used in combination with other agents to treat a wide variety of lymphatic and solid cancers. In addition to being cytotoxic, all are mutagenic and carcinogenic and can lead to secondary malignancies such as acute leukemia.

### A. Cyclophosphamide and ifosfamide (nitrogen mustards)

These drugs are very closely related mustard agents that share most of the same primary mechanisms and toxicities. They are cytotoxic only after generation of their alkylating species, which are produced through hydroxylation by cytochrome P450 (CYP450). These agents have a broad clinical spectrum and are used as single agents or in combinations in the treatment of a wide variety of neoplastic diseases, such as non-Hodgkin lymphoma, sarcoma, and breast cancer.

- Mechanism of action:** *Cyclophosphamide* [sye-kloe-FOSS-fah-mide] is the most commonly used alkylating agent. Both *cyclophosphamide* and *ifosfamide* [eye-FOSS-fah-mide] are first biotransformed to hydroxylated intermediates primarily in the liver by the CYP450 system (Figure 35.18). The hydroxylated intermediates then undergo metabolism to form the active compounds, phosphoramide mustard and acrolein. Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step.
- Pharmacokinetics:** *Cyclophosphamide* is available in oral and IV preparations, whereas *ifosfamide* is IV only. *Cyclophosphamide* is metabolized in the liver to active and inactive metabolites, and minimal amounts are excreted in the urine as unchanged drug. *Ifosfamide* is metabolized primarily by CYP450 3A4 and 2B6 isoenzymes. It is mainly renally excreted.
- Adverse effects:** A unique toxicity of both drugs is hemorrhagic cystitis, which can lead to fibrosis of the bladder. Bladder toxicity has been attributed to acrolein in the urine in the case of *cyclophosphamide* and to toxic metabolites of *ifosfamide*. Adequate hydration as well as IV injection of mesna (sodium 2-mercaptopethane sulfonate), which neutralizes the toxic metabolites, can minimize this problem. Neurotoxicity has been reported in patients on high-dose *ifosfamide*, probably due to the metabolite, chloroacetaldehyde.



**Figure 35.18**

Activation of *cyclophosphamide* and *ifosfamide* by hepatic cytochrome P450.

### B. Nitrosoureas

*Carmustine* [KAR-mus-teen, BCNU] and *lomustine* [LOE-mus-teen, CCNU] are closely related nitrosoureas. Because of their ability to penetrate the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors.

- Mechanism of action:** The nitrosoureas exert cytotoxic effects by an alkylation that inhibits replication and, eventually, RNA and protein synthesis. Although they alkylate DNA in resting cells, cytotoxicity is expressed primarily in cells that are actively dividing. Therefore, nondividing cells can escape death if DNA repair occurs. Nitrosoureas also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins in the targeted cells.
- Pharmacokinetics:** *Carmustine* is administered IV and as chemotherapy wafer implants, whereas *lomustine* is given orally. Because of their lipophilicity, these agents distribute widely in the body and

readily penetrate the CNS. The drugs undergo extensive metabolism. *Lomustine* is metabolized to active products. The kidney is the major excretory route for the nitrosoureas (Figure 35.19).

### C. Streptozotocin

*Streptozotocin* is an antibiotic brought under this group due to its structure containing methyl nitrosourea group attached to glucose. It is used for the treatment of pancreatic cancer and malignant carcinoid tumors.

- Mechanism of action:** Due to its glucose structure, it has higher affinity for pancreas and in experimental animals it causes diabetes by the destruction of islets of Langerhans.
- Pharmacokinetics:** It shows a very short half-life after intravenous administration of 15 minutes. Only a fraction of drug (20%) is excreted in urine in the unmetabolized form.
- Adverse effects:** Nausea, vomiting, elevation of hepatic enzymes, and renal toxicity are reported. *Streptozotocin* should not be combined with other nephrotoxic agents. It is also reported to cause hematological toxicity in some patients.

### D. Procarbazine (methylhydrazines)

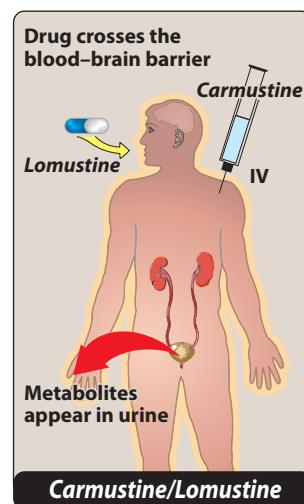
*Procarbazine* is a methylhydrazine derivative used for the treatment of Hodgkin's disease and malignant brain tumors. MOPP is a chemotherapy regimen consisting of *mechlorethamine*, *vincristine*, *procarbazine*, and *prednisone*. One of the components of MOPP regimen for treating Hodgkin's disease has been now largely replaced with other drugs and regimens.

- Mechanism of action:** Upon administration, *procarbazine* is converted by cytochromes of the liver into a highly reactive alkylating species which in turn methylates DNA. It is extensively metabolized and excreted.
- Adverse effects:** *Procarbazine* causes leukopenia and thrombocytopenia. Gastrointestinal side effects are very common. It is a weak mono-amino oxidase (MAO) inhibitor and blocks the metabolism of catecholamines. It is highly carcinogenic, mutagenic, and teratogenic and is associated with the risk of developing acute leukemia in patients undergoing treatment with this agent.

### E. Dacarbazine and temozolamide (tiazenes)

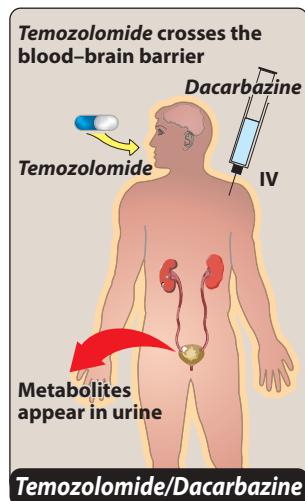
*Dacarbazine* [dah-KAR-bah-zeen] is an alkylating agent that must undergo biotransformation to an active metabolite, methyltriazeno-imidazole carboxamide (MTIC). The metabolite is responsible for the alkylating activity of this agent by forming methylcarbonium ions that attack the nucleophilic groups in the DNA molecule. The cytotoxic action of *dacarbazine* has been attributed to the ability of its metabolite to methylate DNA on the O-6 position of guanine. *Dacarbazine* has found use in the treatment of melanoma and Hodgkin lymphoma.

*Temozolamide* [te-moe-ZOE-loe-mide] is related to *dacarbazine*, because both must undergo biotransformation to an active metabolite,



**Figure 35.19**

Administration and fate of *carmustine*/*lomustine*. IV = intravenous.



**Figure 35.20**

Administration and fate of *temozolomide* and *dacarbazine*. IV = intravenous.

MTIC, which is likely responsible for the methylation of DNA on the O-6 and N-7 position of guanine. Unlike *dacarbazine*, *temozolomide* does not require the CYP450 system for metabolic transformation, and it undergoes chemical transformation at normal physiological pH. *Temozolomide* also inhibits the repair enzyme, O-6-guanine-DNA alkyltransferase. *Temozolomide* differs from *dacarbazine* in that it crosses the blood–brain barrier and, therefore, is used in the treatment of brain tumors such as glioblastomas and astrocytomas. It is also used in metastatic melanoma. *Temozolomide* is administered intravenously or orally and has excellent bioavailability after oral administration. The parent drug and metabolites are excreted in urine (Figure 35.20).

#### F. Other alkylating agents

*Mechlorethamine* [mek-lor-ETH-ah-meen] was developed as a vesicant (nitrogen mustard) during World War I. Its ability to cause lymphocytopenia led to its use in lymphatic cancers. *Melphalan* [MEL-fah-lan], a phenylalanine derivative of nitrogen mustard, is used in the treatment of multiple myeloma. This is a bifunctional alkylating agent that can be given orally, although the plasma concentration differs from patient to patient due to variation in intestinal absorption and metabolism. The dose of *melphalan* is carefully adjusted by monitoring the platelet and white blood cell counts. *Chlorambucil* [clor-AM-byoo-sil] is another bifunctional alkylating agent that is used in the treatment of chronic lymphocytic leukemia. *Busulfan* [byoo-SUL-fan] is an oral agent that is effective against chronic granulocytic leukemia. This agent can cause pulmonary fibrosis (“busulfan lung”). Like other alkylating agents, all of these agents are leukemogenic. *Bendamustine* is administered through the intravenous route over a period of 30 minutes which is approved for the treatment of chronic lymphoid leukemia and non-Hodgkin’s lymphoma.

## VI. MICROTUBULE INHIBITORS

The mitotic spindle is part of a larger, intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells. The mitotic spindle consists of chromatin plus a system of microtubules composed of the protein tubulin. The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells that are formed when a eukaryotic cell divides. Several plant-derived substances used as anticancer drugs disrupt this process by affecting the equilibrium between the polymerized and depolymerized forms of the microtubules, thereby causing cytotoxicity. The microtubule inhibitors are summarized in Figure 35.21.

#### A. Vincristine and vinblastine (Vinca alkaloids)

*Vincristine* [vin-KRIS-teen] (VX) and *vinblastine* [vin-BLAS-teen] (VBL) are structurally related compounds derived from the periwinkle plant, *Vinca rosea*. They are, therefore, referred to as the Vinca alkaloids. A less neurotoxic agent is *vinorelbine* [ye-NOR-el-been] (VRB). Although the Vinca alkaloids are structurally similar, their therapeutic indications are different. They are generally administered in combination

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
<i>Vincristine</i>	IV	Neurotoxicity, constipation	<i>Phenytoin, phenobarbital, carbamazepine, azole antifungal drugs</i>	CBC, hepatic function, peripheral neuropathy	Vesicants; IT administration may result in death
<i>Vinblastine</i>	IV	Myelosuppression, neurotoxicity		CBC, hepatic function	
<i>Vinorelbine</i>	IV	Granulocytopenia			
<i>Paclitaxel</i>	IV	Neutropenia, neurotoxicity, alopecia, N, V	<i>Repaglinide, gemfibrozil, rifampin (CYP2C8)</i>	CBC, hepatic function, peripheral neuropathy	Hypersensitivity reactions (dyspnea, urticaria, hypotension); require premedications
<i>Docetaxel</i>	IV	Neutropenia, neurotoxicity, fluid retention, alopecia, N, V, D	<i>Ketoconazole, ritonavir (CYP3A4)</i>		

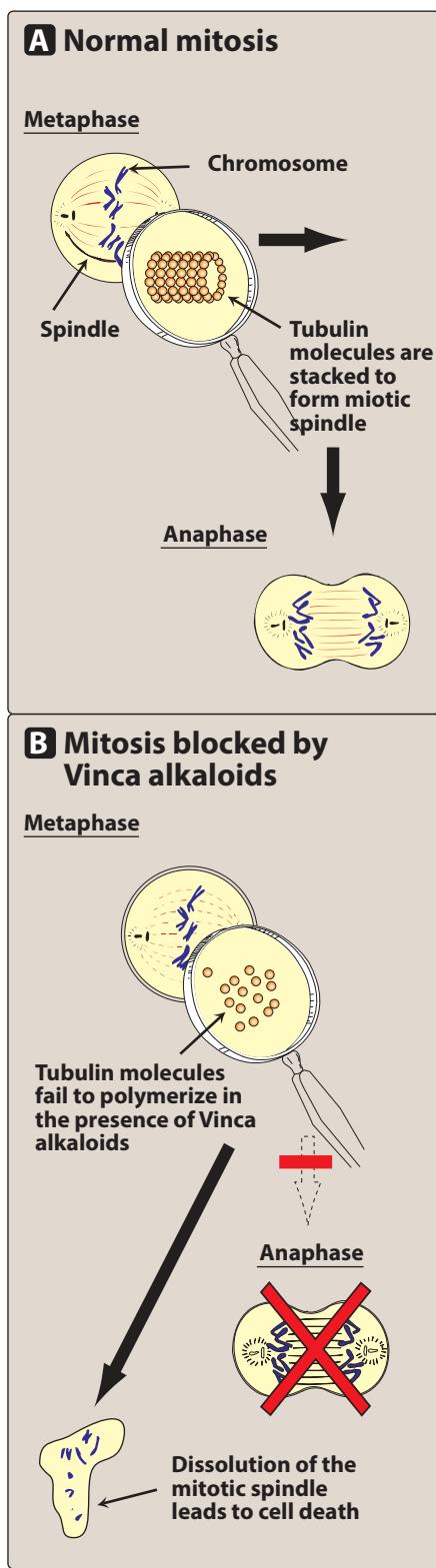
CBC = complete blood count; D = diarrhea; IT = intrathecal; IV = intravenous; N = nausea; V = vomiting.

### Figure 35.21

Summary of microtubule inhibitors. (For drug dosages, refer to Appendix at the end of the book.)

with other drugs. *VX* is used in the treatment of acute lymphoblastic leukemia in children, Wilms tumor, Ewing soft-tissue sarcoma, and Hodgkin and non-Hodgkin lymphomas, as well as some other rapidly proliferating neoplasms. [Note: *VX* (former trade name, Oncovin) is the “O” in the R-CHOP regimen for lymphoma. Due to relatively mild myelosuppressive activity, *VX* is used in a number of other protocols.] *VBL* is administered with *bleomycin* and *cisplatin* for the treatment of metastatic testicular carcinoma. It is also used in the treatment of systemic Hodgkin and non-Hodgkin lymphomas. *VRB* is beneficial in the treatment of advanced non-small cell lung cancer, either as a single agent or with *cisplatin*.

- Mechanism of action:** These agents are cell cycle-specific and phase-specific, because they block mitosis in metaphase (M-phase). Their binding to the microtubular protein, tubulin, blocks the ability of tubulin to polymerize to form microtubules. Instead, paracrystalline aggregates consisting of tubulin dimers and the alkaloid drug are formed. The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation (Figure 35.22).
- Pharmacokinetics:** IV injection of these agents leads to rapid cytotoxic effects and cell destruction. This, in turn, can cause hyperuricemia due to the oxidation of purines that are released from fragmenting DNA molecules. The Vinca alkaloids are concentrated and metabolized in the liver by the CYP450 pathway and eliminated in bile and feces. Dosage adjustment is required in patients with impaired hepatic function or biliary obstruction.
- Adverse effects:** *VX* and *VBL* are both associated with phlebitis or cellulitis if extravasation occurs during injection, as well as nausea, vomiting, diarrhea, and alopecia. *VBL* is a potent myelosuppressant, whereas peripheral neuropathy (paresthesias, loss of reflexes, foot drop, and ataxia) and constipation are more common with *VX*. These agents should not be administered intrathecally. This potential drug error can result in death, and special precautions should be in place for administration.

**Figure 35.22**

Mechanism of action of the microtubule inhibitors.

## B. Paclitaxel and docetaxel (taxanes)

*Paclitaxel* [PAK-li-tax-eI] was the first member of the taxane family to be used in cancer chemotherapy. Semisynthetic *paclitaxel* is available through chemical modification of a precursor found in the needles of Pacific or Himalayan yew species. An albumin-bound form is also available. Substitution of a side chain resulted in *docetaxel* [doe-see-TAX-eI], which is the more potent of the two drugs. *Paclitaxel* has good activity against advanced ovarian cancer and metastatic breast cancer, as well as non-small cell lung cancer when administered with *cisplatin*. *Docetaxel* is commonly used in prostate, breast, GI, and non-small cell lung cancers.

- Mechanism of action:** Both drugs are active in the G<sub>2</sub>/M-phase of the cell cycle, but unlike the Vinca alkaloids, they promote polymerization and stabilization of the polymer rather than disassembly, leading to the accumulation of microtubules (Figure 35.23). The microtubules formed are overly stable and nonfunctional, and chromosome desegregation does not occur. This results in death of the cell.
- Pharmacokinetics:** These agents undergo hepatic metabolism by the CYP450 system and are excreted via the biliary system. Dosages should be reduced in patients with hepatic dysfunction.
- Adverse effects:** The dose-limiting toxicities of *paclitaxel* and *docetaxel* are neutropenia and leukopenia. Peripheral neuropathy is also a common adverse effect with the taxanes. [Note: Because of serious hypersensitivity reactions (including dyspnea, urticaria, and hypotension), patients who are treated with *paclitaxel* should be premedicated with *dexamethasone* and *diphenhydramine*, as well as with an H<sub>2</sub> receptor antagonist.]

## VII. STEROID HORMONES AND THEIR ANTAGONISTS

Tumors that are sensitive to steroid hormones may be either 1) hormone responsive, in which the tumor regresses following treatment with a specific hormone; or 2) hormone dependent, in which removal of a hormonal stimulus causes tumor regression; or 3) both. Removal of hormonal stimuli from hormone-dependent tumors can be accomplished by surgery (for example, in the case of orchietomy—surgical removal of one or both testes—for patients with advanced prostate cancer) or by drugs (for example, in breast cancer, treatment with the antiestrogen *tamoxifen* prevents estrogen stimulation of breast cancer cells; Figure 35.24). For a steroid hormone to influence a cell, that cell must have intracellular (cytosolic) receptors that are specific for that hormone (Figure 35.25A).

### A. Tamoxifen (estrogen receptors modulators)

*Tamoxifen* [taH-MOX-ih-fen] is a selective estrogen modulator (SERM). It is an estrogen antagonist in breast tissue and an agonist in other tissues, such as bone and the endometrium. *Tamoxifen* is used for first-line therapy in the treatment of estrogen receptor-positive breast cancer. It is also used for prevention of breast cancer in high-risk women.

- Mechanism of action:** *Tamoxifen* competes with estrogen for binding to estrogen receptors in the breast tissue and inhibits estrogen-induced growth of breast cancer (Figure 35.25B).

The result is a depletion (down-regulation) of estrogen receptors, and the growth-promoting effects of the natural hormone and other growth factors are suppressed.

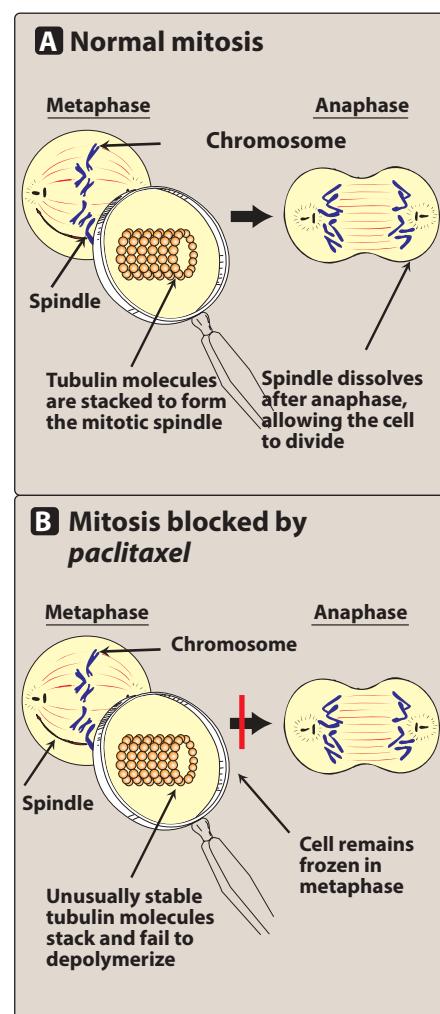
2. **Pharmacokinetics:** *Tamoxifen* is effective after oral administration. It is partially metabolized by the liver. Some metabolites possess estrogen antagonist activity, whereas others have agonist activity. Unchanged drug and metabolites are excreted predominantly through the bile into the feces. *Tamoxifen* is an inhibitor of CYP3A4 and P-glycoprotein.
3. **Adverse effects:** Adverse effects caused by *tamoxifen* include hot flashes, nausea, vomiting, skin rash, and vaginal bleeding and discharge (due to estrogenic activity of the drug and some of its metabolites in the endometrial tissue). *Tamoxifen* has the potential to cause endometrial cancer. Other toxicities include thromboembolism and effects on vision.

### B. Fulvestrant and raloxifene

*Fulvestrant* [fool-VES-trant] is an estrogen receptor antagonist that is given via intramuscular injection to patients with hormone receptor-positive metastatic breast cancer. This agent binds to and causes estrogen receptor down-regulation on tumors and other targets. *Raloxifene* [ral-OKS-i-feen] is an oral SERM that blocks estrogen effects in the uterine and breast tissues, while promoting effects in the bone to inhibit resorption. This agent reduces the risk of estrogen receptor-positive invasive breast cancer in postmenopausal women. Both drugs are known to cause hot flashes, arthralgias, and myalgias.

### C. Estrogens

A high dose of *estrogen* is known to reduce testosterone levels through the negative feedback mechanism in the hypothalamo-hypophyseal axis. The side effects associated with *estrogens* are stroke, myocardial infarction, pulmonary embolism, impotence, and loss of libido in man while treating for prostate cancer. Considering the side effects



**Figure 35.23**

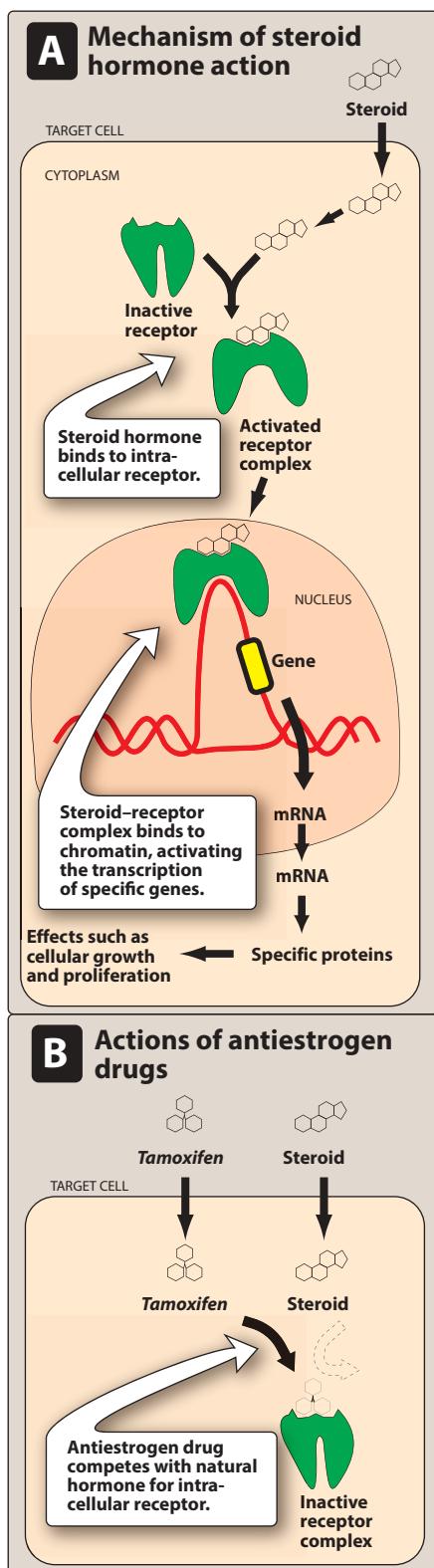
*Paclitaxel* stabilizes microtubules, rendering them nonfunctional.

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
<i>Tamoxifen</i>	PO	Hot flashes, N, V, vaginal bleeding, hypercalcemia, thromboembolism	<i>Warfarin, rifampin</i>	Vaginal bleeding, new breast lumps	May cause endometrial cancer
<i>Anastrozole and letrozole</i>	PO	Hot flashes, N, joint pain, ischemic cardiovascular events, osteoporosis	Estrogen-containing products	Hepatic function, bone mineral density monitoring, cholesterol monitoring	Contraindicated in premenopausal or pregnant women
<i>Leuprolide, goserelin, triptorelin</i>	Depot, Sub-Q, IM	Tumor flare, hot flashes, asthenia, gynecomastia		Bone mineral density monitoring, serum testosterone, PSA	
<i>Flutamide, nilutamide, bicalutamide</i>	PO	Hot flashes, N, gynecomastia, pain, constipation	<i>Warfarin</i>	Hepatic function, PSA	Combined with LHRH agonists or surgical castration

CBC = complete blood count; IM = intramuscular; LHRH = luteinizing hormone-releasing hormone; N = nausea; PO = oral administration; PSA = prostate-specific antigen; Sub-Q = subcutaneous; V = vomiting.

**Figure 35.24**

Summary of steroid hormones and their antagonists. (For drug dosages, refer to Appendix at the end of the book.)

**Figure 35.25**

Action of steroid hormones and antiestrogen agents. mRNA = messenger RNA.

associated with estrogens and availability of other safer alternatives, estrogen therapy is not used. *Diethylstilbestrol*, a synthetic estrogen, and its phosphate derivative, *fostesterol*, are used for treating prostate carcinoma.

#### D. Aromatase inhibitors

The aromatase reaction is responsible for extra-adrenal synthesis of estrogen from androstenedione, which takes place in liver, fat, muscle, skin, and breast tissues, including breast malignancies. Peripheral aromatization is an important source of estrogen in postmenopausal women. Aromatase inhibitors decrease the production of estrogen in these women.

- Anastrozole and letrozole:** *Anastrozole* [an-AS-troe-zole] and *letrozole* [LE-troe-zole] are nonsteroidal aromatase inhibitors. These agents are considered first-line drugs for the treatment of breast cancer in postmenopausal women. They are orally active and cause almost a total suppression of estrogen synthesis. *Anastrozole* and *letrozole* do not predispose patients to endometrial cancer. Both drugs are extensively metabolized in the liver, and metabolites and parent drug are excreted primarily in the urine.
- Exemestane:** A steroidal, irreversible inhibitor of aromatase, *exemestane* [ex-uh-MES-tane], is well absorbed after oral administration and widely distributed. Hepatic metabolism occurs via the CYP3A4 isoenzyme. Because the metabolites are excreted in urine, the doses of the drug must be adjusted in patients with renal failure. Major toxicities are nausea, fatigue, and hot flashes. Alopecia and dermatitis have also been noted.

#### E. Leuprolide, goserelin, and triptorelin (GnRH analogs)

GnRH is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropin hormones: 1) luteinizing hormone (LH), the primary stimulus for the secretion of testosterone by the testes, and 2) follicle-stimulating hormone (FSH), which stimulates the secretion of estrogen. *Leuprolide* [loo-PROE-lide], *goserelin* [GOE-se-rel-in], and *triptorelin* [TRIP-to-rel-in] are synthetic analogs of GnRH. As GnRH analogs, they occupy the GnRH receptor in the pituitary, which leads to its desensitization and, consequently, inhibition of release of FSH and LH. Thus, both androgen and estrogen synthesis are reduced (Figure 35.26). Response to *leuprolide* in prostatic cancer is equivalent to that of orchectomy with regression of tumor and relief of bone pain. These drugs have some benefit in premenopausal women with advanced breast cancer and have largely replaced estrogens in therapy for prostate cancer. *Leuprolide* is available as 1) a subcutaneous daily injection, 2) a subcutaneous depot injection, or 3) an intramuscular depot injection to treat metastatic carcinoma of the prostate. *Goserelin acetate* is a subcutaneous implant, and *triptorelin pamoate* is injected intramuscularly. Levels of androgen in prostate cancer patients may initially rise, but then fall to castration levels. The adverse effects of these drugs, including impotence, hot flashes, and tumor flare, are minimal compared to those experienced with estrogen treatment.

## F. Antiandrogens

*Flutamide* [FLOO-ta-mide], *nilutamide* [nye-LOO-ta-mide], *bicalutamide* [bye-ka-LOO-ta-mide], and *enzalutamide* [enz-a-LOO-ta-mide] are oral antiandrogens used in the treatment of prostate cancer. They compete with the natural hormone for binding to the androgen receptor and prevent its action in the prostate (Figure 35.24). Adverse effects include gynecomastia, constipation, nausea, and abdominal pain. Rarely, liver failure has occurred with *flutamide*. *Nilutamide* can cause visual problems.

## VIII. PLATINUM COORDINATION COMPLEXES

### A. Cisplatin, carboplatin, and oxaliplatin

*Cisplatin* [SIS-pla-tin] was the first member of the platinum coordination complex class of anticancer drugs, but because of severe toxicity, *carboplatin* [KAR-boe-pla-tin] was developed. The potency, pharmacokinetics, patterns of distribution, and dose-limiting toxicities differ significantly (Figure 35.27) between the two drugs. *Cisplatin* has synergistic cytotoxicity with radiation and other chemotherapeutic agents. It has found wide application in the treatment of solid tumors, such as metastatic testicular carcinoma in combination with *VBL* and *bleomycin*, ovarian carcinoma in combination with *cyclophosphamide*, or alone for bladder carcinoma. *Carboplatin* is used when patients cannot be vigorously hydrated, as is required for *cisplatin* treatment, or if they suffer from kidney dysfunction or are prone to neuro- or ototoxicity. *Oxaliplatin* [ox-AL-i-pla-tin] is a closely related analog of *carboplatin* used in the setting of colorectal cancer.

- Mechanism of action:** The mechanism of action for these agents is similar to that of the alkylating agents. In the high-chloride milieu of the plasma, *cisplatin* persists as the neutral species, which enters the cell and loses chloride in the low-chloride milieu. It then binds to guanine in DNA, forming inter- and intrastrand cross-links. The resulting cytotoxic lesion inhibits both polymerases for DNA replication and RNA synthesis. Cytotoxicity can occur at any stage of the cell cycle, but cells are most vulnerable to the actions of these drugs in the G<sub>1</sub>- and S-phases.
- Pharmacokinetics:** These agents are administered via IV infusion. *Cisplatin* and *carboplatin* can also be given intraperitoneally for ovarian cancer and intra-arterially to perfuse other organs. The highest concentrations of the drugs are found in the liver and kidney and in intestinal, testicular, and ovarian cells, but little penetrates into the CSF. The renal route is the main pathway of excretion.
- Adverse effects:** Severe, persistent vomiting occurs for at least 1 hour after administration of *cisplatin* and may continue for as long as 5 days. Premedication with antiemetic agents is required. The major limiting toxicity is dose-related nephrotoxicity, involving the distal convoluted tubule and collecting ducts. This can be prevented by aggressive hydration. Other toxicities include ototoxicity with high-frequency hearing loss and tinnitus. Unlike *cisplatin*, *carboplatin* causes only mild nausea and vomiting, and it

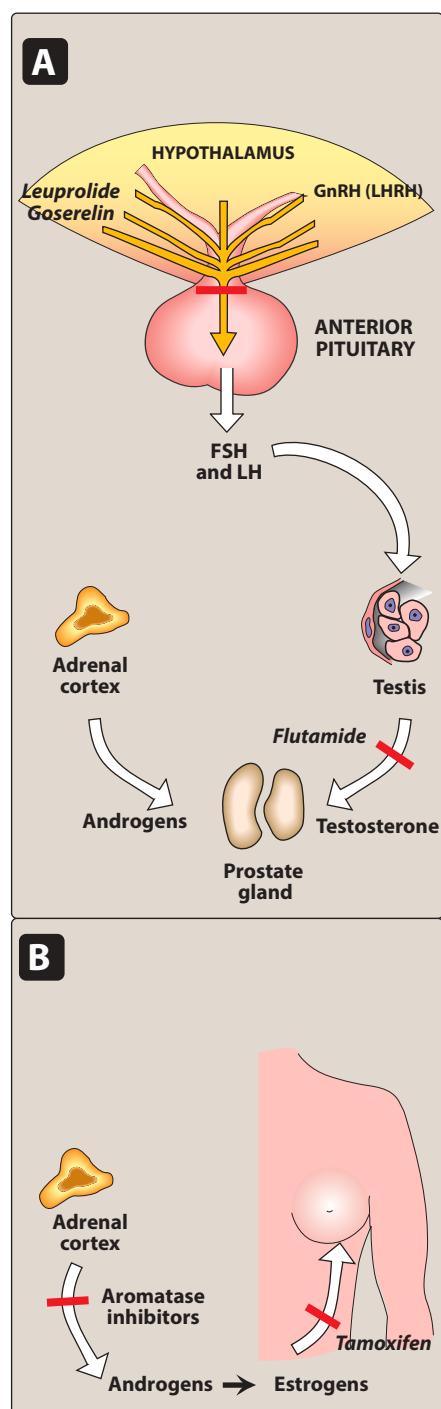


Figure 35.24

Effects of some anticancer drugs on the endocrine system. **A.** In therapy for prostatic cancer. **B.** In therapy of postmenopausal breast cancer. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; LHRH = luteinizing hormone-releasing hormone.

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
<i>Cisplatin</i>	IV, IP, IA	Neurotoxicity, myelosuppression, ototoxicity, N, V, electrolyte wasting, infusion reaction, nephrotoxicity	Anticonvulsants	CBC, CMP, electrolytes, hearing	Aggressive pre- and posthydration required, high incidence of N/V
<i>Carboplatin</i>	IV, IP, IA	Myelosuppression, N, V, infusion reaction	Aminoglycosides	CBC	Dose calculated using AUC
<i>Oxaliplatin</i>	IV	Neurotoxicity, N, V, infusion reaction, hepatotoxicity, myelosuppression	Warfarin	CBC, neurologic function, hepatic function	Cold-related and cumulative peripheral neuropathy

AUC = area under the curve; CBC = complete blood count; CMP = complete metabolic panel; IA = intra-arterially; IP = intraperitoneally; IV = intravenous; N = nausea; V = vomiting.

**Figure 35.27**

Summary of platinum coordination complexes. (For drug dosages, refer to Appendix at the end of the book.)

is rarely nephro-, neuro-, or ototoxic. The dose-limiting toxicity is myelosuppression. *Oxaliplatin* has a distinct adverse effect of cold-induced peripheral neuropathy that usually resolves within 72 hours of administration. It also causes myelosuppression and cumulative peripheral neuropathy. Hepatotoxicity has also been reported. These agents may cause hypersensitivity reactions ranging from skin rashes to anaphylaxis.

## IX. TOPOISOMERASE INHIBITORS

These agents exert their mechanism of action via inhibition of topoisomerase enzymes, a class of enzymes that reduce supercoiling of DNA (Figure 35.28).

### A. Camptothecins (topoisomerase II inhibitors)

Camptothecins are plant alkaloids originally isolated from the Chinese tree *Camptotheca*. *Irinotecan* [eye-rin-oh-TEE-kan] and *topotecan* [toe-poe-TEE-kan] are semisynthetic derivatives of *camptothecin* [camp-toe-THEE-sin]. *Topotecan* is used in metastatic ovarian cancer when primary therapy has failed and also in the treatment of small cell lung cancer. *Irinotecan* is used with 5-FU and *leucovorin* for the treatment of colorectal carcinoma.

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
<i>Irinotecan</i>	IV	Diarrhea, myelosuppression, N, V	CYP3A4 substrates	CBC, electrolytes	Acute and delayed (life-threatening) diarrhea
<i>Topotecan</i>	IV, PO	Myelosuppression, N, V	P-glycoprotein inhibitors (PO)	CBC	Diarrhea common with PO
<i>Etoposide</i>	IV, PO	Myelosuppression, hypotension, alopecia, N, V		CBC	May cause secondary malignancies (leukemias)

CBC = complete blood count; IV = intravenous; N = nausea; PO = oral administration; V = vomiting.

**Figure 35.28**

Summary of topoisomerase inhibitors. (For drug dosages, refer to Appendix at the end of the book.)

- Mechanism of action:** These drugs are S-phase specific and inhibit topoisomerase I, which is essential for the replication of DNA in human cells (Figure 35.29). SN-38 (the active metabolite of *irinotecan*) is approximately 1000 times as potent as *irinotecan* as an inhibitor of topoisomerase I. The topoisomerases relieve torsional strain in DNA by causing reversible, single-strand breaks.
- Adverse effects:** Bone marrow suppression, particularly neutropenia, is the dose-limiting toxicity for *topotecan*. Frequent blood counts should be performed in patients receiving this drug. Myelosuppression is also seen with *irinotecan*. Acute and delayed diarrhea with *irinotecan* may be severe and require treatment with *atropine* during the infusion or high doses of *loperamide* in the days following the infusion.

### B. Etoposide (topoisomerase I inhibitors)

*Etoposide* [e-toe-POE-side] is a semisynthetic derivative of the plant alkaloid, podophyllotoxin. This agent blocks cells in the late S- to G<sub>2</sub> phase of the cell cycle, and the major target is topoisomerase II. Binding of the drug to the enzyme–DNA complex results in persistence of the transient, cleavable form of the complex and, thus, renders it susceptible to irreversible double-strand breaks (Figure 35.30). *Etoposide* finds its major clinical use in the treatment of lung cancer and in combination with *bleomycin* and *cisplatin* for testicular carcinoma. *Etoposide* may be administered either IV or orally. Dose-limiting myelosuppression (primarily leukopenia) is the major toxicity.

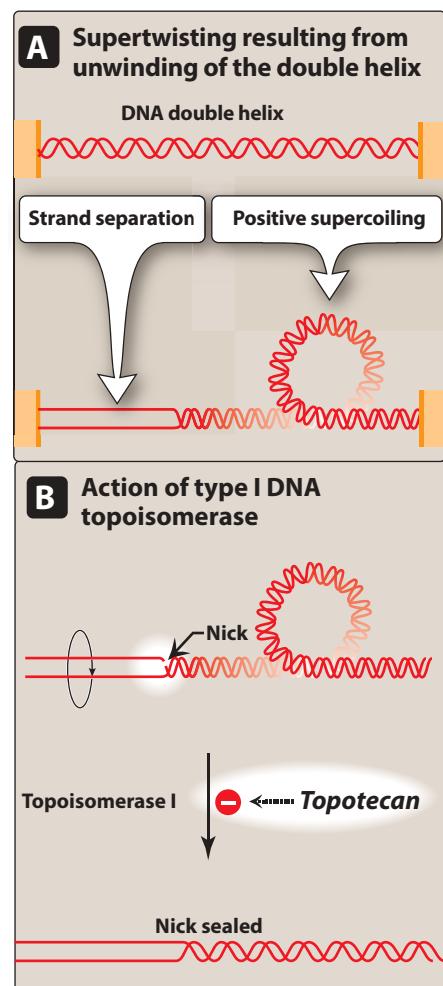
*Teniposide* is another derivative administered by the intravenous route having a longer terminal half-life compared to *etoposide*. The mechanism of action is similar to that of *etoposide*. It is used for the refractory ALL in children. Apart from GI side effects, myelosuppression has also been associated with its usage.

## X. ANTIBODIES

Monoclonal antibodies (Figure 35.31) are an active area of drug development for anticancer therapy and other non-neoplastic diseases, because they are directed at specific targets and often have different adverse effect profiles as compared to traditional chemotherapy agents. [Note: Monoclonal antibodies also find application in a number of other disorders, such as inflammatory bowel disease, psoriasis, and rheumatoid arthritis.] All of these agents are administered intravenously, and infusion-related reactions are common.

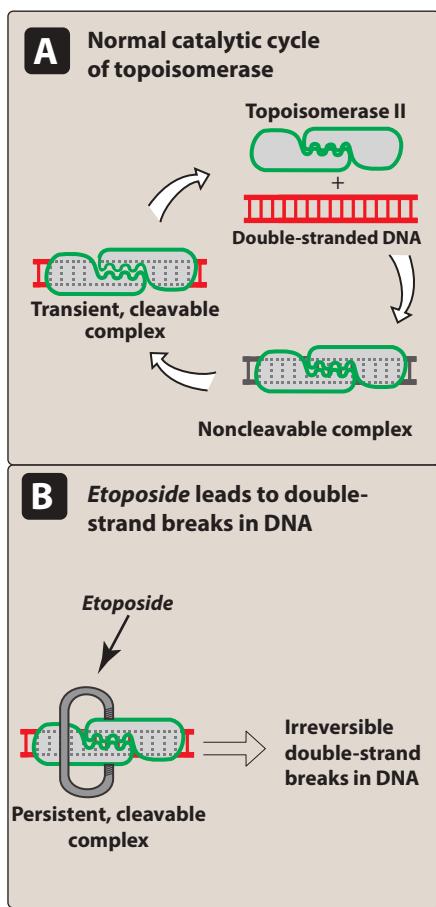
## XI. TYROSINE KINASE INHIBITORS

The tyrosine kinases are a family of enzymes that are involved in several important processes within a cell, including signal transduction and cell division. [Note: At least 50 tyrosine kinases mediate cell growth or division by phosphorylation of signaling proteins. They have been implicated in the development of many neoplasms.] The tyrosine kinase inhibitors are



**Figure 35.29**

Action of type I DNA topoisomerases.

**Figure 35.30**

Mechanism of action of etoposide.

administered orally, and these agents have a wide variety of applications in the treatment of cancer (Figure 35.32).

## XII. IMMUNOTHERAPY

Immunotherapy with intravenous immune checkpoint inhibitors is a rapidly evolving option for cancer treatment. The goal of immune checkpoint inhibitors is to block the checkpoint molecules, such as the programmed-death (PD-1) receptor, that normally help to keep the immune system in check. By blocking these molecules, the immune system is better able to attack the tumor and cause destruction. The two most commonly used checkpoint inhibitors are *pembrolizumab* [PEMBRO-LIZ-ue-mab] and *nivolumab* [nye-VOL-ue-mab]. The adverse reaction profiles of these agents consist of potentially severe and even fatal immune-mediated adverse events. This is because turning off the immune checkpoints allows attack of the tumor, but can also lead to unchecked autoimmune response to normal tissues. Adverse events include diarrhea, colitis, pneumonitis, hepatitis, nephritis, neurotoxicity, dermatologic toxicity in the form of severe skin rashes, and endocrinopathies such as hypo- or hyperthyroidism. Patients should be closely monitored for the potential development of signs and symptoms of toxicity and promptly treated with corticosteroids if necessary.

## XIII. MISCELLANEOUS AGENTS

### A. Abiraterone acetate

*Abiraterone* [ab-er-AT-er-own] acetate is an oral agent used in the treatment of metastatic castration-resistant prostate cancer. *Abiraterone acetate* is used in conjunction with *prednisone* to inhibit the CYP17 enzyme (an enzyme required for androgen synthesis), resulting in reduced testosterone production. Coadministration with *prednisone* is required to help lessen the effects of mineralocorticoid excess resulting from CYP17 inhibition. Hepatotoxicity may occur, and patients should be closely monitored for hypertension, hypokalemia, and fluid retention. Joint and muscle discomfort, hot flushes, and diarrhea are common adverse effects with this agent.

### B. Immunomodulating agents

*Thalidomide* [tha-LEHDO-mide], *lenalidomide* [len-ah-LEHDO-mide], and *pomalidomide* [poma-LEHDO-mide] are oral agents used in the treatment of multiple myeloma. Their exact mechanism of action is not clear, but they possess antimyeloma properties including antiangiogenic, immune-modulation, anti-inflammatory, and anti-proliferative effects. These agents are often combined with *dexamethasone* or other chemotherapeutic agents. Adverse effects include, thromboembolism, myelosuppression, fatigue, rash, and constipation. *Thalidomide* was previously given to pregnant women to prevent morning sickness. However, severe birth defects were prevalent in children born to mothers who used *thalidomide*. *Lenalidomide* and *pomalidomide* are structural variants of *thalidomide* and because of their structural similarities, these drugs are contraindicated in pregnancy.

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	MONITORING PARAMETERS	NOTES
<i>Bevacizumab</i>	Binds VEGF and prevents binding of VEGF to its receptors on endothelial cells  Inhibits vascularization of the tumor	Hypertension, GI perforation, proteinuria, wound healing problems, bleeding	BP, urine protein, signs and symptoms of bleeding	Hold for recent or upcoming surgical procedures
<i>Cetuximab</i>	Binds to EGFR and competitively inhibits the binding of epidermal growth factor and other ligands  Inhibits tumor cell growth and increases apoptosis	Skin rash, electrolyte wasting, infusion reaction, diarrhea	Electrolytes, vital signs during infusion	Premedication with antihistamine required before infusion; rash equated with increased response
<i>Daratumumab</i>	Binds to the transmembrane protein CD38 on multiple myeloma cells and causes cell lysis	Infusion reactions, diarrhea, fatigue, pyrexia	CBC with differential, vital signs during infusion	Can bind CD38 on red blood cells Type and screen patients before starting therapy Premedication with antihistamines, antipyretics, and corticosteroids required
<i>Ramucirumab</i>	Binds VEGF receptor 2 and blocks binding of VEGF receptor ligands	Proteinuria, hypertension, wound healing problems, bleeding	BP, urine protein, signs and symptoms of bleeding	Hold for recent or upcoming surgical procedures
<i>Rituximab</i>	Targets the CD20 antigen expressed on the surface of pre-B lymphocytes and mature B lymphocytes	Fatal infusion reaction, TLS, mucocutaneous reactions, PML	Vital signs during infusion, TLS labs	Fatal reactivation of hepatitis B Premedication required before infusion Increased risk of nephrotoxicity when given with <i>cisplatin</i>
<i>Trastuzumab</i>	Inhibits the proliferation of human tumor cells that overexpress HER2	Cardiomyopathy, infusion-related fever and chills, pulmonary toxicity, headache, nausea/vomiting	LVEF, CBC, pulmonary toxicity due to infusion reaction	Embryo-fetal toxicity Neutropenia in combination with chemotherapy Premedication with antihistamine and <i>acetaminophen</i> required

BP = blood pressure; CBC = complete blood count; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor protein 2; GI = gastrointestinal; LVEF = left ventricular ejection fraction; PML = progressive multifocal leukoencephalopathy; TLS = tumor lysis syndrome; VEGF = vascular endothelial growth factor.

**Figure 35.31**

Summary of monoclonal antibodies. (For drug dosages, refer to Appendix at the end of the book.)

### C. Proteasome inhibitors

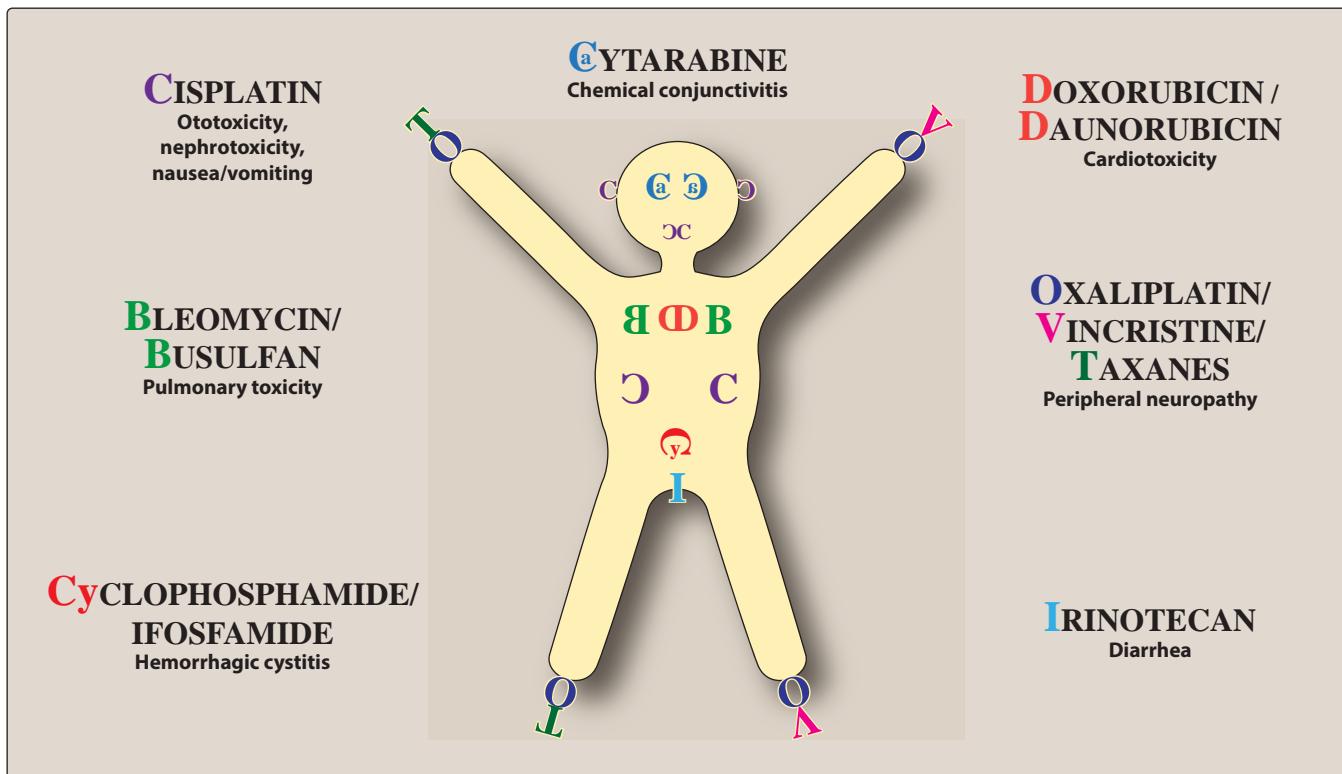
*Bortezomib* [bore-TEZ-o-mib], *ixazomib* [ix-az-O-mib], and *carfilzomib* [kar-FIL-zo-mib] are proteasome inhibitors commonly used as the backbone therapy in the treatment of multiple myeloma. These agents work by inhibiting proteasomes, which in turn prevents the degradation of pro-apoptotic factors, thus leading to a promotion in programmed cell death (apoptosis). Malignant cells readily depend on suppression of the apoptotic pathway; therefore, proteasome inhibition works well in multiple myeloma. *Bortezomib* can be administered IV, but the subcutaneous route is preferred because it is associated with less neuropathy. Other adverse effects include myelosuppression, diarrhea, nausea, fatigue, and herpes zoster reactivation. Patients should receive antiviral prophylaxis if they are receiving therapy with *bortezomib*. *Ixazomib* is an oral agent with an adverse effect profile similar to *bortezomib*. *Carfilzomib* is administered intravenously, and common adverse effects include myelosuppression, fatigue, nausea, diarrhea, and fever. “Chemo Man” is a useful tool to help remember the most common toxicities of these drugs (Figure 35.33).

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
<i>Afatinib</i>	Inhibits EGFR tyrosine kinase	Diarrhea, rash, stomatitis, paronychia, nausea, vomiting, pruritus	P-gp inhibitors and inducers	CBC, CMP	Administer on an empty stomach Reduce dose for significant diarrhea Use effective contraception for female patients
<i>Dabrafenib</i>	Inhibits mutated BRAF kinases	Pyrexia, rash, arthralgia, cough, embryo-fetal toxicity	CYP3A4 inhibitors and substrates; CYP2C8 inhibitors and substrates; substrates of CYP2C9, CYP2C19, or CYP2B6	Glucose, symptoms of heart failure or bleeding, CBC, BMP, INR (if warfarin)	Use effective contraception for female patients Administer on empty stomach May cause new primary malignancies
<i>Dasatinib</i>	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, fluid retention, diarrhea	CYP3A4 substrates, acid-reducing agents	CBC, BCR-ABL, electrolytes	QT prolongation
<i>Erlotinib</i>	Inhibits EGFR tyrosine kinase	Rash, ILD, hepatotoxicity	CYP3A4 substrates, acid-reducing agents, warfarin	CMP	Rash equated with increased response
<i>Ibrutinib</i>	Inhibits Bruton's tyrosine kinase	Neutropenia, thrombocytopenia, diarrhea, anemia, pain, rash, nausea, bruising, fatigue, hemorrhage, pyrexia	CYP3A inhibitors and inducers	CBC, CMP, atrial fibrillation, BP, tumor lysis syndrome	Avoid grapefruit juice and Seville oranges Can cause hepatitis B reactivation Use effective contraceptive
<i>Idelalisib</i>	Inhibits phosphatidylinositol 3-kinase	Diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, rash, neutropenia, infection	CYP3A inducers and substrates	CBC, LFTs, pulmonary symptoms, infection	Use effective contraception for female patients
<i>Imatinib</i>	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, fluid retention, CHF	CYP3A4 substrates, warfarin	CBC, BCR-ABL	Monitor for development of heart failure
<i>Nilotinib</i>	Inhibits BCR-ABL kinase	Myelosuppression, QT prolongation, hepatotoxicity	CYP3A4 substrates, acid-reducing agents	CBC, BCR-ABL, electrolytes	QT prolongation Administer on empty stomach
<i>Osimertinib</i>	Inhibits EGFR tyrosine kinase	Diarrhea, rash, dry skin, nail toxicity, fatigue	Strong CYP3A inducers	CBC, ECG, electrolytes	Use effective contraceptive for female patients
<i>Pazopanib</i>	Multi-tyrosine kinase inhibitor	Diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting	CYP3A4 inhibitors, inducers, and substrates; CYP2D6 or CYP2C8 substrates; simvastatin; drugs that reduce gastric pH	ECG, electrolytes, thyroid function tests, LFTs, UA, CBC, BP	Use effective contraceptive for female patients
<i>Sorafenib</i>	Inhibits multiple intracellular and cell surface kinases	Hypertension, hand-foot syndrome, rash, diarrhea, fatigue	CYP3A4 inducers, warfarin	BP, CMP	Wound healing complications, cardiac events
<i>Sunitinib</i>	Multi-tyrosine kinase inhibitor	Hypertension, hand-foot syndrome, rash, diarrhea, fatigue, hepatotoxicity, hypothyroidism	CYP3A4 substrates	BP, CMP, TSH	Monitor for development of heart failure
<i>Trametinib</i>	Reversible inhibitor of mitogen-activated extracellular kinases	Pyrexia, rash, diarrhea, vomiting, lymphedema	CYP2C8 substrates, P-gp	Fever, new cutaneous malignancies, serum glucose, LVEF, CBC, CMP	Used in combination with <i>dabrafenib</i> Administer on empty stomach
<i>Vemurafenib</i>	Inhibits mutated BRAF serine-threonine kinase	Arthralgia, rash, alopecia, fatigue, photosensitivity, pruritus, skin papilloma	CYP3A4 inhibitors and inducers, CYP1A2 substrates	ECG, electrolytes, CMP, uveitis	May cause new primary cutaneous malignancies Use effective contraception in female patients

BMP = basic metabolic panel; BP = blood pressure; CBC = complete blood count; CHF = congestive heart failure; CMP = complete metabolic panel; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; ILD = interstitial lung disease; INR = international normalized ratio; LFT = liver function test; LVEF = left ventricular ejection fraction; P-gp = P-glycoprotein; TSH = thyroid-stimulating hormone; UA = urinalysis.

**Figure 35.32**

Summary of tyrosine kinase inhibitors.

**Figure 35.33**

Chemo Man—a summary of toxicity of chemotherapeutic agents.

## Study Questions

Choose the ONE best answer.

- 35.1 A patient is about to undergo three cycles of chemotherapy prior to surgery for bladder cancer. Which best describes chemotherapy in this setting?
- Adjuvant
  - Neoadjuvant
  - Palliative
  - Maintenance

Correct answer = B. Chemotherapy given *before* the surgical procedure in an attempt to shrink the cancer is referred to as neoadjuvant chemotherapy. Chemotherapy is indicated when neoplasms are disseminated and are not amenable to surgery (palliative). Chemotherapy is also used as a supplemental treatment to attack micrometastases following surgery and radiation treatment, in which case it is called adjuvant chemotherapy. Chemotherapy given in lower doses to assist in prolonging a remission is known as maintenance chemotherapy.

- 35.2 A 45-year-old man is being treated with ABVD chemotherapy for Hodgkin lymphoma. He presents for cycle 4 of planned 6 cycles with a new-onset cough. He states it started a week ago and he also feels like he has a little trouble catching his breath. Which drug in the ABVD regimen is the most likely cause of his pulmonary toxicity?

- Doxorubicin (adriamycin)
- Bleomycin
- Vinblastine
- Dacarbazine

Correct answer = B. Pulmonary toxicity is the most serious adverse effect of bleomycin, progressing from rales, cough, and infiltrate to potentially fatal fibrosis. The pulmonary fibrosis that is caused by bleomycin is often referred to as “bleomycin lung.”

35.3 A patient is about to begin therapy with doxorubicin and cyclophosphamide. Which test should be ordered for baseline assessment before treatment?

- A. Baseline PFTs
- B. Baseline stress test
- C. Baseline echocardiogram
- D. Baseline urinalysis

35.4 A 64-year-old man is scheduled to undergo chemotherapy for rhabdomyosarcoma, and the regimen includes ifosfamide. Which is most appropriate to include in chemotherapy orders for this patient?

- A. IV hydration, mesna, and frequent urinalyses
- B. Leucovorin and frequent urinalyses
- C. Allopurinol and frequent urinalyses
- D. IV hydration, prophylactic antibiotics, and frequent urinalyses

35.5 Development of signs of which condition should be monitored in patients receiving chemotherapy with ifosfamide?

- A. Hand-foot syndrome
- B. Rash
- C. Cardiotoxicity
- D. Neurotoxicity

35.6 Which chemotherapy drug can cause nephrotoxicity, neurotoxicity, ototoxicity, electrolyte abnormalities, and severe nausea and vomiting?

- A. Cyclophosphamide
- B. Oxaliplatin
- C. Etoposide
- D. Cisplatin

35.7 A patient was mistakenly administered vincristine instead of cytarabine intrathecally. What is the likely outcome of this drug error?

- A. Neuropathy
- B. Death
- C. Renal failure
- D. Hearing loss

35.8 The appearance of a facial rash with cetuximab is associated with a(n)

- A. negative response to therapy.
- B. positive response to therapy.
- C. drug allergy.
- D. infusion reaction.

Correct answer = C. Irreversible, dose-dependent cardiotoxicity, apparently a result of the generation of free radicals and lipid peroxidation, is the most serious adverse reaction of anthracyclines, such as doxorubicin. Cardiac function should be assessed prior to therapy and then periodically throughout therapy.

Correct answer = A. A unique toxicity of ifosfamide is hemorrhagic cystitis. This bladder toxicity has been attributed to toxic metabolites of ifosfamide. Adequate hydration as well as IV injection of mesna (sodium 2-mercaptopethane sulfonate), which neutralizes the toxic metabolites, can minimize this problem. Frequent urinalyses to monitor for red blood cells should be ordered. Leucovorin is used with methotrexate or 5-FU (not ifosfamide). Allopurinol has a drug interaction with ifosfamide and is not an agent that prevents hemorrhagic cystitis. IV fluids are correct; however, mesna is also needed.

Correct answer = D. A fairly high incidence of neurotoxicity has been reported in patients on high-dose ifosfamide, probably due to the metabolite, chloroacetaldehyde. Hand-foot syndrome is an adverse effect of 5-FU and derivatives. Rash is possible with many drugs, but is not the most appropriate answer here. Cardiotoxicity is an adverse effect of the anthracyclines.

Correct answer = D. Cisplatin can cause renal failure, neuropathy, hearing loss, electrolyte wasting, and significant nausea and vomiting. Oxaliplatin rarely causes ototoxicity or nephrotoxicity. Cyclophosphamide and etoposide have myelosuppression as the dose-limiting toxicity.

Correct answer = B. Death. Vincristine is fatal if given intrathecally.

Correct answer = B. Patients undergoing therapy with an EGFR inhibitor such as cetuximab often develop an acneiform-like rash on the face, chest, upper back, and arms. The appearance of such a rash has been correlated with an increased response as compared to patients who do not experience a rash during therapy.

- 35.9 Rituximab is an agent that requires a slow initial infusion due to the possibility of an infusion reaction. Which is believed to be the cause of this reaction?
- A. Allergic reaction to the drug
  - B. Tumor lysis syndrome
  - C. Activation of complement resulting in the release of tumor necrosis factor and interleukins
  - D. Reactivation of hepatitis
- 35.10 Patients should receive antiviral prophylaxis for herpes zoster while undergoing treatment with which agent for multiple myeloma?
- A. Dabrafenib
  - B. Ipilimumab
  - C. Cisplatin
  - D. Bortezomib

Correct answer = C. Patients receiving rituximab may experience an infusion reaction, usually on the first cycle. Hypotension, bronchospasm, and angioedema may occur. Chills and fever may occur, especially in patients with high circulating levels of neoplastic cells, because of rapid activation of complement which results in the release of tumor necrosis factor- $\alpha$  and interleukins. Pretreatment with diphenhydramine, acetaminophen, and corticosteroids and a slower infusion rate can lessen the chance of this reaction.

Correct answer = D. Bortezomib is known to cause herpes zoster reactivation in patients receiving treatment for multiple myeloma. Patients should receive antiviral prophylaxis while on bortezomib therapy.



# Antiprotozoal Drugs

Marylee V. Worley and Jonathan C. Cho

# 36

## I. OVERVIEW

Protozoan parasites that cause human diseases are prevalent in underdeveloped tropical and subtropical countries, where sanitary conditions, hygienic practices, and control of the vectors of transmission are inadequate. However, with increased world travel, protozoal diseases are no longer confined to specific geographic locales. Because they are unicellular eukaryotes, the protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens. Therefore, protozoal diseases are less easily treated than bacterial infections, and many of the antiprotozoal drugs cause serious toxic effects in the host, particularly on cells showing high metabolic activity. Most antiprotozoal agents have not proven to be safe for pregnant patients. This chapter discusses the drugs used in the treatment of Amebiasis, Malaria, Trichomoniasis, Trypanosomiasis, Leshmaniasis, and Giardiasis.

Drugs used to treat protozoal infections are listed in [Figure 36.1](#).

## II. CHEMOTHERAPY FOR AMEBIASIS

Amebiasis (amebic dysentery) is an infection of the intestinal tract caused by *Entamoeba histolytica*. *E. histolytica* is endemic in developing countries and is mainly transmitted via the fecal–oral route or through ingestion of contaminated food or water. Most infected individuals are asymptomatic but can exhibit varying degrees of illness depending on host factors and formation of trophozoites. The diagnosis is established by isolating *E. histolytica* from feces. Due to the risk of developing invasive disease and acting as a potential source of infection for others, therapy is indicated for acutely ill patients and asymptomatic carriers of *E. histolytica*. A summary of the life cycle of *E. histolytica* is presented in [Figure 36.2](#). Therapeutic agents for amebiasis are classified as luminal, systemic, or mixed amebicides according to the site of action ([Figure 36.2](#)). For example, luminal amebicides act on the parasite in the lumen of the bowel, whereas systemic amebicides are effective against amebas in the intestinal wall and liver. Mixed amebicides are effective against both the luminal and the systemic forms of the disease, although luminal concentrations are too low for single-drug treatment.

### A. Mixed amebicides

1. **Metronidazole:** *Metronidazole* [me-troe-NYE-da-zole], a nitroimidazole, is the mixed amebicide of choice for treating amebic infections. [Note: *Metronidazole* is also used in the treatment

### AMEBIASIS

*Metronidazole*  
*Tinidazole*  
*Ornidazole*  
*Secnidazole*  
*Satranidazole*  
*Chloroquine*  
*Dehydroemetine*  
*Iodoquinol*  
*Paromomycin*

### GIARDIASIS

*Metronidazole*  
*Tinidazole*  
*Nitazoxanide*

### MALARIA

*Artemether/lumefantrine*  
*Chloroquine*  
*Primaquine*  
*Pyrimethamine*  
*Quinine/quinidine*  
*Mefloquine*  
*Atovaquone-proguanil*

### TRYPANOSOMIASIS

*Pentamidine*  
*Benznidazole*  
*Eflornithine*  
*Melarsoprol*  
*Nifurtimox*  
*Suramin*

### LEISHMANIASIS

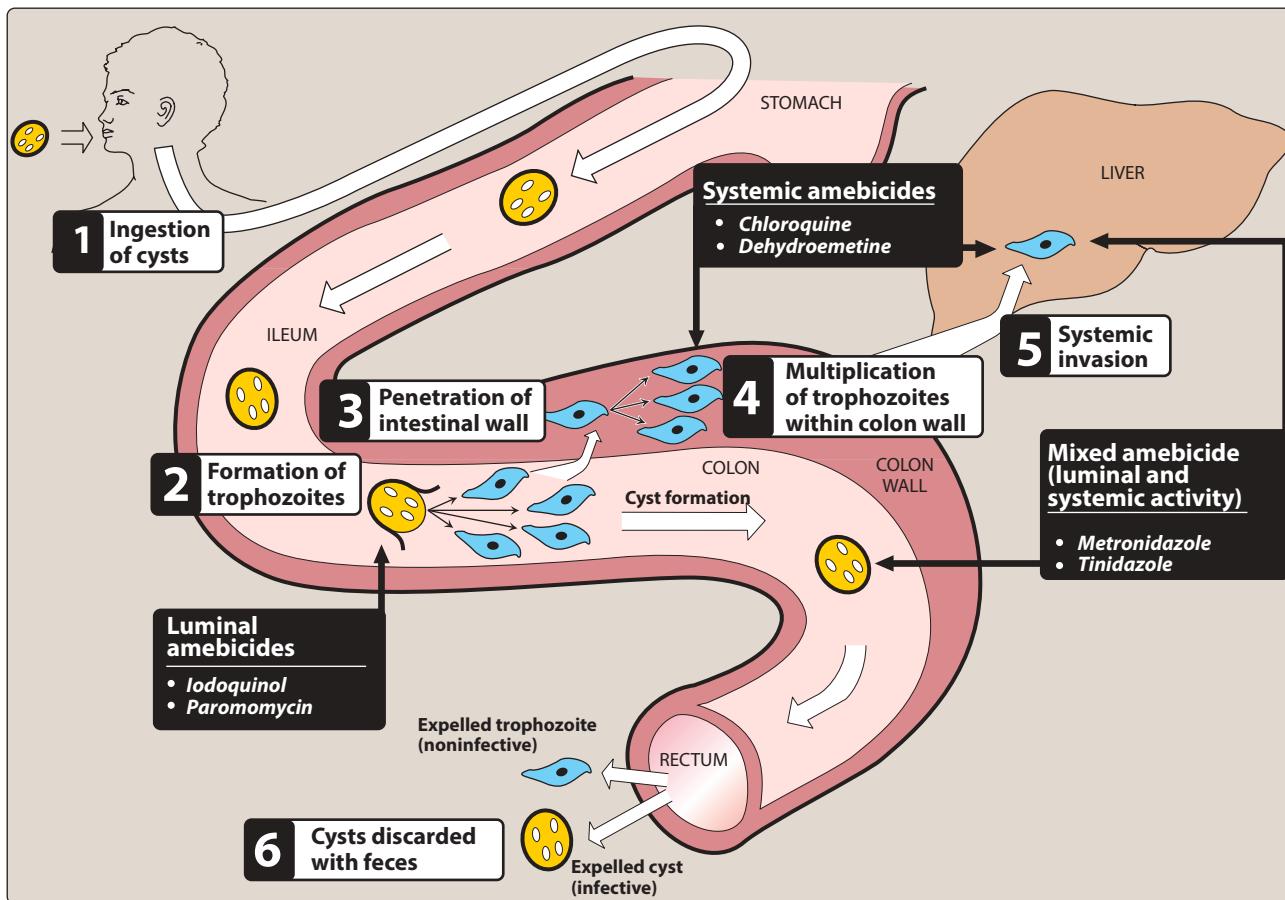
*Miltefosine*  
*Sodium stibogluconate*

### TOXOPLASMOSIS

*Pyrimethamine*

### Figure 36.1

Summary of antiprotozoal agents.  
(For drug dosages, refer to Appendix at the end of the book.)



**Figure 36.2**

Life cycle of *Entamoeba histolytica*, showing the sites of action of amebicidal drugs.

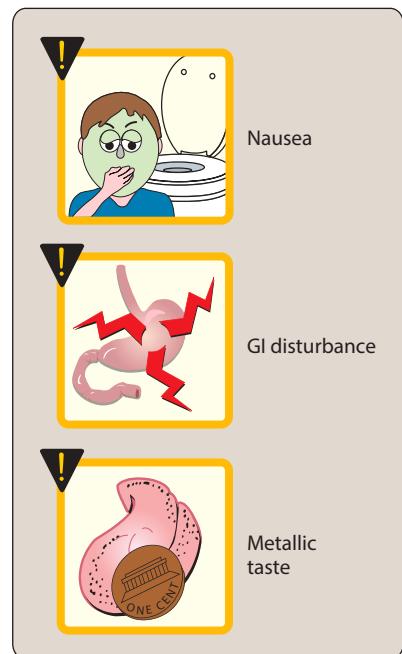
of infections caused by *Giardia lamblia*, *Trichomonas vaginalis*, anaerobic cocci, anaerobic gram-negative bacilli (for example, *Bacteroides* species), and anaerobic gram-positive bacilli (for example, *Clostridium difficile*).]

a. **Mechanism of action:** Amebas and anaerobic organisms possess ferredoxin-like, low-redox-potential, electron transport proteins that participate in metabolic electron removal reactions. It is a prodrug which requires a reactive activation of the nitro group by susceptible microbes. The nitro group of *metronidazole* is able to serve as an electron acceptor, by a radical-mediated mechanism that targets DNA and also by forming reduced cytotoxic compounds, resulting in death of the *E. histolytica* trophozoites and anaerobes. *Metronidazole* catalytically recycles itself by the loss of electron, but increasing levels of oxygen ( $O_2$ ) can inhibit the cytotoxic action of *metronidazole*. Resistance to *metronidazole* is also documented with *T. vaginalis*, *G. lamblia*, and other anaerobic/microaerophilic bacteria but is not seen with *E. histolytica*.

b. **Pharmacokinetics:** *Metronidazole* is completely and rapidly absorbed after oral administration. [Note: For the treatment of amebiasis, it is usually administered with a luminal amebicide,

such as *iodoquinol* or *paromomycin*. This combination provides cure rates of greater than 90%.] *Metronidazole* distributes well throughout body tissues and fluids. Therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid (CSF). Metabolism of the drug depends on hepatic oxidation of the *metronidazole* side chain by mixed-function oxidase, followed by glucuronidation. Therefore, concomitant treatment with inducers of the cytochrome P450, such as *phenobarbital*, enhances the rate of metabolism, and inhibitors, such as *cimetidine*, prolong the plasma half-life of *metronidazole*. The drug accumulates in patients with severe hepatic disease. The parent drug and its metabolites are excreted in the urine. *Metronidazole* used at a dose of 400 mg thrice a day for mild cases and 800 mg thrice a day for severe cases for a duration of 7 to 10 days depends upon the type of infection. During colorectal and pelvic surgery, it is used along with other antibiotics to cover the entire spectrum of aerobic and anaerobic microbes. It can conveniently be administered through slow intravenous infusion as well.

- c. **Adverse effects:** The most common adverse effects are nausea, vomiting, epigastric distress, and abdominal cramps (**Figure 36.3**). An unpleasant, metallic taste is commonly experienced due to the excretion of metabolites in the saliva. Other effects include oral moniliasis (yeast infection of the mouth) and, rarely, neurotoxicity (dizziness, vertigo, and numbness or paresthesia), which may necessitate discontinuation of the drug. If taken with alcohol, a *disulfiram*-like reaction may occur (see Chapter 48).
- 2. **Tinidazole:** *Tinidazole* [tye-NI-da-zole] is a second-generation nitroimidazole that is similar to *metronidazole* in spectrum of activity, absorption, adverse effects, and drug interactions. It is used for the treatment of amebiasis, amebic liver abscess, giardiasis, and trichomoniasis. *Tinidazole* is as effective as *metronidazole*, but it is more expensive. Alcohol consumption should be avoided during therapy. Due to its longer half-life ( $t_{1/2}$  is 12 hours; *tinidazole* can be administered conveniently in the form of a single dose of 2 g in adults and at a dose of 30 to 50 mg/kg in children). For anaerobic infections, it is administered as a prophylactic single dose of 2 g before colorectal surgery and a dose of 500 mg twice daily for 2 weeks for *Helicobacter pylori* infections
- 3. **Ornidazole:** The spectrum and mechanism of *ornidazole* are similar to those of *metronidazole*. *Ornidazole* is reported to have longer  $t_{1/2}$  like *tinidazole*; therefore, for chronic intestinal amoebiasis and asymptomatic cyst passers, *ornidazole* is used at a dose of 0.5 g twice daily for 5 to 7 days. Alcohol consumption should be avoided during this therapy.
- 4. **Satranidazole:** *Satranidazole* is also a congener of *nitroimidazole* having longer  $t_{1/2}$  of 14 hours. It has been reported to have a better side effect profile compared to *metronidazole*. It is used at a dose of 0.3 g twice daily for 3 to 5 days.
- 5. **Secnidazole:** The mechanism of action and spectrum of *secnidazole* are similar to those of *metronidazole*. *Secnidazole* has a potential advantage over *metronidazole* in that it can be administered



**Figure 36.3**

Adverse effects of *metronidazole*.  
GI = gastrointestinal.

as a single dose since its plasma  $t_{1/2}$  is of 17 to 29 hours. After a single dose of 2 g, plasma *secnidazole* remains above the minimum inhibitory concentration (MIC) of sensitive organisms for the treatment of intestinal amebiasis, giardiasis, and bacterial vaginosis. However, *metronidazole* should be considered the drug of choice for life-threatening anaerobic infections.

## B. Luminal amebicides

After treatment of invasive intestinal or extraintestinal amebic disease is complete, a luminal agent, for example, 8-hydroxyquinolines such as *quinodochlor* and *idoquinol*, benzamides such as *diloxanide furoate* and *nitazoxanide*, and antibiotics such as *paromomycin*, should be administered for treatment of the asymptomatic colonization state.

1. **8-hydroxyquinolines:** Many 8-hydroxyquinolines, such as *ido-chloro hydroxyquinoline* (*quinodochlor*) and *diiodohydroxyquin* (*idoquinol*), were developed and widely employed in the past. They share similar properties in spectrum and action. They are amebicidal against *E. histolytica* and are effective against the luminal trophozoite and cyst forms. However, their efficacy is inferior to that of *diloxanide furoate*. Absorption in the intestine is variable; they have a longer half-life of 12 hours. They are metabolized in the liver and excreted by the kidney. The unabsorbed portion of the drug reaches the lower bowel and acts on luminal trophozoite and cyst forms. 8-Hydroxyquinolines cause rashes, diarrhea, and dose-related peripheral neuropathy, including a rare optic neuritis. They cause green stools and pruritis and can also cause iodism. Long-term use of this drug should be avoided due to the possibility of developing iodism evidenced by ptalism, coryza, frontal headache, emaciation, skin eruptions, goiter, etc. People sensitive to iodine might get acute reaction with chills, hyperthermia, angioedema, and cutaneous hemorrhages. They are also used for the treatment of giardiasis and for the local treatment of fungal, trichomonas vaginitis, and bacterial infections. *Quinodochlor* is used at a dose of 250 to 500 mg three times a day and *idoquinol* is used at a dose of 250 mg three times a day for 2 weeks.
2. **Amide derivatives:** This class of benzamides such as *diloxanide furoate* and *nitazoxanide* is every effective as compared to 8-hydroxyquinolines as luminal amebicides. They are furoate esters that get hydrolyzed in the intestine and release diloxanide which is absorbed. Although the mechanism of action is not well documented, after absorption it is metabolized into glucuronide products and excreted in urine. In a single dose, amide derivatives show a clinical cure rate of 80% to 90% in asymptomatic cyst passers. It is well tolerated and reported to have side effects such as flatulence, diarrhea or cramping, nausea, headache, disorientation or dizziness, and rarely diplopia. It is administered orally at a dose of 500 mg three times a day for 5 to 10 days.
  - a. **Nitazoxanide:** *Nitazoxanide* is an oral, broad-spectrum, anti-parasitic agent having a structure similar to *niclosamide*. It has been approved for the treatment of cryptosporidiosis and giardiasis in children. It inhibits the growth of trophozoids of

*Giardia intestinalis*, *E. histolytica*, and *T. vaginalis*. It is reported to interfere with PFOR (pyruvate decarboxylating, catalyzed by pyruvate:ferredoxin oxidoreductase) enzyme-dependent electron transfer reaction. Thereby, it is also active against *metronidazole*-resistant giardiasis. It is also effective against intestinal parasites such as *H. nana*, *Strongyloides stercoralis*, *A. lumbricoides*, *Enterobius vermicularis*, *Ancylostoma duodenale*, and *Fasciola hepatica* and certain microaerophilic bacteria such as *C. difficile* and *H. pylori*. *Nitazoxanide* has also been identified as a first-in-class broad-spectrum anti-viral drug for the treatment of influenza and others. It is used at a dose of 500 mg twice daily for 3 to 7 days (depends upon the type of infection). It has been reported to have side effects such as abdominal pain, nausea, constipation, headache, and dizziness. It has also been used along with other agents for *H. pylori* eradication.

### 3. Antibiotics:

- a. **Paromomycin:** *Paromomycin* [par-oh-moe-MYE-sin], an aminoglycoside antibiotic, is only effective against the luminal forms of *E. histolytica*, because it is not significantly absorbed from the gastrointestinal tract. *Paromomycin* is directly amebicidal and also exerts its antiamebic actions by reducing the population of intestinal flora. Gastrointestinal distress and diarrhea are the principal adverse effects. Along with *metronidazole*, it is used for the treatment of amebic colitis and amebic liver abscess. It is used as a single agent against *E. histolytica* luminal amebicides. For the treatment of giardiasis during the first trimester of pregnancy, *paromomycin* is an alternative when *nitroimidazoles* are contraindicated. It is used at an oral dose of 500 mg three times a day for 7 days for amoebiasis, cryptosporidiosis, and giardiasis.
- b. **Tetracycline:** *Tetracycline* is known to have a moderate effect on *E. histolytica*. The older tetracyclines are known to have incomplete absorption in the intestine reaching higher concentration in the colon which kills the flora.

## C. Systemic amebicides

These drugs are useful for treating extraintestinal amebiasis, such as liver abscesses, and for treating intestinal wall infections caused by amebas.

1. **Chloroquine:** *Chloroquine* [KLOR-oh-kwin] is used in combination with *metronidazole* (or as a substitute for one of the *nitroimidazoles* in the case of intolerance) to treat amebic liver abscesses. It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis. Therapy should be followed with a luminal amebicide. *Chloroquine* is also effective in the treatment of malaria.
2. **Emetine:** *Emetine* is an alkaloid derived from the roots of ipecac (*Cephaelis ipecacuanha*). It is a very potent amebicide and kills trophozoites but does not have any action on cysts. It is a potent emetic when administered orally; therefore, it is administered as injection 60 mg once daily. Due to its systemic side effects such

CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	No treatment; <i>iodoquinol</i> or <i>paromomycin</i> in nonendemic areas
Diarrhea/dysentery Extraintestinal	<i>Metronidazole</i> (plus <i>iodoquinol</i> or <i>paromomycin</i> ) in nonendemic areas
Amebic liver abscess	<i>Metronidazole</i> (or <i>tinidazole</i> ) plus <i>iodoquinol</i> or <i>paromomycin</i> ; poor response: aspirate or add <i>chloroquin</i>

**Figure 36.4**

Some commonly used therapeutic options for the treatment of amebiasis.

as nausea, vomiting, diarrhea, weakness, ECG changes, hypotension, and myocarditis, it is rarely used. It is replaced with *dehydroemetine* due to comparatively lesser side effects.

3. **Dehydroemetine:** *Dehydroemetine* [de-hye-dro-EM-e-teen] is an alternative agent for the treatment of amebiasis. The drug inhibits protein synthesis by blocking chain elongation. Intramuscular injection is the preferred route, since it is an irritant when taken orally. The use of this ipecac alkaloid is limited by its toxicity, and it has largely been replaced by *metronidazole*. Adverse effects include pain at the site of injection, nausea, cardiotoxicity (arrhythmias and congestive heart failure), neuromuscular weakness, dizziness, and rash. A summary of the treatment of amebiasis is shown in Figure 36.4.

Sporadic cases of invasive amebiasis occur worldwide, but the disease is most prevalent throughout south-east Asia including the Indian subcontinent, south-east and west Africa, and Central and South America. In places where there is a high risk of reinfection, neither chemoprophylaxis nor mass chemotherapy offers an effective means of control. Prevention is dependent upon eliminating fecal contamination of food, hands, and water supplies. Luminal amebicides are active primarily against organisms in the colonic contents, and systemic amebicides are active against organisms responsible for invasive disease. In nonendemic areas, carriers (symptomless patients) should be treated with a luminal amebicide which reduces the risk of transmission and protects the patient from invasive amebiasis. Diloxanide furoate is most widely used, but other compounds, including clefamide, etofamide, and teclozan, are also effective.

When the risk of reinfection is high, treatment is not warranted except for mothers responsible for preparing food within a family or for individuals who, as a result of their occupation or lifestyles, are particularly likely to infect others.

All patients with invasive disease require treatment, first with a systemically active compound and subsequently with a luminal amebicide in order to eliminate any surviving organisms in the colon. The availability of metronidazole—and several other 5-nitroimidazoles, including ornidazole, tinidazole, and secnidazole—has made the management of most cases simpler and safer. Parenteral formulations of metronidazole, ornidazole, and tinidazole are available for patients who are too ill to take drugs by mouth. Newer nitroimidazoles have almost similar efficacy and lesser side effects compared to metronidazole and can be administered as a single dose; therefore, the cheapest available preparation should be used in amebic dysentery and in bacterial vaginosis. Amebic liver abscess of up to 10 cm can be cured with metronidazole without drainage. Clinical defervescence should occur during the first 3 to 4 days of treatment. Failure of metronidazole therapy may be an indication for surgical intervention. Treatment with a luminal agent should also follow.

#### D. Treatment for trichomoniasis

Trichomoniasis is caused by the anaerobic, flagellated protozoan parasite called *T. vaginalis*. It is a major nonviral, sexually transmitted infection causing troublesome obstetrical and gynecological problems such as vulvovaginitis. Although drugs such as *nitroimidazoles* are effective,

they require close monitoring and, if required, repeated courses are essential. Nitroimidazoles such as *metronidazole*, *tinidazole*, or *secnidazole*, either as a single higher dose or as daily doses for a week's time, are followed for treatment. If required, repeated doses are considered 6 weeks after treatment. Intravaginal administration of *idodoquin/quino-dochlor* at a dose of 200 mg for 2 weeks or *povidone-iodine* vaginal inserts 400 mg daily for 2 weeks are used.

### III. CHEMOTHERAPY FOR GIARDIASIS

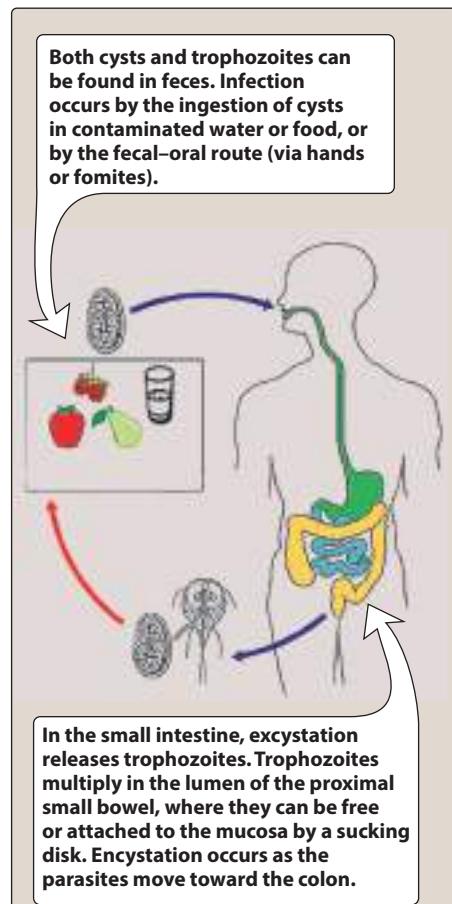
*Giardia lamblia* is the most commonly diagnosed intestinal parasite in the United States. It has two life cycle stages: 1) the binucleate trophozoite with four flagella and 2) the drug-resistant, four-nucleate cyst (Figure 36.5). Ingestion usually occurs from fecally contaminated drinking water or food, leading to infection. The trophozoites exist in the small intestine and divide by binary fission. Occasionally, cysts are formed that pass out in stools. Although some infections are asymptomatic, severe diarrhea can occur, which can be very serious in immunocompromised patients. The treatment of choice is oral *metronidazole* for 5 days. An alternative is a single dose of *tinidazole* or another 5-nitroimidazole, which are as effective as *metronidazole* in the treatment of giardiasis. *Nitazoxanide* [nye-ta-ZOX-a-nide], a nitrothiazole derivative, is also approved for the treatment of giardiasis. [Note: *Nitazoxanide* may also be used for cryptosporidiosis (a diarrheal illness most commonly seen in immunocompromised patients) caused by the parasite *Cryptosporidium parvum*.] For giardiasis, *nitazoxanide* is administered as a 3-day course of oral therapy. The anthelmintic drug *albendazole* may also be efficacious for giardiasis, and *paromomycin* is sometimes used for treatment of giardiasis in pregnant patients.

### IV. CHEMOTHERAPY FOR MALARIA

Malaria is an acute infectious disease caused by five species of the protozoal genus *Plasmodium*. It is transmitted to humans through the bite of a female *Anopheles* mosquito. The classic presentation of malaria begins with headache and fatigue, followed by fever, chills, and sweats. *Plasmodium falciparum* is the most dangerous species and the primary cause of severe malaria, causing an acute, rapidly fulminating disease characterized by persistent high fever, hyperparasitemia, and organ system dysfunction. *P. falciparum* infection can lead to capillary obstruction, cerebral malaria, and death within days without prompt treatment. *Plasmodium vivax*, *malariae*, and *ovale* cause a milder form of the disease; however, the *P. vivax* and *P. ovale* species can also remain dormant in the liver (hypnozoite stage) which can cause relapses months or years later. *Plasmodium knowlesi* is an uncommon form of malaria, previously thought to infect only nonhuman primates, which causes human infections, sometimes severe, in Southeast Asia. Resistance acquired by *Plasmodium* to antiprotozoal drugs has led to new therapeutic challenges, particularly in the treatment of *P. falciparum*. A summary of the life cycle of the parasite and the sites of action of the antimalarial drugs are presented in Figure 36.6.

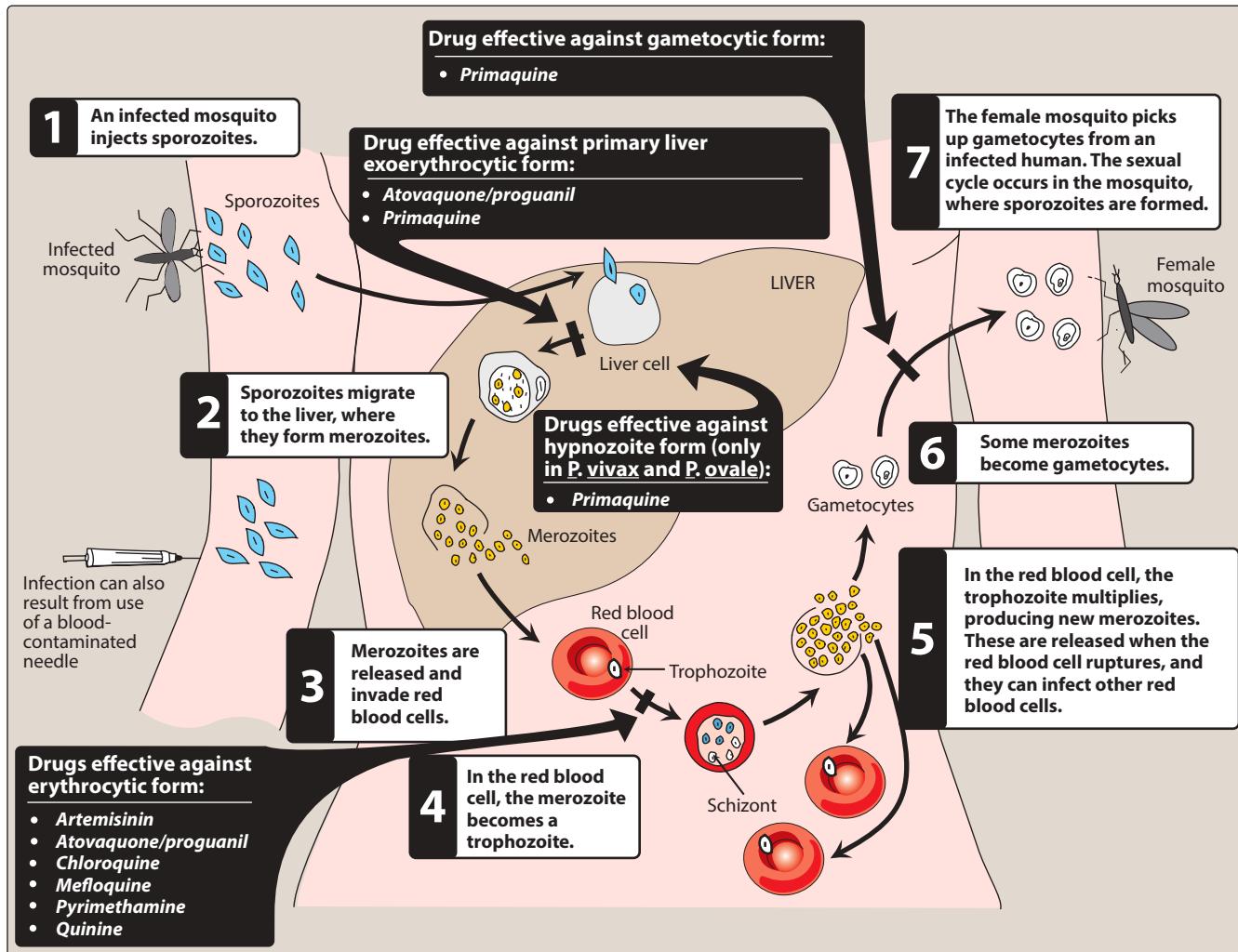
#### A. Primaquine

*Primaquine* [PRIM-a-kwin], an 8-aminoquinoline, is an oral antimalarial drug that eradicates primary exoerythrocytic (liver) forms of plasmodia and the hypnozoites of recurring malarias (*P. vivax* and *P. ovale*).



**Figure 36.5**

Life cycle of *Giardia lamblia*.

**Figure 36.6**

Life cycle of the malarial parasite, showing the sites of action of antimarial drugs.

[Note: *Primaquine* is the only agent that prevents relapses of the *P. vivax* and *P. ovale* malarias, which may remain in the liver in the hypnozoite form after the erythrocytic form of the disease is eliminated.] The sexual (gametocytic) forms of all plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thereby interrupting transmission of the disease. [Note: *Primaquine* is not effective against the erythrocytic stage of malaria and, therefore, it cannot be used monotherapy for treatment.]

- 1. Mechanism of action:** While not completely understood, metabolites of *primaquine* are believed to act as oxidants that severely disrupt the metabolic processes of plasmodial mitochondria. The metabolites are responsible for the schizonticidal action, as well as for the hemolysis and methemoglobinemia encountered as toxicities.
- 2. Pharmacokinetics:** *Primaquine* is well absorbed after oral administration and is not concentrated in tissues. It is rapidly oxidized to many compounds, primarily the deaminated drug. Which

compound possesses the schizonticidal activity has not been established. The drug is minimally excreted in the urine.

- Adverse effects:** *Primaquine* is associated with drug-induced hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency (Figure 36.7). Large doses of the drug may cause abdominal discomfort (especially when administered in combination with *chloroquine*) and occasional methemoglobinemia. *Primaquine* should not be used during pregnancy. All *Plasmodium* species may develop resistance to *primaquine*.

## B. Chloroquine

*Chloroquine* is a synthetic 4-aminoquinoline that had been the mainstay of antimalarial therapy for many years; however, the use is now limited due to *P. falciparum* resistance, which is seen in almost all malaria-endemic areas, except some parts of Central America. *Chloroquine* is less effective against *P. vivax* malaria. *Chloroquine* is used in the prophylaxis of malaria for travel to areas with known *chloroquine*-sensitive malaria. It is also effective in the treatment of extraintestinal amebiasis.

- Mechanism of action:** Although the mechanism of action is not fully understood, the processes essential for the antimalarial action of *chloroquine* are outlined in Figure 36.8. After traversing the erythrocytic and plasmoidal membranes, *chloroquine* (a diprotic weak base) is concentrated in the acidic food vacuole of the malarial parasite, primarily by ion trapping. In the food vacuole, the parasite digests the host cell's hemoglobin to obtain essential amino acids. However, this process also releases large amounts of soluble heme, which is toxic to the parasite. To protect itself, the parasite polymerizes the heme to hemozoin (a pigment), which is sequestered in the food vacuole. *Chloroquine* specifically binds to heme, preventing its polymerization to hemozoin. The increased pH and the accumulation of heme result in oxidative damage to the phospholipid membranes, leading to lysis of both the parasite and the red blood cell. *Chloroquine phosphate* is used at a dose

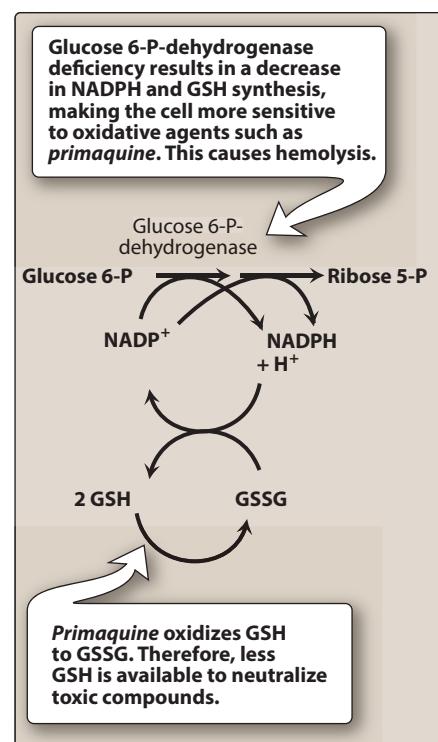


Figure 36.7

Mechanism of *primaquine*-induced hemolytic anemia. GSH = reduced glutathione; GSSG = oxidized glutathione; NADP<sup>+</sup> = nicotinamide adenine dinucleotide phosphate; NADPH = reduced nicotinamide adenine dinucleotide phosphate.

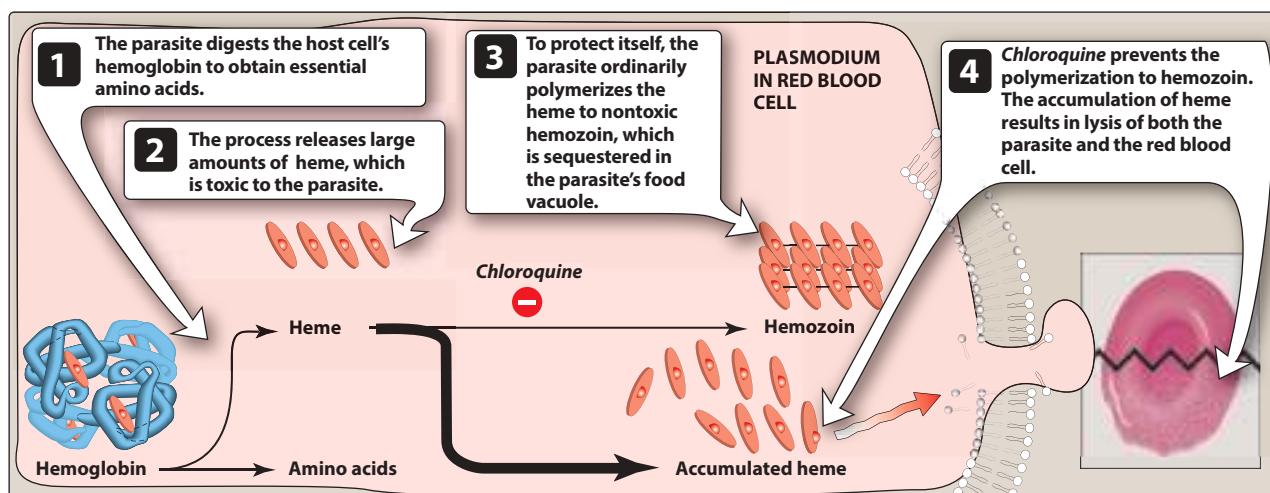
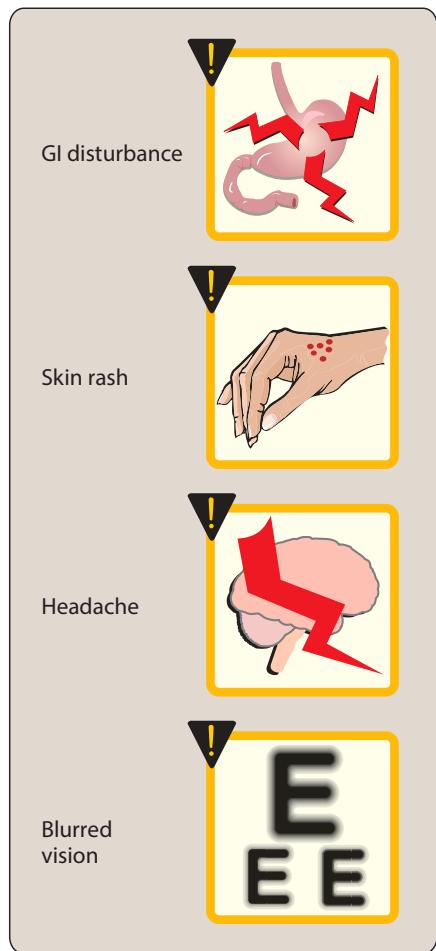


Figure 36.8

Action of *chloroquine* on the formation of hemozoin by *Plasmodium* species.

**Figure 36.9**

Some adverse effects commonly associated with *chloroquine*.  
GI = gastrointestinal.

equivalent to its base (*chloroquine*). Different schedules are used for the treatment of *P. vivax*, *P. ovale*, *P. malariae*, *P. falciparum*, and resistant forms. They are updated time to time by the regulatory and health authorities depending upon the prevalence. Generally, *chloroquine* is given as 600 mg (10 mg/kg) followed by 300 mg (5 mg/kg) three times a day for 2 days followed by *primaquine* 15 mg (0.25 mg/kg) for 2 weeks as a gametocidal to complete the therapy. Resistant falciparum malaria is handled with the help of combination therapy with drugs such as *artesunate*, *lumifantrine*, and *mefloquine*. Alternative regimens using *quinine*, *doxycycline*, *clindamycin* or *arterolane*, and *piperaquine* are also available to handle the drug resistant in *P. falciparum* infestation.

2. **Pharmacokinetics:** *Chloroquine* is rapidly and completely absorbed following oral administration. The drug has a very large volume of distribution and concentrates in erythrocytes, liver, spleen, kidney, lung, melanin-containing tissues, and leukocytes. It persists in erythrocytes. The drug also penetrates the central nervous system (CNS) and traverses the placenta. *Chloroquine* is dealkylated by the hepatic mixed-function oxidase system, and some metabolic products retain antimalarial activity. Both parent drug and metabolites are excreted predominantly in urine.
3. **Adverse effects:** Adverse effects are minimal at low prophylactic doses. At higher doses, gastrointestinal upset, pruritus, headaches, and blurred vision may occur (Figure 36.9). An ophthalmologic examination should be routinely performed during extended use due to potential retinal toxicity. Discoloration of the nail beds and mucous membranes may be seen on chronic administration. *Chloroquine* should be used cautiously in patients with hepatic dysfunction, severe gastrointestinal problems, or neurologic disorders. Patients with psoriasis or porphyria should not be treated with *chloroquine*, because an acute attack may be provoked. *Chloroquine* can prolong the QT interval, and use of other drugs that also cause QT prolongation should be avoided if possible.

### C. Mefloquine

*Mefloquine* [MEF-lo-kwin] is a 4-methanolquinoline, structurally related to *quinine*, which is an effective agent for prophylaxis from all plasmodia and for treatment when used in combination with an *artemisinin* derivative for infections caused by multidrug-resistant forms of *P. falciparum*. Its exact mechanism of action remains undetermined. Resistant strains have been identified, particularly in Southeast Asia. *Mefloquine* is well absorbed after oral administration and is widely distributed to tissues. It has a long half-life (20 days) because of enterohepatic recirculation and its concentration in various tissues. The drug undergoes extensive metabolism and is primarily excreted via the bile into the feces. Adverse reactions at high doses range from nausea, vomiting, and dizziness to disorientation, hallucinations, and depression. Because of the potential for neuropsychiatric reactions, *mefloquine* is usually reserved for treatment of malaria when other agents cannot be used. ECG abnormalities and cardiac arrest are possible if *mefloquine* is taken concurrently with *quinine* or *quinidine*.

#### D. Quinine

*Quinine* [KWYE-nine], an alkaloid originally isolated from the bark of the cinchona tree, interferes with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite. It is reserved for severe infections and for *chloroquine*-resistant malarial strains. *Quinine* is usually administered in combination with *doxycycline*, *tetracycline*, or *clindamycin*. Taken orally, *quinine* is well distributed throughout the body. The major adverse effect of *quinine* is cinchonism, a syndrome causing nausea, vomiting, tinnitus, and vertigo. These effects are reversible and are not reasons for suspending therapy. However, *quinine* treatment should be suspended if hemolytic anemia occurs.

#### E. Amodiaquine

*Amodiaquine* is a congener of *chloroquine* but less bitter. It is not widely used in all the countries but it still has therapeutic benefit in tropical countries. *Amodiaquine* is well tolerated up to 35 mg/kg administered over a period of 3 days for uncomplicated *P. falciparum* malaria. Upon oral administration, it is converted to *monodesethyl-amodiaquine* by hepatic enzymes and this metabolite is responsible for its therapeutic efficacy. It is used at a dose of 25 to 35 mg/kg over a period of 3 days and available as 200 mg tablets and in suspension form for pediatric use. The side effects of *amodiaquine* are similar to those of *chloroquine* but with a lesser frequency. The metabolite has a longer plasma half-life of 9 to 18 days. *Artesunate* combined with *amodiaquine* is the first line of treatment in many African countries and approved in India for *P. falciparum* malaria. Neutropenia has been reported when it is administered in children and HIV patients undergoing antiretroviral drug therapy.

#### F. Piperaquine

*Piperaquine* is another congener of *chloroquine* having a similar mechanism of action. It is a lipophilic compound absorbed well after oral administration. It reaches  $C_{max}$  at 2 hours but has the longest plasma half-life of 3 to 5 weeks. It is more effective when combined with *dihydroartemisinin* in the ratio of 8:1 (for *piperaquine* and *dihydroartemisinin*). It is found to be well tolerated in children and adults. This combination has been extensively studied in many of the Asian countries and it has been found to be equivalent to other combinations such as *artemether-lumefantrin*. A number of clinical trials, showing the combination of *dihydroartemisinin/piperaquine*, has been reported as highly effective in the treatment of uncomplicated *P. falciparum* malaria. Nausea, vomiting, and dizziness have been reported to be less as compared to *artesunate* with *mefloquine*. However, some cases of prolongation of the corrected QT interval have been reported in this combination.

#### G. Tafenoquine

*Tafenoquine* is an investigational 8-aminoquinoline, for the prevention of *P. vivax* relapse. *Tafenoquine* has a long half-life and the potential for more convenient dosing, compared with the currently recommended 14-day *primaquine* regimen.

## H. Lumefantrine

*Lumefantrine* is also called *benflumetol* (belongs to the class of arylamino alcohol drugs such as *mefloquine*). It is used for the treatment of uncomplicated malaria due to *P. falciparum* and *chloroquine*-resistant strains. It is effective against the erythrocytic phase of *Plasmodium* species. It is administered in combination with *artemether* for improved efficacy and for the treatment of *chloroquine*-resistant species.

## I. Proquanil

*Proquanil* is a biguanide derivative, also called *chloroguanide*. A cyclic metabolite, cycloguanil, formed by the structural rearrangement selectively inhibits both plasmoidal dihydrofolate reductase and thymidylate synthase which are crucial for the parasite to de novo synthesis of *purine* and *pyrimidine*. It has been reported to have a wider safety margin. In the drug-sensitive *P. falciparum* malaria, it is effective in the primary liver stage as well as in the asexual stage in RBCs. In *P. vivax* malaria, latent tissue stages are not affected; therefore, relapses do happen upon the discontinuation of *proguanil*. It is used at a dose of 200 to 300 mg/day. The side effects reported with *proquanil* are nausea and diarrhea in the lower doses. As a first-line monotherapy or prophylaxis, it is not encouraged due to the development of resistance but can be used in combination with *atovoquone*. This combination is used as a once-a-day therapy for 3 days. Its therapeutic use in combination has been justified in the resistant infections of *P. falciparum* which is not resistant to *atorvoquone*.

## J. Pyrimethamine

*Pyrimethamine* [peer-i-METH-a-meen] inhibits plasmoidal dihydrofolate reductase required for the synthesis of tetrahydrofolate (a cofactor needed for synthesis of nucleic acids). *Pyrimethamine* is structurally related to cycloguanil. It acts as a blood schizonticide and a strong sporonticide when the mosquito ingests it with the blood of the human host. *Pyrimethamine* is not used alone for malaria; it is available as a fixed-dose combination with *sulfadoxine*, a sulfonamide antimicrobial. Resistance to this combination has developed, so it is usually administered with other agents, such as *artemisinin* derivatives. *Pyrimethamine* in combination with *sulfadiazine* is also used against *Toxoplasma gondii*. If megaloblastic anemia occurs with *pyrimethamine* treatment, it may be reversed with *leucovorin*. **Figure 36.10** shows some therapeutic options in the treatment of malaria.

## K. Artemisinin

*Artemisinin* [ar-te-MIS-in-in] is derived from the sweet wormwood plant which has been used in traditional Chinese medicine (from the plant Qin-hao-su), for many centuries. *Artemisinin* and its derivatives are recommended first-line agents for the treatment of multidrug-resistant *P. falciparum* malaria. The activity of *artemisinin* derivatives is due to the reductive scission of the peroxide bridge by reduced heme-iron. It happens in the acidic environment of vacuole of the

TYPE OF MALARIA	DOSE
<u>P. vivax</u> malaria	<i>Chloroquine</i> 25 mg/kg divided over 3 days orally—that is, 10 mg/kg on day 1, 10 mg/kg on day 2, and 5 mg/kg on day 3 <i>Primaquine</i> 0.25 mg/kg daily orally for 14 days <sup>1</sup>
<u>P. falciparum</u> malaria	<i>Artemisinin-based combination therapy (ACT)</i> <sup>2</sup> consisting of following: (ACT_SP) <i>Artesunate</i> 4 mg/kg body weight daily for 3 days plus <i>Sulfadoxine</i> (25 mg/kg) <sup>3</sup> And <i>Single-dose primaquine</i> 0.75 mg/kg body weight on day 2 In northeastern states (ACT-AL): <i>Artemether</i> 20 mg plus <i>Lumefantrine</i> 120 mg In case of no response to ACT (clinically and parasitologically within 72 hours), oral <i>quinine</i> 648 mg every 8 hours for 7 to 10 days with <i>tetracycline</i> (in adults and children over 8 years) 500 mg twice daily for 7 to 10 days/ <i>doxycycline</i> 3 mg/kg once daily <sup>4</sup>
<u>P. falciparum</u> malaria uncomplicated in pregnancy	First trimester: <i>Quinine</i> salt 10 mg/kg 3 times daily for 7 days Second and third trimesters: <i>ACT</i> as above
<u>P. vivax</u> malaria in pregnancy	<i>Chloroquine</i> as above
Mixed infection ( <u>P. vivax</u> + <u>P. falciparum</u> ) case	To be treated as <u>P. falciparum</u>
Treatment of <u>P. ovale</u> and <u>P. malariae</u> cases	Treat <u>P. ovale</u> as <u>P. vivax</u> and <u>P. malariae</u> as <u>P. falciparum</u>
Severe malaria (an emergency)	Two options, either <i>Artesunate</i> 2.4 mg/kg IV or IM given on admission (time = 0 hour); then at 12 hours and 24 hours and then once a day. <i>Artesunate</i> powder should be diluted in 5% sodium bicarbonate provided in the pack only Or <i>Artemether</i> 3.2 mg/kg IM given on admission and then 1.6 mg/kg per day Or <i>Artemether</i> 150 mg IM daily for 3 days in adults only (not recommended for children) followed by a full course of ACT when the patient can take orally. Avoid ACT containing <i>mefloquine</i> in cerebral malaria due to neuropsychiatric complications associated with it Or Initial parenteral treatment for at least 48 hours: <i>Quinine</i> 20 mg/kg as loading dose on admission followed by a maintenance dose of 10 mg/kg 8 hourly in 5% dextrose/dextrose saline over a period of 4 hours or divided IM injection. The infusion rate should not exceed 5 mg/kg/hr. NEVER GIVE BOLUS INJECTION OF QUININE. If parenteral <i>quinine</i> therapy needs to be continued beyond 48 hours, reduce dose to 7 mg/kg 8 hourly followed by <i>quinine</i> 10 mg/kg 8 hourly with <i>doxycycline</i> 3 mg/kg once daily

<sup>1</sup>Primaquine is contraindicated in pregnant women, infants, and individuals with G6PD deficiency.<sup>2</sup>ACT is not to be given in the first trimester of pregnancy.<sup>3</sup>Sulfadoxine + Pyrimethamine (SP) is contraindicated in a child of age under 5 months; treat with alternate ACTs.<sup>4</sup>To be reported to the concerned district authorities.**Figure 36.10**

Treatment of malaria.

parasite when it digests hemoglobin. Moreover, the formation of toxic adducts and intermediates is also responsible for its action. It causes more rapid clearance of the parasite and clinical improvement. In three to four cycles of treatment over a period of 6 to 8 days, it is enough to get the extensive parasite clearance from blood. Owing to its tolerable side effect profile, it is recommended for nonpregnant adults and children. Addition of another antimalarial agent, or artemisinin-based combination therapy (ACT), is recommended to prevent the development of resistance. Artesunate is a semisynthetic artemisinin for oral administration. Other derivatives are also available for intramuscular (*artesunate* and *artemether*),

intravenous (*artesunate*), and rectal (*artesunate*) modes of administration. Although oral bioavailability is low (30%), rapid higher levels are seen in the plasma, metabolized by CYP2B6 and CYP3A4 in the liver and excreted. *Artesunate* is a microsomal enzyme autoinducer which enhances its own clearance.

#### L. Artesunate-based combination therapy (ACT)

One orally available ACT includes a tablet with *artemether* coformulated with *lumefantrine* [AR-te-meth-er/loo-me-FAN-tree-n] and is used for the treatment of uncomplicated malaria. [Note: *Lumefantrine* is an antimalarial drug similar in action to *quinine* or *mefloquine*.] *Artesunate* [ar-TEZ-oo-nate] may be combined with *sulfadoxine-pyrimethamine*, *mefloquine*, *clindamycin*, or others. The antimalarial action of *artemisinin* derivatives involves the production of free radicals resulting from cleavage of the drug's endoperoxide bridge by heme-iron in the parasite food vacuole. Oral, rectal, intramuscular (IM), and intravenous (IV) preparations are available, but the short half-lives preclude the use of these drugs for prophylaxis. Adverse effects include nausea, vomiting, and diarrhea. High doses may cause prolongation of the QT interval. Hypersensitivity reactions and rash have occurred. A recent meta-analysis revealed that in high transmission settings, *dihydroartemisinin-piperaquine* is found to be superior to *artemether + lumefantrine*, *artesunate + sulfadoxine-pyrimethamine*, and *artesunate + amodiaquine* for preventing recurrent parasitemias before day 28. This study has also reported that *dihydroartemisinin-piperaquine* combination may also have an improved post-treatment prophylactic effect lasting for up to 6 weeks, and this effect may be present even when *primaquine* is given to achieve radical cure.

#### M. Sulfonamide-pyrimethamine

The synergistic combination of long-acting sulfonamides, a malarial dihydropteroate synthase inhibitor, and *pyrimethamine*, a tetrahydrofolate reductase inhibitor, enhances the antimalarial action. This combination had extensive use in the clinical settings for malaria, especially for the erythrocyte stage. Resistance for this combination occurred due to the point mutations in the dihydropteroate synthase gene in the malaria. This combination is highly helpful in *chloroquine*-resistant *P. falciparum* malaria. Due to sulfonamide moiety, adverse effects such as exfoliative dermatitis and Stevens-Johnson syndrome are observed. It is not effective in *P. vivax* malaria. Tablets with *sulfadoxine* or *sulfamethopyrazine* at a dose of 500 mg along with *pyrimethamine* 25 mg are available. It is not used in individuals allergic to sulfonamides. It is usually administered as a single dose of three tablets (1500 mg *sulfadoxine* with 75 mg *pyrimethamine*) for adults. This combination is also used in toxoplasmosis.

#### N. Atovaquone-proguanil

The combination of *atovaquone-proguanil* [a-TOE-va-kwone pro-GWA-nil] is effective for *chloroquine*-resistant strains of *P. falciparum*, and it is used in the prevention and treatment of malaria for travelers from outside malaria-endemic areas. *Atovaquone-proguanil* is

not routinely used in endemic areas due to propensity for emergence of high-level resistance. *Atovaquone* is a hydroxynaphthoquinone which inhibits mitochondrial processes including electron transport, as well as ATP and pyrimidine biosynthesis. *Cycloguanil*, the active triazine metabolite of *proguanil*, inhibits plasmoidal dihydrofolate reductase, thereby preventing DNA synthesis. *Atovaquone* may also be used to treat *Babesia* sp. and *Pneumocystis jirovecii*. *Proguanil* is metabolized via CYP2C19, an isoenzyme that is known to exhibit a genetic polymorphism resulting in poor metabolism of the drug in some patients. The combination should be taken with food or milk to enhance absorption. Common adverse effects include nausea, vomiting, abdominal pain, headache, diarrhea, anorexia, and dizziness.

## O. Other antibiotics

*Tetracycline*, *doxycycline*, and *clindamycin* are used for the treatment of malaria. These are slow-acting blood schizonticides and are used in areas where the use of *chloroquine* and *mefloquine* in resistant malaria is predominant. They act by the inhibition of protein synthesis in the parasitic plastid. Due to their slow onset of action, these drugs are not recommended for clinical management. *Doxycycline* is recommended as malaria chemoprophylaxis.

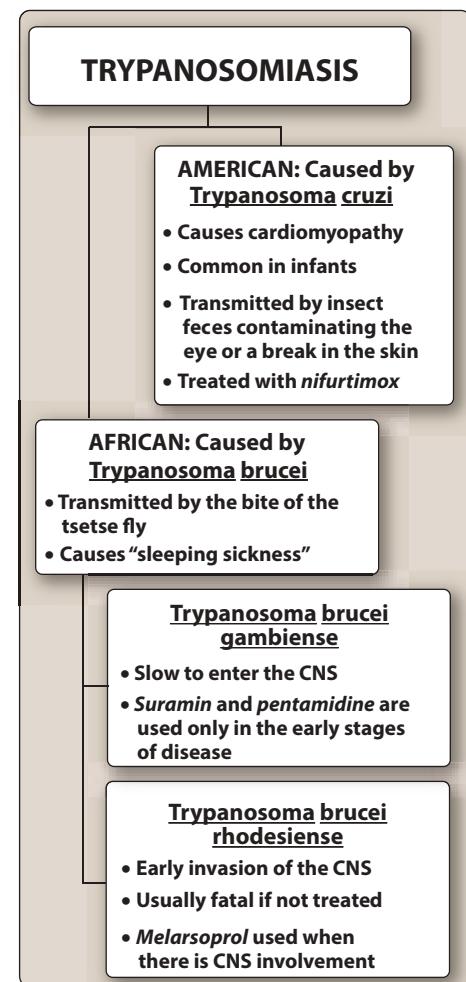
## V. CHEMOTHERAPY FOR TRYPANOSOMIASIS

African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas disease) are two chronic and, eventually, fatal diseases caused by the species of *Trypanosoma* (Figure 36.11). In African sleeping sickness, *T. brucei gambiense* and *T. brucei rhodesiense* initially live and grow in the blood. The parasite later invades the CNS, causing inflammation of the brain and spinal cord that produces the characteristic lethargy and, eventually, continuous sleep. Chagas disease is caused by *T. cruzi* and is endemic in Central and South America. Antitrypanosomal drugs are outlined below.

### A. Pentamidine

*Pentamidine* [pen-TAM-i-deen] is active against a variety of protozoal infections, including African trypanosomiasis due to *T. brucei gambiense*, for which it is used to treat the early stages of disease (hemolymphatic stage without CNS involvement). *Pentamidine* is also an alternative for prophylaxis or treatment of infections caused by *P. jirovecii*. [Note: *P. jirovecii* is an atypical fungus that causes pneumonia in immunocompromised patients, such as those with HIV infection. *Trimethoprim/sulfamethoxazole* is preferred in the treatment of *P. jirovecii* infections; however, *pentamidine* is an alternative in individuals who are allergic to sulfonamides.] *Pentamidine* is also an alternative drug for the treatment of leishmaniasis.

1. **Mechanism of action:** *T. brucei* concentrates *pentamidine* by an energy-dependent, high-affinity uptake system. [Note: Resistance is associated with the inability to concentrate the drug.] Although its mechanism of action has not been defined, evidence exists



**Figure 36.11**

Summary of trypanosomiasis.  
CNS = central nervous system.

that the drug interferes with parasite synthesis of RNA, DNA, phospholipids, and proteins.

2. **Pharmacokinetics:** *Pentamidine* is administered intramuscularly or intravenously for the treatment of trypanosomiasis and pneumonia caused by *P. jirovecii*. [Note: For prophylaxis of *P. jirovecii* pneumonia, *pentamidine* is administered via a nebulizer.] The drug distributes widely and is concentrated in the liver, kidney, adrenals, spleen, and lungs. Because it does not enter the CSF, it is ineffective against the late stages (CNS involvement) of trypanosomiasis. The drug is not metabolized, and it is excreted very slowly in the urine.
3. **Adverse effects:** Serious renal dysfunction may occur, which is reversible on discontinuation. Other adverse reactions include hyperkalemia, hypotension, pancreatitis, ventricular arrhythmias, and hyperglycemia. Plasma glucose should be monitored, as life-threatening hypoglycemia can occur.

## B. Suramin

*Suramin* [SOO-ra-min] is used primarily in the early stage (without CNS involvement) of African trypanosomiasis due to *T. brucei rhodesiense*. It is very reactive and inhibits many enzymes, especially those involved in energy metabolism, which appears to be the mechanism correlated with trypanocidal activity. *Suramin* must be injected intravenously. It binds to plasma proteins and does not penetrate the blood-brain barrier well. It has a long elimination half-life (greater than 40 days) and is mainly excreted unchanged in the urine. Although infrequent, adverse reactions include nausea and vomiting, shock and loss of consciousness, acute urticaria, blepharitis, and neurologic problems, such as paresthesia, photophobia, and hyperesthesia of the hands and feet. Renal insufficiency may occur, but tends to resolve with discontinuation of treatment. Acute hypersensitivity reactions may occur, and a test dose should be given prior to drug administration.

## C. Melarsoprol

*Melarsoprol* [mel-AR-so-prol], a trivalent arsenical compound, is the only medication available for the treatment of late stages of African trypanosomal infections (CNS involvement) due to *T. brucei rhodesiense*. The drug reacts with sulfhydryl groups of various substances, including enzymes in both the organism and the host. Some resistance has been noted, and it may be due to decreased transporter uptake of the drug. *Melarsoprol* is administered by slow IV injection and can be very irritating to the surrounding tissue. Adequate trypanocidal concentrations appear in the CSF, making *melarsoprol* the agent of choice in the treatment of *T. brucei rhodesiense*, which rapidly invades the CNS. The host readily oxidizes *melarsoprol* to a relatively nontoxic, pentavalent arsenic compound. The drug has a very short half-life and is rapidly excreted in urine. The use of *melarsoprol* is limited by CNS toxicity, including reactive encephalopathy, which can be fatal in 10% of cases. Other adverse effects include peripheral neuropathy, hypertension, hepatotoxicity, and albuminuria. Hypersensitivity reactions may also occur, and febrile reactions may follow injection. Hemolytic

anemia has been seen in patients with glucose-6-phosphate dehydrogenase deficiency.

#### D. Eflornithine

*Eflornithine* [ee-FLOOR-nih-theen] is an irreversible inhibitor of ornithine decarboxylase. Inhibition of this enzyme halts the production of polyamines in the parasite, thereby leading to cessation of cell division. The IV formulation of *eflornithine* is a first-line treatment for late-stage African trypanosomiasis caused by *T. brucei gambiense*. [Note: Topical *eflornithine* is used as a treatment for unwanted facial hair in women.] The short half-life of *eflornithine* necessitates frequent IV administration, making the treatment regimen difficult to follow. *Eflornithine* is less toxic than *melarsoprol*, although the drug is associated with anemia, seizures, and temporary hearing loss.

#### E. Nifurtimox

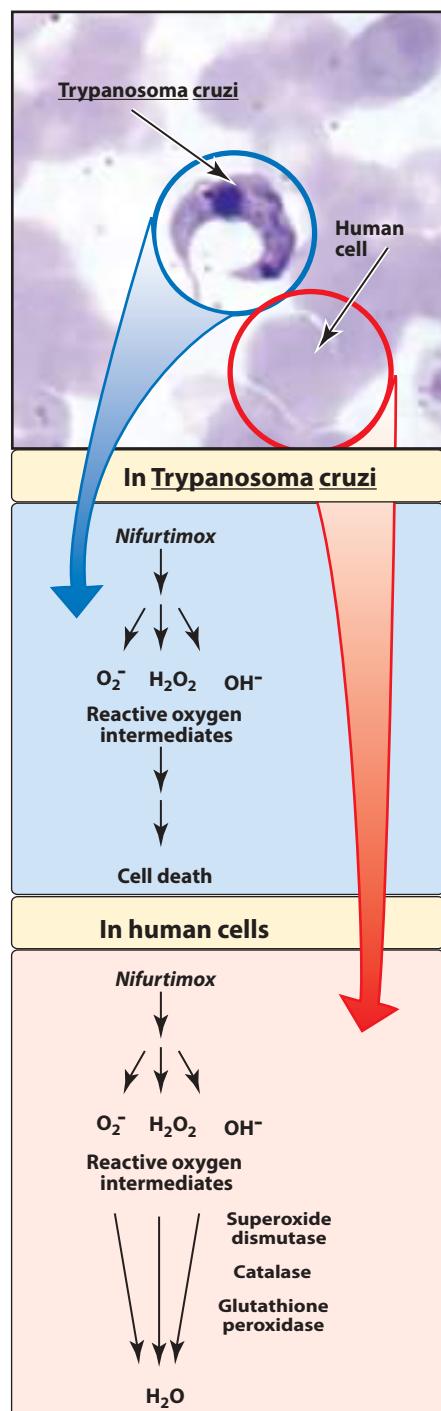
*Nifurtimox* [nye-FER-tim-oks] is used in the treatment of *T. cruzi* infections (Chagas disease), although treatment of the chronic stage of such infections has led to variable results. It may also be useful for the treatment of late-stage *T. brucei gambiense* in combination with *eflornithine*. Being a nitroaromatic compound, *nifurtimox* undergoes reduction and eventually generates intracellular oxygen radicals, such as superoxide radicals and hydrogen peroxide (Figure 36.12). These highly reactive radicals are toxic to *T. cruzi*. *Nifurtimox* is administered orally. It is extensively metabolized, and the metabolites are excreted mainly in the urine. Adverse effects are common following chronic administration, particularly among the elderly. Major toxicities include hypersensitivity reactions (anaphylaxis, dermatitis) and gastrointestinal problems that may be severe enough to cause weight loss. Peripheral neuropathy is relatively common, and headache and dizziness may also occur.

#### F. Benznidazole

*Benznidazole* [benz-NI-da-zole] is a nitroimidazole derivative with a mechanism of action similar to *nifurtimox*. It tends to be better tolerated than *nifurtimox* and is an alternative for the treatment of Chagas disease. Adverse effects include dermatitis, peripheral neuropathy, insomnia, and anorexia.

## VI. CHEMOTHERAPY FOR LEISHMANIASIS

Leishmaniasis, called “kala-azar” in Hindi, is a protozoal infection caused by various species of the genus *Leishmania*. There are three manifestations of leishmaniasis: cutaneous, mucocutaneous, and visceral. [Note: In the visceral type (liver and spleen), the parasite is in the bloodstream and if untreated is fatal.] Leishmaniasis is transmitted by the bite of infected sandflies. For visceral leishmaniasis, parenteral treatments may include *amphotericin B* (see Chapter 33) and pentavalent antimonials, such as *sodium stibogluconate* or *meglumine antimoniate* with *pentamidine* and *paromomycin* as alternative agents. *Miltefosine* is an orally active agent for visceral leishmaniasis. The choice of agent depends on the species



**Figure 36.12**

Generation of toxic intermediates by *nifurtimox*.

of *Leishmania*, host factors, and resistance patterns noted in area of the world where the infection is acquired.

### A. Sodium stibogluconate

The pentavalent antimonial *sodium stibogluconate* [stib-o-GLOO-kone-nate] is a prodrug which is reduced to the active trivalent antimonial compound. The exact mechanism of action has not been determined. Because it is not absorbed after oral administration, *sodium stibogluconate* must be administered parenterally, and it is distributed in the extravascular compartment. Metabolism is minimal, and the drug is excreted in urine. Adverse effects include injection site pain, pancreatitis, elevated liver enzymes, arthralgias, myalgias, gastrointestinal upset, and cardiac arrhythmias. Resistance to the pentavalent antimoniais has developed.

### B. Miltefosine

*Miltefosine* [mil-te-FOE-zeen] is the first orally active drug for visceral leishmaniasis and can also treat cutaneous and mucocutaneous forms of the disease. The precise mechanism of action is not known, but *miltefosine* appears to interfere with phospholipids and sterols in the parasitic cell membrane to induce apoptosis. Nausea and vomiting are common adverse reactions. The drug is teratogenic and should be avoided in pregnancy.

### C. Amphotericin B

Pharmacology of the polyene antifungal *amphotericin B* has been discussed in this chapter. It is a hydrophobic agent known to exhibit nephrotoxicity; therefore, it is formulated as liposomal *amphotericin B* to reduce the higher concentrations reaching kidney. *Amphotericin B* is highly effective in kala-azar. Moreover, liposome *amphotericin B* is used for safety, and liposomes (phospholipid vesicles) are also capable of delivering *amphotericin* inside the circulating macrophages and reticuloendothelial cells in spleen and liver where amastigotes survive. Liposome *amphotericin B*, administered at a dose of 15 mg/kg over 3 to 5 days, showed a cure rate of 98%. A single dose of 10 mg/kg has also been reported to have similar efficacy. It is also effective against sodium stibogluconate-resistant infections. [Figure 36.12](#) depicts drugs used in the treatment of leishmaniasis, their contraindications, and precautions to be taken during treatment.

## VII. CHEMOTHERAPY FOR TOXOPLASMOSIS

One of the most common infections in humans is caused by the protozoan *T. gondii*, which is transmitted to humans when they consume raw, inadequately cooked infected meat, or accidentally ingest oocysts from cat feces. An infected pregnant woman can transmit *T. gondii* to her fetus. The treatment of choice for this condition is a combination of *sulfadiazine* and *pyrimethamine*. *Leucovorin* is commonly administered to protect against folate deficiency. [Note: At the first appearance of a rash, *pyrimethamine* should be discontinued, because hypersensitivity to this drug can be severe.] *Pyrimethamine* with *clindamycin*, or the combination of *trimethoprim* and

*sulfamethoxazole*, are alternative treatments. *Trimethoprim/sulfamethoxazole* is used for prophylaxis against toxoplasmosis (as well as *P. jirovecii*) in immunocompromised patients.

## VIII. CHEMOTHERAPY FOR LYMPHATIC FILARIASIS

Lymphatic filariasis, commonly known as elephantiasis, is a painful and profoundly disfiguring disease. In communities where filariasis is transmitted, all ages are affected. While the infection may be acquired during childhood, its visible manifestations may occur later in life, causing temporary or permanent disability. In endemic countries, lymphatic filariasis has a major social and economic impact. The disease is caused by three species of thread-like nematode worms, known as filariae—*Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. The adult male and female worms together form “nests” in the human lymphatic system.

Filarial infection can cause a variety of clinical manifestations, including lymphedema of the limbs, genital disease (hydrocele, chylocele, and swelling of the scrotum and penis), and recurrent acute attacks, which are extremely painful and are accompanied by fever (Figure 36.13). The vast majority of infected people are asymptomatic, but virtually all of them have subclinical lymphatic damage and as many as 40% have kidney damage, with proteinuria and hematuria.

*Diethylcarbamazine (DEC)* rapidly kills microfilaria and can kill some, but not all adults of both *Wuchereria* and *Brugia*. *DEC* exerts no direct lethal effect on microfilariae but apparently modifies them so that they are eliminated by the host's immune defence mechanism. *DEC* is well absorbed following oral administration with peak plasma concentrations reaching within 1 to 2 hours. The elimination half-life ranges from 10 to 12 hours. If the urine is alkalinized, renal excretion of the unchanged drug is prevented and the half-life of the drug increases. Adverse reactions to *DEC* may either be due to a direct effect of the drug or occur as a response to the pharmacodynamic effect of the drug on the worm.

The standard dose of *DEC* is 6 mg/kg, given in three divided doses after food over a period of 12 days, which reduces microfilaremia levels by approximately 80% to 90% in several days. In cases of heavy parasitic load, in order to decrease the side effects of the *DEC*, start with a lower dose (1 to 3 mg/kg) once a day initially. Drug reactions due to dying worm may commence after the start of the medical treatment. These reactions may be local or systemic. Systemic reactions include fever, headache, myalgia, vomiting, weakness, and asthma; they usually result from the rapid destruction of microfilariae and perhaps adult worms, specially in heavily infected individuals. Local reactions include lymphadenitis, abscess formation, and transient lymphedema. These symptoms develop within 2 days, often within 12 hours, after initiation of the treatment, and persist for 3 to 4 days.

*DEC* should not be administered to patients who may also have onchocerciasis as *DEC* can worsen onchocercal eye disease. In patients with loiasis, *DEC* can cause serious adverse reactions, including encephalopathy and death. The risk and severity of the adverse reactions are related to *Loa loa* microfilarial density. The drug is not recommended during pregnancy though no teratogenic effect has been reported so far. The side effects of *DEC* therapy may be reduced with spacing in between the two doses like a single dose of 6 mg/g once weekly, twice monthly, or once monthly. *DEC* treatment of microfilaremic patients and with acute symptoms eliminates the episodes of acute lymphatic inflammation that may prevent the development

of obstructive lesions, hence reducing the incidence of chyluria. The drug is rapidly excreted and nontoxic; it can be repeated at 1 month following completion of the first course. Multiple courses of treatment may be required which may be repeated at an interval of 6 months. Peripheral eosinophilia often accompanies the infection with this parasite that should resolve with the response of the treatment. If peripheral eosinophilia and/or clinical symptoms persist after treatment, peripheral blood should be re-examined for microfilaremia/or circulating antigen.

*Ivermectin* kills microfilariae only but not the adult worm and can be given as a single dose of 400 mg/kg. Although *ivermectin* leads to rapid clearance of microfilariae, sustained reductions at 6 months or longer after treatment are equivalent or better with a single 6 mg/kg dose of *DEC*. This is consistent with *DEC* having a greater effect on adult worms. *Ivermectin* can also be used with *DEC* as a single dose that gives more rapid clearance of microfilariae and recurrence is delayed. The side effects of *ivermectin* are similar to those of *DEC* with additional neurotoxicity. *Albendazole* 400 mg as a single dose in combination with *ivermectin* is more effective in clearing microfilariae than *albendazole* or *ivermectin* alone.

All people with filariasis who have microfilaremia or a positive antigen test should receive antifilarial drug treatment to eliminate microfilariae. Infected patients can be treated with one of the following regimens:

- Management of morbidity and disability prevention (MMDP) in lymphatic filariasis require a broad strategy involving both secondary and tertiary prevention. Secondary prevention includes simple hygiene measures, such as basic skin care and exercise, to prevent adenolymphangitis (ADL), commonly called “acute attacks,” and progression of lymphedema to elephantiasis. For management of hydrocele, surgery may be appropriate. [Figure 36.13](#) depicts the clinical manifestations of lymphatic filariasis and their management. Tertiary prevention includes psychological and socioeconomic support for people with disabling conditions to ensure that they have equal access to rehabilitation services and opportunities for health, education, and income.
- Elimination of lymphatic filariasis is possible by interrupting the transmission cycle. Providing treatment on a large scale to entire communities where the infection is present can stop the spread of infection. This strategy of preventive chemotherapy, called mass drug administration (MDA), involves a combined dose of two medicines given annually to an entire at-risk population.

The following recommended drug regimens must be administered once a year for at least 5 years, with a coverage of at least 65% of the total at-risk population:

- *Diethylcarbamazine citrate (DEC)* 6 mg/kg + *albendazole* 400 mg Or *Ivermectin* 150 µg/kg + 400 mg *albendazole* (in areas that are also endemic for onchocerciasis).
- *Albendazole* 400 mg alone preferably twice per year (in areas that are also endemic for *Loa loa*).

These medicines have a limited effect on adult parasites but effectively reduce microfilariae from the bloodstream and prevent the spread of microfilaria to mosquitoes. Adult worms can remain viable for years. Therefore, it is necessary to deliver several rounds of MDA. At least five rounds are recommended to reduce infections in the community to levels below a threshold at which mosquitoes are unable to continue spreading the parasites from person to person and new infections are prevented.

CLINICAL MANIFESTATION	TREATMENT
Acute dermatolymphangio-adenitis	Antibiotics, antipyretics, analgesics
Lymphoedema and elephantiasis	Hygiene, anti-bacterial creams, antifungal creams
Hydrocoele	Surgery

**Figure 36.13**

Clinical manifestations of lymphatic filariasis and their management.

Vector control is supplemental to the core strategy of MDA and can enhance elimination efforts by reducing the mosquito density and preventing human–mosquito contact. Malaria control interventions such as residual spraying and sleeping under long-lasting insecticidal nets have collateral benefits in reducing transmission of lymphatic filariasis.

## Study Questions

Choose the ONE best answer.

- 36.1 After the acute infection, which medication is given to treat the asymptomatic colonization state of *E. histolytica*?
- A. Chloroquine
  - B. Iodoquinol
  - C. Metronidazole
  - D. Primaquine
- 36.2 A group of college students are traveling to a chloroquine-resistant malaria area for a mission trip. Which medication can be used to both prevent and treat malaria in these students?
- A. Pyrimethamine
  - B. Artemisinin
  - C. Atovaquone–proguanil
  - D. Hydroxychloroquine
- 36.3 Which agent is available as an oral therapy for the treatment of visceral leishmaniasis?
- A. Artemether/lumefantrine
  - B. Miltefosine
  - C. Nitazoxanide
  - D. Tinidazole
- 36.4 A 27-year-old woman is diagnosed with African trypanosomal infection due to *T. brucei gambiense*. Which medication would be the best for this patient?
- A. Eflornithine
  - B. Suramin
  - C. Sodium stibogluconate
  - D. Metronidazole
- 36.5 Which agent is the only medication to treat late stages of trypanosomal infections due to *T. brucei rhodesiense*?
- A. Artemether/lumefantrine
  - B. Melarsoprol
  - C. Nitazoxanide
  - D. Tinidazole

Correct answer = B. Iodoquinol, diloxanide furoate, and paromomycin are luminal amebicides that are usually administered with mixed or systemic amebicides to treat the asymptomatic colonization state. Chloroquine is a systemic amebicide and an antimalarial. Metronidazole is a mixed amebicide. Primaquine is an antimalarial.

Correct answer = C. The combination of atovaquone–proguanil has been used for both prevention and treatment of malaria in chloroquine-resistant areas. Pyrimethamine is not recommended for prophylaxis of malaria. Artemisinin and its derivatives are not used for prophylaxis, only treatment of malaria. Hydroxychloroquine is only an alternative treatment or prophylaxis option in chloroquine-sensitive regions.

Correct answer = B. Miltefosine is the only oral agent available for the treatment of visceral leishmaniasis. All the other drugs are orally administered, but artemether/lumefantrine is used for the treatment of malaria, nitazoxanide is used for the treatment of giardiasis or cryptosporidiosis, and tinidazole is effective for amebiasis or giardiasis.

Correct answer = A. Eflornithine is indicated for the treatment of African trypanosomiasis caused by *T. brucei gambiense*. Suramin is used for the treatment of first-stage African trypanosomiasis due to *T. brucei rhodesiense*. Sodium stibogluconate is used for the treatment of leishmaniasis. Metronidazole is used for the treatment of amebiasis and giardiasis.

Correct answer = B. Melarsoprol is the only agent available for the treatment of late-stage trypanosomal infections due to *T. brucei rhodesiense*. All the other drugs are used for other indications; artemether/lumefantrine is used for the treatment of malaria, nitazoxanide is used for the treatment of giardiasis or cryptosporidiosis, and tinidazole is effective for amebiasis or giardiasis.

36.6 A 42-year-old man returned from a camping trip and is diagnosed with Giardia lamblia. Which medication would be considered the treatment of choice?

- A. Chloroquine
- B. Nifurtimox
- C. Paromomycin
- D. Metronidazole

36.7 Which statement regarding paromomycin is correct?

- A. Paromomycin is only effective against the luminal forms of E. histolytica.
- B. The principle adverse effects are optic neuritis and peripheral neuropathy.
- C. Paromomycin is considered a nitroimidazole.
- D. If taken with alcohol, a disulfiram-like reaction may occur.

36.8 Which treatment option is *most* appropriate for a patient diagnosed with uncomplicated malaria due to P. ovale?

- A. Artesunate plus mefloquine
- B. Doxycycline
- C. Chloroquine
- D. Chloroquine plus primaquine

36.9 Which antiprotozoal agent is active against Toxoplasma gondii?

- A. Metronidazole
- B. Pyrimethamine
- C. Leucovorin
- D. Miltefosine

36.10 A 32-year-old pregnant woman is traveling abroad to a malaria-endemic country with known chloroquine resistance. Which prophylactic regimen is *most* appropriate?

- A. Doxycycline
- B. Mefloquine
- C. Primaquine
- D. Artemether-lumefantrine

Correct answer = D. Metronidazole is used for the treatment of amebiasis and giardiasis. Chloroquine is used for the treatment of malaria and extraintestinal amebiasis. Nifurtimox is indicated for the treatment of American trypanosomiasis (Chagas disease) caused by T. cruzi. Paromomycin is used for the treatment of luminal forms of E. histolytica.

Correct answer = A. Paromomycin is an aminoglycoside antibiotic, known as a luminal amebicide. It is only active effective against the luminal forms of E. histolytica because it is not significantly absorbed from the gastrointestinal tract. The principle adverse effects are gastrointestinal distress and diarrhea. The nitroimidazoles should be avoided with alcohol consumption due to the risk of a disulfiram-like reaction.

Correct answer = D. Chloroquine plus primaquine is the most appropriate treatment option due to the species of malaria, P. ovale, which causes relapses from the dormant hypnozoite form unless primaquine is added. Chloroquine by itself would treat the acute infection; however, it would not prevent relapse of the disease. Doxycycline is only used for prophylaxis or as a combination with other antimalarial medications for treatment. Artesunate plus mefloquine would be more appropriate to treat severe malaria; however, neither agent would prevent the relapsing form of the disease caused by P. ovale.

Correct answer = B. Pyrimethamine is active against T. gondii and in combination with sulfadiazine is the treatment of choice for toxoplasmosis. Metronidazole is active against amebiasis and giardiasis. Leucovorin can be used during the treatment of toxoplasmosis; however, its actions are to protect against folate deficiency caused by the treatment and the drug itself does not have antiprotozoal activity. Miltefosine is used for leishmaniasis.

Correct answer = B. Mefloquine is one of the preferred regimens for malaria prophylaxis in a pregnant woman. Doxycycline and primaquine are not recommended for use in pregnancy. Artemether-lumefantrine is only recommended for the treatment, not prophylaxis, of malaria.

# Anthelmintic Drugs

Jonathan C. Cho and Marylee V. Worley

# 37

## I. OVERVIEW

Nematodes, trematodes, and cestodes are three major groups of helminths (worms) that infect humans. Anthelmintic drugs (Figure 37.1) are aimed at metabolic targets that are present in the parasite but either are absent from or have different characteristics than those of the host. Figure 37.2 illustrates the high incidence of helminthic infections worldwide. Most anthelmintics target eliminating the organisms from the host, as well as controlling spread of infections.

## II. DRUGS FOR THE TREATMENT OF NEMATODES

Nematodes are elongated roundworms that possess a complete digestive system. They cause infections of the intestine as well as the blood and tissues.

### A. Benzimidazoles

Mebendazole, albendazole, and thiabendazole are the congeners of benzimidazole derivatives.

1. **Mebendazole:** Mebendazole [me-BEN-da-zole], a synthetic benzimidazole compound, is a first-line agent for the treatment of infections caused by whipworms (*Trichuris trichiura*), pinworms (*Enterobius vermicularis*), hookworms (*Necator americanus* and *Ancylostoma duodenale*), and roundworms (*Ascaris lumbricoides*). Mebendazole and benzimidazoles, as a class, act by binding to parasite  $\beta$ -tubulin and inhibiting microtubule polymerization in the parasite. Affected parasites are expelled in the feces. It is well tolerated generally. Its adverse effects include abdominal pain, nausea, vomiting, and diarrhea. Mebendazole should not be used in pregnant women. [Note: Many anthelmintics should be avoided in pregnancy (Figure 37.3); however, in mass prevention or treatment programs, certain agents (for example, mebendazole or albendazole) may be used in the second or third trimester.] Mebendazole has poor bioavailability (22%) due to its extensive first-pass metabolism. It is used at a dose of 100 mg chewable tablets or 100 mg/5 ml suspension. The dose for children above 2 years is the same as the adult dose but for 1 to 2 years, it is half the adult dose. A single oral dose is adequate for pinworm infestations, whereas for roundworm, hookworm, and whipworm infestations it is given 100 mg twice daily for 3 days. In case of trichinosis, it is usually taken 200 mg twice daily for 4 days.

### CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR NEMATODES

*Albendazole*  
*Mebendazole*  
*Triclabendazole*  
*Diethylcarbamazine*  
*Ivermectin*  
*Pyrantel pamoate*  
*Thiabendazole*

### CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR TREMATODES

*Praziquantel*

### CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR CESTODES

*Albendazole*  
*Niclosamide*

Figure 37.1

Summary of anthelmintic agents.

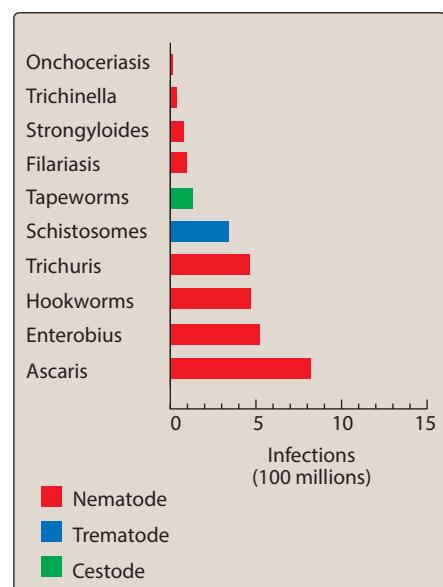
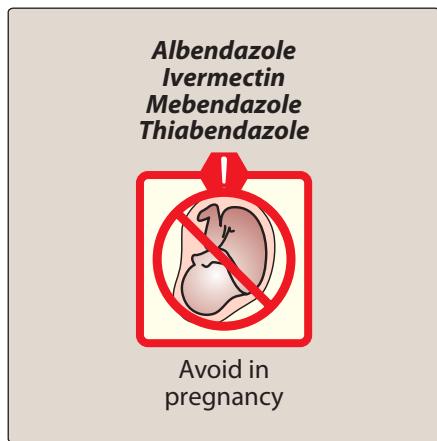


Figure 37.2

Relative incidence of helminth infections worldwide.

**Figure 37.3**

Albendazole, ivermectin, mebendazole, and thiabendazole should be avoided in pregnancy.

**2. Albendazole:** Albendazole is another derivative of benzimidazole which is superior to *mebendazole* in curing hookworm and trichuriasis in children. Due to its active metabolite, albendazole sulfoxide, it is also found to be superior to *mebendazole* in all tissue-residing worm infestations. It is converted to inactive metabolite and excreted in urine. It is the drug of choice for treating cystic hydatid disease due to *Echinococcus granulosus* and *Taenia solium* infestations. It is administered at a dose of 400 mg twice daily in adults and 15 mg/kg in children for varying durations depending on the infestation. Absorption is reported to be erratic after oral administration and it is enhanced by fatty food. A single dose of 400 mg is adequate for the treatment of soil transmitted helminths (STH) such as enterobiasis, ascariasis, trichuriasis, and hookworm. Similar to *mebendazole*, it is highly effective for the treatment of infestations with intestinal nematodes such as *A. lumbricoides*, *T. trichuria*, and hookworms. It is used for AIDS patients suffering from microsporidial intestinal infections, *Capillaria philippinensis*. *Albendazole* therapy is reported to have fewer side effects such as nausea, vomiting, diarrhea, and epigastric pain. Rarely it can cause dizziness and headache.

### B. Pyrantel pamoate

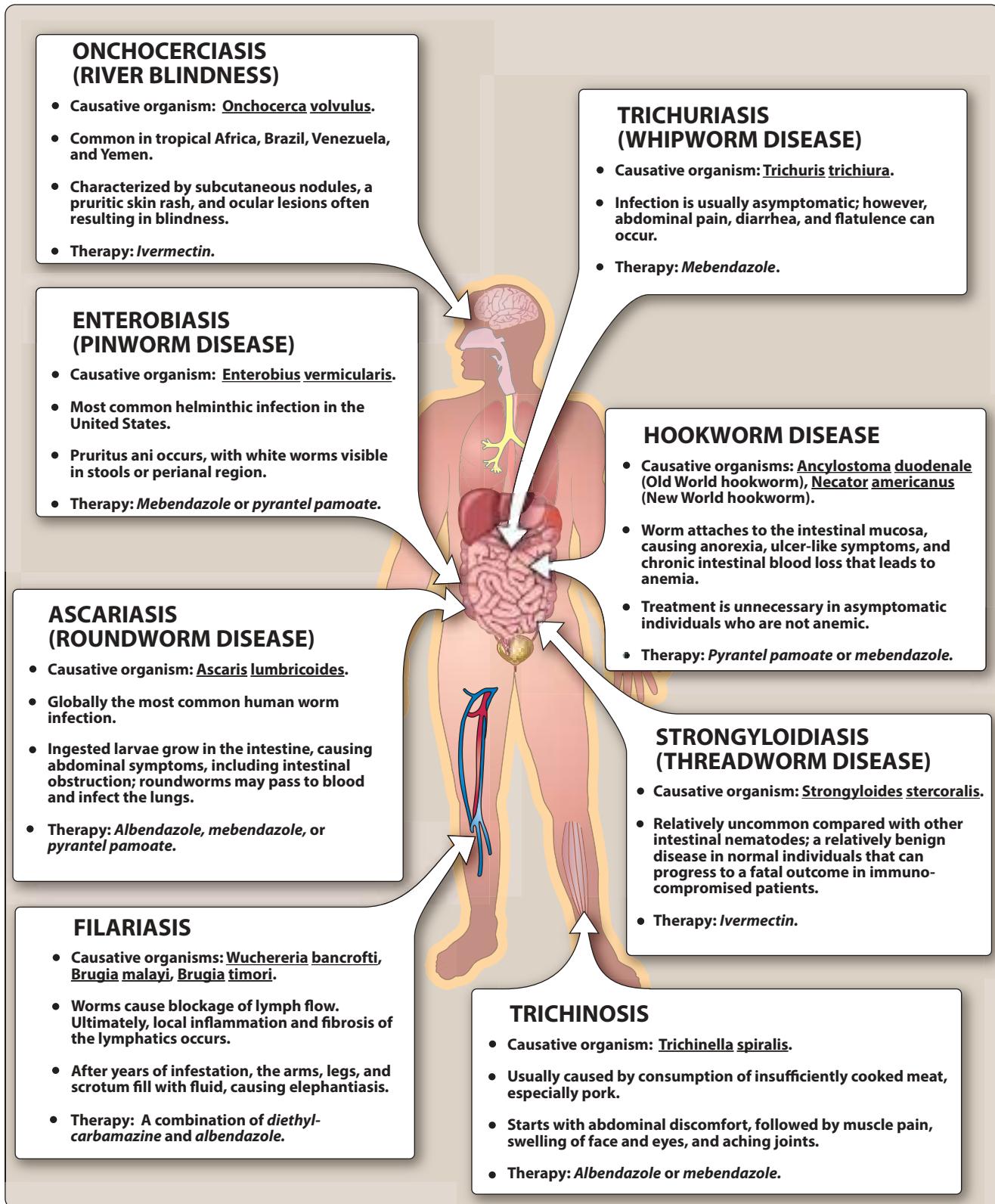
*Pyrantel pamoate* [pi-RAN-tel PAM-oh-ate] is also effective in the treatment of infections caused by roundworms, pinworms, and hookworms (Figure 37.4). *Pyrantel pamoate* is poorly absorbed after oral administration and is only effective against intestinal infections. It acts as a depolarizing, neuromuscular-blocking agent, causing release of acetylcholine and inhibition of cholinesterase, leading to paralysis of the worm and subsequent expulsion. Adverse effects are mild and include nausea, vomiting, and diarrhea.

### C. Thiabendazole

*Thiabendazole* [thye-a-BEN-da-zole], a synthetic benzimidazole, is a potent broad-spectrum anthelmintic agent. Current use of *thiabendazole* is limited to the topical treatment of cutaneous larva migrans (creeping eruption). Because of its toxic effects and removal from the market in many countries, it has been largely replaced by other agents.

### D. Tetramisole and levamisole

*Tetramisole* is an old agent and its optical isomer *levamisole* has been found to be more active for the treatment of ascariasis and ancylostomiasis and is kept as second-line therapy. Neural stimulation in the worm causing tonic paralysis is expected to be the mechanism of action on the worms. For ascariasis, *tetramisole* is used as a single dose of 150 mg for adults 100 mg for children with a body weight of 20 to 39 kg and 50 mg with a body weight of 10 to 19 kg. For ancylostomiasis, it is used as two doses in a day in a gap of 12 hours.

**Figure 37.4**

Characteristics of and therapy for commonly encountered nematode infections.

### E. Piperazine

*Piperazine* is highly effective against *A. lumbricoides* and *Enterobius vermicularis*. It is expelled from the intestine by peristalsis by causing flaccid paralysis in the worms. It acts as a GABA agonist and causes induction of chloride conductance on the ascaris muscle membrane. However, *piperazine* has been replaced by *benimidazoles* in the recent past for the treatment of *Ascaris*. After oral administration, *benimidazoles* is absorbed and after metabolism it is excreted through urine. Nausea, vomiting, abdominal discomfort, and CNS excitation at high dose have been reported with this agent. It is contraindicated in patients with epilepsy and renal insufficiency. It is used at a dose of 4 g once a day for 2 days for *Ascaris* infestation. For pinworm infestation, it is used at a dose of 50 mg/kg once daily for 7 days and repeated after 3 weeks for the eradication.

### F. Ivermectin

*Ivermectin* [eye-ver-MEK-tin] is the drug of choice for the treatment of cutaneous larva migrans, strongyloidiasis, and onchocerciasis (river blindness, although not curative due to lack of activity in adult worms). [Note: *Ivermectin* is also useful in the treatment of pediculosis (lice) and scabies.] *Ivermectin* targets the glutamate-gated chloride channel receptors. Chloride influx is enhanced, and hyperpolarization occurs, resulting in paralysis and death of the worm. The drug is given orally and does not readily cross the blood-brain barrier. *Ivermectin* should not be used in pregnancy (Figure 37.3). It is extensively metabolized by CYP3A4, and it is not excreted in urine. Therefore, dosage reduction is not required in case of kidney disease. The killing of the microfilaria in onchocerciasis can result in a dangerous Mazzotti reaction (fever, headache, dizziness, somnolence, and hypotension). The severity of this reaction is related to parasite load. Antihistamines or steroids may be given to ameliorate the symptoms. *Ivermectin* is administered as a single dose of 150 to 200 µg/kg every 6 to 12 months for the treatment of onchocerciasis and filariasis over a period of 5 to 6 years. A single dose of 0.2 mg/kg is effective against scabies and pediculosis. It is well tolerated by an uninfected person; however, parasite kill-induced side effects vary with the organism. It is reported to have a side effect profile such as itching, giddiness, headache, hypotension, tachycardia, myalgia, arthralgia, and facial and peripheral edema which responds well to glucocorticoid therapy.

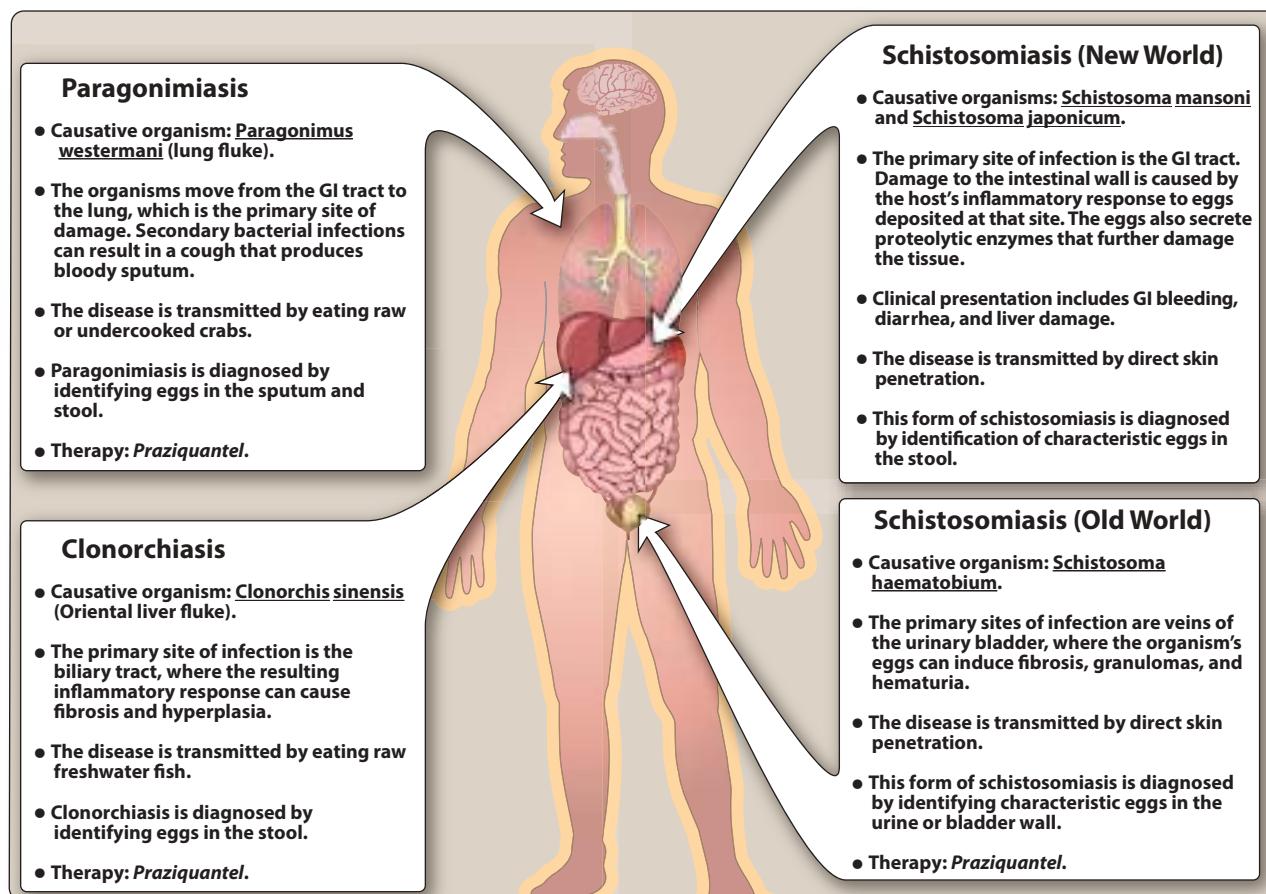
### G. Diethylcarbamazine

*Diethylcarbamazine* [dye-eth-il-kar-BAM-a-zeen] is the drug of choice for filariasis caused by infection with *Wuchereria bancrofti*, *Brugia malayi*, or *Brugia timori*. It kills the microfilariae and has activity against adult worms. [Note: In countries where filariasis is endemic, a combination of antifilarial drugs (either *diethylcarbamazine* and *albendazole* or *ivermectin* and *albendazole*) may be used annually as preventive chemotherapy.] *Diethylcarbamazine* is rapidly absorbed following oral administration with meals and is excreted mainly in the urine. Adverse effects may include fever, nausea, vomiting, arthralgia, and headache. [Note: Patients suspected of having onchocerciasis should

be given *ivermectin* and *albendazole* because *diethylcarbamazine* can accelerate blindness and cause severe Mazzotti reactions. In India, *diethylcarbamazine* is used for filariasis eradication programs and tropical pulmonary eosinophilia. Microfilarial forms of susceptible filarial species are first affected by this agent. Microfilaria of *Onchocerca volvulus* rapidly disappears from skin after the administration of this agent. Used at a dose of 2 mg/kg three times a day, it produces rapid relief within a few days but the adult worm survives in the lymphatics; therefore, a prolonged therapy is required. A dosage therapy of 72 to 126 mg/kg spread across 12 to 21 days was found to be satisfactory. Repeated drug therapy is required in a gap of 3 to 4 weeks to get complete eradication. It has a limited role in the chronic filariasis causing lymphatic obstruction. *Diethylcarbamazine* (6 mg/kg) along with *albendazole* (400 mg) is used to control mass transmission of filariasis in endemic areas by reducing microfilaremia.

### III. DRUGS FOR THE TREATMENT OF TREMATODES

The trematodes (flukes) are leaf-shaped flatworms that are generally characterized by the tissues they infect (for example, liver, lung, intestinal, or blood; Figure 37.5).



**Figure 37.5**

Characteristics of and therapy for commonly encountered trematode infections. GI = gastrointestinal.

### A. Praziquantel

*Praziquantel* [pray-zi-KWON-tel] is an agent of choice for the treatment of all forms of schistosomiasis, other trematode infections, and cestode infections such as taeniasis. *Praziquantel* causes contraction and paralysis of parasites by increasing the permeability of the cell membrane to calcium. It is rapidly absorbed after oral administration and should be taken with food. The drug is extensively metabolized, and the inactive metabolites are excreted primarily in the urine. Common adverse effects include dizziness, malaise, and headache as well as gastrointestinal upset. *Dexamethasone*, *phenytoin*, *rifampin*, and *carbamazepine* may increase the metabolism of *praziquantel*. *Cimetidine* causes increased *praziquantel* levels. *Praziquantel* is contraindicated for the treatment of ocular cysticercosis, because destruction of the organism in the eye may cause irreversible damage. It is used at a single dose of 10 mg/kg for *T. saginata* and *T. solium* and is used at 15 to 25 mg/kg thrice a day for 1 day for *Hymenolepis nana* and *Diphyllobothrium latum*. In neurocysticercosis, schistosoma, and other flukes, it is used at a higher dose for varying periods.

## IV. DRUGS FOR THE TREATMENT OF CESTODES

The cestodes, or “true tapeworms,” typically have a flat, segmented body and attach to the host’s intestine (Figure 37.6). Like the trematodes, the tapeworms lack a mouth and a digestive tract throughout their life cycle.

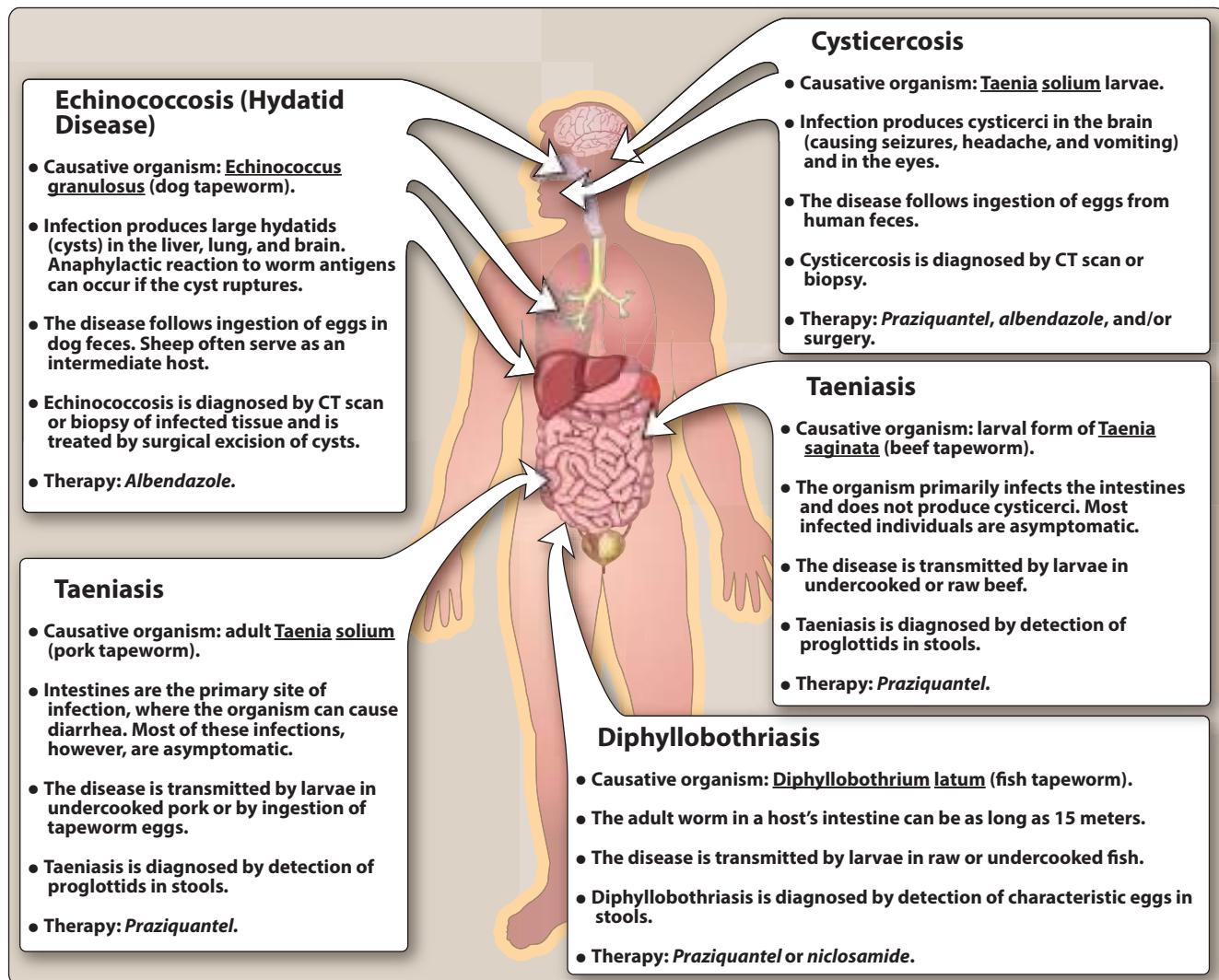
### A. Niclosamide

*Niclosamide* [ni-KLOE-sa-mide] (no longer available in the United States) is an alternative to *praziquantel* for the treatment of taeniasis, diphyllobothriasis, and other cestode infections. It inhibits the mitochondrial phosphorylation of adenosine diphosphate (ADP) in the parasite, making it lethal for the cestode’s scolex and segments but not for the ova. A laxative is administered prior to oral administration to purge the bowel of all dead segments and to enhance digestion and liberation of the ova. Alcohol should be avoided within 1 day of *niclosamide* use.

*Niclosamide* is formulated as 0.5 g chewable tablets. Two tablets are administered orally and another two tablets after a gap of 1 hour. For children aged 2 to 6 years, the dose is 1 g. After the dose, a saline cathartic is given to pull the worms out.

### B. Albendazole

*Albendazole* [al-BEN-da-zole], another benzimidazole, inhibits microtubule synthesis and glucose uptake in nematodes and is effective against most nematodes known. Its primary therapeutic application, however, is in the treatment of cestodal infestations, such as cysticercosis and hydatid disease (caused by the larval stage of *E. granulosus*). [Note: *Albendazole* is also very effective in treating microsporidiosis, a

**Figure 37.6**

Characteristics of and therapy for commonly encountered cestode infections. CT = computed tomography.

fungal infection.] *Albendazole* is erratically absorbed after oral administration, but absorption is enhanced by a high-fat meal. It undergoes extensive first-pass metabolism in the liver, including formation of an active sulfoxide, and its metabolites are primarily excreted in the bile. When used in short-course therapy (1 to 3 days) for nematodal infestations, adverse effects are mild and transient and include headache and nausea. Treatment of hydatid disease (3 months) has a risk of hepatotoxicity and, rarely, agranulocytosis or pancytopenia. Medical treatment of neurocysticercosis is associated with inflammatory responses to dying parasites in the CNS, including headache, vomiting, fever, and seizures.

## Study Questions

Choose the ONE best answer.

- 37.1 A 32-year-old man is diagnosed with whipworm disease after he spent the summer working outside without shoes. Which would be the best treatment option?
- A. Pyrantel pamoate
  - B. Mebendazole
  - C. Thiabendazole
  - D. Diethylcarbamazine
- 37.2 Which combination would be appropriate to use for preventative chemotherapy in countries with endemic filariasis and endemic onchocerciasis?
- A. Pyrantel pamoate and mebendazole
  - B. Ivermectin and diethylcarbamazine
  - C. Albendazole and diethylcarbamazine
  - D. Ivermectin and albendazole
- 37.3 Which statement best describes the mechanism of action of pyrantel pamoate?
- A. Acts as a depolarizing neuromuscular blocking agent leading to paralysis of the worm
  - B. Binds to  $\beta$ -tubulin and inhibits the assembly of the microtubules polymerization in the parasite
  - C. Inhibits the mitochondrial phosphorylation of adenosine diphosphate (ADP) in the parasite
  - D. Inhibits glucose uptake leading to parasite death
- 37.4 Which is the best treatment option for treatment of cutaneous larva migrans?
- A. Pyrantel pamoate
  - B. Diethylcarbamazine
  - C. Ivermectin
  - D. Niclosamide
- 37.5 Which medication used to treat river blindness targets chloride channels and can cause a Mazzotti reaction?
- A. Ivermectin
  - B. Praziquantel
  - C. Pyrantel pamoate
  - D. Albendazole

Correct answer = B. Mebendazole is the drug of choice for treating whipworm. Thiabendazole is not a preferred treatment option for many nematode infections due to its toxicity.

Correct answer = D. Ivermectin and albendazole should be used as combination therapy for filariasis in patients that could also be infected with onchocerciasis due to the propensity of diethylcarbamazine to accelerate blindness in patients at risk for river blindness.

Correct answer = A. Pyrantel pamoate acts as a depolarizing, neuromuscular-blocking agent, causing release of acetylcholine and inhibition of cholinesterase, leading to paralysis and intestinal expulsion of the worm.

Correct answer = C. Ivermectin is the drug of choice for treatment of cutaneous larva migrans, which is usually self-limiting; however, treatment will shorten the course of the disease.

Correct answer = A. Ivermectin targets the parasite's glutamate-gated chloride channel receptors. Chloride influx and hyperpolarization occur, resulting in paralysis of the worm. The killing of the microfilaria in onchocerciasis can result in a dangerous Mazzotti reaction. This can happen with ivermectin or diethylcarbamazine.

- 37.6 A 48-year-old immigrant from Mexico presents with seizures and other neurologic symptoms. Eggs of *T. solium* are found in a stool specimen. A magnetic resonance image of the brain shows many cysts, some of which are calcified. Which drug would be of benefit to this individual?
- A. Ivermectin
  - B. Pyrantel pamoate
  - C. Albendazole
  - D. Diethylcarbamazine
- 37.7 Which drug works by increasing the permeability of the cell membrane to calcium?
- A. Albendazole
  - B. Ivermectin
  - C. Niclosamide
  - D. Praziquantel
- 37.8 When used for treatment of taeniasis, a laxative is usually administered prior to oral administration of which drug?
- A. Mebendazole
  - B. Diethylcarbamazine
  - C. Niclosamide
  - D. Pyrantel pamoate
- 37.9 A 37-year-old man presents with diarrhea and gastrointestinal bleeding. Eggs of *S. mansoni* are found upon examination of a stool specimen. The patient has a history of seizures and is currently on phenytoin. Metabolism of which medication will be increased due to his current drug regimen?
- A. Ivermectin
  - B. Praziquantel
  - C. Thiabendazole
  - D. Niclosamide
- 37.10 When used for longer treatment, such as hydatid disease, which medication is associated with risks of hepatotoxicity and agranulocytosis?
- A. Albendazole
  - B. Diethylcarbamazine
  - C. Niclosamide
  - D. Ivermectin

Correct answer = C. The symptoms and other findings for this patient are consistent with neurocysticercosis. Albendazole is the drug of choice for the treatment of this infestation. The other drugs are not effective against the larval forms of tapeworms.

Correct answer = D. Praziquantel works by increasing the permeability off the cell membrane to calcium, causing contracture and paralysis of the parasites.

Correct answer = C. A laxative is administered prior to oral administration of niclosamide to purge the bowel of all dead segments and to enhance digestion and liberation of the ova.

Correct answer = B. Dexamethasone, phenytoin, rifampin, and carbamazepine may increase the metabolism of praziquantel.

Correct answer = A. When used in short-course therapy, albendazole is associated with adverse effects such as headache and nausea. When used for treatment of hydatid disease (3 months) there is a risk of hepatotoxicity and, rarely, agranulocytosis or pancytopenia.



# Immunosuppressants

Jennifer Jebrock and Jane Revollo

# 38

## I. OVERVIEW

The importance of the immune system in protecting the body against harmful foreign molecules is well recognized. The immune system is one of the most complex organ systems in the body, which can make it difficult to manipulate. Immunosuppressants are drugs that reduce the activation or efficacy of the immune system to treat certain conditions, such as autoimmune diseases, or to lower the body's ability to reject a transplanted organ. Autoimmune diseases can arise when the immune system mistakenly identifies an individual's own tissues as foreign and directs a destructive response against them. The goal of treatment for these diseases is to use drug therapy to stop this inappropriate and harmful process. In the case of organ transplantation, foreign tissue is purposely implanted into the recipient, but the goal remains the same—to use drug therapy to limit the damage inflicted by the immune system and potential rejection of the transplanted organ. Transplantation of organs and tissues (for example, kidney, heart, or bone marrow) has become routine due to improved surgical techniques and better tissue typing. Available drugs now more selectively inhibit rejection of transplanted tissues while preventing the patient from immunological compromise and prolonging the life of transplanted organs (Figure 38.1). Earlier drugs were nonselective, and patients frequently succumbed to infection due to suppression of both the antibody-mediated (humoral) and the cell-mediated arms of the immune system. Today, the principal approach to immunosuppressive therapy is to alter lymphocyte function using drugs or antibodies against immune proteins. Because of their severe toxicities when used as monotherapy, a combination of immunosuppressive agents, usually at lower doses, is generally employed. Immunosuppressive drug regimens typically consist of two to four agents with different mechanisms of action that disrupt various levels of T-cell activation. [Note: Although this chapter focuses on immunosuppressive agents in the context of organ transplantation, these agents may be used in the treatment of other disorders. For example, *cyclosporine* may be useful in the treatment of psoriasis, and various monoclonal antibodies have applications in a number of disorders, including rheumatoid arthritis, multiple sclerosis, Crohn's disease, and ulcerative colitis.]

The immune activation cascade can be described as a three-signal model (Figure 38.2). Signal 1 constitutes T-cell triggering at the CD3 receptor complex by an antigen on the surface of an antigen-presenting cell (APC). Signal 1 alone is insufficient for T-cell activation and requires signal 2. Signal 2, also referred to as co-stimulation, occurs when CD80 and CD86

### ANTIBODIES

*Alemtuzumab*  
*Antithymocyte globulins*  
*Basiliximab*  
*Rituximab*

### CALCINEURIN INHIBITORS

*Cyclosporine*  
*Tacrolimus*

### COSTIMULATION BLOCKER

*Belatacept*

### mTOR INHIBITORS

*Everolimus*  
*Sirolimus*

### ANTIPROLIFERATIVES

*Azathioprine*  
*Mycophenolate mofetil*  
*Mycophenolate sodium*

### ADRENOCORTICOIDS

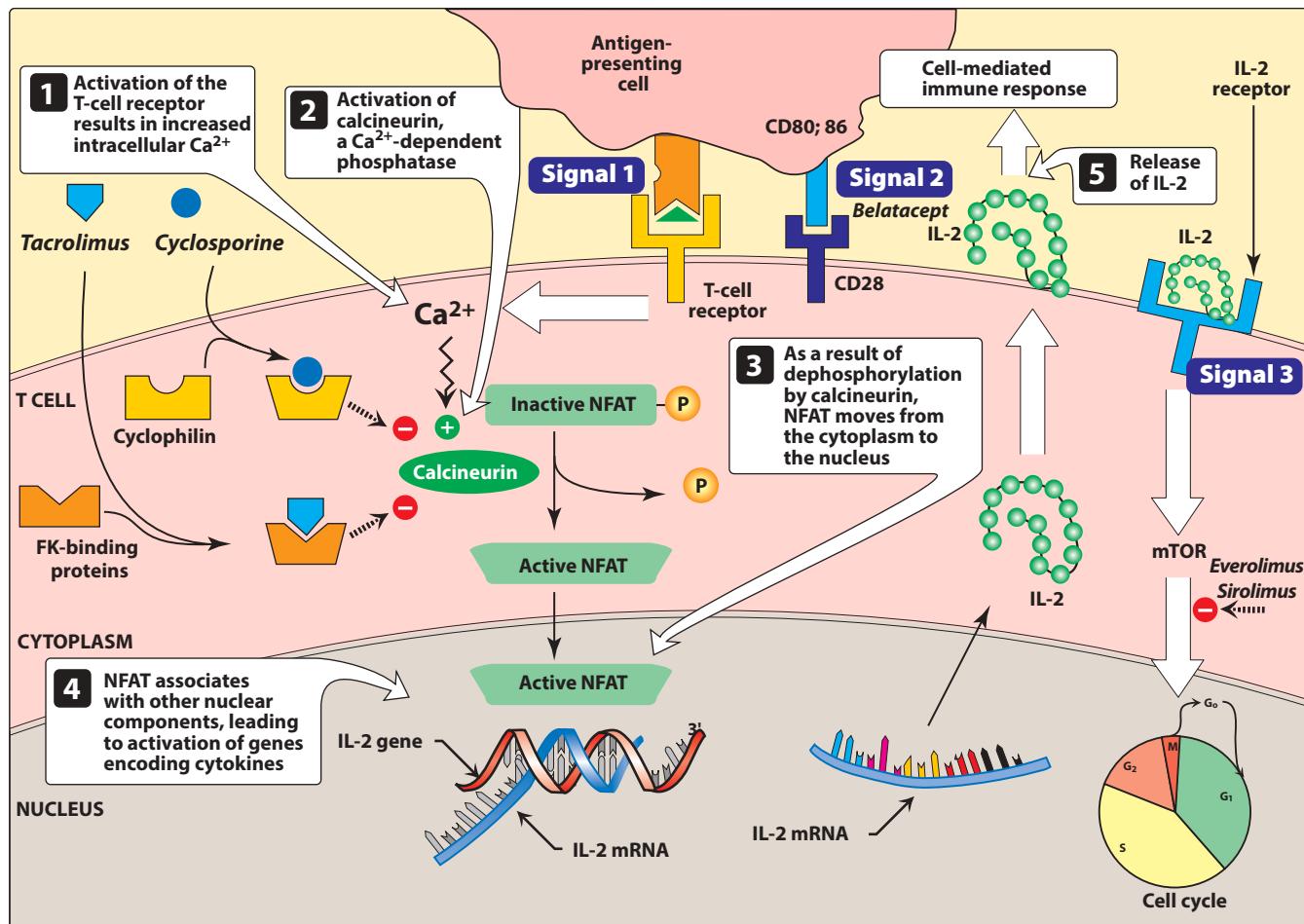
*Methylprednisolone*  
*Prednisolone*  
*Prednisone*

### OTHER

*Bortezomib*  
*Intravenous immunoglobulin*

### Figure 38.1

Immunosuppressant drugs.  
mTOR = mammalian target of rapamycin. (For drug dosages, refer to Appendix at the end of the book.)



**Figure 38.2**

Mechanism of action of immunosuppressive agents. IL-2 = interleukin 2; mRNA = messenger RNA; mTOR = mammalian target of rapamycin; NFAT = nuclear factor of activated T.

(also known as B7.1 and B7.2) on the surface of APCs engage CD28 on T-cells. Both signals 1 and 2 activate several intracellular signal transduction pathways, one of which is the calcium–calcineurin pathway. These pathways trigger the production of cytokines such as interleukin (IL)-2. IL-2 then binds to the IL-2 receptor (also known as CD25) on the surface of other T-cells, thereby providing signal 3 activating the cell cycle via mammalian target of rapamycin (mTOR) and leading to T-cell proliferation.

Immunosuppressants can be broadly categorized by their place in therapy and their mechanism of action. More potent immunosuppressant drugs, such as monoclonal and polyclonal antibodies, are often used in induction therapy, which powerfully suppresses the immune system at the time of transplant, allowing the new organ to start functioning in the recipient and preventing early graft rejection. Maintenance immunosuppressant drugs, on the other hand, are less potent and provide long-term immunological protection for the transplanted organs, with lower risk of infection than with the induction drugs. As noted above, maintenance immunosuppressant medications are frequently combined in regimens to maintain adequate immunosuppression while minimizing adverse effects.

## II. INDUCTION AND REJECTION IMMUNOSUPPRESSANT MEDICATIONS

The use of antibodies plays a central role in prolonging allograft survival. [Note: An allograft is transplant of an organ or tissue from one person to another who is not genetically identical.] Antibodies are prepared by immunization of either rabbits or horses with human lymphoid cells (producing a mixture of polyclonal antibodies or monoclonal antibodies) or by hybridoma technology (producing antigen-specific monoclonal antibodies). Hybridomas are produced by fusing mouse antibody-producing cells with tumor cells. Hybrid cells are selected and cloned, and the antibody specificity of the clones is determined. Clones of interest can be cultured in large quantities to produce clinically useful amounts of the desired antibody. Recombinant DNA technology can also be used to replace part of the mouse gene sequence with human genetic material, thus “humanizing” the antibodies and making them less antigenic. The names of monoclonal antibodies conventionally contain “xi” or “zu” if they are chimerized or humanized, respectively. The suffix “-mab” (monoclonal antibody) identifies the category of drug. The polyclonal antibodies, although relatively inexpensive to produce, are variable and less specific, which is in contrast to monoclonal antibodies, which are homogeneous and specific (Figure 38.3).

DRUG	CLASS	MECHANISM OF ACTION	INDICATIONS	ADVERSE EFFECTS
<i>Alemtuzumab</i>	Humanized monoclonal antibody (CD52)	Binds to CD52 on B and T lymphocytes, causing T- and B-cell depletion	Induction, treatment of rejection	Infusion-related effects (chills, fever), severe and prolonged leukopenia, neutropenia, thrombocytopenia, infections (CMV, HSV, and other viruses/fungi)
<i>Antithymocyte globulins</i>	Polyclonal antibodies	T-cell depletion	Induction, treatment of rejection	Infusion-related effects (chills, fever), leukopenia, thrombocytopenia, pulmonary edema, infections due to CMV or other viruses, skin rash
<i>Basiliximab</i>	Chimeric monoclonal antibody	Binds to CD25 (IL-2R) and inhibits IL-2 mediated T-cell proliferation (nondepleting)	Induction	Generally well tolerated vs. placebo
<i>Bortezomib</i>	Proteasome inhibitor	Proteasome inhibition leads to plasma cell depletion	Treatment of antibody-mediated rejection	Leukopenia, anemia, thrombocytopenia, nausea/vomiting, diarrhea, peripheral neuropathy, hypotension, hepatotoxicity (less common)
<i>Intravenous Immunoglobulin (IVIg)</i>	Immune globulin	Antibodies, B cells	Induction for highly sensitized patients, treatment of rejection	Infusion-related reactions, headache, hypotension, hemolytic anemia, pulmonary edema, thromboembolic events, aseptic meningitis, acute renal failure
<i>Methylprednisolone</i>	Corticosteroid	Nonspecific interleukin and TNF inhibition	Induction, treatment of rejection, maintenance	HTN, HLD, hyperglycemia, peripheral edema, mood disturbance, osteoporosis, weight gain
<i>Rituximab</i>	Chimeric monoclonal antibody	CD20 <sup>+</sup> B-cell depletion	Induction, treatment of rejection	Infusion-related effects (chills, fever), infections (reactivation of hepatitis B virus, CMV, and other viruses/fungi), PML, leukopenia, thrombocytopenia, mucocutaneous reactions

CMV = cytomegalovirus; HLD = hyperlipidemia; HSV = herpes simplex virus; HTN = hypertension; IL = interleukin; PML = progressive multifocal leukoencephalopathy; TNF = tumor necrosis factor.

**Figure 38.3**

Medications used for induction and/or rejection immunosuppressant therapy.

### A. Antithymocyte globulins

Antithymocyte globulins are polyclonal antibodies produced by isolating  $\gamma$ -globulin fractions of serum obtained from rabbits or horses after immunization with human thymocytes. They cause depletion of circulating T-cells and apoptosis of activated T-cells. Rabbit preparations are preferred over horse preparations because of greater potency and less toxicity.

*Antithymocyte globulin, rabbit* is primarily used at the time of transplantation to prevent early allograft rejection, along with other immunosuppressive agents. It may also be used to treat severe rejection episodes or corticosteroid-resistant acute rejection. It is usually used for 3 to 10 days to produce profound lymphopenia that may last beyond 1 year.

The antibodies are slowly infused intravenously and their half-life extends from 3 to 9 days. Premedication with corticosteroids, *acetaminophen*, and antihistamines may help reduce infusion-related reactions. Prolonged use may be associated with profound immunosuppression and an increased risk of opportunistic infections and/or post-transplant lymphoproliferative disease (PTLD).

### B. Basiliximab

*Basiliximab* [bass-il-IX-im-ab] is a chimeric murine/human monoclonal antibody that binds to the  $\alpha$  chain of the IL-2 receptor (CD25) on activated T-cells and, thus, interferes with the proliferation of these cells. Blockade of this receptor foils the ability of any antigenic stimulus to activate the T-cell response system.

*Basiliximab* is approved for prophylaxis of acute rejection in renal transplantation in combination with *cyclosporine* and corticosteroids. This may allow for reduced doses or delayed introduction of calcineurin inhibitors. The drug may be beneficial in those with delayed graft function and may reduce the risk of calcineurin inhibitor-associated renal failure. *Basiliximab* is not T-cell depleting and, therefore, is mainly used in induction protocols as opposed to the treatment of rejection. *Basiliximab* is given as an IV infusion. The serum half-life of *basiliximab* is about 7 days. Usually, two doses of this drug are administered—the first at 2 hours prior to transplantation and the second at 4 days after the surgery. The drug is generally well tolerated.

### C. Alemtuzumab

*Alemtuzumab* [AL-em-TOOZ-ue-mab] is a humanized monoclonal antibody that binds to CD52 on both T- and B-cells, resulting in depletion of both lymphoid cell lines. Depletion of T- and B-cells is observed soon after infusion and recovery of these cells is gradual. T-cells recover over 6 to 12 months, and B-cells recover in 6 months or less. It is approved for the treatment of chronic lymphocytic leukemia, but has been used in transplantation as an induction and anti-rejection agent for both acute cellular rejection and antibody-mediated rejection due to its activity against both T- and B-cells. Due to its potent and prolonged immunosuppressive effect, it is recommended to initiate or continue prophylaxis for *Pneumocystis pneumonia* and herpes viruses after administration of *alemtuzumab*.

*Alemtuzumab* was removed from the United States market by the manufacturer in 2012 in preparation for relabeling for use in multiple sclerosis, but it can still be obtained through the Campath Distribution Program for use in transplant patients.

#### D. Rituximab

*Rituximab* [ri-TUX-i-mab] is a chimeric monoclonal antibody against the antigen CD20 on pre B-cells, mature B-cells, and memory B-cells. *Rituximab* causes B-cell depletion by inducing B-cell lysis and blocking B-cell activation and eventual maturation to antibody-forming plasma cells. Existing plasma cells do not express the CD20 antigen and, therefore, are unaffected by *rituximab*. The drug is approved for use in the treatment of B-cell lymphomas, PTLD, and rheumatoid arthritis. The benefit of using *rituximab* in transplantation is for antibody removal, which has been utilized in ABO (blood type) incompatible transplants, desensitization protocols, and treatment of antibody-mediated rejection (AMR).

Intravenous administration of *rituximab* leads to rapid and sustained depletion of B-lymphocytes, with B-cell counts returning to normal within 9 to 12 months. *Rituximab* has a boxed warning for reactivation of JC virus leading to progressive multifocal leukoencephalopathy (PML) which has been reported in the nontransplant population. Activation of hepatitis B infection has also been reported following treatment, and hepatitis serologies should be monitored.

#### E. Bortezomib

AMR involves the production of high levels of antibodies by plasma cells, either newly made from B-cells or from those that existed prior to transplant. One mechanism to control AMR is to target antibody production by plasma cells. *Bortezomib* [bor-TEZ-oh-mib] is a proteasome inhibitor that leads to cell cycle arrest and apoptosis of normal plasma cells, thereby decreasing antibody production in sensitized patients.

*Bortezomib* is approved for the treatment of multiple myeloma, but it has been adapted for use in the treatment of AMR in transplant patients. It can be administered via intravenous bolus or subcutaneous injection, so it has a low potential for infusion-related reactions. *Bortezomib* is metabolized primarily by cytochrome P450 enzymes and hepatic dysfunction has rarely been reported when multiple cycles are given.

#### F. Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) contains immunoglobulins prepared by human plasma pooled from many donors. It has an immunomodulatory effect and is often used for autoimmune diseases, pretransplant desensitization protocols, and treatment of AMR. The immunomodulatory effects on T- and B-cells occur at high doses, and it is also used at lower doses to prevent infection by replacing immunoglobulins removed during plasmapheresis. The mechanism of action is not well defined, but high doses of IVIG appear to induce

B-cell apoptosis and modulate B-cell signaling. It also inhibits binding of antibodies to the transplanted graft and activation of the complement system. The serum half-life of IVIG is about 3 to 4 weeks.

Adverse effects of IVIG include headache, fever, chills, myalgias, and hypotension/hypertension, which can be reduced by slowing the infusion rate. Serious adverse effects are rare and can include aseptic meningitis, acute renal failure, and thrombotic events.

### III. MAINTENANCE IMMUNOSUPPRESSANT MEDICATIONS

Maintenance immunosuppressants are intended to provide adequate immunosuppression to prevent allograft rejection, while minimizing infection, malignancy, and drug-induced adverse effects. Often they are combined in regimens of two to four drugs, using medications with different mechanisms of action to minimize drug toxicity. These drugs can be further divided into four main classes: 1) calcineurin inhibitors (*cyclosporine* and *tacrolimus*), 2) co-stimulation blockers (*belatacept*), 3) mTOR inhibitors (*sirolimus* and *everolimus*), and 4) antiproliferatives (*mycophenolate* and *azathioprine*) (Figure 38.4).

DRUG	CLASS	INDICATIONS	PHARMACOKINETICS	ADVERSE EFFECTS
<i>Azathioprine</i>	Antiproliferative	SOT (renal), RA	Activated by glutathione S-transferase DDIs ( <i>allopurinol</i> , <i>warfarin</i> )	Myelosuppression, nausea, vomiting, diarrhea, pancreatitis, hepatotoxicity
<i>Belatacept</i>	Costimulation blockade	SOT (renal)	Elimination half-life ~10 days	Anemia, leukopenia
<i>Cyclosporine</i>	Calcineurin inhibitor	SOT (renal, liver, heart), psoriasis, RA, acute GVHD	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD, hyperglycemia, hyperkalemia, hirsutism, gingival hyperplasia, neurotoxicity, nephrotoxicity
<i>Everolimus</i>	mTOR inhibitor	SOT (renal, liver), oncology	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD (particularly TG, TC), stomatitis, proteinuria, impaired wound healing, rash, myelosuppression
<i>Methyl-prednisolone</i> , <i>prednisolone</i> , <i>prednisone</i>	Corticosteroid	Numerous indications	Activated to <i>prednisolone</i>	HTN, HLD, hyperglycemia, peripheral edema, mood disturbance, osteoporosis, weight gain
<i>Mycophenolate</i>	Antiproliferative	SOT (renal, liver, heart)	Metabolism by glucuronidation DDI (bile acid sequestrants)	Leukopenia, thrombocytopenia, nausea, vomiting, diarrhea
<i>Sirolimus</i>	mTOR inhibitor	SOT (renal), lymphangioleiomyomatosis	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD (particularly TG, TC), stomatitis, proteinuria, impaired wound healing, rash, myelosuppression, pneumonitis
<i>Tacrolimus</i>	Calcineurin inhibitor	SOT (renal, liver, heart)	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD, hyperglycemia, hyperkalemia, alopecia, neurotoxicity (hand tremor, headache, seizure), nephrotoxicity

DDI = drug-drug interaction; GVHD = graft-versus-host disease; HLD = hyperlipidemia; HTN = hypertension; mTOR = mammalian target of rapamycin; RA = rheumatoid arthritis; SOT = solid organ transplant; TC = total cholesterol; TG = triglycerides.

**Figure 38.4**

Medications used for maintenance immunosuppressant therapy.

### A. Calcineurin inhibitors

Calcineurin inhibitors *cyclosporine* [sye-kloe-SPOR-een] and *tacrolimus* [tac-RO-li-mus] block signal transduction through the calcium-calcineurin pathway, activated downstream of signal 1, to impair T-cell activation. Calcineurin, a calcium-dependent protein phosphatase, dephosphorylates the transcription factor Nuclear Factor of Activated T-cells (NFAT), allowing NFAT to enter the T-cell nucleus and bind to DNA, leading to transcription and production of cytokines, including IL-2. *Cyclosporine* binds to cyclophilin, whereas *tacrolimus* binds a protein called FK-binding protein (FKBP). These drug–protein complexes inhibit the activity of calcineurin, thereby preventing T-cell activation. *Tacrolimus* is the preferred calcineurin inhibitor due to its decreased rate of allograft rejection as compared to *cyclosporine*. Although it is approved for renal, liver, and heart transplant, *tacrolimus* is the mainstay of maintenance immunosuppressants for all solid organ transplants.

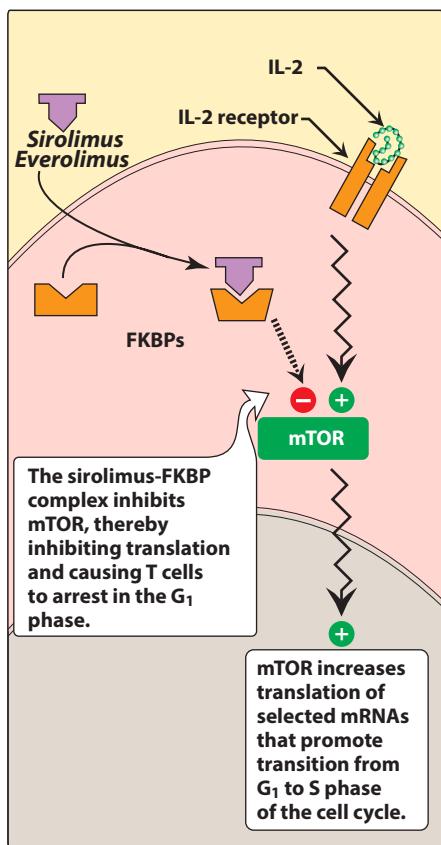
Enzymes CYP3A4, CYP3A5, and P-glycoprotein (P-gp) expressed in the gastrointestinal tract and liver are responsible for the interindividual variability in oral absorption and metabolism of *cyclosporine* and *tacrolimus*. Dosing titration is based on 12-hour trough levels, with goal trough levels varying between different organs, time from transplant, and transplant center-specific protocols.

One of the primary limitations to the use of calcineurin inhibitors is nephrotoxicity, which has led to the development of regimens using these agents in combination with other immunosuppressant drugs. As with all immunosuppressants, infections are possible with the use of calcineurin inhibitors, and recipients are often given prophylactic medications post-transplant. Hirsutism, or excessive hair growth, is a common adverse effect of *cyclosporine*.

### B. Costimulation blocker

*Belatacept* [bel-a-TA-sept], a second-generation costimulation blocker, is a recombinant fusion protein of CTLA-4, which, like CD28, binds to CD80 and CD86 on APCs. Binding of *belatacept* to CD80 and CD86 prevents CD28 from binding to those molecules and, thus, inhibits signal 2 of the T-cell activation pathway. *Belatacept* is approved for kidney transplantation in combination with *basiliximab*, *mycophenolate mofetil*, and corticosteroids. This drug can substitute for calcineurin inhibitors to avoid the detrimental long-term nephrotoxic, cardiovascular, and metabolic complications seen with *cyclosporine* and *tacrolimus*. [Note: The first-generation costimulation blocker *abatacept* is approved for rheumatoid arthritis.]

*Belatacept* is the first IV maintenance immunosuppressant and is dosed in two phases. Initially, it is administered four times in the first month at a higher dose to build up drug levels and then decreased to once-monthly dosing. After 4 months, the dose is also decreased. Monthly dosing may be beneficial in patients for whom medication compliance is an issue. Clearance of *belatacept* is not affected by age, sex, race, renal, or hepatic function. *Belatacept* increases the risk of PTLD, particularly of the central nervous system. Therefore, it is contraindicated in patients who are seronegative to Epstein-Barr virus (EBV), a common cause of PTLD. Serological titers to EBV are typically obtained to confirm exposure.



**Figure 38.5**

Mechanism of action of *sirolimus* and *everolimus*. FKBP = FK-binding protein; IL = interleukin; mRNA = messenger RNA; mTOR = mammalian target of rapamycin.

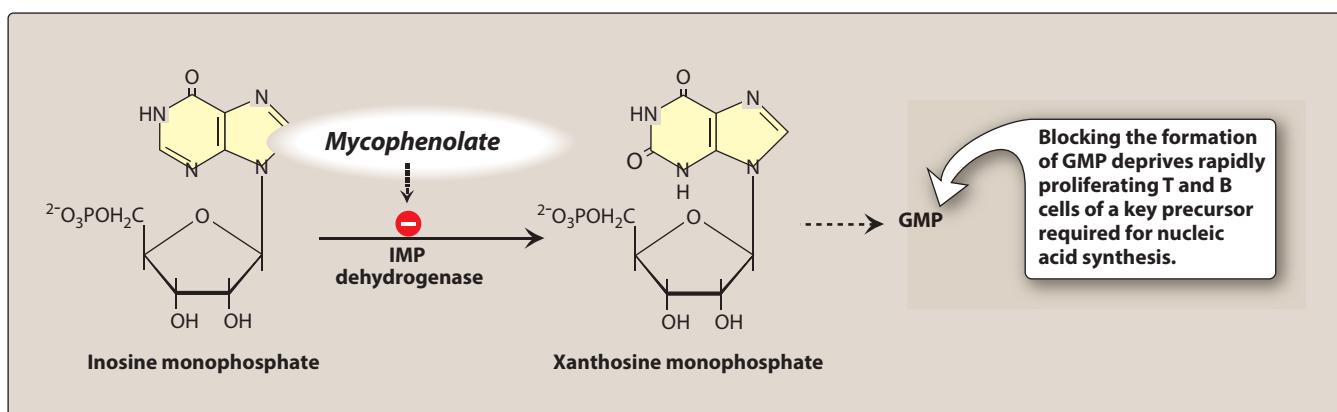
### C. mTOR inhibitors

*Sirolimus* [sih-RO-lih-mus] (also known as *rapamycin*) and *everolimus* [e-ve-RO-lih-mus] inhibit the protein mTOR, blocking the signal transduction pathway activated by signal 3. Progression into the cell cycle and T-cell proliferation is subsequently prevented (Figure 38.5). The mTOR inhibitors are commonly used in multidrug regimens, frequently to minimize the dose of calcineurin inhibitors and spare their nephrotoxic adverse effects.

Like the calcineurin inhibitors, both *sirolimus* and *everolimus* are metabolized by CYP3A4, are substrates for P-gp, and are subject to numerous drug–drug interactions. Both agents require drug monitoring of trough concentrations to optimize therapy. *Sirolimus* has a longer half-life than the calcineurin inhibitors or *everolimus*, and is dosed only once daily, which may improve medication compliance. The anti-proliferative action of *sirolimus* is also valuable in cardiology where *sirolimus*-coated stents are used to inhibit restenosis of the blood vessels by reducing proliferation of the endothelial cells. *Everolimus* is also used in oncology to treat many different types of cancer, including breast, renal cell, and neuroendocrine tumors. However, the doses for tumor treatment are higher than those used in transplantation.

### D. Antiproliferatives

The antiproliferatives *azathioprine* [ay-za-THYE-oh-preen] and *mycophenolate* [mye-koe-FEN-oh-late] block lymphocyte proliferation by inhibiting nucleic acid synthesis. *Azathioprine*, which was one of the first agents to achieve widespread use in organ transplantation, is a prodrug that is converted first to *6-mercaptopurine* (*6-MP*) and then to the corresponding nucleotide analog, thioinosinic acid. The analog is incorporated into nucleic acid chains and blocks further elongation of the DNA. *Mycophenolate* is a potent, reversible, noncompetitive inhibitor of inosine monophosphate dehydrogenase, which blocks the de novo formation of guanosine phosphate (Figure 38.6). Because lymphocytes are unable to utilize the salvage pathway of nucleotide synthesis, *mycophenolate* effectively blocks T- and B-cell proliferation by eliminating de novo production of guanosine.



**Figure 38.6**

Mechanism of action of *mycophenolate*. GMP = guanosine monophosphate; IMP = inosine-59-monophosphate.

These medications are used as adjunctive immunosuppressant agents, primarily with calcineurin inhibitors with or without corticosteroids. However, *mycophenolate* has largely replaced *azathioprine* in this role due to its improved safety and efficacy profile. The main dose-limiting adverse effect of *azathioprine* is bone marrow suppression. *Allopurinol* inhibits the metabolism of *azathioprine*, thereby enhancing the adverse effects of *azathioprine*. Thus, concomitant use of *allopurinol* requires a significant reduction in *azathioprine* dose.

*Mycophenolate* is available in two formulations: 1) as a prodrug *mycophenolate mofetil* and 2) as an active drug *mycophenolic acid*. *Mycophenolate mofetil* is rapidly hydrolyzed in the gastrointestinal tract to *mycophenolic acid*. Glucuronidation of *mycophenolic acid* in the liver produces an inactive metabolite, but enterohepatic recirculation occurs, prolonging the effect of the drug. *Mycophenolic acid* is an enteric-coated tablet designed to theoretically reduce the gastrointestinal upset commonly experienced with *mycophenolate mofetil*.

### E. Cytotoxic agents for immunosuppression

Some of the cytotoxic agents used in anticancer therapy have also showed immunosuppression by suppressing clonal expression of T and B lymphocytes; therefore, they are employed in immunosuppression. *Azathioprine*, *chlorambucil*, and *cyclophosphamide* are used in various autoimmune conditions. *Methotrexate* has been used as a first-line agent in conditions such as severe psoriasis, myasthenia gravis, uveitis, and pemphigus.

### F. Corticosteroids

The corticosteroids (see Chapter 26) were the first pharmacologic agents to be used as immunosuppressives, both in transplantation and in various autoimmune disorders. They are still one of the mainstays for attenuating rejection episodes. For transplantation, the most common agents are *prednisone* and *methylprednisolone*, whereas *prednisone* and *prednisolone* are used for autoimmune conditions. [Note: In transplantation, they are used in combination with agents described previously in this chapter.] The steroids are used to suppress acute rejection of solid organ allografts and in chronic graft-versus-host disease. In addition, they are effective against a wide variety of autoimmune conditions, including refractory rheumatoid arthritis, systemic lupus erythematosus, temporal arthritis, and asthma. The exact mechanism responsible for the immunosuppressive action of the corticosteroids is unclear. The T-lymphocytes are most affected. The steroids are able to rapidly reduce lymphocyte populations by lysis or redistribution. On entering cells, they bind to the glucocorticoid receptor. The complex passes into the nucleus and regulates the transcription of DNA. Among the genes affected are those involved in inflammatory responses. The use of these agents is associated with numerous adverse effects. For example, they are diabetogenic and can cause hypercholesterolemia, cataracts, osteoporosis, and hypertension with prolonged use. Consequently, efforts are being directed toward reducing or eliminating the use of steroids in the maintenance of allografts.

## IV. THERAPEUTIC DRUG MONITORING OF IMMUNOSUPPRESSANTS

Immunosuppressants require therapeutic drug monitoring because of their narrow therapeutic index and significant inter-individual variability in blood concentrations, especially for *cyclosporine*, *tacrolimus*, *sirolimus*, and *mycophenolic acid*. This variability in blood levels can be because of factors such as age, gender, drug-disease interactions, drug-nutrient interactions, renal and hepatic insufficiency, inflammation and infection, and polymorphism. For details, see Chapter 1.

### Study Questions

Choose the ONE best answer.

- 38.1 A 45-year-old man who received a renal transplant 3 months ago and is being maintained on tacrolimus, prednisone, and mycophenolate mofetil is found to have increased creatinine levels and a kidney biopsy indicates severe rejection. Which course of therapy would be appropriate?
- A. Increased dose of prednisone
  - B. Treatment with rabbit antithymocyte globulin
  - C. Treatment with sirolimus
  - D. Treatment with azathioprine
- 38.2 Which combination of immunosuppressive drugs should be avoided?
- A. Basiliximab, belatacept, mycophenolate mofetil, and prednisone
  - B. Tacrolimus, mycophenolate mofetil, and prednisone
  - C. Tacrolimus, cyclosporine, and prednisone
  - D. Tacrolimus, sirolimus, and prednisone
- 38.3 Which drug used to prevent allograft rejection can cause hyperlipidemia?
- A. Basiliximab
  - B. Belatacept
  - C. Mycophenolate mofetil
  - D. Sirolimus
- 38.4 Which drug specifically inhibits calcineurin in the activated T lymphocytes?
- A. Basiliximab
  - B. Tacrolimus
  - C. Sirolimus
  - D. Mycophenolate mofetil

Correct answer = B. This patient is apparently undergoing an acute rejection of the kidney. The most effective treatment would be administration of an antibody. Increasing the dose of prednisone may have some effect but would not be enough to treat the rejection. Sirolimus is used prophylactically with cyclosporine to prevent renal rejection but is less effective when an episode is occurring. Azathioprine has no benefit over mycophenolate.

Correct answer = C. Tacrolimus and cyclosporine are both calcineurin inhibitors and have the same mechanism of action. Immunosuppressive drug regimens should work synergistically at different places in the T-cell activation cascade. Additionally, cyclosporine and tacrolimus are both extremely nephrotoxic and when used together would cause harm to patients. All of the other combinations are reasonable.

Correct answer = D. Patients who are receiving sirolimus can develop elevated cholesterol and triglyceride levels, which can be controlled by statin therapy. None of the other agents has this adverse effect.

Correct answer = B. Tacrolimus binds to FKBP-12, which, in turn, inhibits calcineurin and interferes in the cascade of reactions that synthesize interleukin-2 (IL-2) and lead to T-lymphocyte proliferation. Although basiliximab also interferes with T-lymphocyte proliferation, it does so by binding to the CD25 site on the IL-2 receptor. Sirolimus, while also binding to FKBP-12, does not inhibit calcineurin. Mycophenolate mofetil exerts its immunosuppressive action by inhibiting inosine monophosphate dehydrogenase, thus depriving the cells of guanosine, a key component of nucleic acids.

38.5 An 18-year-old woman who received a kidney transplant 6 months ago comes in to clinic complaining of facial hair growth and does not want to take an immunosuppressant anymore. Which treatment option would be the most appropriate to address her concerns?

- A. Switch cyclosporine to tacrolimus.
- B. Switch mycophenolate mofetil to sirolimus.
- C. Stop prednisone and add methylprednisolone.
- D. Switch mycophenolate mofetil to mycophenolic acid.

38.6 Which immunosuppressant medication avoids the need for therapeutic drug monitoring?

- A. Cyclosporine
- B. Tacrolimus
- C. Mycophenolate mofetil
- D. Sirolimus

38.7 Which clinical situation is *least appropriate* for immunosuppression with sirolimus?

- A. A patient with primary renal failure
- B. A patient who has failed calcineurin inhibitors due to neurotoxicity
- C. A patient who is 6 months postliver transplant and the incision site is fully healed
- D. A patient with an abnormal lipid profile

38.8 Which statement is correct regarding the difference between induction immunosuppression (IS) and maintenance IS?

- A. Maintenance IS is less important than induction IS for long-term graft survival.
- B. Induction IS is more intense than maintenance IS.
- C. Maintenance IS includes lymphocyte-depleting antibodies, while induction IS does not.
- D. Induction IS increases the risk of infection, while maintenance IS does not.

Correct answer = A. Hirsutism, or excessive hair growth, is a well-known adverse effect of cyclosporine. Many patients experience dark, coarse facial or body hair growth while taking cyclosporine. Switching cyclosporine to tacrolimus would eliminate this adverse effect and keep the patient on a calcineurin inhibitor that is effective in preventing rejection. Mycophenolate and prednisone are not known to cause hirsutism.

Correct answer = C. Calcineurin inhibitors (cyclosporine and tacrolimus) and mTOR inhibitors (sirolimus and everolimus) require therapeutic drug monitoring in order to maximize efficacy (prevent rejection episodes) and minimize toxicity (adverse effects). Mycophenolate mofetil is the correct answer since there is no role for routine monitoring with this medication.

Correct answer = D. A patient with an abnormal lipid profile is a poor candidate for immunosuppression with sirolimus, since this medication is known to cause or exacerbate hyperlipidemia, particularly triglycerides and total cholesterol. A patient with primary renal failure would be a candidate for sirolimus, since it does not cause nephrotoxicity as calcineurin inhibitors do. It would be appropriate to switch a patient who has failed calcineurin inhibitors due to neurotoxicity to sirolimus for immunosuppression since it is not associated with that adverse effect. Sirolimus is known to impair wound healing, but a patient with a fully healed incision site could appropriately be placed on sirolimus.

Correct answer = B. Induction IS is more intense than maintenance IS, as it provides IS during the intraoperative and early postoperative period to combat the body's initial immune response to the transplanted graft. Both maintenance and induction IS are important for the long-term survival of the graft. Lymphocyte-depleting antibodies are used as induction IS and not as maintenance. Although induction IS is more potent, all IS (both induction and maintenance) can increase the risk of infection.

38.9 A 39-year-old man is admitted 3 months after liver transplant with increased liver function tests. A liver biopsy is performed and the results show acute and severe rejection. The team decides to start treatment with antithymocyte globulin, rabbit. What additional drug therapy is required for appropriate administration of this medication?

- A. No additional medications are required.
- B. Diphenhydramine, acetaminophen
- C. Diphenhydramine, toradol, corticosteroids
- D. Diphenhydramine, acetaminophen, corticosteroids

38.10 A 21-year-old woman is admitted to receive a kidney transplant from her father. Since she has a low-to-moderate risk of rejection, she will receive induction with the antibody basiliximab. Which statement indicates the uniqueness of the therapy she is receiving compared with other antibody agents?

- A. Basiliximab is generally well tolerated and does not require premedications prior to administration.
- B. Basiliximab binds to CD52 and targets B- and T-lymphocytes.
- C. Basiliximab is used only in combination with antithymocyte globulin.
- D. Basiliximab targets B-cells, not T-cells.

Correct answer = D. Infusion-related reactions are common with the administration of antithymocyte globulins due to cytokine release. Common symptoms include chills, fever, hypotension, and pulmonary edema. Premedication with acetaminophen, diphenhydramine, and corticosteroids should be administered 30 minutes prior to the start of the infusion to prevent this syndrome. Although diphenhydramine and acetaminophen are correct, corticosteroids are also needed as premedication. Toradol is not the most appropriate for use as premedication for antithymocyte globulin.

Correct answer = A. Basiliximab does not require premedication since it is a nondepleting agent and would not be expected to cause cytokine release or infusion reactions. It can be used in combination with antithymocyte globulin, but most commonly it is used alone. Basiliximab binds to CD25 (not CD52) and affects T-cells. It does not have any affect on B-cells.

# UNIT VII

## Special Topics in Pharmacology

# Histamine and Serotonin

Nancy Hart and Carol Motycka

39

### I. OVERVIEW

Histamine and serotonin, along with prostaglandins, belong to a group of endogenous compounds called autacoids. These heterogeneous substances have widely differing structures and pharmacologic activities. They all have the common feature of being formed by the tissues on which they act and, therefore, function as local hormones. [Note: The word “autacoid” comes from the Greek words “autos,” which means self, and “akos,” which means medicinal agent or remedy.] The autacoids also differ from circulating hormones in that they are produced by many tissues rather than in specific endocrine glands. The drugs described in this chapter are either autacoids or autacoid antagonists (compounds that inhibit the synthesis of certain autacoids or that interfere with their interactions with receptors).

### II. HISTAMINE

Histamine is a chemical messenger mostly generated in mast cells. Histamine, via multiple receptor systems, mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and neurotransmission in parts of the brain. Histamine has no clinical applications, but agents that inhibit the action of histamine (antihistamines or histamine receptor blockers) have important therapeutic applications. [Figure 39.1](#) provides a summary of the antihistamines.

#### A. Location, synthesis, and release of histamine

1. **Location:** Histamine is present in practically all tissues, with significant amounts in the lungs, skin, blood vessels, and GI tract. It is found at high concentration in mast cells and basophils. Histamine

#### ANTIHISTAMINES

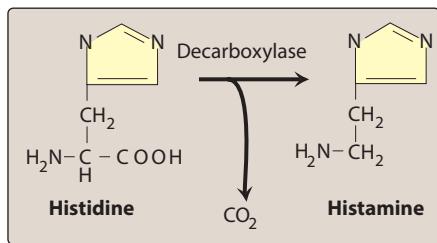
Sedating  
*Diphenhydramine*  
*Dimenhydrinate*  
*Chlorpheniramine*  
*Brompheniramine*  
*Doxylamine*  
Nonsedating  
*Fexofenadine*  
*Cetirizine*  
*Levocetirizine*  
*Loratadine*  
*Desloratadine*  
Mast cell stabilizers  
*Hydroxyzine*  
*Ketotifen*

#### ANTIHISTAMINES AND MAST CELL STABILIZERS

*Azelastine*  
*Olopatadine*  
*Alcaftadine*  
*Bepotastine*  
*Clemastine*  
*Cyproheptadine*  
*Emedastine*  
Motion sickness and nausea  
*Cyclizine*  
*Meclizine*  
*Promethazine*  
*Dimenhydrinate*  
*Triprolidine*

**Figure 39.1**

Summary of antihistamines. (For drug dosages, refer to Appendix at the end of the book.)

**Figure 39.2**

Biosynthesis of histamine.

functions as a neurotransmitter in the brain. It also occurs as a component of venoms and in secretions from insect stings.

2. **Synthesis:** Histamine is an amine formed by the decarboxylation of the amino acid histidine by the enzyme histidine decarboxylase, which is expressed in cells throughout the body, including neurons, gastric parietal cells, mast cells, and basophils (Figure 39.2). In mast cells, histamine is stored in granules. If histamine is not stored, it is rapidly inactivated by the enzyme amine oxidase.
3. **Release of histamine:** Most often, histamine is just one of several chemical mediators released in response to stimuli. The stimuli for release of histamine from tissues may include destruction of cells as a result of cold, toxins from organisms, venoms from insects and spiders, and trauma. Allergies and anaphylaxis can also trigger significant release of histamine.

## B. Mechanism of action

Histamine released in response to certain stimuli exerts its effects by binding to various types of histamine receptors ( $\text{H}_1$ ,  $\text{H}_2$ ,  $\text{H}_3$ , and  $\text{H}_4$ ).  $\text{H}_1$  and  $\text{H}_2$  receptors are widely expressed and are the targets of clinically useful drugs. Histamine has a wide range of pharmacologic effects that are mediated by both  $\text{H}_1$  and  $\text{H}_2$  receptors. For example, the  $\text{H}_1$  receptors are important in producing smooth muscle contraction and increasing capillary permeability (Figure 39.3). Histamine promotes vasodilation of small blood vessels by causing the vascular endothelium to release nitric oxide. In addition, histamine can enhance the secretion of proinflammatory cytokines in several cell types and in local tissues. Histamine  $\text{H}_1$  receptors mediate many pathological processes, including allergic rhinitis, atopic dermatitis, conjunctivitis, urticaria, bronchoconstriction, asthma, and anaphylaxis. Moreover, histamine stimulates the parietal cells in the stomach, causing an increase in acid secretion via the activation of  $\text{H}_2$  receptors.

## C. Role in allergy and anaphylaxis

The symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic shock and allergic reactions. These include contraction of airway smooth muscle, stimulation of secretions, dilation and increased permeability of the capillaries, and stimulation of sensory nerve endings. Symptoms associated with allergy and anaphylactic shock result from the release of certain mediators from their storage sites. Such mediators include histamine, serotonin, leukotrienes, and the eosinophil chemotactic factor of anaphylaxis. In some cases, these mediators cause a localized allergic reaction, producing, for example, actions on the skin or respiratory tract. Under other conditions, these mediators may cause a full-blown anaphylactic response. It is thought that the difference between these two situations results from differences in the sites from which mediators are released and in their rates of release. For example, if the release of histamine is slow enough to permit its inactivation before it enters the bloodstream, a local allergic reaction results. However, if histamine release is too fast for efficient inactivation, a full-blown anaphylactic reaction occurs.

### III. H<sub>1</sub> ANTIHISTAMINES

The term antihistamine refers primarily to the classic H<sub>1</sub>-receptor blockers. The H<sub>1</sub>-receptor blockers can be divided into first- and second-generation drugs (Figure 39.4). The older first-generation drugs are still widely used because they are effective and inexpensive. However, most of these drugs penetrate the central nervous system (CNS) and cause sedation. Furthermore, they tend to interact with other receptors, producing a variety of unwanted adverse effects. By contrast, the second-generation agents are specific for peripheral H<sub>1</sub> receptors. The second-generation antihistamines are made polar, mainly by adding carboxyl groups (for example, *cetirizine* is the carboxylated derivative of *hydroxyzine*), and, therefore, these agents do not penetrate the blood-brain barrier and cause less CNS depression than the first-generation drugs. Among the second-generation agents, *desloratadine* [des-lor-AH-tah-deen], *fexofenadine* [fex-oh-FEN-a-deen], and *loratadine* [lor-AT-a-deen] show the least sedation (Figure 39.5). *Cetirizine* [seh-TEER-ih-zeen] and *levocetirizine* [lee-voe-seh-TEER-ih-zeen] are partially sedating second-generation agents.

#### A. Actions

The action of all H<sub>1</sub>-receptor blockers is qualitatively similar. Most of these compounds do not influence the formation or release of histamine. Rather, they block the receptor-mediated response of a target tissue. They are much more effective in preventing symptoms than reversing them once they have occurred. However, most of these agents have additional effects unrelated to their ability to block H<sub>1</sub> receptors. These effects reflect binding of the H<sub>1</sub>-receptor antagonists to cholinergic, adrenergic, or serotonin receptors (Figure 39.6). For example, *ciproheptadine* [SYE-proe-HEP-ta-deen] also acts as a serotonin antagonist on the appetite center, resulting in appetite stimulation. Antihistamines such as *azelastine* [a-ZEL-uh-steen] and *ketotifen* [kee-toe-TYE-fen] also have mast cell-stabilizing effects in addition to their histamine receptor-blocking effects.

#### B. Therapeutic uses

- Allergic and inflammatory conditions:** H<sub>1</sub>-receptor blockers are useful in treating and preventing allergic reactions caused by antigens acting on immunoglobulin E antibody. For example, oral antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria because histamine is the principal mediator released by mast cells. They are used for the management of anaphylactic reaction to quickly control urticaria, itching, and edema but antihistaminics show only partial protection against the hypotension. Ophthalmic antihistamines, such as *azelastine*, *olopatadine* [oh-loe-PAT-a-deen], *ketotifen*, and others, are useful for the treatment of allergic conjunctivitis. However, the H<sub>1</sub>-receptor blockers are not indicated in treating bronchial asthma, because histamine is only one of several mediators that are responsible for causing bronchial reactions. [Note: *Epinephrine* has actions on smooth muscle that are opposite to those of histamine. It acts via β<sub>2</sub> receptors on smooth muscle, causing cAMP-mediated relaxation. Therefore, *epinephrine* is the drug of choice in treating

#### H<sub>1</sub> Receptors

##### EXOCRINE EXCRETION

Increased production of nasal and bronchial mucus, resulting in respiratory symptoms.

##### BRONCHIAL SMOOTH MUSCLE

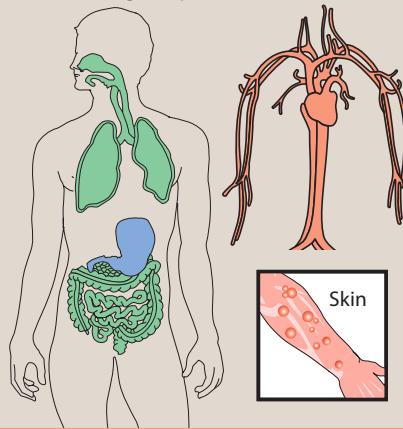
Constriction of bronchioles results in symptoms of asthma and decreased lung capacity.

##### INTESTINAL SMOOTH MUSCLE

Constriction results in intestinal cramps and diarrhea.

##### SENSORY NERVE ENDINGS

Causes itching and pain.



#### H<sub>1</sub> and H<sub>2</sub> Receptors

##### CARDIOVASCULAR SYSTEM

Lowers systemic blood pressure by reducing peripheral resistance. Causes positive chronotropism (mediated by H<sub>2</sub> receptors) and a positive inotropism (mediated by both H<sub>1</sub> and H<sub>2</sub> receptors).

##### SKIN

Dilation and increased permeability of the capillaries results in leakage of proteins and fluid into the tissues. In the skin, this results in the classic “triple response”: wheal formation, reddening due to local vasodilation, and flare (“halo”).

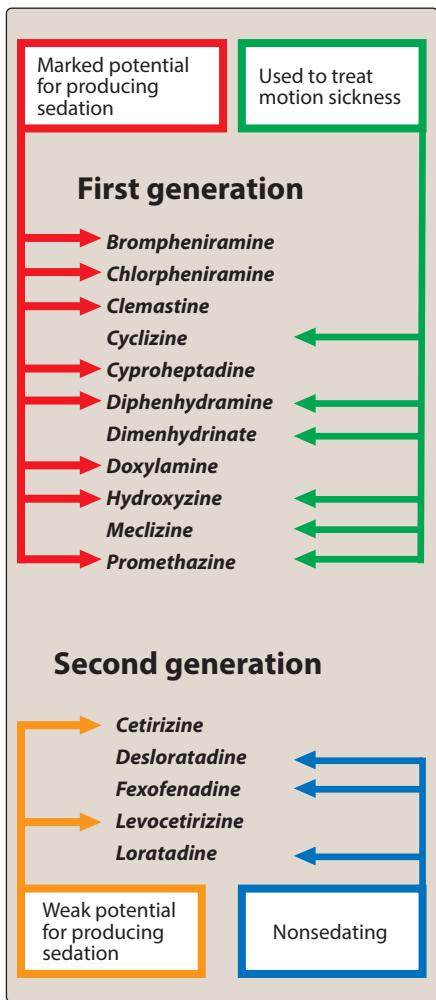
#### H<sub>2</sub> Receptors

##### STOMACH

Stimulation of gastric hydrochloric acid secretion.

**Figure 39.3**

Actions of histamine.

**Figure 39.4**

Summary of therapeutic advantages and disadvantages of some H<sub>1</sub> histamine receptor-blocking agents.

systemic anaphylaxis and other conditions that involve massive release of histamine.] Antihistamines are routinely used for common cold formulas, but they can provide only symptomatic relief by decreasing the rhinorrhea and sneezing.

- Motion sickness and nausea:** Along with the antimuscarinic agent scopolamine, certain H<sub>1</sub>-receptor blockers, such as *diphenhydramine* [dye-fen-HYE-dra-meen], *dimenhydrinate* [dye-men-HYE-dri-nate] (a chemical combination of *diphenhydramine* and a chlorinated theophylline derivative), *cyclizine* [SYE-kli-zeen], *meclizine* [MEK-li-zeen], and *promethazine* [proe-METH-a-zeen], are the most effective agents for prevention of the symptoms of motion sickness. They are usually not effective if symptoms are already present and, thus, should be taken prior to expected travel. The antihistamines prevent or diminish nausea and vomiting mediated by both the chemoreceptor and the vestibular pathways. The antiemetic action of these medications seems to be due to their blockade of central H<sub>1</sub> and M<sub>1</sub> muscarinic receptors. *Meclizine* is also useful for the treatment of vertigo associated with vestibular disorders.
- Somnifacients:** Although they are not the medications of choice, many first-generation antihistamines, such as *diphenhydramine* and *doxylamine* [dox-IL-a-meen], have strong sedative properties and are used in the treatment of insomnia. The use of first-generation H<sub>1</sub> antihistamines is contraindicated in the treatment of individuals working in jobs in which wakefulness is critical. The second-generation antihistamines have no value as somnifacients.

### C. Pharmacokinetics

H<sub>1</sub>-receptor blockers are well absorbed after oral administration, with maximum serum levels occurring at 1 to 2 hours. The average plasma half-life is 4 to 6 hours, except for that of *meclizine* and the second-generation agents, which is 12 to 24 hours, allowing for once-daily dosing. First-generation H<sub>1</sub>-receptor blockers are distributed in all tissues, including the CNS. All first-generation H<sub>1</sub> antihistamines and some second-generation H<sub>1</sub> antihistamines, such as *desloratadine* and *loratadine*, are metabolized by the hepatic cytochrome P450 system. *Levocetirizine* is the active enantiomer of *cetirizine*. *Cetirizine* and *levocetirizine* are excreted largely unchanged in urine, and *fexofenadine* is excreted largely unchanged in feces. After a single oral dose, the onset of action occurs within 1 to 3 hours. *Azelastine*, *olopatadine*, *keto-tifen*, *alcaftadine* [al-KAF-ta-deen], *bepotastine* [bep-oh-TAS-teen], and *emedastine* [em-e-DAS-teen] are available in ophthalmic formulations that allow for more targeted tissue delivery. *Azelastine* and *olopatadine* have intranasal formulations, as well.

### D. Adverse effects

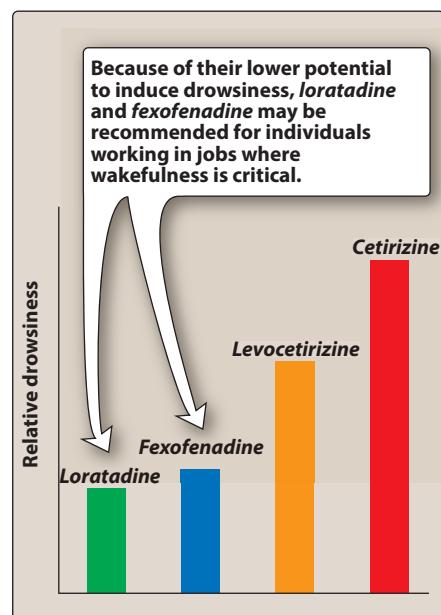
First-generation H<sub>1</sub>-receptor blockers have a low specificity, interacting not only with histamine receptors but also with muscarinic cholinergic receptors, α-adrenergic receptors, and serotonin receptors (Figure 39.6). The extent of interaction with these receptors and, as a result, the nature of the side effects vary with the structure of the

drug. Some side effects may be undesirable, and others may be of therapeutic value. Furthermore, the incidence and severity of adverse reactions for a given drug varies between individual subjects.

**1. Sedation:** First-generation H<sub>1</sub> antihistamines, such as *chlorpheniramine* [klor-fen-IR-a-meen], *pheniramine*, *diphenhydramine*, *hydroxyzine* [hye-DROX-ee-zeen], and *promethazine*, bind to H<sub>1</sub> receptors and block the neurotransmitter effect of histamine in the CNS. The most frequently observed adverse reaction is sedation (Figure 39.7); however, *diphenhydramine* may cause paradoxical hyperactivity in young children. Other central actions include fatigue, dizziness, lack of coordination, and tremors. Elderly patients are more sensitive to these effects. Sedation is less common with the second-generation drugs, since they do not readily enter the CNS. Second-generation H<sub>1</sub> antihistamines are specific for peripheral H<sub>1</sub> receptors.

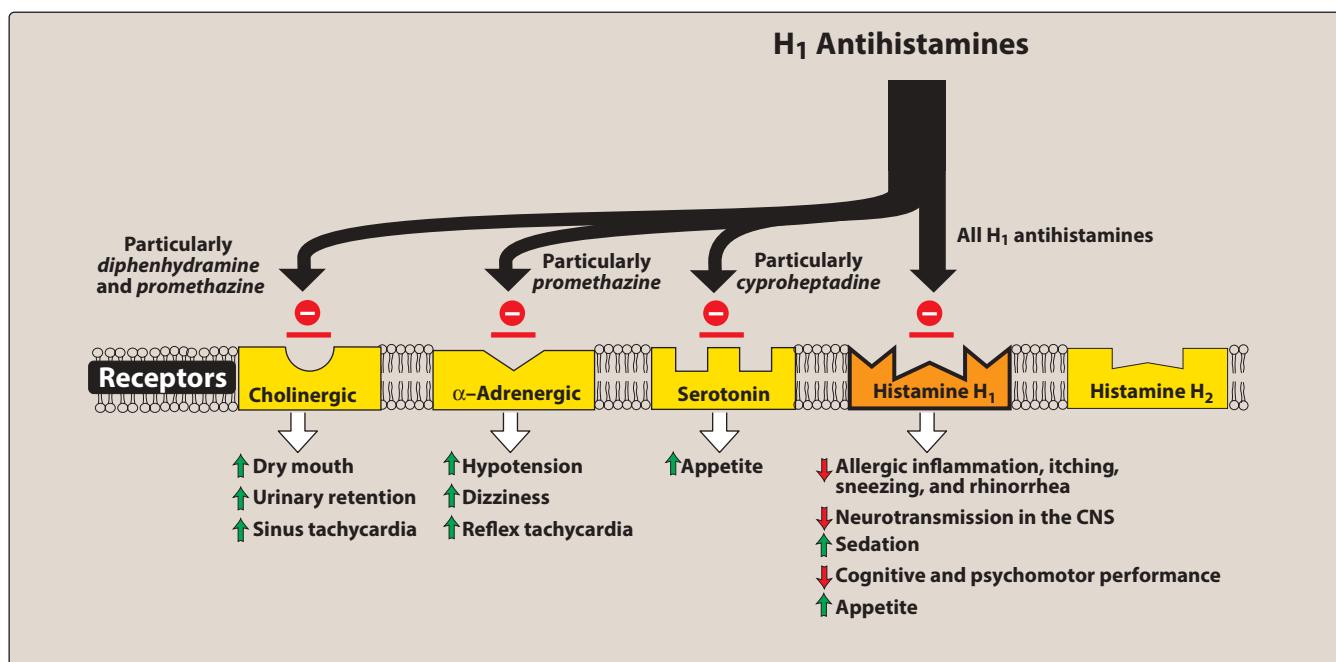
**2. Other effects:** First-generation antihistamines exert anticholinergic effects, leading to dryness in the nasal passage and oral cavity. They also may cause blurred vision and retention of urine. The most common adverse reaction associated with second-generation antihistamines is headache. Topical formulations of *diphenhydramine* can cause local hypersensitivity reactions such as contact dermatitis.

**3. Drug interactions:** Interaction of H<sub>1</sub>-receptor blockers with other drugs can cause serious consequences, such as potentiation of effects of other CNS depressants, including alcohol. Patients taking monoamine oxidase inhibitors (MAOIs), for example *phenelzine*, should not take antihistamines because the MAOIs can exacerbate the sedative and anticholinergic effects of antihistamines. In addition, the first-generation antihistamines (*diphenhydramine* and



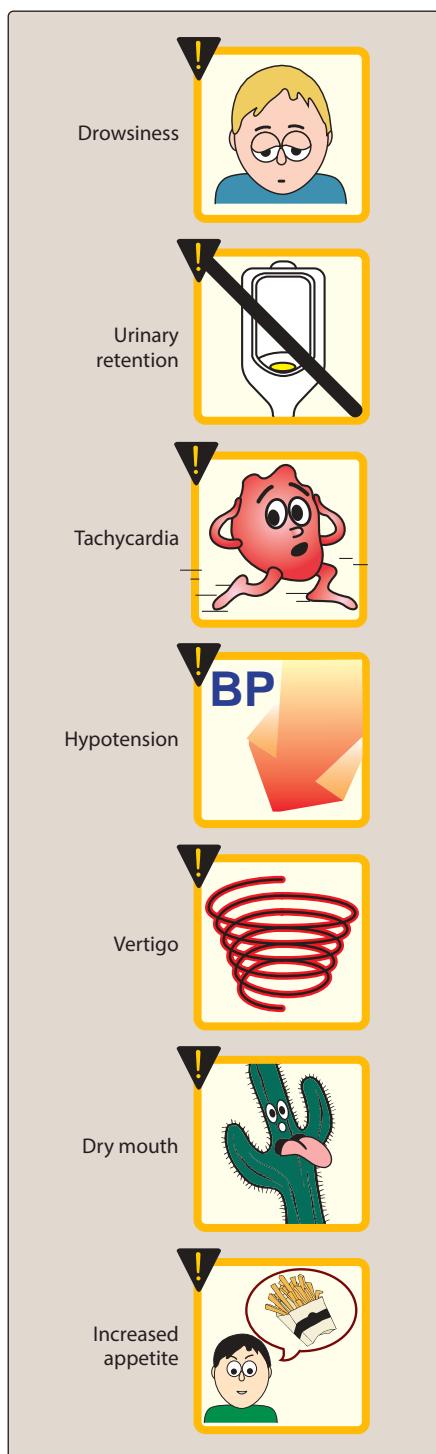
**Figure 39.5**

Relative potential for causing drowsiness in patients receiving second-generation H<sub>1</sub> antihistamines.



**Figure 39.6**

Effects of H<sub>1</sub> antihistamines at histamine, adrenergic, cholinergic, and serotonin-binding receptors. CNS = central nervous system.



**Figure 39.7**

Some adverse effects observed with antihistamines. BP = blood pressure. Bupropion/Naltrexone CONTRAVE.

others) with anticholinergic (antimuscarinic) actions may decrease the effectiveness of cholinesterase inhibitors (*donepezil*, *rivastigmine*, and *galantamine*) in the treatment of Alzheimer's disease.

- Overdoses: Although the margin of safety of H<sub>1</sub>-receptor blockers is relatively high and chronic toxicity is rare, acute poisoning is relatively common, especially in young children. The most common and dangerous effects of acute poisoning are those on the CNS, including hallucinations, excitement, ataxia, and convulsions. If untreated, the patient may experience a deepening coma and collapse of the cardiorespiratory system.

### E. Other uses of antihistaminics

Although antihistaminics are used in cough formulas, they do not have any cough-suppressant property—that is, how they create symptomatic relief through anticholinergic action. Antihistaminics that have anticholinergic activity can be used in the initial stages of Parkinson's disease; however, they are inferior to other agents.

## IV. HISTAMINE H<sub>2</sub>-RECEPTOR BLOCKERS

Histamine H<sub>2</sub>-receptor blockers have little, if any, affinity for H<sub>1</sub> receptors. Although antagonists of the histamine H<sub>2</sub> receptor (H<sub>2</sub> antagonists or H<sub>2</sub>-receptor blockers) block the actions of histamine at all H<sub>2</sub> receptors, their chief clinical use is as inhibitors of gastric acid secretion in the treatment of ulcers and heartburn. The H<sub>2</sub>-receptor blockers *cimetidine*, *ranitidine*, *famotidine*, and *nizatidine* are discussed in Chapter 42.

## V. SEROTONIN

Serotonin (also called 5-hydroxytryptamine or 5HT) is a neurotransmitter within the enteric nervous system and the CNS. It plays a role in vasoconstriction, inhibition of gastric secretion, and stimulation of smooth muscle contraction. It is present in plant and animal kingdom and its effect is often encountered in venoms of wasps and scorpions. Within the gastrointestinal (GI) tract, it may serve as a local hormone to influence GI motility and secretion. Within the brain, the serotonergic neurons affect mood, appetite, body temperature regulation, and sleep. While serotonin has no therapeutic uses, selective serotonin agonists find clinical utility in the management of several disorders, such as depression and migraine headache.

### A. Location, synthesis, and release of serotonin

- Location:** Serotonin is largely present within the enterochromaffin cells of the gastrointestinal tract. It is also found in storage granules in platelets and the raphe nuclei of the brainstem.
- Synthesis:** Serotonin (also known as 5-hydroxytryptamine, 5-HT) is synthesized from the amino acid L-tryptophan. L-tryptophan undergoes hydroxylation of the indole ring to form L-5-hydroxy-tryptophan, followed by decarboxylation to form 5-hydroxytryptamine.
- Release of serotonin:** Following synthesis, serotonin is stored in vesicles and is released by exocytosis of the vesicle in response to an action potential. The activity of serotonin is terminated by

uptake into the neuron and platelets. Metabolism occurs mainly via monoamine oxidase.

### B. Mechanism of action

There are seven families of 5-HT receptor subtypes, with numeric subscripts 1 through 7. Most of these are G protein-coupled receptors, while the 5-HT<sub>3</sub> receptor is a ligand-gated cation channel. The 5-HT<sub>1</sub> and 5-HT<sub>2</sub> receptors have several subtypes denoted by letters (for example, 5-HT<sub>2C</sub>). Serotonin has a wide range of effects that are mediated by the different types of serotonin receptors. For example, serotonin activity at 5-HT<sub>2C</sub> receptors in the CNS may cause a reduction in appetite, and stimulation of 5-HT<sub>3</sub> receptors in the GI tract and vomiting center may trigger emesis. [Note: 5-HT<sub>3</sub> receptor antagonists are highly effective for the management of chemotherapy-induced or postsurgical nausea and vomiting; see Chapter 42.]

### C. Therapeutic uses

Selective serotonin agonists have a variety of clinical indications, depending on the receptor specificity. Serotonin has a role in the pathophysiology of clinical depression, and agents such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are effective therapies for this condition (see Chapter 10). The clinical use of serotonin agonists in the management of migraine and obesity is further described below.

## VI. DRUGS USED TO TREAT HEADACHE DISORDERS

The most common types of headaches are migraine, tension-type, and cluster headaches. Migraines can usually be distinguished from cluster headaches and tension-type headaches by the characteristics as shown in [Figure 39.8](#). Patients with severe migraine headaches report one to five attacks per month

	MIGRAINE	CLUSTER	TENSION TYPE
Family history	Yes	No	Yes
Sex	Females more often than males	Males more often than females	Females more often than males
Onset	Variable	During sleep	Under stress
Location	Usually unilateral	Behind or around one eye	Bilateral in band around head
Character and severity	Pulsating, throbbing	Excruciating, sharp, steady	Dull, persistent, tightening
Duration	2–72 hours per episode	15–90 minutes per episode	30 minutes to 7 days per episode
Associated symptoms	Visual auras, sensitivity to light and sound, pale facial appearance, nausea and vomiting	Unilateral or bilateral sweating, facial flushing, nasal congestion, lacrimation, pupillary changes	Mild intolerance to light and noise, anorexia

**Figure 39.8**

Characteristics of migraine, cluster, and tension-type headaches.

of moderate-to-severe pain which is usually unilateral. Headache disorders significantly affect quality of life and result in considerable healthcare costs. Management of headaches involves avoidance of headache triggers (for example, alcohol, chocolate, and stress) and use of abortive treatments for acute headaches, as well as prophylactic therapy in patients with frequent or severe migraines (Figure 39.9). Serotonin agonists (triptans and ergot alkaloids) are effective as abortive agents in the treatment of migraines.

### A. Types of migraine

There are two main types of migraine headaches. The first, migraine without aura, is a severe, unilateral, pulsating headache that typically

	ROUTE	DOSE
<b>Triptans:</b>		
<i>Almotriptan</i>	Oral	<b>6.25–25 mg/day, once or twice a day</b>
<i>Eletriptan</i>	Oral	<b>20–80 mg/day, twice a day</b>
<i>Frovatriptan</i>	Oral	<b>2.5–7.5 mg/day, up to thrice a day</b>
<i>Naratriptan</i>	Oral	<b>1–5 mg/day, once in 4-hour interval</b>
<i>Rizatriptan</i>	Oral	<b>5–30 mg/day, once in 2-hour interval</b>
<i>Sumatriptan</i>	Oral/intranasal/subcutaneous	<b>Oral = 25–200 mg/day, once in 2 hours if required</b> <b>Intranasal = 5–40 mg/day, once in 2 hours if required</b> <b>Subcutaneous = 6–12 mg/day, twice a day with 1 hour interval</b>
<i>Zolmitriptan</i>	Oral/intranasal	<b>Oral: 1–10 mg/day (once in 2 hr)</b> <b>Intranasal = 5–10 mg/day, once in 2 hours if required</b>
<b>Ergots:</b>		
<i>Dihydroergotamine</i>	Sublingual/IM/subcutaneous/IV/intranasal	<b>Sublingual = 2–6 mg/day, 30 minutes of interval</b> <b>Subcutaneous/IM = 1–3 mg/day, once in 1-hour interval</b> <b>IV = 1–2 mg/day, once in 1-hour interval</b> <b>Intranasal = 1–3 mg/day, once in 15 minutes on both nostrils</b>
<i>Ergotamine</i>	Oral/sublingual/suppository	<b>Oral:</b> <b>Adult = 1–6 mg/day or 1–10 mg/week, with 30 minutes of interval</b> <b>Children = 1–3 mg/day or 1–5 mg/week, with 30 minutes of interval</b> <b>Sublingual = 2–6 mg/day, with 30 minutes of interval</b> <b>Suppository = 2–10 mg/week, once in 1 hour interval</b>
<b>Other agents:</b>		
<b>NSAIDs (refer to Chapter 40):</b>		
<i>Aspirin, Ibuprofen, Indomethacin, ketorolac</i>		
<i>Naproxen</i>		
<b>Prophylactic medications:</b>		
<b>Anticonvulsants (refer to Chapter 12)</b>		
<b>β-Blockers (refer to Chapter 7)</b>		
<b>Calcium channel blockers (refer to Chapter 16)</b>		
<b>Tricyclic antidepressants (refer to Chapter 10)</b>		

**Figure 39.9**

Summary of drugs used to treat migraine headache and their dosages. Modified from D. D. Dubose, A. C. Cutlip, and W. D. Cutlip. Migraines and other headaches: an approach to diagnosis and classification. Am. Fam. Physician 51: 1498 (1995).

lasts from 2 to 72 hours. These headaches are often aggravated by physical activity and are accompanied by nausea, vomiting, photophobia (hypersensitivity to light), and phonophobia (hypersensitivity to sound). The majority of patients with migraine do not have aura. In the second type, migraine with aura, the headache is preceded by neurologic symptoms called auras, which can be visual, sensory, and/or cause speech or motor disturbances. Most commonly, these prodromal symptoms are visual (flashes, zigzag lines, and glare) and occur approximately 20 to 40 minutes before headache pain begins. In the 15% of migraine patients whose headache is preceded by an aura, the aura itself allows diagnosis. The headache in migraines with or without auras is similar. Women are threefold more likely than men to experience either type of migraine.

### B. Biologic basis of migraine headaches

The first manifestation of migraine with aura is a spreading depression of neuronal activity accompanied by reduced blood flow in the most posterior part of the cerebral hemisphere. This hypoperfusion gradually spreads forward over the surface of the cortex to other contiguous areas of the brain. The vascular alteration is accompanied by functional changes. The hypoperfusion persists throughout the aura and well into the headache phase. Patients who have migraine without aura do not show hypoperfusion. However, the pain of both types of migraine may be due to extracranial and intracranial arterial vasodilation, which leads to release of neuroactive molecules, such as substance P, neurokinin A, and calcitonin gene-related peptide.

### C. Symptomatic treatment of acute migraine

Acute treatments can be classified as nonspecific (symptomatic) or migraine specific. Nonspecific treatment includes analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and antiemetics (for example, *prochlorperazine*) to control vomiting. Opioids are reserved as rescue medication when other treatments for a severe migraine are not successful. Migraine-specific therapy includes triptans and ergot alkaloids, which are 5-HT<sub>1B/1D</sub> receptor and 5-HT<sub>1D</sub> receptor agonists, respectively. It has been proposed that activation of 5-HT<sub>1</sub> receptors by these agents leads either to vasoconstriction or to inhibition of the release of proinflammatory neuropeptides on the trigeminal nerve innervating cranial blood vessels.

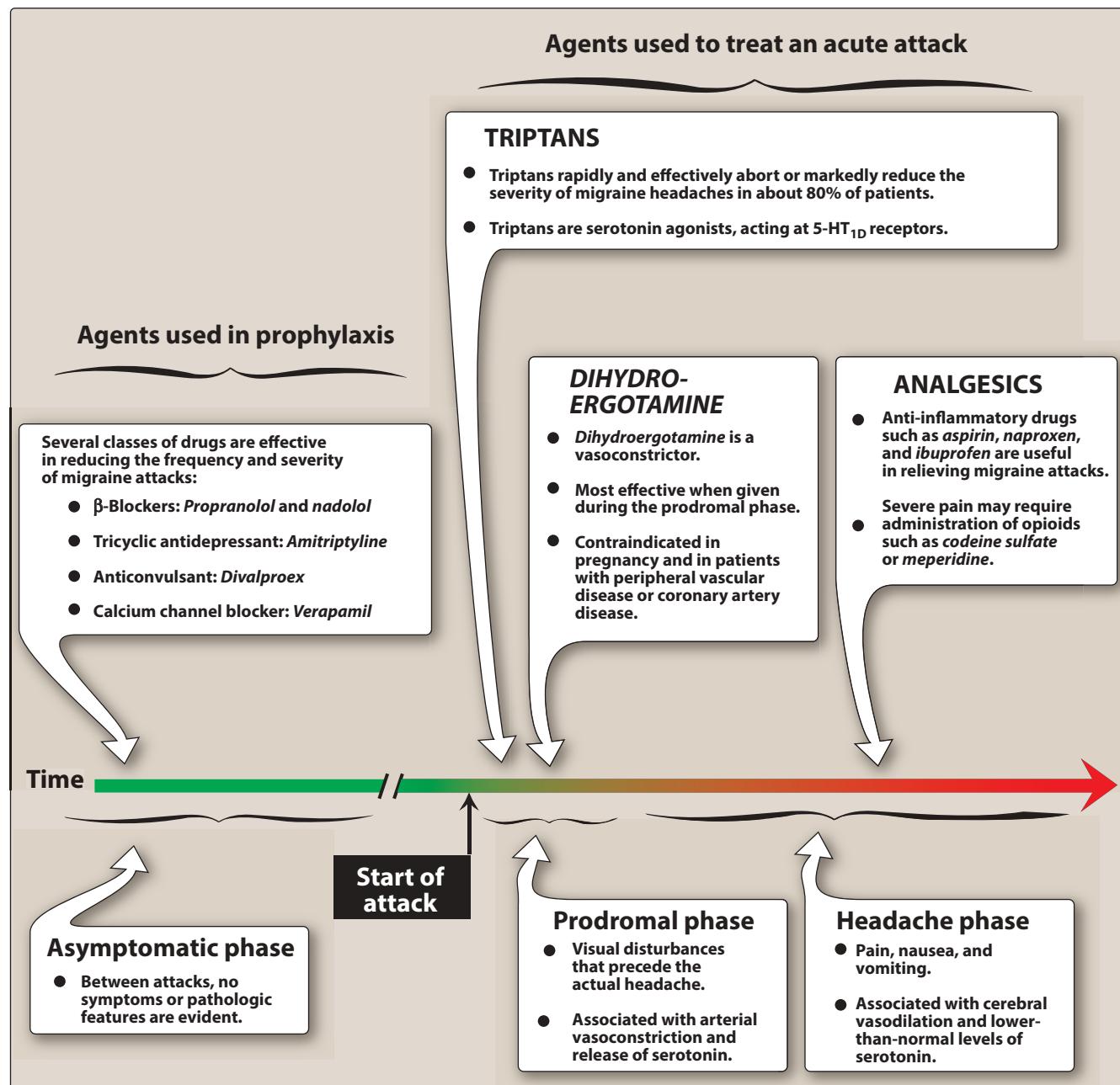
- 1. Triptans:** This class of drugs includes *almotriptan* [al-moe-TRIP-tan], *eletriptan* [el-e-TRIP-tan], *frovatriptan* [froe-va-TRIP-tan], *naratriptan* [nar-a-TRIP-tan], *rizatriptan* [rye-za-TRIP-tan], *sumatriptan* [soo-ma-TRIP-tan], and *zolmitriptan* [zole-ma-TRIP-tan]. *Sumatriptan* was the first available triptan and is the prototype of this class. These agents rapidly and effectively abort or markedly reduce the severity of migraine headaches in about 70% of patients. The triptans are serotonin agonists, acting at a subgroup of serotonin receptors found on small peripheral nerves that innervate the intracranial vasculature. The nausea that occurs with *dihydroergotamine* and the vasoconstriction caused by *ergotamine* (see below) are much less pronounced with the triptans. *Sumatriptan* is given subcutaneously, intranasally, or orally

(*sumatriptan* is also available in a combination product with *naproxen*). *Zolmitriptan* is available orally and by nasal spray. All other agents are taken orally. The onset of the parenteral drug *sumatriptan* is about 20 minutes, compared with 1 to 2 hours when the drug is administered orally. The drug has a short duration of action, with an elimination half-life of 2 hours. Headache commonly recurs within 24 to 48 hours after a single dose of drug, but in most patients, a second dose is effective in aborting the headache. *Frovatriptan* is the longest acting triptan, with a half-life of more than 24 hours. Individual response to triptans varies, and a trial of more than one triptan may be necessary before treatment is successful. Elevation of blood pressure and other cardiac events have been reported with triptan use. Therefore, triptans should not be administered to patients with risk factors for coronary artery disease without performing a cardiac evaluation prior to administration. Other adverse events with the use of triptans include pain and pressure sensations in the chest, neck, throat, and jaw. Dizziness and malaise have also been seen with the use of triptans.

2. **Ergot alkaloids:** Ergot is the dried sclerotium of the fungus *Claviceps purpura* which grows on rye plant. Ergot alkaloids such as ergotamine and ergonovine are potent bioactive compounds. *Ergotamine* [er-GOT-a-meen] and *dihydroergotamine* [dye-hye-droe-er-GOT-a-meen], a semisynthetic derivative of *ergotamine*, are ergot alkaloids approved for the treatment of migraine headaches. The action of the ergot alkaloids is complex, with the ability to bind to 5-HT<sub>1</sub> receptors, α receptors, and dopamine receptors. 5-HT<sub>1</sub> receptors located on intracranial blood vessels are targets that cause vasoconstriction with the use of these agents. *Ergotamine* is currently available sublingually and is mostly effective when used in the early stages of the migraine. It is also available as an oral tablet or suppository containing both *ergotamine* and caffeine. *Ergotamine* is used with strict daily and weekly dosage limits due to its ability to cause dependence and rebound headaches. *Dihydroergotamine* is administered intravenously or intranasally and has an efficacy similar to that of *sumatriptan*. The use of *dihydroergotamine* is limited to severe cases of migraines. Nausea is a common adverse effect. *Ergotamine* and *dihydroergotamine* are contraindicated in patients with angina and peripheral vascular disease because they are significant vasoconstrictors. Apart from migraine, ergot alkaloids such as *ergonocine* and *methylergonovine* are used as uterotonic in postpartum women. After intravenous administration, the effect can be observed within 10 minutes. The plasma half-life of *methylergonovine* is between 0.5 and 2 hours. Considering this action of ergot alkaloids on the uterus, it is contraindicated in patients who have migraine during pregnancy or who are likely to become pregnant. Ergot alkaloids are known to cause fetal distress and miscarriage in pregnant women.
3. **Nonspecific therapies:** Other therapies for acute migraine attacks include analgesics, antiemetics, nonsteroidal anti-inflammatory drugs, and corticosteroids.

#### D. Prophylaxis for migraine headache

Therapy to prevent migraine is indicated if the attacks occur two or more times a month and if the headaches are severe or complicated by serious neurologic signs.  $\beta$ -Blockers are the drugs of choice for migraine prophylaxis; however, calcium channel blockers, anticonvulsants, and tricyclic antidepressants have also shown effectiveness in migraine prevention (Figure 39.10).



**Figure 39.10**

Drugs useful in the treatment and prophylaxis of migraine headaches.

### E. Drugs for tension and cluster headache

Analgesics (NSAIDs, *acetaminophen*, *aspirin*) are used for symptom relief of tension headaches, and *caffeine* and *butalbital* are often combined with *acetaminophen* or *aspirin*. Triptans, along with inhalation of 100% oxygen, are used as first-line abortive strategies for cluster headache.

## VII. DRUGS FOR OBESITY

The term “obesity” is given to individuals with a body mass index (BMI) 30 kg/m<sup>2</sup> or greater. Obesity is due in part to an energy imbalance; however, it is now well understood that genetics, metabolism, behavior, environment, culture, and socioeconomic status play a role in obesity, as well. Serotonin agonists have been used in the treatment of obesity for the appetite suppression that they produce. Drugs for obesity are considered effective if they demonstrate at least a 5% greater reduction in body weight as compared to placebo (no treatment). The majority of drugs approved to treat obesity have short-term indications for usage. A summary of medications for obesity is provided in [Figure 39.11](#).

### A. Serotonin agonists

The first serotonin agonists used for weight loss, *fenfluramine* and *dexfenfluramine*, were withdrawn from the market following an increase in potentially fatal adverse effects, including valvulopathy.

DRUG NAME	ROUTE OF ADMINISTRATION	COMMENTS
<b>Nonspecific 5HT<sub>2C</sub> receptor agonists:</b>		
<i>Fenfluramine</i>	Oral	Discontinued by FDA
<i>Dexfenfluramine</i>	Oral	Discontinued by FDA
<b>Specific 5HT<sub>2C</sub> receptor agonist:</b>		
<i>Lorcasirin</i>	Oral	10–20 mg/day, twice a day
<b>Appetite suppressants:</b>		
<i>Phentermine</i>	Oral	12–30 mg/day, once a day
<i>Diethylpropion</i>	Oral	25–75 mg/day, up to thrice a day
<b>Lipase inhibitor:</b>		
<i>Orlistat</i>	Oral	120–360 mg/day, thrice a day at 1 hour after meal
<b>Glucagon-like peptide-1 (GLP-1) receptor agonist:</b>		
<i>Liraglutide</i>	Subcutaneous	0.6–1.8 mg/day, once a day
<b>Combination drugs:</b>		
<i>Bupropion/naltrexone</i>	Oral	<i>Naltrexone</i> 8 mg/ <i>bupropion</i> 90 mg, 1–4 tablets/wk
<i>Pentermine/topiramate</i>	Oral	<i>Pentermine</i> = 3.75–15 mg/day, <i>topiramate</i> = 23–92 mg/day, once a day in morning

**Figure 39.11**

Summary of the drugs used for the treatment of obesity and their doses.

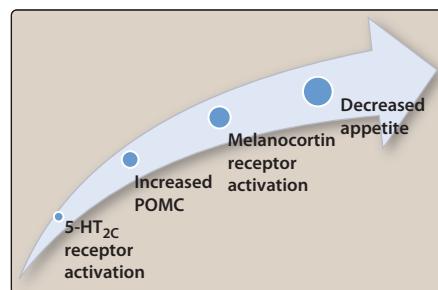
Valvulopathy, which may lead to pulmonary hypertension, is linked to 5-HT<sub>2B</sub> receptors. *Lorcaserin* [lor-KAS-er-in] is a serotonin agonist with selectivity for the 5-HT<sub>2C</sub> serotonin receptor. In contrast to many other weight-loss drugs, it is used for chronic weight management.

1. **Mechanism of action:** *Lorcaserin* selectively activates 5-HT<sub>2C</sub> receptors, which are almost exclusively found in the central nervous system. This activation, in turn, stimulates pro-opiomelanocortin (POMC) neurons, which activate melanocortin receptors, thereby causing a decrease in appetite (Figure 39.12). If a patient does not lose at least 5% of their body weight after 12 weeks of use, the drug should be discontinued.
2. **Pharmacokinetics:** *Lorcaserin* is extensively metabolized in the liver to two inactive metabolites that are then eliminated in the urine. *Lorcaserin* has not been studied for use in severe hepatic impairment and is not recommended in severe renal impairment.
3. **Adverse effects:** The most common adverse effects observed with *lorcaserin* are nausea, headache, dry mouth, dizziness, constipation, and lethargy. Although rare, mood changes and suicidal ideation can occur. The development of life-threatening serotonin syndrome or neuroleptic malignant syndrome has been reported with the use of serotonin agonists. Therefore, patients should be monitored for the emergence of these conditions while on *lorcaserin*. Because of the increased risk of serotonin syndrome, concomitant use of *lorcaserin* with selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, MAOIs, or other serotonergic drugs should be avoided. As mentioned in the preceding text, valvulopathy has been associated with the use of 5-HT<sub>2B</sub> receptor agonists. Although the incidence of valvulopathy was not significantly increased in studies of *lorcaserin* (5HT<sub>2c</sub> receptor agonist), patients should still be monitored for the development of this condition. For that reason, individuals with a history of heart failure should use this agent with caution.

## B. Other agents for obesity

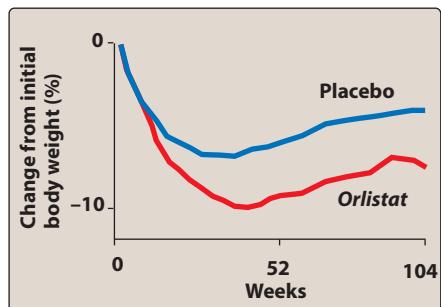
In addition to *lorcaserin*, several agents with varying mechanisms of action are available for weight loss and the management of obesity.

1. **Appetite suppressants:** *Phentermine* [FEN-ter-meen] and *diethylpropion* [dye-eth-ill-PROE-pee-on] are appetite suppressants. They exert pharmacologic action by increasing the release of norepinephrine and dopamine from the nerve terminals and by inhibiting reuptake of these neurotransmitters, thereby increasing levels of neurotransmitters in the brain. The increase in norepinephrine signals a “fight-or-flight” response by the body, which, in turn, decreases appetite. Tolerance to the weight loss effect of these agents develops within weeks, and weight loss typically plateaus. An increase in the dosage generally does not result in further weight loss, and discontinuation of the drug is usually recommended once the plateau is reached. The anorexiants are classified as controlled substances due to the potential



**Figure 39.12**

*Lorcaserin* mechanism of action.  
POMC = pro-opiomelanocortin.

**Figure 39.13**

Effect of *orlistat* treatment on body weight.

for dependence or abuse. Dry mouth, headache, insomnia, and constipation are common adverse effects. Heart rate and blood pressure may be increased with these agents. Therefore, these drugs should be avoided in patients with a history of uncontrolled hypertension, cardiovascular disease, arrhythmias, heart failure, or stroke. Concomitant use of anorexiants with monoamine oxidase inhibitors (MAOIs) or other sympathomimetics should be avoided.

2. **Lipase inhibitor:** *Orlistat* [OR-lih-stat] is the only agent in a class of antiobesity drugs known as lipase inhibitors. It is indicated for weight loss or weight maintenance. *Orlistat* is a pentanoic acid ester that inhibits gastric and pancreatic lipases, thus decreasing the breakdown of dietary fat into smaller molecules that can be absorbed. Administration of *orlistat* decreases fat absorption by about 30%. The loss of calories from decreased absorption of fat is the main cause of weight loss. Figure 39.13 shows the effects of *orlistat* treatment. The clinical utility of *orlistat* is limited by gastrointestinal adverse effects, including oily spotting, flatulence with discharge, fecal urgency, and increased defecation. These effects may be minimized through a low-fat diet and the use of concomitant *cholestyramine*. *Orlistat* is contraindicated in pregnancy and in patients with chronic malabsorption syndrome or cholestasis. The drug also interferes with the absorption of fat-soluble vitamins and  $\beta$ -carotene. Patients should be advised to take a multivitamin supplement that contains vitamins A, D, E, and K and  $\beta$ -carotene. *Orlistat* can also interfere with the absorption of other medications, such as *amiodarone*, *cyclosporine*, and *levothyroxine*, and clinical response to these medications should be monitored if *orlistat* is initiated. The dose of *levothyroxine* should be separated from *orlistat* by at least 4 hours.
3. **Glucagon-like peptide-1 (GLP-1) receptor agonist:** *Liraglutide* is an injectable GLP-1 receptor agonist that is indicated for obesity. See Chapter 24 for a full discussion of GLP-1 receptor agonists.
4. **Combination therapy:** The combination of *phentermine* and *topiramate* has been approved for long-term use in the treatment of obesity. Initial studies of the anticonvulsant *topiramate* observed weight loss in patients taking the medication. Because of the sedating effects of *topiramate*, the stimulant *phentermine* was added to counteract sedation and promote additional weight loss. If a patient does not achieve a 5% weight loss after 12 weeks on the highest dose of this medication, then it should be discontinued. It is also important to note that this medication should not be stopped abruptly as seizures may be precipitated. *Topiramate* has been associated with birth defects including cleft palate, and, thus, the combination of *phentermine/topiramate* is contraindicated in pregnancy. *Bupropion* and *naltrexone* is another combination therapy approved for chronic weight management. Important characteristics of the medications for obesity are summarized in Figure 39.14.

DRUG	TARGET	MECHANISM OF ACTION	PHARMACOKINETICS	ADVERSE EFFECTS
Bupropion + naltrexone	Bupropion: CNS-POMC neuron stimulation  Naltrexone: CNS—blocks autoinhibitory feedback of the hypothalamic melanocortin system	Combination regulates the mesolimbic reward system and results in appetite suppression	Extensive metabolism through CYP2D6	Nausea, headache, dry mouth, dizziness, constipation, suicidal ideation
Liraglutide	GLP-1 receptor agonist	Slows gastric emptying and increases satiety	Excretion through the kidneys and metabolism in the liver	Nausea and vomiting, pancreatitis, hypoglycemia, acute gall bladder disease, elevated heart rate, suicidal ideation
Lorcaserin	CNS—5-HT <sub>2C</sub> receptor agonist	Appetite suppression	Extensive metabolism in the liver	Nausea, headache, dry mouth, dizziness, constipation, suicidal ideation, lethargy
Orlistat	GI system—inhibits gastric and pancreatic lipase	Fat absorption decreased by ~30%, which decreases overall caloric intake	Minimal systemic absorption	GI symptoms such as oily spotting, flatulence, fecal urgency, and increased defecation
Phentermine	CNS—increase in NE and dopamine release and reuptake inhibition	Appetite suppression	Excretion through the kidneys	Dry mouth, headache, insomnia, constipation  Possible heart rate and blood pressure increases
Diethylpropion	CNS—increase in NE and dopamine release and reuptake inhibition	Appetite suppression	Excretion mainly through the kidneys	Dry mouth, headache, insomnia, constipation  Possible heart rate and blood pressure increases
Phentermine + topiramate	Phentermine: CNS—increase in NE and dopamine release and reuptake inhibition  Topiramate: CNS—increase in GABA	Appetite suppression and increased satiety	Excretion primarily through the kidneys with limited hepatic metabolism	Paresthesia, altered taste, dizziness, insomnia, dry mouth, constipation  Contraindicated in pregnancy

CNS = central nervous system; GABA =  $\gamma$ -aminobutyric acid; GI = gastrointestinal; GLP = glucagon-like peptide; NE = norepinephrine; POMC = pro-opiomelanocortin.

**Figure 39.14**

Characteristics of the medications for obesity.

## Study Questions

Choose the ONE best answer.

- 39.1 A 43-year-old heavy machine operator complains of seasonal allergies. Which medication is most appropriate for management of his allergy symptoms?
- Diphenhydramine
  - Doxylamine
  - Hydroxyzine
  - Fexofenadine

Correct answer = D. The use of first-generation H<sub>1</sub> antihistamines is contraindicated in the treatment of pilots and others who must remain alert. Because of its lower potential to induce drowsiness, fexofenadine may be recommended for individuals working in jobs in which wakefulness is critical.

- 39.2 Which statement concerning H<sub>1</sub> antihistamines is correct?
- A. Second-generation H<sub>1</sub> antihistamines are relatively free of adverse effects.
  - B. Because of the established long-term safety of first-generation H<sub>1</sub> antihistamines, they are the first choice for allergic rhinitis.
  - C. The motor coordination involved in driving an automobile is not affected by the use of first-generation H<sub>1</sub> antihistamines.
  - D. H<sub>1</sub> antihistamines can be used in the treatment of acute anaphylaxis.
- 39.3 Which histamine receptor antagonist is known to enter the central nervous system readily and cause sedation?
- A. Hydroxyzine
  - B. Cetirizine
  - C. Desloratadine
  - D. Loratadine
- 39.4 Which drug is an H<sub>1</sub>-receptor antagonist that also has serotonin receptor antagonism on the appetite center, with the ability to stimulate appetite?
- A. Hydroxyzine
  - B. Loratadine
  - C. Diphenhydramine
  - D. Cyproheptadine
- 39.5 Which drug for headache is contraindicated in patients with peripheral vascular disease?
- A. Ergotamine
  - B. Aspirin
  - C. Acetaminophen
  - D. Naproxen
- 39.6 A 29-year-old woman complains of migraine headaches associated with early onset vomiting. Currently, she uses ibuprofen as needed for her migraines, but it is not very effective. Which triptan would be ideal for this patient?
- A. Naratriptan
  - B. Zolmitriptan
  - C. Frovatriptan
  - D. Almotriptan

Correct answer = A. Second-generation H<sub>1</sub> antihistamines are preferred over first-generation agents because they are relatively free of adverse effects. Driving performance is adversely affected by first-generation H<sub>1</sub> antihistamines. Epinephrine, not antihistamine, is an acceptable treatment for acute anaphylaxis. Second-generation H<sub>1</sub> antihistamines penetrate the blood-brain barrier to a lesser degree than the first-generation drugs.

Correct answer = A. Choices B, C, and D are all second-generation antihistamines that cross the blood-brain barrier to a much lesser extent than hydroxyzine. Hydroxyzine is the only drug that crosses the blood-brain barrier easily.

Correct answer = D. Cyproheptadine has significant serotonin antagonism and is known to increase appetite.

Correct answer = A. Ergotamine is contraindicated in peripheral vascular disease because it is a significant vasoconstrictor.

Correct answer = B. Although all of the triptans listed are available as an oral tablet, this patient suffers from vomiting associated with her migraines. Zolmitriptan and sumatriptan are available as an intranasal dosage form, which would be ideal for this patient.

- 39.7 A 35-year-old woman is having several severe migraines per month. The migraines are usually relieved with one or two doses of triptan drugs. Which is most appropriate for prophylaxis to reduce the frequency of her migraines?
- A. Dihydroergotamine
  - B. Ibuprofen
  - C. Propranolol
  - D. Sumatriptan
- 39.8 A 27-year-old married woman is asking about treatment options for obesity. She recently stopped taking her birth control medications, as she felt they were contributing to her weight gain. Which medication should be avoided in this patient?
- A. Phentermine/topiramate
  - B. Orlistat
  - C. Diethylpropion
  - D. Lorcaserin
- 39.9 A fellow healthcare provider is concerned about prescribing orlistat to adolescent patients. Many of his adolescent patients are stopping the medication during the first month of treatment. Which side effect is the most likely reason the adolescents are stopping orlistat?
- A. Valvulopathy
  - B. Suicidal ideation
  - C. Drowsiness
  - D. Flatulence
- 39.10 A 38-year-old obese man with depression is considering a weight loss medication following several failed attempts with diet and exercise. Which medication could be considered in this individual?
- A. Liraglutide
  - B. Bupropion + naltrexone
  - C. Orlistat
  - D. Lorcaserin

Correct answer = C.  $\beta$ -Blockers such as propranolol are used for prophylaxis to reduce the frequency of migraines. The other medications are all used to treat an acute migraine headache.

Correct answer = A. Although patients should not take any medications to lose weight during pregnancy, the topiramate component of this medication is especially dangerous, since it can be teratogenic. Because this patient stopped her birth control medicine, she is at risk of becoming pregnant and developing birth defects while also on this medication.

Correct answer = D. Flatulence is a very common side effect with orlistat, along with several other GI disturbances. For adolescents, these side effects may be embarrassing and difficult to manage. It is important to counsel patients about these gastrointestinal side effects with orlistat and recommend a low-fat diet as well as cholestyramine to counteract the effects should they become bothersome. The other side effects listed have been seen with other obesity medications, but not with orlistat.

Correct answer = C. Only orlistat has not been associated with suicidal ideation. All of the other drugs listed may cause suicidal ideation and would not be advisable for an individual with depression. Also, with a history of depression, the patient may be taking a medication that could increase serotonin levels. The addition of lorcaserin, a serotonin receptor agonist, could lead to serotonin syndrome further excluding it from the list of possible options.



# Anti-inflammatory, Antipyretic, and Analgesic Agents

40

Eric Dietrich, Amy Talana, and Thirumurthy Velpandian

## I. OVERVIEW

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair. When healing is complete, the inflammatory process usually subsides. However, inappropriate activation of the immune system can result in inflammation and immune-mediated diseases such as rheumatoid arthritis (RA). Normally, the immune system can differentiate between self and non-self. In RA, white blood cells (WBCs) view the synovium as non-self and initiate an inflammatory attack. WBC activation leads to stimulation of T lymphocytes which recruit and activate monocytes and macrophages. These cells secrete proinflammatory cytokines, including tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-1, into the synovial cavity, ultimately leading to joint destruction and other systemic abnormalities characteristic of RA. In addition to T lymphocyte activation, B lymphocytes are also involved and produce rheumatoid factor and other autoantibodies to maintain inflammation. These defensive reactions cause progressive tissue injury, resulting in joint damage and erosions, functional disability, pain, and reduced quality of life. Pharmacotherapy for RA includes anti-inflammatory and/or immunosuppressive agents that modulate/reduce the inflammatory process, with the goals of reducing inflammation and pain, and halting or slowing disease progression. The agents discussed in this chapter (Figure 40.1) include nonsteroidal anti-inflammatory drugs (NSAIDs), celecoxib, paracetamol, and disease-modifying antirheumatic drugs (DMARDs). Additionally, agents used for the treatment of gout are reviewed.

## II. PROSTAGLANDINS

NSAIDs act through inhibition of the synthesis of prostaglandins. Thus, an understanding of NSAIDs requires comprehension of the actions and biosynthesis of prostaglandins—unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure. [Note: These compounds are sometimes referred to as eicosanoids; “eicosa” refers to the 20 carbon atoms.]

### NONSELECTIVE CYCLOOXYGENASE INHIBITORS

#### Salicylates

*Aspirin*  
*Diflunisal*  
*Methyl salicylate*  
*Sodium salicylate (salsalate)*

#### Propionic acid derivatives

*Ibuprofen*  
*Fenoprofen*  
*Flurbiprofen*  
*Ketoprofen*  
*Naproxen*  
*Oxaprozin*

#### Acetic acid derivatives

*Ketorolac*  
*Etodolac*  
*Indomethacin*  
*Nabumetone*  
*Tolmetin*

#### Fenamaets

*Mephenamic acid*

#### Oxicams

*Piroxicam*  
*Tenoxicam*

#### Pyrazolines

*Metamizol (dipyrone)*  
*Propiphenazole*

#### Para-amino phenol derivative

*Paracetamol*

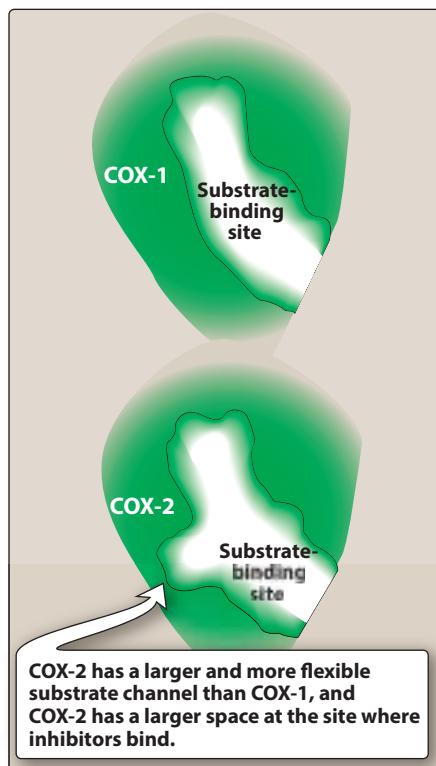
### Figure 40.1

Summary of anti-inflammatory drugs.  
(Figure continues on next page)

<b>Others</b>
<i>Propiphenazone</i>
<i>Metamizol (dipyrone)</i>
<b>PREFERENTIAL COX-2 INHIBITORS</b>
<i>Diclofenac</i>
<i>Nimesulide</i>
<i>Aceclofenac</i>
<i>Meloxicam</i>
<i>Etodolac</i>
<b>SELECTIVE COX-2 INHIBITORS</b>
<i>Celecoxib</i>
<i>Parcoxicib</i>
<i>Etoricoxicib</i>

**Figure 40.1** (Continued)

Summary of anti-inflammatory drugs. COX = cyclooxygenase.

**Figure 40.2**

Structural differences in active sites of cyclooxygenase (COX)-1 and COX-2.

### A. Role of prostaglandins as local mediators

Prostaglandins and related compounds are produced in minute quantities by virtually all tissues. They generally act locally on the tissues in which they are synthesized and are rapidly metabolized to inactive products at their sites of action. Therefore, prostaglandins do not circulate in the blood in significant concentrations. Thromboxanes and leukotrienes are related compounds that are synthesized from the same precursors as the prostaglandins.

### B. Synthesis of prostaglandins

Arachidonic acid is the primary precursor of the prostaglandins and related compounds, and it is present as a component of the phospholipids of cell membranes. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A<sub>2</sub> via a process controlled by hormones and other stimuli. There are two major pathways in the synthesis of eicosanoids from arachidonic acid, the cyclooxygenase and the lipoxygenase pathways.

- Cyclooxygenase pathway:** Eicosanoids with ring structures (that is, prostaglandins, thromboxanes, and prostacyclins) are synthesized via the cyclooxygenase pathway. Two related isoforms of the cyclooxygenase enzymes exist. Cyclooxygenase-1 (COX-1) is responsible for the physiologic production of prostanoids, whereas cyclooxygenase-2 (COX-2) causes the elevated production of prostanoids that occurs in sites of chronic disease and inflammation. COX-1 is a constitutive enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive and kidney functions. COX-2 is constitutively expressed in tissues such as the brain, kidney, and bone. Its expression at other sites is increased during states of chronic inflammation. Differences in binding site shape have permitted the development of selective COX-2 inhibitors (Figure 40.2). Additionally, expression of COX-2 is induced by inflammatory mediators such as TNF- $\alpha$  and IL-1 but can also be pharmacologically inhibited by glucocorticoids (Figure 40.3), which may contribute to the significant anti-inflammatory effects of these drugs.
- Lipoxygenase pathway:** Alternatively, several lipoxygenases can act on arachidonic acid to form leukotrienes (Figure 40.3). Antileukotriene drugs, such as zileuton, zafirlukast, and montelukast, are treatment options for asthma (see Chapter 41).

### C. Actions of prostaglandins

Actions of prostaglandins are mediated by their binding to a variety of distinct G-coupled protein receptors in cell membranes. Prostaglandins and their metabolites act as local signals that fine-tune the response of a specific cell type. Their functions vary depending on the tissue and the specific enzymes within the pathway that are available at that particular site. For example, the release of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) from platelets during tissue injury triggers the recruitment of new platelets for aggregation and local vasoconstriction. However,

prostacyclin ( $\text{PGI}_2$ ), produced by endothelial cells, has opposite effects, inhibiting platelet aggregation and producing vasodilation. The net effect on platelets and blood vessels depends on the balance of these two prostanoids.

#### D. Therapeutic uses of prostaglandins

Prostaglandins have a major role in modulating pain, inflammation, and fever. They control many physiological functions, such as acid secretion and mucus production in the gastrointestinal (GI) tract, uterine contractions, and renal blood flow. Prostaglandins are among the chemical mediators released in allergic and inflammatory processes. Therefore, they find use for the disorders discussed below (Figure 40.4).

#### E. Alprostadil

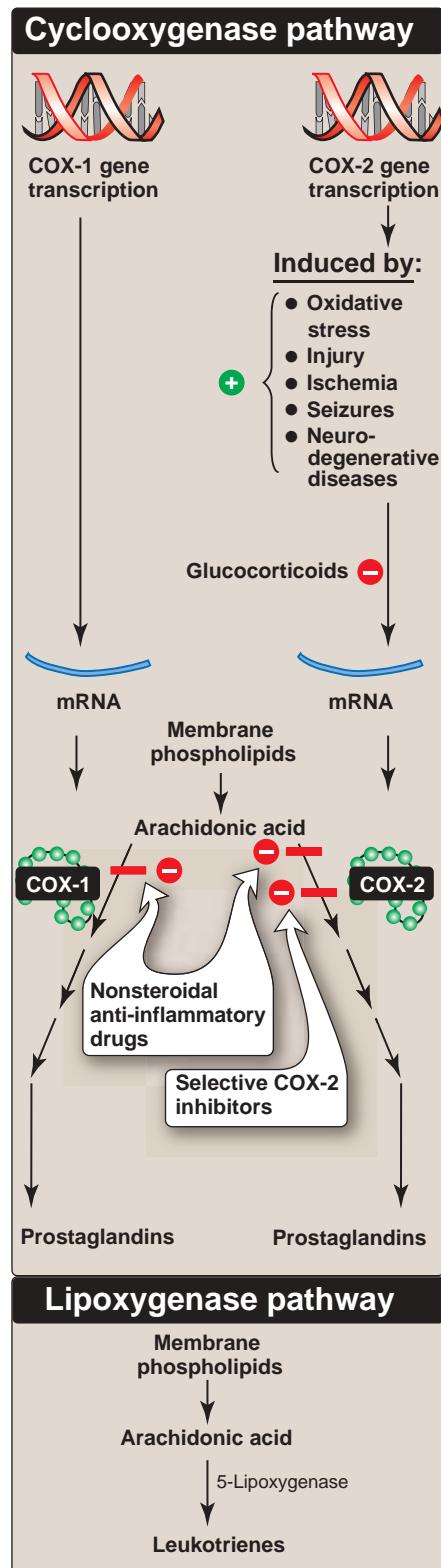
*Alprostadil* [al-PROS-ta-dil] is a  $\text{PGE}_1$  analog that is naturally produced in tissues such as seminal vesicles and cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus.  $\text{PGE}_1$  maintains the patency of the ductus arteriosus during pregnancy. The ductus closes soon after delivery to allow normal blood circulation between the lungs and the heart. In neonates with congenital heart conditions, infusion of *alprostadil* keeps the ductus open, allowing time until surgical correction is possible. *Alprostadil* is also used for erectile dysfunction (see Chapter 43).

#### F. Lubiprostone

*Lubiprostone* [loo-bee-PROS-tone] is a  $\text{PGE}_1$  derivative indicated for the treatment of chronic idiopathic constipation, opioid-induced constipation, and irritable bowel syndrome with constipation. It stimulates chloride channels in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion (see Chapter 42). Nausea and diarrhea are the most common adverse effects of *lubiprostone* (Figure 40.5). Nausea can be decreased if taken with food.

#### G. Misoprostol

*Misoprostol* [mye-soe-PROST-ole], a  $\text{PGE}_1$  analog, is used to protect the mucosal lining of the stomach during chronic NSAID treatment. *Misoprostol* interacts with prostaglandin receptors on parietal cells within the stomach, reducing gastric acid secretion. Furthermore, *misoprostol* has a GI cytoprotective effect by stimulating mucus and bicarbonate production. This combination of effects decreases the incidence of NSAID-induced gastric ulcers. [Note: There is a combination product containing the NSAID *diclofenac* and *misoprostol*.] *Misoprostol* is also used off-label in obstetric settings for labor induction, since it increases uterine contractions by interacting with prostaglandin receptors in the uterus. *Misoprostol* has the potential to induce abortion. Therefore, the drug is contraindicated during pregnancy. Its use is limited by common adverse effects including diarrhea and abdominal pain.



**Figure 40.3**

Synthesis of prostaglandins and leukotrienes. COX = cyclooxygenase.

PROSTAGLANDIN E1 ANALOGS
<i>Alprostadil</i>
<i>Lubiprostone</i>
<i>Misoprostol</i>
PROSTAGLANDIN F <sub>2α</sub> ANALOGS
<i>Bimatoprost</i>
<i>Latanoprost</i>
<i>Tafluprost</i>
<i>Travoprost</i>
PROSTACYCLIN ANALOGS
<i>Epoprostenol</i>
<i>Iloprost</i>
<i>Treprostinil</i>

**Figure 40.4**

Summary of prostaglandin and prostacyclin analogs.

## H. Prostaglandin F<sub>2α</sub> analogs

*Bimatoprost* [bih-MAT-oh-prost], *latanoprost* [la-TAN-oh-prost], *tafluprost* [TAF-loo-prost], and *travoprost* [TRAV-oh-prost] are PGF<sub>2α</sub> analogs that are indicated for the treatment of open-angle glaucoma. By binding to prostaglandin receptors, they increase uveoscleral outflow, reducing intraocular pressure. They are administered as ophthalmic solutions once a day and are as effective as *timolol* or better in reducing intraocular pressure. *Bimatoprost* increases eyelash prominence, length, and darkness and is approved for the treatment of eyelash hypotrichosis. Ocular reactions include blurred vision, iris color change (increased brown pigmentation), increased number and pigment of eyelashes, ocular irritation, and foreign body sensation.

## I. Prostacyclin (PGI<sub>2</sub>) analogs

*Epoprostenol* [ee-poe-PROST-en-ol], the pharmaceutical form of naturally occurring prostacyclin, and the synthetic analogs of prostacyclin (*ilo-prost* [EYE-loe-prost] and *treprostinil* [tre-PROS-ti-nil]) are potent pulmonary vasodilators that are used for the treatment of pulmonary arterial hypertension. These drugs mimic the effects of prostacyclin in endothelial cells, producing a significant reduction in pulmonary arterial resistance with a subsequent increase in cardiac index and oxygen delivery. These agents have short half-lives. *Epoprostenol* and *treprostinil* are administered as a continuous intravenous infusion, and *treprostinil* is administered orally or via inhalation or subcutaneous infusion. Inhaled *ilo-prost* requires frequent dosing due to the short half-life (Figure 40.6). Dizziness, headache, flushing, and fainting are the most common adverse effects (Figure 40.7). Bronchospasm and cough can also occur after inhalation of *ilo-prost*.

## III. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. The class includes derivatives of salicylic acid (*aspirin* [AS-pir-in], *diflunisal* [dye-FLOO-ni-sal], *salsalate* [SAL-sa-late]), propionic acid (*ibuprofen* [eye-bue-PROE-fen], *fenoprofen* [fen-oh-PROE-fen], *flurbiprofen* [flure-BI-proe-fen], *ketoprofen* [kee-toe-PROE-fen], *naproxen* [na-PROX-en], *oxaprozin* [ox-a-PROE-zin]), acetic acid (*diclofenac* [dye-KLOE-fen-ak], *etodolac* [ee-toe-DOE-lak], *indomethacin* [in-doe-METH-a-sin], *ketorolac* [kee-toe-ROLE-ak], *nabumetone* [na-BUE-me-tone], *sulindac* [sul-IN-dak], *tolmetin* [TOLE-met-in]), enolic acid (*meloxicam* [mel-OKS-i-kam], *piroxicam* [peer-OX-i-kam]), fenamates (*mefenamic* [me-fe-NAM-ik] acid, *meclofenamate* [me-kloe-fen-AM-ate]), and the selective COX-2 inhibitor (*celecoxib* [sel-e-KOX-ib]). They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects. [Note: Differences in safety and efficacy of the NSAIDs may be explained by relative selectivity for the COX-1 or COX-2 enzyme. Inhibition of COX-2 is thought to lead to the anti-inflammatory and analgesic actions of NSAIDs, whereas inhibition of COX-1 is responsible for prevention of cardiovascular events and most adverse events.]

**Figure 40.5**

Some adverse reactions to *lubiprostone*.

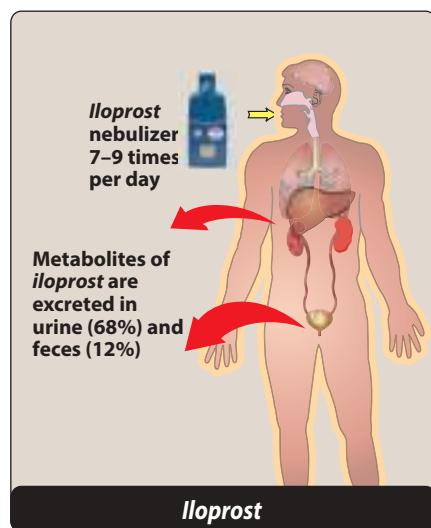
## A. Aspirin and other NSAIDs

*Aspirin* can be thought of as a traditional NSAID, but it exhibits anti-inflammatory activity only at relatively high doses that are rarely used. It is used more frequently at lower doses to prevent cardiovascular events such as stroke and myocardial infarction (MI). *Aspirin* is often differentiated from other NSAIDs since it is an irreversible inhibitor of cyclooxygenase activity.

1. **Mechanism of action:** *Aspirin* is a weak organic acid that irreversibly acetylates and, thus, inactivates cyclooxygenase (Figure 40.8). The other NSAIDs are reversible inhibitors of cyclooxygenase. The NSAIDs, including *aspirin*, have three major therapeutic actions: they reduce inflammation (anti-inflammatory), pain (analgesic effect), and fever (antipyretic effect; Figure 40.9). However, not all NSAIDs are equally effective in each of these actions.
  - a. **Anti-inflammatory actions:** Inhibition of cyclooxygenase diminishes the formation of prostaglandins and, thus, modulates aspects of inflammation mediated by prostaglandins. NSAIDs inhibit inflammation in arthritis, but they neither arrest the progression of the disease nor induce remission.
  - b. **Analgesic action:** PGE<sub>2</sub> is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE<sub>2</sub> synthesis, the sensation of pain can be decreased. As COX-2 is expressed during times of inflammation and injury, it is thought that inhibition of this enzyme is responsible for the analgesic activity of NSAIDs. No single NSAID has demonstrated superior efficacy over another, and they are generally considered to have equivalent analgesic efficacy. The NSAIDs are used mainly for the management of mild-to-moderate pain arising from musculoskeletal disorders. One exception is *ketorolac*, which can be used for more severe pain, but for only a short duration.
  - c. **Antipyretic action:** Fever occurs when the set point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE<sub>2</sub> synthesis, which is stimulated when endogenous fever-producing agents (pyrogens), such as cytokines, are released from WBCs that are activated by infection, hypersensitivity, malignancy, or inflammation. The NSAIDs lower body temperature in patients with fever by impeding PGE<sub>2</sub> synthesis and release, resetting the “thermostat” back towards normal. This rapidly lowers the body temperature of febrile patients by increasing heat dissipation through peripheral vasodilation and sweating. NSAIDs have no effect on normal body temperature.

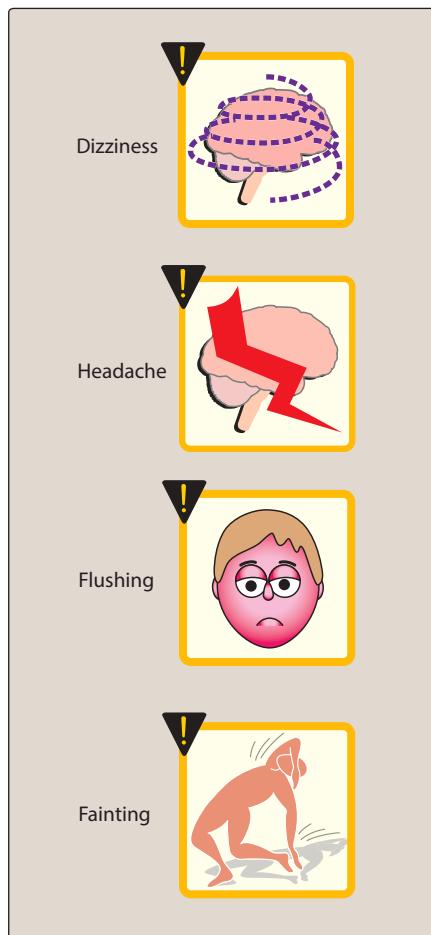
### 2. Therapeutic uses:

- a. **Anti-inflammatory and analgesic uses:** NSAIDs are used in the treatment of osteoarthritis, gout, RA, and common conditions requiring analgesia such as (for example, headache, arthralgia, myalgia, and dysmenorrhea). Combinations of opioids and NSAIDs may be effective in treating pain caused by malignancy. Furthermore, the addition of NSAIDs may lead to an opioid-sparing effect, allowing for lower doses of opioids to be utilized. The salicylates exhibit analgesic activity



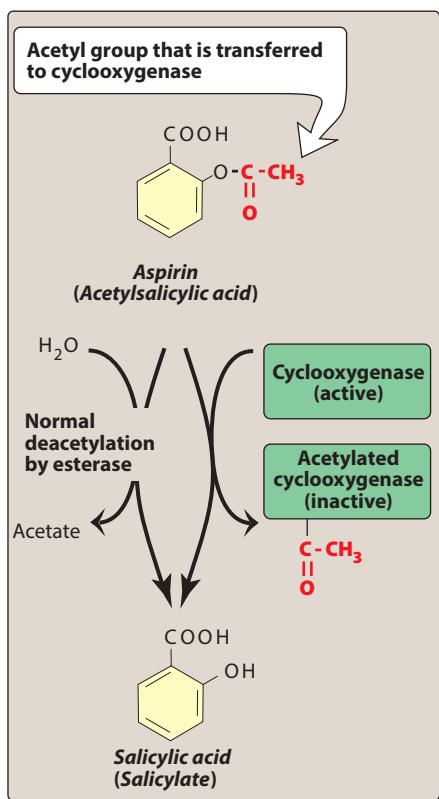
**Figure 40.6**

Administration and fate of *ilo prost*.

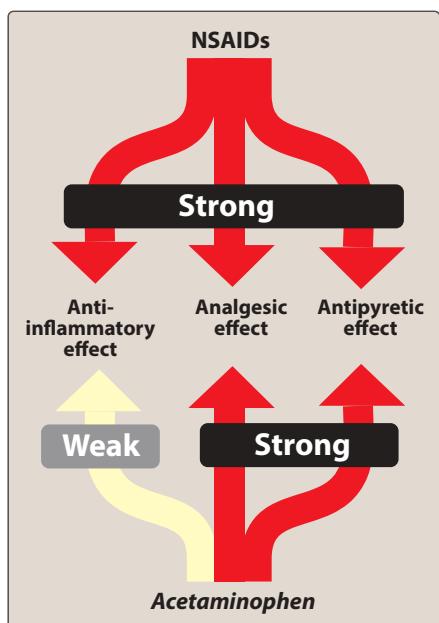


**Figure 40.7**

Some adverse reactions to *ilo prost*.

**Figure 40.8**

Metabolism of *aspirin* and acetylation of cyclooxygenase by *aspirin*.

**Figure 40.9**

Actions of nonsteroidal anti-inflammatory drugs (NSAIDs) and *paracetamol*.

at lower doses. Only at higher doses do these drugs show anti-inflammatory activity (Figure 40.10). For example, two 325-mg *aspirin* tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity.

- b. **Antipyretic uses:** *Aspirin*, *ibuprofen*, and *naproxen* may be used to treat fever. [Note: *Aspirin* should be avoided in patients less than 19 years old with viral infections, such as varicella (chickenpox) or influenza, to prevent Reye's syndrome—a syndrome that can cause fulminating hepatitis with cerebral edema, often leading to death.]

- c. **Cardiovascular applications:** *Aspirin* irreversibly inhibits COX-1-mediated production of TXA<sub>2</sub>, thereby reducing TXA<sub>2</sub>-mediated vasoconstriction and platelet aggregation and the subsequent risk of cardiovascular events (Figure 40.11). The antiplatelet effects persist for the life of the platelet. Low doses of *aspirin* (75 to 162 mg—commonly 81 mg) are used prophylactically to reduce the risk of recurrent cardiovascular events, transient ischemic attacks (TIAs), stroke, and death in patients with a history of previous MI, TIA, or stroke. Chronic use of *aspirin* allows for continued inhibition as new platelets are generated. *Aspirin* is also used acutely to reduce the risk of death in acute MI and in patients undergoing certain revascularization procedures. *Aspirin* is used at a dose of 0.3 to 0.6 mg tablets three to four times a day in rheumatic fever. It is available as 350 mg tablets with or without enteric coating (to avoid its release in stomach). It is also available as a dispersible tablet as Disprin (*aspirin* 350 mg along with calcium carbonate and citric acid) and should be taken after adding it in a cup of water and while in an effervescent stage. Injectable *aspirin* has been available as lysine acetylsalicylate.

- d. **External applications:** *Salicylic acid* is used topically to treat acne, corns, calluses, and warts. *Methyl salicylate* ("oil of wintergreen") is used externally as a cutaneous counterirritant in liniments, such as arthritis creams and sports rubs. *Diclofenac* is available in topical formulations (gel or solution) for treatment of osteoarthritis in the knees or hands. In order to avoid systemic toxicity of NSAIDs and for prolonged application in painful musculoskeletal conditions such as sports injuries, rheumatoid arthritis, osteoarthritis, joint pains, ankylosing spondylitis, sprains, and tenosynovitis, topical application is preferred for localized drug therapy. The thin-film application of drug on the localized part above the skin causes topical NSAIDs to penetrate up to dermis. Localized inflammation might increase the drug penetration and disposition, and systemic drug exposure after topical application is very low. Counterirritants are also used along with the NSAIDs in drug formulations to give more localized relief. A higher degree of interindividual variability has been seen upon with the localized drug response. Drugs such as *diclofenac* (1%), *nimesulide* (1%), *piroxicam* (0.5%), and *ibuprofen* (10%) are used in the form of ointment or gel for topical application. In addition, ocular formulations of *ketorolac* and *flurbiprofen* are available for the management of seasonal allergic conjunctivitis and inflammation and pain related to ocular surgery.

e. **Migraine abortive and prophylactic uses:** NSAIDs are used as abortive therapy in case of mild-to-moderate migraine (that is, occasional throbbing headaches and no major impairment of functioning). The choice of acute migraine treatments depends on rapidity of onset, headache severity, associated symptoms (for example, nausea/vomiting), and patient preference. Acute treatment is most effective when given within 15 minutes of pain onset and when pain is mild. Rule out rebound syndrome prior to initiating therapy. If rebound is present, prevention and acute migraine medications may not be effective. If a patient does not respond to one to two adequate doses of a given NSAID during a migraine episode, or in patients with moderate-to-severe headache, with nausea or vomiting or rapid progression to severe headache, add other drugs, tryptans or parenteral NSAIDs (Diclofenac). See also Chapter 39.

### 3. Pharmacokinetics:

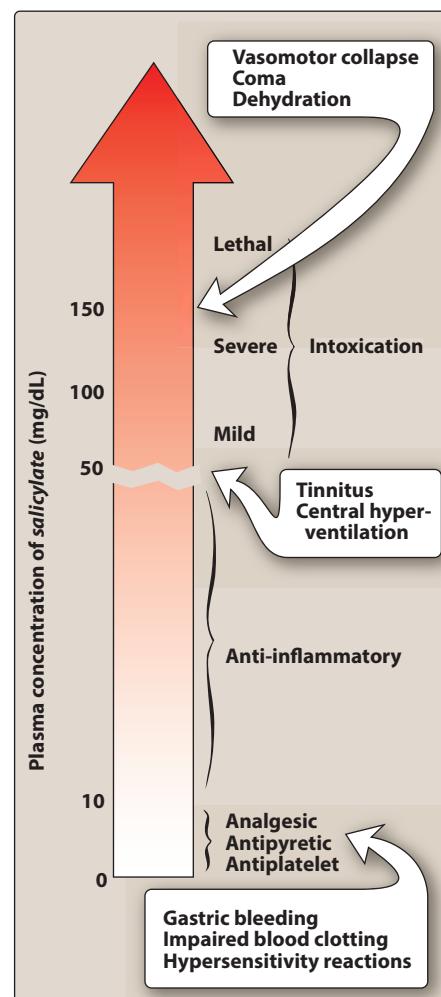
a. **Aspirin:** After oral administration, *aspirin* is rapidly deacetylated by esterases in the body to produce salicylate. Unionized salicylates are passively absorbed mainly from the upper small intestine. Salicylates (except for *diflunisal*) cross both the blood–brain barrier and the placenta and are absorbed through intact skin (especially *methyl salicylate*). Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in first-order elimination and a serum half-life of 3.5 hours. At anti-inflammatory dosages of *aspirin* (more than 4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, leading to a half-life of 15 hours or more (Figure 40.12). Salicylate is secreted into the urine and can affect uric acid excretion. Therefore, *aspirin* should be avoided in gout, if possible, or in patients taking *probencid*.

b. **Other NSAIDs:** Most NSAIDs are well absorbed after oral administration and circulate highly bound to plasma proteins. The majority are metabolized by the liver, mostly to inactivate metabolites. Few (for example, *nabumetone* and *sulindac*) have active metabolites. Excretion of active drug and metabolites is primarily via the urine.

### 4. Adverse events:

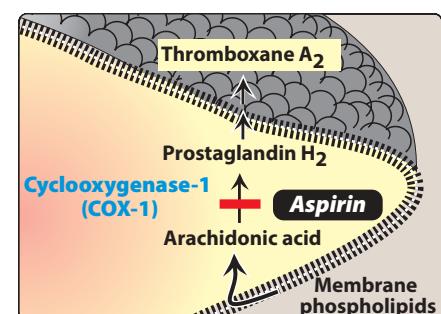
Because of the adverse event profile, it is preferable to use NSAIDs at the lowest effective dose for the shortest duration possible.

a. **Gastrointestinal:** These are the most common adverse effects of NSAIDs, ranging from dyspepsia to bleeding. Normally, production of prostacyclin ( $\text{PGI}_2$ ) inhibits gastric acid secretion, and  $\text{PGE}_2$  and  $\text{PGF}_{2\alpha}$  stimulate synthesis of protective mucus in both the stomach and the small intestine. Agents that inhibit COX-1 reduce beneficial levels of these prostaglandins, resulting in increased gastric acid secretion, diminished mucus protection, and increased risk for GI bleeding and ulceration. Agents with a higher relative selectivity for COX-1 may have a higher risk for GI events compared to those with a lower relative selectivity for COX-1 (that is, higher COX-2 selectivity). NSAIDs should be taken with food or fluids to diminish GI upset. If NSAIDs are used in patients at high risk for GI events, proton-pump inhibitors or *misoprostol* should be used concomitantly to prevent NSAID-induced ulcers (see Chapter 42).



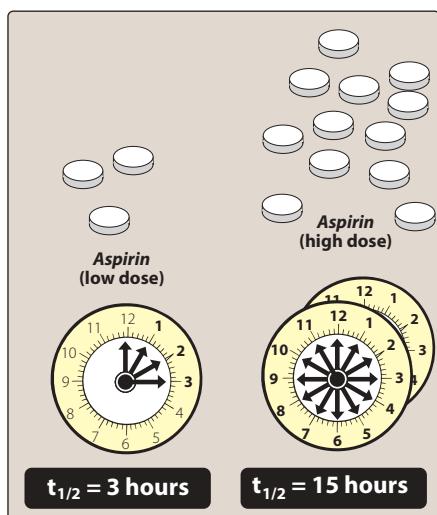
**Figure 40.10**

Dose-dependent effects of salicylate.

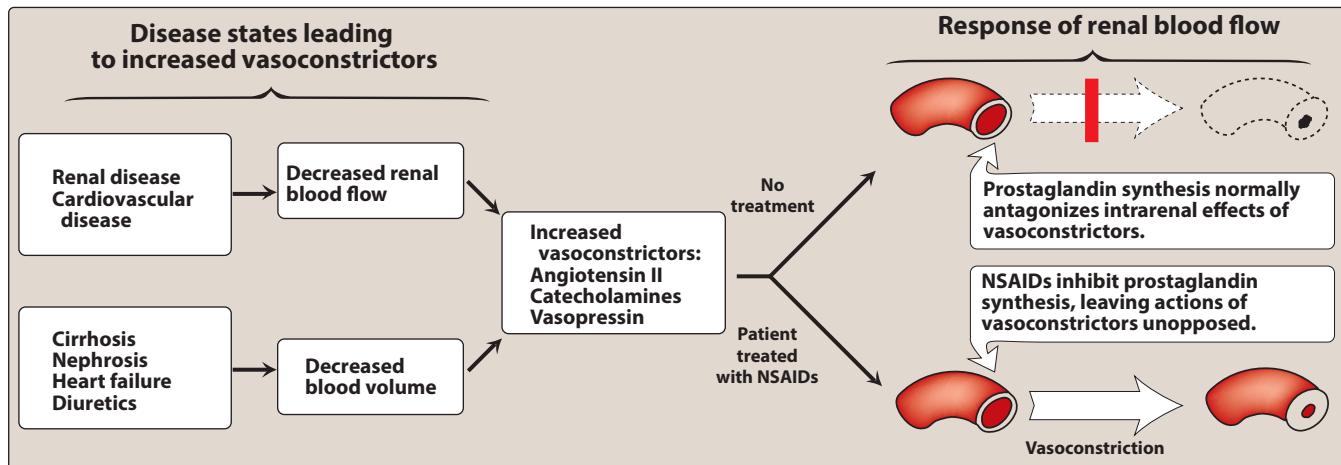


**Figure 40.11**

Aspirin irreversibly inhibits platelet cyclooxygenase-1.

**Figure 40.12**Effect of dose on the half-life of *aspirin*.

- b. Increased risk of bleeding (antiplatelet effect):** As described above, *aspirin* inhibits COX-1 mediated formation of TXA<sub>2</sub> and reduces platelet aggregation for the lifetime of the platelet (3 to 7 days). Platelet aggregation is the first step in thrombus formation, and the antiplatelet effect of *aspirin* results in a prolonged bleeding time. For this reason, *aspirin* is often withheld for at least 1 week prior to surgery. NSAIDs other than *aspirin* are not utilized for their antiplatelet effect but can still prolong bleeding time, especially when combined with anticoagulants. Concomitant use of NSAIDs and *aspirin* can prevent *aspirin* from binding to cyclooxygenase. Patients who take *aspirin* for cardioprotection should avoid concomitant NSAID use if possible or take *aspirin* at least 30 minutes prior to the NSAID.
- c. Renal effects:** NSAIDs prevent the synthesis of PGE<sub>2</sub> and PG<sub>I<sub>2</sub></sub>, prostaglandins that are responsible for maintaining renal blood flow (Figure 40.13). Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema. Patients with a history of heart failure or kidney disease are at particularly high risk. These effects can also mitigate the beneficial effects of antihypertensive medications. In susceptible patients, NSAIDs have led to acute kidney injury.
- d. Cardiac effects:** Agents such as *aspirin*, with a very high degree of COX-1 selectivity at low doses, have a cardiovascular protective effect thought to be due to a reduction in the production of TXA<sub>2</sub>. Agents with higher relative COX-2 selectivity have been associated with an increased risk for cardiovascular events, possibly by decreasing PG<sub>I<sub>2</sub></sub> production mediated by COX-2. An increased risk for cardiovascular events, including MI and stroke, has been associated with all NSAIDs except *aspirin*. All NSAIDs carry a boxed warning regarding the increased risk for cardiovascular events. Use of NSAIDs, other than *aspirin*, is discouraged in patients with established cardiovascular disease. For patients with cardiovascular disease in whom NSAID treatment cannot be avoided, *naproxen* may be the least likely to be harmful.

**Figure 40.13**

Renal effect of NSAIDs inhibition of prostaglandin synthesis. NSAIDs = nonsteroidal anti-inflammatory drugs.

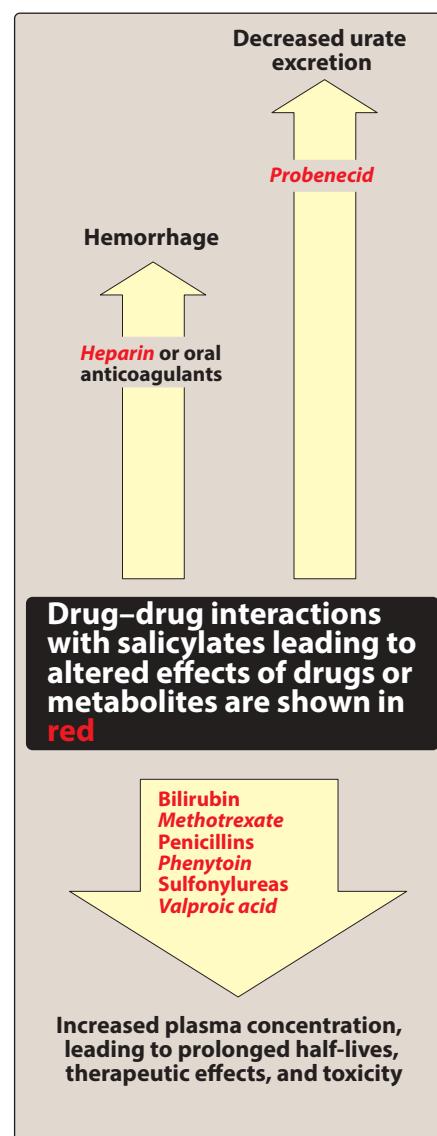
- e. **Other adverse effects:** NSAIDs are inhibitors of cyclooxygenases and, therefore, inhibit the synthesis of prostaglandins but not of leukotrienes. For this reason, NSAIDs should be used with caution in patients with asthma, as inhibition of prostaglandin synthesis can cause a shift toward leukotriene production and increase the risk of asthma exacerbations. Central nervous system (CNS) adverse effects, such as headache, tinnitus, and dizziness, may occur. Approximately 15% of patients taking *aspirin* experience hypersensitivity reactions. Symptoms of true allergy include urticaria, bronchoconstriction, and angioedema. Patients with severe hypersensitivity to *aspirin* should avoid using NSAIDs. *Aspirin* is both an NSAID and uricosuric at high doses.
- f. **Drug interactions:** Salicylate is roughly 80% to 90% plasma protein bound (albumin) and can be displaced from protein-binding sites, resulting in increased concentration of free salicylate. Alternatively, *aspirin* can displace other highly protein-bound drugs, such as *warfarin*, *phenytoin*, or *valproic acid*, resulting in higher free concentrations of these agents (Figure 40.14).
- g. **Toxicity:** Large doses of *aspirin* cause hypoglycemia and glycosuria along with depletion of glycogen in liver and muscles. Mild salicylate toxicity is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears). When large doses of salicylate are administered, severe salicylate intoxication may result (Figure 40.10). Restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure may occur. Children are particularly prone to salicylate intoxication; ingestion of as little as 10 g of *aspirin* can be fatal.
- h. **Pregnancy:** NSAIDs should be used in pregnancy only if benefits outweigh risks to the developing fetus. [Note: *Paracetamol* is preferred if analgesic or antipyretic effects are needed during pregnancy.] In the third trimester, NSAIDs should generally be avoided due to the risk of premature closure of the ductus arteriosus.

## B. Diflunisal

*Diflunisal*, a fluorinated derivative of salicylic acid which is more potent than that of *aspirin* in anti-inflammatory effect, however, lacks antipyretic effect due to poor CNS penetration. *Diflunisal* is used in cases of pain due to arthritis and is used at an oral dose of 1 g two to three times a day followed by 0.5 g twice a day. *Diflunisal* has low propensity to cause GI and antiplatelet side effects.

## C. Propionic acid derivatives

The compounds that belong to this group, shown in Figure 40.1, share similar pharmacodynamic properties with a slight variation in pharmacokinetics. They are nonselective cyclooxygenase inhibitors. Analgesic, anti-inflammatory, and antipyretic properties are somewhat equivalent or inferior to the analgesic dose of *aspirin*. However, they are



**Figure 40.14**

Drugs interacting with salicylates.

better tolerated than *aspirin*; therefore, they are used for pain caused by different types of arthritis. They also have different degrees of effect on platelets as seen with *aspirin*. Amongst all, *naproxen* is found to have higher analgesic efficacy.

#### D. Ibuprofen

*Ibuprofen* is a commonly prescribed analgesic having weak anti-inflammatory activity. It is used at a dose of 400 to 600 mg three times a day. It has a very weak antiplatelet activity and shares common side effects of other NSAIDS. *Fenoprofen* and *oxaprozin* are similar to *ibuprofen* in their pharmacology.

#### E. Naproxen

Apart from analgesic property, *naproxen* also shows good anti-inflammatory property. Therefore, it is used for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendonitis, dysmenorrhea, bursitis, and migraine. The plasma half-life of *naproxen* is 14 hours in young and it doubles in elderly patients due to age-related decrease in renal function. It is used at a dose of 250 mg two to three times a day.

#### F. Ketoprofen

Apart from being analgesic, *ketoprofen* has also been reported to stabilize lysosomal membranes and antagonize the action of bradykinin. *Ketoprofen* is used at a dose of 50–100 mg two to three times a day.

#### G. Flurbiprofen

*Flurbiprofen* is a fluorinated propionic acid derivative known to have similar activity and toxicity profile like *ibuprofen*. It is also used as anti-inflammatory for topical application in ophthalmic conditions. It is used as 0.03% eye drops instilled four times a day.

#### H. Indomethacin

*Indomethacin* is approximately 20 times more potent nonselective inhibitor of COX pathway compared to *aspirin*. It is an acetic acid derivative. It inhibits infiltration of polymorphonuclear leukocytes and suppresses the biosynthesis of mucopolysaccharides. It is a potent anti-inflammatory with the analgesic and antipyretic properties equivalent to *aspirin*. It also causes vasoconstriction which might be independent of its effect on COX pathway. It is used for the closure of persistent patent ductus arteriosus in premature infants weighing 500 to 1750 g, and it can be administered by the intravenous route (three doses of 0.1 to 0.2 mg/kg administered 12 hourly). Due to a higher incidence of adverse effects, *indomethacin* is not used as a first-line drug for many inflammatory conditions such as arthritis of various origins. It is only used in refractory cases such as Bartter's syndrome due to enhanced prostaglandin synthesis. *Sulindac* is a prodrug and a congener of *indomethacin*. Its active sulfide metabolite is more than 500 times potent COX inhibitor compared to *sulindac* but less potent

than *indomethacin*. No distinct advantage has been shown as compared to *indomethacin* except a lesser extent of GI-related side effects.

#### I. Kетаролак

Among NSAIDs, *kетаролак* is an aryl acetic acid derivative with a potent analgesic having comparatively a lesser anti-inflammatory property. In the control of postoperative pain, it is equivalent to that of *morpheine*. Its use is limited to acute pain control for shorter periods. It is absorbed orally as well as administered through intramuscular or intravenous routes. Adverse effects include somnolence, dizziness, headache, GI-related side effects, and pain at the site of injection. A transient rise in liver enzymes has also been reported. *Kетаролак* is metabolized in the liver and excreted in urine. It is used at a dose of 10 to 20 mg four times a day (maximum of 90 mg/day).

#### J. Этодолак

*Etodolac* is an acetic acid derivative. It is another agent in this group that has lesser GI-related side effects due to more selectivity toward COX-2. It is used at a dose of 200 to 400 mg three times a day for postoperative analgesia. It is also used as a uricosuric for the treatment of gout and as analgesic for the treatment of different types of arthritis.

#### K. Набуметоне

*Nabumetone* is an acetic acid derivative. It is a prodrug and upon conversion, it shows potent nonselective COX inhibition. It has been reported to have low GI-related side effects with good analgesic, anti-inflammatory, and antipyretic activity. It is used for the treatment of different types of arthritis and soft-tissue injuries. It is well absorbed orally and converted to active metabolites in the liver, and the inactivated metabolites are excreted through bile. It shows a longer plasma half-life, thereby enabling once-a-day therapy. It is used in the dose of 500 mg tablets given once a day.

#### L. Фенаматес

*Fenamates* is an acetic acid derivative. Fenamic acid is a molecule which, especially in its ester form, *fenamate*, serves as a parent structure for several NSAIDs, including *mefenamic acid*, *tolfenamic acid*, *flufenamic acid*, and *meclofenamic acid*. These drugs are commonly referred to as “anthranilic acid derivatives” or “fenamates” because fenamic acid is a derivative of *anthranilic acid*.

#### M. Мифенаминовая кислота

*Mefenamic acid* is an acetic acid derivative. Its action is similar to other NSAIDs with analgesic, antipyretic, and weak anti-inflammatory activities. It is used for short-term pain relief in conditions such as dysmenorrhea and soft-tissue injuries. It is not used for arthritis. GI side effects and diarrhea are common. Transient elevation of hepatic enzymes is seen. It rarely causes autoimmune hemolytic anemia, which is potentially serious in nature. *Mephenamic acid* is used at a dose of 250 to 500 mg three times a day.

## N. Piroxicam

*Piroxicam* is an oxicam. It is a potent anti-inflammatory with good analgesic and antipyretic compounds. It is a nonselective and reversible COX inhibitor known to have longer activity. It is completely absorbed, metabolized, and eliminated through kidney. Due to its longer half-life after slower onset of action, it reaches a good steady-state level enabling single-dose administration per day. It is used for rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. However, due to serious skin reactions besides GI-related side effects, it is not considered a first-line therapy for arthritis.

*Piroxicam* is used at a dose of 10 to 20 mg once a day. *Tenoxicam* is used at a dose of 20 mg/day.

## O. Apazone (azapropazone)

Apazone is an oxicam. Apart from anti-inflammatory, analgesic, and antipyretic activity, it is also known to have potent uricosuric activity. It is used for different types of arthritis, ankylosing spondylitis, and gout. It is reserved when other safer NSAIDs fail to achieve required activity. It is used at a dose of 600 mg three times a day. Its side effects are similar to those of nonselective COX inhibitors. GI-related side effects, headache, and vertigo have been reported.

## P. Diclofenac

Although *diclofenac* is a commonly used NSAID, it is classified as acetic acid derivative due to its preferential activity on COX-2 (similar to *celecoxib*). It is a potent compound, having good analgesic, antipyretic, and anti-inflammatory activities, as compared to *naproxen*, *indomethacin*, etc. Upon oral administration, it is absorbed well but undergoes extensive first-pass metabolism. It accumulates in synovial fluid; therefore, its pharmacological activity is more than its plasma half-life and correlation. It is metabolized in liver and excreted through urine and bile. It is not recommended for children, nursing mothers, and pregnant women. GI-related adverse effects are similar to those of *celecoxib*; however, transient elevation of liver enzymes is observed. Like other NSAIDs, it increases the risk for cardiovascular events, including MI and stroke. It is used at a dose of 50 mg three times a day or 75 mg twice daily. It is also administered as 75 mg intramuscular injection. Its ethyl ammonium salt is used for making ointments for topical applications (used as 1% topical gel or ointment). It is also used as 0.1% eye drop for ocular inflammatory conditions.

## Q. Aceclofenac

*Aceclofenac* is a preferential COX-2 inhibitor. It is another phenylacetic acid derivative and has properties similar to *diclofenac*. It shows higher COX-2 selectivity compared to *diclofenac*. NSAIDs may impair the ability of the chondrocyte to repair its damaged extracellular matrix in osteoarthritic cartilage; however, *aceclofenac* is reported to increase the synthesis of proteoglycans and hyaluronic

acid in a dose-dependent manner. It is used at a dose of 100 mg twice daily.

#### R. Etodolac

*Etodolac* is a preferential COX-2 inhibitor. It is similar to *diclofenac* and *aceclofenac* having higher selectivity for COX-2 and is well absorbed orally. Its side effects are similar to those of other agents. It is used at a dose of 200 to 400 mg twice daily.

#### S. Meloxicam

*Meloxicam* is a preferential COX-2 inhibitor. Although it belongs to the category of oxicams, it shows preferentiality to COX-2 as compared to piroxicam. Its pharmacological activities are similar to piroxicam but its gastric site effects are much lesser. It is used at a dose of 7.5 to 15 mg once daily.

#### T. Nimesulide

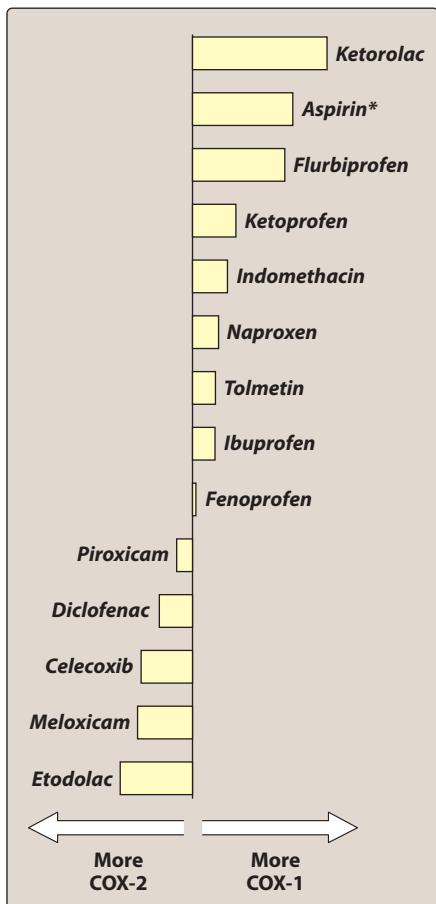
*Nimesulide* is a preferential COX-2 inhibitor. It is an arylsulfonanilide derivative lacking an acidic group like most of the NSAIDs. It was developed in Europe and is used in most of the countries. Apart from preferential COX inhibition, it is reported to reduce the generation of reactive oxygen species in neutrophils, decrease in cytokine like TNF- $\alpha$  release, and inhibit PAF synthesis and matrix metalloproteinase activity in cartilage by the activation of glucocorticoid receptors. Its anti-inflammatory, analgesic, and antipyretic activities are comparable with other NSAIDs. People who have *aspirin*-induced allergy are reported to tolerate *nimesulide*. *Nimesulide* has rapid and complete absorption after oral administration. It is rapidly distributed into the synovial fluid and exists for a longer period despite the fall in plasma levels. Its adverse effect profile is similar to that of other COX-2 inhibitors. It is metabolized in liver and excreted through kidney. Hepatotoxicity of *nimesulide* has been considered similar to that of other NSAIDs. However, its use in children has been banned in many countries including India. It is used at a dose of 100 mg twice daily for arthritis, cancer, thrombophlebitis, bursitis, dysmenorrhea, renal colic, postoperative conditions, etc.

#### U. Metamizol

*Metamizol* is a pyrazoline derivative. It is an aminopyridine derivative that has analgesic and antipyretic properties but weak anti-inflammatory property. It has been reported to cause agranulocytosis; therefore, it is banned in USA. However, it is used in India and other European countries without any serious toxicities. Mild GI irritation and GI-related side effects have been reported. It is used at a dose of 0.5 to 1.5 g orally or by intramuscular or intravenous routes.

#### V. Propiphenazone

*Propiphenazone* is a pyrazoline derivative. It is similar to the pyrazoline derivative *metamizole*, which is used in India. It is extensively used as



**Figure 40.15**

Relative selectivity of some commonly used NSAIDs. Data shown as the logarithm of their ratio of IC<sub>80</sub> (drug concentration to achieve 80% inhibition of cyclooxygenase).

\*Aspirin graphed for IC<sub>50</sub> value due to it showing significantly more COX-1 selectivity at lower doses and graph using higher concentrations does not accurately reflect the usage or selectivity of aspirin. Adapted from T. D. Warner, F. Giuliano, I. Vojnovic, et al. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. Proc. Natl. Acad. Sci. U. S. A. 96: 7563 (1999).

an over-the-counter product for headache and fever during common cold and other mild pain, either alone or in combination with other antipyretics such as *paracetamol*. It is used at the dose of 150 to 600 mg three times a day along with *paracetamol* or with *caffeine*.

## W. Celecoxib

*Celecoxib* [SEL-e-KOX-ib], a selective COX-2 inhibitor, is significantly more selective for inhibition of COX-2 than COX-1 (Figure 40.15). Unlike the inhibition of COX-1 by *aspirin* (which is irreversible), the inhibition of COX-2 is reversible.

1. **Therapeutic uses:** *Celecoxib* is approved for the treatment of RA, osteoarthritis, and acute pain. *Celecoxib* has similar efficacy to NSAIDs in the treatment of pain.
2. **Pharmacokinetics:** *Celecoxib* is readily absorbed after oral administration. It is extensively metabolized in the liver by cytochrome P450 (CYP2C9) and the metabolites are excreted in feces and urine. The half-life is about 11 hours, and the drug may be dosed once or twice daily. The dosage should be reduced in those with moderate hepatic impairment, and *celecoxib* should be avoided in patients with severe hepatic or renal disease.
3. **Adverse effects:** Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects. *Celecoxib* is associated with less GI bleeding and dyspepsia than other NSAIDs. However, this benefit is lost when *aspirin* is added to *celecoxib* therapy. Patients who are at a high risk of ulcers and require *aspirin* for cardiovascular prevention should avoid the use of *celecoxib*. Like other NSAIDs, *celecoxib* has a similar risk for cardiovascular events. Patients who have had anaphylactoid reactions to *aspirin* or nonselective NSAIDs may be at risk for similar effects with *celecoxib*. Inhibitors of CYP2C9, such as *fluconazole*, may increase serum levels of *celecoxib*.

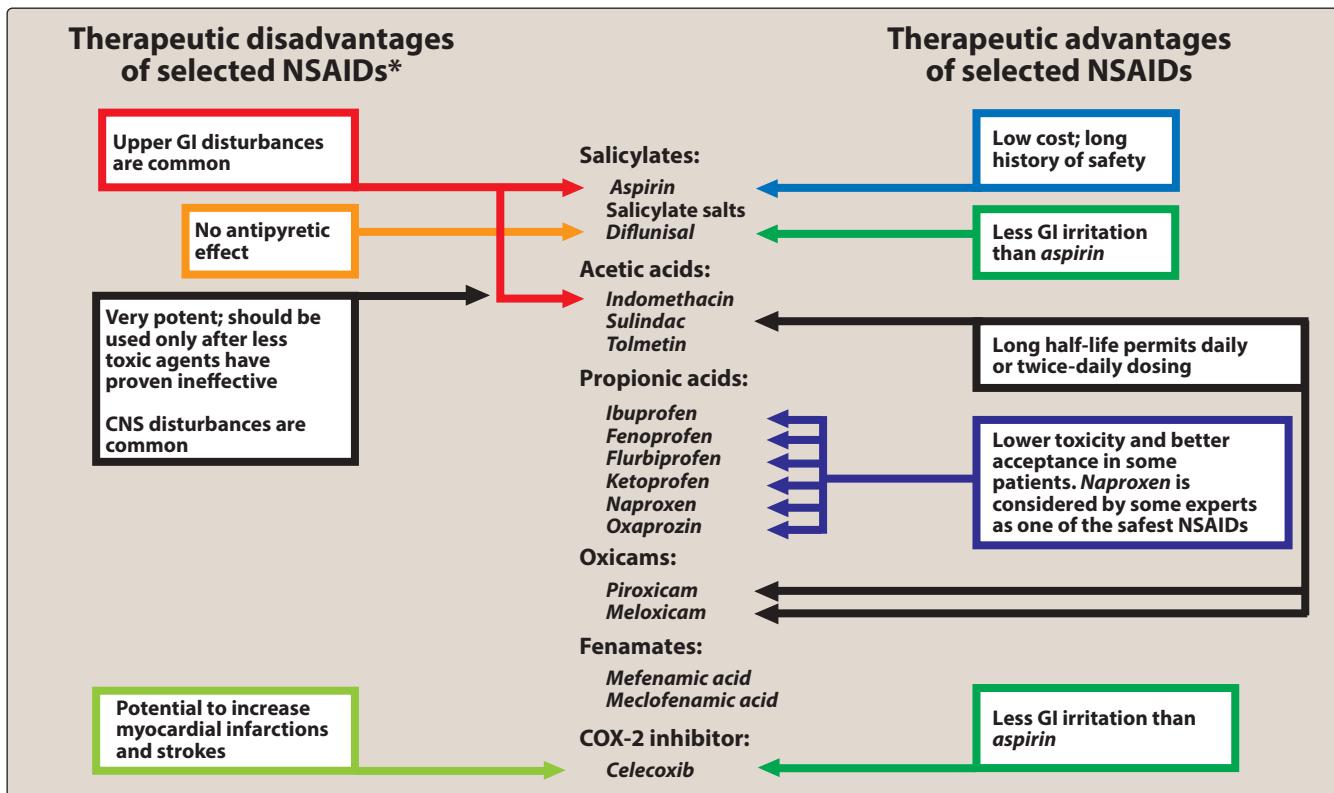
Figure 40.16 summarizes some of the therapeutic advantages and disadvantages of members of the NSAID family.

## X. Etoricoxib

*Etoricoxib* is another highly selective COX-2 inhibitor suitable for once-a-day therapy for various arthritis conditions, ankylosing spondylitis, surgical pain, etc. As compared to others in this group, *etoricoxib* shows very low GI-related side effects. However, it has been reported to have the risk of cardiovascular events and stroke. It is used at an oral dose of 60 to 120 mg once a day.

## Y. Parecoxib and valdecoxib

*Parecoxib* is one of the selective COX-2 inhibitors. *Valdecoxib* has been modified suitably as a prodrug which is suitable for injection after demethylation. Therefore, it can be used for postoperative conditions by intravenous or intramuscular routes. *Valdecoxib* has been reported to cause severe skin reactions and *parecoxib* injection shares such risk due to its active metabolite conversion into *valdecoxib*. It is used at a dose of 40 mg two to three times a day either orally or as intramuscular/intravenous injections.

**Figure 40.16**

Summary of nonsteroidal anti-inflammatory agents (NSAIDs). CNS = central nervous system; COX-2 = cyclooxygenase-2; GI = gastrointestinal. \*As a group, with the exception of aspirin, these drugs may have the potential to increase risk of myocardial infarction and stroke.

## IV. PARACETAMOL (ACETAMINOPHEN)

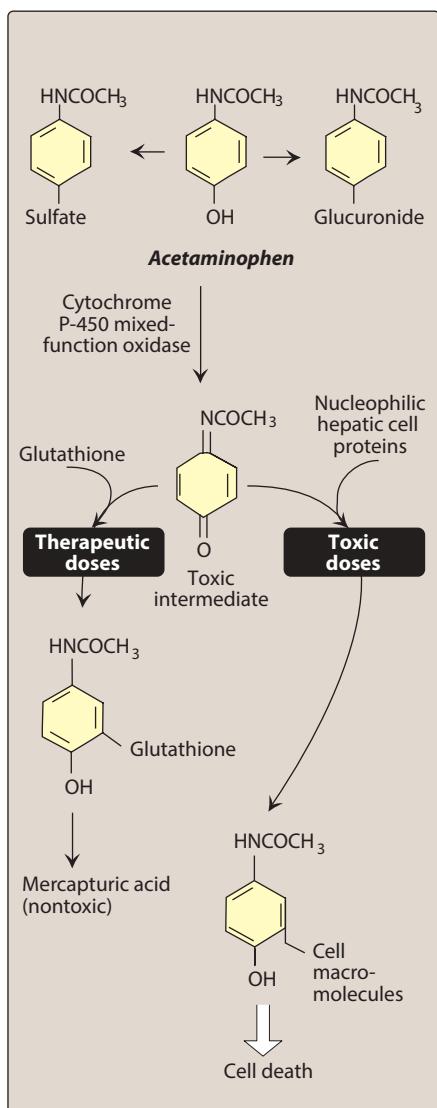
*Paracetamol* [Para-SEET-a-Mol] (*N*-acetyl-*p*-aminophenol or APAP) inhibits prostaglandin synthesis in the CNS, leading to antipyretic and analgesic effects. *Paracetamol* has less effect on cyclooxygenase in peripheral tissues (due to peripheral inactivation), which accounts for its weak anti-inflammatory activity. *Paracetamol* does not affect platelet function or increase bleeding time. It is not considered an NSAID.

### A. Therapeutic uses

*Paracetamol* is used for the treatment of fever and relief of pain. It is useful in patients with gastric complaints/risks with NSAIDs and those who do not require the anti-inflammatory action of NSAIDs. *Paracetamol* is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with *aspirin*).

### B. Pharmacokinetics

*Paracetamol* is rapidly absorbed from the GI tract and undergoes significant first-pass metabolism. It is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of *paracetamol* is hydroxylated to form *N*-acetyl-*p*-benzoquinoneimine, or NAPQI, a highly



**Figure 40.17**

Metabolism of *paracetamol*.

reactive metabolite that can react with sulphydryl groups and cause liver damage. At normal doses of *paracetamol*, NAPQI reacts with the sulphydryl group of glutathione produced by the liver, forming a nontoxic substance (Figure 40.17). *Paracetamol* and its metabolites are excreted in urine. The drug is also available in intravenous and rectal formulations.

### C. Adverse effects

At normal therapeutic doses, *paracetamol* has few significant adverse effects. With large doses of *paracetamol*, the available glutathione in the liver becomes depleted, and NAPQI reacts with the sulphydryl groups of hepatic proteins (Figure 40.17). Hepatic necrosis, a serious and potentially life-threatening condition, can result. Patients with hepatic disease, viral hepatitis, or a history of alcoholism are at a higher risk of *paracetamol*-induced hepatotoxicity. [Note: *N-acetylcysteine* is an antidote in cases of overdose (see Chapter 46).] *Paracetamol* should be avoided in patients with severe hepatic impairment. It is used at a dose of 325 to 650 mg three to five times a day and the total adult dose of *paracetamol* per day is restricted to 2600 mg.

## V. TRADITIONAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDs)

Traditional DMARDs (*methotrexate*, *hydroxychloroquine*, *leflunomide*, or *sulfasalazine*) are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues. Following diagnosis of RA, these agents should be started as soon as possible to delay progression of the disease. Monotherapy may be initiated with any of the traditional DMARDs, although *methotrexate* is generally preferred. For patients with inadequate response to monotherapy, a combination of traditional DMARDs, or use of a TNF inhibitor or non-TNF biologic agent may be needed. NSAIDs or glucocorticoids can also be used for their anti-inflammatory actions.

### A. Methotrexate

*Methotrexate* [meth-oh-TREX-ate] is a folic acid antagonist that inhibits cytokine production and purine nucleotide biosynthesis, leading to immunosuppressive and anti-inflammatory effects. It has become a mainstay of treatment in patients with rheumatoid arthritis. Response to *methotrexate* usually occurs within 3 to 6 weeks of starting treatment. Other traditional DMARDs, TNF inhibitors, or non-TNF biologic agents can be added to *methotrexate* if there is inadequate response to monotherapy with this agent. Doses of *methotrexate* required for RA treatment are much lower than those needed in cancer chemotherapy and generally administered once weekly, thereby minimizing adverse effects. Common adverse effects of *methotrexate* when used for RA are mucosal ulceration and nausea. Cytopenias (particularly leukopenia), cirrhosis of the liver, and an acute pneumonia-like syndrome may occur with chronic administration. [Note: Supplementation with *folic acid* may improve tolerability of *methotrexate* and reduce gastrointestinal and hepatic adverse effects.] Periodic liver function tests, complete blood counts, and monitoring for signs of infection are recommended. *Methotrexate* is contraindicated in pregnancy.

## B. Hydroxychloroquine

*Hydroxychloroquine* [hye-drox-ee-KLOR-oh-kwin] is used for early, mild RA and may be combined with *methotrexate*. Its mechanism of action in autoimmune disorders is unknown, and onset of effects takes 6 weeks to 6 months. *Hydroxychloroquine* has less adverse effects on the liver and immune system than other DMARDs. However, it may cause ocular toxicity, including irreversible retinal damage and corneal deposits, CNS disturbances, GI upset, and skin discoloration and eruptions.

## C. Leflunomide

*Leflunomide* [le-FLOO-no-mide] is an immunomodulatory agent that preferentially causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH). After biotransformation, *leflunomide* becomes a reversible inhibitor of DHODH, an enzyme necessary for pyrimidine synthesis (Figure 40.18). *Leflunomide* may be used as monotherapy in patients who have intolerance or contraindications to use of *methotrexate* in RA, or it may be used in combination with *methotrexate* for patients with suboptimal response to *methotrexate* alone. Common adverse effects include headache, diarrhea, and nausea. Other effects are weight loss, allergic reactions, including a flu-like syndrome, skin rash, alopecia, and hypokalemia. The drug is not recommended in patients with liver disease as it can be hepatotoxic. *Leflunomide* is contraindicated in pregnancy. Monitoring parameters include signs of infection, complete blood count, electrolytes, and liver enzymes.

## D. Sulfasalazine

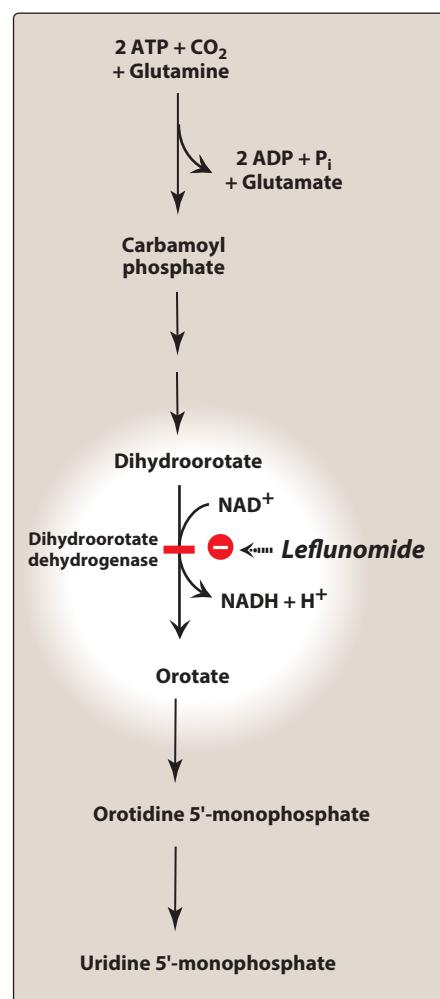
*Sulfasalazine* [sul-fa-SAH-la-zeen] has recommendations for use similar to *leflunomide* in the treatment of RA. Its mechanism of action in treating RA is unclear. The onset of activity is 1 to 3 months, and it is associated with GI adverse effects (nausea, vomiting, anorexia) and leukopenia.

## E. Glucocorticoids

Glucocorticoids (see Chapter 26) are potent anti-inflammatory drugs that are commonly used in patients with RA to provide symptomatic relief and bridge the time until other DMARDs become effective. Glucocorticoids should always be used at the lowest dose and for the shortest duration possible to avoid adverse effects associated with long-term use.

## VI. BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

IL-1 and TNF- $\alpha$  are proinflammatory cytokines involved in the pathogenesis of RA. When secreted by synovial macrophages, IL-1 and TNF- $\alpha$  stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis. The TNF- $\alpha$  inhibitors (*adalimumab*, *certolizumab*, *etanercept*,



**Figure 40.18**

Site of action of *leflunomide*.

*golimumab*, and *infliximab*) are biologic DMARDs which have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function. Clinical response can be seen within 2 weeks of therapy. TNF- $\alpha$  inhibitors are usually employed in RA after a patient has an inadequate response to traditional DMARDs. These agents may be used alone or in combination with traditional DMARDs. If a patient has failed monotherapy with one TNF- $\alpha$  inhibitor, a traditional DMARD may be added, or therapy with a non-TNF biologic agent or a different TNF- $\alpha$  inhibitor may be tried. TNF- $\alpha$  inhibitors should be used cautiously in those with heart failure, as they can cause and/or worsen pre-existing heart failure. An increased risk of lymphoma and other cancers has been observed with the use of TNF- $\alpha$  inhibitors.

Biologic DMARDs include the TNF- $\alpha$  inhibitors as well as the non-TNF biologic agents (*abatacept*, *rituximab*, *tocilizumab*). Like TNF- $\alpha$  inhibitors, non-TNF biologics are generally used in RA after a patient has an inadequate response to traditional DMARDs, and they may be used alone or in combination with traditional DMARDs. If a patient has failed monotherapy with one non-TNF biologic, a trial of another non-TNF biologic with or without *methotrexate* is warranted. Patients receiving biologic DMARDs are at increased risk for infections, such as tuberculosis, fungal opportunistic infections, and sepsis. [Note: TNF- $\alpha$  inhibitors and non-TNF biologic agents should not be used together due to the risk of severe infections.] Reactivation of hepatitis B may occur with use of these agents. Live vaccinations should not be administered to patients taking any of the biologic DMARDs. Characteristics of the TNF- $\alpha$  inhibitors and non-TNF biologic therapies for the treatment of RA are outlined below. [Note: TNF- $\alpha$  inhibitors find use in a number of disorders, such as ulcerative colitis and Crohn's disease (see Chapter 42), psoriasis, and ankylosing spondylitis.]

### A. Adalimumab

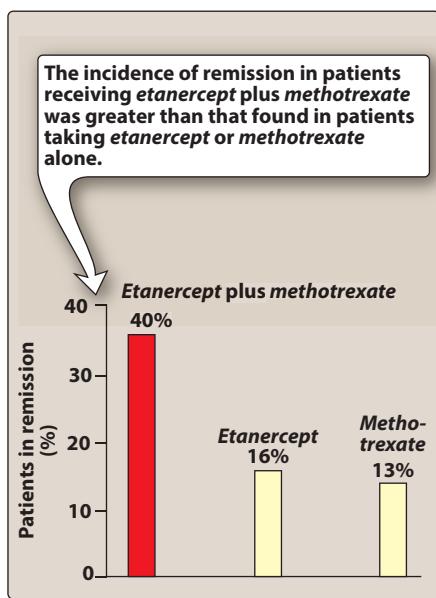
*Adalimumab* [a-dal-AYE-mu-mab] is a recombinant monoclonal antibody that binds to TNF- $\alpha$  and interferes with its activity by blocking interaction of TNF- $\alpha$  with cell surface receptors. *Adalimumab* is administered subcutaneously weekly or every other week. It may cause headache, nausea, agranulocytosis, rash, reaction at the injection site, and increased risk of infections.

### B. Certolizumab pegol

*Certolizumab* [ser-toe-LIZ-oo-mab] is a humanized antibody that neutralizes biological actions of TNF- $\alpha$ . It is combined with polyethylene glycol (pegylated) and is administered every 2 weeks via subcutaneous injection. Its adverse effects are similar to other TNF- $\alpha$  inhibitors.

### C. Etanercept

*Etanercept* [ee-TAN-er-cept] is a genetically engineered fusion protein that binds to TNF- $\alpha$ , thereby blocking its interaction with cell surface TNF- $\alpha$  receptors. The combination of *etanercept* and *methotrexate* is more effective than *methotrexate* or *etanercept* alone in hindering the RA disease process, improving function, and achieving remission (Figure 40.19). *Etanercept* is given subcutaneously once weekly and is generally well tolerated.



**Figure 40.19**

Incidence of remission from the symptoms of RA after 1 year of therapy.

#### D. Golimumab

*Golimumab* [goe-LIM-ue-mab] neutralizes the biological activity of TNF- $\alpha$  by binding to it and blocking its interaction with cell surface receptors. It is administered subcutaneously once a month in combination with *methotrexate*. *Golimumab* may increase hepatic enzymes.

#### E. Infliximab

*Infliximab* [in-FLIX-i-mab] is a chimeric monoclonal antibody composed of human and murine regions. The antibody binds specifically to human TNF- $\alpha$  and inhibits binding with its receptors. This agent is not indicated for monotherapy, as this leads to the development of anti-*infliximab* antibodies and reduced efficacy. *Infliximab* should be administered with *methotrexate*. *Infliximab* is administered as an IV infusion every 8 weeks. Infusion-related reactions, such as fever, chills, pruritus, and urticaria, may occur.

#### F. Abatacept

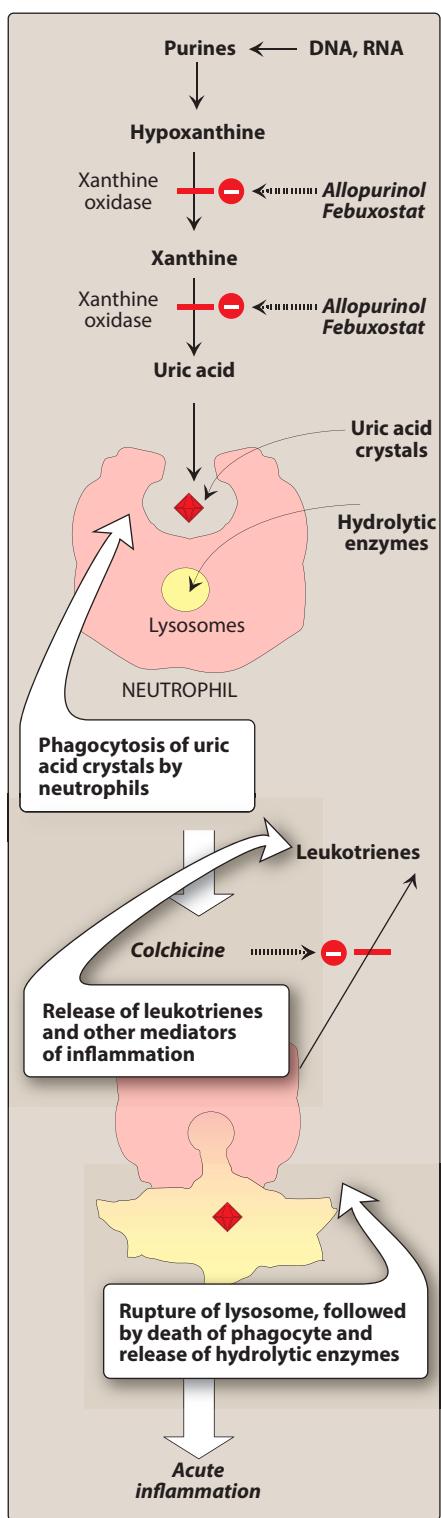
T lymphocytes need two interactions to become activated: 1) the antigen-presenting cell (macrophages or B cells) must interact with the receptor on the T cell and 2) the CD80/CD86 protein on the antigen-presenting cell must interact with the CD28 protein on the T cell. *Abatacept* [a-BAT-ah-cept] is a recombinant fusion protein and costimulation modulator that competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T-cell activation and reducing the inflammatory response. *Abatacept* is administered as an IV infusion every 4 weeks. Common adverse effects include infusion-related reactions, headache, upper respiratory infections, and nausea.

#### G. Rituximab

In RA, B lymphocytes can perpetuate the inflammatory process in the synovium by 1) activating T lymphocytes, 2) producing autoantibodies and rheumatoid factor, and 3) producing proinflammatory cytokines, such as TNF- $\alpha$  and IL-1. *Rituximab* [ri-TUK-si-mab] is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Administration of *rituximab* results in B-cell depletion. *Rituximab* is administered as an intravenous infusion every 16 to 24 weeks. To reduce the severity of infusion reactions, *methylprednisolone* is administered 30 minutes prior to each infusion. Infusion reactions (urticaria, hypotension, and angioedema) are the most common complaints and typically occur during the first infusion.

#### H. Tocilizumab and sarilumab

*Tocilizumab* [toe-si-LIZ-ue-mab] and *sarilumab* [sar-IL-ue-mab] are recombinant monoclonal antibodies that bind to IL-6 receptors and inhibit activity of the proinflammatory cytokine IL-6. Both *tocilizumab* and *sarilumab* are administered as a subcutaneous injection every 2 weeks. *Tocilizumab* may also be administered as an intravenous infusion every 4 weeks. Adverse reactions to *tocilizumab* include elevated liver function tests, hyperlipidemia, neutropenia, hypertension,

**Figure 40.20**

Role of uric acid in the inflammation of gout.

and infusion-related and injection site reactions. Adverse reactions for sarilumab are similar.

## VII. OTHER DRUGS FOR RHEUMATOID ARTHRITIS

Janus kinases are intracellular enzymes that modulate immune cell activity in response to the binding of inflammatory mediators to the cellular membrane. *Tofacitinib* [toe-fa-SYE-ti-nib] is a synthetic small molecule that is an oral inhibitor of Janus kinases. It is indicated for the treatment of moderate-to-severe established RA in patients who have had an inadequate response or intolerance to *methotrexate*. Metabolism of *tofacitinib* is mediated primarily by CYP3A4, and dosage adjustments may be required if the drug is taken with potent inhibitors or inducers of this isoenzyme. Hemoglobin concentrations must be greater than 9 g/dL to start *tofacitinib* and must be monitored during therapy due to the risk for anemia. Likewise, lymphocyte and neutrophil counts should be checked prior to initiation of therapy and monitored during treatment. *Tofacitinib* treatment may also increase the risk for new primary malignancy and opportunistic infections. Due to long-term safety concerns, *tofacitinib* is usually reserved for patients who have inadequate response or intolerance to other agents. [Note: *Anakinra*, *azathioprine*, *cyclosporine*, *gold*, and *minocycline* are other agents used infrequently in the treatment of RA due to their adverse effect profile or the availability of other agents with more proven efficacy.]

## VIII. DRUGS USED FOR THE TREATMENT OF GOUT

Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia). Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals (Figure 40.20). Acute flares of gout usually present as pain, swelling, tenderness, and redness in the affected joints (for example, big toe, knees, ankles, wrists, or elbows). The cause of hyperuricemia in gout is an imbalance between overproduction of uric acid and/or the inability to excrete uric acid renally. Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (6 mg/dL), thus preventing the deposition of urate crystals. This can be accomplished by interfering with uric acid synthesis or increasing uric acid excretion.

### A. Treatment of acute gout

Acute gout attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease. NSAIDs, corticosteroids, and *colchicine* are effective agents for the management of acute gouty arthritis. *Indomethacin* is considered the classic NSAID of choice, although all NSAIDs are likely to be effective in decreasing pain and inflammation. Intra-articular administration of corticosteroids (when only one or two joints are affected) is also appropriate in the acute setting, or systemic corticosteroids for more widespread joint involvement. Patients are candidates for prophylactic urate-lowering therapy if they have more than two attacks

per year or they have chronic kidney disease, kidney stones, or tophi (deposit of urate crystals in the joints, bones, cartilage, or other body structures).

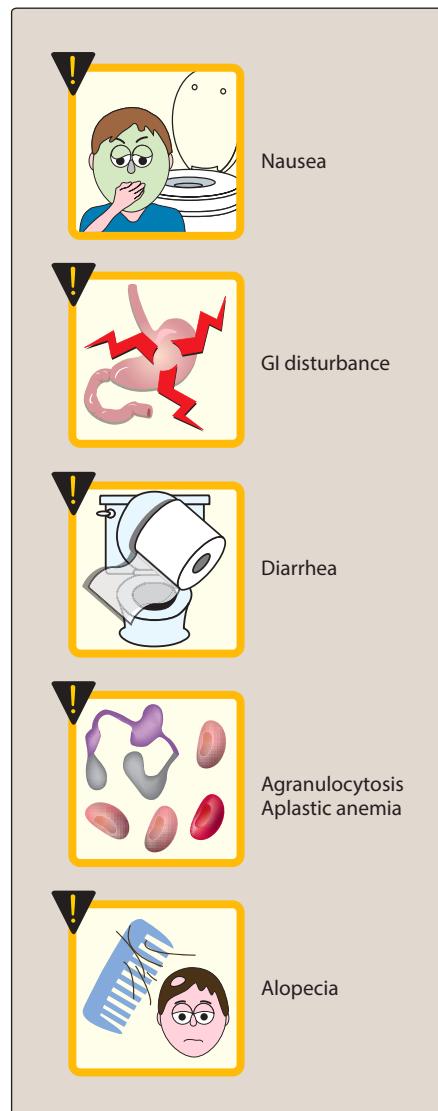
## B. Treatment of chronic gout

Urate-lowering therapy for chronic gout aims to reduce the frequency of attacks and complications of gout. Treatment strategies include the use of xanthine oxidase inhibitors to reduce the synthesis of uric acid or use of uricosuric drugs to increase its excretion. Xanthine oxidase inhibitors (*allopurinol, febuxostat*) are first-line urate-lowering agents. Uricosuric agents (*probenecid*) may be used in patients who are intolerant to xanthine oxidase inhibitors or fail to achieve adequate response with those agents. [Note: Initiation of urate-lowering therapy can precipitate an acute gout attack due to rapid changes in serum urate concentrations. Medications for the prevention of an acute gout attack (low-dose *colchicine*, NSAIDs, or corticosteroids) should be initiated with urate-lowering therapy and continued for at least 6 months.]

## C. Colchicine

*Colchicine* [KOL-chi-seen], a plant alkaloid, is used for the treatment of acute gouty attacks. It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout.

- Mechanism of action:** *Colchicine* binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of neutrophils, thus decreasing their migration into the inflamed joint. Furthermore, *colchicine* blocks cell division by binding to mitotic spindles.
- Therapeutic uses:** The anti-inflammatory activity of *colchicine* is specific for gout, usually alleviating the pain of acute gout within 12 hours. [Note: *Colchicine* must be administered within 36 hours of onset of attack to be effective.] NSAIDs have largely replaced *colchicine* in the treatment of acute gouty attacks for safety reasons. *Colchicine* is also used as a prophylactic agent to prevent acute attacks of gout in patients initiating urate-lowering therapy.
- Pharmacokinetics:** *Colchicine* is administered orally and is rapidly absorbed from the GI tract. *Colchicine* is metabolized by hepatic CYP450 3A4 and other tissues. It undergoes enterohepatic recirculation and exhibits high interpatient variability in the elimination half-life. A portion of the drug is excreted unchanged in the urine.
- Adverse effects:** *Colchicine* may cause nausea, vomiting, abdominal pain, and diarrhea (Figure 40.21). Chronic administration may lead to myopathy, neutropenia, aplastic anemia, and alopecia. The drug should not be used in pregnancy and should be used with caution in patients with hepatic, renal, or cardiovascular disease. Adequate drug holiday must be given between dosages to avoid cumulative toxicity. Dosage adjustments are required in patients taking CYP3A4 inhibitors (for example, *clarithromycin* and *itraconazole*) or P-gp inhibitors (for example, *amiodarone* and *verapamil*) and those with severe renal impairment.



**Figure 40.21**

Some adverse effects of *colchicine*.  
GI = gastrointestinal.

#### D. Allopurinol

*Allopurinol* [al-oh-PURE-i-nole], a xanthine oxidase inhibitor, is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase (Figure 40.20).

1. **Therapeutic uses:** *Allopurinol* is an effective urate-lowering therapy in the treatment of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after chemotherapy) or in renal disease.
2. **Pharmacokinetics:** *Allopurinol* is completely absorbed after oral administration. The primary metabolite alloxanthine (oxypurinol) is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosing. The drug and its active metabolite are excreted in the urine. Dose adjustment is needed if the estimated glomerular filtration rate is less than 30 mL/min/1.73 m<sup>2</sup>.
3. **Adverse effects:** *Allopurinol* is well tolerated by most patients. Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions. The risk is increased in those with reduced renal function. Because acute attacks of gout may occur more frequently during the first several months of therapy, *colchicine*, NSAIDs, or corticosteroids can be administered concurrently.

#### E. Febuxostat

*Febuxostat* [feb-UX-oh-stat] is an oral xanthine oxidase inhibitor structurally unrelated to *allopurinol*. *Febuxostat* is rapidly absorbed after oral administration with the time to reach peak concentration (*t*<sub>max</sub>) being of approximately 1 hour. The drug is highly bound to albumin in blood (~99%) and appears to have a low-to-medium apparent volume of distribution of approximately 0.7 L/kg. *Febuxostat* is indicated for the long-term management of hyperuricemia in patients with gout at a dose of 10 to 120 mg once daily. *Febuxostat* is well tolerated. Its adverse effect profile is similar to that of *allopurinol*, although the risk for rash and hypersensitivity reactions may be reduced. *Febuxostat* does not have the same degree of renal elimination as *allopurinol* and thus requires less adjustment in those with reduced renal function. The most common adverse events include abnormal liver function test results, abdominal pain, diarrhea, headache, joint-related signs and symptoms, and musculoskeletal and connective tissue signs and symptoms. *Febuxostat* should be used with caution in patients with a history of heart disease or stroke, as this agent may be associated with a greater risk of these events as compared to *allopurinol*.

#### F. Probenecid

*Probenecid* [proe-BEN-a-sid] is an oral uricosuric drug. It is a weak organic acid that promotes renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule. At therapeutic doses, it blocks proximal tubular reabsorption of uric acid. *Probenecid* should be avoided if the creatinine clearance is less than 50 mL/min.

Adverse effects include nausea, vomiting, and dermatologic reactions, and, rarely, anemia or anaphylactic reactions. It is used at a dose of 0.25 to 0.5 g twice daily. However, intermittent *colchicine* therapy is indicated to avoid acute precipitation of gout.

### G. Pegloticase

*Pegloticase* [peg-LOE-ti-kase] is a recombinant form of the enzyme urate oxidase or uricase. It acts by converting uric acid to allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys. *Pegloticase* is indicated for patients with gout who fail treatment with standard therapies such as xanthine oxidase inhibitors. It is administered as an IV infusion every 2 weeks. Infusion-related reactions and anaphylaxis may occur with *pegloticase*, and patients should be premedicated with antihistamines and corticosteroids.

## Study Questions

Choose the ONE best answer.

- 40.1 A 64-year-old man presents with mild-to-moderate musculoskeletal back pain. He states he has tried paracetamol without relief. His medical history includes diabetes, hypertension, hyperlipidemia, gastric ulcer (resolved), and coronary artery disease. Which is the most appropriate NSAID regimen to treat this patient's pain?

- A. Celecoxib
- B. Indomethacin and omeprazole
- C. Naproxen and omeprazole
- D. Naproxen

Correct answer = C. This patient is at high risk of future ulcers, due to the history of gastric ulcer. Therefore, using a regimen that includes an agent that is more COX-2 selective or a proton-pump inhibitor is warranted. Therefore, D is incorrect. Choices A and B are incorrect because this patient has significant cardiovascular risk and a history of coronary artery disease. Naproxen is thought of as the safest NSAID regarding cardiovascular disease, though it still can present risks. Therefore, C is correct as it uses the first-choice NSAID with the GI protection of a proton-pump inhibitor.

- 40.2 Which statement is correct regarding the difference between paracetamol and naproxen?

- A. Paracetamol has more anti-inflammatory effects compared with naproxen.
- B. Paracetamol has more GI side effects but less effects on bleeding compared with naproxen.
- C. Paracetamol has less risk for CV events compared with naproxen.
- D. Paracetamol has fewer antipyretic effects than naproxen.

Correct answer = C. While paracetamol inhibits prostaglandin synthesis via COX inhibition, it is inactivated peripherally so it is devoid of systemic GI, CV, and bleeding adverse effects which are hallmarks of NSAIDs like naproxen. However, as paracetamol is active centrally it is still able to maintain antipyretic effects similar to other NSAIDs.

40.3 Which statement correctly describes the proposed mechanism of cardioprotection from low-dose aspirin?

- A. Aspirin preferentially inhibits COX-2 to lead to a relative reduction in thromboxane A2 levels.
- B. Aspirin preferentially inhibits COX-1 to lead to a relative reduction in thromboxane A2 levels.
- C. Aspirin preferentially inhibits COX-2 to lead to a relative reduction in prostacyclin levels.
- D. Aspirin preferentially inhibits COX-1 to lead a relative reduction in prostacyclin levels.

Correct answer = B. At low doses aspirin selectively inhibits COX-1, which reduces the production of thromboxane A2, a substance that promotes vasoconstriction and platelet aggregation. COX-2 activity is thought to lead to relatively higher levels of prostacyclin which causes vasodilation and inhibits platelet aggregation. Selective COX-2 inhibitors, as well as all NSAIDs, may increase the risk for CV events by inhibiting the beneficial production of prostacyclin by COX-2, thereby leading to a relative imbalance of thromboxane A2 and promoting platelet aggregation and vasoconstriction.

40.4 Which statement correctly describes the pathophysiological actions of prostaglandins at a target tissue?

- A. Promote vasoconstriction in the kidneys
- B. Promote sodium and water retention in the kidneys
- C. Decrease secretion of mucus at the lining of the stomach
- D. Decrease secretion of gastric acid in the stomach

Correct answer = D. Prostaglandins, specifically PGE<sub>2</sub> and PG<sub>I<sub>2</sub></sub>, cause vasodilation in the renal arteries; a decrease in prostaglandins from NSAIDs can lead to vasoconstriction of renal arteries as well as sodium and water retention. In the stomach, PG<sub>I<sub>2</sub></sub> inhibits gastric acid secretion, while PGE<sub>2</sub> and PGF<sub>2<sub>α</sub></sub> promote secretion of protective mucus at the stomach lining.

40.5 Which prostaglandin agents can be used to maintain the patency of the ductus arteriosus in neonates with congenital heart problems while awaiting surgery?

- A. Misoprostol
- B. Epoprostenol
- C. Bimatoprost
- D. Alprostadil

Correct answer = D. Misoprostol, a PGE<sub>1</sub> analog, is used for GI protection or labor induction. Epoprostenol, a PG<sub>I<sub>2</sub></sub> analog, is used for the treatment of pulmonary arterial hypertension. Bimatoprost, a PGF<sub>2<sub>α</sub></sub> analog, is used topically in the eye for the treatment of open-angle glaucoma or on the lashes for hypotrichosis. Alprostadil, a PGE<sub>1</sub> analog, is used to maintain patency of the ductus arteriosus in neonates with congenital heart problems. The drug can also be used for erectile dysfunction.

40.6 A 34-year-old woman with RA is planning for pregnancy. Which RA agents are absolutely contraindicated in pregnancy?

- A. Abatacept and rituximab
- B. Adalimumab and certolizumab pegol
- C. Infliximab and etanercept
- D. Methotrexate and leflunomide

Correct answer = D. Both methotrexate and leflunomide are contraindicated in pregnancy. Data is limited in other RA agents to confirm or rule out teratogenicity in pregnancy. The risk of RA treatment on the developing fetus should be weighed against the benefits of improved RA symptoms with these therapies. Any adverse outcomes should be reported to the pregnancy registry.

40.7 Which agent for RA competes with CD28 to prevent full T-cell activation?

- A. Sarilumab
- B. Abatacept
- C. Golimumab
- D. Adalimumab

Correct answer = B. Abatacept is a costimulation modulator that competes with CD28 to prevent its binding on CD80/CD86 protein, resulting in reduced T-cell activation. Golimumab and adalimumab are both TNF- $\alpha$  inhibitors and sarilumab is an IL-6 inhibitor.

- 40.8 Which statement correctly represents the mechanism of action of tofacitinib in the treatment of RA?
- A. TNF- $\alpha$  inhibitor
  - B. Janus kinase inhibitor
  - C. IL-6 receptor blocker
  - D. Dihydrofolate reductase inhibitor
- 40.9 A 54-year-old man with gout is found to have an issue with renal excretion of uric acid. Which drug is an oral agent that would target the cause of his acute gout attacks?
- A. Allopurinol
  - B. Febuxostat
  - C. Probenecid
  - D. Pegloticase
- 40.10 A 64-year-old man presents with signs and symptoms of an acute gouty flare. Which strategy is the *least* likely to acutely improve his gout symptoms and pain?
- A. Naproxen
  - B. Colchicine
  - C. Probenecid
  - D. Prednisone

Correct answer = B. Tofacitinib is an inhibitor of Janus kinases 1, 3, and, to a lesser extent, 2. Methotrexate inhibits dihydrofolate reductase. Etanercept is an example of TNF- $\alpha$  inhibitor, and tocilizumab is an example of an IL-6 inhibitor.

Correct answer = C. Probenecid is a uricosuric agent that increases renal excretion by inhibiting the urate-anion exchanger in the proximal tubule, thereby blocking reabsorption of uric acid and facilitating its excretion. Allopurinol and febuxostat are xanthine oxidase inhibitors which primarily act by decreasing uric acid production. Pegloticase works by increasing renal excretion of uric acid; however, it is an IV infusion.

Correct answer = C. Probenecid is a uricosuric agent indicated to lower serum urate levels to prevent gout attacks. It is not indicated during acute gout flares and should not be started until after the resolution of an acute attack. Naproxen, colchicine, and prednisone all represent viable treatment options that acutely reduce pain and inflammation associated with acute gout attacks.



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# Drugs for Disorders of the Respiratory System

# 41

Kyle Melin

## I. OVERVIEW

Asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis are commonly encountered respiratory disorders. Each of these conditions may be associated with a troublesome cough, which may be the only presenting complaint. Asthma is a chronic disease characterized by hyper-responsive airways that affects over 235 million patients worldwide. This disorder is under-diagnosed and under-treated, creating a substantial burden to individuals and families, and resulting in millions of emergency room visits. COPD is currently the fourth leading cause of death in the world, and is predicted to become the third leading cause of death by 2030. Allergic rhinitis is a common chronic disease and is characterized by itchy, watery eyes, runny nose, and a nonproductive cough that can significantly decrease the quality of life. Each of these respiratory conditions may be managed with a combination of lifestyle changes and medications. Drugs used to treat respiratory conditions can be delivered topically to the nasal mucosa, inhaled into the lungs, or given orally or parenterally for systemic absorption. Local delivery methods, such as nasal sprays or inhalers, are preferred to target affected tissues while minimizing systemic adverse effects. Medications used to treat common respiratory disorders are summarized in [Figure 41.1](#).

## II. PREFERRED DRUGS USED TO TREAT ASTHMA

Asthma is a chronic inflammatory disease of the airways characterized by episodes of acute bronchoconstriction which cause shortness of breath, cough, chest tightness, wheezing, and rapid respiration.

### A. Pathophysiology of asthma

Airflow obstruction in asthma is due to bronchoconstriction that results from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased secretion of mucus ([Figure 41.2](#)). The underlying inflammation of the airways contributes to airway hyper-responsiveness, airflow limitation, respiratory symptoms, and disease chronicity. Asthma attacks may be triggered by exposure to allergens,

MEDICATION	INDICATION
<b>SHORT-ACTING <math>\beta_2</math> ADRENERGIC AGONISTS (SABAs)</b>	
<i>Albuterol</i>	Asthma, COPD
<i>Levalbuterol</i>	Asthma, COPD
<b>LONG-ACTING <math>\beta_2</math> ADRENERGIC AGONISTS (LABAs)</b>	
<i>Arformoterol</i>	COPD
<i>Formoterol</i>	Asthma, COPD
<i>Indacaterol</i>	COPD
<i>Olodaterol</i>	COPD
<i>Salmeterol</i>	Asthma, COPD
<b>INHALED CORTICOSTEROIDS</b>	
<i>Beclomethasone</i>	Allergic rhinitis, Asthma, COPD
<i>Budesonide</i>	Allergic rhinitis, Asthma, COPD
<i>Ciclesonide</i>	Allergic rhinitis, Asthma
<i>Fluticasone</i>	Allergic rhinitis, Asthma, COPD
<i>Mometasone</i>	Allergic rhinitis, Asthma
<i>Triamcinolone</i>	Allergic rhinitis, Asthma
<b>LONG-ACTING <math>\beta_2</math> ADRENERGIC AGONIST/CORTICOSTEROID COMBINATION</b>	
<i>Formoterol/budesonide</i>	Asthma, COPD
<i>Formoterol/mometasone</i>	Asthma, COPD
<i>Salmeterol/fluticasone</i>	Asthma, COPD
<i>Vilanterol/fluticasone</i>	COPD
<b>SHORT-ACTING ANTICHOLINERGIC</b>	
<i>Ipratropium</i>	Allergic rhinitis, COPD
<b>SHORT-ACTING <math>\beta_2</math> AGONIST/SHORT-ACTING ANTICHOLINERGIC COMBINATION</b>	
<i>Albuterol/ipratropium</i>	COPD
<b>LONG-ACTING ANTICHOLINERGIC (LAMA)</b>	
<i>Aclidinium bromide</i>	COPD
<i>Glycopyrrrolate</i>	COPD
<i>Tiotropium</i>	Asthma, COPD
<i>Umeclidinium</i>	COPD
<b>LABA/LAMA COMBINATION</b>	
<i>Formoterol/glycopyrrrolate</i>	COPD
<i>Indacaterol/glycopyrrrolate</i>	COPD
<i>Vilanterol/umeclidinium</i>	COPD
<i>Olodaterol/tiotropium</i>	COPD
<b>LEUKOTRIENE MODIFIERS</b>	
<i>Montelukast</i>	Asthma, Allergic rhinitis
<i>Zafirlukast</i>	Asthma
<i>Zileuton</i>	Asthma
<b>ANTIHISTAMINES (<math>H_1</math>-RECEPTOR ANTAGONISTS)</b>	
<i>Azelastine</i>	Allergic rhinitis
<i>Cetirizine</i>	Allergic rhinitis
<i>Desloratadine</i>	Allergic rhinitis
<i>Fexofenadine</i>	Allergic rhinitis
<i>Loratadine</i>	Allergic rhinitis
<b><math>\alpha</math>-ADRENERGIC AGONISTS</b>	
<i>Oxymetazoline</i>	Allergic rhinitis
<i>Phenylephrine</i>	Allergic rhinitis
<i>Pseudoephedrine</i>	Allergic rhinitis
<b>AGENTS FOR COUGH</b>	
<i>Benzonatate</i>	Cough suppressant
<i>Codeine (with guaifenesin)</i>	Cough suppressant/expectorant
<i>Dextromethorphan</i>	Cough suppressant
<i>Dextromethorphan (with guaifenesin)</i>	Cough suppressant/expectorant
<i>Guaifenesin</i>	Expectorant
<b>OTHER AGENTS</b>	
<i>Benralizumab</i>	Asthma
<i>Cromolyn<sup>1</sup></i>	Asthma, Allergic rhinitis
<i>Mepolizumab</i>	Asthma
<i>Omalizumab</i>	Asthma
<i>Reslizumab</i>	Asthma
<i>Roflumilast</i>	COPD
<i>Theophylline</i>	Asthma, COPD

LABA = long-acting  $\beta_2$  agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting  $\beta_2$  agonist.

<sup>1</sup>Indicates intranasal formulation.

### Figure 41.1

Summary of drugs affecting the respiratory system. (For drug dosages, refer to Appendix at the end of the book.)

exercise, stress, and respiratory infections. Asthma can be episodic (seasonal) or chronic in nature (perennial, status asthmaticus). After the trigger, mast cell degranulation releases mediators such as histamine, proteolytic enzymes, and inflammatory cytokines like TNF- $\alpha$ . The triggering inflammation also synthesizes slow-releasing substances of anaphylaxis such as leukotrienes, prostaglandins, and platelet-activating factor. Activation of gene-responsive elements also causes the production of cytokines and chemokines. The airway inflammatory phase leads to bronchoconstriction, edema, mucus secretion, vasodilation, and activation of sensory nerves. A chronic inflammatory condition can lead to structural modifications in the airway epithelium, causing subepithelial fibrosis, smooth muscle hypertrophy, hyperplasia, angiogenesis, and hyperplasia of mucus-secreting cells. Unlike COPD, cystic fibrosis, and bronchiectasis, asthma is usually not a progressive disease. However, if untreated, asthma may cause airway remodeling, resulting in increased severity and incidence of asthma exacerbations and/or death.

### B. Goals of therapy

Asthma can present as an acute exacerbation which can be mild, moderate-to-severe, or life-threatening. Treatment depends on the severity of asthma. The management algorithm for treating acute asthma in a hospital is depicted in Figure 41.3.

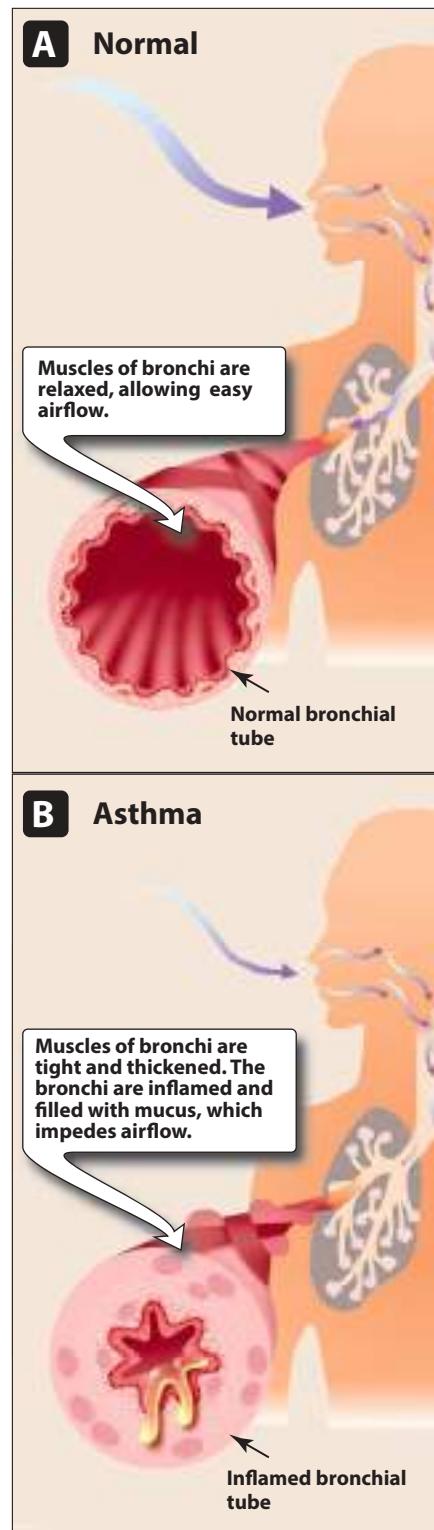
The trigger factor(s) should be identified and avoided, wherever possible, smoking should be stopped, and regular breathing exercises (such as “Pranayama”) should be started. Physical activity and weight loss help in prevention of acute episodes of asthma.

Drug therapy for long-term control of asthma is designed to reverse and prevent airway inflammation. The goals of asthma therapy are to decrease the intensity and frequency of asthma symptoms, prevent future exacerbations, and minimize limitations in activity related to asthma symptoms. First-line drug therapy based on classification of asthma is presented in Figure 41.4. Figure 41.5 depicts the stepwise approach to management of asthma.

### C. $\beta_2$ -Adrenergic agonists

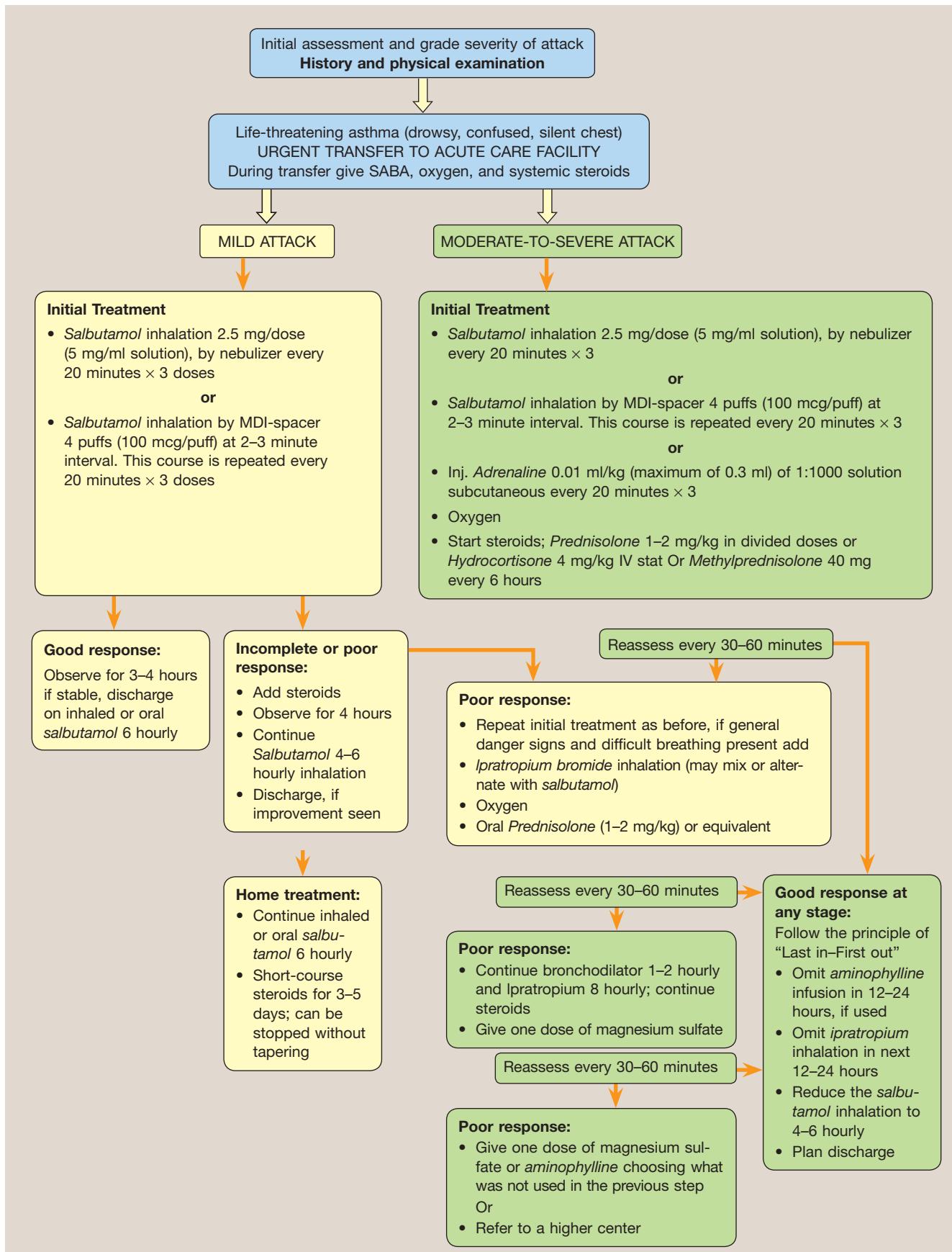
Inhaled  $\beta_2$ -adrenergic agonists directly relax airway smooth muscle. They are used for the quick relief of asthma symptoms (therefore, also referred to as “reliever”) as well as an adjunctive therapy for long-term control of the disease.

- Quick relief:** Short-acting  $\beta_2$  agonists (SABAs) have a rapid onset of action (5 to 30 minutes) and provide relief for 4 to 6 hours. They are used for symptomatic treatment of bronchospasm, providing quick relief of acute bronchoconstriction. All patients with asthma should receive a SABA inhaler for use as needed.  $\beta_2$  agonists have no anti-inflammatory effects, and they should not be used as monotherapy for patients with persistent asthma. However, monotherapy with SABAs may be appropriate for patients with mild, intermittent asthma or exercise-induced bronchospasm. Direct-acting  $\beta_2$ -selective agonists include *salbutamol* and *terbutaline*. These agents provide significant bronchodilation with little of the undesired effect of  $\alpha$  or  $\beta_1$  stimulation (see Chapter 6). Adverse effects, such as tachycardia, hyperglycemia, hypokalemia, hypomagnesemia, and  $\beta_2$ -mediated skeletal muscle tremors are minimized with inhaled delivery versus systemic administration.



**Figure 41.2**

Comparison of bronchi of normal and asthmatic individuals.

**Figure 41.3**

Management algorithm for treating acute asthma in a hospital.

CLASSIFICATION	BRONCHO-CONSTRICATIVE EPISODES	NIGHT TIME SYMPTOMS	RESULTS OF PEAK FLOW OR SPIROMETRY	LONG-TERM CONTROL	QUICK RELIEF OF SYMPTOMS
Grade 1 Mild Intermittent	Asymptomatic and normal between attacks	Less than 2 times a month	Near normal (80% of normal)	No daily medication	Short-acting $\beta_2$ agonist
Grade 2 Mild persistent	More than one time a week but less than one time a day	More than 2 times a month	Near normal (>60% to 80% of normal)	Low-dose ICS	Short-acting $\beta_2$ agonist
Grade 3 Moderate persistent	More than once daily	Once a week	60% to 80% of normal	Low-dose ICS + LABA OR Medium-dose ICS	Short-acting $\beta_2$ agonist ICS/formoterol is an alternative
Grade 4 Severe persistent	Continual; limited physical activity	Frequent	Less than 60% of normal	Medium-dose ICS + LABA OR High-dose ICS + LABA	Short-acting $\beta_2$ agonist ICS/formoterol is an alternative

ICS = inhaled corticosteroid; LABA = long-acting  $\beta_2$  agonist.

**Figure 41.4**

Guidelines for the treatment of asthma. In all asthmatic patients, quick relief is provided by a SABA as needed for symptoms.

2. **Long-term control:** *Salmeterol* [sal-MEE-ter-all] and *formoterol* [for-MOE-ter-all] are long-acting  $\beta_2$  agonists (LABAs) and chemical analogs of *salbutamol*. *Salmeterol* and *formoterol* have a long duration of action, providing bronchodilation for at least 12 hours. Use of LABA monotherapy is contraindicated, and

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Preferred controller choice		Low-dose ICS	Low-dose ICS/LABA	Medium/high-dose ICS/LABA	Refer for add-on treatment with <i>omalizumab</i>
Other controller options	Low-dose ICS	LTRA/low-dose <i>theophylline</i> <sup>1</sup>	Medium/high-dose ICS/low dose ICS + LTRA (Or+ <i>Theophylline</i> )	Add <i>ipratropium/tiotropium/high-dose ICS + LTRA</i> (Or+ <i>Theophylline</i> )	
Reliever	As needed SABA		As needed SABA or low-dose ICS/formoterol <sup>2</sup>		
Symptoms	Intermittent	Persistent			

ICS = inhaled corticosteroid; LABA = long-acting  $\beta_2$  agonist.

**Notes:** Before step-up, check dose, device, adherence, and inhaler technique and correct errors, check for triggers, and comorbidity, if any (allergic rhinitis, sinusitis).

Short step-up for 1–2 weeks during viral infection or exposure to allergens.

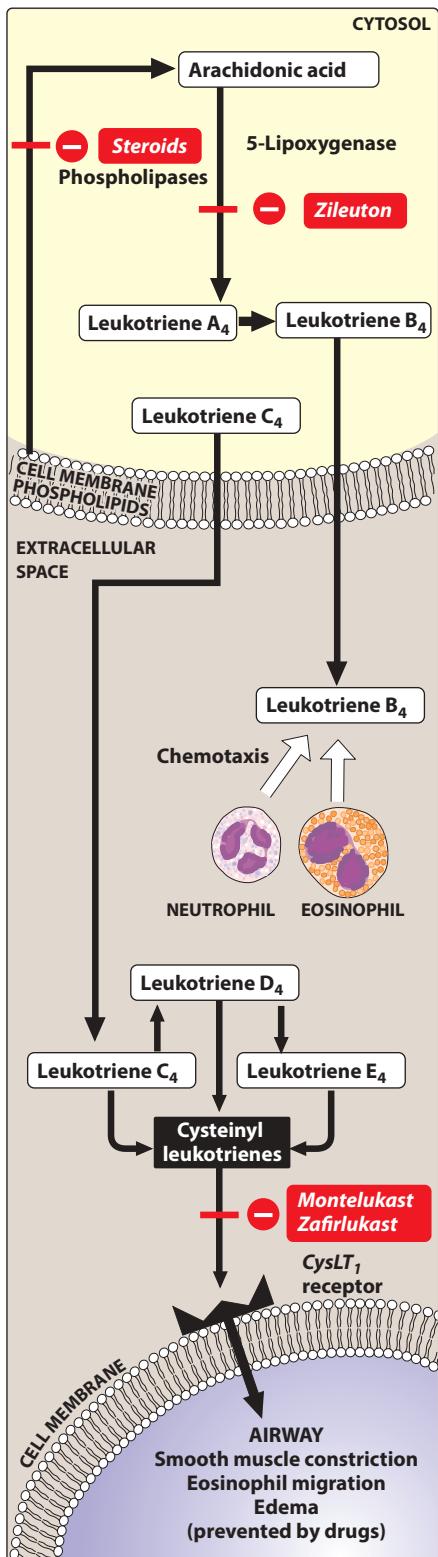
Day-to-day adjustments by patients on ICS as maintenance or reliever therapy. Step down if symptoms controlled for 3 months and at low risk of exacerbation.

<sup>1</sup>For children 6 to 11 years of age, *theophylline* is not recommended; the preferred step 3 treatment is medium-dose ICS

<sup>2</sup>Low-dose ICS/formoterol is reliever for patients prescribed low-dose budesonide/formoterol or beclomethasone/formoterol.

**Figure 41.5**

Stepwise approach to management of asthma.



**Figure 41.6**

Sites of action for various respiratory medications. CysLT<sub>1</sub> = cysteinyl leukotriene-1.

LABAs should be used only in combination with an asthma controller medication, such as an inhaled corticosteroid (ICS). ICS remains the long-term controllers of choice in asthma, and LABAs are considered to be useful adjunctive therapy for attaining control in moderate-to-severe asthma. Some LABAs are available as a combination product with an ICS (Figure 41.1). Although both LABAs are usually used on a scheduled basis to control asthma, adults and adolescents with moderate persistent asthma can use the ICS/formoterol combination for relief of acute symptoms. Adverse effects of LABAs are similar to quick-acting  $\beta_2$  agonists. *Bambuterol* is a prodrug of *terbutaline*. Upon administration, it is slowly released over a period of 24 hours by pseudocholinesterase.

#### D. Corticosteroids

ICS are the drugs of choice for long-term control (preventer) in patients with persistent asthma (Figure 41.4). Corticosteroids (see Chapter 26) inhibit the release of arachidonic acid through inhibition of phospholipase A<sub>2</sub>, thereby producing direct anti-inflammatory properties in the airways (Figure 41.6). To be effective in controlling inflammation, these agents must be used regularly. Treatment of exacerbations or severe persistent asthma may require the addition of a short course of oral or intravenous corticosteroids.

**1. Actions on Lung:** ICS therapy directly targets underlying airway inflammation by decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes), reversing mucosal edema, decreasing the permeability of capillaries, and inhibiting the release of leukotrienes. After several months of regular use, ICS reduce the hyper-responsiveness of the airway smooth muscle to a variety of bronchoconstrictor stimuli, such as allergens, irritants, cold air, and exercise.

#### 2. Routes of administration:

a. **Inhalation:** The development of ICS has markedly reduced the need for systemic corticosteroid treatment to achieve control of asthma symptoms. However, as with all inhaled medications, appropriate inhalation technique is critical to the success of therapy (see section on Inhaler Technique).

b. **Oral/systemic:** Patients with a severe exacerbation of asthma (status asthmaticus) may require intravenous *methylprednisolone* or oral *prednisone* to reduce airway inflammation. In most cases, suppression of the hypothalamic-pituitary-adrenal cortex axis does not occur during the oral *prednisone* "burst" (short course) typically prescribed for an asthma exacerbation. Thus, a dose taper is unnecessary prior to discontinuation.

c. **Adverse effects:** Oral or parenteral corticosteroids have a variety of potentially serious adverse effects (see Chapter 26), whereas ICS, particularly if used with a spacer, have few systemic effects. ICS deposition on the oral and laryngeal mucosa can cause oropharyngeal candidiasis (due to local immune suppression) and hoarseness. Patients should be instructed to rinse the mouth in a "swish-and-spit" method

with water following use of the inhaler to decrease the chance of these adverse events. Due to the potential for serious adverse effects, chronic maintenance with oral corticosteroids should be reserved for patients who are not controlled on an ICS.

### III. ALTERNATIVE DRUGS USED TO TREAT ASTHMA

These drugs are useful for treatment of asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to corticosteroid treatment. These drugs should be used in conjunction with ICS therapy for most patients.

#### A. Leukotriene modifiers (leukotriene receptor antagonists and lipoxygenase inhibitors)

Leukotrienes (LT) B<sub>4</sub> and the cysteinyl leukotrienes, LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade. 5-Lipoxygenase is found in cells of myeloid origin, such as mast cells, basophils, eosinophils, and neutrophils. LTB<sub>4</sub> is a potent chemoattractant for neutrophils and eosinophils, whereas the cysteinyl leukotrienes constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucus secretion. *Zileuton* [zye-LOO-ton] is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both LTB<sub>4</sub> and the cysteinyl leukotrienes. *Zafirlukast* [za-FIR-loo-kast] and *montelukast* [mon-te-LOO-kast] are selective antagonists of the cysteinyl leukotriene-1 receptor, and they block the effects of cysteinyl leukotrienes (Figure 41.6). These agents are approved for the prevention of asthma symptoms. They should not be used in situations where immediate bronchodilation is required. Leukotriene receptor antagonists have also shown efficacy for the prevention of exercise-induced bronchospasm.

- Pharmacokinetics:** These agents are orally active and highly protein bound. Food impairs the absorption of *zafirlukast*. The drugs undergo extensive hepatic metabolism. *Zileuton* and its metabolites are excreted in urine, whereas *zafirlukast*, *montelukast*, and their metabolites undergo biliary excretion.
- Adverse effects:** Elevations in serum hepatic enzymes may occur with these drugs, requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal. Other effects include headache and dyspepsia. *Zafirlukast* is an inhibitor of cytochrome P450 (CYP) isoenzymes 2C8, 2C9, and 3A4, and *zileuton* inhibits CYP1A2. Coadministration with drugs that are substrates of these isoenzymes may result in increased effects and/or toxicity.

#### B. Mast cell stabilizers

- Cromolyn:** *Cromolyn* [KRO-moe-lin] is a prophylactic anti-inflammatory agent that inhibits mast cell degranulation and release of histamine. It is an alternative therapy for mild persistent asthma and is available as a nebulized solution. Because *cromolyn* is not

a bronchodilator, it is not useful in managing an acute asthma attack. Because of its short duration of action, this agent requires dosing three or four times daily, which affects adherence and limits its use. Adverse effects are minor and include cough, irritation, and unpleasant taste.

2. **Ketotifen:** *Ketotifen* is an antihistaminic reported to have mast cell stabilization activity. It shows moderate antiasthmatic activity on prolonged use. It is useful in patients with allergy such as rhinitis, conjunctivitis, and dermatitis. Unlike *cromolyn*, it induces sedation and dry mouth.

### C. Cholinergic antagonists

The anticholinergic agents block vagally mediated contraction of airway smooth muscle and mucus secretion (see Chapter 5). Inhaled *ipratropium* [IP-ra-TROE-pee-um], a short-acting quaternary derivative of *atropine*, is not recommended for the routine treatment of acute bronchospasm in asthma, as its onset is much slower than inhaled SABAs. However, it may be useful in patients who are unable to tolerate a SABA or patients with asthma-COPD overlap syndrome. *Ipratropium* also offers additional benefit when used with a SABA for the treatment of acute asthma exacerbations in the emergency department. *Tiotropium* [tye-oh-TROE-pee-um], a long-acting anticholinergic agent, can be used as an add-on treatment in adult patients with severe asthma and a history of exacerbations. Adverse effects such as xerostomia and bitter taste are related to local anticholinergic effects.

### D. Methylxanthines

1. **Theophylline:** *Theophylline* [thee-OFF-i-lin] is a bronchodilator that relieves airflow obstruction in chronic asthma and decreases its symptoms. It may also possess anti-inflammatory activity. Although it is precise, the mechanism of action is unclear. It is a nonselective phosphodiesterase inhibitor known to increase cellular cAMP and cGMP levels, which are accounted for the bronchodilation achieved. It is also responsible for its cardiac side effects. Additionally, *theophylline* is reported to play a beneficial role in asthma due to its ability to antagonize adenosine receptors causing bronchoconstriction, induce anti-inflammatory interleukin (IL10) release, prevent the gene transcription of NF- $\kappa$ B, prevent adenosine-induced constriction of blood vessels, inhibit histone decarboxylase-2 by its anti-inflammatory action, and increase circulating catecholamines.

Previously, the mainstay of asthma therapy, *theophylline* has been largely replaced with  $\beta_2$  agonists and corticosteroids due to its narrow therapeutic window, adverse effect profile, and potential for drug interactions. Overdose may cause seizures or potentially fatal arrhythmias. *Theophylline* is metabolized in the liver and is a CYP1A2 and 3A4 substrate. It is subject to numerous drug interactions. Serum concentration monitoring should be performed when *theophylline* is used chronically.

### E. Monoclonal antibodies

*Omalizumab* [OH-ma-LIZ-oo-mab] is a monoclonal antibody that selectively binds to human immunoglobulin E (IgE). This leads to decreased binding of IgE to its receptor on the surface of mast cells and basophils. Reduction in surface-bound IgE limits the release of mediators of the allergic response. The monoclonal antibodies *mepolizumab* [MEP-oh-LIZ-ue-mab], *benralizumab* [ben-ra-LIZ-ue-mab], and *reslizumab* [res-LIZ-ue-mab] are interleukin-5 (IL-5) antagonists. IL-5 is the major cytokine involved in recruitment, activation, and survival of eosinophils in eosinophilic asthma. These agents are indicated for the treatment of severe persistent asthma in patients who are poorly controlled with conventional therapy. Their use is limited by the high cost, route of administration (IV for *reslizumab* and subcutaneous for others), and adverse effect profile. Adverse effects include serious anaphylactic reactions (rare), arthralgias, fever, rash, and increased risk of infections. New malignancies have been reported.

## IV. DRUGS USED TO TREAT CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD is a chronic, irreversible obstruction of airflow that is usually progressive and characterized by persistent symptoms. These may include cough, excess mucus production, chest tightness, breathlessness, difficulty sleeping, and fatigue. Although symptoms are similar to asthma, the characteristic **irreversible** airflow obstruction of COPD is one of the most significant differences between the diseases. Smoking is the greatest risk factor for COPD and is directly linked to the progressive decline of lung function, as demonstrated by forced expiratory volume in 1 second (FEV<sub>1</sub>). Smoking cessation should be recommended regardless of the stage and severity of COPD, or the age of the patient. Drug therapy for COPD is aimed at relief of symptoms and prevention of disease progression. Unfortunately, with the current available care, many patients still experience a decline in lung function over time.

### A. Bronchodilators

Inhaled bronchodilators, including the  $\beta_2$ -adrenergic agonists and anticholinergic agents (muscarinic antagonists), are the foundation of therapy for COPD (Figure 41.7). These drugs increase airflow, alleviate symptoms, and decrease exacerbations. The long-acting bronchodilators, LABAs and long-acting muscarinic antagonists (LAMAs), are preferred as first-line treatment of COPD for all patients except those who are at low risk with less symptoms. LABAs include once-daily *indacaterol* [in-da-KA-ter-ol], *olodaterol* [OH-loe-DAT-er-ol], and *vilanterol* [vy-LAN-ter-ol], as well as the twice-daily inhaled formulations of *arformoterol*, *formoterol*, and *salmeterol*. *Aclidinium* [A-kli-DIN-ee-um], *tiotropium*, *glycopyrrrolate* [GLYE-koe-PIR-oh-late], and *umeclidinium* [ue-ME-kli-DIN-ee-um]) are LAMAs. The combination of an anticholinergic and a  $\beta_2$  agonist may be helpful in patients who have inadequate response to a single inhaled bronchodilator and are at risk of exacerbations.

PATIENT GROUP	RECOMMENDED FIRST CHOICE	RECOMMENDED ESCALATION
<b>A</b> Low risk Fewer symptoms	Bronchodilator: SABA or LABA or Short-acting anticholinergic or LAMA	Try alternative class
<b>B</b> Low risk More symptoms	Long acting bronchodilator: LABA or LAMA	LAMA + LABA
<b>C</b> High risk Fewer symptoms	LAMA	LAMA + LABA or LABA + ICS
<b>D</b> High risk More symptoms	LAMA + LABA	LAMA + LABA + ICS (May consider <i>roflumilast</i> if FEV <sub>1</sub> < 50% predicted and chronic bronchitis)

FEV<sub>1</sub> = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting  $\beta_2$  agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting  $\beta_2$  agonist.

**Figure 41.7**

Guidelines for the pharmacologic therapy of stable chronic obstructive pulmonary disease.

## B. Corticosteroids

The addition of an ICS to a long-acting bronchodilator may improve symptoms, lung function, and quality of life in COPD patients with FEV<sub>1</sub> of less than 60% predicted or patients with symptoms of both asthma and COPD. However, ICS treatment in COPD should be restricted to these patients, since its use is associated with an increased risk of pneumonia. Although often used for acute exacerbations, oral corticosteroids are not recommended for long-term treatment of COPD.

## C. Other agents

*Roflumilast* [roe-FLUE-mi-last] is an oral phosphodiesterase-4 inhibitor used to reduce exacerbations in patients with severe chronic bronchitis. Although its activity is not well defined in COPD, it is theorized to reduce inflammation by increasing levels of intracellular cAMP in lung cells. *Roflumilast* is not a bronchodilator and is not indicated for the relief of acute bronchospasm. Its use is limited by common adverse effects including weight loss, nausea, diarrhea, and headache. In COPD, the use of *theophylline* has largely been replaced by the more effective and tolerable long-acting bronchodilators.

## V. INHALER TECHNIQUE

An appropriate inhaler technique differs between metered-dose inhalers (MDIs) and dry powder inhalers (DPIs). A proper technique is critical to the success of therapy, and the inhaler technique should be assessed regularly.

### A. Metered-dose inhalers and dry powder inhalers

MDIs have propellants that eject the active medication from the canister. Patients should be instructed to exhale before they actuate the inhaler, and then begin to inhale **slowly** as they press the canister and continue inhaling **slowly and deeply** throughout actuation. This technique avoids impaction of the medication onto the laryngeal mucosa and facilitates the drug reaching the site of action in the bronchial smooth muscle. A large fraction (typically 80% to 90%) of inhaled medication (for example, corticosteroids) is either deposited in the mouth and pharynx or swallowed (Figure 41.8). The remaining 10% to 20% of a dose of inhaled glucocorticoids that is not swallowed reaches the site of action in the airway. Use of an appropriate technique with ICS reduces the risk of systemic absorption and adverse effects. DPIs require a different inhaler technique. Patients should be instructed to inhale **quickly** and **deeply** to optimize drug delivery to the lungs. Patients using any type of inhaled corticosteroid device should be instructed to rinse the mouth after use to prevent the development of oral candidiasis.

### B. Spacers

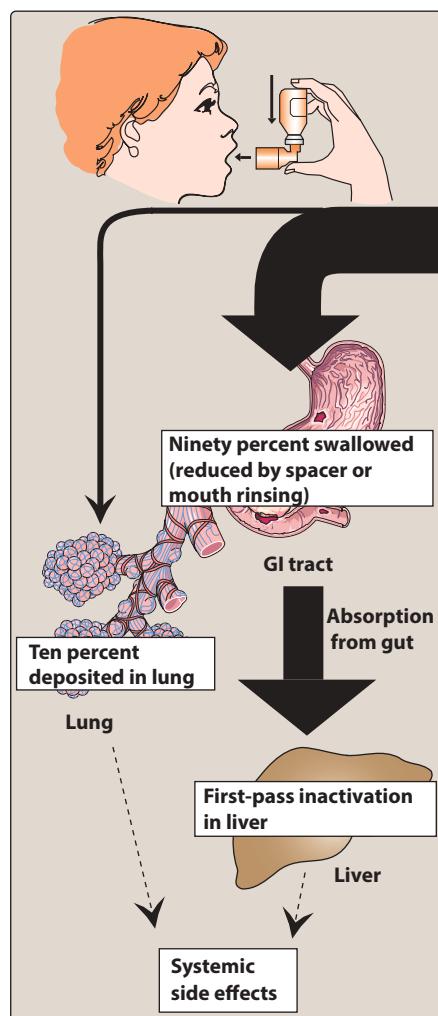
A spacer is a large-volume chamber attached to an MDI. The chamber reduces the velocity of the aerosol before entering the mouth, allowing large drug particles to be deposited in the device. The smaller, higher velocity drug particles are less likely to be deposited in the mouth and more likely to reach the target airway tissue (Figure 41.9). Patients should be advised to wash and/or rinse spacers to reduce the risk of bacterial or fungal growth that may induce an asthma attack.

## VI. DRUGS USED TO TREAT ALLERGIC RHINITIS

Rhinitis is an inflammation of the mucous membranes of the nose and is characterized by sneezing, itchy nose/eyes, watery rhinorrhea, nasal congestion, and sometimes a nonproductive cough. An attack may be precipitated by inhalation of an allergen (such as dust, pollen, or animal dander). The foreign material interacts with mast cells coated with IgE generated in response to a previous allergen exposure. The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors that promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration. Antihistamines and/or intranasal corticosteroids are preferred therapies for allergic rhinitis.

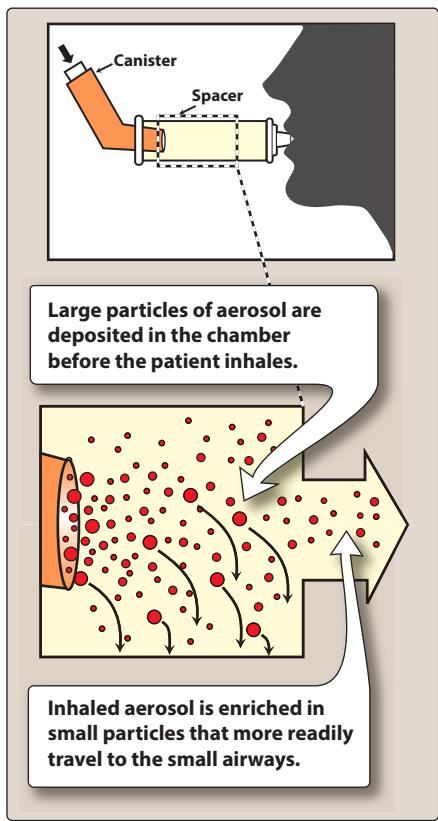
### A. Antihistamines

Oral antihistamines ( $H_1$  receptor antagonists; see Chapter 39) have a fast-onset of action and are useful for the management of symptoms of allergic rhinitis caused by histamine release, such as sneezing, watery rhinorrhea, and itchy eyes/nose. However, they are more effective for prevention of symptoms in mild or intermittent disease, rather than treatment once symptoms have begun. First-generation antihistamines, such as *diphenhydramine* and *chlorpheniramine*, are usually not preferred due to adverse effects, such as sedation, performance impairment, and other anticholinergic effects. The



**Figure 41.8**

Pharmacokinetics of inhaled glucocorticoids. GI = gastrointestinal.



**Figure 41.9**

Effect of a spacer on the delivery of an inhaled aerosol.

second-generation antihistamines (for example, *fexofenadine*, *loratadine*, *desloratadine*, and *cetirizine*) are generally better tolerated. Ophthalmic and nasal antihistamine delivery devices are available for targeted, topical tissue delivery. Examples of topical intranasal antihistamines include *olopatadine* [OH-loe-PA-ta-deen] and *azelastine* [a-ZEL-uh-steen]. Intranasal antihistamines provide increased delivery of the drug with fewer adverse effects. Combinations of antihistamines with decongestants (see the following text) are effective when congestion is a feature of rhinitis, or when patients have no response or incomplete control of symptoms with intranasal corticosteroids.

### B. Corticosteroids

Intranasal corticosteroids, such as *beclomethasone*, *budesonide*, *fluticasone*, *ciclesonide*, *mometasone*, and *triamcinolone*, are the most effective medications for treatment of allergic rhinitis. With an onset of action that ranges from 3 to 36 hours after the first dose, intranasal corticosteroids improve sneezing, itching, rhinorrhea, and nasal congestion. Systemic absorption is minimal, and adverse effects of treatment are localized. These include nasal irritation, nosebleed, sore throat, and, rarely, candidiasis. To minimize systemic absorption, patients should be instructed to avoid deep inhalation during administration into the nose, because the target tissue is the nose, not the lungs or the throat. For patients with chronic rhinitis, improvement may not be seen until 1 to 2 weeks after starting therapy.

### C. $\alpha$ -Adrenergic agonists

Short-acting  $\alpha$ -adrenergic agonists (“nasal decongestants”), such as *phenylephrine*, constrict dilated arterioles in the nasal mucosa and reduce airway resistance. Long-acting *oxymetazoline* [OX-i-me-TAZ-oh-leen] is also available. When administered intranasally, these drugs have a rapid onset of action and show few systemic effects. However, intranasal formulations of  $\alpha$ -adrenergic agonists should be used for no longer than 3 days due to the risk of rebound nasal congestion (*rhinitis medicamentosa*). For this reason, the  $\alpha$ -adrenergic agents are not used in the long-term treatment of allergic rhinitis. Administration of oral  $\alpha$ -adrenergic agonists results in a longer duration of action but also increased systemic effects, such as increased blood pressure and heart rate (see Chapter 6). As with intranasal formulations, regular use of oral  $\alpha$ -adrenergic agonists (*phenylephrine* and *pseudoephedrine*) alone or in combination with antihistamines is not recommended.

### D. Other agents

Intranasal *cromolyn* may be useful in allergic rhinitis, particularly when administered before contact with an allergen. To optimize the therapeutic effect, dosing should begin at least 1 to 2 weeks prior to allergen exposure. Although potentially inferior to other treatments, some leukotriene receptor antagonists are effective for allergic rhinitis as monotherapy or in combination with other agents. They may be a reasonable option in patients who also have asthma. An intranasal formulation of *ipratropium* is available to treat rhinorrhea associated with allergic rhinitis or the common cold. It does not relieve sneezing or nasal congestion.

## VII. DRUGS USED TO TREAT COUGH/ANTITUSSIVE AGENTS

Coughing is an important defense mechanism of the respiratory system in response to irritants and is a common reason for patients to seek medical care. A troublesome cough may represent several etiologies, such as the common cold, sinusitis, and/or an underlying chronic respiratory disease. In some cases, cough may be an effective defense reflex against an underlying bacterial infection and should not be suppressed. Before treating cough, identification of its cause is important to ensure that antitussive treatment is appropriate. The priority should always be to treat the underlying cause of cough when possible.

### A. Opioids

*Codeine* [KOE-deen], an opioid, decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli and decreases mucosal secretion. These therapeutic effects occur at doses lower than those required for analgesia. However, common adverse effects, such as constipation, dysphoria, and fatigue, still occur. In addition, *codeine* has addictive potential which limits its use, given increasing concerns with opioid addiction (see Chapter 14).

*Dextromethorphan* [dex-troe-meth-OR-fan] is a synthetic derivative of *morphine* that has no analgesic effects in antitussive doses. It is a centrally active excitatory amino acid NMDA receptor antagonist and is also reported to antagonize opioid receptors. It has a better adverse effect profile than *codeine* and is equally effective for cough suppression. In low doses, *dextromethorphan* has a low addictive profile. However, it is also a potential drug of abuse, since it may cause dysphoria at high doses. *Guaifenesin* [gwy-e-FEN-e-sin], an expectorant, is available as a single-ingredient formulation and is commonly found in combination cough products with *codeine* or *dextromethorphan*.

Other opioid derivatives such as *pholcodine* and *ethylmorphine* are structurally related to *codeine* and are used as antitussive. *Pholcodine* is long acting while *ethylmorphine* is less constipating.

### B. Nonopioid cough suppressants

1. **Benzonatate:** Unlike the opioids, *benzonatate* [ben-ZOE-na-tate] suppresses the cough reflex through peripheral action. It anesthetizes the stretch receptors located in the respiratory passages, lungs, and pleura. Adverse effects include dizziness, numbness of the tongue, mouth, and throat. These localized effects may be particularly problematic if the capsules are broken or chewed and the drug comes in direct contact with the oral mucosa.
2. **Noscapine:** Although *noscapine* is also isolated from the opium poppy, it is chemically different from the phenanthrene type of alkaloids (morphine type). *Noscapine* acts as a cough suppressant through the nonopioid pathway. Sigma receptors are suggested to be involved in the antitussive mechanism of *noscapine* used for spasmodic cough. Headache and nausea are the side effects reported on its usage.

3. **Chlophedianol:** *Chlophedianol* is a centrally acting antitussive having a slow onset of action along with a longer duration of action. It is reported to cause irritability, vertigo, and dryness of mouth.
4. **Prenoxydiazine:** *Prenoxydiazine* is a locally acting antitussive which desensitizes pulmonary stretch receptors and decreases the impulses arising from lungs. Due to its peripheral action, it is indicated for the bronchial cough.

### C. Mucokinetics and expectorants

Mucokinetics are a class of drugs which aid in the clearance of mucus from the airways and lungs. Such drugs can be further categorized by their mechanism of action:

- Mucolytic agents
- Expectorants
- Surfactants—wetting agents (hypoviscosity agents) and adhesives (that decrease the adhesivity of secretions)

An expectorant (derived from the Latin *expectorare*, to expel or banish) increases the bronchial secretion or reduces its viscosity, facilitating its removal by coughing, and relieves the irritated respiratory tract. Expectorants do not alter ciliary beat frequency or mucociliary clearance. Sodium and potassium citrate or acetate, potassium iodide, guaiacol, guaiphenesin (glyceryl guaiacolate), balsam of tolu, vasaka, and terpin hydrate are commonly used mucolytics. Mucolytics are medications that change the biophysical properties of secretions by degrading the mucin polymers, DNA, fibrin, or F-actin in airway secretions, generally decreasing viscosity. This does not necessarily improve secretion clearance, because sputum that is more viscous but less sticky tends to clear better with cough. Some examples of mucolytics are bromhexine, ambroxol, acetyl cysteine, and carbocisteine. There is no evidence that the currently available expectorants are effective and therefore are not recommended for chronic bronchitis or during acute exacerbation.

Both expectorants and mucolytics are used to increase the output of bronchial secretions, enhance the clearance of bronchial exudate, and promote a productive cough. Saline expectorants stimulate bronchial mucous secretions via a vagally mediated reflex action on the gastric mucosa. However, there are no well-designed studies that support these claims. Examples of these drugs include ammonium chloride, ammonium carbonate, potassium iodide, calcium iodide, and ethylenediamine dihydroiodide. Iodine-containing products are contraindicated in pregnant, and prolonged use can induce goiter and hypothyroidism.

Direct stimulants of respiratory secretions include the volatile oils, such as eucalyptus oil and oil of lemon. They are believed to directly increase respiratory tract secretions. Their efficacy in animals is unknown.

**Guaifenesin** (glyceryl guaiacolate) is a centrally acting muscle relaxant that may also have an expectorant effect. It may stimulate bronchial secretions via vagal pathways. The volume and viscosity of bronchial secretions do not change, but particle clearance from the airways

may accelerate. Guaifenesin is commonly available in many over-the-counter cough syrups in combination with dextromethorphan.

**N-acetylcysteine** is available as a 10% solution that can be nebulized. Its mucolytic effect is the result of the exposed sulphydryl groups on the compound, which interact with disulfide bonds on mucoprotein. Acetylcysteine helps to break down respiratory mucus and enhance clearance. It may also increase the levels of glutathione, which is a scavenger of oxygen-free radicals. N-acetylcysteine has no proven benefit and carry a risk of epithelial damage when administered via aerosol. Aerosolization of acetylcysteine can cause reflex bronchoconstriction due to irritant receptor stimulation, so its use should be preceded by bronchodilator therapy. These drugs also act as antioxidants and may therefore reduce airway inflammation.

Bromhexine/Ambroxol is a derivative of the alkaloid vasicine obtained from Adiantodavasica. It is a potent mucolytic and mucokinetic, capable of inducing thin copious bronchial secretion and, helps in dissolving hard phlegm/mucus plugs. Side effects include rhinorrhea, lacrymation, gastric irritation, and hypersensitivity.

## Study Questions

Choose the ONE best answer.

41.1 A 12-year-old girl with asthma presents to the emergency room with complaints of cough, dyspnea, and wheezing after visiting a riding stable. Which is the most appropriate drug to rapidly reverse her bronchoconstriction?

- A. Inhaled fluticasone
- B. Inhaled beclomethasone
- C. Inhaled salbutamol
- D. Intravenous propranolol

Correct answer = C. Inhalation of a rapid-acting  $\beta_2$  agonist, such as salbutamol, usually provides immediate bronchodilation. An acute asthmatic crisis often requires intravenous corticosteroids, such as methylprednisolone. Inhaled corticosteroids such as beclomethasone and fluticasone treat chronic airway inflammation but do not provide any immediate effect. Propranolol is a nonselective  $\beta$ -blocker and would aggravate the bronchoconstriction.

41.2 A 9-year-old girl has severe asthma that required three hospitalizations in the past year. She is now receiving therapy that has greatly reduced the frequency of severe attacks. Which drug is most likely responsible for this benefit?

- A. Inhaled salbutamol
- B. Inhaled ipratropium
- C. Inhaled fluticasone
- D. Oral zafirlukast

Correct answer = C. Administration of an inhaled corticosteroid such as fluticasone significantly reduces the frequency of severe asthma attacks. This benefit is accomplished with minimal risk of the severe systemic adverse effects of oral corticosteroid therapy. The  $\beta_2$  agonist salbutamol is used to treat acute asthma symptoms. Ipratropium has more common use in COPD and sometimes in the acute management of acute asthma exacerbations. Zafirlukast may reduce the severity of attacks, but not to the same degree or consistency as fluticasone (or other corticosteroids).

41.3 A 68-year-old man has COPD with moderate airway obstruction. Despite using salmeterol twice daily, he reports continued symptoms of shortness of breath with mild exertion. Which agent is an appropriate addition to his current therapy?

- A. Systemic corticosteroids
- B. Salbutamol
- C. Tiotropium
- D. Roflumilast

Correct answer = C. The addition of an anticholinergic bronchodilator to the LABA salmeterol would be appropriate and provide additional therapeutic benefit. Systemic corticosteroids are used to treat exacerbations in patients with COPD, but not recommended for chronic use. The addition of a SABA (salbutamol) is less likely to provide additional benefit since the patient is already using medication with the same mechanism of action. Roflumilast is not indicated, since the patient only has moderate airway obstruction.

41.4 A 58-year-old woman with COPD has been hospitalized three times in the past year for COPD exacerbations. She reports only mild symptoms between exacerbations. Her regimen for the past year has included inhaled salmeterol twice daily and inhaled tiotropium once daily. Her current FEV<sub>1</sub> is below 60%. Which is an appropriate change in her drug therapy?

- A. Discontinue the tiotropium.
- B. Discontinue the salmeterol.
- C. Change the salmeterol to a combination product that includes both a LABA and an inhaled corticosteroid (for example, salmeterol/fluticasone DPI).
- D. Add theophylline.

Correct answer = C. The addition of an inhaled corticosteroid may provide additional benefit since the patient has significant airway obstruction and frequent exacerbations requiring hospitalization. It is not routinely recommended to discontinue a long-acting bronchodilator unless the patient experiences an adverse effect or experiences no therapeutic benefit. In this case, the patient reports mild symptoms in between exacerbations, suggesting she may benefit from both bronchodilators. Theophylline is an oral bronchodilator that is beneficial to some patients with stable COPD. However, because of its toxic potential, its use is not routinely recommended.

41.5 A 32-year-old man with a history of opioid addiction presents with cough due to a viral upper respiratory system infection. Which is appropriate symptomatic treatment for cough in this patient?

- A. Guaifenesin/dextromethorphan
- B. Guaifenesin/codeine
- C. Benzonatate
- D. Montelukast

Correct answer = C. Benzonatate suppresses the cough reflex through peripheral action and has no abuse potential. Dextromethorphan, an opioid derivative, and codeine, an opioid, both have abuse potential. Montelukast is not indicated for cough suppression.

41.6 Because of its anti-inflammatory mechanism of action, which drug requires regular administration for the treatment of asthma?

- A. Tiotropium
- B. Salmeterol
- C. Mometasone
- D. Salbutamol

Correct answer = C. Inhaled corticosteroids have direct anti-inflammatory properties on the airways and require regular dosing to be effective. Tiotropium is used more frequently for the treatment of COPD. It does not have anti-inflammatory effects like the corticosteroids. Salmeterol and salbutamol are both bronchodilators, but do not have anti-inflammatory properties.

41.7 Which agent is a preferred antihistamine for the management of allergic rhinitis?

- A. Chlorpheniramine
- B. Diphenhydramine
- C. Phenylephrine
- D. Cetirizine

Correct answer = D. Chlorpheniramine and diphenhydramine are first-generation antihistamines and are usually not a preferred treatment due to their increased risk of adverse effects, such as sedation, performance impairment, and other anticholinergic effects. Phenylephrine is short-acting  $\alpha$ -adrenergic agonist (“nasal decongestant”). Cetirizine is a second-generation antihistamine and is generally better tolerated, making it a preferred agent for allergic rhinitis.

41.8 Which medication inhibits the action of 5-lipoxygenase and consequently the action of leukotriene B<sub>4</sub> and the cysteinyl leukotrienes?

- A. Cromolyn
- B. Zafirlukast
- C. Zileuton
- D. Montelukast

Correct answer = C. Zileuton is the only 5-lipoxygenase inhibitor available. While zafirlukast and montelukast both inhibit the effects of leukotrienes, they do so by blocking the receptor. Cromolyn inhibits mast cell degranulation and the release of histamine.

41.9 Which statement describes appropriate inhaler technique for a dry powder inhaler?

- A. Inhale slowly and deeply just before and throughout actuation of the inhaler.
- B. Use a large-volume chamber (spacer) to decrease deposition of drug in the mouth caused by improper inhaler technique.
- C. Inhale quickly and deeply to optimize drug delivery to the lungs.
- D. Rinse mouth in a “swish-and-spit” method with water prior to inhaler use to decrease the chance of adverse events.

Correct answer = C. “Quick and deep” inhalation is required for effective use of a DPI. Inhaling “slowly and deeply” and the use of a spacer describe techniques associated with an MDI, not DPI. Rinsing the mouth may be appropriate for either type of inhaler if the medication being administered is an inhaled corticosteroid; however, this should always be done following inhaler use, not prior to use.

41.10 Which category of allergic rhinitis medications is most likely to be associated with rhinitis medicamentosa (rebound nasal congestion) with prolonged use?

- A. Intranasal corticosteroid
- B. Intranasal decongestant
- C. Leukotriene antagonist
- D. Oral antihistamine

Correct answer = B. Intranasal decongestants should be used no longer than 3 days due to the risk of rebound nasal congestion (rhinitis medicamentosa). For this reason, the  $\alpha$ -adrenergic agents should not be used in the long-term treatment of allergic rhinitis. The other agents may be used as chronic therapies.



# Gastrointestinal and Antiemetic Drugs

42

Carol Motycka and Adonice Khoury

## I. OVERVIEW

This chapter describes drugs used to treat six common medical conditions involving the gastrointestinal (GI) tract: 1) peptic ulcers and gastroesophageal reflux disease (GERD), 2) chemotherapy-induced emesis, 3) diarrhea, 4) constipation, 5) irritable bowel syndrome (IBS), and 6) inflammatory bowel disease (IBD). Many drugs described in other chapters also find application in the treatment of GI disorders. For example, the *meperidine* derivative *diphenoxylate*, which decreases peristaltic activity of the gut, is useful in the treatment of severe diarrhea. Other drugs are used almost exclusively to treat GI tract disorders. For example, H<sub>2</sub> receptor antagonists and proton-pump inhibitors (PPIs) are used to heal peptic ulcers.

## II. DRUGS USED TO TREAT PEPTIC ULCER DISEASE AND GASTROESOPHAGEAL REFLUX DISEASE

The two main causes of peptic ulcer disease are infection with gram-negative *Helicobacter pylori* and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Increased hydrochloric acid (HCl) secretion and inadequate mucosal defense against gastric acid also play a role (faulty roof and acid rain). Treatment approaches include 1) eradicating the *H. pylori* infection, 2) reducing secretion of gastric acid with the use of PPIs or H<sub>2</sub> receptor antagonists, and/or 3) providing agents that protect the gastric mucosa from damage, such as *misoprostol* and *sucralfate*. Figure 42.1 summarizes agents that are effective in treating peptic ulcer disease.

### A. Antimicrobial agents

Patients with peptic ulcer disease (duodenal or gastric ulcers) who are infected with *H. pylori* require antimicrobial treatment. Infection with *H. pylori* is diagnosed via endoscopic biopsy of the gastric mucosa or various noninvasive methods, including serology, fecal antigen tests, and urea breath tests (Figure 42.2). Figure 42.3 shows a biopsy sample in which *H. pylori* is discovered on the gastric mucosa. Eradication of *H. pylori* with various combinations of antimicrobial drugs results in rapid healing of active ulcers and low recurrence rates (less than 15% compared with 60% to 100% per year for ulcers healed with acid-reducing therapy alone). Currently, quadruple therapy of *bismuth*

### ANTIMICROBIAL AGENTS (for eradication of *H. pylori*)

*Amoxicillin*  
*Bismuth compounds*  
*Clarithromycin*  
*Metronidazole*  
*Tetracycline*

### H<sub>2</sub>-HISTAMINE RECEPTOR BLOCKERS

*Cimetidine*  
*Ranitidine*  
*Nizatidine*  
*Famotidine*

### PROTON-PUMP INHIBITORS (PPIs)

*Omeprazole*  
*Pantoprazole*  
*Lansoprazole*  
*Rabeprazole*  
*Esomeprazole*  
*Dexlansoprazole*

### PROSTAGLANDINS

*Misoprostol*

### ANTIMUSCARINIC AGENTS

*Dicyclomine*

### ANTACIDS

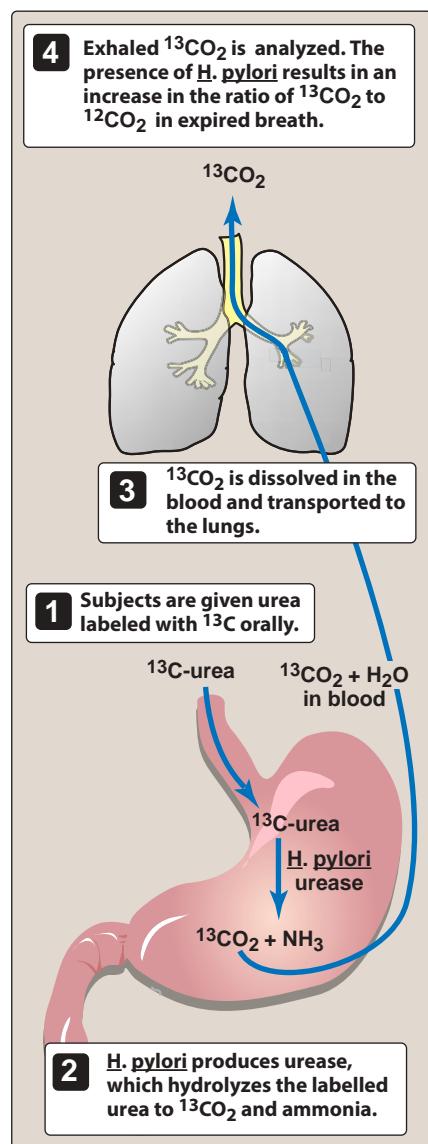
*Aluminum hydroxide*  
*Calcium carbonate*  
*Magnesium hydroxide*  
*Sodium bicarbonate*

### MUCOSAL PROTECTIVE AGENTS

*Bismuth subsalicylate*  
*Sucralfate*

### Figure 42.1

Summary of drugs used to treat peptic ulcer disease. (For drug dosages, refer to Appendix at the end of the book.)

**Figure 42.2**

Urea breath test, one of several non-invasive methods for detecting presence of *Helicobacter pylori*. Modified from D. Cave, Hosp. Pract. (1992).

**Figure 42.3**

*Helicobacter pylori* in association with gastric mucosa.

subsalicylate, metronidazole, and tetracycline plus a PPI is a recommended first-line option. Bismuth quadruple therapy is particularly attractive in patients with any previous macrolide exposure or who are allergic to penicillin. This usually results in a 90% or greater eradication rate. Triple therapy consisting of a PPI combined with amoxicillin (metronidazole may be used in penicillin-allergic patients) plus clarithromycin is a preferred treatment when rates of clarithromycin resistance are low and the patient has no prior exposure to macrolide antibiotics. Figure 42.4 depicts the treatment regimens for *H. pylori* infection. Confirm eradication of *H. pylori* after therapy in patients with *H. pylori*-associated ulcer, continued dyspeptic symptoms, mucosa-associated lymphoid tissue lymphoma, and resection of gastric cancer.

### B. $\text{H}_2$ receptor antagonists

Gastric acid secretion is stimulated by acetylcholine, histamine, and gastrin (Figure 42.5). The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases, which in turn stimulates the  $\text{H}^+/\text{K}^+$ -adenosine triphosphatase (ATPase) proton pump to secrete hydrogen ions in exchange for  $\text{K}^+$  into the lumen of the stomach. By competitively blocking the binding of histamine to  $\text{H}_2$  receptors, these agents reduce the secretion of gastric acid. Drugs such as cimetidine, ranitidine, famotidine, roxatidine, and nizatidine are used to inhibit basal, food-stimulated, and nocturnal secretion of gastric acid, reducing acid secretion by approximately 70%. Cimetidine was the first  $\text{H}_2$  receptor antagonist. However, its utility is limited by its adverse effect profile and drug-drug interactions.

- Actions:** The histamine  $\text{H}_2$  receptor antagonists act selectively on  $\text{H}_2$  receptors in the stomach, without effects on  $\text{H}_1$  receptors. They are competitive antagonists of histamine and are fully reversible.
- Therapeutic uses:** The use of these agents has decreased with the advent of PPIs.
  - Peptic ulcers:** All four agents are equally effective in promoting the healing of duodenal and gastric ulcers. However, recurrence is common if *H. pylori* is present and the patient is treated with these agents alone. Patients with NSAID-induced ulcers should be treated with PPIs, because these agents heal and prevent future ulcers more effectively than do  $\text{H}_2$  receptor antagonists.
  - Acute stress ulcers:** These drugs are given as an intravenous infusion to prevent and manage acute stress ulcers associated with high-risk patients in the intensive care setting. However, because tolerance may occur with these agents, PPIs are also used for this indication.
  - Gastroesophageal reflux disease:**  $\text{H}_2$  receptor antagonists are effective for the treatment of heartburn or gastroesophageal reflux disease (GERD).  $\text{H}_2$  receptor antagonists act by decreasing acid secretion; therefore, they may not relieve symptoms of heartburn for up to 45 minutes. Antacids more quickly and efficiently neutralize stomach acid, but their action is short-lived. For these reasons, PPIs are now used preferentially in the treatment of GERD, especially for patients with severe and frequent heartburn.

Type	Regimen	Duration	Eradication Rate	Comments
<b>First line (preferred):</b>				
Standard triple therapy	PPI, amoxicillin 1 g, and clarithromycin 500 mg twice daily	7–10 days (up to 14 days)	70–85%	Preferred
	PPI, clarithromycin 500 mg, and metronidazole 500 mg twice daily	10–14 days	70–85%	—
If the patient does not tolerate triple therapy, switch to sequential regimen				
Sequential therapy	PPI and amoxicillin 1 g twice daily, followed by PPI, clarithromycin 500 mg, and tinidazole 500 mg or metronidazole 500 mg twice daily	10 days (5 days for each regimen)	> 4%	—
<b>Second line:</b>				
Non-bismuth-based quadruple therapy (concomitant therapy)	PPI, amoxicillin 1 g, clarithromycin 500 mg, and tinidazole 500 mg or metronidazole 500 mg twice daily	10 days	90%	Less complex than sequential therapy with similar eradication rates
Bismuth-based quadruple therapy	Bismuth subsalicylate 525 mg or subcitrate 300 mg, metronidazole 250 mg, and tetracycline 500 mg, four times daily; and PPI twice daily	10–14 days	75–90%	May also be used if first-line therapy fails
Levofloxacin-based triple therapy	PPI and amoxicillin 1 g twice daily, and levofloxacin 500 mg once daily	10 days	—	Needs validation; should be used as salvage therapy only

PPI = proton-pump inhibitor

**Notes:** Tab. Omeprazole 20 mg Or Lansoprazole 30 mg Or Pantoprazole 40 mg Or Rabeprazole 20 mg Or Esomeprazole 40 mg 2 times a day (Esomeprazole can be taken once daily). All medicines to be taken 15 to 30 minutes before meals.

**Figure 42.4**

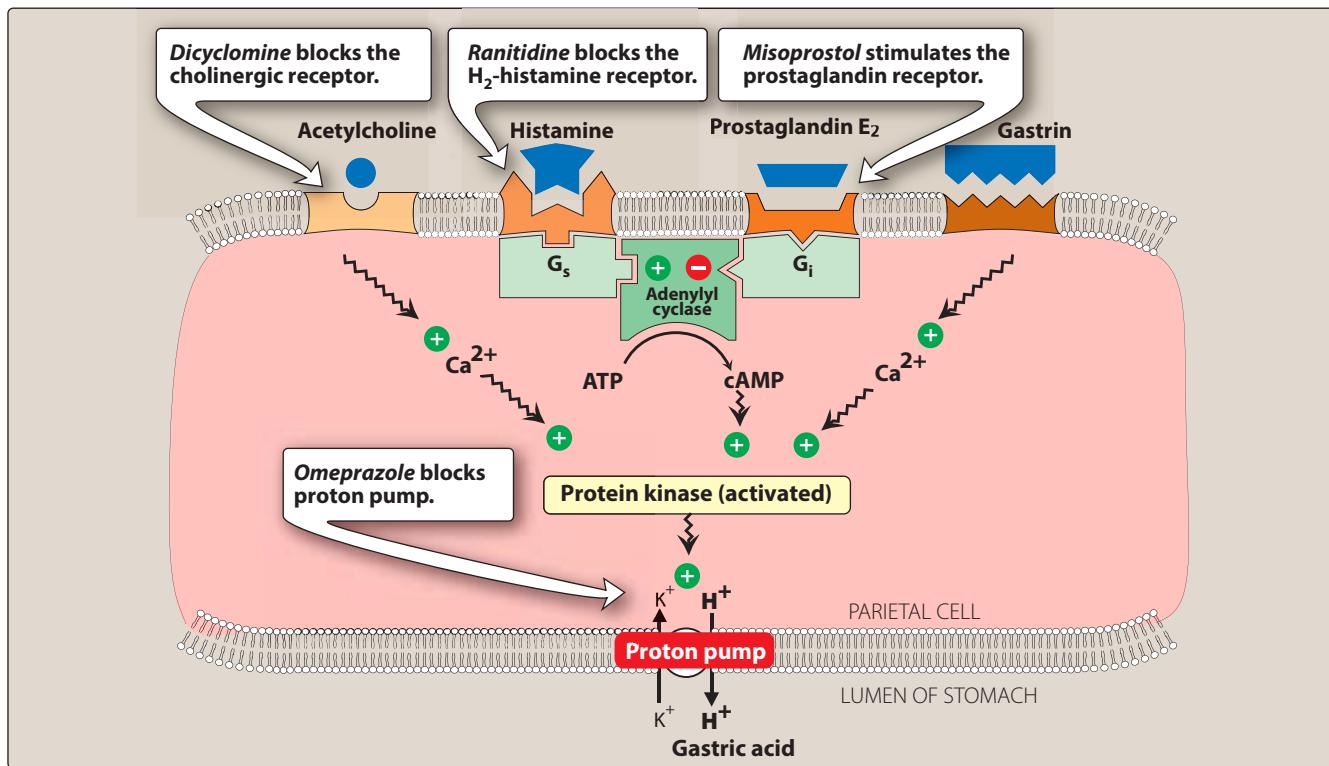
Treatment regimens for *Helicobacter pylori* infection.

**3. Pharmacokinetics:** After oral administration, the H<sub>2</sub> receptor antagonists distribute widely throughout the body (including into breast milk and across the placenta) and are excreted mainly in urine. *Cimetidine*, *ranitidine*, and *famotidine* are also available in intravenous formulations. The half-life of these agents may be increased in patients with renal dysfunction, and dosage adjustments are needed.

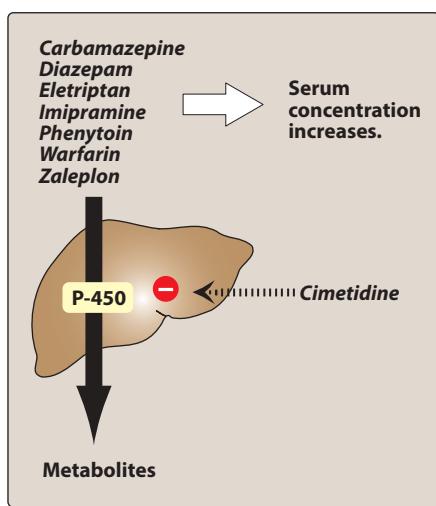
**4. Adverse effects:** In general, the H<sub>2</sub> receptor antagonists are well tolerated. However, *cimetidine* can have endocrine effects (displaces dihydrotestosterone from its binding site), such as gynecomastia and galactorrhea (continuous release/discharge of milk) because it acts as a nonsteroidal antiandrogen. Other central nervous system effects such as confusion and altered mentation occur primarily in elderly patients and after intravenous administration. H<sub>2</sub> receptor antagonists may reduce the efficacy of drugs that require an acidic environment for absorption, such as *ketoconazole*. *Cimetidine* inhibits several cytochrome P450 isoenzymes and can interfere with the metabolism of many drugs, such as *warfarin*, *phenytoin*, and *clopidogrel* (Figure 42.6).

### C. Inhibitors of the H<sup>+</sup>/K<sup>+</sup>-ATPase proton pump

The proton-pump inhibitors (PPIs) bind to the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme system (proton pump) and suppress the secretion of hydrogen ions into the gastric lumen. The membrane-bound proton pump is the final

**Figure 42.5**

Effects of acetylcholine, histamine, prostaglandin E<sub>2</sub>, and gastrin on gastric acid secretion by the parietal cells of stomach. G<sub>s</sub> and G<sub>i</sub> are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenyl cyclase.

**Figure 42.6**

Drug interactions with cimetidine.  
Modified from F. E. Silverstein, D. Y. Graham, and J. R. Senior. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann. Intern. Med. 123: 241 (1995).

step in the secretion of gastric acid (Figure 42.5). The available PPIs include *lansoprazole* [lan-SO-pra-zole] (and its isomer *dexlansoprazole*), *esomeprazole* [es-oh-MEH-pra-zole], *omeprazole* [oh-MEH-pra-zole], *pantoprazole* [pan-TOE-pra-zole], and *rabeprazole* [rah-BEH-pra-zole].

- Actions:** These agents are prodrugs with an acid-resistant enteric coating to protect them from premature degradation by gastric acid. The coating is removed in the alkaline duodenum, and the prodrug, a weak base, is absorbed and transported to the parietal cell. There, it is converted to the active drug and forms a stable covalent bond with the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme. It takes about 18 hours for the enzyme to be resynthesized, and acid secretion is inhibited during this time. At standard doses, PPIs inhibit both basal and stimulated gastric acid secretion by more than 90%. An oral product containing *omeprazole* combined with *sodium bicarbonate* for faster absorption is also available. Some degree of difference has been observed between the individual agents for their acid stability.
- Therapeutic uses:** The PPIs are superior to the H<sub>2</sub> antagonists in suppressing acid production and healing ulcers. Thus, they are the preferred drugs for the treatment of GERD, erosive esophagitis, active duodenal ulcer, and pathologic hypersecretory conditions such as Zollinger-Ellison syndrome. PPIs reduce the risk of bleeding from ulcers caused by *aspirin* and other NSAIDs and may be used for prevention or treatment of NSAID-induced ulcers. PPIs are also used for stress ulcer prophylaxis and management. Finally, PPIs are combined with antimicrobial regimens used to eradicate *H. pylori*.

**3. Pharmacokinetics:** These agents are effective orally. For maximum effect, PPIs should be taken 30 to 60 minutes before breakfast or the largest meal of the day. [Note: Some of them are formulated as dual delayed-release formulation and can be taken without regard to food.] *Esomeprazole*, *lansoprazole*, and *pantoprazole* are also available in intravenous formulations. Although the plasma half-life of these agents is only a few hours, they have a long duration of action due to covalent bonding with the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme. Metabolites of these agents are excreted in urine and feces.

**4. Adverse effects:** The PPIs are generally well tolerated. *Omeprazole* and *esomeprazole* may decrease the effectiveness of *clopidogrel* because they inhibit CYP2C19 and prevent the conversion of *clopidogrel* to its active metabolite. Concomitant use of these PPIs with *clopidogrel* is not recommended. PPIs may increase the risk of fractures, particularly if the duration of use is 1 year or greater (Figure 42.7). Prolonged acid suppression with PPIs (and H<sub>2</sub> receptor antagonists) may result in low vitamin B<sub>12</sub> because acid is required for its absorption in a complex with intrinsic factor. Elevated gastric pH may also impair the absorption of *calcium carbonate*. *Calcium citrate* is an effective option for calcium supplementation in patients on acid suppressive therapy, since absorption of the citrate salt is not affected by gastric pH. Diarrhea and *Clostridium difficile* colitis may occur in patients receiving PPIs. Patients must be counseled to discontinue PPI therapy and contact their physician if they have diarrhea for several days. Additional adverse effects may include hypomagnesemia and an increased incidence of pneumonia.

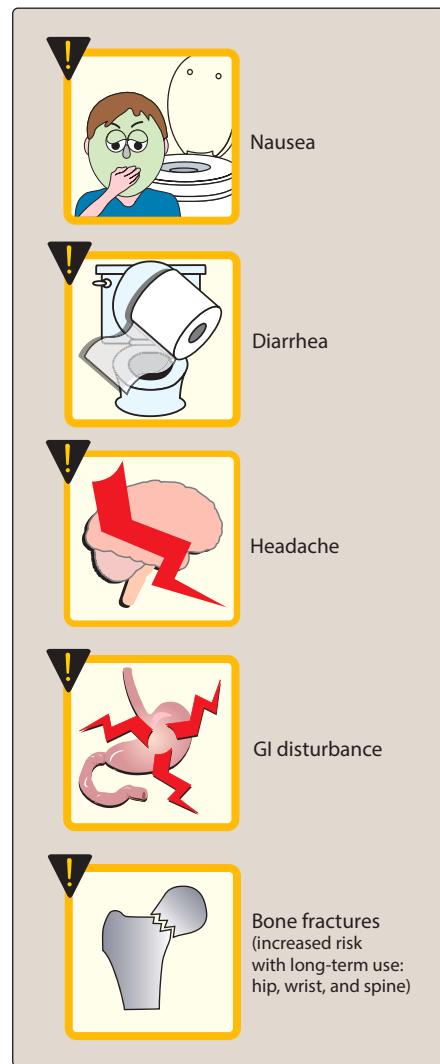
#### D. Prostaglandins

Prostaglandin E, produced by the gastric mucosa, inhibits secretion of acid and stimulates secretion of mucus and bicarbonate (cytoprotective effect). A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. *Misoprostol* [mye-soe-PROST-ole], an analog of prostaglandin E<sub>1</sub>, is approved for the prevention of NSAID-induced gastric ulcers (Figure 42.8). Prophylactic use of *misoprostol* should be considered in patients who take NSAIDs and are at moderate-to-high risk of NSAID-induced ulcers, such as elderly patients and those with previous ulcers. *Misoprostol* is contraindicated in pregnancy, since it can stimulate uterine contractions and cause miscarriage. Dose-related diarrhea is the most common adverse effect and limits the use of this agent. Thus, PPIs are preferred agents for the prevention of NSAID-induced ulcers.

#### E. Antacids

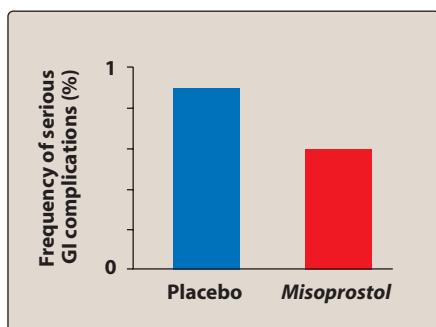
Antacids are weak bases that react with gastric acid to form water and a salt to diminish gastric acidity. Because pepsin (a proteolytic enzyme) is inactive at a pH greater than 4, antacids also reduce pepsin activity.

**1. Chemistry:** Antacid products vary widely in their chemical composition, acid-neutralizing capacity, sodium content, and palatability. The efficacy of an antacid depends on its capacity to neutralize gastric HCl and on whether the stomach is full or empty. Food delays stomach emptying, allowing more time for the antacid to react and prolonging the duration of action. Commonly used antacids are combinations of salts of aluminum



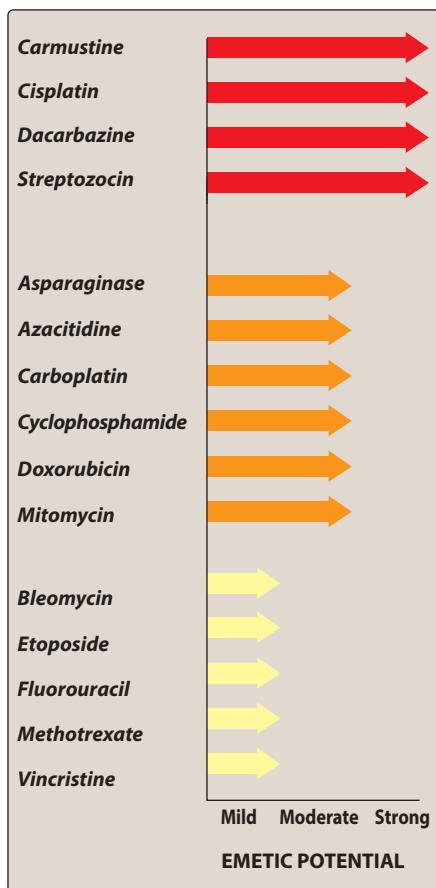
**Figure 42.7**

Some adverse effects of proton pump therapy. GI = gastrointestinal. Modified from S. M. Grunberg, and P. J. Hesketh. Control of chemotherapy-induced emesis. N. Engl. J. Med. 329: 1790 (1993).



**Figure 42.8**

*Misoprostol* reduces serious gastrointestinal (GI) complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs.



**Figure 42.9**

Comparison of emetic potential of anticancer drugs. From data of S. Bilgrami, and B. G. Fallon. Chemotherapy-induced nausea and vomiting. Easing patients' fear and discomfort with effective antiemetic regimens. Postgrad. Med. 94: 55 (1993).

and magnesium, such as *aluminum hydroxide* and *magnesium hydroxide* [ $\text{Mg}(\text{OH})_2$ ]. *Calcium carbonate* [ $\text{CaCO}_3$ ] reacts with HCl to form  $\text{CO}_2$  and  $\text{CaCl}_2$  and is also a commonly used preparation. Systemic absorption of *sodium bicarbonate* [ $\text{NaHCO}_3$ ] can produce transient metabolic alkalosis and produce a significant sodium load. Therefore, this antacid is not recommended.

- Therapeutic uses:** Antacids are used for symptomatic relief of peptic ulcer disease, heartburn, and GERD. They should be administered after meals for maximum effectiveness. [Note: *Calcium carbonate* preparations are also used as calcium supplements for the prevention of osteoporosis.] *Magaldrate* is a hydrated complex of hydroxy magnesium aluminate that releases aluminum hydroxide upon reaction with acid. This complex shows sustained as well as higher acid neutralizing capacity upon administration.
- Adverse effects:** *Aluminum hydroxide* tends to cause constipation, whereas *magnesium hydroxide* tends to produce diarrhea. Preparations that combine these agents aid in normalizing bowel function. Absorption of the cations from antacids ( $\text{Mg}^{2+}$ ,  $\text{Al}^{3+}$ ,  $\text{Ca}^{2+}$ ) is usually not a problem in patients with normal renal function; however, accumulation and adverse effects may occur in patients with renal impairment.

## F. Mucosal protective agents

Also known as cytoprotective compounds, these agents have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

- Sucralfate:** This complex of *aluminum hydroxide* and sulfated sucrose binds to positively charged groups in proteins of both normal and necrotic mucosa. By forming complex gels with epithelial cells, *sucralfate* [soo-KRAL-fate] creates a physical barrier that protects the ulcer from pepsin and acid, allowing the ulcer to heal. Although *sucralfate* is effective for the treatment of duodenal ulcers and prevention of stress ulcers, its use is limited due to the need for multiple daily dosing, drug-drug interactions, and availability of more effective agents. Because it requires an acidic pH for activation, *sucralfate* should not be administered with PPIs,  $\text{H}_2$  antagonists, or antacids. *Sucralfate* is well tolerated, but it can bind to other drugs and interfere with their absorption.
- Bismuth subsalicylate:** This agent is used as a component of quadruple therapy to heal *H. pylori*-related peptic ulcers. In addition to its antimicrobial actions, it inhibits the activity of pepsin, increases secretion of mucus, and interacts with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer.

## III. DRUGS USED TO CONTROL CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Although nausea and vomiting occur in a variety of conditions (for example, motion sickness, pregnancy, and GI illnesses) and are always unpleasant for the patient, the nausea and vomiting produced by chemotherapeutic agents demands especially effective management. Nearly 70% to 80% of patients who undergo chemotherapy experience nausea and/or vomiting. Several factors influence the incidence and severity of chemotherapy-induced nausea and vomiting (CINV), including the specific chemotherapeutic drug (Figure 42.9); the dose, route, and schedule of administration; and patient

variables. For example, young patients and women are more susceptible than older patients and men, and 10% to 40% of patients experience nausea and/or vomiting in anticipation of chemotherapy (anticipatory vomiting). CINV not only affects quality of life but can also lead to rejection of potentially curative chemotherapy. In addition, uncontrolled vomiting can produce dehydration, profound metabolic imbalances, and nutrient depletion.

### A. Mechanisms that trigger vomiting

Two brainstem sites have key roles in the vomiting reflex pathway. The chemoreceptor trigger zone (CTZ) is located in the area postrema (a circumventricular structure at the caudal end of the fourth ventricle). It is outside the blood–brain barrier. Thus, it can respond directly to chemical stimuli in the blood or cerebrospinal fluid. The second important site, the vomiting center, which is located in the lateral reticular formation of the medulla, coordinates the motor mechanisms of vomiting. The vomiting center also responds to afferent input from the vestibular system, the periphery (pharynx and GI tract), and higher brainstem and cortical structures. The vestibular system functions mainly in motion sickness.

### B. Emetic actions of chemotherapeutic agents

Chemotherapeutic agents can directly activate the medullary CTZ or vomiting center. Several neuroreceptors, including dopamine receptor type 2 and serotonin type 3 (5-HT<sub>3</sub>), play critical roles. Often, the color or smell of chemotherapeutic drugs (and even stimuli associated with chemotherapy) can activate higher brain centers and trigger emesis. Chemotherapeutic drugs can also act peripherally by causing cell damage in the GI tract and by releasing serotonin from the enterochromaffin cells of the small intestine. Serotonin activates 5-HT<sub>3</sub> receptors on vagal and splanchnic afferent fibers, which then carry sensory signals to the medulla, leading to the emetic response.

### C. Antiemetic drugs

Considering the complexity of the mechanisms involved in emesis, it is not surprising that antiemetics represent a variety of classes (Figure 42.10) and offer a range of efficacies (Figure 42.11). This group contains a wide range of drugs that belong to antihistamines, anticholinergics, antidopaminergics, selective 5-HT receptor antagonists, neuroleptics, neurokinin 1 antagonists, and their combinations.

Motion sickness sometimes is bothersome during travelling and with use of advanced visual information technologies such as 3D visuals mimicking reality. Motion sickness arises from a mismatch between sensory inputs from the visual and vestibular systems. Agents with anticholinergic and antihistaminic properties are the drug of choice for motion sickness and they are taken before commencement of the journey.

Incidence of morning sickness accompanied by nausea and vomiting is reported in 85% of pregnant women. The most severe form, hyperemesis gravidarum, affects up to 3% of women and can have significant adverse physical and psychological consequences. Clinical studies found for the mild symptoms of nausea and emesis of pregnancy, ginger, pyridoxine, antihistamines, and *metoclopramide* are found to provide greater benefit. For moderate symptoms, *pyridoxine-doxylamine*, *promethazine*, and *metoclopramide* are beneficial. *Ondansetron* is associated with improvement for a range of symptom severity, and in severe cases corticosteroids may have some added benefit.

### PHENOTHIAZINES

*Prochlorperazine*

### 5-HT3 SEROTONIN RECEPTOR ANTAGONISTS

*Dolasetron*

*Granisetron*

*Ondansetron*

*Palonosetron*

### SUBSTITUTED BENZAMIDES

*Metoclopramide*

### BUTYROPHENONES

*Droperidol*

*Haloperidol*

### BENZODIAZEPINES

*Alprazolam*

*Lorazepam*

### CORTICOSTEROIDS

*Dexamethasone*

*Methylprednisolone*

### SUBSTANCE P/NEUROKININ-1 RECEPTOR ANTAGONIST

*Aprepitant*, *Fosaprepitant*

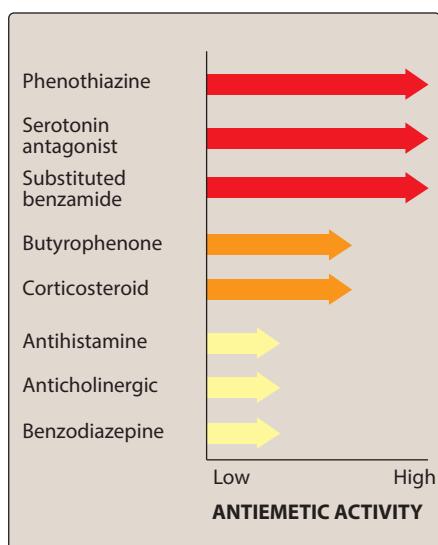
*Netupitant*\*

*Rolapitant*

**Figure 42.10**

Summary of drugs used to treat CINV.

\*In combination with *palonosetron*.



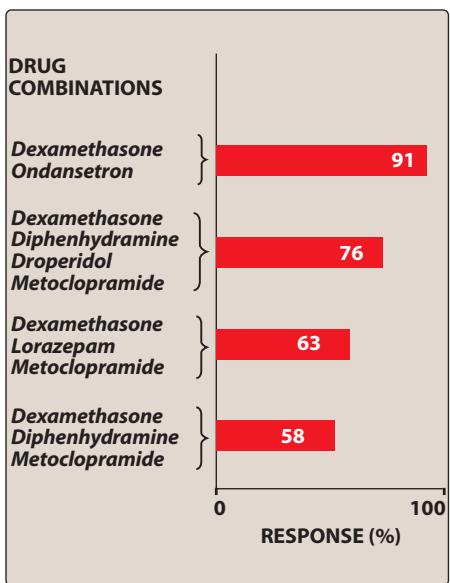
**Figure 42.11**

Efficacy of antiemetic drugs.

1. **Anticholinergics:** Anticholinergic drugs, especially the muscarinic receptor antagonist *scopolamine*, also called *hyoscine*, are used predominately for motion sickness. By blocking the cholinergic pathway link between vestibular apparatus and vomiting centers, *hyoscine* exhibit its action as antiemetic. Since it has a shorter duration of action, it cannot be used for longer journeys. It is also formulated as a transdermal patch (applied behind pinna) which can deliver the drug over a period of 3 days. Apart from *hyoscine*, *dicyclomine* has also been used as a prophylaxis for motion sickness.
2. **Antihistamines:** Antihistaminics, such as *diphenhydramine* and *dimenhydrinate*, known to have antiemetic property, are also used for motion sickness and to a lesser extent for morning sickness. Antiemetic effects of antihistaminics are due to their nonspecific action of anticholinergic and antidopaminergic activities apart from their action on histamine receptors. However, sedation and anticholinergic side effects such as dryness of mouth are associated with its use. *Dimenhydrinate*, *meclizine*, and *cyclizine*, are very useful in motion sickness but are ineffective against substances that act directly on the CTZ. *Doxylamine* is an antihistaminic effective for “morning sickness” in early pregnancy. *Doxylamine-pyridoxine* is recommended as a first-line treatment for nausea and vomiting during pregnancy and it is commonly prescribed. *Meclizine* shows lesser sedation along with longer duration (24 hours) of action; it is used for sea sickness. Acute vestibular symptoms may be ameliorated by antiemetic and vestibular-suppressant drugs such as *cinnarizine* or *flunarizine* but these drugs have extrapyramidal side effects and should be used cautiously by older patients.
3. **Phenothiazines:** Phenothiazines, such as *prochlorperazine* [pro-klor-PER-ah-zeen], act by blocking dopamine receptors in the CTZ. *Prochlorperazine* is effective against low or moderately emetogenic chemotherapeutic agents (for example, *fluorouracil* and *doxorubicin*). Although increasing the dose improves antiemetic activity, adverse effects are dose limiting. *Promethazine*, used for motion sickness, is a centrally acting phenothiazine derivative having weak antidopaminergic effect. By acting through D2 receptors, older generation neuroleptics such as *phenothiazines* and *haloperidol* exhibit antiemetic property.
4. **5-HT<sub>3</sub> receptor blockers:** The 5-HT<sub>3</sub> receptor antagonists include *dolasetron* [dol-A-seh-tron], *granisetron* [gra-NI-seh-tron], *ondansetron* [on-DAN-seh-tron], *palonosetron* [pa-low-NO-seh-tron], and *ramosetron*. These agents selectively block 5-HT<sub>3</sub> receptors in the periphery (visceral vagal afferent fibers) and in the CTZ. This class of agents is important in treating CINV, because of their superior efficacy and longer duration of action. These drugs can be administered as a single dose prior to chemotherapy (intravenously or orally) and are efficacious against all grades of emetogenic therapy. *Ondansetron* and *granisetron* prevent emesis in 50% to 60% of *cisplatin*-treated patients. These agents are also useful in the management of postoperative nausea and vomiting. 5-HT<sub>3</sub> antagonists are extensively metabolized by the liver; however, only *ondansetron* requires dosage adjustments in hepatic insufficiency. Excretion is via the urine. QT prolongation can occur with high doses of *ondansetron* and *dolasetron*. For this reason, the indication for CINV prophylaxis was withdrawn for intravenous

*dolasetron*. *Ramosetron* is developed in Japan and available for use in Asian countries. Its pharmacology is similar to *ondansetron*. It is used for CINV by injecting intravenously before chemotherapy. It is orally administered once daily where a lesser degree of CINV is expected.

5. **Substituted benzamides:** One of several substituted benzamides with antiemetic activity, *metoclopramide* [met-oh-kloe-PRAH-mide], is effective at high doses against the emetogenic *cisplatin*, preventing emesis in 30% to 40% of patients and reducing emesis in the majority of patients. *Metoclopramide* accomplishes this through inhibition of dopamine in the CTZ. Antidopaminergic adverse effects, including extrapyramidal symptoms, limit long-term high-dose use. *Metoclopramide* enhances gastric motility and is useful for patients with gastroparesis.
6. **Butyrophenones:** *Droperidol* [droe-PER-i-doll] and *haloperidol* [hal-oh-PER-i-doll] act by blocking dopamine receptors. The butyrophenones are moderately effective antiemetics. *Droperidol* had been used most often for sedation in endoscopy and surgery, usually in combination with opioids or benzodiazepines. However, it may prolong the QT<sub>c</sub> interval and should be reserved for patients with inadequate response to other agents.
7. **Domperidone:** *Domperidone* is a D2 receptor antagonist, structurally related to butyrophenones in the upper gastrointestinal tract. Its antiemetic and prokinetic actions are similar to those of *metoclopramide*. As it crosses the blood-brain barrier poorly, its extrapyramidal side effects are rare but can cause hyperprolactinemia. It can cause mild galactorrhea (used for the induction of lactation) in females, dry mouth, and headache. Its antiemetic activity is through its penetration at the blood-brain barrier-deficient chemoreceptor trigger zone (CTZ). It is absorbed orally and shows poor bioavailability due to extensive first-pass metabolism. It has a plasma half-life of 7 hours. Health Canada released a warning regarding the use of *domperidone*, because of its association with life-threatening arrhythmias and death.
8. **Benzodiazepines:** The antiemetic potency of *lorazepam* [lor-A-ze-pam] and *alprazolam* [al-PRAH-zoe-lam] is low. Their beneficial effects may be due to their sedative, anxiolytic, and amnestic properties. These same properties make benzodiazepines useful in treating anticipatory vomiting. Concomitant use of alcohol should be avoided due to additive CNS depressant effects.
9. **Corticosteroids:** *Dexamethasone* [dex-a-MEH-tha-sone] and *methylprednisolone* [meth-ill-pred-NIH-so-lone], used alone, are effective against mildly to moderately emetogenic chemotherapy. Most frequently, they are used in combination with other agents. Their antiemetic mechanism is not known, but it may involve blockade of prostaglandins.
10. **Substance P/neurokinin-1 receptor antagonist:** *Aprepitant* [ah-PRE-pih-tant], *netupitant* [net-UE-pi-tant], and *rolapitant* [net-UE-pi-tant] target the neurokinin receptor in the vomiting center and block the actions of substance P. [Note: *Fosaprepitant* is a prodrug of *aprepitant* that is administered intravenously.] These oral agents are indicated for highly or moderately emetogenic

**Figure 42.12**

Effectiveness of antiemetic activity of some drug combinations against emetic episodes in the first 24 hours after *cisplatin* chemotherapy.

chemotherapy regimens, and they are usually administered with *dexamethasone* and a 5-HT<sub>3</sub> antagonist. Unlike most 5-HT<sub>3</sub> antagonists, these agents are effective for the delayed phase of CINV which occurs 24 hours or more after chemotherapy. *Aprepitant* and *rolapitant* undergo hepatic metabolism, primarily by CYP3A4. Coadministration with strong inhibitors or inducers of CYP3A4 (for example, *clarithromycin* or *St. John's wort*, respectively) should be avoided. *Aprepitant* is an inducer of CYP3A4 and CYP2C9, and it also exhibits dose-dependent inhibition of CYP3A4. Therefore, it may affect the metabolism of other drugs that are substrates of these isoenzymes and is subject to numerous drug interactions. *Rolapitant* is a moderate inhibitor of CYP2D6. Fatigue, diarrhea, abdominal pain, and hiccups are adverse effects of this class.

- Combination regimens:** Antiemetic drugs are often combined to increase efficacy or decrease toxicity (Figure 42.12). Corticosteroids, most commonly *dexamethasone*, increase antiemetic activity when given with high-dose *metoclopramide*, a 5-HT<sub>3</sub> antagonist, *phenothiazine*, *butyrophenone*, or a *benzodiazepine*. Antihistamines, such as *diphenhydramine*, are often administered in combination with high-dose *metoclopramide* to reduce extrapyramidal reactions or with corticosteroids to counter *metoclopramide*-induced diarrhea. Addition of a substance P/neurokinin-1 receptor antagonist to a 5-HT<sub>3</sub> antagonist and *dexamethasone* is beneficial in highly emetogenic regimens, especially those with delayed CINV.

#### IV. THERAPEUTIC USE OF ANTIEMETIC DRUGS

Antiemetics are indicated to control vomiting, especially when profuse and protracted vomiting may lead to fluid, electrolyte, or acid-base disturbances or is causing distress to the patient or owner. Antiemetic drugs are commonly used to prevent vomiting predicted to occur with the use of emetic drugs, for example, anticancer drugs and amphotericin. Use of antiemetic agents for chemotherapy-induced vomiting should take into account individual patient risk factors (for example, sex, age, history of alcohol use, and previous emesis with chemotherapy). Postoperative nausea and vomiting frequently occur in the first 24 hours after anesthesia and surgery. *Dexamethasone*, *prochlorperazine*, *hyoscine* (using a transdermal patch), *cyclizine*, and 5-HT<sub>3</sub> receptor antagonists are all effective for preventing postoperative vomiting.

Nausea is common in pregnancy. High doses of pyridoxine (vitamin B<sub>6</sub>) or nonpharmacological therapy ground ginger may be effective. Hyperemesis gravidarum, severe morning sickness which begins in the first trimester, can lead to marked maternal weight loss, dehydration, electrolyte disturbances, and vitamin deficiencies. Avoid drugs, whenever possible; however, if vomiting arises in pregnancy doxylamine, promethazine, *prochlorperazine*, *metoclopramide*, or *ondansetron* at bed time is used for short-term treatment. For more severe vomiting, intravenous rehydration and nutritional supplementation (particularly thiamine in hyperemesis gravidarum) will be necessary.

Use of antiemetics is not necessary if vomiting is intermittent, the patient is not distressed, and correction of fluid and electrolyte imbalances can easily be achieved.

#### A. Inappropriate use of antiemetics

Use of antiemetics in the following situations is inappropriate:

- Gastrointestinal obstruction—antiemetics may delay diagnosis.
- Gastrointestinal toxicity/gastroenteritis—antiemetics may prevent the patient from eliminating the toxin.
- Systemic hypotension—the phenothiazines and  $\alpha_2$ -adrenergic antagonists, when used in high doses, can intensify hypotension.

### V. ANTIDIARRHEALS

Diarrhea is a condition of having at least three loose or liquid bowel movements (or more frequently than usual) in a day lasting for less than 14 days. Diarrhea can be accompanied by painful abdominal cramps, nausea, fever, bloating, and generalized weakness. It often lasts for a few days and can result in dehydration due to loss of fluids in stool, especially in young children and older people. Symptoms of dehydration in adults can include thirst, lack of energy, passing less urine than normal, dizziness or lightheadedness, and loss of skin colour and turgor. Symptoms of mild-to-moderate dehydration in children can include dry mouth, decreased urination, irritability, listlessness, and less tears when crying. Signs of severe dehydration in children include sunken eyes, cheeks or belly or a sunken fontanelle. People with diarrhea, especially the very young and the very elderly, are at risk of becoming rapidly dehydrated. This requires immediate medical attention.

The most common cause of the gastroenteritis are due to either a virus, bacteria, or parasite. Parasites include particularly protozoa (for example, *Cryptosporidium* spp., *Giardia* spp., *Entamoeba histolytica*). Infectious diarrhea due to norovirus in adults and rotavirus in children is the most common cause of diarrhea worldwide and is the leading cause of death in childhood. Bacterial diarrhea are caused by infections by *Salmonella* spp., *Shigella* spp., and some strains of *Escherichia coli*. These infections are often acquired from contaminated food or water with viruses or bacteria. Diarrhea can be prevented by improved sanitation, clean drinking water, hand washing with soap, exclusive breast-feeding up to 6 months, and rotavirus vaccination. The rotavirus vaccine is given as 2 or 3 doses as part of the routine childhood immunization schedule at 2 months, 4 months, and sometimes also at 6 months.

#### A. Antibiotics

Since diarrhea is a self-limiting illness and most deaths are caused by dehydration, the mainstay of treatment in diarrhea is rehydration with oral rehydration solution (ORS). Increased motility of the GI tract and decreased absorption of fluid are major factors in diarrhea. Because acute diarrhea is most often self-limited and caused by viruses, routine antibiotic use is not recommended for most adults with non-severe, watery diarrhea. Therefore, the role of antimicrobial agents in the management of infective diarrhea is limited and these agents are

indicated in case of bacillary dysentery as in shigellosis, campylobacteriosis, *Clostridium difficile*, traveler's diarrhea, and protozoal infections. Additionally, the overuse of antibiotics can lead to resistance, harmful eradication of normal flora, prolongation of illness (for example, superinfection with *C. difficile*), prolongation of carrier state (for example, delayed excretion of *Salmonella*), induction of Shiga toxins (for example, from Shiga toxin-producing *E. coli*), and increased cost. Antibiotics may be considered in patients with traveler's diarrhea, old patients, immunocompromised, severely ill, or septic patients. Probiotics have been shown to have some efficacy in diarrhea by stimulating the immune system and competing for binding sites on intestinal epithelial cells. However, further scrutiny is required to determine the magnitude of their effect as many species are generally categorized as probiotics, but even closely related strains may have different clinical effects.

### B. Zinc supplementation

Zinc supplementation (20 mg per day for 10 days in children older than 2 months) may play a crucial role in treating and preventing acute diarrhea, in children. A decrease in the risk of dehydration and in the duration and severity of the diarrheal episode by 20% to 40% has been observed. However, additional research is needed to evaluate potential benefits of zinc supplementation in the adult population.

### C. Rehydration therapy

Oral rehydration therapy (ORT) is the cornerstone of treatment and is by far the safest, most physiologic, and most effective way to provide rehydration and maintain hydration in children with acute diarrhea worldwide, as recommended by the WHO. The reduced osmolarity ORS (250 mOsm/L or less) decreases stool outputs, episodes of emesis, and the need for intravenous rehydration without increasing hyponatremia, compared with the standard ORS (osmolarity 311 mOsm/L). Not all commercial ORT formulas promote optimal absorption of electrolytes, water, and nutrients. The ideal solution has a low osmolarity (210 to 250 mOsm/L) and a sodium content of 50 to 60 mmol/L. In addition, maintenance fluids are given for replacement of losses. Educate caregivers in methods necessary to replace this amount of fluid. Small amounts of fluid at frequent intervals minimize discomfort and vomiting. Early refeeding decreases intestinal permeability caused by infections, reduces the duration of illness, and improves nutritional outcomes. In case of severe-to-moderate dehydration, the patient requires intravenous lactated Ringer solution or normal saline (20 ml/kg until perfusion and mental status improve), followed by 100 ml/kg ORS over 4 hours or 5% dextrose, or half-normal saline intravenously at twice-maintenance fluid rates.

## VI. OTHER ANTIDIARRHEAL DRUGS

Antidiarrheal drugs include antimotility agents, adsorbents, and drugs that modify fluid and electrolyte transport (Figure 42.13).

### A. Antimotility agents

Two drugs that are widely used to control diarrhea are *diphenoxylate* [dye-fen-OX-see-late] and *loperamide* [loe-PER-ah-mide]. Both are analogs of *meperidine* and have opioid-like actions on the gut. They activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis. At the usual doses, they lack analgesic effects. *Loperamide* is used for the general treatment of acute diarrhea, including traveler's diarrhea. Because these drugs can contribute to toxic megacolon, they should not be used in young children or in patients with severe colitis.

### B. Adsorbents

Adsorbent agents, such as *aluminum hydroxide* and *methylcellulose* [meth-ill-CELL-you-lowse], are used to control diarrhea. Presumably, these agents act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa. They are much less effective than antimotility agents, and they can interfere with the absorption of other drugs.

### C. Agents that modify fluid and electrolyte transport

*Bismuth subsalicylate*, used for prevention and treatment of traveler's diarrhea, decreases fluid secretion in the bowel. Its action may be due to its salicylate component as well as its coating action. Adverse effects may include black tongue and black stools.

## VII. LAXATIVES

Constipation is defined as a decrease in frequency and liquidity of stool compared to the normal pattern in a particular individual. Laxatives are commonly used in the treatment of constipation to accelerate the motility of the bowel, soften the stool, and increase the frequency of bowel movements. These drugs are classified on the basis of their mechanism of action (Figure 42.14). Laxatives increase the potential for loss of pharmacologic effect of poorly absorbed, delayed-acting, and extended-release oral preparations by accelerating their transit through the intestines. They may also cause electrolyte imbalances when used chronically. Many of these drugs have a risk of dependency for the user. Lifestyle advice, fluid intake, fiber, and exercise must be continued throughout laxative therapy. Acute constipation may be a part of a more serious illness such as acute bowel obstruction. Red flag signs which point toward other causes of constipation include a persistent unexplained change in the bowel habit, especially in an elderly person whose bowel habits have always been regular, unexplained weight loss, iron deficiency anemia, fever, nocturnal symptoms, severe, persistent constipation which is unresponsive to treatment, palpable mass in the abdomen or pelvis, persistent rectal bleeding without anal symptoms, narrowing of stool caliber, family history of colon cancer, or inflammatory bowel disease.

### DRUGS USED IN DIARRHEA

*Oral rehydration therapy (ORS)*

*Probiotics*

*Zinc*

### ANTIMOTILITY AGENTS

*Diphenoxylate + atropine*

*Loperamide*

### ADSORBENTS

*Aluminum hydroxide*

*Methylcellulose*

### AGENTS THAT MODIFY FLUID AND ELECTROLYTE TRANSPORT

*Bismuth subsalicylate*

### Figure 42.13

Summary of drugs used to treat diarrhea.

Stimulant and irritant laxatives (can cause abdominal cramps due to increased intestinal motility. They generally act by stimulating nerves to induce peristalsis and also decrease water reabsorption from the colon).			
EXAMPLES	ROUTE	ACTS WITHIN	EXTRA MEASURES AND CONTRAINDICATIONS
<b>Habit forming:</b>			
<i>Bisacodyl</i>	Oral 5–15 mg or rectal (supps or liquid) once a day	10–12 hours	Oral medication should not be used for long-term treatment, which could cause loss of tone on the colon and hypokalemia Not to be used in cases of intestinal obstruction, for example, fecal impaction
<i>Senna</i>	Oral 17.6–26.4 mg at bedtime	10–12 hours	May cause the urine to be colored brown or red Not to be used in cases of intestinal obstruction Not to be used for long-term treatment, which could cause loss of tone on the colon and hypokalemia
<i>Castor oil</i>	Oral solution 15–60 ml once in constipation; 16 hours before procedure	6–12 hours	Decreases net absorption of fluid and electrolytes and stimulates peristalsis It acts on the small intestine
<b>Bulk laxatives:</b>			
<i>Methylcellulose Bran</i>	Oral Dose varies 1 heaping tablespoon (2 g) in 8 oz water a day to every 8 hours	8–12 hours	Dietary fiber supplements of poorly digestible polysaccharides and celluloses derived principally from cereal grains, wheat bran, and psyllium Form gels in the large intestine causing water retention and intestinal distension, thereby increasing peristaltic activity Should be used cautiously in immobile patients because of potential for causing intestinal obstruction These preparations must be taken with water or they may cause obstruction
<b>Saline and osmotic laxatives:</b>			
<i>Magnesium salts: Magnesium hydroxide and magnesium citrate</i>	Oral (40–80 mmol of magnesium ion); dissolve one dose in 8 ounces of water	Within 2 hours	Rarely used Distend the bowel by attracting water into the bowel, increasing the volume of the stool, and also increasing intestinal activity Only for short-term use for rapid evacuation of the bowel Not to be used for intestinal obstruction Avoid dehydration and maintain oral fluids It may cause electrolyte imbalance, especially in young children or patients with renal insufficiency
<i>Isotonic polyethylene glycol (PEG) solution</i>	Oral 125–250 ml		Used as colonic lavage solutions to prepare gut for radiologic or endoscopic procedures Used in smaller volumes as an osmotic (but not hyperosmotic) agent Causes less cramping and gas than other laxatives
<i>Sodium picosulfate</i>	Oral 10 mg at night	Usually within 3 hours of the first dose	Often used for bowel evacuation prior to investigations or surgery Not to be used for intestinal obstruction or for long-term use Side effects include nausea, vomiting, and abdominal cramps
<b>Lubricant laxatives:</b>			
<i>Glycerol</i>	Rectal suppositories	20 minutes	Lubricates the anorectum Mild irritant effect which stimulates defecation There are no significant side effects or contraindications for their use

**Figure 42.14**

Summary of drugs used to treat constipation, precautions, and their contraindications. (Figure continues on next page)

EXAMPLES	ROUTE	ACTS WITHIN	EXTRA MEASURES AND CONTRAINDICATIONS
<i>Mineral oil (liquid paraffin)</i>	Oral liquid 15–45 mL/day, single or divided doses	8 hours	Lubricates the intestine and facilitate passage of stool by decreasing water absorption from the intestine Used for acute or subacute management of constipation Unpalatable Mineral oil usage should probably be limited to rectal administration because of the risk of aspiration pneumonia Long-term use is accompanied by concerns about lipid pneumonia, lymphoid hyperplasia, and foreign body reactions
<b>Osmotic laxatives:</b>			
<i>Lactulose</i>	Oral 15–20 ml at night	~48 hours accumulative	Broken down to form lactic, formic, and acetic acids in the colon, which stimulate peristalsis; increases osmotic pressure, causing fluid accumulation, colon distension, soft stools, and defecation Not to be used in patients with abdominal obstruction Can cause flatulence and abdominal cramps Fluid intake must be increased when taking these medications
<b>Stool softeners (see also bulk-forming laxatives and docusate sodium):</b>			
<i>Docusate sodium</i>	Oral or rectal	24–48 hours	Has detergent and emulsifying properties which also soften the stool It is given in patients who should avoid straining during defecation. Docusate is effective acutely. It does not induce defecation Not to be used long term as tachyphylaxis develops with long-term use Can cause abdominal cramps Not to be used in patients with intestinal obstruction Not to be used concomitantly with mineral oil
<b>Rectal suppositories and enemas (enemas general act by causing rectal distention and sometimes irritation of the rectal mucosa. Although generally safe, enemas may cause serious damage to the rectum by misinsertion resulting in trauma to the rectal mucosa):</b>			
<i>Rectal phosphates</i>	Rectal suppositories or enemas	Within 30 minutes	Have a direct osmotic and stimulant effect Only for short-term use; produce rapid bowel evacuation as in acute severe constipation or subacute intestinal obstruction Not to be used in patients with abdominal obstruction or acute gastrointestinal conditions Not for use in patients with neurogenic bowel
<i>Rectal sodium citrate enema</i>	Administered as an enema	Within 30 minutes	Only for short-term use to produce rapid bowel evacuation Not to be used in patients with abdominal obstruction or acute gastrointestinal conditions Case should be taken in patients where sodium salts are contraindicated, for example, cardiac failure
<b>Chloride channel activators:</b>			
<i>Lubiprostone</i>	Orally 8 mcg twice a day in irritable bowel syndrome; 24 mcg twice a day in chronic idiopathic constipation and opioid-induced constipation	30–60 minutes	Acts locally and enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. It increases intestinal fluid secretion to assist in GI motility, thereby decreasing symptoms of constipation (for example, abdominal pain, bloating, straining, hard stools) Used in chronic idiopathic constipation; opioid-induced constipation in patients with chronic, noncancer pain; and for women with constipation caused by irritable bowel syndrome.

**Note:** Laxatives should not be used for long-term use and review and look for other underlying problems if not effective after 1 week. Do not use to relieve gastrointestinal symptoms of an unknown cause. Depletion of fluids and electrolytes may result from their chronic use.

**Figure 42.14 (Continued)**

Summary of drugs used to treat constipation, precautions, and their contraindications.

### A. Irritants and stimulants

1. **Senna:** This agent is a widely used stimulant laxative. Its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides. Taken orally, senna causes evacuation of the bowels within 6 to 12 hours. It also causes water and electrolyte secretion into the bowel. In combination products with a *docusate*-containing stool softener, it is useful in treating opioid-induced constipation.
2. **Bisacodyl:** Available as suppositories and enteric-coated tablets, *bisacodyl* is a potent stimulant of the colon. It acts directly on nerve fibers in the mucosa of the colon.
3. **Castor oil:** This agent is broken down in the small intestine to ricinoleic acid, which is very irritating to the stomach and promptly increases peristalsis. Pregnant patients should avoid *castor oil* because it may stimulate uterine contractions. Use of *castor oil* is generally not recommended due to poor palatability and potential for GI adverse effects.

### B. Bulk laxatives

The bulk laxatives include hydrophilic colloids (from indigestible parts of fruits and vegetables). They form gels in the large intestine, causing water retention and intestinal distension, thereby increasing peristaltic activity. Similar actions are produced by *methylcellulose*, psyllium (Ispaghula/isabgol husk), and bran. They should be used cautiously in patients who are immobile because of their potential for causing intestinal obstruction. *Psyllium* can reduce the absorption of other oral drugs, and administration of other agents should be separated from *psyllium* by at least 2 hours.

### C. Saline and osmotic laxatives

Saline cathartics, such as *magnesium citrate* and *magnesium hydroxide*, are nonabsorbable salts (anions and cations) that hold water in the intestine by osmosis. This distends the bowel, increasing intestinal activity and producing defecation in a few hours. Electrolyte solutions containing *polyethylene glycol* (PEG) are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures. PEG powder for solution without electrolytes is also used as a laxative and has been shown to cause less cramping and gas than other laxatives. *Lactulose* is a semisynthetic disaccharide sugar that acts as an osmotic laxative. It cannot be hydrolyzed by GI enzymes. Oral doses reach the colon and are degraded by colonic bacteria into lactic, formic, and acetic acids. This increases osmotic pressure, causing fluid accumulation, colon distension, soft stools, and defecation. *Lactulose* is also used for the treatment of hepatic encephalopathy, due to its ability to reduce ammonia levels.

### D. Stool softeners (emollient laxatives or surfactants)

Surface-active agents that become emulsified with the stool produce softer feces and ease passage of stool. These include *docusate sodium* and *docusate calcium*. They may take days to become effective and are often used for prophylaxis rather than acute treatment. Stool softeners should not be taken concomitantly with *mineral oil* because of the potential for absorption of the *mineral oil*.

### E. Lubricant laxatives

*Mineral oil* (liquid paraffin) and *glycerin suppositories* are lubricants and act by facilitating the passage of hard stools. *Mineral oil* should be taken orally in an upright position to avoid its aspiration and potential for lipid or lipoid pneumonia.

### F. Chloride channel activators

*Lubiprostone* [loo-bee-PROS-tone] works by activating chloride channels to increase fluid secretion in the intestinal lumen. This eases the passage of stools and causes little change in electrolyte balance. *Lubiprostone* is used in the treatment of chronic constipation and irritable bowel syndrome with constipation (IBS-C), particularly because tolerance or dependency has not been associated with this drug. Also, drug-drug interactions appear minimal because metabolism occurs quickly in the stomach and jejunum.

## VIII. GASTROKINETIC AGENTS

### A. Cisapride

*Cisapride* is the first agent approved with prokinetic activity. By the activation of 5-HT<sub>4</sub> receptors, it induces peristaltic movements in the intestine by releasing acetyl choline in myenteric interneurons. It also exhibits a weak 5-HT<sub>3</sub> antagonism which suppresses inhibitory transmission in the myenteric plexus. It also stimulates cAMP-dependent Cl<sup>-</sup> secretion in the colon, thereby augmenting increased water content in the stools. It stimulates the propulsion (motility)—that is, gastrointestinal smooth muscle motility and decreases the transit time of gastrointestinal contents down the length of the tract. As this action has been seen throughout the alimentary tract (from esophagus to colon), its action has also been called “pan-prokinetic.” Moreover, it also improves the tone of the lower esophageal sphincter; hence, it is highly effective for gastroesophageal reflux disease (GERD). *Cisapride* is metabolized by CYP3A4, thereby having several drug interactions. A potential drug interaction is expected to increase *cisapride* metabolism reaching higher concentrations in the plasma causing “torsades de pointes” (ventricular arrhythmia). It is due to the activation of HERG channels (inward rectifying potassium channels in heart causing QT prolongation). Therefore, the use of this agent is banned in many countries or highly restricted. Its use has been reported to cause side effects such as diarrhea, abdominal cramps, flatulence, headache, stuffy nose, and cough. Therefore, in this group of benamides, other congeners which have no or lesser effect on HERG channels are in use.

*Mosapride*, a congener of *cisapride* having similar action, is reported to have no risk of arrhythmia in clinical trials. It is metabolized by CYP3A4 and therefore has potential for drug interactions with the concomitant use of azole antifungals, erythromycin, etc. It is highly effective for the gastrointestinal disorders, including chronic gastritis, gastroesophageal reflux disease, chronic constipation, diabetic gastroparesis, and functional dyspepsia. *Mosapride* was generally well tolerated, but diarrhea/loose stools, abdominal pain, dry mouth, malaise, and headache have been reported in <5% of patients.

IBS-C AGENTS
<i>Linaclotide</i>
<i>Lubiprostone</i>
IBS-D AGENTS
<i>Alosetron</i>
<i>Eluxadoline</i>
<i>Rifaximin</i>
AGENTS FOR IBS-C AND IBS-D
<i>Dicyclomine</i>
<i>Hyoscyamine</i>

#### Figure 42.15

Summary of drugs used to treat irritable bowel syndrome. IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea.

#### B. Prucalopride

*Prucalopride* is a highly selective serotonin 5-HT<sub>4</sub> receptor agonist which exhibits its action similar to *cisapride*. It is used for constipation, predominantly irritable bowel syndrome, or chronic constipation. As it is reported to have no effect on Q-T prolongation in the clinical studies, it is found to be safe unlike *cisapride*. Diarrhea, abdominal discomfort, headache, nausea, diarrhea, and fatigue are the common side effects reported.

#### C. Itopride

*Itopride* is a benzamide derivative similar to *cisapride* and *mosapride*, but its activity differs significantly from them. It is a dopamine D2 receptor antagonist and an acetylcholine esterase inhibitor. It accelerates gastric emptying, improves gastric tension and sensitivity, and has an antiemetic action. *Itopride* has been identified to have equiefficacy with *cisapride* in functional dyspepsia. As it is not being metabolized by CYP3A4, the drug interaction-related risk of ventricular arrhythmia is not encountered. It is metabolized by flavin mono-oxygenases, and *itopride* is considered a safer prokinetic agent. Diarrhea/loose stools, abdominal pain, and headache are the general side effects, and rarely gynecomastia and galactorrhea are reported. The risk of extrapyramidal effects is reported to be low with *itopride*.

### IX. IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is characterized by chronic abdominal pain and altered bowel habits in the absence of an organic cause. IBS may be classified as constipation predominant (IBS-C), diarrhea predominant (IBS-D), or a combination of both. Diet and psychosocial modifications play an important role in the management of the disease, as well as drug therapy (Figure 42.15). Key characteristics of medications used for the treatment of IBS-C and IBS-D are provided in Figure 42.16.

DRUG	INDICATION	MECHANISM OF ACTION	ADVERSE EFFECTS
<i>Linaclotide</i>	IBS-C <sup>1</sup>	Increases intestinal fluid secretion via increased cGMP	Diarrhea, abdominal pain, flatulence, and abdominal distention Do not use in children < 17 years old
<i>Lubiprostone</i>	Women with IBS-C <sup>1</sup>	Chloride channel activator	Nausea and vomiting, dyspepsia, headache, dizziness, and hypotension
<i>Alosetron</i>	Women with severe IBS-D	5-HT <sub>3</sub> antagonist	Constipation, nausea and vomiting, heartburn, ischemic colitis (rare)
<i>Eluxadoline</i>	IBS-D	μ-Opioid receptor agonist	Constipation, abdominal pain, nausea, pancreatitis (rare) Possible risk of dependence and overdose
<i>Rifaximin</i>	Short-term use in IBS-D	Decreases bacterial load (structural analog of <i>rifampin</i> )	Nausea, fatigue, headache, dizziness, peripheral edema, and risk of <i>Clostridium difficile</i> infection
<i>Dicyclomine</i>	IBS-C and IBS-D	Antimuscarinic; decreases GI spasms and motility	Anticholinergic effects such as drowsiness and dry mouth
<i>Hyoscyamine</i>	IBS-C and IBS-D	Antimuscarinic; decreases GI spasms and motility	Anticholinergic effects such as drowsiness and dry mouth Overdose may produce hallucinations, arrhythmias, and nausea and vomiting

cGMP = cyclic guanosine monophosphate; IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea; GI = gastrointestinal.

<sup>1</sup>Also indicated for the treatment of chronic constipation.

#### Figure 42.16

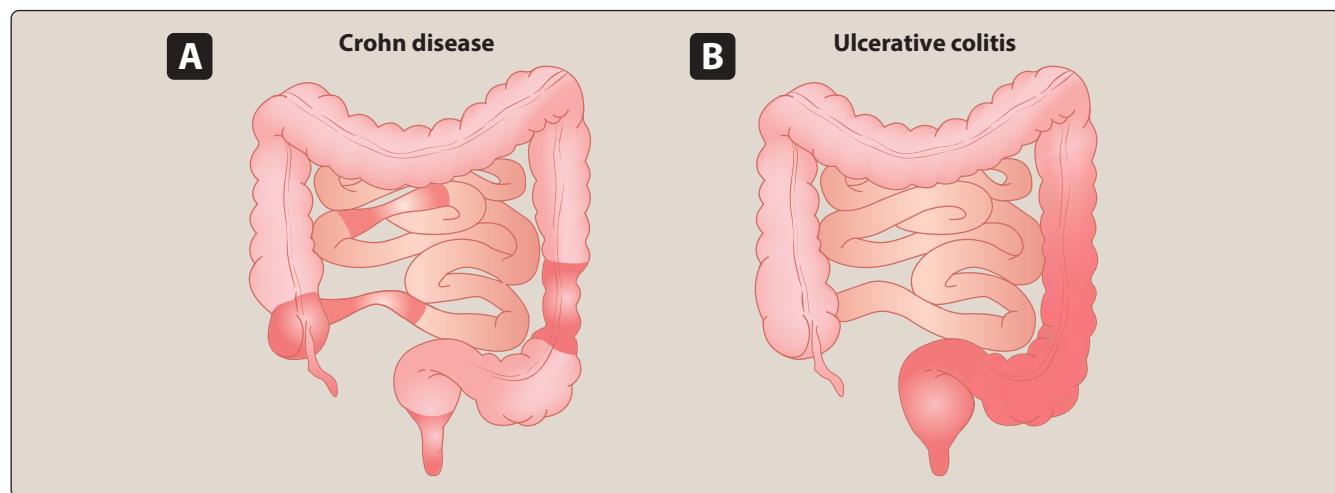
Characteristics of drugs used to treat irritable bowel syndrome. (For drug dosages, refer to Appendix at the end of the book.)

## X. DRUGS USED TO TREAT INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a group of idiopathic chronic intestinal conditions characterized by immune-mediated GI tract inflammation in response to bacterial antigens in the intestinal lumen. The most common subtypes of IBD are Crohn's disease (CD) and ulcerative colitis (UC). CD can affect any portion of the GI tract from the mouth to the anus in a noncontinuous fashion and is characterized by transmural inflammation. UC usually affects the rectum. It may extend continuously to affect other parts of the colon and is characterized by inflammation limited to the mucosal layer (Figure 42.17). Severity, extent of disease, and risk of complications guide treatment of IBD. Remission of IBD can be induced with the use of rectal and oral 5-aminosalicylates (5-ASAs), corticosteroids (rectal, oral locally delivered and systemic), and biologic agents (TNF- $\alpha$  inhibitors,  $\alpha$ 4-integrin inhibitors, and the IL-12/23 inhibitor *ustekinumab*). Drugs used to maintain remission are the same as those used for induction. The immunomodulators (*azathioprine*, *6-mercaptopurine*, and *methotrexate*) are additional agents used in the maintenance of remission in IBD. Figure 42.18 summarizes agents used in the treatment of inflammatory bowel disease.

### A. 5-Aminosalicylates

Two types of 5-ASA compounds exist, the azo compounds and the *mesalamine* compounds. The azo compounds are prodrugs that consist of a 5-ASA molecule bound via an azo (N=N) bond to another molecule. These include *balsalazide* [bal-SAL-a-zide], *olsalazine* [ole-SAL-a-zeen], and *sulfasalazine* [SUL-fa-SAL-a-zeen]. The oral *mesalamine* [me-SAL-a-meen] compounds consist of single 5-ASA molecules enclosed within an enteric coat or a semipermeable membrane. The first 5-ASA agent used in the treatment of IBD, *sulfasalazine*, is a prodrug consisting of 5-ASA linked to sulphydryl groups. Colonic bacteria cleave *sulfasalazine* to produce 5-ASA



**Figure 42.17**

Distribution patterns of disease with skip lesions in Crohn's disease (A) and continuous involvement of the colon (B), beginning with the rectum, in ulcerative colitis.

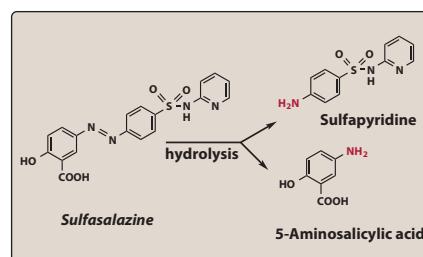
**5-AMINOSALICYLATES***Oral formulation**Balsalazide**Mesalamine**Olsalazine**Sulfasalazine**Rectal formulation**Mesalamine enema**Mesalamine suppository***CORTICOSTEROIDS***Oral formulation**Budesonide delayed-release**Budesonide extended-release**Hydrocortisone**Prednisone**Methylprednisolone**Intravenous formulation**Hydrocortisone**Methylprednisolone**Rectal formulation**Budesonide foam**Hydrocortisone suppository**Hydrocortisone enema**Hydrocortisone foam***BIOLOGIC AGENTS***TNF- $\alpha$  inhibitors**Adalimumab**Certolizumab**Golimumab**Infliximab* *$\alpha$ 4-Integrin inhibitor**Vedolizumab**IL-12/13 inhibitor**Ustekinumab***IMMUNOMODULATORS***Azathioprine**6-Mercaptopurine**Methotrexate***Figure 42.18**

Agents used in the treatment of inflammatory bowel disease. (For drug dosages, refer to Appendix at the end of the book.)

(mesalamine) and sulfapyridine (Figure 42.19). When it became known that 5-ASA was responsible for the efficacy of *sulfasalazine* while sulfapyridine was mainly responsible for its adverse effects, unlinked 5-ASA formulations were produced. However, unlinked 5-ASA is rapidly absorbed with only 20% reaching the site of action in the terminal ileum and colon. Therefore, other azo-bonded compounds and various formulations of *mesalamine* were developed to limit absorption of 5-ASA in the proximal gastrointestinal tract and allow increased drug delivery to the colon. These formulations differ in their sites of topical delivery within the intestinal tract and dosing frequency (Figure 42.20). Compared to *sulfasalazine*, the *mesalamine* formulations and the other azo compounds have improved tolerability with similar efficacy, making them the mainstay of therapy in UC.

- Actions:** The 5-ASAs exhibit anti-inflammatory and immunosuppressive properties that are the main determinants of their efficacy in IBD. The exact mechanism of action of 5-ASA is unknown but is thought to be due in part to 1) inhibition of cytokine synthesis, 2) inhibition of leukotriene and prostaglandin synthesis, 3) scavenging of free radicals, 4) inhibition of T-cell proliferation, activation, and differentiation, and 5) impairment of leukocyte adhesion and function. 5-ASA is thought to act via topical interaction with the intestinal mucosa and the mechanisms are the same with both oral and rectal administration.
- Therapeutic uses:** The 5-ASA drugs are the mainstay of treatment in UC. All 5-ASA formulations and *sulfasalazine* are indicated in UC for induction and maintenance of remission. Current guidelines recommend these agents as first line for mild-to-moderate disease. Use of 5-ASA drugs in CD is limited due to a general lack of efficacy.
- Pharmacokinetics:** 5-ASA (*mesalamine*) pharmacokinetics are variable and dependent on the route of administration (for example, rectal vs. oral), type of oral formulation (Figure 42.20) and disease activity. Absorption of 5-ASA increases with more severe disease and decreases with decreasing pH. In UC, 5-ASAs work by local effect. Therefore, the 5-ASA preparations deliver drug to the colon for maximal intestinal exposure. Absorption of rectally administered *mesalamine* and systemic exposure depends on rectal retention time. Due to the topical mechanism of action, differences in systemic exposure are not related to efficacy but may be important for adverse effects. *Sulfasalazine* is administered orally, with the sulfapyridine component having significant absorption (60% to 80%).
- Adverse effects:** Adverse effects of *sulfasalazine* occur in up to 45% of patients, with the majority due to the sulfapyridine component. Headache, nausea, and fatigue are most common and are dose-related. Serious reactions include hemolytic anemia, myelosuppression, hepatitis, pneumonitis, nephrotoxicity, fever, rash, and Stevens–Johnson syndrome. Treatment should be discontinued at the first sign of skin rash or hypersensitivity. *Sulfasalazine* reversibly impairs male fertility. *Sulfasalazine* also inhibits intestinal folate absorption, and folate supplementation is recommended with chronic use. The newer *mesalamine* formulations are well tolerated; headache and dyspepsia are the most common adverse effects. Rarely, acute interstitial nephritis may occur and renal

function should be monitored in patients receiving *mesalamine*. Watery diarrhea occurs in up to 20% of patients treated with *olsalazine*. Some formulations of *mesalamine* depend on pH for their release (Figure 42.20), and coadministration of drugs that increase pH (for example, PPIs, H<sub>2</sub> receptor antagonists, and antacids) may result in increased systemic absorption and premature release of 5-ASA before reaching the site of action. Concomitant use should be avoided or another formulation of 5-ASA that is non-pH dependent should be used (for example, *olsalazine* and *balsalazide*).



**Figure 42.19**

Sulfasalazine metabolism.

## B. Corticosteroids

Corticosteroids are used in IBD for their anti-inflammatory effects as they are in other inflammatory conditions (see Chapter 26). Although very effective at inducing remission in IBD, long-term maintenance with corticosteroids should be avoided due to the deleterious effects of chronic use. Rectal formulations (for example, *hydrocortisone* enema and *budesonide* foam) have fewer adverse effects than systemic steroids but use is limited to left-sided disease in UC. Enteric release preparations of oral *budesonide* deliver corticosteroid to a portion of inflamed intestine. This agent has minimal systemic adverse effects due to low bioavailability resulting from extensive first-pass hepatic metabolism. Delayed-release *budesonide* delivers drug to the terminal ileum and proximal large bowel and is used in ileocecal CD. Extended-release *budesonide* delivers drug throughout the colon and is used in UC patients with pancolitis. Although systemic exposure is less than other corticosteroids, the use of *budesonide* in extended maintenance of remission is limited due to concerns with long-term use.

DRUG	BRAND(S)	ROUTE	DOSING FREQUENCY	FORMULATION	SITE OF DELIVERY
<i>Balsalazide</i>	Colazal	PO	Three times daily	5-ASA azo bonded to inert carrier molecule; release dependent on cleavage by colonic bacteria	Colon
<i>Mesalamine</i>	Apriso	PO	Once daily	pH-dependent ( $\geq 6$ ) delayed release with extended-release matrix core	Colon
	Asacol, Asacol HD	PO	Three times daily	pH-dependent ( $\geq 7$ ) delayed release	Distal ileum, colon
	Canasa	Rectal	Once daily	Suppository	Rectum
	Lialda	PO	Once daily	pH-dependent ( $\geq 7$ ) delayed-release multimatrix system	Distal ileum, colon
	Pentasa	PO	Four times daily	Ethyl cellulose membrane controlled-release micropellets	Entire small intestine, colon
	Rowasa	Rectal	Once daily	Liquid enema	Rectum, sigmoid colon
<i>Olasalazine</i>	Dipentum	PO	Twice daily	5-ASA azo bonded to another 5-ASA molecule; release dependent on cleavage by colonic bacteria	Colon

**Figure 42.20**

5-Aminosalicylate formulations.

### C. Biologic agents

The TNF- $\alpha$  inhibitors,  $\alpha$ -4 integrin inhibitors, and the IL-12/23 inhibitor *ustekinumab* are biologic agents used in the management of IBD. Use of these agents is associated with an increased risk for infection. Patients should be evaluated for tuberculosis and treatment for latent TB should be considered prior to the use of these drugs. Many of these agents have other therapeutic indications such as rheumatoid arthritis (see Chapter 40) or psoriasis (see Chapter 45). The actions, pharmacokinetics, and adverse effects of these drugs in other conditions are similar in IBD.

1. **TNF- $\alpha$  inhibitors:** TNF- $\alpha$  inhibitors are parenteral agents that are effective for both induction and maintenance of remission in IBD. *Infliximab* [in-FLIX-ih-mab] and *adalimumab* [AY-da-LIM-ue-mab] are indicated in both moderate-to-severe CD and UC. *Certolizumab* [SER-toe-LIZ-oo-mab] is indicated for moderate-to-severe CD, and *golimumab* [goe-LIM-ue-mab] is indicated for moderate-to-severe UC. The TNF- $\alpha$  inhibitors are generally reserved as second-line agents in patients with UC who have failed 5-ASAs, are unresponsive to or dependent on corticosteroids, or who present with more severe disease. In CD, the TNF- $\alpha$  inhibitors have a first-line role in patients with moderate-to-severe disease and those at higher risk of progression and worse outcomes. These agents are associated with the development of immunogenicity and antidrug antibodies that can result in loss of response in a significant proportion of patients.
2.  **$\alpha$ -4 Integrin inhibitors:**  $\alpha$ -4 Integrins are adhesion molecules that promote leukocyte migration to sites of inflammation. Use of  $\alpha$ -4 integrin inhibitors reduces lymphocyte migration into the intestinal mucosa and inflammation. The use of  $\alpha$ -4 integrin inhibitors in IBD is reserved for disease refractory to TNF- $\alpha$  inhibitors. *Vedolizumab* [VE-doe-LIZ-ue-mab] exhibits specific binding to  $\alpha$ -4/ $\beta$ -7 integrin and is indicated for refractory UC and CD. The most common adverse reactions include headache, arthralgia, nausea, fatigue, and musculoskeletal pain.
3. **IL-12/23 inhibitor:** *Ustekinumab* [YOO-sti-KIN-ue-mab] inhibits the cytokines IL-12 and IL-23 involved in lymphocyte activation. It is indicated for psoriasis, psoriatic arthritis, and induction and maintenance of remission in CD in patients refractory to or intolerant of TNF- $\alpha$  inhibitors, immunomodulators, or corticosteroids. Common adverse effects include headache, arthralgia, infection, nausea, and nasopharyngitis.

### D. Immunomodulators

The immunomodulator drugs most often used in IBD are *methotrexate* and the thiopurines *azathioprine* and *6-mercaptopurine* (6-MP). *Methotrexate* (MTX) also has therapeutic applications in cancer, rheumatoid arthritis, and psoriasis (see Chapters 38, 40, and 45) and *azathioprine* is sometimes used in kidney transplant (see Chapter 35). The actions, pharmacokinetics, and adverse effects of the immunomodulators in other conditions are similar in IBD.

1. **Methotrexate:** MTX is a structural analog of folic acid that inhibits the production of folinic acid. The exact mechanism of action in CD is unknown. Only intramuscular or subcutaneous

administration of *MTX* has efficacy in CD. *MTX* is a recommended monotherapy option for maintenance of remission in CD, but is not recommended in maintenance for UC. Common adverse effects of *MTX* are headache, nausea, vomiting, abdominal discomfort, serum aminotransferase elevations, and rash. Daily administration of folic acid is effective at reducing the incidence of GI adverse effects and is recommended in patients receiving *MTX*.

2. **Thiopurines:** The thiopurines *azathioprine* and *6-mercaptopurine* (*6-MP*) are oral medications that have corticosteroid-sparing effects in patients with UC and CD. They are considered first line as monotherapy for maintenance of remission. Use of thiopurines in IBD is limited by concerns of toxicity, including bone marrow suppression and hepatotoxicity. Monitoring of complete blood counts and liver function tests is recommended in all patients treated with a thiopurine.

## Study Questions

Choose the ONE best answer.

- 42.1 A 68-year-old patient with cardiac failure is diagnosed with ovarian cancer. She begins using cisplatin but becomes nauseous and suffers from severe vomiting. Which drug would be most effective to counteract the emesis in this patient without exacerbating her cardiac problem?
- A. Droperidol
  - B. Dolasetron
  - C. Prochlorperazine
  - D. Palonosetron

Correct answer = D. Palonosetron is a 5-HT<sub>3</sub> antagonist that is effective against drugs with high emetogenic activity, such as cisplatin. Although dolasetron is also in this category, its propensity to affect the heart makes it a poor choice for this patient. Droperidol is only a moderately effective antiemetic and has the potential to prolong the QTc interval, so it is preferred in this patient. The antiemetic effect of prochlorperazine, a phenothiazine, is most beneficial against anticancer drugs with moderate-to-low emetogenic properties.

- 42.2 A 45-year-old woman complains of severe persistent heartburn and an unpleasant, acid-like taste in her mouth. The clinician suspects that she has gastroesophageal reflux disease. Which drug is most appropriate?
- A. An antacid such as aluminum hydroxide
  - B. Dicyclomine
  - C. Granisetron
  - D. Esomeprazole

Correct answer = D. It is appropriate to treat this patient with a proton-pump inhibitor (PPI) to reduce acid production and promote healing. An H<sub>2</sub> receptor antagonist might also be effective, but the PPIs are preferred. An antacid would decrease gastric acid, but its effects are short lived compared to those of the PPIs and H<sub>2</sub> receptor antagonists. Dicyclomine is an antimuscarinic drug that is mainly used as an antispasmodic for IBS. The 5-HT<sub>3</sub> receptor antagonist granisetron is an antiemetic and not appropriate for the treatment of GERD.

- 42.3 A couple celebrating their 30th wedding anniversary are given a trip to Peru to visit Machu Picchu. Because of past experiences while traveling, they ask their doctor to prescribe an agent in case they experience diarrhea. Which drug would be effective?
- A. Omeprazole
  - B. Loperamide
  - C. Famotidine
  - D. Lubiprostone

Correct answer = B. Loperamide is the only drug that has antidiarrheal activity. Omeprazole is a proton-pump inhibitor, famotidine antagonizes the H<sub>2</sub> receptor to reduce acid production, and lubiprostone is indicated for chronic constipation or IBS-C.

42.4 A 27-year-old woman who is 34 weeks' pregnant is on bed rest and is experiencing mild constipation. Which drug is most appropriate for her?

- A. Castor oil
- B. Docusate
- C. Mineral oil
- D. Loperamide

Correct answer = B. Although its effects are not immediate, docusate may be used for mild constipation and is generally considered safe in pregnancy. Castor oil should not be used in pregnancy because of its ability to cause uterine contractions. Mineral oil should not be used in bedridden patients due to the possibility of aspiration. Loperamide is used for diarrhea, not constipation.

42.5 Which drug has been known to cause discoloration of the tongue?

- A. Amoxicillin
- B. Omeprazole
- C. Bismuth subsalicylate
- D. Lubiprostone

Correct answer = C. Bismuth subsalicylate compounds may cause a harmless black discoloration of the tongue. The other agents have not been associated with this effect.

42.6 An elderly woman with a recent history of myocardial infarction is seeking a medication to help treat her occasional heartburn. She is currently taking several medications, including aspirin, clopidogrel, simvastatin, metoprolol, and lisinopril. Which drug should be avoided in this patient?

- A. Calcium citrate
- B. Famotidine
- C. Omeprazole
- D. Ranitidine

Correct answer = C. Omeprazole may possibly decrease the efficacy of clopidogrel because it inhibits the conversion of clopidogrel to its active form.

42.7. Extrapyramidal symptoms (EPS) have been associated with which drug?

- A. Metoclopramide
- B. Sucralfate
- C. Aprepitant
- D. Bisacodyl

Correct answer = A. Only metoclopramide has been associated with EPS. This is due to its ability to inhibit dopamine activity.

42.8 Which agent for gastrointestinal problems is contraindicated in pregnancy?

- A. Calcium carbonate
- B. Famotidine
- C. Lansoprazole
- D. Misoprostol

Correct answer = D. Misoprostol, a synthetic prostaglandin analog, is contraindicated in pregnancy because it may stimulate uterine contractions. The other medications may be used during pregnancy for the treatment of heartburn (common in pregnancy) or peptic ulcer disease.

42.9 A patient presents with a 2-month history of crampy right lower quadrant abdominal pain. Results of endoscopy are consistent with moderate Crohn's disease involving the terminal ileum and proximal large intestine. Which drug is best to initiate in this patient at this time?

- A. Extended-release budesonide
- B. Delayed-release budesonide
- C. Mesalamine enema
- D. Ustekinumab

Correct answer = B. Delayed-release budesonide is indicated in Crohn's disease because it releases in the terminal ileum and proximal large bowel and is effective in inducing remission. Extended-release budesonide, although effective at inducing remission, is only indicated in ulcerative colitis because it does not release in the small bowel and would not be expected to be effective in this patient's ileal disease. Mesalamine enema is only effective on the distal large intestine. Ustekinumab is only indicated in patients who are refractory or intolerant to TNF- $\alpha$  inhibitors.

42.10 A patient with a history of ulcerative colitis well controlled on mesalamine (Apriso) presents with epigastric pain and dark tarry stools. He is found to have a duodenal ulcer and is prescribed esomeprazole for 8 weeks. At follow-up 2 weeks later, his epigastric pain and dark tarry stools are resolved. However, he reports having increased lower abdominal pain and increased stool frequency. Which change in drug therapy is appropriate at this time?

- A. Change esomeprazole to omeprazole due to interaction with mesalamine (Apriso).
- B. Discontinue esomeprazole.
- C. Change mesalamine (Apriso) to mesalamine (Asacol).
- D. Change mesalamine (Apriso) to olsalazine (Dipentum).

Correct answer = D. The patient seems to be having increased symptoms of ulcerative colitis after starting the PPI, esomeprazole. The pH-dependent release formulations of mesalamine have a significant interaction with the PPIs which may lead to early release and loss of efficacy. A is incorrect because omeprazole is expected to have the same interaction. B is incorrect because this patient still requires therapy with a PPI. C is incorrect because Asacol is also pH-dependent release and is likely to be affected. D is correct because olsalazine is not pH-dependent and release relies on cleavage by colonic bacteria.



# Drugs for Urologic Disorders

43

Katherine Vogel Anderson and Kaylie Smith

## I. OVERVIEW

Erectile dysfunction (ED) and benign prostatic hyperplasia (BPH) are common urologic disorders in males. ED is the inability to maintain penile erection for the successful performance of sexual activity. ED has many physical and psychological causes, including vascular disease, diabetes, medications, depression, and sequelae to prostatic surgery. BPH is usually a nonmalignant enlargement of the prostate, which occurs naturally as men age. As the prostate grows in size, lower urinary tract symptoms develop, which can significantly impact a patient's quality of life. A summary of drugs for ED and BPH is provided in **Figure 43.1**.

## II. DRUGS USED TO TREAT ERECTILE DYSFUNCTION

Therapy for ED includes penile implants, intrapenile injections of *alprostadil*, intraurethral suppositories of *alprostadil*, and oral phosphodiesterase-5 (PDE-5) inhibitors. Because of the efficacy, ease of use, and safety of PDE-5 inhibitors, these drugs are first-line therapy for ED.

### A. Phosphodiesterase-5 inhibitors

Four PDE-5 inhibitors *sildenafil* [sil-DEN-a-fil], *vardenafil* [var-DEN-na-fil], *tadalafil* [ta-DAL-a-fil], and *avanafil* [a-VAN-a-fil] are approved for the treatment of ED. [Note: *Sildenafil* and *tadalafil* are also indicated to treat pulmonary hypertension, although the dosage regimen differs for this indication.] All four PDE-5 inhibitors are equally effective in treating ED, and the adverse effect profiles of the drugs are similar. However, these agents differ in the duration of action and the effects of food on drug absorption.

- Mechanism of action:** Sexual arousal results in smooth muscle relaxation of the corpus cavernosum, increasing the inflow of blood (**Figure 43.2**). The mediator of this response is nitric oxide (NO). NO activates guanylyl cyclase, which forms cyclic guanosine monophosphate (cGMP) from guanosine triphosphate. cGMP produces smooth muscle relaxation through a reduction in the intracellular Ca<sup>2+</sup> concentration. The duration of action of cyclic nucleotides is controlled by the action of phosphodiesterase (PDE). At least

### DRUGS FOR ERECTILE DYSFUNCTION

*Alprostadil*  
*Avanafil*  
*Sildenafil*  
*Tadalafil*  
*Vardenafil*

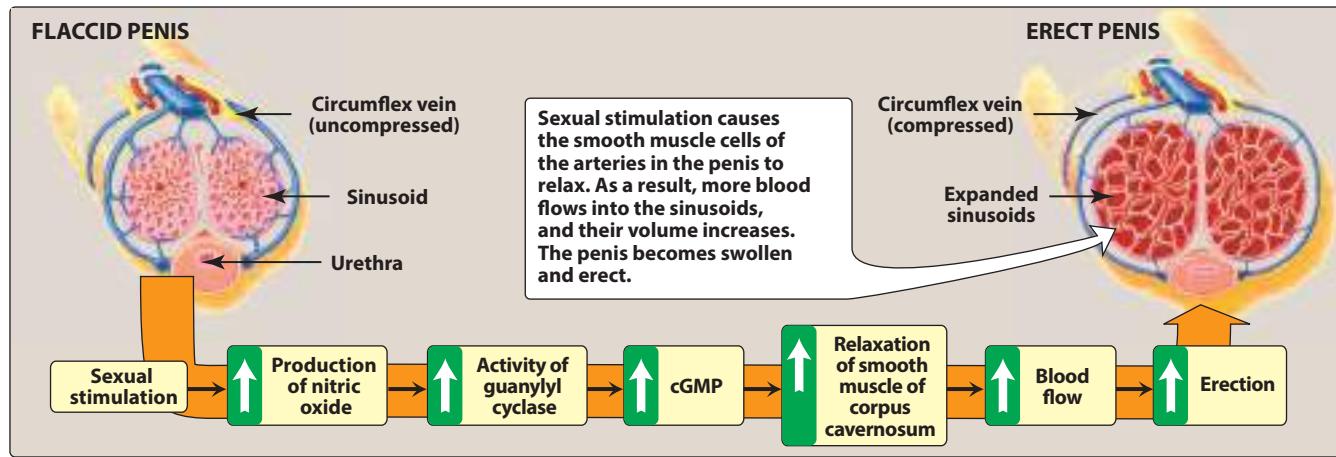
**α-BLOCKERS**  
*Alfuzosin*  
*Doxazosin*  
*Prazosin*  
*Silodosin*  
*Tamsulosin*  
*Terazosin*

**5-α REDUCTASE INHIBITORS**  
*Dutasteride*  
*Finasteride*

**COMBINATION PRODUCT**  
*Dutasteride/tamsulosin*

### Figure 43.1

Summary of drugs used for the treatment of urologic disorders. (For drug dosages, refer to Appendix at the end of the book.)

**Figure 43.2**

Mechanism of penile erection. cGMP = cyclic guanosine monophosphate.

A	Time to peak concentration
Avanafil	30–45 min
Sildenafil	60 min
Vardenafil	60 min
Tadalafil	120 min

B	Half-life
Avanafil	5 hr
Sildenafil	3–4 hr
Vardenafil	4–5 hr
Tadalafil	18 hr

C	Food interaction*
Avanafil	No
Sildenafil	Yes
Vardenafil	Yes
Tadalafil	No

**Figure 43.3**

Some properties of phosphodiesterase inhibitors. \*Delay in time to reach peak drug concentration when taken with high-fat foods.

11 isozymes of PDE have been characterized. *Sildenafil*, *avanafil*, *tadalafil*, and *avanafil* inhibit PDE-5, the isozyme responsible for degradation of cGMP in the corpus cavernosum. The action of PDE-5 inhibitors is to increase the flow of blood into the corpus cavernosum at any given level of sexual stimulation. At recommended doses, PDE-5 inhibitors have no effect in the absence of sexual stimulation.

2. **Pharmacokinetics:** *Sildenafil* and *avanafil* have similar pharmacokinetic properties. Both drugs should be taken approximately 1 hour prior to anticipated sexual activity, with erectile enhancement observed for up to 4 hours after administration. Thus, administration of *sildenafil* and *avanafil* must be timed appropriately with regard to anticipated sexual activity. The absorption of both drugs is delayed by consumption of a high-fat meal. *Vardenafil* is also available in an orally disintegrating tablet (ODT) formulation, which is not affected by a high-fat meal. However, the bioavailability of the ODT formulation may be decreased by water, and therefore the ODT should be placed under the tongue and not administered with liquids. The *vardenafil* ODT provides a higher systemic bioavailability than the *vardenafil* film-coated oral tablet, and these products are not interchangeable. *Tadalafil* has a slower onset of action (Figure 43.3) than *sildenafil* and *vardenafil*, but a significantly longer half-life of approximately 18 hours. As such, it is approved for once-daily dosing (in addition to as-needed dosing). This results in enhanced erectile function for up to 36 hours. Furthermore, the absorption of *tadalafil* is not clinically influenced by food. The timing of sexual activity is less critical for *tadalafil* because of its prolonged duration of effect. Of all the PDE-5 inhibitors, *avanafil* has the quickest onset of action. It should be taken 30 minutes prior to sexual activity. All PDE-5 inhibitors are metabolized by the cytochrome P450 3A4 (CYP3A4) isoenzyme. Dosage adjustments for *sildenafil*, *tadalafil*, and *vardenafil* are recommended in patients with mild-to-moderate hepatic dysfunction. PDE-5 inhibitors should be avoided in patients with severe hepatic impairment. For patients

with severe renal dysfunction, the dose of *sildenafil* and *tadalafil* should be reduced, and daily-dose *tadalafil* and as needed *avafil* are contraindicated in these patients.

3. **Adverse effects:** The most frequent adverse effects of the PDE-5 inhibitors are headache, flushing, dyspepsia, and nasal congestion. These effects are generally mild, and men with ED rarely discontinue treatment because of side effects. Disturbances in color vision (loss of blue/green discrimination) may occur with PDE-5 inhibitors, likely due to inhibition of PDE-6 which is involved in the photoreceptor signal transduction in the retina (a PDE found in the retina that is important in color vision). *Tadalafil*, however, does not appear to disrupt PDE-6, and reports of changes in color vision have been rare with this medication. The incidence of these reactions appears to be dose-dependent. Sudden hearing loss has also been reported with the use of PDE-5 inhibitors, perhaps due to changes in sinus pressure because of vasodilation. *Tadalafil* has been associated with back pain and myalgias, likely because of inhibition of PDE-11, an enzyme found in skeletal muscle. There is an inherent cardiac risk associated with sexual activity. Therefore, PDE-5 inhibitors should be used with caution in patients with a history of cardiovascular disease or those with strong risk factors for cardiovascular disease. PDE-5 inhibitors should not be used more than once per day for the treatment of erectile dysfunction. All of the PDE-5 inhibitors have the potential to cause priapism (a painful, prolonged erection). Although this is a rare side effect, it is a medical emergency.
4. **Drug interactions:** Because of the ability of PDE-5 inhibitors to potentiate the hypotensive activity of NO, administration of these medications in combination with organic nitrates (for example, *nitroglycerin* products, *isosorbide dinitrate*, or *isosorbide mononitrate*) is contraindicated. PDE-5 inhibitors may produce additive blood pressure-lowering effects when used in patients taking  $\alpha$ -adrenergic antagonists for treatment of hypertension and/or alleviation of symptoms associated with BPH. The combination of PDE-5 inhibitors and  $\alpha$ -adrenergic antagonists should be used with caution. Patients should be on a stable dose of the  $\alpha$ -adrenergic antagonist prior to the initiation of the PDE-5 inhibitor, and the PDE-5 inhibitor should be started at a low dose if this combination is used. Doses of PDE-5 inhibitors may need to be reduced in the presence of potent inhibitors of CYP3A4, such as *clarithromycin*, *ritonavir*, and other protease inhibitors. Because of QT prolongation, the combination of *vardenafil* and *dronedarone* should be avoided.

## B. Alprostadil

*Alprostadil* [al-PRAHST-uh-dill] is synthetic prostaglandin E1 (PGE1). In the penile tissue, PGE1 allows for relaxation of the smooth muscle in the corpus cavernosum. *Alprostadil* is available as an intraurethral suppository and an injectable formulation. Although PDE-5 inhibitors are considered first-line therapy for the treatment of ED, *alprostadil* may be used for patients who are not candidates for oral therapies. In contrast to oral agents, *alprostadil* acts locally, which may reduce the occurrence of adverse effects.

1. **Mechanism of action:** *Alprostadil* causes smooth muscle relaxation by an unknown mechanism. It is believed that *alprostadil* increases concentrations of cyclic AMP (cAMP) within cavernosal tissue. As a result, protein kinase is activated, allowing trabecular smooth muscle relaxation and dilation of cavernosal arteries. Increased blood flow to the erection chamber compresses venous outflow, so that blood is entrapped leading to penile tumescence (erection) to help in intercourse and erection may occur.
2. **Pharmacokinetics:** Systemic absorption of *alprostadil* is minimal. If any *alprostadil* is systemically absorbed, it is quickly metabolized. Therefore, it is either administered as a corpus cavernosal injection on the penis using a very fine needle or administered as a urethral suppository. The onset of action of *alprostadil* is 5 to 10 minutes when given as a urethral suppository and 2 to 25 minutes when administered by injection. The resulting erection may last for 30 to 60 minutes, or longer, depending upon the particular patient.
3. **Adverse effects:** Since *alprostadil* is not systemically absorbed, adverse systemic effects are rare. However, hypotension or headache is a possibility due to PGE1-induced vasodilation. Locally, adverse effects of *alprostadil* include penile pain, urethral pain, and testicular pain. Bleeding from the insertion or injection of *alprostadil* is rare. Hematoma, ecchymosis, and rash are possible from *alprostadil* injection, although these adverse effects are also rare. *Alprostadil* administration may lead to priapism.

### C. Papaverine or phentolamine

The combination of *papaverine*, a direct smooth muscle relaxant (an alkaloid isolated from opium poppy but having different structure unlike *morphine*), and *phentolamine*, nonselective  $\alpha$ -adrenergic blocker known to cause vasodilation are used together to induce penile erection. *Papaverine* and *phentolamine* are directly injected into corpus cavernosum for the effect. Though priapism is a common problem, it is an emergency situation, where the reversal is achieved by withdrawing blood from the corpus cavernosum or by injecting vasoconstrictors such as *phenylephrine*. Moreover, self-injection requires adequate skills and the injection can cause local hematoma, infection, and damage of the smooth muscle. It is used only in situations where all other pharmacological methods fail.

### D. Androgen substitution therapy

Androgen deficiency is one of the factors responsible for ED. Hypogonadism due to various factors causing ED can be treated by the injection of the esters of *testosterone* or topical or transdermal *testosterone* therapy.

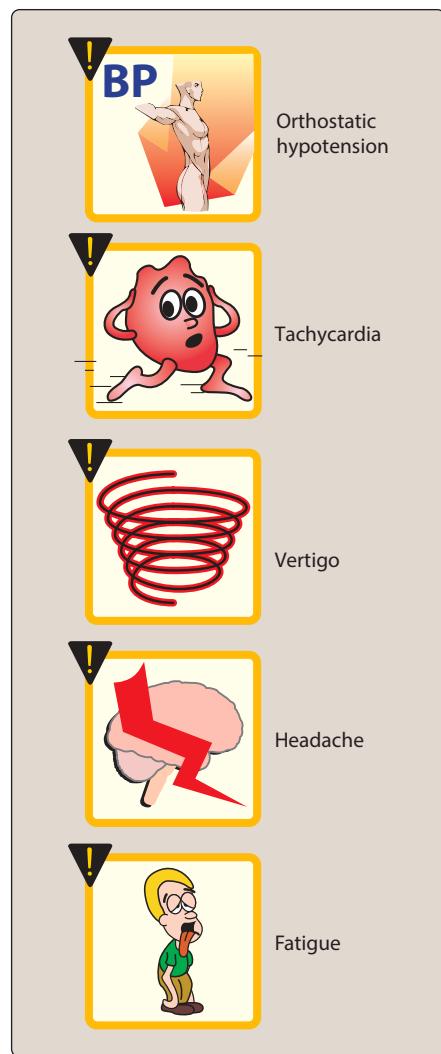
## III. BENIGN PROSTATIC HYPERPLASIA

Three classes of medications are used to treat BPH:  $\alpha_1$ -adrenergic antagonists, 5- $\alpha$  reductase inhibitors, and phosphodiesterase-5 (PDE-5) inhibitors.

## A. $\alpha_1$ -Adrenergic antagonists

*Terazosin* [ter-AY-zoe-sin], *doxazosin* [dox-AY-zoe-sin], *tamsulosin* [tam-SUE-loh-sin], *alfuzosin* [al-FUE-zoe-sin], and *silodosin* [sil-oh-DOE-sin] are selective competitive blockers of the  $\alpha_1$  receptor. All drugs with their dosage and receptor specificity which are indicated for the treatment of BPH are shown in Figure 43.1. *Prazosin* is an  $\alpha$ -blocker that is used off-label in the treatment of BPH. However, current guidelines do not endorse the use of *prazosin* for BPH. Please refer to Chapter 7 for a discussion of  $\alpha$ -blockers in the setting of hypertension.

- Mechanism of action:**  $\alpha_{1A}$  Receptors are found in the prostate,  $\alpha_{1B}$  receptors are found in the prostate and vasculature, and  $\alpha_{1D}$  receptors are found in the vasculature. By blocking the  $\alpha_{1A}$  and  $\alpha_{1B}$  receptors in the prostate, the  $\alpha$ -blockers cause prostatic smooth muscle relaxation, which leads to improved urine flow. As *doxazosin*, *terazosin*, and *alfuzosin* also have blockade on  $\alpha_{1B}$  apart from  $\alpha_{1A}$  receptors, they can cause decrease in blood pressure by reducing peripheral vascular resistance. In contrast, *tamsulosin* and *silodosin* have less of an effect on blood pressure because they are more selective for the prostate-specific  $\alpha_{1A}$  receptor.
- Pharmacokinetics:** The  $\alpha$ -blockers are well absorbed following oral administration. When taken with food, the absorption of *tamsulosin*, *alfuzosin*, and *silodosin* is increased. Therefore, for best efficacy, these agents should be taken with food or after a meal, typically supper. *Doxazosin*, *alfuzosin*, *tamsulosin*, and *silodosin* are metabolized through the cytochrome P450 system. *Silodosin* is also a substrate for P-glycoprotein (P-gp). *Terazosin* is metabolized in the liver, but not through the CYP system. In general, the  $\alpha$ -blockers have a half-life of 8 to 22 hours, with peak effects 1 to 4 hours after administration. *Silodosin* requires dosage adjustment in renal impairment and is contraindicated in patients with severe renal dysfunction.
- Adverse effects:**  $\alpha$ -Blockers may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension. Because *tamsulosin* and *silodosin* are more selective for the  $\alpha_{1A}$  receptors found on the smooth muscle of the prostate, they have relatively minimal effects on blood pressure, although dizziness and orthostasis may occur. By blocking  $\alpha$  receptors in the ejaculatory ducts and impairing smooth muscle contraction, inhibition of ejaculation and retrograde ejaculation have been reported. Several of these agents have a caution about “floppy iris syndrome,” a condition in which the iris billows in response to intraoperative eye surgery (Figure 43.4)
- Drug interactions:** Drugs that inhibit CYP3A4 and CYP2D6 (for example, *verapamil*, *diltiazem*) may increase the plasma concentrations of *doxazosin*, *alfuzosin*, *tamsulosin*, and *silodosin*, whereas drugs that induce the CYP450 system (for example, *carbamazepine*, *phenytoin*, and *St. John's wort*) may decrease plasma concentrations. *Alfuzosin* may prolong the QT interval, so it should be used with caution with other drugs that cause QT prolongation (for example, class III antiarrhythmics). Because *silodosin* is a substrate for P-gp, drugs that inhibit P-gp, such as *cyclosporine*, may increase *silodosin* concentrations.



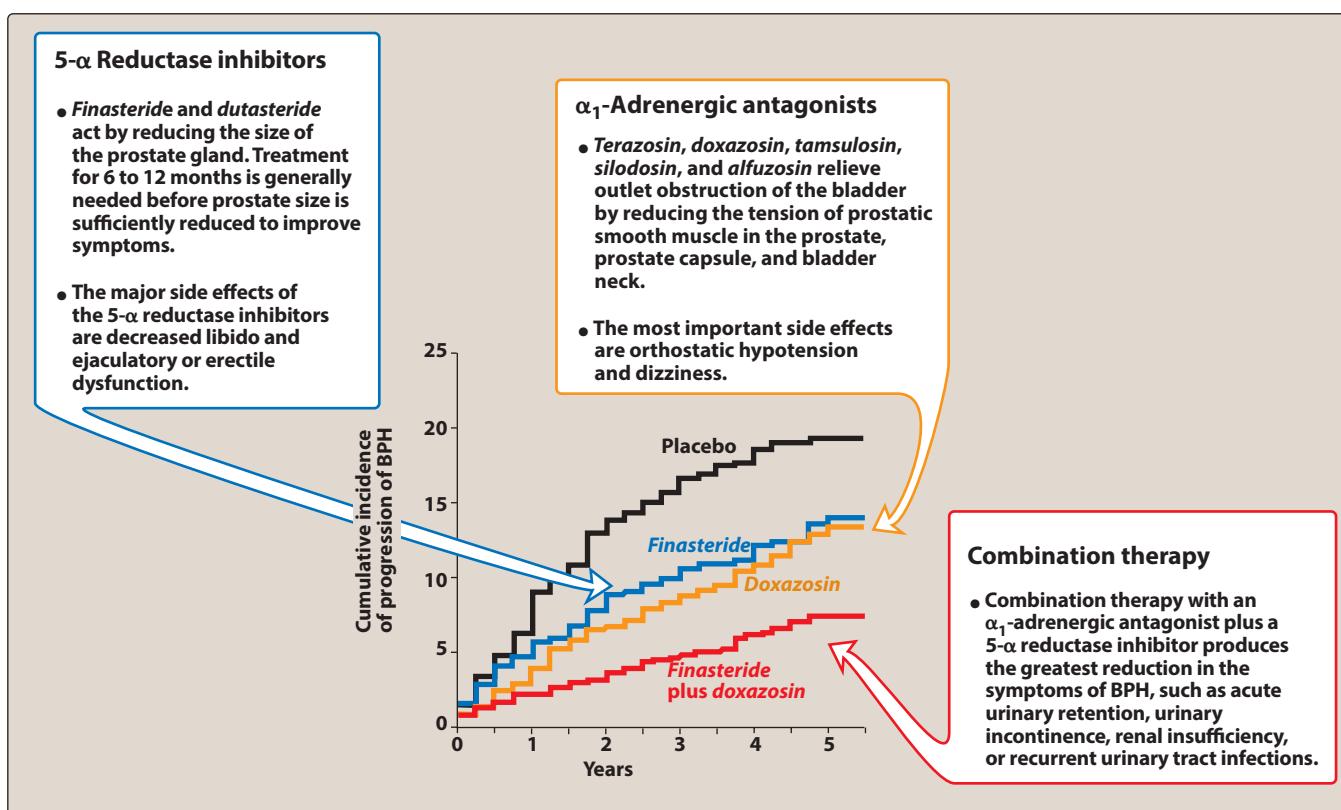
**Figure 43.4**

Some adverse effects commonly observed with nonselective  $\alpha$ -blockers.

## B. 5- $\alpha$ Reductase inhibitors

*Finasteride* [fin-AS-ter-ide] and *dutasteride* [doo-TAS-ter-ide] inhibit 5- $\alpha$  reductase. Compared to the  $\alpha$ -blockers, which provide patients with relief from BPH symptoms within 7 to 10 days, these agents may take up to 12 months to relieve symptoms.

**1. Mechanism of action:** Both *finasteride* and *dutasteride* inhibit the enzyme 5- $\alpha$  reductase, which is responsible for converting testosterone to the more active dihydrotestosterone (DHT). DHT is an androgen that stimulates prostate growth. By reducing DHT, the prostate shrinks and urine flow improves. Compared with *finasteride*, *dutasteride* is more potent and causes a greater decrease in DHT. *Finasteride* inhibits only 5- $\alpha$  reductase I iso-enzyme (present predominantly in the male urogenital tract) but *dutasteride* blocks both I and II iso-enzymes, thereby reducing plasma DHT levels more than *finasteride*. In order for the 5- $\alpha$  reductase inhibitors to be effective, the prostate must be enlarged. Since it takes several months for 5- $\alpha$  reductase inhibitors to reduce the prostate size, it is appropriate to use these agents in combination with an  $\alpha$ -blocker to provide relief of symptoms. *Dutasteride* and *tamsulosin* are available as a combination product for this indication. Figures 43.5 and 43.6 summarize important differences between these two classes of agents. *Finasteride* is also used for alopecia, especially for male pattern baldness, as reduction of DHT in scalp and serum prevents hair loss.



**Figure 43.5**

Therapy for benign prostatic hyperplasia (BPH).

	$\alpha_1$ -ADRENERGIC ANTAGONISTS	5- $\alpha$ REDUCTASE INHIBITORS
Decrease in prostate size	No	Yes
Peak onset	2–4 weeks	6–12 months
Decrease in PSA	No	Yes
Sexual dysfunction	+	++
Hypotensive effects	++	–
Commonly used drugs	<i>Tamsulosin</i> and <i>alfuzosin</i>	<i>Finasteride</i> and <i>dutasteride</i>

PSA = prostate-specific antigen.

**Figure 43.6**

Comparisons of treatment for benign prostatic hyperplasia.

- Pharmacokinetics:** Food does not affect the absorption of *finasteride* or *dutasteride*. Both agents are highly protein bound and metabolized by the CYP450 system. The mean plasma elimination half-life of *finasteride* is 6 to 16 hours, while the terminal elimination half-life of *dutasteride* is 5 weeks once steady-state concentrations are achieved (which is typically after 6 months of therapy).
- Adverse effects:** The 5- $\alpha$  reductase inhibitors cause sexual side effects, such as decreased ejaculate, decreased libido, ED, gynecomastia, and oligospermia. *Finasteride* and *dutasteride* are teratogenic. Women who are pregnant or of childbearing age should not handle or ingest either agent, as this may lead to serious birth defects involving the genitalia in a male fetus. Although both agents are metabolized by the CYP450 system, drug interactions are rare. It is not ideal to use a 5- $\alpha$  reductase inhibitor with testosterone, since both *finasteride* and *dutasteride* inhibit the conversion of testosterone to its active form, DHT.

### C. Phosphodiesterase-5 inhibitor

*Tadalafil* is the only PDE-5 inhibitor approved for the treatment of BPH. PDE-5 is present in the prostate and bladder. As such, inhibition of PDE-5 by *tadalafil* allows for vasodilation and relaxation of the smooth muscle of the prostate and bladder, which thereby improves symptoms of BPH.

## Study Questions

Choose the ONE best answer.

- 43.1 Which is CORRECT regarding the mechanism of action of phosphodiesterase-5 (PDE-5) inhibitors?
- PDE-5 inhibitors increase prostaglandin production.
  - PDE-5 inhibitors enhance the effect of nitric oxide.
  - PDE-5 inhibitors cause vasoconstriction of the erection chamber.
  - PDE-5 inhibitors antagonize cyclic GMP.

Correct answer = B. PDE-5 inhibitors enhance the effect of nitric oxide by preventing the breakdown of cGMP. PDE-5 inhibitors do not affect prostaglandin production. Although blood is drawn to the erection chamber, PDE-5 inhibitors allow for this via vasodilation, not vasoconstriction. PDE-5 inhibitors prevent the breakdown of cGMP but do not antagonize its action.

- 43.2 When selecting between the available PDE-5 inhibitors for treatment of ED, which is an important consideration?
- Tadalafil has the shortest half-life of the PDE-5 inhibitors.
  - Sildenafil should be given with food to increase absorption.
  - Vardenafil ODT doses are not equal to film-coated vardenafil doses.
  - Avanafil should be taken at least 1 hour before intercourse.
- 43.3 A patient who is taking a PDE-5 inhibitor for ED is diagnosed with angina. Which antianginal medication would be of particular concern in this patient?
- Metoprolol
  - Diltiazem
  - Amlodipine
  - Nitroglycerin
- 43.4 Which BEST describes the mechanism of action of alprostadil?
- Alprostadil blocks cGMP.
  - Alprostadil blocks nitric oxide.
  - Alprostadil increases PDE-5.
  - Alprostadil increases cAMP.
- 43.5 Which is CORRECT regarding local administration of alprostadil?
- Local administration of alprostadil allows for low systemic absorption.
  - Local administration of alprostadil increases the chance of drug interactions.
  - Local administration of alprostadil is accomplished by application of a cream.
  - Local administration of alprostadil causes changes in color vision.
- 43.6 Which is the BEST description of the mechanism of action of dutasteride?
- Dutasteride blocks 5- $\alpha$  reductase.
  - Dutasteride blocks  $\alpha_{1A}$  receptors.
  - Dutasteride blocks PDE-5.
  - Dutasteride blocks  $\alpha_{1A}$  and  $\alpha_{1B}$  receptors.
- 43.7 A patient is worried about starting terazosin because he is very sensitive to side effects of medications. Which adverse effect would be most expected in this patient?
- Erectile dysfunction
  - Gynecomastia
  - Dizziness
  - Vomiting

Correct answer = C. The ODT dosage form of vardenafil provides a high systemic concentration of vardenafil, which is higher than that provided by the film-coated tablets. As such, the doses are not interchangeable. Tadalafil has the longest half-life of all PDE-5 inhibitors. Food may delay sildenafil absorption. Avanafil has the quickest onset of action and may be taken 30 minutes before intercourse.

Correct answer = D. Nitrates, such as nitroglycerin, can cause life-threatening hypotension when taken with PDE-5 inhibitors. While metoprolol, diltiazem, and amlodipine may all lower blood pressure, the interaction with PDE-5 inhibitors is not relevant.

Correct answer = D. Through an unknown mechanism, alprostadil (a synthetic prostaglandin) increases levels of cAMP, causing smooth muscle relaxation. Alprostadil does not affect cGMP, nitric oxide, or PDE-5.

Correct answer = A. Local administration of alprostadil allows for minimal systemic absorption. This makes alprostadil associated with few drug interactions. Alprostadil is administered by injection or urethral suppository, not a cream. Because there is little systemic absorption, and alprostadil does not affect PDE-6, changes in color vision are not likely.

Correct answer = A. Dutasteride blocks 5- $\alpha$  reductase. Dutasteride does not affect  $\alpha_{1A}$  receptors,  $\alpha_{1B}$  receptors, or PDE-5.

Correct answer = C. Because of the  $\alpha$ -blocking properties, terazosin commonly causes dizziness (this may be related to orthostatic hypotension). ED and gynecomastia would be unexpected with  $\alpha$ -blockers. While most drugs may cause nausea and vomiting, terazosin is much more likely to cause dizziness.

- 43.8 Which describes an important difference between terazosin and tamsulosin?
- A. Terazosin blocks  $\alpha_{1A}$  receptors, whereas tamsulosin blocks  $\alpha_{1A}$  and  $\alpha_{1B}$  receptors.
  - B. Terazosin blocks  $\alpha_{1A}$  and  $\alpha_{1B}$  receptors, whereas tamsulosin blocks  $\alpha_{1A}$  receptors.
  - C. Terazosin blocks 5- $\alpha$  reductase, whereas tamsulosin blocks PDE-5.
  - D. Terazosin must be taken with food, whereas tamsulosin can be taken on an empty stomach.
- 43.9 Which is CORRECT regarding finasteride?
- A. Finasteride is associated with significant hypotension.
  - B. Finasteride is associated with birth defects.
  - C. Finasteride is effective within 2 weeks of initiation.
  - D. Finasteride is renally eliminated.
- 43.10 A 70-year-old man with BPH and an enlarged prostate continues to have urinary symptoms after an adequate trial of tamsulosin. Dutasteride is added to his therapy. In addition to tamsulosin, he is also taking hydrochlorothiazide, testosterone, and vardenafil as needed before intercourse. Which of his medications could have an interaction with dutasteride?
- A. Hydrochlorothiazide
  - B. Tamsulosin
  - C. Testosterone
  - D. Vardenafil

Correct answer = B. Tamsulosin is more selective for the  $\alpha_{1A}$  receptor, found in the prostate. Terazosin blocks  $\alpha_{1A}$ ; however, terazosin also blocks  $\alpha_{1B}$ . Neither one blocks 5- $\alpha$  reductase nor PDE-5. Tamsulosin should be taken with food, while terazosin does not need to be taken with food.

Correct answer = B. Because finasteride inhibits the conversion of testosterone to its active form, it may cause significant developmental defects in the male genitalia of a developing fetus. As such, it is contraindicated in pregnancy. Unlike the  $\alpha$ -blockers, the 5- $\alpha$  reductase inhibitors are not associated with hypotension. Finasteride may take up to 12 months before it is effective. Finasteride is metabolized via CYP450 and is not renally eliminated.

Correct answer = C. Because dutasteride prevents the conversion of testosterone to the more active form, DHT, these medications have an interaction. Essentially, dutasteride prevents testosterone from "working." Hydrochlorothiazide does not interfere with the metabolism of dutasteride, and dutasteride does not have any effect on the blood pressure-lowering effects of hydrochlorothiazide. Tamsulosin is appropriate in combination with a 5- $\alpha$  reductase inhibitor when the prostate is enlarged. Vardenafil is only prescribed as needed, and the two drugs do not have a pharmacokinetic interaction.



# Drugs for Anemia

Lori Dupree

44

## I. OVERVIEW

Anemia is defined as a below-normal plasma hemoglobin concentration resulting from a decreased number of circulating red blood cells or an abnormally low total hemoglobin content per unit of blood volume. General signs and symptoms of anemia include fatigue, palpitations, shortness of breath, pallor, dizziness, and insomnia. Anemia can be caused by chronic blood loss, bone marrow abnormalities, hemolysis, infections, malignancy, endocrine deficiencies, renal failure, and a number of other disease states. A large number of drugs cause toxic effects on blood cells, hemoglobin production, or erythropoietic organs, which, in turn, may cause anemia. Nutritional anemias are caused by dietary deficiencies of substances such as iron, folic acid, and vitamin B<sub>12</sub> (*cyanocobalamin*) that are necessary for normal erythropoiesis. Individuals with a genetic predisposition to anemia, such as sickle cell disease, can benefit from pharmacologic treatment with actions beyond nutritional supplementation, such as *hydroxyurea*. While severe anemia can be temporarily corrected by transfusion of packed cell or whole blood, a summary of agents used for the treatment of mild-to-moderate anemia is provided in [Figure 44.1](#).

## II. AGENTS USED TO TREAT ANEMIAS

### A. Iron

Iron is stored in the intestinal mucosal cells, liver, spleen, and bone marrow as ferritin (an iron–protein complex) and delivered to the marrow for hemoglobin production by transferrin, a transport protein. Iron deficiency, the most common nutritional deficiency, results from a negative iron balance due to depletion of iron stores and/or inadequate intake, such as acute or chronic blood loss, menstruating or pregnant women, or periods of accelerated growth in children. In addition to general signs and symptoms of anemia, iron deficiency anemia may cause pica (hunger for ice, dirt, paper, etc.), koilonychias (upward curvature of the finger and toe nails), and soreness and cracking at the corners of the mouth. Treatment with an iron preparation is justified only in the presence of a demonstrable iron-deficiency state. Before starting treatment, it is important to exclude any serious underlying cause of the anemia (for example, gastric erosion and gastrointestinal cancer).

Prophylaxis with an iron preparation may be appropriate in pregnancy, in menorrhagia, in malabsorption, after subtotal or total gastrectomy, in hemodialysis patients, and in the management of low birth weight infants such as preterm neonates.

### TREATMENT OF ANEMIA

Oral preparations (available as tablets, capsules [extended release, film coated], suspension, chewable tablets)  
\*Iron salt—ferrous sulfate, ferrous gluconate, ferrous fumarate, ferrous carbonate anhydrous, ferrous succinate  
Iron carbonyl iron  
Iron polysaccharide complex (iron polymaltose)  
Combination of iron salts, vitamins, and minerals  
Folic acid  
Cyanocobalamin (vitamin B<sub>12</sub>)  
Parenteral iron preparations  
Iron dextran complex  
Iron sucrose  
Ferric carboxymaltose  
Hormones produced by kidney  
Epoetin alfa (EPO)  
Darbepoetin

### BIOLOGIC RESPONSE MODIFIERS

*Filgrastim*  
*Pegfilgrastim*  
*Sargramostim*  
*Tbo-filgrastim*

### TREATMENT OF SICKLE CELL ANEMIA

*Hydroxyurea*  
*Iron antagonist*  
*Deferrioxamine*

**Figure 44.1**

Summary of drugs for the treatment of anemia, dose, and route of administration. \*Elemental iron may vary markedly from one or more preparation. (For drug dosages, refer to Appendix at the end of the book.)

1. **Mechanism of action:** Supplementation with elemental iron corrects the iron deficiency. An oral dose of 3 to 5 mg/kg body weight (100 to 180 mg/day) of oral elemental iron is administered in divided doses two to three times daily for patients with iron deficiency anemia.
2. **Pharmacokinetics:** Iron is absorbed after oral administration. Acidic conditions in the stomach keep iron in the reduced ferrous form, which is the more soluble form. Iron is then absorbed in the duodenum. [Note: The amount absorbed depends on the current body stores of iron. If iron stores are adequate, less iron is absorbed. If stores are low, more iron is absorbed.] The relative percentage of iron absorbed decreases with increasing doses. Oral preparations include ferrous sulfate, ferrous fumarate, ferrous gluconate, polysaccharide–iron complex, and carbonyl iron formulations. The percentage of elemental iron varies in each oral iron preparation (Figure 44.2). Parenteral formulations of iron, such as iron dextran, sodium ferric gluconate, ferumoxytol, ferric carboxymaltose, and iron sucrose, are also available. Iron salts should be given by mouth unless there are good reasons for using another route such as vomiting or poor tolerability of oral iron, continuing blood loss, or malabsorption. Parenteral iron, when given with erythropoietins, may also play a role in the management of chemotherapy-induced anemia. It can also be used in specific patient groups and in case of chronic renal failure in patients on dialysis. Depending on the preparation used,

IRON FORMULATION	ELEMENTAL IRON (%)	NOTES
<i>Ferrous gluconate</i>	12	<ul style="list-style-type: none"> <li>Less elemental iron, but similar tolerability to <i>ferrous sulfate</i></li> </ul>
<i>Ferric ammonium citrate</i>	18	<ul style="list-style-type: none"> <li>Less bioavailable than ferrous salts</li> <li>Must be reduced to ferrous form in the intestine</li> </ul>
<i>Ferrous sulfate</i>	20	<ul style="list-style-type: none"> <li>Most common oral iron supplement</li> <li>Low cost with good effectiveness and tolerability</li> </ul>
<i>Ferrous sulfate, anhydrous</i>	30	<ul style="list-style-type: none"> <li>Extended-release formulation of <i>ferrous sulfate</i> (once-daily dosing)</li> <li>Higher cost than <i>ferrous sulfate</i></li> </ul>
<i>Ferrous fumarate</i>	33	<ul style="list-style-type: none"> <li>Similar effectiveness and tolerability to <i>ferrous sulfate</i></li> <li>Almost no taste compared to other iron salts</li> </ul>
<i>Carbonyl iron</i>	100	<ul style="list-style-type: none"> <li>Microparticles of purified iron</li> <li>Dissolves in the stomach to form HCl salt to be absorbed</li> <li>Less toxic than iron salts due to slower absorption rate (continued iron release for 1 to 2 days)</li> </ul>
<i>Polysaccharide-iron complex</i>	100	<ul style="list-style-type: none"> <li>Tasteless and odorless</li> <li>Once-daily elemental iron dose similar to twice-daily <i>ferrous sulfate</i></li> </ul>

**Figure 44.2**

Characteristics of various iron formulations.

parenteral iron is given as a total dose or in divided doses. Further treatment should be guided by monitoring hemoglobin and serum iron concentrations. Ferrous salts show only marginal differences among themselves in efficiency of absorption of iron. Hemoglobin regeneration rate is little affected by the type of salt used provided sufficient iron is given, and in most patients the speed of response is not critical. Thus, the choice of preparation is usually decided by the incidence of side effects and cost.

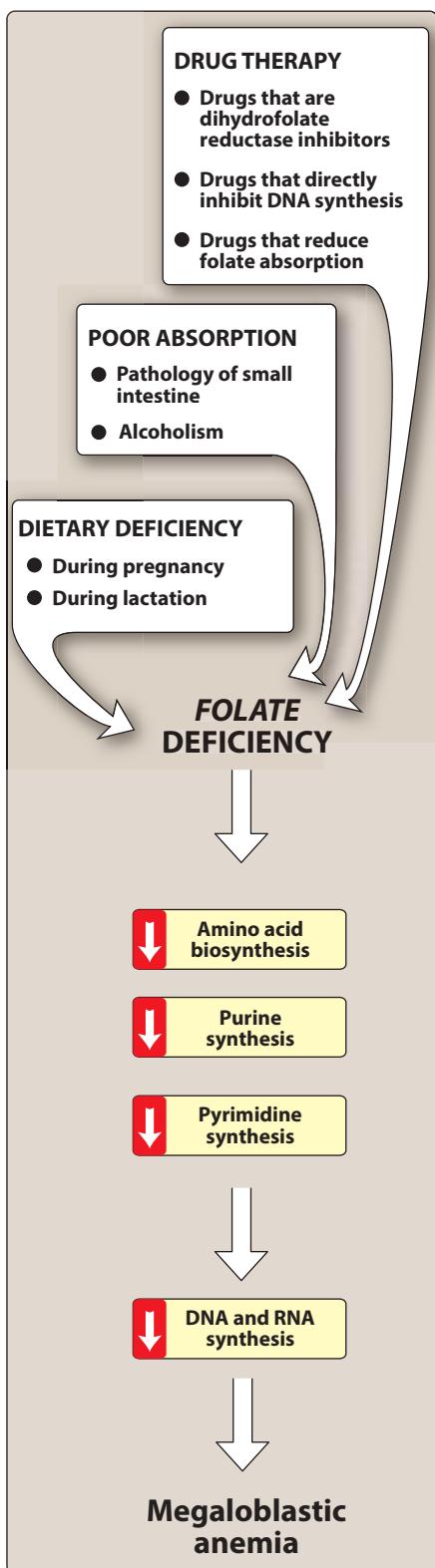
Carbonyl iron is a micronized metallic iron formulation. It has been reported to be absorbed slowly and better tolerated as compared to other forms of iron. Although its bioavailability is reported to be low as compared to ferrous sulfate, it has been found to have a higher safety margin in terms of iron toxicity. Modified-release preparations of iron are available for once-daily dosage, but have no therapeutic advantage and are not recommended. These preparations are formulated to release iron gradually; the low incidence of side effects may reflect the small amounts of iron available for absorption as the iron is carried past the first part of the duodenum into an area of the gut where absorption may be poor.

a. **Compound preparations:** Several preparations containing folic acid are used during pregnancy in women who are at a high risk of developing iron and folic acid deficiency and for prevention of neural tube defects in women planning a pregnancy. However, the small doses of folic acid contained in these preparations are inadequate for the treatment of megaloblastic anemias.

Some oral preparations contain ascorbic acid to aid absorption of the iron but the therapeutic advantage of such preparations is minimal and may be costlier. Similarly, there is no justification for the inclusion of Vitamin B group (except folic acid for pregnant women).

3. **Adverse effects:** Excess of iron is having a highly toxic value. Accidental overdosage ( $>60$  mg/kg) of iron formulation can produce fatal consequences. It can cause vomiting, hematemesis, diarrhea, abdominal pain, acidosis, cardiovascular collapse and death. A quick toxicological management is essential. In therapeutic doses, gastrointestinal (GI) disturbances caused by local irritation (abdominal pain, constipation, nausea, diarrhea) and dark stools are the most common adverse effects of oral iron supplements. Parenteral iron formulations may be used in those who cannot tolerate or inadequately absorb oral iron, as well as those receiving *erythropoietin* with hemodialysis or chemotherapy. Fatal hypersensitivity and anaphylactoid reactions can occur in patients receiving parenteral iron (mainly *iron dextran* formulations). A test dose should be administered prior to *iron dextran*. In addition, intravenous iron should be used cautiously in the presence of active infections. [Note: Iron is essential for bacterial growth.]

Iron supplementation is indicated in the treatment of iron deficiency anemia, in megaloblastic anemia B12, and in folic acid therapy but the underlying cause for iron deficiency needs to be evaluated before supplementation.

**Figure 44.3**

Causes and consequences of folic acid depletion.

- a. **Treatment of iron poisoning:** Acute overdosage (prevalent in children) of iron needs to be reduced by gastric lavage with sodium bicarbonate solution to prevent further absorption of iron. *Desferroxamine* injection (50 mg/kg repeated based on serum levels), intramuscularly or intravenously (10 to 15 mg/kg/hr to a maximum of 75 mg/kg/day), is used as an antidote to chelate ion. Periodic serum level monitoring is essential while continuing with *desferroxamine* therapy. In the absence of *desferroxamine*, diethylene triamine penta-acetic acid (DTPA) or calcium EDTA can be used.

### B. Folic acid (folate)

The primary use of *folic acid* is in treating deficiency states that arise from inadequate levels of the vitamin. Folate deficiency may be caused by 1) increased demand (for example, pregnancy and lactation), 2) poor absorption caused by pathology of the small intestine, 3) alcoholism, or 4) treatment with drugs that are dihydrofolate reductase inhibitors (for example, *methotrexate* and *trimethoprim*), drugs that directly inhibit DNA synthesis (for example, *azathioprine* and *zidovudine*), or drugs that reduce folate absorption (for example, *phenytoin* and *phenobarbital*). Folinic acid (N5-Formyl-THF), also called "leucovorin," is the active coenzyme of folic acid which is used for the rescue of normal cells while treating cancer with a higher dose of *methotrexate*. Folinic acid is also used to enhance the anticancer efficacy of *5-fluorouracil*. A primary result of folic acid deficiency is megaloblastic anemia (large-sized red blood cells), which is caused by diminished synthesis of purines and pyrimidines. This leads to an inability of erythropoietic tissue to make DNA and, thereby, proliferate (Figure 44.3). [Note: To avoid neurological complications of vitamin B<sub>12</sub> deficiency, it is important to evaluate the basis of the megaloblastic anemia prior to instituting therapy. Both vitamin B<sub>12</sub> and folate deficiency can cause similar symptoms.]

*Folic acid* is rapidly absorbed in the jejunum unless abnormal pathology is present. Oral *folic acid* administration is nontoxic and at high doses, excess vitamin is excreted in the urine. Rare hypersensitivity reactions to parenteral injections have been reported.

### C. Cyanocobalamin and hydroxocobalamin (vitamin B<sub>12</sub>)

Deficiencies of *vitamin B<sub>12</sub>* can result from either low dietary levels or, more commonly, poor absorption of the vitamin due to the failure of gastric parietal cells to produce intrinsic factor (as in pernicious anemia), or a loss of activity of the receptor needed for intestinal uptake of the vitamin. Nonspecific malabsorption syndromes or gastric resection can also cause *vitamin B<sub>12</sub>* deficiency. In addition to general signs and symptoms of anemia, *vitamin B<sub>12</sub>* deficiency anemia may cause tingling (pins and needles) in the hands and feet, difficulty walking, dementia and, in extreme cases, hallucinations, paranoia, or schizophrenia. [Note: *Folic acid* administration alone reverses the hematologic abnormality and, thus, masks the *vitamin B<sub>12</sub>* deficiency, which can then proceed to severe neurologic dysfunction and disease. The cause of megaloblastic anemia needs to be determined in order to be specific in terms of treatment. Therefore, megaloblastic anemia should

not be treated with *folic acid* alone but, rather, with a combination of *folic acid* and *vitamin B<sub>12</sub>*. Predominantly, vitamin B<sub>12</sub> deficiency has been seen in strict vegetarians such as vegans. Therefore, it is essential to understand the dietary habits of the patients suffering from anemia. Vitamin B<sub>12</sub> also has independent metabolic functions, as it gets converted to active coenzymes such as adenosyl cobalamin and methylcobalamin which are involved in metabolism. Vitamin B<sub>12</sub> deficiency can also cause neuropathy as it is required for the synthesis of myelin.

The vitamin may be administered orally (for dietary deficiencies), intramuscularly, or deep subcutaneously (for pernicious anemia). Intramuscular *hydroxocobalamin* [hye-drox-oh-koe-BAL-a-min] is preferred since it has a rapid response, is highly protein bound, and maintains longer plasma levels. In patients with malabsorption, such as in bariatric surgery (surgical treatment for obesity), vitamin B<sub>12</sub> supplementation as *cyanocobalamin* [sye-an-oh-koe-BAL-a-min] is required daily in high oral doses or monthly by the parenteral route. For neurological defects due to diabetes, alcoholic, and other forms of peripheral neuropathy, vitamin B<sub>12</sub> is substituted in a dose of 1.5 mg/day. This vitamin is nontoxic even in large doses. In pernicious anemia, therapy must be continued for life.

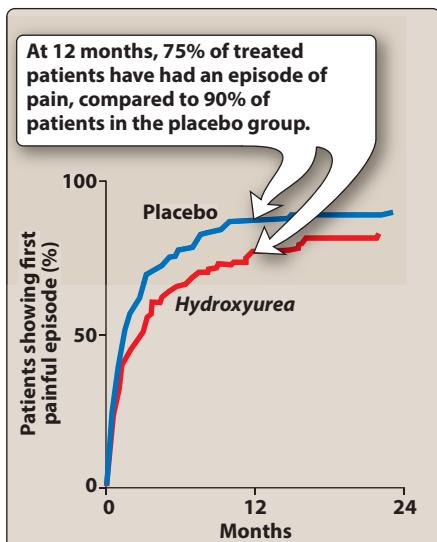
#### D. Erythropoietin and darbepoetin

Peritubular cells in the kidneys respond to hypoxia and synthesize and release erythropoietin [ee-rith-ro-POE-e-tin; EPO], a glycoprotein. EPO stimulates stem cells to differentiate into proerythroblasts and promotes the release of reticulocytes from the marrow and initiation of hemoglobin formation. Thus, EPO regulates red blood cell proliferation and differentiation in bone marrow. Human *erythropoietin* (*epoetin alfa*), produced by recombinant DNA technology, is effective in the treatment of anemia caused by end-stage renal disease, human immunodeficiency virus infection, bone marrow disorders, prematurity, and malignancy. A long-acting form of *erythropoietin*, *darbepoetin* [dar-be-POE-e-tin], has a half-life about three times that of *epoetin alfa* due to the addition of two carbohydrate chains. These agents are well tolerated and are administered intravenously in renal dialysis patients or subcutaneously for other indications. Side effects such as blood pressure elevation and arthralgia may occur in some cases. [Note: The former may be due to increases in peripheral vascular resistance and/or blood viscosity.] In addition, iron supplementation may be required to ensure an adequate response.

When *epoetin alfa* is used to target hemoglobin concentrations over 11 g/dL, serious cardiovascular events (such as thrombosis and severe hypertension), increased risk of death, shortened time to tumor progression, and decreased survival have been observed. The recommendations for all patients receiving *epoetin alfa* or *darbepoetin* include a minimum effective dose that does not exceed a hemoglobin level of 12 g/dL, and a hemoglobin level that does not rise by more than 1 g/dL over a 2-week period. Additionally, if the hemoglobin level exceeds 10 g/dL, doses of *epoetin alfa* or *darbepoetin* should be reduced or treatment should be discontinued. Neither agent has any value in the acute treatment of anemia due to their delayed onset of action.

### III. AGENTS USED TO TREAT NEUTROPENIA

Myeloid growth factors or granulocyte colony-stimulating factors (G-CSF), such as *filgrastim* [fil-GRAS-tim], *tbo-filgrastim*, and *pegfilgrastim* [peg-fil-GRAS-tim], and granulocyte-macrophage colony-stimulating factors (GM-CSF), such as *sargramostim* [sar-GRA-moe-stim], stimulate granulocyte production in the marrow to increase the neutrophil counts and reduce the duration of severe neutropenia. These agents are typically used prophylactically to reduce the risk of neutropenia following chemotherapy and bone marrow transplantation. *Filgrastim* and *sargramostim* can be dosed either subcutaneously or intravenously, whereas *tbo-filgrastim* and *pegfilgrastim* are dosed subcutaneously only. The main difference between the available agents is in the frequency of dosing. *Filgrastim*, *tbo-filgrastim*, and *sargramostim* are dosed once a day beginning 24 to 72 hours after chemotherapy, until the absolute neutrophil count (ANC) reaches 5000 to 10,000/ $\mu$ L. *Pegfilgrastim* is a pegylated form of G-CSF, resulting in a longer half-life when compared to the other agents, and is administered 24 hours after chemotherapy, as a single dose, rather than once daily. Monitoring of ANC is typically not necessary with *pegfilgrastim*. There is no evidence to show superiority of one agent over another in terms of efficacy, safety, or tolerability. Bone pain is a common adverse effect with these agents.



**Figure 44.4**

Effect of treatment with *hydroxyurea* on the percentage of sickle cell patients experiencing the first painful episode.

### IV. AGENTS USED TO TREAT SICKLE CELL DISEASE

#### A. Hydroxyurea

*Hydroxyurea* [high-DROX-ee-YOUR-ee-ah] is an oral ribonucleotide reductase inhibitor that can reduce the frequency of painful sickle cell crises (Figure 44.4). In sickle cell disease, *hydroxyurea* increases fetal hemoglobin (HbF) levels, thus diluting the abnormal hemoglobin S (HbS). Polymerization of HbS is delayed and reduced in treated patients, so that painful crises are not caused by sickled cells blocking capillaries and causing tissue anoxia. A clinical response may take 3 to 6 months. Important side effects of *hydroxyurea* include bone marrow suppression and cutaneous vasculitis. It is important that *hydroxyurea* is administered under the supervision of a physician experienced in the treatment of sickle cell disease. *Hydroxyurea* is also used off-label to treat acute myelogenous leukemia, psoriasis, and polycythemia vera.

Figure 44.5 provides a summary of medications used in the management of anemia.

MEDICATION	ADVERSE EFFECTS	DRUG INTERACTIONS	MONITORING PARAMETERS
<b>Treatment of anemia:</b>			
<i>Cyanocobalamin/B<sub>12</sub></i>	Injection site pain Arthralgia Dizziness Headache Nasopharyngitis Anaphylaxis	Proton-pump inhibitors—may decrease oral absorption of vitamin B <sub>12</sub>	Vitamin B <sub>12</sub> Folate Iron
<i>Erythropoietin/epoetin alfa</i>	Edema Pruritus Nausea/vomiting Hypertension CVA Thrombosis	<i>Darbepoietin alfa</i> —duplication of therapy can lead to increase adverse events	H/H Serum ferritin Blood pressure
<i>Darbepoietin alfa</i>	Edema Dyspnea Hypertension CVA Thrombosis	<i>Epoetin alfa</i> —duplication of therapy can lead to increase adverse events	H/H Serum ferritin Blood pressure
<i>Folic acid</i>	Bad taste in mouth Nausea Confusion Irritability	<i>Cholestyramine</i> —may interfere with absorption	CBC Serum folate
<i>Iron</i>	Pruritus N/V/D Headache Anaphylaxis	<i>Deferoxamine</i> —chelates iron <i>Dimercaprol</i> —chelates iron	H/H Serum iron TIBC Transferrin Reticulocyte count
<b>Treatment of sickle cell anemia:</b>			
<i>Hydroxyurea</i>	Myelosuppression Skin ulcer Secondary leukemia Elevated liver enzymes	HIV medications— <i>hydroxyurea</i> can decrease CD4 counts Salicylates—increase bleeding risk <i>Probenecid</i> —↑ uric acid	CBC

CBC = complete blood count; CVA = cerebrovascular accident; H/H = hemoglobin and hematocrit; N/V/D = nausea/vomiting/diarrhea; TIBC = total iron binding capacity.

**Figure 44.5**

Medications for the management of anemia.

## Study Questions

Choose the ONE best answer.

- 44.1 Which is an appropriate treatment for a nutritional anemia that presents as a hunger for ice and/or upward curvature of the fingernails?
- Vitamin B<sub>12</sub> (cyanocobalamin)
  - Folic acid
  - Vitamin D
  - Iron

Correct answer = C. Vitamin B<sub>12</sub>, folic acid, and iron deficiencies all contribute to anemia, but iron deficiency is associated with pica (hunger for ice or dirt) and koilonychia (upward curvature of toenails/fingernails). Vitamin D deficiency does exist but does not cause anemia.

- 44.2 Which iron supplement contains the highest percentage of elemental iron?
- Ferrous sulfate
  - Carbonyl iron
  - Ferrous gluconate
  - Ferric ammonium citrate
- 44.3 A 56-year-old woman is discovered to have megaloblastic anemia. Her past medical history is significant for alcoholism. Which would be the best treatment option for this patient?
- Oral vitamin B<sub>12</sub>
  - Parenteral vitamin B<sub>12</sub>
  - Oral folic acid
  - Oral vitamin B<sub>12</sub> with oral folic acid
- 44.4 A 60-year-old woman presents to her primary care physician complaining of dizziness and fatigue. Following laboratory testing, the patient is diagnosed with iron deficiency anemia, and oral iron supplementation is needed. Which would be the most appropriate dosing regimen for the patient?
- Ferrous fumarate 325 mg once daily
  - Ferrous gluconate 256 mg once daily
  - Polysaccharide–iron complex 150 mg two to three times daily
  - Ferrous sulfate 325 mg two to three times daily
- 44.5 A 63-year-old female patient with anemia secondary to chronic kidney disease and a hemoglobin level of 8.6 g/dL is treated with epoetin alfa. Eight days after the initial dose of epoetin alfa, the patient's hemoglobin is 10.5 g/dL. Which would be the next step in the management of this patient's anemia?
- Discontinue epoetin alfa.
  - Discontinue epoetin alfa and initiate darbepoetin.
  - Continue epoetin alfa.
  - Increase the dose of epoetin alfa.
- 44.6 Which drug would be beneficial to reduce the frequency of painful crises in a patient with sickle cell disease?
- Epoetin alfa
  - Filgrastim
  - Hydroxyurea
  - Sargramostim

Correct answer = B. Ferrous sulfate contains 20% (or 30% in the anhydrous formulation), ferrous gluconate contains 12%, and ferric ammonium citrate contains 18% of elemental iron. These are all well below the percent of elemental iron in carbonyl iron, which contains 100% elemental iron.

Correct answer = D. The patient has a history of alcoholism, which would suggest folic acid deficiency anemia. However, folic acid administration alone reverses the hematologic abnormality and masks possible vitamin B<sub>12</sub> deficiency, which can then proceed to severe neurologic dysfunction and disease. The cause of megaloblastic anemia needs to be determined in order to be specific in terms of treatment. Therefore, megaloblastic anemia should not be treated with folic acid alone but, rather, with a combination of folic acid and vitamin B<sub>12</sub>.

Correct answer = D. The recommended dose of iron supplementation in iron deficiency anemia is typically about 150 mg of elemental iron in two to three divided doses. Extended-release formulations (such as polysaccharide–iron complex) may be dosed once daily. Ferrous sulfate 325 mg contains approximately 65 mg of elemental iron, ferrous fumarate 325 mg contains about 107 mg elemental iron, ferrous gluconate 256 mg contains approximately 30 mg elemental iron, and polysaccharide–iron complex 150 mg contains 150 mg elemental iron.

Correct answer = A. Hemoglobin has increased to more than 10 g/dL and more than 1 g/dL in 2 weeks, so epoetin alfa should be discontinued or the dose reduced. Switching to darbepoetin, continuing epoetin alfa, or increasing the dose of epoetin alfa would continue to increase hemoglobin and lead to increased risk of cardiovascular events.

Correct answer = C. Clinical evidence supports the use of hydroxyurea for reducing the frequency and severity of painful sickle cell crises during the course of sickle cell disease. Epoetin alfa helps increase hemoglobin and red blood cell production in anemias secondary to chronic kidney disease, HIV, bone marrow disorders, and other disorders. Filgrastim and sargramostim stimulate granulocyte production in the marrow to increase the neutrophil counts and reduce the duration of severe neutropenia.

- 44.7 After completing his last cycle of chemotherapy, a 68-year-old man received a dose of pegfilgrastim prophylactically to reduce his risk of neutropenia. Twenty-four hours later, he returned to clinic to receive an additional dose of pegfilgrastim and was told he did not need another dose. Which would explain the rationale behind this recommendation?
- A. Absolute neutrophil count is above 1,000/ $\mu$ L
  - B. Pegfilgrastim is given as single dose
  - C. Next dose of pegfilgrastim is due 72 hours after the first dose
  - D. Next dose of pegfilgrastim is due 48 hours after the first dose
- 44.8 A patient has been taking ferrous sulfate 325 mg twice daily for 2 weeks and is complaining of a bad taste after each dose. Which once-daily, oral iron formulations would improve tolerability and provide a similar total daily dose of elemental iron as twice-daily ferrous sulfate?
- A. Ferric ammonium citrate 25 mg
  - B. Ferrous gluconate 100 mg
  - C. Ferrous sulfate, anhydrous 142 mg
  - D. Polysaccharide–iron complex 150 mg
- 44.9 Which patient with iron deficiency anemia would need the parenteral form of iron replacement?
- A. 22-year-old woman with heavy menstrual periods.
  - B. 58-year-old man with end stage renal disease on hemodialysis.
  - C. 32-year-old woman in the first trimester of pregnancy.
  - D. 40-year-old man with a diabetic foot infection.
- 44.10 An 81-year-old woman presents to the emergency department with progressive weakness, fatigue, confusion, and reports of seeing people in her house who were trying to hurt her but who were not physically present. Her physical exam was positive for pallor but negative for koilonychias or cracking at the corners of the mouth. Which deficiency would be the highest priority in this patient's workup?
- A. Vitamin B<sub>12</sub>
  - B. Iron
  - C. Folate
  - D. Calcium

Correct answer = B. Pegfilgrastim is a pegylated form of G-CSF and has a longer half-life; therefore, it is administered as a single dose with no additional doses needed. Monitoring of the ANC is not necessary with pegfilgrastim due to the pharmacokinetics of the drug.

Correct answer = D. Once-daily polysaccharide–iron complex (150 mg = 150 mg elemental iron) is tasteless and odorless, with a similar total daily dose of elemental iron as ferrous sulfate 325 mg twice daily (130 mg elemental iron/day). Once-daily ferric ammonium citrate 25 mg (4.5 mg elemental iron) is less bioavailable than twice-daily ferrous sulfate. Ferrous sulfate and ferrous gluconate have similar tolerability, but once-daily ferrous gluconate has less elemental iron (12 mg elemental iron). Ferrous sulfate, anhydrous has better tolerability with the extended-release formulation, but has less elemental iron (43 mg elemental iron) administered once daily compared to twice-daily ferrous sulfate.

Correct answer = B. Clinical evidence supports the use of parenteral iron over oral iron in hemodialysis patients due to a significantly greater increase in hemoglobin levels and lower incidence of treatment-related adverse events. Parenteral iron is also preferred in patients who cannot tolerate oral iron or who have iron malabsorption. Patients with heavy menstrual periods, who are pregnant, or who have chronic disease states, such as diabetes, and infections, should be administered an initial trial of oral iron.

Correct answer = A. Based on the presentation of confusion and hallucinations, vitamin B<sub>12</sub> deficiency should be considered the highest priority. Second priority would be to assess folate deficiency, since symptoms are similar to vitamin B<sub>12</sub> deficiency. Iron would be the third priority due to the patient's age, even without the presence of koilonychias or cracking of the mouth. Last priority would be to assess age-related deficiencies in calcium which could lead to fatigue as well as muscle cramps, poor appetite, and abnormal heart rhythms.



# Drugs for Dermatologic Disorders

45

Stacey Curtis and Cary Mobley

## I. OVERVIEW

The skin is a complex and dynamic organ comprising cells, tissues, and biomolecules that coordinate to provide many interdependent functions, including protection from environmental insults from noxious chemicals, infectious pathogens, and ultraviolet radiation, as well as serving vital functions in wound repair, sensation, thermoregulation, and vitamin D synthesis. This chapter focuses on drugs that are used for some of the more common skin conditions including psoriasis, acne, rosacea, infections, pigmentation disorders, and alopecia. Drugs for acne, superficial bacterial infections, and rosacea are summarized in [Figure 45.1](#). [Note: Agents for fungal infections of the skin are covered in Chapter 33.]

## II. TOPICAL PREPARATIONS

The skin is composed of two main layers, the epidermis and the dermis ([Figure 45.2](#)). The epidermis is composed of several layers of keratinocytes, with the outermost layer, the stratum corneum, serving as the primary barrier to external insults. The dermis, located between the epidermis and the subcutaneous tissue, is composed of connective tissue and contains many specialized structures, such as sweat glands, sebaceous glands, hair follicles, and blood vessels. Defects in skin structure and function induced by genetics and by environmental insults can lead to numerous dermatological conditions, many of which can be controlled or cured with the use of drug therapy.

Use of topical agents for treatment of dermatologic disorders is not only convenient, but also can minimize systemic adverse effects. Common topical dosage forms include sprays, powders, lotions, creams, pastes, gels, ointments, and foams. The choice of which dosage form to use for a particular condition involves factors such as occlusiveness, ease of application, patient acceptance, and drug potency. The choice also includes factors such as stratum corneum thickness and integrity, as well as the type, location, and extent of the lesions being treated.

## III. AGENTS FOR ACNE

Acne vulgaris (common acne) is a common skin disorder that occurs in about 85% of individuals 12 to 24 years of age, coinciding with an increase in androgen production. [Note: Use of oral contraceptives may

### TOPICAL AGENTS FOR ACNE

*Retinoids  
Tretinoin  
Alitretinoin  
Adapalene  
Bexarotene  
Tazarotene  
Salicylic acid  
Azelaic acid  
Benzoyl peroxide  
Systemic retinoid  
Isotretinoin  
Acitretin  
Etretinate  
Bexarotene  
Topical and Oral antibiotics  
Minocycline  
Clindamycin  
Doxycycline  
Erythromycin*

### AGENTS FOR SUPERFICIAL BACTERIAL INFECTIONS

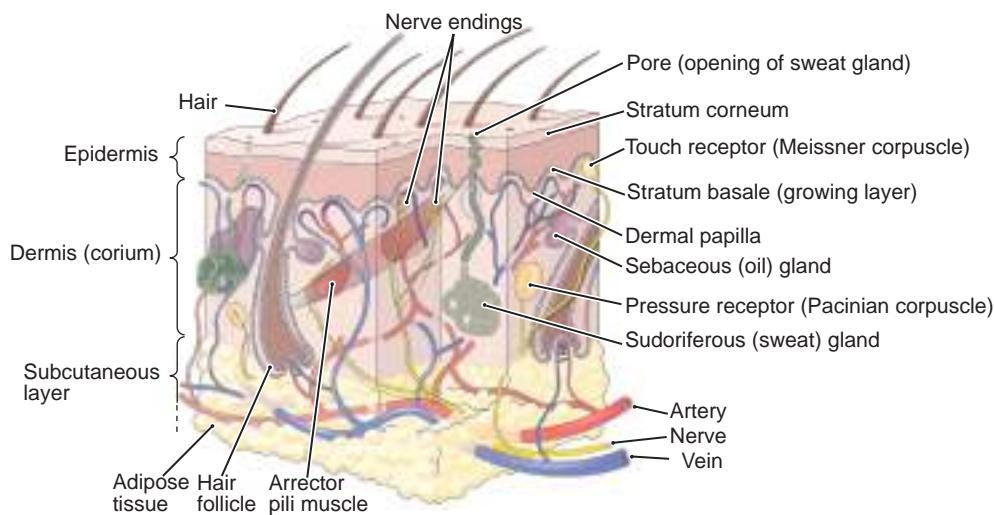
*Bacitracin  
Gentamicin  
Mupirocin  
Neomycin  
Polymyxin  
Retapamulin*

### AGENTS USED FOR ROSACEA

*Azelaic acid  
Brimonidine  
Oxymetazoline  
Pimecrolimus  
Sulfacetamide sodium  
Doxycycline  
Metronidazole*

**Figure 45.1**

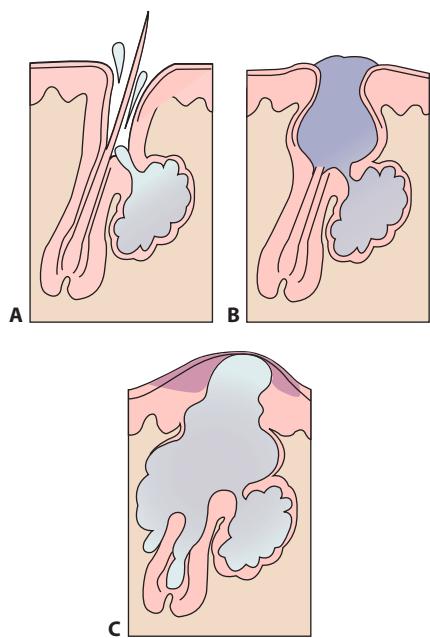
Summary of drugs for acne, superficial bacterial infections, and rosacea. (For drug dosages, refer to Appendix at the end of the book.)



**Figure 45.2**  
Cross-section of the skin.

help decrease circulating levels of free androgen and reduce symptoms of acne in females (see Chapter 25). It begins with excessive proliferation and adhesion of skin cells that form a keratin plug (microcomedone), which closes the hair follicle (Figure 45.3). Within the closed hair follicle, skin cells are shed and sebum production continues. This causes the follicle to dilate to form a comedone.

The sebum serves as a nutrient for the proliferation of *Propionibacterium acnes*, which, along with other factors, triggers an inflammatory response that causes the formation of a pustule or papule—the pimple. If this progresses, the follicular wall can rupture, leading to the formation of an inflamed nodule. Different medications can be used alone or in combination to affect one or more of these pathological components to clear the acne lesions.



**Figure 45.3**  
Acne vulgaris. **A.** Normal sebaceous gland and hair follicle. **B.** Comedone formation. **C.** Pustule formation.

### A. Antibiotics

Topical and oral antibiotics are commonly used in acne, with oral antibiotics reserved for moderate-to-severe acne. The use of antibiotics in acne is based not only on their antibacterial effects, but also on anti-inflammatory properties, which can be significant for some antibiotics, such as the tetracyclines. The most common topical antibiotics used are *clindamycin* [klin-da-MYE-sin] (solution or 1% gel or solution), *erythromycin* [er-ITH-roe-MYE-sin] (3% cream, gel, or lotion) and *nafcillin* (1% cream). The most common oral antibiotics used for acne are the tetracyclines, *doxycycline* [DOX-i-SYE-kleen] and *minocycline* [mi-no-SYE-kleen], and the macrolides, *erythromycin* and *azithromycin* [a-ZITH-roe-MYE-sin]. Topical forms tend to be well tolerated. For oral tetracyclines, common adverse effects are gastrointestinal disturbances and photosensitivity, and for the macrolides, gastrointestinal disturbances are common. The most significant concern in the use of both topical and oral antibiotics is the development of bacterial resistance. Some measures that can be taken to limit the development of resistance include using antibiotics only in combination with other

acne agents, using oral antibiotics for the shortest time possible, and using low-dose oral antibiotics (subantimicrobial dosing) when possible. Also, once acne lesions are clear, patients should follow topical maintenance therapy with effective nonantibiotic topical agents, such as benzoyl peroxide and the retinoids. Antibiotics are covered in more detail in Chapters 30 and 31.

### B. Azelaic acid

*Azelaic acid* [aze-eh-LAY-ik] is a naturally occurring dicarboxylic acid that has antibacterial activity against *P. acnes* through its ability to inhibit protein synthesis. It also exhibits anti-inflammatory activity, inhibits the division and differentiation of keratinocytes, and shows comedolytic activity. *Azelaic acid* also exhibits a lightening effect on hyperpigmented skin, which makes it useful in patients who experience dyspigmentation as a consequence of inflammatory acne. It is available as a cream and a gel, and the major adverse effects are mild and transient pruritus, burning, stinging, and tingling.

### C. Benzoyl peroxide

*Benzoyl peroxide* [BEN-zoyl per-OX-ide] is a commonly used topical medication that improves acne primarily through its bactericidal action, where its oxidizing activity is lethal for *P. acnes*. It shows no bacterial resistance. The agent also reduces inflammation and has comedolytic activity. It is available in topical washes, foams, creams, and gels. The major adverse effects are dry skin, irritation, and bleaching of bedding and clothing. It may also cause contact dermatitis in some patients.

### D. Dapsone

*Dapsone* [DAP-sone] is a sulfone that exhibits both anti-inflammatory and antibacterial activity and is effective at reducing inflammatory acne lesion counts, with some reduction in non-inflammatory lesions as well. Its anti-inflammatory activity derives partly from its ability to interfere with neutrophilic function and to reduce the production of TNF- $\alpha$  by mononuclear cells. It is available as a topical gel with the most common adverse effects being transient oiliness, dryness, and erythema, which may be at least in part due to the nondrug part of the formulation.

### E. Retinoids

Retinoids are Vitamin A derivatives that interact with retinoid receptors to regulate gene expression in a manner that normalizes keratinocyte differentiation and reduces their hyperproliferation (giving them comedolytic activity). They also reduce sebum production and inflammation. These diverse effects make retinoids useful for acne, as well as a variety of other conditions, including psoriasis and severe rosacea. For acne vulgaris, the topical retinoids *tretinoin* [TRET-i-no-in], *adapalene* [a-DAP-a-leen] (0.1% gel), and *tazarotene* [ta-ZAR-oh-teen] are used for mild and moderate forms, whereas the oral retinoid *isotretinoin* [eye-so-TRET-i-no-in] is reserved for severe nodular forms

of acne. Topical retinoids such as *tazarotene* (0.05% to 0.1% gel) are also used for psoriasis.

Adverse effects of the topical retinoids include erythema, desquamation, burning, and stinging. These effects often decrease with time. Other potential adverse effects include dry mucous membranes and photosensitivity. Patients should be cautioned to wear sunscreen. Though their systemic absorption is generally limited, use should be avoided during pregnancy, particularly topical *tazarotene*, which is the most teratogenic of the three topical retinoids for acne. Oral *isotretinoin*, used in severe acne, has potentially serious adverse effects including psychiatric effects and birth defects. It is contraindicated in women who are pregnant or intend to become pregnant.

#### F. Salicylic acid

Topical *salicylic* [sal-i-SIL-ik] acid, a  $\beta$ -hydroxy acid, penetrates the pilosebaceous unit and works as an exfoliant to clear comedones. Its comedolytic effects are not as pronounced as those of the retinoids. The drug has mild anti-inflammatory activity and is keratolytic at higher concentrations. *Salicylic acid* is used as a treatment for mild acne and is available in many over-the-counter facial washes and medicated treatment pads. Mild skin peeling, dryness, and local irritation are adverse effects.

#### G. Sulfacetamide sodium

*Sulfacetamide sodium* [SUL-fa-SET-a-mide SOE-dee-um] interferes with bacterial growth and is often combined with sulfur, a keratolytic agent. The combination is used to treat inflammatory acne lesions when present. It is also used to treat rosacea (see the following text). The product is available as cleanser, cream, foam, gel, lotion, pads, suspension, and a wash. The most common adverse effects include contact dermatitis, erythema, pruritus, Stevens–Johnson syndrome, and xeroderma.

### IV. AGENTS FOR SUPERFICIAL BACTERIAL INFECTIONS

Several gram-positive and gram-negative bacteria can cause various superficial skin infections, such as folliculitis and impetigo, as well as deeper infections, such as erysipelas and cellulitis. In more severe cases, these infections can lead to ulceration and systemic infections. This section covers topical antibacterial agents that can be used for the treatment and prevention of certain superficial skin infections.

#### A. Bacitracin

*Bacitracin* [bas-i-TRAY-sin] is a peptide antibiotic active against many gram-positive organisms. It is used mainly in topical formulations; if used systemically, it is toxic. *Bacitracin* is mostly used for the prevention of skin infections after burns or minor scrapes. It is frequently found in combination products with *neomycin* and/or *polymyxin* (see the following text). It is available as an ointment.

## B. Gentamicin

*Gentamicin* [GEN-ta-MYE-sin] interferes with bacterial protein synthesis targeting gram-negative organisms. This agent is often used in combination with other agents to treat skin infections caused by gram-negative organisms. It is available as a cream and an ointment. Topical use of this agent rarely causes systemic side effects.

## C. Mupirocin

*Mupirocin* [mue-PIR-oh-sin] is a protein synthesis inhibitor targeting gram-positive organisms. It is useful in treating impetigo (a contagious skin infection caused by streptococci or staphylococci; **Figure 45.4**) and other serious gram-positive skin infections, including infections caused by *methicillin-resistant Staphylococcus aureus*. It is available as a cream and an ointment. [Note: Intranasal *mupirocin* may be used to eradicate colonization with *methicillin-resistant S. aureus* and reduce the risk of infection in hospitalized patients.] The most common adverse effects are pruritus, skin rash, and burning.



**Figure 45.4**

Impetigo on the face.

## D. Neomycin

*Neomycin* [nee-oh-MY-sin] interferes with bacterial protein synthesis and is active primarily against gram-negative organisms, with some activity against gram-positive organisms. This agent is often formulated with other topical anti-infectives, such as *bacitracin* and *polymyxin* to treat skin infections. The combination is available as an ointment. Common adverse effects associated with the combination agents include contact dermatitis, erythema, rash, and urticaria.

## E. Polymyxin

*Polymyxin* [paw-lee-MIX-in] *B* is a cyclic hydrophobic peptide that disrupts the bacterial cell membrane of gram-negative organisms. As noted above, it is commonly combined with *bacitracin* ("double antibiotic") and *neomycin* with *bacitracin* ("triple antibiotic") in topical products used for the prevention of skin infections after minor skin trauma. These combinations are available as ointments.

## F. Retapamulin

*Retapamulin* [RE-te-PAM-ue-lin] is a protein synthesis inhibitor active against gram-positive organisms. It is indicated for the treatment of impetigo. The only available dosage form is an ointment and the most common adverse effects are pruritus and skin irritation.

# V. AGENTS USED FOR ROSACEA

Rosacea is a common inflammatory disorder affecting the central portion of facial skin. Common clinical features include facial erythema (flushing) and inflammatory lesions that are similar to acne lesions. The signs, symptoms, and severity determine the treatment for this disorder. *Azelaic acid*

is one potential treatment for rosacea. Other topical and oral products for rosacea are described below.

#### A. Brimonidine

*Brimonidine* [bri-MOE-ni-deen] is an  $\alpha_2$  adrenoceptor agonist that reduces erythema through vasoconstriction. It is available as a gel and its major adverse effects are burning, localized warm feeling, and flushing. [Note: *Brimonidine* ophthalmic solution is used for the treatment of glaucoma.]

#### B. Doxycycline

*Doxycycline* [DOX-i-SYE-kleen] is an antibacterial agent used orally at low doses, where it exerts its effects on rosacea, not by killing bacteria, but rather through its anti-inflammatory effects. It is available as a capsule and tablet and its major adverse effects include diarrhea, nausea, dyspepsia, and nasopharyngitis.

#### C. Metronidazole

*Metronidazole* [me-troe-NI-da-zole] is an antibacterial agent used topically for rosacea. It is believed to work in rosacea through anti-inflammatory or immunosuppressive effects, rather than through its antibacterial effects. It is available as a cream, gel, and lotion and its major adverse effects are burning, erythema, skin irritation, xeroderma, and acne vulgaris.

#### D. Oxymetazoline

*Oxymetazoline* [ox-e-meh-TAZ-oh-lean] is an  $\alpha_1$  adrenoceptor agonist that reduces erythema through vasoconstriction. It is available as a cream and its major adverse effects are application site dermatitis, worsening inflammatory lesions, site pruritus, site erythema, and a burning sensation.

#### E. Pimecrolimus

*Pimecrolimus* [pim-e-KROE-li-mus] is a topical calcineurin inhibitor/immunosuppressant agent that decreases inflammation. It is available as a cream, and its major adverse effects are burning, irritation, pruritus, and erythema.

### VI. AGENTS FOR PIGMENTATION DISORDERS

The color of skin is derived from melanin produced by melanocytes in the basal layer of the epidermis. When the melanocytes are damaged, the melanin levels are affected, which ultimately leads to pigmentation disorders. If the body does not make enough melanin, the skin gets lighter (hypopigmentation). If the body makes too much melanin, the skin gets darker (hyperpigmentation). Pigmentation disorders can be widespread and affect many areas of the skin or they can be localized. Agents used for pigmentation disorders are discussed below and summarized in [Figure 45.5](#).

DRUG	DOSE
<b>Agents for pigmentation disorders:</b>	
<i>Hydroquinone</i>	4% topical application
<i>Methoxsalen</i>	20 mg oral capsule taken along with milk or food before 4 hours of UV radiation therapy
<i>Trisoralen</i>	20–40 mg oral tablet before 2–4 hours of UVA exposure and two to three times a week with 48-hour interval
<i>Tazarotene</i>	0.05–0.1% topical gel application daily in the evening
<b>Agents for psoriasis:</b>	
<i>Apremilast</i>	10–60 mg/day, twice a day
<i>Dithranol</i>	1% solution
<i>Coal tar</i>	1–15% topical application
<i>Salicylic acid</i>	2–6% cream used topically
<i>Acitretin</i>	25–50 mg/day oral once a day with the main meal
<i>Adalimumab</i>	SC injection 80 mg as initial dose followed by 40 mg/wk as maintenance dose
<i>Brodalumab</i>	SC injection of 210 mg for 0, 1, and 2 weeks followed by 210 mg every 2 weeks
<i>Calcipotriene</i>	0.005% ointment, apply once or twice
<i>Calcitriol</i>	0.25–0.5 mcg/day capsule or liquid 0.5–1.5 µg/weekly thrice through IV
<i>Certolizumab pegol</i>	SC infusion 400 mg or 200 mg every 2 weeks
<i>Etanercept</i>	50 mg twice a week for 3 months followed by 50 mg/wk SC Pediatric: 0.8 mg/kg/wk up to 50 mg/wk SC
<i>Golimumab</i>	50 mg/mon subcutaneous
<i>Guselkumab</i>	100 mg at weeks 0 and 4 and then at 8 weeks thereafter subcutaneously
<i>Infliximab</i>	5 mg/kg at 0, 2, and 6 weeks and then every 8 weeks intravenously
<i>Ixekizumab</i>	Initial dose of 160 mg followed by 80 mg every 2 weeks for 12 weeks followed by 80 mg every 4 weeks SC
<i>Methotrexate</i>	Psoriasis: 10–25 mg once weekly for oral, IM, SC, or IV
<i>Secukinumab</i>	150–300 mg/wk SC for 0 to 4 weeks followed by 150–300 mg every 4 weeks
<i>Ustekinumab</i>	Psoriasis, psoriatic arthritis: 45–90 mg SC initially and 4 weeks later followed by 45–90 mg every 12 weeks
<i>Tacrolimus</i>	0.03–0.1% topical ointment for adults and 0.03 for children of age 3–11 years
<i>Pimecrolimus</i>	1% topical application twice daily
<b>Agents for alopecia:</b>	
<i>Finasteride</i>	1 mg/day oral
<i>Minoxidil</i>	2–5% topical solution

**Figure 45.5**

Summary of drug for pigmentation disorders, psoriasis, and alopecia.

## A. Demelanizing agents

- Hydroquinone:** *Hydroquinone* [HYE-droe-KWIN-one] is a topical skin-whitening agent that reduces hyperpigmentation associated with freckles and melasma (brown to gray-brown patches on the skin; [Figure 45.6](#)). It is often used in combination with topical retinoids to treat the signs of photoaging. The mechanism of action of *hydroquinone* is through inhibition of the tyrosinase, an enzyme required for melanin synthesis. *Hydroquinone* lightens the skin temporarily and is commonly used as a 4% preparation. It should not be used in higher concentrations, or in excessive quantities for



**Figure 45.6**

Melasma on the face. From Jensen S: Pocket Guide for Nursing Health Assessment: A Best Practice Approach, 2<sup>nd</sup> Edition. Wolters Kluwer (2011).



**Figure 45.7**

The palm is frequently affected by vitiligo.

an extended duration, as it is associated with possible carcinogenicity. The most common adverse effect is local skin irritation. *Monobenzone* is a monobenzyl ether of *hydroquinone* which upon topical use is used as an ointment (20%). It is known to cause permanent depigmentation in 4 to 6 months. It is reported to have skin irritation, contact dermatitis, ocular side effects, and exogenous ochronosis.

### B. Melanizing agents

1. **Methoxsalen:** *Methoxsalen* [meth-OX-a-len] is a psoralen photoactive agent that stimulates melanocytes and is used as a repigmentation agent for patients with vitiligo (Figure 45.7). It is administered as a dose of 10 mg tablet for oral use. Its plasma half-life is 1 hour but the photosensitization of skin persists up to 8 hours or more. It must be photoactivated by UV radiation to form a DNA adduct inhibiting DNA replication by a method called PUVA (psoralen plus UVA radiation). *Methoxsalen* inhibits cell proliferation and promotes cell differentiation of epithelial cells. Topical *methoxsalen* (0.1% to 1% used as ointment or solution) may be used for small patches of vitiligo, and oral therapy is used for more widespread disease. Because of the possibilities for aging of the skin and carcinogenicity, it is used with caution. *Psoralen* is used as 10 mg tablet or 1% topical ointment. *Trioxsalen* is used as 5 mg tablets or 0.2% topical lotion.
2. **Tazarotene:** *Tazarotene* is a topical retinoid which decreases hyperpigmentation and is sometimes used to treat the signs of photoaging. It is available as a cream, foam, and gel. The most common adverse effects include itching, burning, erythema, rash, and dryness.

## VII. AGENTS FOR PSORIASIS

Psoriasis is a chronic autoimmune skin disease that manifests as epidermal hyperplasia and dermal inflammation, which can range from mild to disabling. It is a condition that has significant genetic associations and it tends to wax and wane, with flare-ups that can be triggered by a number of environmental factors including stress and skin trauma. There are several forms of psoriasis, with the most common form being plaque psoriasis. Plaque psoriasis is characterized by the presence of sharply demarcated, thick, erythematous plaques that are usually covered by dry silvery white scales (Figure 45.8). The plaques range in size from 1 square centimeter to several square centimeters. In mild-to-moderate cases these plaques cover less than 5% of the body surface area, but in more severe cases, they can cover more than 20% of the body. Therapies may target inflammation and the abnormal immune response, as well as epidermal hyperproliferation.

### A. Apremilast

*Apremilast* [a-PRE-mi-last] is an oral agent approved for moderate-to-severe plaque psoriasis. It works by inhibiting phosphodiesterase-4, which ultimately leads to reduced production of several inflammatory mediators in psoriasis. The most common adverse effects are diarrhea, nausea, and headache. Depression may also

occur. Strong CYP450 inducers (for example, *carbamazepine* and *phenytoin*) may reduce the efficacy of *apremilast*, and co-administration is not recommended.

### B. Anthralin (Dithranol)

*Anthralin* is an anthracene derivative that has been reported to be the most effective topical treatment of stable plaque psoriasis. It has been reported to restore cell differentiation by mitochondrial dysfunction, preventing the activation of T-cells, decreasing keratinocyte proliferation. Overnight therapy with 1% is indicated for the topical use. Short contact *anthralin* therapy (SCAT) is adopted (20 minutes to 1 hour before removal) for the treatment of scaly plaques of psoriasis on the body or the scalp which are not responding to other treatments. The side effects of *anthralin* therapy include skin irritation and staining of the applied area and clothes. Triethanolamine is used for the removal of *anthralin* residue remaining in the skin.

### C. Coal tar

Coal tar is a thick, black liquid obtained while distilling bituminous coal. It is reported to contain phenolic compounds such as benzene, naphthalene, phenols, and aniline. On exposure to light, it causes photoexcitation by UV-A (320 to 380 nm) and retards hyperproliferation of keratinocytes by suppressing DNA synthesis. It is conventionally applied in an alcoholic solution (containing 1% to 15% coal tar) with salicylic acid on the psoriatic plaques. A preparation containing crude coal tar is also frequently used as a part of an inpatient or daily dressing regimen. It is used for psoriasis of scalp, palmoplantar, and chronic plaque. This therapy is expected to improve psoriasis 1 month after the initiation of the treatment and remission is also longer than with any other agent. Common side effects include strong odor, severe skin irritation, stinging folliculitis, and formation of keratoacanthomas. Coal tar exposure is considered a carcinogenic occupational hazard but its relevance to topical therapy during psoriasis is not yet studied.

### D. Salicylic acid

Topical salicylic acid (2% to 6%) is a well-recognized keratolytic agent and has been used for psoriasis for many years. A combination containing steroid with salicylic acid is used as a first line of treatment on thick, scaly plaques in palm, scalp, trunk, and soles but must not be used on eyes, genitals, and mucous membrane. It can also be combined with topical calcineurin inhibitors. Salicylic acid therapy for psoriasis suffers from a major problem of a potential chronic or acute systemic intoxication, called "salicylism," which has symptoms of nausea, vomiting, tinnitus, metabolic acidosis, oral mucosa burning, etc. Therefore, it should be used more than 20% of the body surface area.

### E. Methotrexate

*Methotrexate* [meth-oh-TREX-ate] is the most commonly used systemic therapy for psoriasis. The drug is used in more severe forms of psoriasis and its primary mechanism of action is due to immunosuppressive action, resulting from its ability to reduce DNA synthesis in



**Figure 45.8**

Psoriasis. A large, scaly, erythematous plaque.

cells of the immune system, particularly T-lymphocytes. *Methotrexate* is available in oral and injectable dosage forms. Among the common potential adverse effects are nausea, diarrhea, mouth ulcers, hair loss, and skin rashes. The primary long-term risk is the potential for liver damage, and therefore periodic liver function tests are required for patients using *methotrexate*.

## F. Retinoids

Retinoids normalize keratinocyte differentiation and reduce hyperproliferation and inflammation. *Tazarotene* is a topical retinoid used for the treatment of plaque psoriasis. Adverse effects are similar to other topical retinoids described for acne. *Acitretin* [a-si-TRE-tin] is a second-generation retinoid used orally in the treatment of pustular forms of psoriasis. It is administered in the dose of 0.5 to 0.75 mg/kg per day orally. Similar to oral *isotretinoin* used in acne, *acitretin* is teratogenic and women must avoid pregnancy for at least 3 years after the use of this drug (due to its long duration of teratogenic potential). Ethanol is contraindicated with this agent. Cheilitis, pruritus, peeling skin, and hyperlipidemia are common adverse effects. Due to side effects, it is reserved for severe forms of psoriasis.

## G. Topical corticosteroids

Topical corticosteroids have been a mainstay of psoriasis therapy for over 50 years and are used in variety of other skin conditions as well. The available agents differ in potencies and are formulated in a variety of dosage forms, including solutions, lotions, creams, ointments, gels, and shampoo (Figure 45.9). Upon binding to intracellular corticosteroid receptors, these agents produce numerous effects that can be beneficial for psoriasis, including anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive effects. Potential adverse effects, especially with the long-term use of potent corticosteroids, include skin atrophy, striae, acneiform eruptions, dermatitis, local infections, and hypopigmentation. In children, excessive use of potent agents applied to a large surface area can cause systemic toxicity, including possible depression of the hypothalamic–pituitary–adrenal axis and growth retardation.

## H. Topical calcineurin inhibitors

Calcineurin inhibitors such as *tacrolimus* ointment (0.03% and 0.1%) and *pimecrolimus* cream (1%) are in use for mild-to-moderate atopic dermatitis and psoriasis. They are found to be safer and effective in patients with facial, intertriginous, and genital psoriasis. They are reported to have transient side effects such as stinging sensation upon application.

## I. Vitamin D analogs

*Calcipotriene* [kal-sih-poh-TRY-een] and *calcitriol* [kal-si-TRYE-oil] are synthetic vitamin D<sub>3</sub> (calcitriol) derivatives used topically to treat plaque psoriasis. They bind to the same receptors as calcitriol to

LOW STRENGTH	INTERMEDIATE STRENGTH	HIGH STRENGTH	VERY HIGH STRENGTH
<b>Aclometasone dipropionate 0.05% (c, o)</b>	<b>Betamethasone dipropionate 0.05% (c)</b>	<b>Amcinonide 0.1% (c, l, o)</b> <b>Betamethasone dipropionate, augmented 0.05% (c, l)</b>	<b>Betamethasone dipropionate 0.05% (o, g)</b>
<b>Clocortolone pivalate 0.1% (c)</b> <b>Fluocinolone acetonide 0.01% solution (s)</b>	<b>Desonide 0.05% (c, l, o)</b>	<b>Desoximetasone 0.05% (c)</b>	<b>Clobetasol propionate 0.05% (c, g, o)</b>
<b>Hydrocortisone base or acetate 0.25% to 2.5% (o, c)</b>	<b>Fluocinolone acetonide 0.025% (c, o)</b>	<b>Diflorasone diacetate 0.05% (o, c)</b>	<b>Diflorasone diacetate 0.05% (o)</b>
<b>Triamcinolone acetonide 0.025% (c, l, o)</b>	<b>Flurandrenolide 0.025 to 0.5% (c, o)</b> <b>Fluticasone propionate 0.005% to 0.05% (o, c)</b> <b>Hydrocortisone butyrate 0.1% (c, o, s)</b> <b>Hydrocortisone valerate 0.2% (c, o)</b> <b>Mometasone furoate 0.1% (c, o, l)</b> <b>Triamcinolone acetonide 0.1% to 0.2% (c, o)</b>	<b>Fluocinonide 0.05% (c, g, o, s)</b> <b>Halcinonide 0.1% (c, o)</b> <b>Triamcinolone acetonide 0.5% (c, o)</b>	<b>Fluocinonide 0.1% (c)</b> <b>Flurandrenolide 0.05% (l)</b> <b>Halobetasol 0.05% (c, o)</b>

c = cream; g = gel; o = ointment; s = solution.

**Figure 45.9**

Potency of various topical corticosteroids.

inhibit keratinocyte proliferation, enhance keratinocyte differentiation, and inhibit certain inflammatory elements. *Calcipotriene* is available in cream, ointment, solution, and foam formulations, and *calcitriol* is available as an ointment. Potential adverse effects include itching, dryness, burning, irritation, and erythema.

## J. Biologic agents

Biologics are agents isolated from natural sources, including humans, animals, and microorganisms. They can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances. The biologics approved for psoriasis are all injectable, antibody-based proteins produced by recombinant DNA technology. They are used for moderate-to-severe psoriasis and their mechanism of action results from their interaction with specific cytokines that induce or mediate T-cell effector function, which is important in autoimmune diseases such as psoriasis. For example, several biologics target TNF- $\alpha$ , which plays multiple roles in psoriasis pathogenesis, including the stimulation of keratinocyte proliferation, neutrophils, and the release of pro-inflammatory cytokines. The TNF- $\alpha$  blockers include *etanercept* [ee-TAN-er-sept], *infliximab* [in-FLIKS-e-mab], *adalimumab* [a-da-LIM-yoo-mab], *certolizumab pegol* [ser-toe-LIZ-oo-mab PEG-oI],

and *golimumab* [goe-LIM-ue-mab]. Biologics that target other cytokines important in psoriasis pathogenesis include the anti-IL-12/IL-23 medication, *ustekinumab* [YOO-st-KIN-ue-mab]; the anti-IL-23 medication, *guselkumab* [gue-sel-KOO-mab]; and the anti-IL-17A medications, *secukinumab* [SEK-ue-KIN-ue-mab], *ixekizumab* [IX-ee-KIZ-ue-mab], and *brodalumab* [broe-DAL-ue-mab]. Though each agent has specific potential risks and adverse effects, among the adverse effects that they share include injection or infusion reactions and increased risk of infections due to their suppression of the immune system. In addition, because they are foreign proteins, there is a risk for the development of antidrug antibodies, which may affect efficacy over the course of therapy.

## VIII. AGENTS FOR ALOPECIA

Alopecia (baldness) is the partial or complete loss of hair from areas where hair normally grows. The most common type of hair loss is androgenic alopecia (also known as male pattern baldness) which can occur in men or women. Trichogenic agents are used to stimulate hair growth and slow the progression of hair loss.

### A. Finasteride

*Finasteride* [fih-NAH-steh-ride] is an oral 5- $\alpha$  reductase inhibitor that blocks conversion of testosterone to the potent androgen 5- $\alpha$  dihydrotestosterone (DHT). High levels of DHT can cause the hair follicle to miniaturize and atrophy. *Finasteride* decreases scalp and serum DHT concentrations, thus inhibiting a key factor in the etiology of androgenic alopecia. [Note: *Finasteride* is used in higher doses for the treatment of benign prostatic hyperplasia (see Chapter 43).] Adverse effects include decreased libido, decreased ejaculation, and erectile dysfunction. The drug should not be used or handled in pregnancy, as it can cause hypospadias in a male fetus. Like *minoxidil*, use must be continued to maintain therapeutic benefits.

### B. Minoxidil

*Minoxidil* [min-OX-i-dil], originally used as a systemic antihypertensive, was noted to have the adverse effect of increased hair growth. This adverse effect was turned into a therapeutic application in the treatment of alopecia. For hair loss, the drug is available as a non-prescription topical foam or solution, without systemic hypotensive effects. *Minoxidil* is effective at halting hair loss in both men and women and may produce hair growth in some patients. Although the mechanism of action is not fully known, it is believed to act, at least in part, by shortening the rest phase of the hair cycle. The drug must be used continuously to maintain effects on hair growth. The main adverse effects include erythema and pruritus.

## Study Questions

Choose the ONE best answer.

45.1 Which is correct regarding the use of isotretinoin in the treatment of acne?

- A. It is used topically in the treatment of acne.
- B. It acts primarily on the corticosteroid receptors.
- C. It is used for milder forms of acne.
- D. It is contraindicated in pregnancy.

Correct answer = D. Isotretinoin is an oral retinoid reserved for more severe forms of acne. Retinoic acids play an important role in mammalian embryogenesis. Excessive amounts of retinoids such as isotretinoin have been shown to cause teratogenicity, but the exact molecular mechanism is not known.

45.2 Which drug is a topically applied antibiotic that is thought to work through anti-inflammatory effects to treat rosacea?

- A. Brimonidine
- B. Doxycycline
- C. Metronidazole
- D. Benzoyl peroxide

Correct answer = C. Metronidazole is an antibacterial agent used topically for rosacea. It is believed to work in rosacea through anti-inflammatory or immunosuppressive effects. Doxycycline is also used for its anti-inflammatory effects, but is used orally rather than topically.

45.3 Which drug is taken orally for more severe forms of psoriasis?

- A. Etanercept
- B. Calcipotriene
- C. Tazarotene
- D. Methotrexate

Correct answer = D. Methotrexate is the most commonly used systemic therapy for psoriasis. It is used in more severe forms of psoriasis and is available as an oral tablet and injection.

45.4 Which is correct regarding trichogenic agents?

- A. Topically applied minoxidil is known for its hypotensive effects.
- B. Once hair regrowth has been established with topically applied minoxidil, hair growth will be maintained after discontinuing its use.
- C. Finasteride inhibits the 5- $\alpha$  reductase enzyme that controls the production of DHT from testosterone.
- D. Both oral and topical minoxidil are commonly used for alopecia.

Correct answer = C. Androgenic alopecia is associated with DHT concentrations, and finasteride is known to inhibit the 5- $\alpha$  reductase enzyme required for the formation of DHT from testosterone. Only topical minoxidil is used for the treatment of alopecia. Both minoxidil and finasteride must be continued to maintain effects on hair growth.

45.5 A 12-year-old child has extensive psoriatic lesions covering his back. Which topical therapy would, with continuous use, most likely prevent him from reaching his full adult height?

- A. Clobetasol propionate
- B. Salicylic acid
- C. Calcipotriene
- D. Calcitriol

Correct answer = A. Excessive use of potent corticosteroids applied to a large surface area can cause systemic toxicity, including growth retardation.

- 45.6 A 17-year-old female has darkened spots on her face following resolution of acne lesions. Which agent is the best choice to treat her acne, if one of the goals of therapy is to lighten these spots?
- A. Benzoyl peroxide
  - B. Azelaic acid
  - C. Clindamycin
  - D. Dapsone
- 45.7 A 26-year-old woman is diagnosed with pustular psoriasis. She is getting married in 1 year and she would like to become pregnant and start a family within a year of her marriage. Which agent should be avoided for treatment of her psoriasis because the duration of its teratogenic potential may affect her plans for pregnancy?
- A. Methotrexate
  - B. Triamcinolone acetonide
  - C. Infliximab
  - D. Acitretin
- 45.8 A patient has been using topical minoxidil to manage his baldness for several years, but now wants to stop using the medication. What is the likely consequence of discontinuing this medication?
- A. Hair loss will resume.
  - B. Hair growth will be maintained.
  - C. Hair color will start to turn gray.
  - D. Blood pressure will increase.
- 45.9 A 16-year-old female has mild acne on her face. Which agent is the least appropriate choice for treating her acne?
- A. Benzoyl peroxide
  - B. Topical clindamycin
  - C. Oral doxycycline
  - D. Adapalene
- 45.10 Which topical antibacterial agent targets gram-negative bacteria?
- A. Gentamicin
  - B. Bacitracin
  - C. Mupirocin
  - D. Retapamulin

Correct answer = B. Azelaic acid exhibits a lightening effect on hyperpigmented skin, which makes it useful in patients who experience dyspigmentation as a consequence of inflammatory acne. The other agents do not lighten the skin.

Correct answer = D. Acitretin is teratogenic and women must avoid pregnancy for at least 3 years after the use of this drug (due to the long duration of teratogenic potential).

Correct answer = A. Topical minoxidil must be used continuously to maintain effects on hair growth. Minoxidil does not affect hair color, and topical minoxidil does not affect blood pressure.

Correct answer = C. Oral antibiotics, such as doxycycline, are reserved for moderate-to-severe acne.

Correct answer = A. Gentamicin interferes with bacterial protein synthesis targeting gram-negative organisms and is often used in combination with other agents to treat skin infections caused by gram-negative organisms.

# Clinical Toxicology

Dawn Sollee and Emily Winograd

# 46

## I. OVERVIEW

For thousands of years, poisons and the study of them (toxicology) have been woven into the rich fabric of the human experience. Homer and Aristotle described the poison arrow; Socrates was executed with poison hemlock; lead poisoning may have helped bring down the Roman Empire; Marilyn Monroe, Elvis Presley, and Michael Jackson all fatally overdosed on prescription medications. Toxins can be inhaled, insufflated (snorted), orally ingested, injected, and absorbed dermally (Figure 46.1). An understanding of the varied mechanisms of toxicity helps to develop an approach to treatment. This chapter provides an overview of the emergent management of the poisoned patient, as well as a brief review of some of the more common and interesting toxins, their mechanisms, clinical presentations, and clinical management.

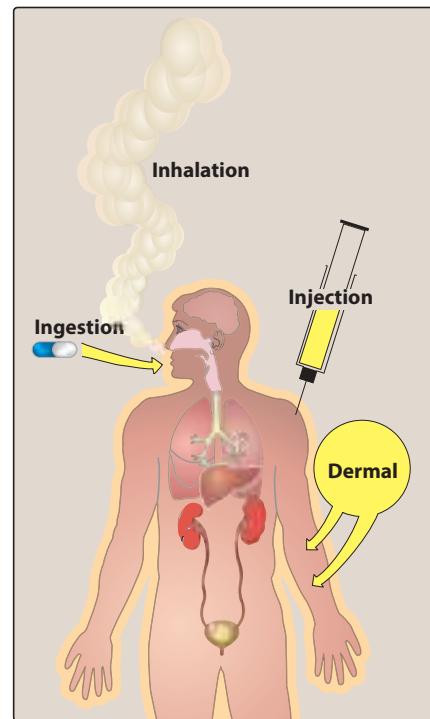
A stepwise care approach to a patient of poisoning is helpful in successful management.

### A. Stepwise care approach

- Diagnosis—suspect and identify poison, if possible.
- Treatment includes basic principles, antidotes, symptomatic, and supportive.
- Anticipate complications, preserve evidence, and prevent sequelae as well as recurrence.

## II. EMERGENCY TREATMENT OF THE POISONED PATIENT

The first principle in the management of the poisoned patient is high index of suspicion of poisoning in case of sudden onset and persistence of symptoms along with increasing severity of symptoms in a group, for example, food poisoning or industrial poisoning. Unexplained nausea, vomiting, diarrhea, drowsiness or coma, euphoria, increased psychomotor activity, convulsions, delirium, and unusual breath smell are symptoms which in the absence of disease need careful evaluation for suspected poisoning. Identification of the substance should not take precedence over the first step, since the process is slow and unreliable and further lack of proper history might add to confusion. Action of poisons is modified by physical factors such as quantity, form, chemical combination, dilution, route of administration, and host factors like age, idiosyncrasy, sleep, food, and use (abuse) of multiple substances.



**Figure 46.1**

Routes of exposure for toxins.

Attention to CAB (Circulation, Airway, and Breathing) of resuscitation is utmost priority at all times. The basic principle is to treat the patient, not the poison. Poisoned patients may deteriorate rapidly. Care for all patients who are critically ill or under evaluation for possible toxin exposure or ingestion, particularly when the history is uncertain, should begin in a monitored treatment area where the development of central nervous system depression, hemodynamic instability, or seizures can be rapidly recognized and addressed.

Airway, breathing, and circulation are assessed and addressed initially, along with any other immediately life-threatening toxic effect (for example, profound increases or decreases in blood pressure, heart rate, respirations, body temperature, or any dangerous dysrhythmias). Acid/base and electrolyte disturbances, *acetaminophen* and salicylate blood levels, and results of other appropriate drug screens can be further assessed as laboratory results are obtained. After administering oxygen, obtaining intravenous access, and placing the patient on a cardiac monitor, the poisoned patient with altered mental status should be considered for administration of the “coma cocktail.” The coma cocktail consists of intravenous dextrose to treat hypoglycemia, a possible toxicological cause of altered mental status, *naloxone* to treat possible opioid or *clonidine* toxicity, and *thiamine* for ethanol-induced Wernicke encephalopathy.

#### **A. Removal of poison: decontamination**

Once the patient is stabilized, decontamination can occur—that is, removal of poison from the person or person from the poison. After getting quick information about the type of exposure, the decontamination step is adopted as a first-aid measure. The cloth soiled with poison is removed and the exposed surface is washed with an adequate amount of clean water. Chemical or poison exposure to eye requires wash with saline (irrigating solution) to reach neutral pH. In case of exposures such as toxic gases, the affected person must be brought out to an open ventilated place and if required artificial respiration be given. Gastrointestinal (GI) decontamination with gastric lavage, activated charcoal, or whole bowel irrigation (utilizing a polyethylene glycol electrolyte balanced solution) for ingestions, once a mainstay in the management of ingested toxins, has a less significant role in poisoning treatment today. With rare exceptions, gastric lavage, whole bowel irrigation, and administration of syrup ipecac are no longer recommended. Therapy should be administered preferably within 1 hour of ingestion. Several substances do not adsorb to activated charcoal (for example, lead and other heavy metals, *iron*, *lithium*, *potassium*, and alcohols), limiting the use of activated charcoal unless there are coingested products. Also, charcoal should not be administered in cases of ingestion of caustic substances, metals, or hydrocarbons. Induction of emesis is contraindicated in cases of corrosive poisoning, in unconscious patients, and in those who have swallowed petroleum products. Mechanical tickling of the throat with fingers, spatula, or tongue depressor will induce vomiting. Sometimes, syrup ipecac (10 to 20 ml) may be used followed by half a glass of water but it is contraindicated in children aged less than 6 months.

#### **B. Elimination enhancement**

Elimination of poisonous substances can be enhanced by use of diuretics such as *frusemide*, *ethacrynic acid*, and *acetazolamide* and of osmotic substances such as urea and mannitol. Forced alkaline

diuresis treatment is done in patients of barbiturate intoxication. Other effective measures to eliminate ionizable substances are peritoneal dialysis, hemodialysis, and exchange transfusions.

- Hemodialysis:** The elimination of some medications/toxins may be enhanced by hemodialysis if certain properties are met, such as low protein binding, small volume of distribution, small molecular weight, and water solubility of the toxin. Examples of medications or substances that can be removed with hemodialysis include methanol, ethylene glycol, salicylates, *theophylline*, *phenobarbital*, and *lithium*.
- Urinary alkalinization:** Alkalization of the urine enhances the elimination of salicylates or *phenobarbital*. Increasing the urine pH with intravenous *sodium bicarbonate* transforms the drug into an ionized form that prevents reabsorption, thereby trapping it in the urine to be excreted by the kidney. The goal urine pH is 7.5 to 8, while ensuring the serum pH does not exceed 7.55.
- Multiple dose-activated charcoal:** Multiple dose-activated charcoal enhances the elimination of certain drugs (for example, *phenobarbital*, *digoxin*, *carbamazepine*, alkaloids such as *atropine*, *morphine*, *reserpine*, and *theophylline*). Activated charcoal is extremely porous and has a high surface area, which creates a gradient across the lumen of the gut. Medications traverse from areas of high concentration to low concentration, promoting absorbed medication to cross back into the gut to be adsorbed by the activated charcoal. In addition, activated charcoal blocks the reabsorption of medications that undergo enterohepatic recirculation (such as *phenytoin*), by adsorbing the substance to the activated charcoal (Figure 46.2). Bowel sounds must be present prior to each activated charcoal dose to prevent obstruction. As mentioned earlier, charcoal should not be administered in cases of ingestion of caustic substances, metals, or hydrocarbons. In patients who are at risk for aspiration, endotracheal intubation and head-of-bed elevation should be performed before charcoal administration.

### C. Antidote (Figure 46.3)

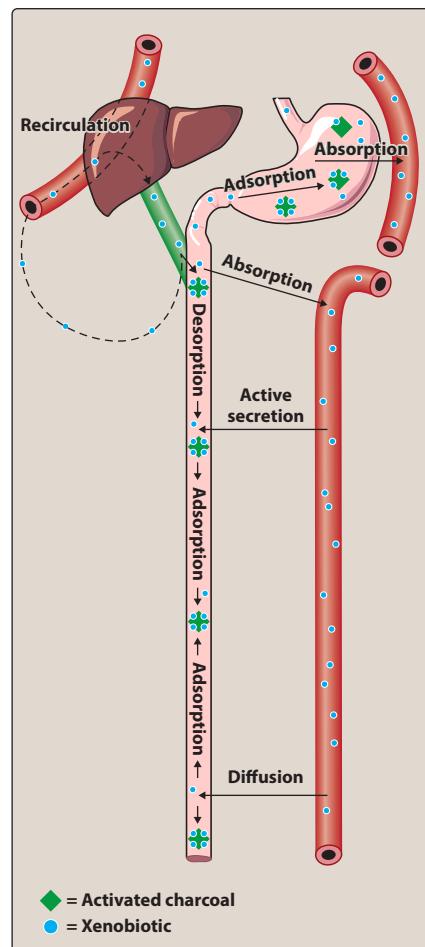
After removal of the ingested poison (absorption of the ingested poison), antidotes play an important role in the management of most toxins and are essentially life-saving when used as early as possible in the treatment of toxins with known antidotes (for example, *N*-acetylcysteine, *naloxone*, and *pyridoxine*). Chelating drugs are used in cases of poisoning with heavy metals and occasionally with other drugs.

### D. Ongoing supportive measures

Most symptoms (for example, agitation, sedation, coma, cerebral edema, hypertension, arrhythmias, renal failure, and hypoglycemia) are treated with the usual supportive measures.

Fluid and electrolyte disturbances are managed with proper laboratory investigations and assessment of intake and output.

Careful monitoring of vital signs such as temperature, pulse, respiration, and blood pressure is mandatory. Metabolic needs get increased by about 10% and then the temperature rises by about  $0.8^{\circ}\text{C}$ . Hyperthermia is treated with aggressive sedation and physical cooling measures rather than with antipyretics. Hypothermia delays detoxification and excretion of poison due to reduced metabolism and circulatory disturbances.



**Figure 46.2**

Mechanism of multiple dose-activated charcoal.

<b>A</b>	
<b>POISON</b>	<b>ANTIDOTE AND DOSE</b>
Carbon monoxide	Pure oxygen
Cyanide	Sodium nitrite (3% soln, 0.2 ml/kg, IV over 2 min) followed by sodium thiosulfate (25% soln, 1 ml/kg, IV over 10–20 minutes)
Nitrate and nitrites	If methemoglobinemia, treat with methylene blue
Organophosphates	Inj. Atropine 0.05 mg/kg, IV every 10 minutes until signs of atropinism Inj. PAM 25–50 mg/kg, IV in older children, and 250 mg IV in infants over 5–10 minutes, 8 hourly up to 36 hours; Adults 1 g IV repeated every 3–4 hours as needed, preferably as a constant infusion of 250–400 mg/kg
Anticholinergics	Inj. Physostigmine 0.56 mg slow IV over 5 minutes (atropine gp); repeated every 10 minutes till a maximum of 2 mg
Narcotics (opium)	Inj. Naloxone 0.05–0.1 mg/kg IV or intratracheal titrated to symptom reversal, from birth up to 5 years or 20 kg of weight; at times, a minimum of 2 mg should be used
Methyl alcohol	Ethyl alcohol (ethanol) or fomepizole
Methaemoglobinemia	Methylene blue 1–2 mg/kg over 5 minutes
Phenothiazine	Inj. Diphenhydramine 1–2 mg/kg
Iron	Inj. Desferrioxamine 15 mg/kg/hr IV in 100–200 ml 5% glucose soln (maximum 80 mg/kg in 24 hours or 6–8 g/day; 100 mg of desferrioxamine binds 8.5 mg of iron)
Paracetamol N-acetyl cysteine	Oral initially 140 mg/kg, then 4 hourly up to 72 hours. IV 150 mg/kg by infusion over 15 minutes followed by 50 mg/kg 4 hourly for 72 hours
Benzodiazepines	Adults: Diazepam Inj. Flumazenil. Initial dose: 0.2 mg IV one time over 30 seconds; 0.5 mg may be given every minute (most patients respond to 1 to 3 mg; max total dose 3 mg). Patients responding partially at 3 mg may receive additional doses up to 5 mg. Resedation doses: 0.5 mg every 20 minutes to a total of 1 mg/dose and 3 mg/hr Children: 1–17 years: Initial dose: 0.01 mg/kg IV over 15 seconds. Repeat doses: 0.01 mg/kg given over 15 seconds; may repeat 0.01 mg/kg after 45 seconds, then every minute to a maximum total cumulative dose of 0.05 mg/kg

<b>B</b>	
<i>Acetaminophen (paracetamol)</i>	<i>Oral or IV N-acetylcysteine</i> , if hepatotoxicity is likely. A loading dose of 150 mg/kg in 200 ml of 5% D/W given over 15 minutes is followed by a maintenance doses of 50 mg/kg in 500 ml of 5% D/W given over 4 hours, then 100 mg/kg in 1000 ml of 5% D/W given over 16 hours. For children, dosing may need to be adjusted to decrease the total volume of fluid delivered. The <i>N-acetylcysteine</i> is most effective if given within 8 hours of <i>acetaminophen</i> ingestion. After 24 hours, the benefit is questionable, but it should still be given. If the degree of toxicity is uncertain, <i>N-acetylcysteine</i> should be given until toxicity is ruled out. The oral loading dose of <i>N-acetylcysteine</i> is 140 mg/kg. This dose is followed by 17 additional doses of 70 mg/kg every 4 hours. Oral <i>acetylcysteine</i> is unpalatable; it is given diluted 1:4 in a carbonated beverage or fruit juice and may still cause vomiting.
<i>Arsenic</i>	<i>Dimercaprol</i> (British anti-lewisite [BAL]) Or <i>Succimer</i> (dimercaptosuccinic acid [DMSA]) Or <i>Dimerval</i> (dimercaptopropane sulfonate) [DMPS])
<i>Lead</i>	<i>Succimer</i> or <i>D-penicillamine</i> orally in case blood lead levels (BLLs) are higher than 45 µg/dl Or parenteral <i>edetate</i> (EDTA) <i>calcium disodium</i> (CaNa <sub>2</sub> EDTA). In lead encephalopathy, parenteral <i>dimercaprol</i> is a drug of choice. With high BLLs (>100 µg/dl), dimercaprol is used in conjunction with CaNa <sub>2</sub> EDTA.
<i>Isoniazid</i>	<i>Diazepam</i> 5–10 mg IV for seizure control; repeat dose as necessary. <i>Pyridoxine</i> in a dose equivalent to the suspected maximum amount of <i>isoniazid</i> ingested (that is, gram-per-gram replacement). If the dose of <i>isoniazid</i> not known, 5 g of <i>pyridoxine</i> IV over 5 to 10 minutes.

**Figure 46.3**

Commonly available specific antidotes. (Figure continues on next page)

<b>Digitalis</b>	<b>Digoxin immune Fab (Digibind)</b> in case of severe, acute digitalis toxicity and correction of hyperkalemia, hypokalemia, and hypomagnesemia to reverse dysrhythmias. Reconstitute digoxin immune Fab 40-mg vial with 4 ml of sterile water for IV injection over 30 minutes via a 0.22-μm membrane filter or in an unstable clinical situation, can be given as IV bolus. Administer reconstituted solution immediately or, if refrigerated, used within 4 hours. In acute, intentional overdose, administration of four to six vials as a loading dose, followed by 0.5 mg/min for 8 hours and then 0.1 mg/min for about 6 hours.								
<b>Heparin</b>	<p><b>Protamine IV</b> depending on the dose of heparin (1 mg of protamine neutralizes ~100 units of heparin); maximum dose: 50 mg;</p> <p><b>Heparin overdosage, following intravenous administration</b>—consider duration of time since heparin administration to adjust the protamine dosage since IV blood heparin concentrations decrease rapidly after administration as below:</p> <table border="1"> <thead> <tr> <th>TIME ELAPSED</th> <th>DOSE OF PROTAMINE (MG) TO NEUTRALIZE 100 UNITS OF HEPARIN</th> </tr> </thead> <tbody> <tr> <td>Immediate</td> <td>1–1.5</td> </tr> <tr> <td>30–60 min</td> <td>0.5–0.75</td> </tr> <tr> <td>&gt;2 hr</td> <td>0.25–0.375</td> </tr> </tbody> </table> <p><b>Heparin overdosage, following subcutaneous injection:</b> 1–1.5 mg protamine IV per 100 units heparin</p>	TIME ELAPSED	DOSE OF PROTAMINE (MG) TO NEUTRALIZE 100 UNITS OF HEPARIN	Immediate	1–1.5	30–60 min	0.5–0.75	>2 hr	0.25–0.375
TIME ELAPSED	DOSE OF PROTAMINE (MG) TO NEUTRALIZE 100 UNITS OF HEPARIN								
Immediate	1–1.5								
30–60 min	0.5–0.75								
>2 hr	0.25–0.375								
<b>Warfarin</b>	Transfusions of packed red blood cells (RBCs), fresh frozen plasma (FFP), and if PT is elevated, IV/ oral vitamin K <sub>1</sub> . 1–2.5 mg orally lowers the INR to <5 within 24 hours or 5–10 mg slow IV infusion over 30 minutes								

**Figure 46.3** (Continued)

Commonly available specific antidotes.

A comatose patient needs careful supervision for clear airway, proper oxygenation, prevention of aspiration of gastric contents by proper positioning, frequent change of position, and care of bladder, bowels, skin, eyes, and buccal mucosa. Antibiotics for infections are given according to the needs.

Drug-induced hypotension and arrhythmias may not respond to the usual drug treatments. For refractory hypotension, *dopamine*, *epinephrine*, other vasopressors, an intra-aortic balloon pump, or even extracorporeal circulatory support may be needed.

Seizures are first treated with benzodiazepines. *Phenobarbital* or *phenytoin* may be required.

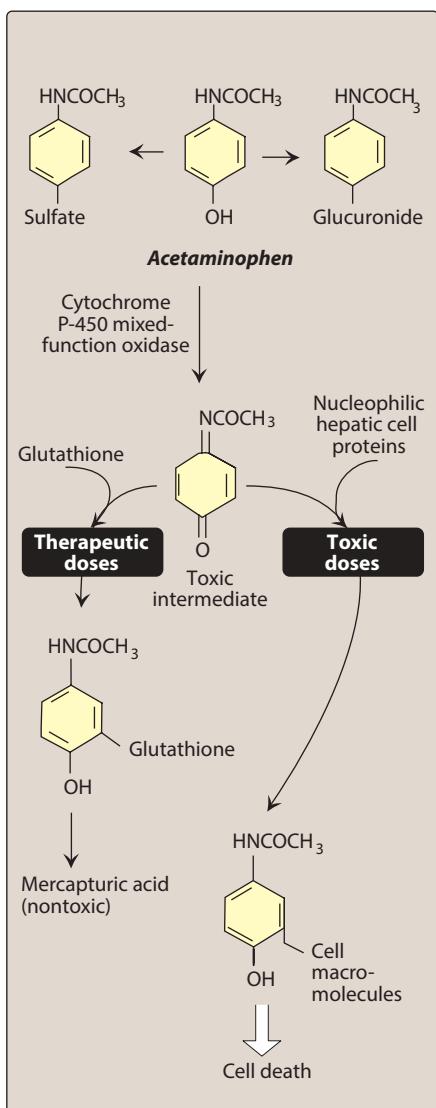
## E. Complications arising commonly in poisoning

Anticipating complications arising due to poisoning and their proper management help in a successful outcome. Prevention of sequelae such as strictures following corrosive poisoning is done by using corticosteroids. Corticosteroids are useful in petroleum product poisoning to treat shock and lung syndrome and to prevent pulmonary fibrosis.

Preserving evidence for medicolegal purposes and toxicological studies is the responsibility of the attending physician. Urine, stool, gastric contents (vomited or aspirated), blood and food samples, and viscera should be preserved.

## F. Prevention

Preventing recurrence of poisoning is by proper labeling (household products and prescription drugs); keeping medicines, cosmetics, and household products separately; storing such substances in cabinets that are locked and inaccessible to children; and providing

**Figure 46.4**

Metabolism of acetaminophen.

**Phase 1 (0 to 24 hours):** loss of appetite, nausea, vomiting, general malaise

**Phase 2 (24 to 72 hours):** abdominal pain, increased liver enzymes

**Phase 3 (72 to 96 hours):** liver necrosis, jaundice, encephalopathy, renal failure, death

**Phase 4 (> 4 days to 2 weeks):** complete resolution of symptoms and organ failure

**Figure 46.5**

Phases of acetaminophen toxicity.

psychiatric consultation to patients who have taken drugs with suicidal intention. Use of child-resistant containers with safety caps reduces the number of poisoning deaths in children. Limiting the amount of OTC (over-the-counter) analgesics in a single container and eliminating confusing and redundant formulations or fixed-dose combinations reduce the severity of poisoning, particularly with *acetaminophen*, *aspirin*, or *ibuprofen*.

Public education measures to encourage storage of substances in their original containers (for example, not placing insecticides in drink bottles) are also important. Use of imprint identifications on solid drugs helps to prevent confusion and errors by patients, pharmacists, and healthcare practitioners.

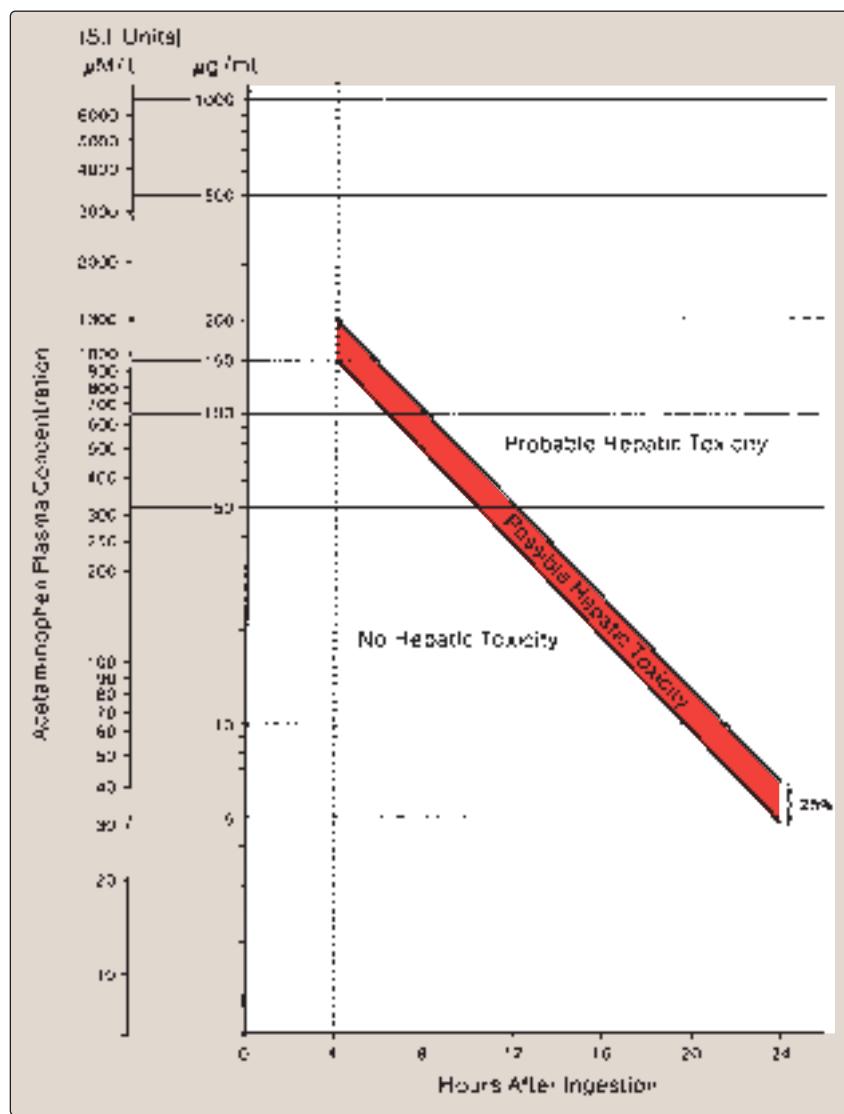
### III. SELECT PHARMACEUTICAL AND OCCUPATIONAL TOXICITIES

#### A. Acetaminophen (Paracetamol)

*Acetaminophen* produces toxicity when normal metabolic pathways become saturated, leading to the production of a hepatotoxic metabolite (*N*-acetyl-p-benzoquinone imine, NAPQI) (Figure 46.4). After therapeutic doses of *acetaminophen*, the liver generates glutathione, which detoxifies NAPQI. However, in overdose, glutathione is depleted, leaving the metabolite to produce toxicity. There are four phases typically describing *acetaminophen* toxicity (Figure 46.5). The antidote for *acetaminophen* toxicity, *N*-acetylcysteine (NAC), works as a glutathione precursor and glutathione substitute, and assists with sulfation. NAC may also function as an antioxidant to aid in recovery. NAC is most effective when initiated within 8 to 10 hours of ingestion. The Rumack-Matthew nomogram (Figure 46.6), which is based on the time of ingestion and the serum *acetaminophen* level, is utilized after an acute ingestion to determine if NAC therapy is needed. The nomogram is helpful to predict *acetaminophen* toxicity when levels can be obtained between 4 and 24 hours postingestion.

#### B. Alcohols

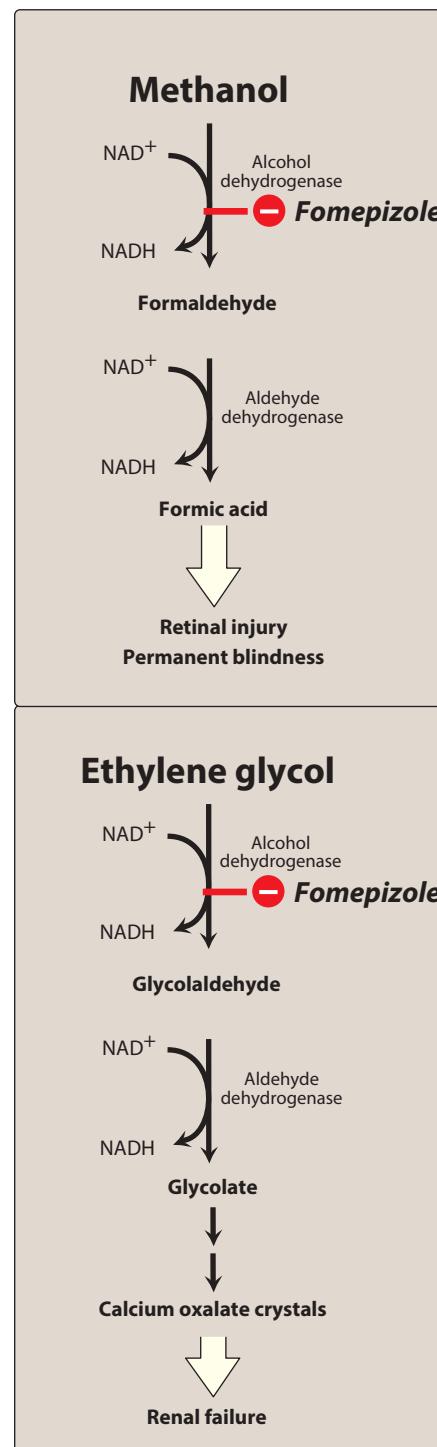
- Methanol (wood alcohol) and ethylene glycol:** Methanol is found in products such as windshield washer fluid and model airplane fuel. Ethylene glycol is most commonly found in radiator anti-freeze. In India, the primary reason for methanol poisoning is the consumption of country liquor or methylated spirit. Epidemic poisonings are not rare due to distilling and fermenting errors and beverage contamination. These primary alcohols cause CNS depression. Methanol gets converted by alcohol dehydrogenase into formaldehyde as metabolic intermediate which in turn gets converted to formic acid by aldehyde dehydrogenase. The lethal dose of methanol is approximately 30 to 240 mL or 1 gram per kilogram. Blindness can happen even with the minimum ingestion of 30 mL of methanol. Conversion of formic acid is responsible for severe toxicity which includes blindness or even death. Retinal damage is primarily due to the formic acid's oxidative stress. Methanol follows zero-order pharmacokinetics such as ethanol. Methanol poisoning is manifested by vomiting, severe epigastric pain, disorientation, hyperventilation, dyspnea, bradycardia,

**Figure 46.6**

Rumack-Matthew nomogram for acetaminophen poisoning. Acetaminophen concentration plotted vs. time after exposure to predict potential toxicity and antidote use. Reprinted with permission from B. H. Rumack. Acetaminophen overdose in children and adolescents. Pediatr. Clin. North Am. 33: 691 (1986).

and hypotension. If untreated, methanol ingestion may produce blindness, metabolic acidosis, seizures, and coma. In general, treatment for methanol poisoning includes supportive care which includes intravenous sodium bicarbonate infusion, *fomepizole*, ethanol, dialysis, and supplementation of folate. [Note: Ethanol is an alternative antidote, if *fomepizole* is not available.]

As ethanol has more affinity for alcohol dehydrogenase, it can saturate the enzyme at the concentration of 100 mg/dl; therefore, ethanol can retard the metabolism of methanol into formaldehyde and formic acid. It prevents the formation of toxic metabolites and allows the parent alcohol to be excreted by the kidney (Figure 46.7). Ethanol is usually administered as a 10% solution in water through a nasogastric tube. In the absence of pure ethanol,

**Figure 46.7**

Metabolism of methanol and ethylene glycol.

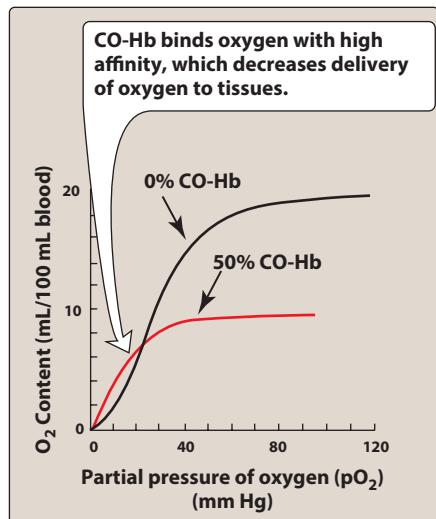
to make 10% solution, commercial alcoholic preparations such as whisky, gin, or brandy can be diluted appropriately for this purpose. Ethanol substitution therapy can cause hypoglycemia which needs to be corrected. Hemodialysis is often utilized to remove the toxic acids that are already produced. This treatment need to continue for a prolonged period, and periodic alcohol measurement in blood needs to monitored. In addition, cofactors are administered to encourage metabolism to nontoxic metabolites (folate for methanol, *thiamine* and *pyridoxine* for ethylene glycol).

Ethylene glycol is metabolized into toxic products such as glycolic, glyoxylic, and oxalic acids. *Fomepizole* [foe-MEP-i-zole] inhibits this oxidative pathway by blocking alcohol dehydrogenase. Ethylene glycol ingestion may lead to renal failure, hypocalcemia, metabolic acidosis, and heart failure. The treatment of ethylene glycol ingestion should be treated in a similar manner to that of methanol poisoning.

- Isopropanol (rubbing alcohol, isopropyl alcohol):** This secondary alcohol is metabolized to acetone via alcohol dehydrogenase. Acetone cannot be further oxidized to carboxylic acids, and therefore, acidemia does not occur. Because isopropyl alcohol is not metabolized to a toxic metabolite, no antidote is necessary to treat an isopropyl alcohol ingestion. Isopropanol is a known CNS depressant (approximately twice as intoxicating as ethanol) and GI irritant. Treatment centers on supportive care.

### C. Carbon monoxide

Carbon monoxide is a colorless, odorless, and tasteless gas. It is a natural by-product of the combustion of carbonaceous materials, and common sources of this gas include automobiles, poorly vented furnaces, fireplaces, wood-burning stoves, kerosene space heaters, house fires, charcoal grills, and generators. Following inhalation, carbon monoxide rapidly binds to hemoglobin to produce carboxyhemoglobin. The binding affinity of carbon monoxide to hemoglobin is 230 to 270 times greater than that of oxygen. Consequently, even low concentrations of carbon monoxide in the air can produce significant levels of carboxyhemoglobin. In addition, bound carbon monoxide increases hemoglobin affinity for oxygen at the other oxygen-binding sites. This high-affinity binding of oxygen prevents the unloading of oxygen at the tissues, further reducing oxygen delivery (Figure 46.8). The presence of this highly oxygenated blood may produce “cherry red” skin. Carbon monoxide toxicity can also occur following inhalation or ingestion of methylene chloride found in paint strippers. Once absorbed, methylene chloride is metabolized to carbon monoxide through the hepatic cytochrome P450 pathway. The symptoms of carbon monoxide intoxication are consistent with hypoxia, including headache, dyspnea, lethargy, confusion, and drowsiness. Higher exposure levels can lead to seizures, coma, and death. The management of a carbon monoxide-poisoned patient includes prompt removal from the source of carbon monoxide, and institution of 100% oxygen by a nonrebreathing face mask or an endotracheal tube. In patients with severe intoxication, oxygenation in a hyperbaric chamber is recommended.



**Figure 46.8**

Effect of carbon monoxide on the oxygen affinity of hemoglobin.  
CO-Hb = carbon monoxyhemoglobin.

## D. Cyanide

Cyanide is one of the toxic products of combustion produced during house fires. Its principal toxicity occurs as a result of the inactivation of the enzyme cytochrome oxidase (cytochrome a<sub>3</sub>), leading to the inhibition of cellular respiration. Therefore, even in the presence of oxygen, tissues with a high oxygen demand, such as the brain and heart, are adversely affected. Death can occur quickly due to arrest of oxidative phosphorylation and production of adenosine triphosphate. The antidote, *hydroxocobalamin* (vitamin B<sub>12a</sub>), is administered intravenously to bind the cyanide and produce *cyanocobalamin* (vitamin B<sub>12</sub>) without the adverse effects of hypotension or methemoglobin production seen with older antidotes. The older cyanide antidote kit consists of *sodium nitrite* to form cyanomethemoglobin and *sodium thiosulfate* to accelerate the production of thiocyanate, which is much less toxic than cyanide and is quickly excreted in urine. To avoid the oxygen-carrying capacity becoming too low in patients with smoke inhalation and cyanide toxicity, the induction of methemoglobin with *sodium nitrite* should be avoided unless the carboxyhemoglobin concentration is less than 10%.

## E. Iron

The incidence of pediatric iron toxicity has greatly diminished during the past two decades due to education and changes in packaging and labeling of iron products. Iron is radiopaque and may show up on an abdominal radiograph if the product contains a sufficient concentration of elemental iron. Toxic effects can be expected with ingestions as little as 20 mg/kg of elemental iron, and doses of 60 mg/kg may be lethal. Each iron salt contains a different concentration of elemental iron (Figure 46.9). A serum iron level should be obtained, since levels between 500 and 1000 µg/dL have been associated with shock and levels higher than 1000 µg/dL with death. Patients with iron toxicity usually present with nausea, vomiting, and abdominal pain. Depending on the amount of elemental iron ingested, the patient may experience a latent period or may progress quickly to hypovolemia, metabolic acidosis, hypotension, and coagulopathy. Ultimately, hepatic failure and multisystem failure, coma, and death may occur. *Deferoxamine* [de-fer-OKS-a-meen], an iron-specific chelator, binds free iron, creating ferrioxamine, which is excreted in the urine. Hypotension may occur if rapid intravenous boluses of *deferoxamine* are administered instead of a continuous infusion.

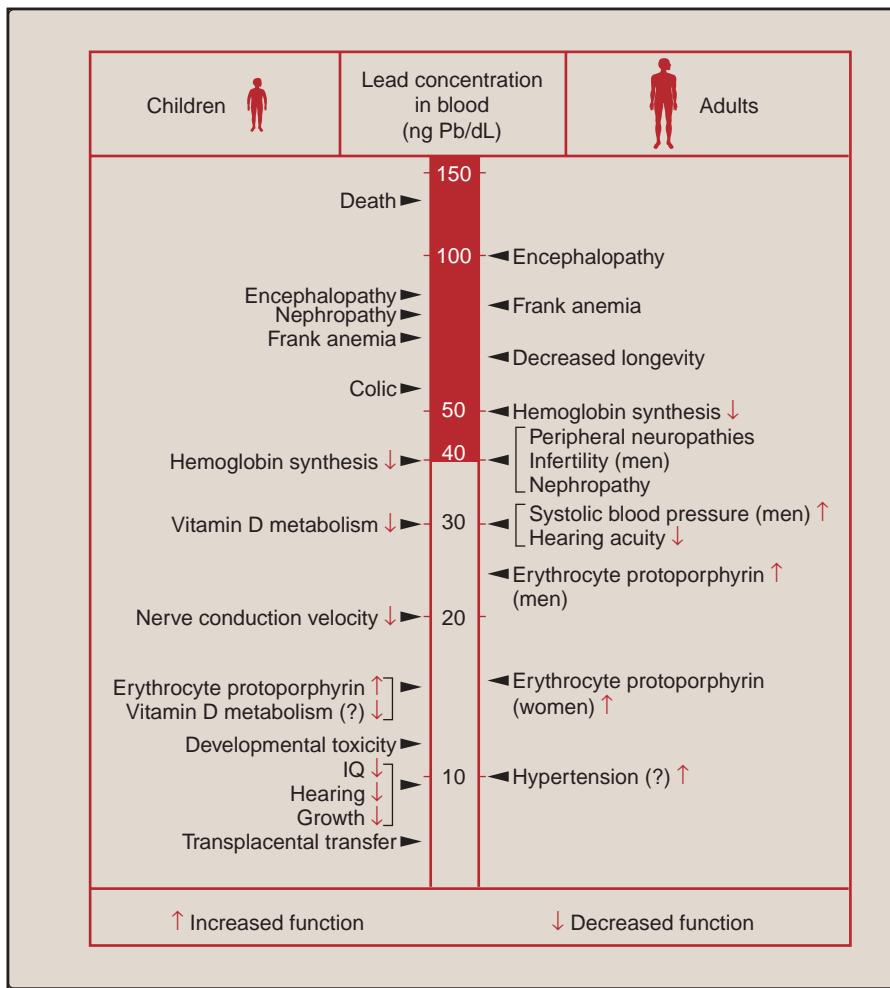
## F. Lead

Lead is ubiquitous in the environment, with sources of exposure including old paint, drinking water, industrial pollution, food, and contaminated dust. Most chronic exposure to lead occurs with inorganic lead salts, such as those in paint used in housing constructed prior to 1978. Adults absorb about 10% of ingested lead, whereas children absorb about 40%. Inorganic forms of lead are initially distributed to the soft tissues and more slowly redistribute to bone, teeth, and hair. Lead impairs bone formation and causes increased calcium deposition in long bones visible on x-ray. Ingested lead is radiopaque and may appear on an abdominal radiograph if present in the GI tract. Lead has an apparent blood half-life of about 1 to 2 months,

CONTENT	ELEMENTAL IRON (%)
<i>Ferrous fumarate</i>	33
<i>Ferrous gluconate</i>	12
<i>Ferrous sulfate</i>	20

**Figure 46.9**

Elemental iron contained in various iron preparations.

**Figure 46.10**

Comparison of effects of lead on children and adults. From the Centers for Disease Control and Prevention. <http://wonder.cdc.gov/>.

whereas its half-life in the bone is 20 to 30 years. Chronic exposure to lead can have serious effects on several tissues (Figure 46.10). Early symptoms of lead toxicity can include discomfort and constipation (and, occasionally, diarrhea), whereas higher exposures can produce painful intestinal spasms. CNS effects from lead include headaches, confusion, clumsiness, insomnia, fatigue, and impaired concentration. As the disease progresses, clonic convulsions and coma can occur. Death is rare, given the ability to treat lead intoxication with chelation therapy. Blood levels of 5 to 20 µg/dL in children have been shown to lower IQ in the absence of other symptoms. Finally, lead can cause hypochromic, microcytic anemia as a result of a shortened erythrocyte life span and disruption of heme synthesis.

Multiple chelators can be utilized in the treatment of lead toxicity. When levels are greater than 45 µg/dL, but less than 70 µg/dL in children, *succimer [dimercaptosuccinic acid (DMSA)]*, an oral chelator, is the treatment of choice. With lead levels greater than 70 µg/dL or if encephalopathy is present, dual parenteral therapy is required with *dimercaprol* given intramuscularly and *calcium disodium edetate*

given intravenously. *Dimercaprol* is suspended in peanut oil and should not be given to those with a peanut allergy.

### G. Organophosphate and carbamate insecticides

These insecticides exert their toxicity through inhibition of acetylcholinesterase, with subsequent accumulation of excess acetylcholine producing nicotinic (mydriasis, fasciculations, muscle weakness, tachycardia, hypertension) and muscarinic (diarrhea, urination, miosis, bradycardia, bronchorrhea, emesis, lacrimation, salivation) effects. Carbamates reversibly bind to acetylcholinesterase, whereas organophosphates undergo an aging process to ultimately irreversibly inactivate the enzyme. Organophosphate nerve agents, such as sarin, soman, and tabun, have the same mechanism of action, but the aging process is much more rapid compared to insecticides. *Atropine*, a muscarinic receptor antagonist, and *pralidoxime*, an oxime to reactivate cholinesterase, should be administered intravenously or intramuscularly to treat the muscarinic and nicotinic effects, respectively (see Chapter 4).

## IV. ANTIDOTES

Specific chemical antidotes for poisoning have been developed for a number of chemicals or classes of toxicants (Figure 46.3). This is not an all-inclusive list.

### Study Questions

Choose the ONE best answer.

46.1 A 3-year-old boy is brought to the emergency department by his mother, who reports that he has been crying continuously and “does not want to play or eat” for the past few days. She also states that he has not had regular bowel movements, with mostly constipation and occasional diarrhea, and frequently complains of abdominal pain. The child now has an altered level of consciousness, is difficult to arouse, and begins to seize. The clinician rules out infection and other medical causes. Upon questioning, the mother states that the house is in an older neighborhood, that her house has not been remodeled or repainted since the 1940s, and that the paint is chipping around the windows and doors. The child is otherwise breathing on his own and urinating normally. Which toxin would you expect to be producing such severe effects in this child?

- A. Iron
- B. Lead
- C. Carbon monoxide
- D. Cyanide

Correct answer = B. Lead poisoning is common among children in older homes painted before lead was removed from paint. Paint chips with lead are easily ingested by toddlers, and excessively high lead levels can lead to the signs and symptoms described plus clumsiness, confusion, headaches, coma, constipation, intestinal spasms, and anemia. Death is rare when chelation therapy is instituted. Iron can produce abdominal pain, but more often would cause diarrhea, vomiting, and volume loss. Carbon monoxide would affect the entire household, depending on the source. Clinical effects from carbon monoxide would include headache, nausea, and CNS depression. If he had cyanide poisoning, death would have occurred quickly following respiratory arrest of oxidative phosphorylation and production of adenosine triphosphate, but this child has been exhibiting symptoms over several days.

46.2 A 41-year-old male jeweler presents to the emergency department after he was found unconscious on the floor of the shop by a coworker. The coworker states that the patient complained of being cold this morning around 8 AM (the central heat was broken, and the outdoor temperature was 34°F) and that since noon, he had been complaining of headache, drowsiness, confusion, and nausea. The clinician notices that he has cherry red skin. What is the most likely toxin causing his signs and symptoms?

- A. Ethylene glycol
- B. Cyanide
- C. Acetaminophen
- D. Carbon monoxide

Correct answer = D. Although watch makers and other professionals who use electroplating may be at higher risk for cyanide exposure because many plating baths use cyanide-containing ingredients (for example, potassium cyanide), this patient shows signs of carbon monoxide poisoning, such as cherry red skin, headache, confusion, nausea, and drowsiness leading to unconsciousness. The history also leads us to believe that this person may have been using a space heater to stay warm, which would be consistent with the description. A carboxyhemoglobin level should be obtained to confirm the exposure. Cyanide in low doses from such an occupational exposure can present with loss of consciousness, flushing, headache, and confusion. Chronically, workers may develop a rash after handling cyanide solutions. Also, an odor of bitter almonds may be present. An arterial blood gas and a venous blood gas could be obtained and compared to determine if cyanide is present (a lack of oxygen extraction would be present on the venous side). Ethylene glycol toxicity may cause alterations in mental status, but the history did not include anything suggesting a toxic alcohol ingestion. Acetaminophen toxicity is not consistent with this presentation.

46.3 A 50-year-old migrant field worker comes to the emergency department and complains of diarrhea, tearing, nausea and vomiting, and sweating. The clinician notices that he looks generally anxious and has fine fasciculations in the muscles of the upper chest as well as pinpoint pupils. Which antidote should he receive first?

- A. *N*-acetylcysteine
- B. Sodium nitrite
- C. Deferoxamine
- D. Atropine

Correct answer = D. Atropine is appropriate for this patient, who has symptoms consistent with organophosphate (insecticide) poisoning. The mnemonic DUMBELS (diarrhea, urination, miosis, bronchorrhea/bradycardia, emesis, lacrimation, salivation) can be used to remember the signs and symptoms of cholinergic toxicity. An anticholinergic antidote, atropine, controls these muscarinic symptoms, whereas the antidote pralidoxime treats the nicotinic symptoms like fasciculations (involuntary muscle quivering or twitching). *N*-acetylcysteine is the antidote for acetaminophen overdose and acts as a sulfhydryl donor. Sodium nitrite is one of the antidotes included in the old cyanide antidote kit (sodium nitrite and sodium thiosulfate). Deferoxamine is the chelating agent for iron.

46.4 A 45-year-old man presented to the emergency department 18 hours after ingesting an unknown product. On presentation, he is tachycardic, hypertensive, tachypneic, and complaining of flank pain. A metabolic panel is obtained, and the patient has a large anion gap acidosis, an increased creatinine, and hypocalcemia. Which substance was most likely ingested?

- A. Methanol
- B. Acetaminophen
- C. Ethylene glycol
- D. Iron

Correct answer = C. Ethylene glycol produces a metabolic acidosis from the toxic metabolites. The formation of calcium oxalate crystals, which can be found on urinalysis, leads to hypocalcemia and renal failure. The treatment regimen for this patient would include intravenous fomepizole, if some of the parent compound was still present, and hemodialysis. Methanol may produce a metabolic acidosis as well, but its target organ of toxicity is the eyes instead of the kidneys as with ethylene glycol. Acetaminophen toxicity may produce upper quadrant pain within the first 24 hours, but vital sign abnormalities are not usually found during this time frame. Iron toxicity may also produce a metabolic acidosis and tachycardia. However, hypocalcemia does not occur.

46.5 A 27-year-old woman presents to the emergency department 6 hours after reportedly ingesting 20 tablets of acetaminophen 500 mg. An acetaminophen level is drawn, but it has to be sent out to another lab and will not return for another 6 hours. What is the most appropriate next step in management of this patient?

- A. Administer a dose (50 g) of activated charcoal.
- B. Start empirical *N*-acetylcysteine therapy.
- C. Wait for the level to return and then decide what to do.
- D. Draw a NAPQI level.

Correct answer = B. *N*-acetylcysteine should be started empirically on the basis of the history, and then, once the level returns and is plotted on the Rumack-Matthew nomogram, a final decision on whether to continue therapy can be made. Activated charcoal would not be of any benefit 6 hours post-acetaminophen ingestion. The optimal time frame to give *N*-acetylcysteine is within 8 to 10 hours post-ingestion. So, waiting on the level to return would put the patient more than 12 hours post-ingestion. Therefore, initiation of *N*-acetylcysteine therapy should happen, if possible during the optimal time frame. Clinicians are unable to draw a NAPQI level and therefore cannot utilize this to guide therapy.

46.6 A 15-year-old girl presents to the emergency department with CNS depression. She is slightly bradycardic and slightly hypotensive. Upon further questioning, the mother admits that the patient was found with an open bottle of clonidine. Which antidote might be beneficial for this patient?

- A. Flumazenil
- B. Atropine
- C. Deferoxamine
- D. Naloxone

Correct answer = D. Naloxone has a reversal rate of the CNS effects of approximately 50% in clonidine ingestions. Flumazenil reverses benzodiazepines and has no effect on clonidine. Atropine is an anticholinergic agent and would not improve the CNS depression. Deferoxamine is the chelator for iron.

46.7 A 45-year-old woman presents to the emergency department with a complaint of persistent vomiting. The patient appears intoxicated, but an ethanol level returns as negative and her basic metabolic panel is unremarkable. Which substance did she probably ingest?

- A. Isopropyl alcohol
- B. Methanol
- C. Ethylene glycol
- D. Ethanol

Correct answer = A. Isopropyl alcohol produces twice as much CNS depression as ethanol and is known to cause GI distress. Isopropyl alcohol is metabolized to acetone, so a metabolic acidosis does not result (which is in contrast to the acidosis generated by methanol and ethylene glycol). The ethanol level was negative, eliminating ethanol as an ingestion.

46.8 A 5-year-old boy is brought in to the health care facility for being irritable and failure to thrive. He is drowsy, and his vital signs are normal. The doctor diagnoses him with lead toxicity when the blood lead level returns as 75 µg/dL. Which chelator regimen should be started?

- A. Dimercaprol
- B. Calcium disodium edetate
- C. Both dimercaprol and calcium disodium edetate
- D. Succimer

46.9 A healthy 2-year-old boy ingested one of his mother's 2 mg clonazepam tablets 1 hour ago. The child presented to the emergency department with CNS depression but a normal heart rate and blood pressure. His bedside glucose check is also normal. Which antidote might be helpful?

- A. Flumazenil
- B. Naloxone
- C. Physostigmine
- D. Fomepizole

46.10 A 47-year-old man with a history of a seizure disorder, maintained on phenytoin, presented to the emergency department with salicylate toxicity. The salicylate level was 50 mg/dL (15 to 35 mg/dL therapeutic range) and the phenytoin level was 15 mg/L (10 to 20 mg/L therapeutic range). What therapy can be considered to enhance the elimination of salicylate without impacting the phenytoin?

- A. Multiple doses of activated charcoal
- B. Urinary alkalinization
- C. Whole bowel irrigation
- D. Urinary acidification

Correct answer = C. Dual parenteral therapy with dimercaprol and calcium disodium edetate is indicated if encephalopathy is present, or if the lead level is greater than 70 µg/dL in a child. Dimercaprol intramuscular therapy is initiated 4 hours prior to the intravenous administration of calcium disodium edetate when both medications are required. Succimer (dimercaptosuccinic acid, DMSA) is utilized when the lead level is greater than 45 µg/dL but less than 70 µg/dL, without encephalopathy.

Correct answer = A. Flumazenil is a competitive benzodiazepine antagonist that reverses the CNS depression from benzodiazepines such as clonazepam. After flumazenil administration, re sedation usually occurs, since the duration of the benzodiazepine is longer than that of the flumazenil. Naloxone reverses the effects from opioids and clonidine, not benzodiazepines. Physostigmine is the antidote for anticholinergic toxicity. Fomepizole is the antidote for methanol or ethylene glycol toxicity.

Correct answer = B. Urinary alkalinization enhances the elimination of the salicylate but does not affect the therapeutic phenytoin level. Multiple doses of activated charcoal would lower the concentration of both medications, rendering the phenytoin subtherapeutic. Whole bowel irrigation is another GI decontamination modality involving administration of large quantities (up to 2 L/hr in adults) of a polyethylene glycol-balanced electrolyte solution via a nasogastric tube until the patient generates clear rectal effluent.

# Antisnake Venom

Shyamal R. Sinha and Sangeeta Sharma

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## I. OVERVIEW

WHO classifies snakebite as a neglected tropical disease. Envenoming is a significant public health problem in tropical and subtropical regions. Snakebite is an acute life-threatening, time-limiting medical emergency. It is a preventable public health hazard often faced by rural population in tropical and subtropical countries with heavy rainfall and humid climate. Snakebite is a common occupational hazard affecting farmers, plantation workers, and others, resulting in thousands of deaths each year. Since snakebite is an environmental, occupational, and climatic hazard and mostly affect farmers, plantation workers, herdsmen, fishermen, snake restaurant workers, and other food producers, it results in tens of thousands of deaths each year and chronic physical handicap in many cases.

There are more than 2000 species of snakes in the world and about 300 species are found in India out of which 52 are venomous. The venomous snakes found in India belong to three families Elapidae, Viperidae, and hydrophinae (Sea Snakes). The most common Indian elapids are *Naja naja* (Indian Cobra), *Bungarus caeruleus* (Indian krait), *Daboia russelii* (Russells' viper), and *Echis carinatus* (saw-scaled viper). **Figure 47.1** lists some common snakes and the families they belong to. The clinical effects of envenoming by the same species of snake are almost similar except a few regional variations. Kraits are active during night hours, often biting a person sleeping on the floor bed. Maximum Viper and Cobra bites occur during the day or early darkness, while watering the plantation or walking barefoot in grown grass or soybean crops.

Although the total number of bites may be more than 5 to 6 lakhs, only 30% are venomous bites. On the basis of Million Death Study, nonfatal bites may be as high as 1.4 million per year. Snakes are found all over the world except in Antarctica, Iceland, Greenland, Madagascar, Ireland, and New Zealand. Most snakes are found in tropical regions. Snakes are found in many habitats including water. They eat their prey whole and are able to consume prey three times larger than the diameter of their head. Venomous snakes inject their prey with venom, while constrictors squeeze their prey.

This chapter provides an overview of the types of poisonous snakes, their toxins, and clinical manifestations and management of a snake bite. **Figure 47.1**.

FAMILY	NAMES
Viperidae	Saw-scaled viper, Russell's viper
Elapidae	Indian cobra, Common krait
Crotalidae	Pit viper
Hydrophidae	Sea snakes
Colubridae	Grass snakes and garter snakes

**Figure 47.1**

Common poisonous snakes.

## II. PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Venomous snakes are so called because they produce venom, which is basically modified saliva. It is discharged with the purpose of killing prey or disabling predators and delivered by grooved or hollow fangs in the upper jaw. Glands producing venom are found below each eye. Snake venom is mostly made up of water, but its venomous effects are from a complex mixture of proteins, enzymes, nonenzymatic polypeptide, toxins, and non-toxic proteins.

A clinical presentation of a snakebite victim depends upon the species of snake. The venomous effects vary (Figure 47.2) due to the amount of venom injected, site of bite, area covered or uncovered, dry or incomplete bite, multiple bites, venom injection in vessel, weight of the victim, and time elapsed between the bite and administration of antisnake venom (ASV).

The patient can present in any of the four clinical syndromes or with overlapping syndrome: 1) progressive weakness (neuroparalytic/neurotoxic), 2) bleeding (vasculotoxic/hemotoxic), 3) myotoxic, and 4) painful progressive swelling (Figure 47.2). There may be considerable overlap of clinical features.

The clinical features may be localized to the site of the bite or they may be systemic. The pathological effects of venom on one hand may not be noticed for about 6 hours; on the other hand, the effects may last for a few weeks.

The venom effects produced may be local or systemic.

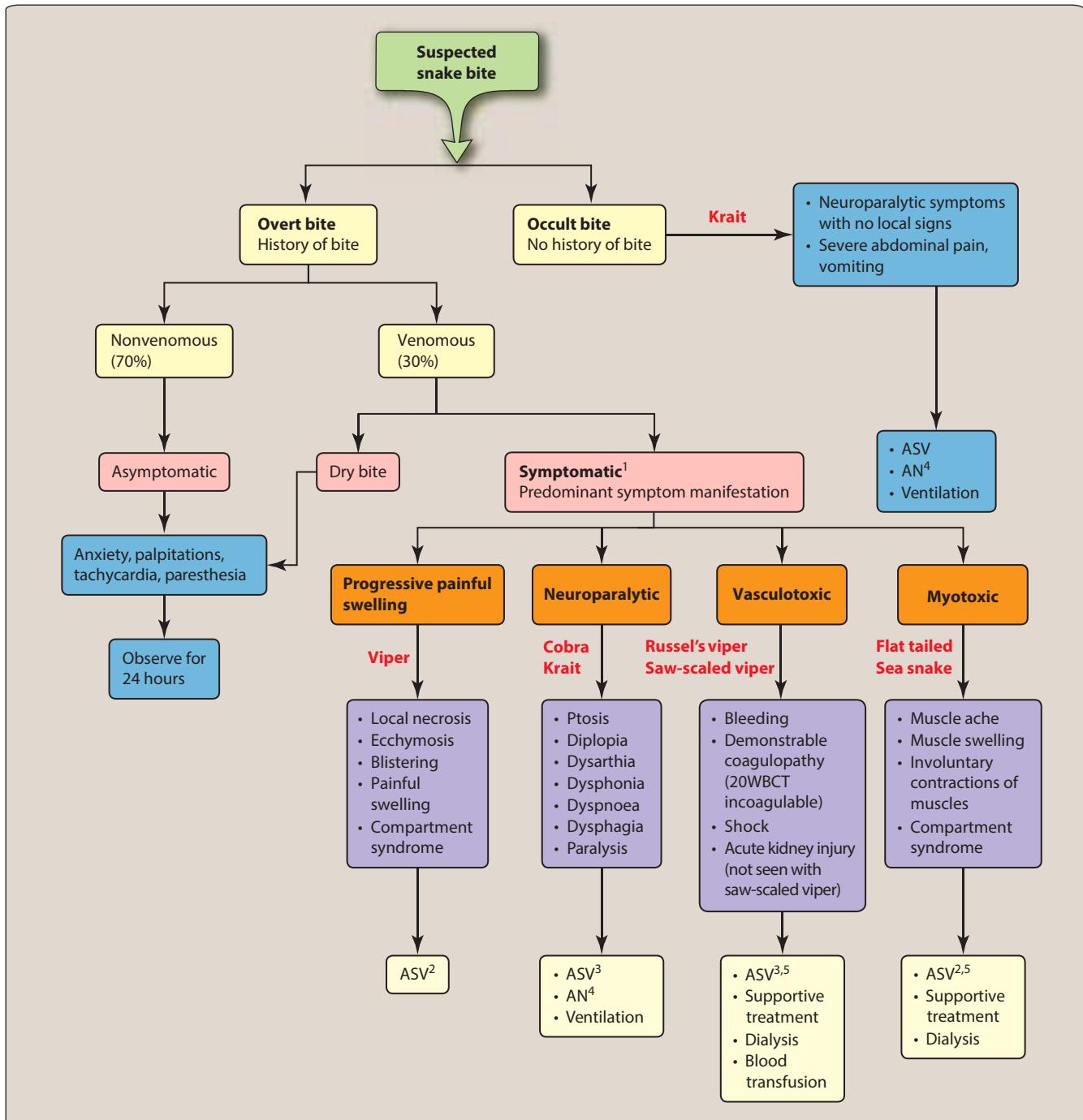
### A. Local effects

Local effects are confined to the part of the body that has been bitten (local bleeding, pain, inflammation, blistering, necrosis around the fang marks). The enzymes in the venom cause destruction of the tissues locally with hemolysis and muscle necrosis leading to further spread of the venom (Figure 47.3).

### B. Systemic effects

Systemic effects are on the organs and tissues away from the part of the body that has been bitten. These effects may be neurologic, cardiovascular, or thrombogenic depending on the type of snake and its toxin released.

1. **Neuroparalytic/Neurologic:** Predominantly in case of elapids (cobra, krait). The neurotoxins can cause pre- or postsynaptic blockade, depending on the type of the snake that has bitten. Postsynaptic neurotoxins are polypeptides that target the neuromuscular junction. They bind to the acetylcholine receptor on the muscle end-plate, blocking neurotransmitter binding, thus causing paralysis. The response to *neostigmine* is satisfactory. This is typical of a cobra bite. The presynaptic neurotoxins are modified phospholipase A2 toxins which target the terminal axon of the neuromuscular junction causing first the release of the neurotransmitter and then extensive damage to the axonal structure with progressive flaccid paralysis thereafter as seen in Krait poisoning. *Neostigmine* causes no response in this type of paralysis. The neurologic effects include drowsiness, paresthesia, abnormalities of taste and smell, ptosis, external ophthalmoplegia, paralysis of



<sup>1</sup>Even though present as predominant manifestation but there may be overlap of syndrome as well.

<sup>2</sup>ASV indicated in rapidly developing swelling only. Purely localized swelling with or without bite marks is not an indication of ASV.

<sup>3</sup>For reaction to antisnake venom (ASV) Dose of Adrenaline 0.5 mg IM (in children 0.01 mg/kg)

<sup>4</sup>"AN" injection Atropine 0.6 mg followed by neostigmine (1.5mg) IV stat (in children Inj. Atropine 0.05 mg/kg followed by Inj. Neostigmine 0.04 mg/kg IV.) Repeat neostigmine 0.5 mg (in children 0.01mg/kg) with atropine every 30 minutes for 5 doses. Thereafter taper dose at 1 hour, 2 hours, 6 hours and 12 hours. Positive response is measured as 50% or more recovery of the ptosis in one hour. If no response after 3<sup>rd</sup> dose stop AN injection. **No AN injection in confirmed krait bite.**

<sup>5</sup>Specific ASV for sea snake and Pit viper bite is not available in India. However, available ASV may have some advantage by cross reaction.

**Note:** The snake species shown above are indicative only. Russell's viper envenoming in Tamil Nadu and some other areas commonly causes paralysis. The venom of this species varies considerably across its range in India.

**Figure 47.2**

Clinical syndromes of snakebite—that is, progressive weakness (neuroparalytic/neurotoxic), bleeding (vasculotoxic/hemotoxic), myotoxic, and painful progressive swelling and its management.



**Figure 47.3**

Swollen part of the limb after snakebite; bleeding can be seen.



**Figure 47.4**

Ptosis (drooping eyelids) due to cobra envenomation. It is a neurotoxic effect. Source: Mabel Cordeiro Vasnaik (2012). Snake envenomation. In David, Suresh S. (Chief Ed.). *Textbook of Emergency Medicine*. Delhi: Wolters Kluwer.

facial muscles and other muscles innervated by the cranial nerves, and aphonia (Figure 47.4).

## 2. **Vasculotoxic:**

- a. **Thrombogenic:** Russell's viper venom contains serine proteases and other procoagulant enzymes that are thrombin-like or activate factor X, prothrombin, and other clotting factors causing consumption coagulopathy. This is due to the vasculotoxic effect of the viper venom. This leads to spontaneous systemic bleeding from gums, epistaxis, bleeding into the tears, bleeding into the mucosae, hemoptysis, hematemesis, rectal bleeding or melena, hematuria, vaginal bleeding, antepartum hemorrhage in pregnant women, and intracranial hemorrhage.
- b. **Cardiovascular effects:** Predominantly in case of Russell's viper. Certain cardiotoxins are phospholipases causing cellular injury of skeletal, smooth, and cardiac muscles to produce paralysis and cardiac asystole. Some cardiotoxins cause irreversible depolarization of the cell membrane and systolic cardiac arrest. As muscles undergo lysis and also following massive hemolysis or rhabdomyolysis, there is hyperkalemia that depresses cardiac function. The effects include collapse, shock, hypotension, cardiac arrhythmias, cardiac failure, pulmonary edema, and respiratory failure.

## 3. **Painful progressive swelling (PPS):** Progressive painful swelling is indicative of local venom toxicity. It is prominent in Russel's viper bite, saw-scaled viper bite, and cobra bite. This is associated with the following:

- Local necrosis which often has a rancid smell. The limb is swollen and the skin is taut and shiny. Blistering with reddish black fluid at and around the bite site. Skip lesions around the main lesion are also seen.
- Ecchymoses due to venom action destroying the blood vessel wall.
- Significant painful swelling potentially involving the whole limb and extending onto the trunk.
- Compartment syndrome presents invariably.
- Regional tender enlarged lymphadenopathy.

## 4. **Occult snakebite:**

- Krait bite victims often present in the early morning with paralysis with no local signs and no bite marks.
- The snakebite victim gets up in the morning with severe epigastric/umbilical pain with vomiting persisting for 3 to 4 hours and followed by typical neuroparalytic symptoms within the next 4 to 6 hours. There is no history of snakebite.
- Unexplained respiratory distress in children in the presence of ptosis or sudden onset of acute flaccid paralysis in a child (locked-in syndrome) are highly suspicious symptoms in endemic areas, particularly of krait bite envenomation. Sometimes, patients may present with throat, chest, or joint pain.

### III. MANAGEMENT OF SNAKEBITE

#### A. Diagnosis

Snakebite is a medical emergency. Therefore history, symptoms, and signs must be obtained quickly. Assess circulation, airway, and breathing and deal with any life-threatening symptoms on presentation. Vasculotoxic patients presenting with bleeding from multiple orifices with hypotension, reduced urine output, obtunded mentation (drowsy, confused), and cold extremities need urgent attention and ICU care for volume replacement, pressor support, dialysis and infusion of blood and blood products.

Neuroparalytic patients presenting with respiratory paralysis, tachypnea or bradypnea or paradoxical respiration (only moving abdomen), obtunded mentation, and peripheral skeletal muscle paralysis need urgent ventilator management with endotracheal intubation, ventilation bag, or ventilator assistance.

Other noncritical patients can be evaluated to decide the severity of their illness. Management of all snakebite victims includes the following.

- Establish large-bore intravenous access and start normal saline slow infusion.
- Before removal of the tourniquet/ligatures, test for the presence of a pulse distal to the tourniquet. If the pulse is absent, ensure a doctor is present before removal of ligatures.
- In case of a clinically confirmed venomous bite, remove tourniquet only after starting the loading dose of ASV and keep *atropine neostigmine* injection ready. In case of multiple ligatures, all the ligatures can be released in an Emergency Room EXCEPT the most proximal one, which should only be released after admission and all preparations.
- Carry out a medical assessment including history and physical examination every 1–2 hourly and record bite site, local swelling, painful tender and enlarged local lymph glands, persistent bleeding from the bite wound, blood pressure, pulse rate, bleeding (gums, nose, vomit, stool, or urine), level of consciousness, drooping eyelids, and other signs of paralysis. ***The Glasgow Coma scale cannot be used to assess the level of consciousness of patients paralyzed by neurotoxic venoms.***
- Check for 20 minutes Whole Blood Clotting Test (20 WBCT) at admission and in case clotted, monitor every hour for the first 3 hours and every 6 hours for the remaining 24 hours to detect evolving venom-induced DIC. In case test is nonclotting, repeat 6 hours after administration of a loading dose of ASV. **Figure 47.5** depicts the method and precautions to be taken while doing 20WBCT. In case of neurotoxic envenomation, repeat clotting test after 6 hours. Use a new, clean, dry test tube. If clotted, carry out every 1 hour from admission for 3 hours and then 6 hourly for 24 hours. If the test is nonclotting, repeat 6 hours after administration of a loading dose of ASV.
- Check distal pulses and monitor if there is presence of gross swelling. The presence of a pulse does not rule out compartment syndrome.
- Examine the snake carefully, if brought, and identify, if possible. Take one smart phone photograph of the snake, dead or alive, if available, for confirmation by an expert.



**Figure 47.5**

20-minute whole blood clotting test (20WBCT).

Victims of snakebite may suffer from any or all of the following:

- No physical effects other than the fang/tooth puncture due to bites by nonvenomous snakes, animals other than snakes (lizards, fish, rodent, spiders), and dry bite by a venomous snake.

#### **Examination of the bite site.**

- Examine the bite site and look for fang marks or any signs of local envenomation. Fang marks or their patterns have no role to determine whether the biting species was venomous or nonvenomous or the amount of venom injected, severity of systemic poisoning, and nature of poisoning—Elapidae or viperidae venom. Some species such as krait may leave no bite marks.
- Local envenoming confined to the bitten part of the body: These effects may be transient, resolving in hours or a few days. They may persist for a few weeks or may be debilitating, sometimes permanently, due to local necrotic effects of venom and complicating infections.
- Systemic envenoming involving organs and tissues distant from the bitten part of the body: These effects may be transient, life threatening and debilitating, and persistent, sometimes permanently.
- Effects of anxiety prompted by the frightening experience of being bitten (real or imagined) and by exaggerated beliefs about the potency and speed of action of snake venoms. The symptoms may mislead the treating personnel.
- Effects of first-aid and other prehospital treatments that may cause misleading clinical features.

Though to a large extent the manifestation of snakebite depends upon the species of snake, unfortunately, in many cases the biting snake is not seen, and if it is, its description by the victim is often misleading. Therefore, identification of the type of snake should not hold the treatment. At times, the bite mark might not be visible (for example, in the case of krait). The clinical manifestations of the patient may not correlate with the species of snake brought as evidence.

## **B. Treatment**

### **1. First-aid measures and some do's and don'ts are shown in Figure 47.6:**

- Admit all confirmed or suspected victims of snakebite and keep them under observation for 24 hours. Observe for signs of envenomation.
- Administer ASV therapy as soon as there is evidence of envenomation.
- In case of dry bite, symptoms due to anxiety and sympathetic over-activity due to stress or panic may sometimes mimic early envenoming symptoms. Thus, clinicians may have difficulties in determining whether envenoming occurred or not.
- Local wound care should be taken care of by cleaning the bite site with povidone-iodine solution (but do not apply any dressing). Leave blisters alone allowing them to break spontaneously and heal. If there is local necrosis, excise and apply saline dressings. Surgical decompression may be necessary in some cases.

DO'S	IMPORTANT DON'TS
<p><b>First-Aid Measures</b></p> <p>Shift the victim to the nearest health facility (PHC/hospital) IMMEDIATELY after providing first aid where optimal medical care with antisnake venom (ASV) is available.</p> <p><b>At The Community or Village Level</b></p> <ul style="list-style-type: none"> <li>Check history of snakebite and look for obvious evidence of a bite (fang puncture marks, bleeding, swelling of the bitten part, etc.).</li> <li>Reassure the patient as around 70% of all snakebites are from nonvenomous species and there is treatment for venomous snakebite.</li> <li>Immobilize the limb in the same way as a fractured limb (in the recovery position [prone, on the left side]) with airway protected.</li> <li>Splint should extend the entire length of the limb, immobilizing all joints of the bitten limb. May use any rigid object as a splint, for example, spade, piece of wood or tree branch, rolled-up newspapers, and ruler), <i>but do NOT block the blood supply or apply pressure.</i></li> <li>Nil by mouth till the victim reaches a medical health facility.</li> <li>Arrange transport of the patient to medical care as quickly, safely, and passively as possible by vehicle ambulance (toll free no. 102/108/etc.), boat, bicycle, motorbike, stretcher, etc., whichever is readily available. If no other transport is available, a motorbike may be used <i>but a third person should sit behind the patient.</i></li> <li>The victim must not run or drive himself to reach a health facility.</li> <li>Remove shoes, rings, watches, jewelry, and tight clothing from the bitten area.</li> <li>Leave the blisters undisturbed.</li> </ul> <p><b>At a Healthcare Facility</b></p> <ul style="list-style-type: none"> <li>Admit all victims of confirmed or suspected snakebite and observe for 24 hours for signs of envenomation.</li> <li>Provide first-aid measures and supportive measures immediately.</li> <li>Administer ASV therapy as soon as there is evidence of envenomation.</li> </ul>	<ul style="list-style-type: none"> <li>Do NOT attempt to kill/catch the snake.</li> <li>Discard traditional first-aid methods (black stones, scarification) and alternative medical/herbal therapy.</li> <li>Do NOT wash wound and interfere with the bite wound (incisions, suction, rubbing, massage, tattooing, application of herbs or chemicals, cryotherapy, cauterization).</li> <li>Do NOT apply or inject antisnake venom (ASV) locally.</li> <li>Do NOT tie tourniquets as they may cause gangrenous limbs.</li> <li>If the victim is expected to reach the hospital in more than 30 minutes but less than 3 hours, crepe bandage may be applied by a <i>qualified medical personnel only</i> till the patient is shifted to the hospital. The bandage is wrapped over the bitten area as well as the entire limb with the limb placed in a splint. It should be capable of admitting a finger beneath it.</li> </ul>

**Figure 47.6**

Some do's and don'ts while providing first-aid measures in snakebite victims.

- Administer booster tetanus toxoid dose. General care includes monitoring pulse, blood pressure, respiration, EKGs for arrhythmias; maintaining adequate hydration; and achieving an intravenous access.
  - Medications include antibiotics. Other medications may include benzodiazepines for anxiety and sedation, opioids for pain, fluid replacement, and vasopressor support for shock.
- 2. Antisnake venom (ASV) therapy:** ASV is the only effective antidote for snake venom and is an essential element of treatment of systemic envenoming. It should be given as soon as it is indicated. The dosage required varies with the degree of envenomation.

Antivenom is immunoglobulin purified from the plasma of a horse, mule, or donkey (equine), or sheep (bovine) that has been immunized with the venoms of one or more species of snake.

“Specific” antivenom implies that the antivenom has been raised against the venom of the snake that has bitten the patient and that it can therefore be expected to contain a specific antibody that will neutralize that particular venom and perhaps the venoms of closely related species (paraspecific neutralization). Monovalent (monospecific) antivenom neutralizes the venom of only one species of snake. Polyvalent (polyspecific) antivenom neutralizes the venoms of several different species of snakes, usually the most important species, from a medical point of view, in a particular geographical area.

Antibodies raised against the venom of one species may have cross-neutralizing activity against other venoms, usually from closely related species. This is known as paraspecific activity.

In India, only polyvalent antisnake venom is available; these are produced against four most important venomous snakes—Naja naja (cobra), B. ceruleus (Indian common krait), Daboi Russelli (Russell's viper), and Echis carinatus (saw-scaled viper). It is raised in horse serum. They are prepared in two forms:

- Lyophilized/freeze dried form (heat stable; to be stored at cool temperature—stored below 25°C; shelf-life 3 to 5 years) which will be reconstituted with 10 mL water to 10 mL of ASV. Mixing is done by swirling and not by vigorous shaking. Do not use, if reconstituted solution is opaque to any extent as it may have been denatured by an inadequate freeze-drying technique.
- Liquid form of ASV (heat labile; ready to use; requires reliable cold chain [stored at 2°C to 8°C and NOT frozen] with a refrigeration shelf-life of 2 years but costlier)—each vial contains 10 mL of ASV. It should be preserved at -20°C to 80°C.

If the integrity of the cold chain is not guaranteed (in remote areas), use of lyophilized ASV is preferred.

The range of venom injected is 5 to 147 mg. Each mL of polyvalent ASV produced in India neutralizes

- 0.6 mg dried Indian cobra venom,
- 0.45 mg dried common krait venom,
- 0.6 mg of dried Russell's venom, and
- 0.45 mg dried saw-scaled viper venom.

The total required dose range is between 10 and 30 vials. Depending on the patient condition, additional vials can be considered.

Pregnant women and children are treated in exactly the same way as other victims. They are given the same dose of ASV as adults as snakes inject the same amount of venom into children and adult.

### 3. Indications:

#### a. Early features of systemic envenoming:

- Hemostatic abnormalities
  - Spontaneous systemic bleeding
  - Noncoagulable blood in 20-minute whole blood clotting test (20 WBCT)

- Neurotoxic signs
  - Ptosis, external ophthalmoplegia, dysphagia, and paralysis
- Cardiovascular abnormalities
  - Shock and cardiac arrhythmia

**b. Local envenoming:**

- Local swelling involving more than half of the bitten limb (in the absence of a tourniquet)
- Rapid extension of swelling
- Development of an enlarged tender lymph node draining the bitten limb

**4. Administration:**

- a. Systemic:** Systemic administration is by intravenous infusion diluted in approximately 5 to 10 mL/kg of body weight or 250 to 500 mL of normal saline or 5% dextrose in case of adults over a period of 1 hour to achieve the effective blood concentration rapidly. An intravenous push injection can be given but slowly (not more than 2 mL/min) which appears to be more cumbersome.

**NEVER** give ASV by the IM route. Antivenom should never be injected into the gluteal region (upper outer quadrant of the buttock) as absorption is exceptionally slow and unreliable and there is always the danger of sciatic nerve damage when the injection is given by an inexperienced person. No ASV test dose must be administered. Skin/conjunctival hypersensitivity testing does not reliably predict early or late antisnake venom reactions and is not recommended.

- b. Local:** Local administration of antivenom at the site of bite is not recommended as it has not shown to be effective and is extremely painful and may produce an increase in the intra-compartmental pressure.

**5. Repeat administration:** The dose should be repeated in the following cases:

- Persistence or recurrence of blood incoagulability (as measured by 20WBCT) after 6 hours of the first dose
- In patients who continue to bleed briskly after 1 to 2 hours of the first dose of ASV.
- Deteriorating neurotoxic or cardiovascular signs after 1 to 2 hours of the first dose of ASV.

**6. Victims who arrive late:** Sometimes victims arrive late after the bite, often after several days, usually with acute kidney injury. Determine the current venom activity such as bleeding in case of viperine envenomation. Perform 20WBCT and determine if any coagulopathy is present; then administer ASV. If no coagulopathy is evident, treat kidney injury, if any.

**a. Prophylactic epinephrine with antisnake venom:**

- Give prophylactic epinephrine (adrenaline) 0.25 mg of 0.1% solution (1:1000 dilution) by subcutaneous injection (children 0.005 mg/kg body weight of 0.1% solution) except in known hypertensive or in patients with cardiovascular disease and draw epinephrine in readiness in two syringes before ASV is administered.

**7. Adverse reactions:**

- a. **Early anaphylactic reactions:** These occur within 10 to 180 minutes of starting the antivenin. Clinical features include urticaria, itching, cough, nausea, vomiting, abdominal colic, diarrhea, and tachycardia.
  - b. **Pyrogenic (endotoxin) reactions:** They develop 1 to 2 hours after starting ASV therapy. Clinical features include fever, rigor, chill, and lower blood pressure.
  - c. **Late (serum sickness type) reactions:** They develop 1 to 12 days after antivenin therapy (mean 7 days). Clinical features include fever, nausea, vomiting, arthralgia, arthritis, diarrhea, itching, recurrent urticaria, myalgia, lymphadenopathy, and proteinuria.
8. **Treatment of early antisnake venom reaction:** Use of histamine, anti-H1 and anti-H2 blockers, corticosteroids, and the rate of intravenous infusion of antivenom between 10 and 120 minutes does not affect the incidence or severity of early antivenom reactions.

## **IV. MANAGEMENT OF NEUROTOXIC (NEUROPARALYTIC) ENVENOMATION**

Antisnake venom treatment alone cannot be relied upon to save the life of a patient with bulbar and respiratory paralysis. Administer the following in addition:

- Oxygen
- Assisted ventilation. If the patient has evidence of bulbar or respiratory paralysis, insert an endotracheal tube with the help of the anesthesiologist, if available, or by a trained medical personnel or use laryngeal mask airway (LMA). If there is evidence of respiratory failure, assist ventilation manually by an anesthetic bag or a mechanical ventilator. The duration of mechanical ventilation in snakebite victims is usually short since neuroparalysis reverses quickly with prompt administration of ASV. Manual ventilation (self-ventilating anesthetic bag) is also effective if the mechanical ventilator is not available. Prolonged assisted ventilation with room air or oxygen is followed by complete recovery in case of Guillain–Barre syndrome and delayed neuropathy following snakebite.
- Administer “*atropine neostigmine (AN)*” schedule as described in the following text. Give one dose of “AN” injection before transferring to a higher center as rapid deterioration of cobra bite neurotoxic syndrome may kill the patient on the way during transfer. Some patients go into a deep coma state but recover completely. Hence, diagnosis of brain death should not be considered.
- Do not give AN in case of a confirmed krait bite.
- The initial dose of ASV is administered over 1 hour. If ASV is not available, refer to a higher facility where ASV is available or if no improvement after the initial dose.

### **A. Atropine neostigmine (AN) dosage schedule**

*Atropine* 0.6 mg followed by *neostigmine* (1.5 mg) to be given IV stat and repeat dose of *neostigmine* 0.5 mg with *atropine* every 30 minutes for 5 doses (in children, Inj. *Atropine* 0.05 mg/kg

followed by Inj. *Neostigmine* 0.04 mg/kg intravenous and repeat dose 0.01 mg/kg every 30 minutes for 5 doses). A fixed-dose combination of *neostigmine* and glycopyrrolate IV can also be used, thereafter to be given as tapering dose at 1 hour, 2 hours, 6 hours, and 12 hours.

Majority of patients improve within the first 5 doses. Observe the patient closely for 1 hour to determine if the *neostigmine* is effective. After 30 minutes, any improvement should be visible by an improvement in ptosis. A positive response to the "AN" trial is measured if 50% or more recovery of the ptosis occurs in 1 hour.

Stop *atropine neostigmine* (AN) dosage schedule if:

- Patient has complete recovery from neuroparalysis. Rarely the patient can have recurrence; carefully watch patients for recurrence.
- Patient shows side effects in the form of fasciculations or bradycardia.

If there is no improvement after 3 doses of *atropine neostigmine*, it indicates a probable krait bite which requires calcium gluconate. Krait affects presynaptic fibers where calcium ion acts as a neurotransmitter.

Improvement by *atropine neostigmine* indicates cobra bite. A few Nilgiri Russel's viper bites victims also improve with this regimen.

## Study Questions

**Choose the ONE best answer.**

47.1 A 35-year-old farmer was working in the fields when he was bitten by a snake. After 3 hours, he started developing ptosis and paralysis of facial muscles. Subsequently, he was taken to a local hospital where he was diagnosed to have suffered from snake bite by a cobra (identified from bite marks). What should be the ideal management of this patient?

- Observe the patient and maintain his vitals.
- Take local care of the wound.
- Administer ASV to the patient.
- Administer ASV, atropine, and neostigmine to the patient.

Correct Answer = D. In this patient, signs of systemic envenomation have developed; hence, ASV has to be administered. In cobra, the toxin is postsynaptic so administration of neostigmine will be beneficial to the patient.

47.2 A 42-year-old female, while working at the garden in the night, was bitten by a snake. She rapidly developed local swelling of the limb and thereafter had ptosis and paralysis of facial muscles. Subsequently, she was taken to a hospital where she was diagnosed to have suffered from snakebite by a krait (identified from bite marks). What should be the ideal management of this patient?

- Observe the patient and maintain his vitals.
- Take local care of the wound.
- Administer ASV to the patient.
- Administer ASV, atropine, and neostigmine to the patient.

Correct Answer = C. In this patient, signs of local and systemic envenomation have developed; hence, ASV has to be administered. In krait, the toxin is presynaptic so administration of neostigmine will not be beneficial for the patient.



# Drugs of Abuse

Carol Motycka and Joseph Spillane

48

## I. OVERVIEW

A boy inhales paint fumes to momentarily escape his surroundings of poverty; a new gang member smokes crack with his friends to feel like he belongs; a curious girl swallows a “Molly” to see what it is like; a prescription drug abuser injects fentanyl-laced heroin to substitute for the pain pills that are more difficult to obtain; and a lonely widower drinks another shot of bourbon to help remember the past and forget the present. In each of these cases, chemicals are being used for nontherapeutic effects on the body or mind. Excessive use or misuse of drugs or alcohol for intoxicating or mind-altering effects is considered substance misuse, and those who misuse substances are considered to have a substance use disorder. **Figure 48.1** provides a list of commonly abused substances.

Substance use disorders occur in many forms and their effects have been witnessed throughout the history of the world. The lure of addictive substances continues to impact people today. In 2015, approximately 10.1% of the population in the United States were current users of some form of illicit substance (**Figure 48.2**), while 6.2% were considered to have an alcohol use disorder, and 4.7% misused prescription medications. Abused substances have become progressively more potent, and their routes of administration have become increasingly effective, resulting in greater risks of addiction (**Figure 48.3**) and toxicity. Some examples of the methods, mechanisms, and clinical manifestations of toxicity of commonly abused substances are discussed in this chapter.

## II. SYMPATHOMIMETICS

Sympathomimetics are stimulants that mimic the sympathetic nervous system, producing “fight-or-flight” responses. Sympathomimetics usually produce a relative increase of adrenergic neurotransmitters at the site of action (**Figure 48.4**), thereby causing effects such as tachycardia, hypertension, hyperthermia, and tachypnea. These agents come from natural

**Figure 48.2**

Past-month illicit drug use among persons aged 12 or older. Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.

### STIMULANTS

*Amphetamines*

*Cocaine*

*Methylenedioxymethamphetamine (MDMA)*

*Cocaine*

*Synthetic cathinones (“bath salts”)*

### HALLUCINOGENS

*Lysergic acid diethylamide (LSD)*

*Marijuana*

*Synthetic cannabinoids*

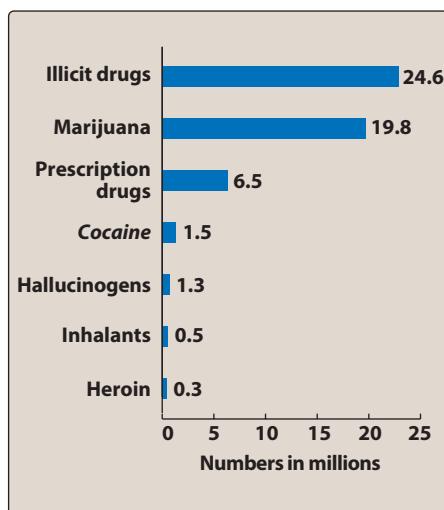
### OTHER DRUGS OF ABUSE

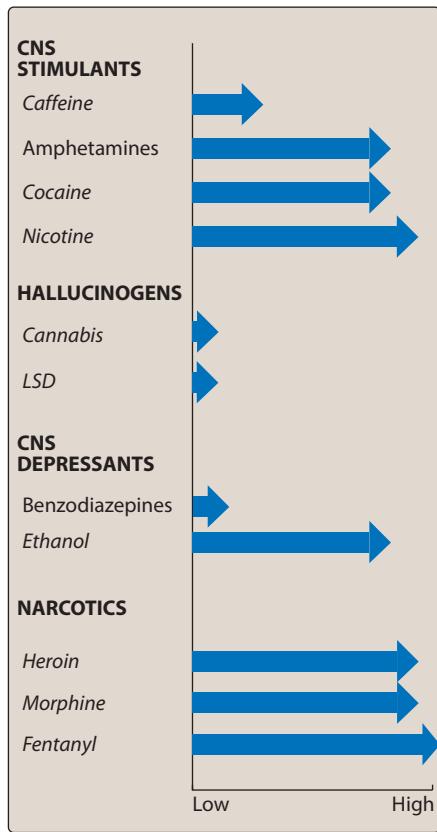
*Ethanol*

*Prescription drugs (particularly opioids)*

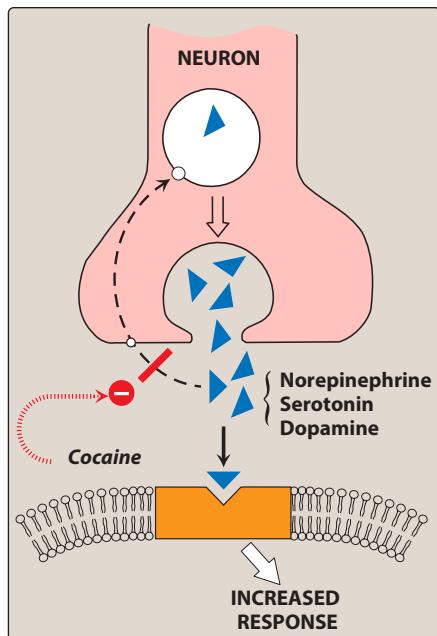
**Figure 48.1**

Summary of commonly abused substances.



**Figure 48.3**

Relative potential for physical dependence of commonly abused substances.

**Figure 48.4**

Mechanism of action of cocaine.

sources, such as plants, or are synthesized in legitimate or clandestine laboratories. Aside from the stimulant effect, many of these agents have a remarkable ability to produce pleasure. Consequently, their addictive potential and monetary value on the illicit market offer a huge profit motive.

### A. Cocaine

*Cocaine* is derived from coca (*Erythroxylum coca*) shrub that grows in the foothills of the Andes Mountains in South America. It causes central nervous system (CNS) stimulation by inhibiting the reuptake of norepinephrine into the adrenergic neuron, thus increasing the availability of catecholamines at the synapse. The profound ability of *cocaine* to stimulate the pleasure center of the human brain is thought to result from inhibition of reuptake of dopamine and serotonin. *Cocaine* has minimal bioavailability when taken by the oral route. Instead, the *cocaine hydrochloride* powder is snorted, or solubilized and injected. The *cocaine* powder cannot be effectively smoked, as it is destroyed upon heating. However, crack *cocaine*, an alkaloidal form, can be smoked. Smoking is an extremely effective route of administration, as the lungs are richly perfused with blood and carry the drug within seconds to its site of action, the brain. This causes an intense euphoria or “rush” that is followed rapidly by an intense dysphoria or “crash.” It is this immediate positive reinforcement, followed rapidly by the negative reinforcement that makes the drug, particularly in this form, so addictive. Like most drugs of abuse, street *cocaine* powder and crack are usually adulterated to increase the bulk, mimic the action, and thereby increase the profitability.

The clinical manifestations of *cocaine* toxicity are a function of its stimulant effects. Common reasons for *cocaine* users to present to the emergency department include psychiatric complaints (depression precipitated by *cocaine* dysphoria, agitation/paranoia), convulsions, hyperthermia, and chest pain. Hyperthermia is caused by *cocaine*-induced CNS stimulation that increases heat production and vasoconstrictive effects of *cocaine* that minimize the ability to dissipate heat. *Cocaine*-related chest pain can be chest muscle pain or cardiac in nature, as *cocaine* causes vasoconstriction of coronary arteries and accelerates the atherosclerotic process. Commonly, *cocaine* is consumed with alcohol, which creates a secondary metabolite cocaethylene. The metabolite is cardiotoxic and further contributes to cardiac issues related to *cocaine* consumption. *Cocaine* chest pain can also be related to pulmonary damage caused by inhalation of this heated impure substance. *Cocaine* convulsions are a natural extension of the CNS stimulant effect (Figure 48.5). *Cocaine* toxicity is treated by calming and cooling the patient. Benzodiazepines, such as *lorazepam*, help to calm the agitated patient and can both treat and prevent convulsions. In addition, the calming effect helps cool the patient and manage hyperthermia. This is an important therapeutic effect, as hyperthermia is one of the major causes of *cocaine* fatalities. The remainder of *cocaine* toxicity is treated with short-acting antihypertensives, anticonvulsants, and symptomatic supportive care.

## B. Amphetamines

Amphetamines such as *methamphetamine* are sympathomimetics with clinical effects very similar to those of *cocaine*. Amphetamines act by enhancing the release of biogenic amines from the storage sites in the nerve terminals. In many cases, these effects may last longer and are associated with more stimulation and less euphoria when compared to *cocaine*. Treatment of *amphetamine* toxicity is similar to that of *cocaine* toxicity. Therapeutic uses of *amphetamines* are presented in Chapter 15.

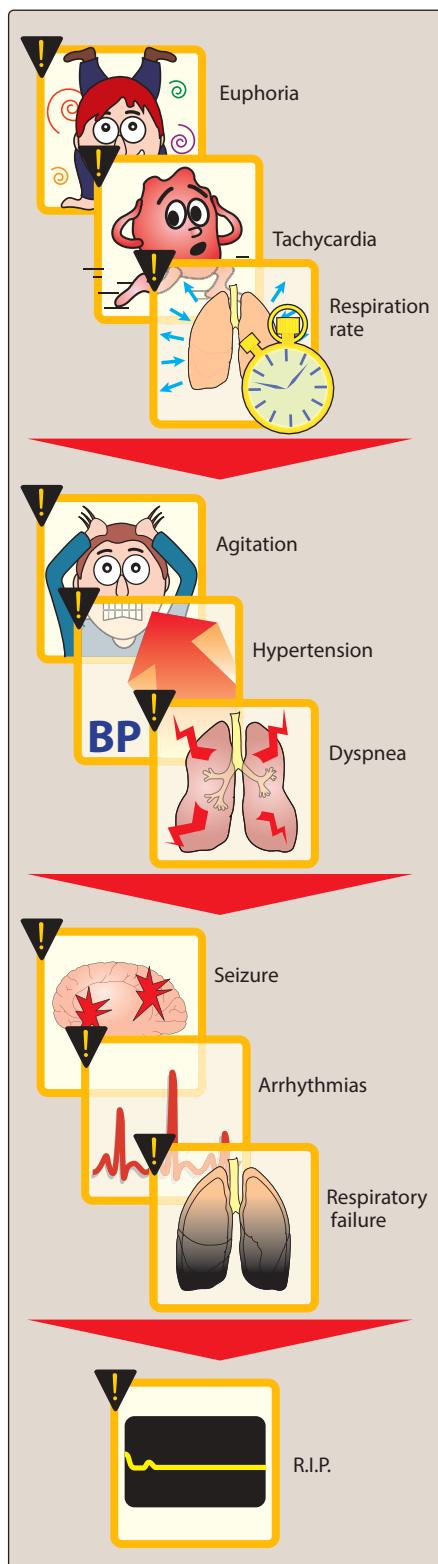
## C. Methyleneatedoxymethamphetamine

*Methyleneatedoxymethamphetamine (MDMA)*, commonly known as *ecstasy* or *molly*, is a hallucinogenic *amphetamine* with profound serotonin-releasing effects (Figure 48.6). However, like most illicit substances, MDMA is often substituted or adulterated with other drugs such as *methylone*. The chemical structure of *methylone* differs from *MDMA* by one carbonyl group (Figure 48.7), but the drug is more profitable to dealers and does not produce the same euphoric effect. Because of *MDMA*'s unique serotonin properties, it is sometimes referred to as an “empathogen,” and tactile stimulation is particularly pleasurable to users. Many users describe a sense of well-being and social interactivity, and sexual offenders have also taken advantage of this property of the drug. Like many *amphetamines*, *MDMA* can cause bruxism (teeth grinding) and trismus (jaw clenching), which explain the baby pacifiers and lollipops that have been popularized among “ravers.” Among the most disturbing properties of *MDMA* abuse is its propensity to cause profound hyperthermia, altered mental status, and serotonin syndrome. Benzodiazepines help to calm and cool the patient, and life-threatening hyperthermia has been treated with neuromuscular blockers and endotracheal intubation to control excessive movement and heat generation. *Cyproheptadine* is a serotonin antagonist that has been used to treat serotonin syndrome; however, one of its practical limitations is that it is only available in an oral formulation.

*Aminorex* is also called “ICE.” It is a cyclic derivative converted from phenylpropanolamine as a synthesis intermediate. Chemically, it is 2-amino-5-phenyl-2-oxazoline. It was originally developed as an anorexiant but withdrawn from the market due to its severe side effect of pulmonary hypertension. It exhibits effects on CNS similar to *amphetamine* and has moderate dependence potential. It is illicitly distributed in many countries.

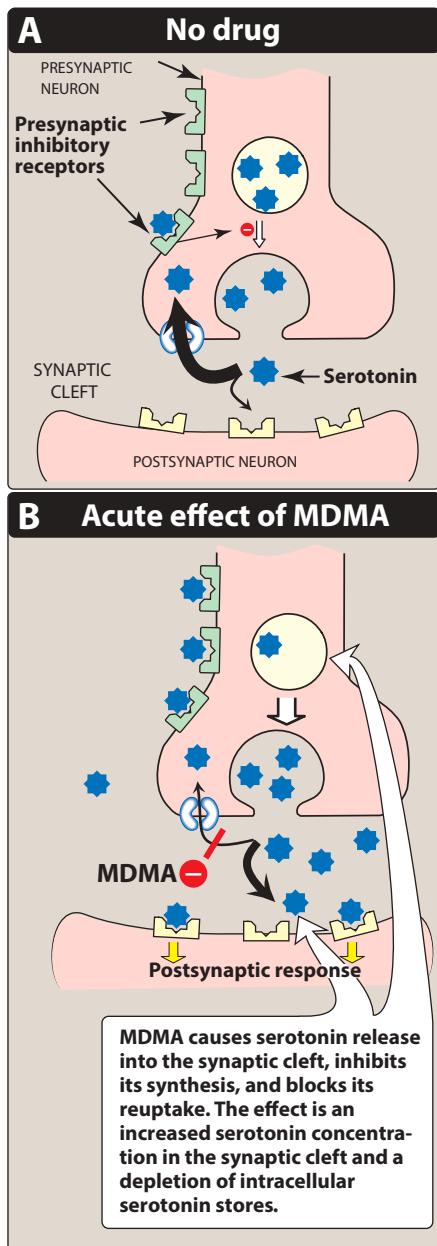
## D. Synthetic cathinones

Cathinone is the psychoactive component in the evergreen shrub *Khat* (*Catha edulis*) native to East Africa and the Arabian Peninsula. Synthetic cathinones, also known as “bath salts,” have become increasingly popular. These products are packaged and labeled as “bath salts” or “pond water cleaner” to circumvent detection, prosecution, and enforcement. Many of these packages read “not for human consumption,” although they are sold with an unstated understanding



**Figure 48.5**

Major effects of *cocaine* use.

**Figure 48.6**

Proposed mechanism of action of methylenedioxymethamphetamine (MDMA).

by the seller and buyer that they produce intoxication. Synthetic cathinones are not easily detected in urine toxicology screens.

*Methcathinone, butylone, methylene dioxypyrovalerone, and naphyrone* are just a few examples of synthetic cathinones. These drugs increase the release and inhibit the reuptake of catecholamines (norepinephrine, epinephrine, and dopamine) in a manner very similar to *cocaine* and *amphetamines*. A rapid onset of *amphetamine*-like stimulation with psychotomimetic effects of variable duration is common with synthetic cathinones. Bath salts are generally snorted or ingested, but they may also be injected. Treatment is similar to the emergent treatment of *amphetamines* and *cocaine*.

### III. HALLUCINOGENS

*Lysergic acid diethylamide (LSD)*, marijuana, and synthetic cannabinoids are substances that fall into this category.

#### A. Lysergic acid diethylamide

*LSD, lysergic acid diethylamide*, is perhaps the most commonly recognized drug in the hallucinogen class. *LSD* was first created from ergot in 1938 by Dr. Albert Hoffman. *LSD* produces its psychedelic effects through serving as a potent partial agonist at 5-HT<sub>2A</sub> receptors. Aside from the very colorful hallucinations, the drug is also responsible for mood alterations, sleep disturbances, and anxiety. Repeated use rapidly produces tolerance through down-regulation of serotonin receptors.

Although physical adverse effects are typically minimal, *LSD* may cause mydriasis, tachycardia, increased blood pressure and body temperature, dizziness, decreased appetite, and sweating. Perhaps, the most troubling side effects are the loss of judgment and impaired reasoning associated with use of *LSD*. This can sometimes be an exaggerated effect with extreme panic, which is known by individuals as a “bad trip,” and may lead to trauma. Recently, a group of synthetic serotonin agonists collectively known as “N-Bomb” have been substituted for *LSD*. Like *LSD*, these agents are used in liquid form or with blotter paper and have resulted in hypertension, convulsions, and accidental traumatic injury and death.

#### B. Marijuana

Cannabis is a plant that has been used by humans for over 10,000 years. *Centuries-old* Chinese documents describe the use of cannabis for clothing production, food, and as an agent to communicate with spirits. In India, cannabis consumption is known from the ancient literature and followed in spiritual practice even today. The leaves of *Cannabis indica* taken orally are called “Bhang,” the dried female inflorescence smoking is called “Ganja,” and the smoking of dried resinous extract from the leaves and flowering tops with tobacco is called “Charas.” Today, marijuana is the most frequently used illicit drug, and the illicit drug that new users are most likely to try (Figure 48.8). Those numbers are expected to grow as liberalization of marijuana laws continues throughout the United States but is banned in India. Although

cannabis is a substance of abuse, it exhibits lowest toxicity. Certain cannabis plants can be used for making rope or clothing; however, the species *Cannabis sativa* is the plant most often used for its psychoactive properties. The main psychoactive alkaloid contained in marijuana is  $\Delta^9$ -tetrahydrocannabinol [tet-ra-HY-dro-can-NAB-i-nol] (*THC*). Growing techniques have evolved over the past 50 years, and *THC* concentrations found in the plant have increased as much as 20-fold during that time period.

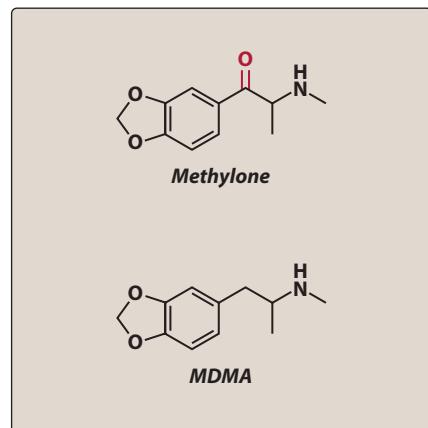
Specific receptors in the brain, cannabinoid or  $CB_1$  receptors, were discovered in the late 1980s and found to be reactive to *THC*. When  $CB_1$  receptors are activated by marijuana, effects include physical relaxation, hyperphagia (increased appetite), increased heart rate, decreased muscle coordination, conjunctivitis, and minor pain control (Figure 48.9). Depending on the social situation, *THC* can produce euphoria, followed by drowsiness and relaxation. Although hallucinations are typically not as robust as those observed with the use of *LSD*, marijuana is often used for the mild hallucinogenic effects that it produces. Marijuana stimulates the amygdala, causing the user to have a sense of novelty to anything the user encounters through an enhancement of sensory activity. For this same reason, heavy users have a down-regulation in their  $CB_1$  receptors, leaving them with a feeling of boredom when not taking the drug. The effects of marijuana on  $\gamma$ -aminobutyric acid (*GABA*) in the hippocampus diminish the capacity for short-term memory in users, and this effect seems to be more pronounced in adolescents. In addition to adversely affecting short-term memory and mental activity, *THC* decreases muscle strength and impairs highly skilled motor activity, such as that required to drive a car. The effects of *THC* appear immediately after smoking marijuana, but maximum effects take about 20 minutes. By 3 hours, the effects largely disappear.

In chronic marijuana users, tolerance develops rapidly, 9% of all users and 17% of adolescent users will develop dependence, and withdrawal has been observed. Marijuana may be found in the body up to 3 months after the last usage in heavy chronic users. For this reason, withdrawal occurs much later in individuals who previously used marijuana heavily. Withdrawal may include cravings, insomnia, depression, pain, and irritability.

Although not well studied for medicinal use, marijuana has been used as an adjuvant in the treatment of chemotherapy-induced nausea and vomiting, cachexia secondary to cancer and AIDS, epilepsy, chronic pain, multiple sclerosis, glaucoma, and anxiety. Synthetic *THC* medications are available as prescription products and include *dronabinol* [*droe-NAB-i-nol*] and *nabilone* [*NA-bi-lone*]. These medications are used for the prevention of CINV. Nabiximols, a medication created from the extract of the *Cannabis sativa* plant, is an oromucosal spray available in several countries throughout the world for the treatment of spasticity in multiple sclerosis.

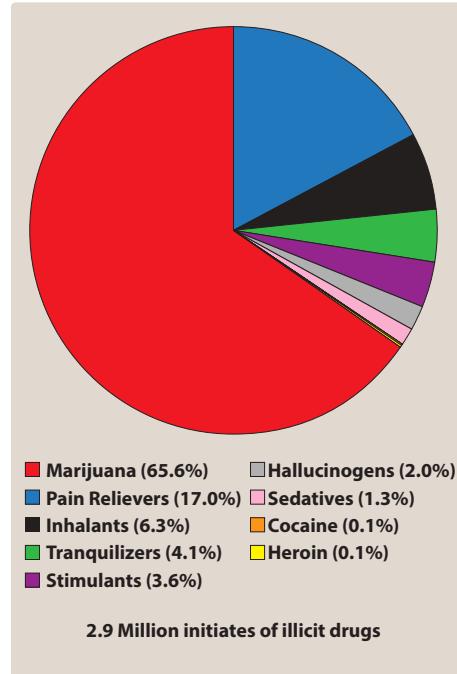
### C. Synthetic cannabinoids

Synthetic cannabinoids are sprayed onto plant material in a process known as dusting. These first-generation products such as "Spice" and "K2" are then smoked to produce intoxication. Since the molecular



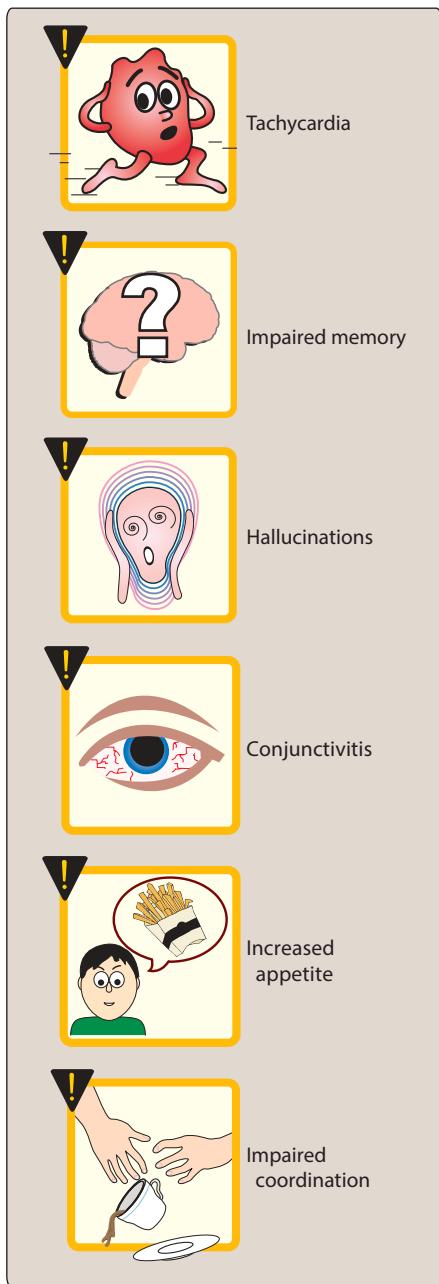
**Figure 48.7**

Comparison of the structures of methylenedioxymethamphetamine and methylone.



**Figure 48.8**

First specific drug associated with initiation of illicit drug use among past year illicit drug initiates aged 12 or older.

**Figure 48.9**

Effects of tetrahydrocannabinol.

structure of synthetic cannabinoids is much different from the cannabinoids found in marijuana plants, users do not test positive for *THC* with traditional drug tests. Sympathomimetic effects may also be seen in users, including tachycardia and hypertension. The greatest danger with the use of these agents includes extreme hallucinations and psychotic reactions. More recent formulations of synthetic cannabinoids and their contaminants have caused convulsions, acute kidney injury, and deaths.

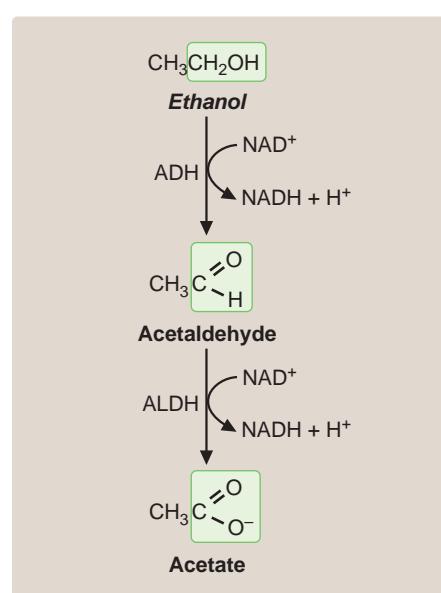
#### IV. ETHANOL

*Ethanol* (*EtOH*) is a clear, colorless hydroxylated hydrocarbon that is the product of fermentation of fruits, grains, or vegetables. *Ethanol* is mainly important in medicine but because of the consequences of abuse and misuse, it is a major cause of deadly automobile accidents, drownings, and fatal falls and is a related factor in many hospital admissions. Alcohol use is common since ancient times and is the most commonly abused substance in modern society, with the prevalence of alcohol use disorder being as high as 12.6% of the population in some regions of the world. Alcoholism decreases life expectancy by 10 to 15 years and impacts one in three families. It is thought that *ethanol* exerts its desired and toxic effects through several mechanisms, including enhanced effects of the inhibitory neurotransmitter GABA, increased release of endogenous opioids, and altered levels of serotonin and dopamine. *Ethanol* is a selective CNS depressant at low doses, resulting in decreased inhibitions and the characteristic loquaciousness or drunken behavior. At high doses, it is a general CNS depressant, which can result in coma and respiratory depression.

Drinking *ethanol* traditionally has been the most common route of administration, although recently the inhalation of aerosolized *ethanol* has gained popularity. *Ethanol* is highly lipid soluble and is absorbed rapidly from the stomach and duodenum, and food (especially milk, fat, and carbohydrates) slows and decreases absorption. Peak *ethanol* levels are generally achieved in 20 minutes to 1 hour of ingestion. The maximum concentration of alcohol in blood after oral consumption depends on many factors such as gender, total quantity, strength of the solution, and duration of consumption. Status of food in the stomach (empty or filled), type of food as well as speed of metabolism and clearance are also the deciding factors. There is a greater subjective feeling of intoxication while levels are ascending (absorption), as compared to when levels are descending. About 95% of *ethanol* is metabolized by alcohol dehydrogenase to acetaldehyde and then by aldehyde dehydrogenase to acetate in the liver (Figure 48.10), and the remainder is excreted in the breath, sweat, and urine. *Ethanol* metabolism by alcohol dehydrogenase follows first-order kinetics at low doses. However, once the blood concentration exceeds 15 to 40 mg/dL/hr, it follows dose-dependent (zero-order) kinetics as the enzymatic processes are saturated and the elimination rate no longer increases with rising concentration with potential major adverse consequences for the individual. Tolerance and toxicity develop in habitual users due to induction of the alcohol hepatic drug metabolizing enzyme. Increased formation of metabolites (acetaldehyde in the liver) results in toxicity leading to organ damage in chronic overconsumption and increased susceptibility to liver injury when heavy drinkers are exposed to drugs, anesthetics, and industrial

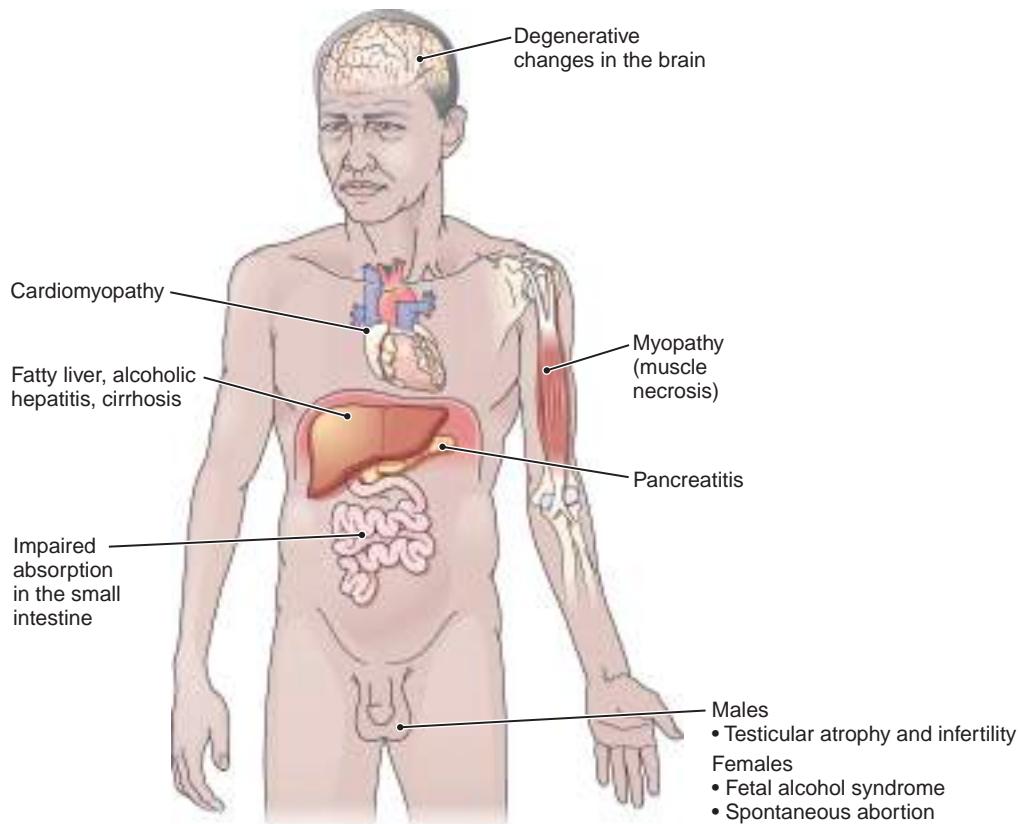
solvents. Binge drinking (an acute substantial dose of alcohol) inhibits hepatic drug metabolism. Marked interethnic variation is seen in the ability to metabolize alcohol. Asians, particularly Japanese, develop flushing, headache, and nausea after small amounts of alcohol as per Caucasian standards. Genetic deficiency of aldehyde dehydrogenase with slow metabolism of acetaldehyde (toxic metabolite) explains these features. Blood concentration of alcohol has medicolegal importance. Because there is a constant blood-to-breath ratio of 2100:1, a breath sample can be used to determine blood alcohol levels. Medical management of acute *ethanol* toxicity includes symptomatic supportive care and *thiamine* and folate administration. Patients with extremely high alcohol levels can be dialyzed, although that is rarely necessary, and could precipitate withdrawal in an alcoholic.

Chronic *ethanol* abuse can cause profound hepatic, cardiovascular, pulmonary, hematologic, endocrine, metabolic, and CNS damage (Figure 48.11). Alcohol dependence varies from social drinkers to individuals drinking at the end of a working day to a person who cannot resist the need and whose whole life is dominated by the quest for alcohol. Sudden cessation of *ethanol* ingestion in a heavy drinker who has developed physical dependence can precipitate withdrawal manifested by tachycardia, sweating, tremor, anxiety, and agitation in 6 hours and an acute psychotic attack (delirium tremens), hallucinations, and convulsions at 72 hours. Alcohol withdrawal is a life-threatening situation



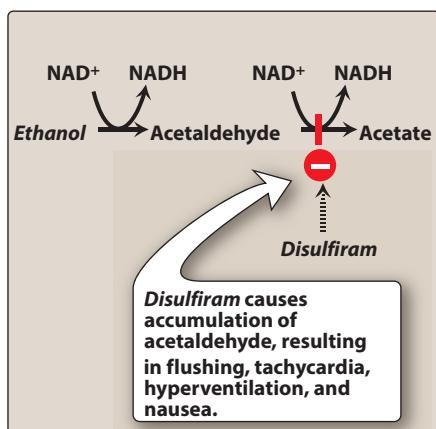
**Figure 48.10**

The pathway of ethanol metabolism.  
 $\text{ADH}$  = alcohol dehydrogenase;  
 $\text{ALDH}$  = acetaldehyde dehydrogenase.



**Figure 48.11**

The effects of chronic alcohol abuse.



**Figure 48.12**

The effect of disulfiram on the metabolism of ethanol.

that should be medically managed with symptomatic/supportive care, short-term benzodiazepines (chlordiazepoxide), and long-term addiction treatment. The drugs used in the treatment of alcohol dependence are given in the following text.

### A. Disulfiram

*Disulfiram* [dye-SUL-fi-ram] blocks the oxidation of acetaldehyde to acetic acid by inhibiting aldehyde dehydrogenase (Figure 48.12). This results in the accumulation of acetaldehyde in the blood and immediate unpleasantness due to flushing, tachycardia, hyperventilation, and nausea. *Disulfiram* has found some use in patients seriously desiring to stop alcohol ingestion. The objective is that patients will find the drinking experience so unpleasant that they will start avoiding alcohol. A conditioned avoidance response is induced so that the patient abstains from alcohol to prevent the unpleasant effects of *disulfiram*-induced acetaldehyde accumulation which occurs within 5 minutes of alcohol intake and consists of fall in blood pressure, sweating, dyspnea, chest pain, nausea, and vomiting. Severe reactions include convulsions and circulatory collapse which may last for several hours. That is why use of *disulfiram* is advocated under supervision in an inpatient setting usually after the fifth day. A *disulfiram*-like reaction occurs with other drugs as well such as *metronidazole*, *chlorpropamide*, *cefamandole*, *procarbazine*, and *griseofulvin*.

Alcohol can induce the metabolism of antiepileptic drugs, contributing to adverse effect on seizure control. Control with oral anticoagulants may be disturbed. Some alcoholic drinks containing tyramine can cause hypertensive crisis in a patient taking monoamine oxidase inhibitors (MAOIs).

Fetal alcohol syndrome (microcephaly, mental retardation, low birth weight babies, poor co-ordination, hypotonia, small eyeballs, and short palpebral fissures) has been reported in 10% of the children of women alcohol abusers. During lactation, even a small amount of alcohol can delay motor development in the child.

### B. Naltrexone

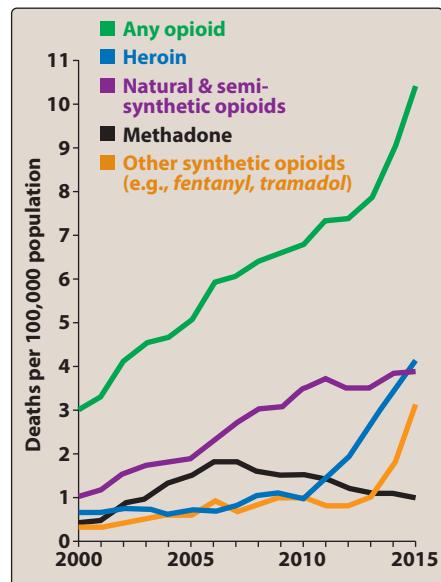
*Naltrexone* [nal-TREX-own] is a competitive and relatively long-acting opioid antagonist that helps decrease cravings for alcohol. It should be used in conjunction with supportive psychotherapy. *Naltrexone* is better tolerated than *disulfiram* and does not produce the aversive reaction that *disulfiram* does.

### C. Acamprosate

*Acamprosate* [a-kam-PROE-sate] is an agent used in alcohol dependence treatment programs and is thought to decrease cravings through its regulatory effects on NMDA-mediated glutamatergic excitation. This agent should also be used in conjunction with supportive psychotherapy. It may cause gastrointestinal adverse effects and cutaneous rashes.

## V. PRESCRIPTION DRUG ABUSE

This chapter has discussed many of the illicit substances that are abused by individuals. It is important to also mention that parts of the world, including the United States and portions of Europe, are currently experiencing an epidemic of prescription drug abuse. Some commonly abused prescription drugs include opioids and benzodiazepines. In the United States, between 1997 and 2007, there was a 600% increase in the prescribing of opioids, and by 2010, enough opioid prescription pain relievers were sold in the United States to medicate every American adult with 5 mg of hydrocodone every 4 hours for 1 month. An increased emphasis on treating pain as the “fifth vital sign,” coupled with an exaggerated belief in the beneficial capacity of these medications and a minimization of their inherent toxicity among the lay public and health professionals, were among the many possible explanations for the epidemic. Recent efforts have been made to decrease the misuse of prescription opioids, which has resulted in an increased use of heroin, often adulterated with *fentanyl* and extremely potent fentanyl derivatives such as *carfentanil*. Reversal of *fentanyl* and its derivatives is much more difficult than reversal of opioids such as *morphine*. This has contributed to a dramatic increase in death rates, with over 33,000 overdose deaths in the United States alone in 2015 (Figure 48.13). Medications for the treatment of opioid toxicity and dependence are reviewed in Chapter 14. In India, cough syrup abuse is prevalent among prescription drugs, especially codeine-containing cough syrups.



**Figure 48.13**

Overdose deaths involving opioids in the United States between 2000 and 2015. From the Centers for Disease Control and Prevention; National Center for Health Statistics. National Vital Statistics System, mortality. CDC WONDER. Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/>.

## Study Questions

### Choose the ONE best answer.

- 48.1 A 15-year-old asthmatic patient has been told that marijuana may help his anxiety. Which adverse effect has been associated with marijuana and may be a reason for this patient to avoid use of marijuana?
- Short-term memory loss
  - Hyperthermia
  - Hepatitis
  - Hyponatremia
- 48.2 A 21-year-old college student is curious about the effects of LSD. She asks what type of risks may be involved with using the drug for the first time. Which is a correct response to her question?
- Exaggerated hallucinations
  - Cardiomyopathy
  - Hyperphagia
  - Bronchitis

Correct answer = A. Short-term memory loss is observed with marijuana use and is more pronounced in adolescents. Hyperthermia, hepatitis, and hyponatremia have not been associated with marijuana use.

Correct answer = A. Exaggerated hallucinations, sometimes known as “bad trips,” may occur, even in first-time users. These hallucinations can lead to extreme panic, which has caused individuals to react in a manner very uncharacteristic of their typical behavior.

48.3 A 58-year-old man is brought into the emergency department following an automobile accident. His blood alcohol level on admission is 280 mg/dL. He has been treated in the past for seizures related to alcohol abuse, and he confirms that he has been drinking heavily over the past month since losing his job. What treatment should be given to this patient if he begins to go into withdrawal while hospitalized?

- A. Acamprosate
- B. Lorazepam
- C. Naltrexone
- D. Disulfiram

48.4 A 35-year-old man has been abusing cocaine and is agitated, tachycardic, hypertensive, and hyperthermic. Which statement is correct regarding treatment in this situation?

- A. This patient should undergo gastric lavage; that is, he should have his stomach pumped immediately.
- B. Atropine should be administered by IV route to reverse the CNS depression which can occur with cocaine toxicity.
- C. Benzodiazepines should be administered to calm the patient and decrease heart rate, blood pressure, and body temperature.
- D. Phenobarbital should be the first choice as an anticonvulsant.

48.5 A 22-year-old man with a history of substance abuse arrives in the emergency department hypertensive, hyperthermic, and tachycardic. He also presents with an altered mental status and hyperreflexia. Which substance is most likely causing these symptoms?

- A. LSD
- B. Bath salts
- C. Heroin
- D. Marijuana

48.6 THC is a psychoactive alkaloid found in:

- A. N-bomb
- B. K2
- C. LSD
- D. Marijuana

Correct answer = B. Should this patient go into alcohol withdrawal, he will likely also have seizures associated with it, given his past history. Benzodiazepines are used to treat seizures associated with alcohol withdrawal. Acamprosate, naltrexone, and disulfiram may be considered at a later time to treat the dependence, but would not be useful in the acute withdrawal setting.

Correct answer = C. Benzodiazepines such as lorazepam have anxiolytic properties and can calm a cocaine-toxic patient, thereby decreasing heart rate and blood pressure. As the patient becomes less agitated, he/she decreases movement and the body temperature drops. In addition, the use of benzodiazepines decreases the chance of the patient experiencing a convulsion and would be the first choice to treat cocaine-induced convulsions.

Correct answer = B. "Bath salts" often contain synthetic cathinones and are labeled, marketed, and sold as something "not for human consumption" to avoid law enforcement and prosecution. In addition, they are usually not detected on urine toxicology screening so often evaluation of symptoms are used to distinguish the substance taken. These products can cause an amphetamine-like sympathomimetic toxidrome, as well as serotonin syndrome, which would be treated with symptomatic/supportive care and possibly a serotonin antagonist (not a serotonin agonist) such as cyproheptadine. LSD and marijuana would produce mostly psychological symptoms such as hallucinations and paranoia and opioids would produce depressive symptoms such as respiratory depression, hyperthermia, and stupor.

Correct answer = D. THC is the main psychoactive alkaloid contained in marijuana. N-bomb is a synthetic hallucinogen derived from mescaline. K2, also known as Spice or synthetic cannabis, is dried plant material which has been sprayed with synthetic chemicals that cause psychoactive effects. K2 does not contain THC. LSD is also a psychoactive drug but contains lysergic acid diethylamide.

48.7 Which drug has clinical effects similar to those of cocaine?

- A. LSD
- B. Marijuana
- C. Methamphetamine
- D. Ethanol

Correct answer = C. Cocaine and methamphetamine have similar stimulant effects such as alertness, anxiety, tachycardia, hypertension, and hyperthermia. This can lead to arrhythmias, stroke, or myocardial infarction. LSD and marijuana cause primarily psychoactive effects such as hallucinations and paranoia, but have negligible to minimal stimulant effects. Ethanol is a depressant which often will produce the opposite effects of stimulants including relaxation, drowsiness, and in high doses hypothermia.

48.8 Which drug leads to the formation of a cardiotoxic metabolite when administered with cocaine?

- A. Lorazepam
- B. Marijuana
- C. Ethanol
- D. Khat

Correct answer = C. Cocaine combined with ethanol forms cocaethylene, which may lead to aggressive and impulsive behaviors as well as the potential for sudden myocardial infarction.

48.9 Which agent is often found as an adulterant in heroin and has led to an increase in overdose deaths?

- A. Spice
- B. Fentanyl
- C. Marijuana
- D. Cathinones

Correct answer = B. Fentanyl and its multitude of derivatives are often found in samples of heroin. Fentanyl derivatives are often many times more potent than heroin or fentanyl, which has led to an alarming number of overdoses in recent years.

48.10 Death secondary to MDMA use has occurred secondary to which adverse effect?

- A. Respiratory depression
- B. Acute kidney injury
- C. CNS depression
- D. Hyperthermia

Correct answer = D. MDMA, or Ecstasy, is a stimulant with similar properties to cocaine. The stimulant effects may include hyperthermia, hypertension, and tachycardia.



# APPENDIX

## DRUGS AND DOSAGES

Thirumurthy Velpandian

### I. ADRENERGIC ANTAGONIST

<b><math>\alpha</math>-BLOCKERS</b>	
<b>Nonselective:</b>	
<i>Phenoxybenzamine (irreversible)</i>	Oral: 20–60 mg/day IV: 1 mg/kg
<i>Phentolamine</i>	IV: 5 mg
<b><math>\alpha_1</math> Selective:</b>	
<i>Prazosin</i>	Oral: 0.5–4 mg (twice or thrice a day)
<i>Doxazosin</i>	Oral: 1–8 mg (once or twice a day)
<i>Terazosin</i>	Oral: 2–10 mg/day
<i>Alfuzosin</i>	Oral: 5–10 mg/day
<b><math>\alpha_1 A</math> Selective:</b>	
<i>Tamsulosin</i>	Oral: 0.4–0.8 mg/day
<b><math>\alpha_2</math> Selective:</b>	
<i>Yohimbine</i>	Oral: 2 mg
<b><math>\beta</math>-BLOCKERS</b>	
<b>Nonselective <math>\beta_1</math> and <math>\beta_2</math>:</b>	
<i>Propranolol</i>	Oral: 40–160 mg/day IV: 2–5 mg
<i>Carvedilol</i>	Oral: 6.25–50 mg/day
<i>Labetalol</i>	Oral: 100–600 mg/day IV: 20–40 mg
<i>Nadolol</i>	Oral: 40–320 mg/day
<i>Penbutolol</i>	Oral: 10–80 mg/day
<i>Pindolol</i>	Oral: 10–30 mg/day
<i>Sotalol</i>	Oral: 160–480 mg/day
<i>Timolol</i>	Topical: 0.25–0.5% (two times a day)
<i>Carteolol</i>	Topical: 1% (two times a day)
<b><math>\beta_1</math> Selective:</b>	
<i>Atenolol</i>	Oral: 25–100 mg/day
<i>Metoprolol</i>	Oral: 50–400 mg/day IV: 5–15 mg
<i>Betaxolol</i>	Topical: 0.5% (two times a day)
<i>Bisoprolol</i>	Oral: 2.5–10 mg/day
<i>Celiprolol</i>	Oral: 100–600 mg/day

<i>Esmolol (ultra short acting)</i>	IV: 0.05–0.5 mg/kg
<i>Nebivolol (vasodilatory)</i>	Oral: 2.5–5 mg/day
<i>Acebutolol (partial agonist)</i>	Oral: 400–1200 mg/day IV: 20–40 mg
<b><math>\beta_1</math> and <math>\beta_2</math> Selective:</b>	
<i>Labetalol</i>	Oral: 100–600 mg/day IV: 20–40 mg
<i>Carvedilol</i>	Oral: 6.25–50 mg/day

### II. OPIOID ANALGESICS: AGONISTS AND ANTAGONISTS

<b>Strong agonists:</b>	
<i>Alfentanil</i>	IV: 3–245 $\mu$ g/kg
<i>Fentanyl</i>	IV: 2–4 $\mu$ g/kg
<i>Heroin</i>	Restricted in India
<i>Morphine</i>	Adult: Oral: 10–50 mg IM: 10–15 mg Epidural/intrathecal: 2–3 mg Children: IM: 0.1–0.2 mg/kg
<i>Hydrocodone</i>	Oral: 20–80 mg/day
<i>Hydromorphone</i>	Oral: 8–32 mg IM/SC: 4–12 mg/day
<i>Levorphanol</i>	Oral: 6–12 mg/day
<i>Meperidine</i>	Oral: Adult = 300–1200 mg/day, children = 1.1–1.8 mg/kg
<i>Methadone</i>	Oral/IM: 2.5–40 mg/day
<i>Oxycodone</i>	Oral: 20–80 mg/day
<i>Oxymorphone</i>	Oral: 5–40 mg
<i>Remifentanil</i>	IV: 0.5–1 1–2 $\mu$ g/kg
<i>Sufentanil</i>	IV/ Epidural: 10–15 $\mu$ g (or) 1–2 $\mu$ g/kg
<b>Moderate/low agonist:</b>	
<i>Codeine</i>	Oral: 30–60 mg

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**Mixed agonist–antagonist and partial agonists:**

<i>Pentazocine</i>	Oral: 50–100 mg IM/SC: 30–60 mg
<i>Buprenorphine</i>	IM/IV/SC: 0.3–0.6 mg Sublingual: 0.2–0.4 mg
<i>Butorphanol</i>	IV/IM: 1–4 mg
<i>Nalbuphine</i>	IV/IM/SC: 40–160 mg/day
<b>Antagonists:</b>	
<i>Naloxone</i>	IV: Adults = 0.4–10 mg, pediatric = 10 µg/kg
<i>Naltrexone</i>	Oral: 50 mg/day
<b>Other analgesics:</b>	
<i>Tramadol</i>	Oral/IV/IM: Adults = 200–600 mg/day, pediatric = 1–2 mg/kg
<i>Tapentadol</i>	Oral: 100–600 mg/day

**III. CENTRAL NERVOUS SYSTEM (CNS) STIMULANTS****PSYCHOMOTOR STIMULANTS**

<b>Methylxanthines:</b>	
<i>Caffeine</i>	Oral: 1600 mg/day
<i>Theophylline</i>	Oral: 100–300 mg 8 hourly
<i>Nicotine</i>	Transdermal: 7–21 mg/day Oral: 6–96 mg/day
<i>Varenicline</i>	Oral: 0.5–1 mg/day
<i>Cocaine</i>	Topical: Maximum up to 3 mg/kg
<i>Amphetamine</i>	Oral: Adults = 5–60 mg/day, children = 2.5–40 mg/day
<i>Methamphetamine</i>	Oral: 20–25 mg/day 12 hourly
<i>Dextroamphetamine</i>	Oral: Adults = 5–60 mg/day, children = 2.5–40 mg/day
<i>Lisdexamfetamine</i>	Oral: 30–70 mg/day
<b>Methylphenidate or mixed amphetamine salts:</b>	
<i>Methylphenidate</i>	Oral: 18–72 mg/day
<i>Dexmethylphenidate</i>	Oral: 5–20 mg/day
<i>Modafinil</i>	Oral: 200–400 mg/day
<i>Armodafinil</i>	Oral: 150–250 mg/day
<b>Selective norepinephrine (noradrenaline) reuptake inhibitors:</b>	
<i>Atomoxetine</i>	Oral: 40–100 mg/day
<i>Hallucinogens</i>	
<i>Lysergic acid diethylamide (LSD)</i>	Restricted in India
<i>Tetrahydrocannabinol (Marijuana)</i>	Restricted in India

**IV. ANTIHYPERTENSIVE DRUGS****Angiotensin converting enzyme inhibitors:**

<i>Captopril</i>	Oral: 50–150 mg/day
<i>Enalapril</i>	Oral: 2.5–40 mg/day
<i>Ramipril</i>	Oral: 1.25–10 mg/day
<i>Lisinopril</i>	Oral: 5–40 mg/day
<i>Quinapril</i>	Oral: 10–40 mg/day
<i>Fosinopril</i>	Oral: 10–40 mg/day

**Angiotensin receptor blockers:**

<i>Losartan</i>	Oral: 50–100 mg/day
<i>Telmisartan</i>	Oral: 20–80 mg/day
<i>Valsartan</i>	Oral: 80–160 mg/day
<i>Candesartan</i>	Oral: 8–16 mg/day

**Angiotensin receptor-neprilysin inhibitor:**

<i>Sacubitril/Valsartan</i>	Oral: 80–160 mg/day
<i>Aldosterone antagonists:</i>	

<i>Spironolactone</i>	Oral: 50–150 mg/day
<i>Eplerenone</i>	Oral: 50–100 mg/day

**β-Adrenoreceptor blockers:**

<i>Bisoprolol</i>	Oral: 2.5–10 mg/day
<i>Carvedilol</i>	Oral: 6.25–50 mg/day
<i>Metoprolol succinate</i>	Oral: 25–200 mg/day
<i>Metoprolol tartrate</i>	Oral: 100–450 mg/day IV: 5–15 mg/day

**Diuretics:**

<i>Metolazone</i>	Oral: 5–20 mg/day
<i>Furosemide</i>	Oral: 20–80 mg/day
<i>Bumetanide</i>	Oral: 1–5 mg/day IV/IM: 2–4 mg/day
<i>Torsemide</i>	Oral: 2.5–20 mg/day

**Direct vaso- and venodilators:**

<i>Hydralazine</i>	Oral: 25–150 mg/day
<i>Isosorbide dinitrate</i>	Oral: 25–150 mg/day Sublingual: 10–40 mg/day
<i>FDC (Hydralazine + Isosorbide dinitrate)</i>	Oral: (30 mg + 56.25 mg) to (60 mg + 112.5 mg) per day

**HCN channel blocker:**

<i>Ivabradine</i>	5–15 mg/day
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**Inotropic agents:**

<i>Digoxin</i>	Oral: 0.125–0.5 mg/day IV/IM: 0.1–0.25 mg
<i>Dobutamine</i>	IV: 2.5–10 µg/kg
<i>Milrinone</i>	IV: 50 µg/kg

**B-Type natriuretic peptide:**

<i>Nesiritide</i>	IV: 2 µg/kg
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## V. ANTIANGINAL DRUGS

DRUG	ROUTE AND DOSAGE
<b>β-Blockers</b>	
<i>Propranolol</i>	Oral: 10–160 mg 6–12 hourly IV: 2–5 mg
<i>Atenolol</i>	Oral: 25–100 mg/day
<i>Bisoprolol</i>	Oral: 2.5–10 mg/day
<i>Metoprolol</i>	Oral: 50–600 mg/day IV: 5–15 mg
<b>Calcium channel blockers (dihydropyridines):</b>	
<i>Amlodipine</i>	Oral: 5–10 mg/day
<i>Nifedipine</i>	Oral: 5–20 mg 8–12 hourly
<i>Felodipine</i>	Oral: 5–10 mg/day
<b>Calcium channel blockers (nondihydropyridines):</b>	
<i>Diltiazem</i>	Oral: 30–60 mg 6–8 hourly
<i>Verapamil</i>	Oral: 40–160 mg 8 hourly IV: 5 mg
<b>Nitrates:</b>	
<i>Nitroglycerin</i>	Sublingual: 0.5 mg Oral: 5–15 mg Transdermal: 14–16 hr/day IV: 5–20 µg/min
<i>Isosorbide dinitrate</i>	Sublingual: 5–10 mg Oral: 10–20 mg Sustained release oral: 20–40 mg
<i>Isosorbide mononitrate</i>	Oral: 20 mg 12 hourly
<b>Sodium channel blocker:</b>	
<i>Ranolazine</i>	Sustained release oral: 0.5–1.0 g 12 hourly

## VI. DRUGS USED IN TREATING DYSFUNCTIONS OF HEMOSTASIS

<b>PLATELET INHIBITORS</b>	
<b>Thromboxane A<sub>2</sub> inhibitor:</b>	
<i>Aspirin (Oral)</i>	75–150 mg/day
<b>Vasodilator and thromboxane A<sub>2</sub> synthesis inhibitor:</b>	
<i>Dipyridamole (Oral)</i>	150–300 mg/day
<b>ADP receptor inhibitors:</b>	
<i>Clopidogrel (Oral)</i>	75 mg/day
<i>Ticlopidine (Oral)</i>	250 mg 12 hourly
<i>Prasugrel (Oral)</i>	5–10 mg/day
<i>Ticagrelor (Oral)</i>	60–90 mg 12 hourly with 75–100 mg Aspirin
<i>Cangrelor (IV)</i>	30 µg/kg bolus followed by 4 µg/kg over 2 hours

<b>Vasodilator and PDE III inhibitor:</b>	
<i>Cilostazol (Oral)</i>	100 mg 12 hourly
<b>GP IIb/IIIa inhibitors:</b>	
<i>Abciximab (IV)</i>	0.25 mg/kg followed by 10 µg/min over 12 hours
<i>Tirofiban (IV)</i>	0.4 µg/kg/min over 30 minutes, followed by 0.1 µg/kg/min over 48–108 hours
<i>Eptifibatide (IV)</i>	180 µg/kg/IV followed by 2 µg/kg/min over 72 hours
<b>ANTICOAGULANTS</b>	
<i>Heparin (IV, SC)</i>	IV: Adults = 5000–10,000 U bolus followed by 750–1000 U/hr, children = 50–100 U/kg SC: 5000 U 8–12 hourly
<b>Low molecular weight heparins:</b>	
<i>Enoxaparin (SC)</i>	20–40 mg/day
<i>Dalteparin (SC)</i>	100–200 U/kg 12–24 hourly
<b>Synthetic parenteral:</b>	
<i>Argatroban (IV)</i>	2–25 µg/kg/min
<i>Fondaparinux (SC)</i>	SC: 5–10 mg/day
<b>Hirudin analogs:</b>	
<i>Bivalirudin (IV)</i>	0.75 mg/kg bolus followed by 1.75 mg/kg/hr
<i>Desirudin (SC)</i>	SC: 15 mg 12 hourly
<i>Warfarin (Oral)</i>	2–10 mg/day
<i>Dabigatran (Oral)</i>	75–150 mg 12 hourly
<i>Apixaban (Oral)</i>	2.5–5 mg 12 hourly
<i>Betrixaban (Oral)</i>	80 mg/day for 35–42 days
<i>Edoxaban (Oral)</i>	30–60 mg/day
<i>Rivaroxaban (Oral)</i>	10–20 mg/day
<b>THROMBOLYTIC AGENTS (IV)</b>	
<i>Streptokinase</i>	IV: 2.5–15 lac IU over 30 minutes to 1 hour, 1 lac IU/hr for 24 hours
<i>Urokinase</i>	IV: 2.5 lac IU over 10 minutes followed by 5 lac IU over 1 hour or 6000 IU/min for 2 hours; 4400 IU/kg over 10 minutes followed by 4400 IU/kg/hr for 12 hours
<i>Alteplase (tPA)</i>	IV: 15 mg bolus followed by 35–50 mg over 30 minutes to 1 hour; 100 mg over 2 hours
<i>Reteplase</i>	IV: 10 mg over 10 minutes, every 30 minutes
<i>Tenecteplase</i>	IV: 0.5 mg/kg
<b>TREATMENT OF BLEEDING</b>	
<i>Protamine sulfate (IV)</i>	0.25–1.5 mg to neutralise 100 units of heparin
<i>Tranexamic acid (Oral, IV)</i>	Oral: 10–15 mg/kg 8–12 hourly or 1–1.5 g 8 hourly IV: 0.5–1 g 8 hourly
<i>Vitamin K1 (phytonadione)</i>	Oral IM: 5–10 mg

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<b>TREATMENT OF BLEEDING</b>	
<i>Idarucizumab (IV)</i>	5 g
<i>Aminocaproic acid (IV)</i>	IV: 1 g/hr for 8 hours Oral: 1–1.25 g/hr for 8 hours

## VII. DRUGS USED IN THE TREATMENT OF OSTEOPOROSIS AND OTHER BONE DISORDERS

<b>HORMONAL REGULATION OF CALCIUM AND PHOSPHATE HOMEOSTASIS</b>	
<i>Calcitonin</i>	IM/SC: 50–100 IU/day 16–32 IU/kg/day
<b>Parathyroid hormone derivative—Teriparatide</b>	SC: 20 µg/day
<b>Vitamin D–Hormone replacement therapy (HRT)</b>	Vit D <sub>3</sub> oral: 400–1000IU/day
<b>ANTIRESORPTIVE AGENTS</b>	
<b>Bisphosphonates:</b>	
<i>Abaloparatide</i>	SC: 80 µg/day
<i>Alendronate</i>	Oral: 5–40 mg/day
<i>Ibandronate</i>	Oral: 2.5 mg/day
<i>Risedronate</i>	Oral: 5 mg/day
<i>Zoledronic acid</i>	IV: 4 mg per week
<b>Monoclonal antibody:</b>	
<i>Denosumab</i>	SC: 120–360 mg every 4 weeks
<b>Drugs for disorders of bone remodeling:</b>	
<i>Etidronate</i>	Oral: 5–20 mg/kg/day
<i>Pamidronate</i>	IV: 30–90 mg/wk
<i>Tiludronate</i>	Oral: 400 mg/day
<b>Selective estrogen receptor modulator:</b>	
<i>Raloxifene</i>	Oral: 60 mg/day

## VIII. ANTIMICROBIAL AGENTS AFFECTING CELL WALL SYNTHESIS (PENICILLINS AND CONGENERS)

CLASSIFICATION/NAME	ROUTE	DOSAGE
<b>Natural penicillins:</b>		
<i>Aqueous penicillin G (benzylpenicillin)</i>	IM or IV	0.5–5 MU IM or IV 6–12 hourly Pediatric: 0.025–0.4 MU/kg/day (4–6 hourly doses)
<i>Penicillin G benzathine</i>	IM	0.6–2.5 MU IM 12–24 hourly

<b>Penicillin G procaine</b>	IM/IV	0.5–1 MU/day
<b>Pencillin V (phenoxyethyl penicillin)</b>	Oral	Oral: 250–500 mg every 6–8 hourly Pediatric: 25–50 mg/kg/day (6 hourly doses)
<b>β-Lactamase-resistant penicillins (antistaphylococcal penicillins; narrow spectrum):</b>		
<i>Methicillin</i>	IV/IM	Discontinued
<i>Cloxacillin</i>	Oral/IV/IM	0.25–0.5 g 6 hourly, IV/IM 0.25–1 g Pediatric: 25–50 mg/kg/day (6 hourly doses)
<i>Nafcillin</i>	IV	1–2 g every 4–6 hours Pediatric: 50–100 mg/kg/day (divided doses)
<i>Oxacillin</i>	IV	0.25–1 g every 4–6 hours Pediatric: 50–100 mg/kg/day (4–6 hourly doses)
<i>Dicloxacillin</i>	Oral	125–250 mg 6 hourly Pediatric: 12.5–25 mg/kg/day 6 hourly
<b>Extended spectrum penicillins (Aminopenicillins):</b>		
<i>Ampicillin</i>	Oral/IV/IM	0.25–2 g every 6 hours Pediatric: 50–150 mg/kg/day
<i>Amoxicillin</i>	Oral/IV/IM	0.25–0.5 g 8 hourly Pediatric: 25–40 mg/kg/day (8 hourly doses)
<i>Bacampicillin</i>	Oral	400–800 mg 12 hourly
<i>Cloxacillin</i>	Oral/IM/IV	250–500 mg 6 hourly 0.25–1 g 6 hourly
<b>Extended spectrum penicillins (antipseudomonals):</b>		
<b>CARBOXYOPENICILLINS</b>		
<i>Carbenicillin</i>	IV/IM	1–5 g IV/1–2 g IM 4–6 hourly
<i>Ticarcillin</i>	IV	3 g IV every 4 hours
<b>UREIDOPENICILLINS</b>		
<i>Azlocillin</i>		Discontinued
<i>Mezlocillin</i>		Discontinued
<i>Piperacillin</i>	IV/IM	IM/IV 100–150 mg/kg/day 8 hourly
<b>β-Lactamase inhibitors (<i>clavulanic acid</i>, <i>sulbactam</i>, <i>tazobactam</i>) and their combinations:</b>		
<i>Amoxicillin + clavulanic acid</i>	Oral/IV/IM	250 mg + 125 mg to 500 mg + 250 mg 8–12 hourly IV/IM 1 g + 0.2 g 6–8 hourly Paediatric: <12 weeks of age: 30 mg/kg/day every 12 hours from 125 mg/5 mL oral suspension 12 weeks and older: 25–45 mg/kg/day every 12 hours from 200 or 400 mg/5 mL oral suspension

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<b>Ampicillin + sulbactam</b>	IV/IM	1 g + 0.5 g–2 g + 1 g every 6–8 hours Pediatric: 1 year or older: 300 mg/kg every 6 hours (200 mg ampicillin + 100 mg sulbactam)
<b>Sultamicillin tosylate</b>	Oral	75–750 mg twice daily
<b>Piperacillin + tazobactam</b>	IV	4 g + 0.5 g 8 hourly by IV Pediatric: 2–9 months age: 80 mg piperacillin/10 mg tazobactam/kg, every 8 hours 9 months and older: 100 mg piperacillin/12.5 mg tazobactam/kg every 8 hours Weighing more than 40 kg, same as adult dose

## IX. ANTIMICROBIAL AGENTS AFFECTING CELL WALL SYNTHESIS (CEPHALOSPORINS AND CONGENERS)

CLASSIFICATION/NAME	ROUTE (IV/IM/ORAL)	DOSAGE
<b>First generation (broad spectrum of activity and low toxicity):</b>		
<b>Cefadroxil</b>	Oral	0.5–1 g/day 12 hourly Pediatric: 30 mg/kg/day 12 hourly
<b>Cefazolin</b>	IV/IM	0.5–1 g/day 8 hourly Pediatric: 25–100 mg/kg/day divided 6 hourly
<b>Cephalexin</b>	Oral	0.25–1 g/day 6 hourly Pediatric: 25–50 mg/kg/day 6 hourly
<b>Cephradine</b>	IV/oral	Discontinued
<b>Second generation (intermediate spectrum; extended gram-negative coverage; active against <i>Enterobacter</i>, <i>Proteus vulgaris</i>, <i>Klebsiella</i>, <i>Haemophilus influenzae</i>):</b>		
<b>Cefaclor</b>	Oral	0.25–1 g 8 hourly
<b>Cefotetan</b>	IV/IM	1–2 g 12 hourly
<b>Cefoxitin</b>	IV	1–2 g 6–8 hourly Pediatric: 75–150 mg/kg/day 6 hourly
<b>Cefprozil</b>	Oral	0.5 g/day 12–24 hourly Pediatric: 7.5–20 mg/kg 12 hourly
<b>Cefuroxime</b>	IM/IV/oral	0.75–1.5 g 8 hourly Pediatric: 50–100 mg/kg/day 6 hourly

**Third generation (extended spectrum of activities and extended gram-negative coverage; *Pseudomonas aeruginosa*; *Serratia*; *Neisseria gonorrhoeae*; activity for *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterobacteriaceae*):**

<b>Cefoperazone</b>	IV/IM	1–3 g IV/IM 12 hourly
<b>Cefotaxime</b>	IV/IM	1–2 g 6–12 hourly Pediatric: 50–100 mg/kg/day 12 hourly
<b>Ceftriaxone</b>	IV/IM	1–4 g/day IV/IM 24 hourly Pediatric: 50–100 mg/kg 12–24 hourly
<b>Ceftazidime</b>	IV/IM	0.5–2 g 8–12 hourly Pediatric: 75–150 mg/kg/day 8 hourly
<b>Cefdinir</b>	Oral	300 mg 12 hourly Pediatric: 7–14 mg/kg 12–24 hourly
<b>Cefixime</b>	Oral	200–400 mg/day 12 hourly Pediatric: 4–8 mg/kg/day 12–24 hourly
<b>Cefpodoxime proxetil</b>	Oral	200 mg 12 hourly Pediatric: 5 mg/kg 12 hourly
<b>Ceftibuten</b>	Oral	200–400 mg 12–24 hourly

**Fourth generation (extended gram-negative coverage; increased activity against *Streptococci* and MRSA):**

<b>Cefepime</b>	IV/IM	0.5–2 g 8–12 hourly Pediatric: 75–120 mg/kg, 8 hourly
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**Fifth generation (extended spectrum against MRSA):**

<b>Ceftaroline</b>	IV	0.6 g 12 hourly as slow IV infusion (1 hr) Pediatric: 8–12 mg/kg 8 hourly slow IV infusion (1 hr)
<b>Ceftabiprole</b>	IV	0.5 g 8 hourly as IV as slow infusion over 2 hours

**Carbapenems:**

<b>Doripenem</b>	IV	0.5 g (slow IV infusion over 1 hr) 8 hourly
<b>FaropenemM</b>	Oral	150–300 mg 8 hourly
<b>Imipenem/cilastatin</b>	IV	0.5 g 6–8 hourly (max 4 g/day) Pediatric: 15–25 mg/kg 6 hourly
<b>Meropenem</b>	IV	0.5–2 g 8 hourly Pediatric: 60–120 mg/kg 8 hourly

**Monobactam:**

<b>Aztreonam</b>	IM/IV	0.5–2 g 6–12 hourly Pediatric: 30 mg/kg 6–8 hourly
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## X. CELL WALL INHIBITORS

DRUG	ROUTE AND DOSAGE
<i>Vancomycin</i>	Oral: 125–500 mg IV: 0.5–1 g
<i>Daptomycin</i>	IV: 4–6 mg/kg
<i>Telavancin</i>	IV: 10 mg/kg/day

## XI. PROTEIN SYNTHESIS INHIBITORS

DRUG	ROUTE AND DOSAGE
<b>First generation (biosynthesis; broad-spectrum antibiotic):</b>	
<i>Tetracycline</i>	Oral 250–500 mg 6–8 hourly
<i>Oxytetracycline</i>	Oral 250–500 mg 6–8 hourly IV 500 mg 6–12 hourly
<i>Telithromycin</i>	Oral: 800 mg once a day
<i>Chlortetracycline</i>	Oral: Adult = 250–500 mg 4–12 hourly Pediatric = 25–50 mg/kg/day
<i>Demeclocycline</i>	Oral: Adult = 300–600 mg/day, twice a day Pediatric = 7–13 mg/kg
<b>Second generation (semisynthetic):</b>	
<i>Doxycycline</i>	200 mg/day initial dose followed by 100–200 mg/day once a day
<i>Minocycline</i>	IV Adult = 200 mg/day as initial dose and 100 mg every 12 hours Children = 4 mg/kg as initial dose and 2 mg/kg every 12 hours Oral: 100 mg once or twice a day
<i>Methacycline</i>	Oral 300–600 mg 12 hourly
<i>Lymecycline</i>	Oral 300–600 mg 12 hourly
<b>Third generation (synthetic; glycylcyclines):</b>	
<i>Tigecycline</i>	100 mg as loading dose, followed by 50 mg in 12 hours in IV for 5–14 days
<b>Aminoglycosides:</b>	
<i>Gentamicin</i>	3–5 mg/kg IM/IV in single dose 0.1–0.3% in topical (eye or skin)
<i>Amikacin</i>	0.75–1.0 g (15 mg/kg/day) IM
<i>Neomycin</i>	0.25–1 g/day orally four times a day, 0.3–0.5% topical
<i>Streptomycin</i>	1000 mg (15 mg/kg) daily or thrice weekly by IM for 30–60 days
<i>Tobramycin</i>	3–5 mg/kg/day IM in 1–3 doses 0.3% eye drops
<b>Macrolides/ketolides:</b>	
<i>Erythromycin</i>	Oral: Adult = 250–500 mg per 6 hours, maximum 4 g/day orally Children = 30–60 mg/kg/day

<i>Roxithromycin</i>	Oral: Adult = 150–300 mg twice a day, 30 minutes before meals Children = 2.5–5 mg/kg twice a day
<i>Azithromycin</i>	Oral: Adult: 500 mg/day 1 hour before or 2 hours after food Children: 10 mg/kg 500 mg for IM
<i>Clarithromycin</i>	Oral: 250–500 mg/day twice a day up to 14 days
<i>Telithromycin</i>	Oral: 800 mg once a day
<b>Macrocyclic:</b>	
<i>Fidaxomicin</i>	Oral 200 mg every 12 hours for 10 days; may take with or without food
<b>Lincosamides:</b>	
<i>Clindamycin</i>	Oral: Adult = 150–300 mg/day four times a day Children = 3 mg/kg four times a day IV 200–600 mg 8 hourly 1% topical application
<b>Oxazolidinones:</b>	
<i>Linezolid</i>	600 mg 12 hourly oral/IV
<i>Tedizolid</i>	Oral: 200 mg 24 hourly
<b>Others:</b>	
<i>Chloramphenicol</i>	Oral: Adult = 250–500 mg 6 hourly Children = 25–50 mg/kg/day 0.5–1% in topically in eye 5–10% topically in ear 1% as skin application
<i>Quinupristin/dalfopristin</i>	7.5 mg/kg every 8–12 hours IV

## XII. FLUOROQUINOLONES

DRUGS	ROUTE AND DOSAGE
<b>First generation (active against gram-negative organisms but not <i>Pseudomonas</i> species):</b>	
<i>Nalidixic acid</i>	Oral: Adult = 1 g 6 hourly, maximum dose of 4 g/day Children = 33–55 mg/kg 6 hourly
<b>Second generation (gram-negative organisms [including <i>Pseudomonas</i> species] plus some gram-positive organisms [<i>Staphylococcus aureus</i> but not <i>Streptococcus pneumoniae</i>] and some atypical pathogens):</b>	
<i>Ciprofloxacin</i>	Oral: 250–750 mg 12 hourly 100–200 mg IV

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<b>Norfloxacin</b>	Oral: 200–400 mg 12 hourly 0.3% topical eye drops
<b>Ofloxacin</b>	Oral: 200–400 mg 12 hourly 200 mg IV 0.3% topical eye drops
<b>Levofloxacin</b>	Oral: 500 mg once a day 500 mg IV
<b>Third generation (as above plus expanded gram-positive coverage [penicillin-sensitive and penicillin-resistant <i>S. pneumoniae</i>] and expanded activity against atypical pathogens):</b>	
<b>Gatifloxacin</b>	0.3–0.5% topical eye drops
<b>Fourth generation (same as for third-generation agents plus broad anaerobic coverage):</b>	
<b>Moxifloxacin</b>	Oral: 400 mg once a day 400 mg IV 0.5% topical eye drops
<b>Gemifloxacin</b>	Oral: 320 mg/day
<b>Inhibitors of folate synthesis:</b>	
<b>Mafenide</b>	1% topical cream
<b>Silver sulfadiazine</b>	1% topical cream
<b>Sulfadiazine</b>	Oral: 0.5–2 g 8 hourly
<b>Sulfasalazine</b>	Oral: Adult = 1–4 g/day Children = 40–60 mg/kg/day
<b>Inhibitors of folate reduction:</b>	
<b>Pyrimethamine</b>	Available as combination with <i>sulfadoxine</i> , <i>sulfapyrazine</i> , and <i>dapsone</i> Oral: Adult = 75 mg/day Children = 25–50 mg/day
<b>Trimethoprim</b>	Combination available with <i>sulfamethoxazole</i> <b>Adult:</b> Oral = 80–160 mg 12 hourly IM = 160 mg 12 hourly IV = 80 mg 12 hourly <b>Children:</b> Oral = 20–40 mg 12 hourly
<b>Combination of inhibitors of folate synthesis and reduction:</b>	
<b>Cotrimoxazole (trimethoprim + sulfamethoxazole)</b>	<b>Adult:</b> Oral: (80 mg + 400 mg) to (160 mg + 800 mg) 12 hourly IM = (160 mg + 800 mg) 12 hourly IV = (80 mg + 400 mg) 12 hourly <b>Children:</b> Oral = (20 mg + 100 mg) to (40 mg + 200 mg) 12 hourly
<b>Urinary tract antiseptics:</b>	
<b>Methenamine</b>	Oral: 3–4 g/day
<b>Nitrofurantoin</b>	Oral: 150–400 mg /day

### XIII. ANTIFUNGAL AGENTS

DRUG	ROUTE	DOSAGE
<b>Polyene:</b>		
<i>Amphotericin B</i> and <i>liposome amphotericin B</i>	IV, oral, topical, intrathecal	IV = 0.3–0.7 mg/kg daily by slow infusion over 4–8 hours (total dose 3–4 g) IV liposome amphotericin B = 3–5 mg/kg/day infused over 2 hours Intrathecal = 0.5 mg Topical = 3% ear drops
<b>Azoles:</b>		
<b>Fluconazole</b>	Oral, IV, topical	Oral = 150 mg weekly (for tinea infection and cutaneous and vaginal candidiasis) For systemic mycosis = 200–400 mg daily oral/IV Topical = 0.3% in eye for fungal keratitis
<b>Ketoconazole</b>	Oral, topical	Oral = 200 mg OD-BD Tropical = 2%
<b>Isavuconazole</b>	Oral, IV	Oral = 200 mg every 8 hours for 2 days followed by 200 mg once daily IV = 200 mg every 8 hours for 2 days followed by 200 mg once daily
<b>Itraconazole</b>	Oral	200 mg OD-BD (for systemic mycosis) 200 mg OD (for vaginal candidiasis and dermatophytosis)
<b>Posaconazole</b>	Oral	200 mg QID or 400 mg BD with meal
<b>Voriconazole</b>	Oral/IV	Oral = 200 mg BD (1 hour and 1 hour after meal) IV = Initially 6 mg/kg 12 hourly 2 doses, then 3–4 mg/kg 12 hourly (drug is to be reconstituted and diluted, and infused at not more than 3 mg/kg/hr)
<b>Pyrimidine analog:</b>		
<b>Flucytosine</b>	Oral	Oral = 50–150 mg/kg/ day in divided doses at 6-hour intervals
<b>Echinocandin derivatives:</b>		
<b>Caspofungin</b>	IV	IV = 70 mg over 1 hour (loading dose), followed by 50 mg IV daily
<b>Micafungin</b>	IV	IV = 150 mg/day
<b>Anidulafungin</b>	IV	IV = 100–200 mg loading dose on Day 1, followed by 50–100 mg daily
<b>Drug for cutaneous mycoses:</b>		
<b>Griseofulvin</b>	Oral	120–250 mg 2–4 times daily (taken with meals)

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DRUG	ROUTE	DOSAGE
<b>Topical azole derivatives:</b>		
<i>Miconazole</i>	Topical	2% topical application 2 to 3 times daily, 100 mg intravaginal nightly
<i>Clotrimazole</i>	Topical	1% topical application twice daily, 100 mg intravaginal at bed time
<i>Econazole</i>	Topical	1% topical application 2 to 3 times daily, 150 mg intravaginal nightly
<i>Sertaconazole</i>	Topical	2% cream 2 times a day for 4 weeks
<i>Sulconazole</i>	Topical	1% cream or solution
<i>Butoconazole</i>	Topical	2% cream
<i>Efinaconazole</i>	Topical	10% topical solution
<i>Oxiconazole</i>	Topical	1% topical
<i>Terconazole</i>	Topical	0.4% and 0.8% intravaginal cream and vaginal suppositories
<i>Tioconazole</i>	Topical	6.5% vaginal cream
<b>Topical allylamine derivatives:</b>		
<i>Terbinafine</i>	Oral/ topical	Oral = 250 mg OD oral Topical = 1% topical application
<i>Butenafine</i>	Topical	1% topical
<i>Naftifine</i>	Topical	1% or 2% cream or gel
<b>Miscellaneous:</b>		
<i>Natamycin (Pimircin)</i>	Topical	5% ophthalmic suspension
<i>Hamycin</i>	Topical	2–5 lac U/g for topical, 4 lac U vaginal application
<i>Ciclopirox olamine</i>	Topical	1% topical and vaginal application
<i>Tolnaftate</i>	Topical	1% topical application
<i>Nystatin</i>	Oral/ topical	Oral = 5 lac U 8 hourly Topical = 1 lac U nightly for vaginal insertion, 10,000 U/ml for buccal application, 1 lac U/g for application over skin and eye
<i>Tavaborole</i>	Topical	5% toenail solution
<i>Undecylenic acid</i>	Topical	5–10% topical application
<i>Benzoic acid</i>	Topical	5% topical
<i>Quiniodochlor</i>	Topical	3–10% topical
<i>Sodium thiosulfate</i>	Topical	20% topical

## XIV. ANTIVIRAL DRUGS

DRUG	ROUTE AND DOSAGE
<b>For respiratory virus infections:</b>	
<i>Amantadine</i>	Oral: Adults = 200 mg/day, elderly = 100 mg/day, children = 5 mg/kg/day
<i>Oseltamivir</i>	Oral: 75–150 mg/day for 5 days
<i>Ribavirin</i>	Oral: Adults = 800 mg/day, children = 10mg/kg/day
<i>Rimantadine</i>	Oral: Adults = 200 mg/day, elderly = 100 mg/day, children = 5 mg/kg/day
<i>Zanamivir</i>	Intranasal: 10–20 mg/day
<b>For hepatic viral infections—Hepatitis B:</b>	
<i>Adefovir</i>	Oral: 10 mg/day
<i>Entecavir</i>	Oral: 0.5–1 mg/day
<i>Lamivudine</i>	Oral: 100 mg/day
<i>Peginterferon α-2a</i>	SC: 0.18 mg/week
<i>Tenofovir alafenamide (TAF)</i>	Oral: 25 mg/day
<i>Tenofovir disoproxil fumarate (TDF)</i>	Oral: Adults = 300 mg/day, children = 150–300 mg/kg/day
<b>For hepatic viral infections—Hepatitis C:</b>	
<i>Daclatasvir</i>	Oral: 60 mg/day for 12 weeks
<i>Elbasvir/grazoprevir</i>	Oral: 50 mg/day elbasvir and 100 mg/day grazoprevir for 12–16 weeks
<i>Glecaprevir/pibrentasvir</i>	Oral: 300 mg/day glecaprevir and 120 mg/day pibrentasvir for 8–16 weeks
<i>Ledipasvir/sofosbuvir</i>	Oral: 90 mg/day ledipasvir and 400 mg/day sofosbuvir for 12–24 weeks
<i>Paritaprevir/ritonavir/ombitasvir</i>	Oral: 25 mg/day ombitasvir, 75 mg/day paritaprevir, and 50 mg/day ritonavir for 12 weeks
<i>Paritaprevir/ritonavir/ombitasvir + dasabuvir</i>	Oral: 25 mg/day ombitasvir, 75 mg/day paritaprevir, 50 mg/day ritonavir, and 500 mg/day dasabuvir for 12–24 weeks
<i>Ribavirin</i>	Oral: Adults = 200 mg 6 hourly, children = 10 mg/kg/day
<i>Simeprevir</i>	Oral: 150 mg/day
<i>Sofosbuvir</i>	Oral: 400 mg/day
<i>Sofosbuvir/velpatasvir</i>	Oral: 400 mg/day sofosbuvir and 100 mg/day velpatasvir for 12 weeks
<i>Sofosbuvir/velpatasvir/voxilaprevir</i>	Oral: 400 mg/day sofosbuvir, 100 mg/day velpatasvir, and 100 mg/day voxilaprevir for 12 weeks
<b>For herpesvirus and cytomegalovirus infections:</b>	
<i>Acyclovir</i>	Oral: 200 mg x 5/day (15 mg/kg/day) IV: 5–10 mg/kg 8 hourly Topical: 5% ointment 6 times/day

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<i>Valacyclovir</i>	Oral: 0.5–2 g/day or 12 hourly
<i>Valganciclovir</i>	Oral: 900 mg/day
<i>Ganciclovir</i>	Oral: 5–10 mg/kg/day
<i>Penciclovir</i>	Topical: 1% cream 2 hourly for 4 days
<i>Cidofovir</i>	IV: 3–5 mg/kg/week for 2 weeks
<i>Famciclovir</i>	Oral: 250–500 mg 8 hourly for 5–10 days
<i>Foscarnet</i>	IV: 40–90 mg/kg 8–12 hourly for 2–3 weeks
<i>Trifluridine</i>	Oral: 35 mg/m <sup>2</sup> 12 hourly

## XV. ANTI-HIV DRUGS

Nucleoside and nucleotide reverse transcriptase inhibitors:	
<i>Zidovudine (AZT, ZDV)</i>	Oral: Adults = 300 mg 12 hourly, children = 180 mg/m <sup>2</sup> 12 hourly
<i>Abacavir (ABC)</i>	Oral: 300 mg 12 hourly
<i>Didanosine (DDI)</i>	Oral: 250–400 mg/day
<i>Stavudine (d4T)</i>	Oral: 30 mg 12 hourly
<i>Emtricitabine (FTC)</i>	Oral: Adults = 200–240 mg/day, children = 3–6 mg/kg/day
<i>Lamivudine (3TC)</i>	Oral: 150 mg 12 hourly
<i>Tenofovir (TAF and TDF)</i>	Oral: 300 mg/day
<i>Zalcitabine (ddC)</i>	Oral: 0.75 mg 8 hourly
Non-nucleoside reverse transcriptase inhibitors:	
<i>Efaviranz (EFV)</i>	Oral: Adults = 600 mg/day, children = 200–600 mg based on body weight
<i>Nevirapine (NVP)</i>	Oral: 200 mg/day to 200 mg 12 hourly after 2 weeks
<i>Delavirdine (DLV)</i>	Oral: 400 mg 8 hourly
Protease inhibitors:	
<i>Atazanavir (ATV)</i>	Oral: 300 mg/day with 100 mg Ritonavir
<i>Fosamprenavir (FPV)</i>	Oral: 700–1400 mg 12 hourly with 100–200 mg Ritonavir
<i>Ritonavir (RTV)</i>	Oral: 600 mg 12 hourly
<i>Lopinavir (LPV)</i>	Oral: 400 mg 12 hourly with 100 mg Ritonavir
<i>Sequnavir (SQV)</i>	Oral: 1000–1200 mg 8–12 hourly with 100 mg Ritonavir
<i>Tipranavir (TPV)</i>	Oral: 500 mg 12 hourly with 200 mg Ritonavir
Integrase strand transfer inhibitor:	
<i>Raltegravir (RAL)</i>	Oral: Adults = 400 mg 12 hourly, 800 mg 12 hourly with <i>Rifampin</i> , children = 300–400 mg 12 hourly based on body weight
Fusion and entry inhibitor	
<i>Enfluvirtide (T 20)</i>	SC: Adults = 90 mg 12 hourly, children = 2 mg/kg–90 mg 12 hourly
<i>Maraviroc (MVC)</i>	Oral: 150–600 mg 12 hourly

## XVI. ANTICANCER DRUGS

DRUG	ROUTE AND DOSAGE
<i>Methotrexate</i>	Oral: 15–30 mg/day for 5 days IM/IV: 20–40 mg/m <sup>2</sup> (BSA) twice weekly or 2.5–15 mg/day
<i>6-Mercaptopurine</i>	Oral: 1.25–2.5 mg/kg/day
<i>Fludarabine</i>	IV: 25 mg/m <sup>2</sup> BSA for 5 days every 28 days
<i>Cladribine</i>	IV: 0.09 mg/kg/day for 7 days
<i>Fluorouracil (5-FU)</i>	IV: 500 mg/m <sup>2</sup> (or) 6–12 mg/kg/day
<i>Capecitabine</i>	Oral: 1250 mg/m <sup>2</sup> twice a day for 2 weeks
<i>Cytarabine</i>	IV/IT: 100 mg/m <sup>2</sup> once or twice a day (or) 1–3 g/day
<i>Azacitidine</i>	IV/SC: 75–100 mg/m <sup>2</sup> /day
<i>Gemcitabine</i>	IV: 1000 mg/m <sup>2</sup> /week

## XVII. ANTITUMOR ANTIBIOTICS

DRUG	ROUTE AND DOSAGE
<i>Doxorubicin</i>	IV: 60–75 mg/m <sup>2</sup> every 3 weeks
<i>Daunorubicin</i>	IV: 30–50 mg/m <sup>2</sup> /day
<i>liposomal doxorubicin</i>	IV: 20–50 mg/m <sup>2</sup>
<i>Epirubicin</i>	IV: 60–90 mg/m <sup>2</sup>
<i>Idarubicin</i>	IV: 12 mg/m <sup>2</sup> /day
<i>Bleomycin</i>	IV/IM: 60 mg/wk (or) 300–400 mg

## XVIII. ALKYLATING AGENTS

DRUG	ROUTE AND DOSAGE
<i>Cyclophosphamide</i>	Oral: 2–3 mg/kg/day IV: 10–15 mg/kg
<i>Ifosfamide</i>	IV: 10–15 mg/kg
<i>Carmustine</i>	IV: 150–200 mg/m <sup>2</sup> every 6 weeks
<i>Lomustine</i>	Oral: 100–130 mg/m <sup>2</sup> every 6 weeks
<i>Dacarbazine</i>	IV: 3.5 mg/kg/day
<i>Temozolamide</i>	Oral/IV: 75–150 mg/m <sup>2</sup> /day
<i>Melphalan</i>	Oral/IV: 10 mg/day and 2–4 mg/day as maintenance dose
<i>Chlorambucil</i>	Oral: 4–10 mg/day and 2 mg/day as maintenance dose
<i>Busulfan</i>	Oral: 2–6 mg/day

## XIX. MICROTUBULE INHIBITORS

DRUG	ROUTE AND DOSAGE
Vincristine	IV: 1.5–2 mg/m <sup>2</sup> /wk
Vinblastine	IV: 0.1–0.15 mg/kg
Vinorelbine	IV: 25–30 mg/m <sup>2</sup> /wk
Paclitaxel	IV: 135–175 mg/m <sup>2</sup> (every 3 weeks)
Docetaxel	IV: 75–100 mg/m <sup>2</sup> (every 3 weeks)

## XX. STEROID HORMONES AND THEIR ANTAGONISTS

DRUG	ROUTE AND DOSAGE
Tamoxifen	Oral: 20–40 mg/day
Ietrozole	Oral: 2.5 mg/day
Anastrozole	Oral: 1 mg/day
Leuproreotide	Depot/IM/SC: 1–3.75 mg
Goserelin	SC: 10.8 mg every 12 weeks
Triptorelin	IM: 3.75–7.5 mg every 4 weeks
Flutamide	Oral: 750 mg/day
Nilutamide	Oral: 150–300 mg/day
Bicalutamide	Oral: 50 mg/day

## XXI. PLATINUM COORDINATION COMPLEXES

DRUG	ROUTE AND DOSAGE
Cisplatin	IV: 50–100 mg/m <sup>2</sup>
Carboplatin	IV: 400 mg/m <sup>2</sup>
Oxaliplatin	IV: 75–85 mg/m <sup>2</sup>

## XXII. TOPOISOMERASE INHIBITORS

DRUG	ROUTE AND DOSAGE
Irinotecan	IV: 125 mg/m <sup>2</sup> /wk
Topotecan	IV: 1.5 mg/m <sup>2</sup> /day
Etoposide	Oral: 100–200 mg <sup>2</sup> /day IV: 50–100 mg/m <sup>2</sup> /day

## XXIII. MONOCLONAL ANTIBODIES

DRUG	ROUTE AND DOSAGE
Bevacizumab	IV: 05–15 mg/kg (every 2–3 weeks)
Cetuximab	IV: 250–400 mg/m <sup>2</sup>
Daratumumab	IV: 16 mg/kg
Ramucirumab	IV: 8 mg/kg (every 2 weeks)

<i>Rituximab</i>	IV: 250–500 mg/m <sup>2</sup>
<i>Trastuzumab</i>	IN: 2–8 mg/kg

## XXIV. ANTIPROTOZOAL AGENTS

DRUG	ROUTE AND DOSAGE
<b>Amebiasis:</b>	
<i>Metronidazole</i>	Oral: Adults = 400–800 mg 8 hourly for 5–10 days, children = 30–50 mg/kg/day IV: 15 mg/kg/hr, 7.5 mg/kg 6–8 hourly
<i>Tinidazole</i>	Oral: Adults = 0.6 g 12 hourly for 5–10 days or 2.0 g/day for 3 days, children = 30–50 mg/kg/day
<i>Ornidazole</i>	Oral: 2 g/day for 3 days or 0.6 g 12 hourly for 5–10 days IV: 0.5–1.0 g
<i>Secnidazole</i>	Oral: Adults = 1.5–2.0 g/day, children = 30 mg/kg
<i>Satranidazole</i>	Oral: 300 mg 12 hourly for 3–5 days
<i>Chloroquine</i>	Oral: 600 mg/day for 2 days followed by 300 mg/day for 2–3 weeks
<i>Dehydroemetine</i>	IM, SC: 60–100 mg/day for maximum 10 days
<i>Iodoquinol</i>	Oral: 650 mg 8 hourly for 14 days
<i>Paromomycin</i>	IM: 15 mg/kg for 21 days
<b>Giardiasis:</b>	
<i>Metronidazole</i>	Oral: 400 mg 8 hourly for 7 days
<i>Tinidazole</i>	Oral: 2 g single dose or 0.6 g/day for 7 days
<i>Nitazoxanide</i>	Oral: Adults = 500 mg 12 hourly for 3 days, children = 7.5 mg/kg
<b>Malaria:</b>	
<i>Artemether/lumefantrine</i>	Oral: Adults = 6 doses over 3-day period of 80 mg Artemether and 480 mg Lumefantrine, children = 6 doses over 3-day period of 20–80 mg Artemether and 120–480 mg Lumefantrine based on body weight
<i>Chloroquine</i>	Oral: Adults = 4 doses over 3-day period of 300–600 mg, children = 150–1000 mg over 3 days
<i>Primaquine</i>	Oral: Adults = 15 mg/day for 2 weeks or 45 mg single dose with Chloroquine, children = 0.25–0.75 mg/kg
<i>Pyrimethamine</i>	Oral: Adults = 25–50 mg/day for 2 days, children = 25 mg/day for 2 days
<i>Quinine/quinidine</i>	Quinine: IV: 20 mg/kg over 4 hours followed by 10 mg/kg over 8 hours, Oral: 600 mg 8 hourly for 7 days Quinidine: Oral: 100–200 mg 8 hourly, IV: 100–300 mg
<i>Mefloquine</i>	Oral: 25 mg/kg divided over 2 days with 4 mg/kg/day Artesunate for 3 days

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<b>Atovaquone-proguanil</b>	Oral: Adults = 1 g/day <i>Atovaquone</i> and 400 mg/day <i>Proguanil</i> for 3 days, children = 125 mg–1 g/day <i>Atovaquone</i> and 50–400 mg/day <i>Proguanil</i> based on body weight
<b>Trypanosomiasis:</b>	
<b>Pentamidine</b>	Intranasal: 300 mg every 4 weeks
<b>Benznidazole</b>	Oral: Children = 5 mg/kg–8 mg/kg divided 12 hourly for 60 days
<b>Eflornithine</b>	IV: 400 mg/kg/day
<b>Melarsoprol</b>	IV: Adult = 3.6 mg/kg/day for 3 days, children = 18–25 mg/kg over 1 month
<b>Nifurtimox</b>	Oral: Adults = 8–10 mg/kg/day for 3–4 months, children = 12.5–20 mg/kg/day for 3–4 months
<b>Suramin</b>	IV: 100–200 mg followed by 10–20 mg/kg/day for 5–7 days
<b>Leishmaniasis:</b>	
<b>Miltefosine</b>	Oral: Adults = 50 mg 12 hourly, children = 2.5 mg/kg/day
<b>Sodium stibogluconate</b>	IM, IV: 20 mg/kg/day for 30 days
<b>Toxoplasmosis:</b>	
<b>Pyrimethamine</b>	Oral: Adults = 25–50 mg/day for 2 days, children = 25 mg/day for 2 days

## XXV. IMMUNOSUPPRESSANT DRUGS

<b>Antibodies:</b>	
<b>Alemtuzumab</b>	IV: 12 mg/day
<b>Antithymocyte globulins</b>	
<b>Basiliximab</b>	IV: Adult = 20 mg 12 hourly, children = 10 mg 12 hourly
<b>Rituximab</b>	IV: 250–500 mg/m <sup>2</sup>
<b>Calcineurin inhibitors:</b>	
<b>Cyclosporine</b>	Oral: 2–15 mg/kg/day IV: 3–5 mg/kg/day
<b>Tacrolimus</b>	Oral: 0.05–0.2 mg/kg 12 hourly 0.03% and 0.1% topical ointment
<b>Costimulation blocker:</b>	
<b>Belatacept</b>	IV: 5–10 mg/kg
<b>mTOR Inhibitors:</b>	
<b>Everolimus</b>	Oral: 2.5–20 mg/day
<b>Sirolimus</b>	Oral: 1 mg/m <sup>2</sup> /day
<b>Antiproliferatives:</b>	
<b>Azathioprine</b>	Oral: 1–5 mg/kg/day
<b>Mycophenolate mofetil</b>	Oral: 1 g twice a day
<b>Mycophenolate sodium</b>	Oral: Adult: 720 mg twice a day, children: 400–720 mg twice a day

## Adrenocorticoids:

<b>Methylprednisolone</b>	Oral: 4–32 mg/day IV: 0.5–1 g
<b>Prednisolone</b>	Oral: 5–60 mg/day IM/intra-articular: 10–40 mg/day
<b>Prednisone</b>	Oral: Adult = 0.5–2 mg/kg/day, children: 0.05–2 mg/kg/day
<b>Others:</b>	
<b>Bortezomib</b>	IV: 1.3 mg/m <sup>2</sup>
<b>Intravenous immunoglobulin</b>	IV: 300–1000 mg/kg

## XXVI. ANTIHISTAMINIC DRUGS

DRUG	ROUTE	DOSAGE
<b>Sedating:</b>		
<b>Diphenhydramine</b>	Oral/IM/IV	Oral = 25–50 mg, 6–8 hourly/day IM or IV = 10–50 mg deep IM or IV
<b>Dimenhydrinate</b>	Oral/IM	25–50 mg oral
<b>Chlorpheniramine</b>	Oral/IM	Oral/IM = 2–4 mg every 6 hours (max 32 mg/day) IV, IM = 5–20 mg Pediatric oral = 0.5 mg every 12 hours (3–5 mon) 1.0 mg every 12 hours (6–8 mon) 1–1.5 every 12 hours (9–18 mon)
<b>Brompheniramine</b>	Oral/IV/IM	Oral: 4–8 mg every 6 hours (max 24 mg/day) IV, IM = 5–20 mg every 6 or 12 hours (max 40 mg/day) Pediatric oral = 0.125 mg/kg every 6 hours (<6 yr)
<b>Doxylamine</b>	Oral	10–20 mg oral/day before bed
<b>Nonsedating:</b>		
<b>Fexofenadine</b>	Oral	Adult = 120–180 mg/day, once or twice a day Children (6–11 yr) = 60 mg/day, twice a day
<b>Cetirizine</b>	Oral	Adults = 5–10 mg/day, once or twice a day Children (6 mon to 5 yr) = 2.5–5 mg/day, once or twice a day
<b>Levocetirizine</b>	Oral	Adult = 2.5–5 mg/day, once a day Children = 2.5 mg/day, once a day
<b>Loratadine</b>	Oral	Adult = 10 mg/day, once a day Children (2–6 yr) = 5 mg/day, once a day

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DRUG	ROUTE	DOSAGE
<i>Desloratadine</i>	Oral	Adult = 5 mg/day, once a day Children (6–11 yr) = 2.5 mg/day, once a day Children (1–5 yr) = 1.25 mg/day, once a day Children (6–11 mon) = 1 mg/day, once a day
<b>Mast cell stabilizers:</b>		
<i>Hydroxyzine</i>	Oral/IM	Oral: Adult = 10–50 mg/day IM: Adult = 25–50 mg/day
<i>Ketotifen</i>	Oral	Adult = 1–2 mg/day, twice a day Children = 0.5 mg/day, twice a day
<b>Antihistamines and mast cell stabilizers:</b>		
<i>Azelastine</i>	Oral/intra-nasal	Oral = 4 mg Intranasal = 0.28 mg
<i>Olopatadine</i>	Topical-ophthalmic (0.1% to 0.2%), intranasal (0.6%)	Ophthalmic: One drop in the affected eye, once a day Intranasal: Two sprays per nostril, twice a day
<i>Alcaftadine</i>	Topical-ophthalmic (0.25%)	One drop in the affected eye, once a day
<i>Emedastine</i>	Topical-ophthalmic (0.05%)	One drop in the affected eye, four times a day
<i>Clemastine</i>	Oral	1–2 mg/day
<i>Cyproheptadine</i>	Oral	Adult = 4–32 mg/day, three times a day Children (7–14 yr) = 4–12 mg/day, twice or thrice a day Children (2–6 yr) = 2–12 mg/day, twice or thrice a day
<i>Bepotastine</i>	Topical-Ophthalmic (1.5%)	One drop in the affected eye, twice a day
<b>Motion sickness and nausea:</b>		
<i>Cyclizine</i>	IM/IV	50–150 mg/day, up to thrice a day
<i>Meclizine</i>	Oral	25–100 mg/day
<i>Promethazine</i>	Oral/suppository/ deep IM or IV	Oral = 25–50 mg, up to thrice a day Deep IM or IV = 12.5–50 mg/day Suppository = 12.5–25 mg/day, twice a day

<i>Dimenhydrinate</i>	Oral/IM/IV	<b>Oral:</b> Adult = 50–400 mg/day, every 4–6 hours Children (6–11 yr) = 25–150 mg/day, every 6–8 hours Children (2–5 yr) = 12.5–75 mg/day, every 6–8 hours <b>IM/IV:</b> Adult = 50–400 mg/day, every 4 hours
<i>Triprolidine</i>	Oral (discontinued in FDA)	<b>Adult:</b> 2.5–10 mg/day, every 6 hours Children (6–12 yr) = 1.25–5 mg/day, every 6 hours

## XXVII. DRUGS AFFECTING THE RESPIRATORY SYSTEM

DRUG	ROUTE AND DOSAGE
<b>Short-acting <math>\beta_2</math> adrenergic agonists (SABAs):</b>	
<i>Albuterol</i>	Oral inhalation: Adults and children (>4 yr) = 2 inhalations (180 $\mu$ g) 4–6 hourly
<i>Levalbuterol</i>	Oral inhalation: Adults and adolescents (>12 yr) = 0.63 mg 6–8 hourly, children (6–11 yr) = 0.31 mg 8 hourly
<b>Long-acting <math>\beta_2</math> adrenergic agonists (LABAs):</b>	
<i>Arformoterol</i>	Oral inhalation: Adults = 15 $\mu$ g 12 hourly
<i>Formoterol</i>	Oral inhalation: Adults and children (>5 yr) = 12 $\mu$ g 12 hourly
<i>Indacaterol</i>	Oral inhalation: Adults = 75 $\mu$ g 24 hourly
<i>Olodaterol</i>	Oral inhalation: Adults = 5 $\mu$ g (2 inhalations) 24 hourly
<i>Salmeterol</i>	Oral inhalation: Adults and children (>4 yr) = 50 $\mu$ g 12 hourly
<b>Inhaled corticosteroids:</b>	
<i>Beclomethasone</i>	Oral inhalation: 100–400 $\mu$ g (2–4 times a day)
<i>Budesonide</i>	Oral inhalation: 200–400 $\mu$ g (2–4 times a day)
<i>Ciclesonide</i>	Inhalation: 80–160 $\mu$ g/day in evening
<i>Fluticasone</i>	Inhalation: 200–1000 $\mu$ g/day
<i>Mometasone</i>	Inhalation: Adult = 440–880 $\mu$ g/day, children = 110 $\mu$ g/day
<i>Triamcinolone</i>	Oral: 4–32 mg/day IM/IA: 5–40 mg
<b>Long-acting <math>\beta_2</math> adrenergic agonists/corticosteroid combination:</b>	
<i>Formoterol/budesonide</i>	Inhalation: Budesonide = 80–160 $\mu$ g and formoterol = 4.5 $\mu$ g (once or twice a day)
<i>Formoterol/mometasone</i>	Inhalation: Mometasone = 100–200 $\mu$ g and formoterol = 5 $\mu$ g (once or twice a day)

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<b>Salmeterol/ fluticasone</b>	Inhalation: <i>Fluticasone</i> = 100–500 µg and <i>salmeterol</i> = 50 µg (twice daily)
<b>Vilanterol/ fluticasone</b>	Inhalation: <i>Fluticasone</i> = 100–200 µg/day and <i>formoterol</i> = 25 µg/day
<b>Short-acting anticholinergic:</b>	
<i>Ipratropium</i>	Inhalation: 40–80 µg (3–4 times a day)
<b>Short-acting β<sub>2</sub> agonist/short-acting anticholinergic combination:</b>	
<i>Albuterol/ Ipratropium</i>	Inhalation: <i>Ipratropium</i> = 0.5 mg and <i>albuterol</i> = 3 mg (up to 4 times a day)
<b>Long-acting anticholinergic (LAMA):</b>	
<i>Aclidinium bromide</i>	Inhalation: 400–800 µg/day
<i>Glycopyrrrolate</i>	Oral: 1–2 mg IM/IV: 0.1–0.3 mg
<i>Tiotropium</i>	Inhalation: 18 µg
<i>Umeclidinium</i>	Inhalation: 62.5 µg/day
<b>LABA/LAMA combination:</b>	
<i>Formoterol/glyco-pyrrolate</i>	Inhalation: <i>Glycopyrrrolate</i> = 18 µg and <i>formoterol</i> = 9.6 µg (twice daily)
<i>Indacaterol/glyco-pyrrolate</i>	Inhalation: <i>Indacaterol</i> = 27.5 µg and <i>glycopyrrrolate</i> = 15.6 µg (twice a day)
<i>Vilanterol/umeclidinium</i>	Inhalation: <i>Umeclidinium</i> = 62.5 µg/day and <i>vilanterol</i> = 25 µg/day
<i>Olodaterol/tiotropium</i>	Inhalation: <i>Olodaterol</i> = 5 µg /day and <i>tiotropium</i> = 5 µg /day
<b>Leukotriene modifiers:</b>	
<i>Montelukast</i>	Oral: Adult = 10 mg/day, children = 4–5 mg/day
<i>Zafirlukast</i>	Oral: Adult = 20 mg (twice a day), children = 10 mg (twice a day)
<i>Zileuton</i>	Oral: 600–2400 mg/day
<b>Antihistamines (H<sub>1</sub>-receptor antagonists):</b>	
<i>Azelastine</i>	Oral: 4 mg Intranasal: 0.28 mg
<i>Cetirizine</i>	Oral: 10 mg
<i>Desloratadine</i>	Oral: 5 mg
<i>Fexofenadine</i>	Oral: 120–180 mg
<i>Loratadine</i>	Oral: 10 mg
<b>α-Adrenergic agonists:</b>	
<i>Oxymetazoline</i>	Topically in nose: 0.025–0.05%
<i>Phenylephrine</i>	Oral: 5–10 mg IM: 2–5 mg IV: 0.1–0.5 mg Topically in nose: 0.25% Topically in eye: 5–10%
<i>Pseudoephedrine</i>	Oral: 30–60 mg (thrice a day)
<b>Agents for cough:</b>	
<i>Benzonatate</i>	Oral: 300–600 mg/day
<i>Codeine (with guaifenesin)</i>	Oral: <i>Codeine</i> = 30 mg and <i>guaifenesin</i> = 600 mg

<b>Dextromethorphan</b>	Oral: Adult = 10–20 mg, children = 2.5–10 mg
<b>Dextromethorphan (with guaifenesin)</b>	Oral: <i>Dextromethorphan</i> = 60 mg/day and <i>guaifenesin</i> = 600 mg/day
<b>Guaifenesin</b>	Oral: 600–1200 mg (twice or thrice a day)
<b>Other agents:</b>	
<i>Benralizumab</i>	SC: 30 mg
<i>Cromolyn</i>	Oral: Adult = 800 mg/day, children = 400 mg/day Inhalation: 6.4 mg
<i>Mepolizumab</i>	SC: 100–300 mg
<i>Omalizumab</i>	SC: 75–375 mg
<i>Reslizumab</i>	IV: 3 mg/kg
<i>Roflumilast</i>	Oral: 0.5 mg/day
<i>Theophylline</i>	Oral: 300–900 mg/day (or) 15 mg/kg/day

## XXVIII. DRUGS USED TO TREAT PEPTIC ULCER DISEASE

DRUG	ROUTE AND DOSAGE
<b>Antimicrobial agents (for eradication of <i>Helicobacter pylori</i>):</b>	
<i>Amoxicillin</i>	750–1000 mg 12 hourly
<i>Bismuth compounds</i>	
<i>Clarithromycin</i>	500 mg 12 hourly
<i>Metronidazole</i>	400 mg 8 hourly
<i>Tetracycline</i>	500 mg 6 hourly
<b>H<sub>2</sub>-Histamine receptor blockers:</b>	
<i>Cimetidine</i>	Oral: 800 mg/day IV: 50 mg/hr
<i>Ranitidine</i>	Oral: 150–300 mg/day Parenteral IM: 50 mg Parenteral IV: 0.1–0.25 mg/kg/hr
<i>Nizatidine</i>	Oral: 300 mg/day
<i>Famotidine</i>	Oral: 20–40 mg/day Parenteral IV: 20 mg 12 hourly or 2 mg/hr
<b>Proton-pump inhibitors (PPIs):</b>	
<i>Omeprazole</i>	Oral: 20–60 mg/day
<i>Pantoprazole</i>	Oral: 20–40 mg/day
<i>Lansoprazole</i>	Oral: 15–30 mg/day
<i>Rabeprazole</i>	Oral: 20 mg/day
<i>Esomeprazole</i>	Oral: 20–40 mg/day
<i>Dexlansoprazole</i>	Oral: 30–60 mg/day
<b>Prostaglandins:</b>	
<i>Misoprostol</i>	Oral: 0.2 mg 6 hourly

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DRUG	ROUTE AND DOSAGE
<b>Antimuscarinic agents:</b>	
Dicyclomine	Oral: 10–20 mg
<b>Antacids:</b>	
Aluminum hydroxide	Gel: 0.6–2.4 g
Calcium carbonate	Oral: 1–2 g/day
Magnesium hydroxide	Oral: 0.4–1.0 g
Sodium bicarbonate	IV: 44.6–50 mEq/5–10 minutes or 2–5 mEq/kg/4–8 hours
<b>Mucosal protective agents:</b>	
Bismuth subsalicylate	Oral: Adults = 524 mg 6 hourly, children = 262–524 mg 6 hourly for 6 weeks
Sucralfate	Oral: 2–4 g/day

## XXIX. DRUGS USED TO TREAT IRRITABLE BOWEL SYNDROME

DRUG	ROUTE AND DOSAGE
Linaclotide	Oral: 145–290 µg/day
Lubiprostone	Oral: 8–24 µg/day
Alosetron	Oral: 1–2 mg/day
Eluxadoline	Oral: 150–200 mg/day in two divided doses
Rifaximin	Oral: 200–550 mg (three times a day)
Dicyclomine	Oral: 20 mg
Hyoscyamine	Oral: Adult = 1.25–3 mg/day, children = 0.375–0.075 mg/day

## XXX. DRUG USED TO TREAT INFLAMMATORY BOWEL DISEASE

DRUG	ROUTE AND DOSAGE
<b>5-Aminosalicylates:</b>	
Balsalazide	Oral: 1.5–2.25 g (twice/thrice a day)
Mesalamine	Oral: 1.2–2.4 g/day Rectal: 4 g
Olsalazine	Oral: 1 g/day (twice a day)
Sulfasalazine	Oral: 1.5–4 g/day
<b>Corticosteroids:</b>	
Budesonide	Oral: 6–9 mg/day Rectal: 2 mg/day
Hydrocortisone	Oral: 20–30 mg/day Rectal: 2 g IV: 100 mg 8 hourly IM: 100–200 mg

Prednisone	Oral: 5 mg
Methylprednisolone	Oral: 4–32 mg/day IV: 0.5–1 g
<b>Biological agents:</b>	
TNF-α inhibitor:	
Adalimumab	SC: Adult = 40–160 mg, children = 10–40 mg
Certolizumab	SC: 200–400 mg
Golimumab	SC: 50 mg/month
Infliximab	IV: 5–10 mg/kg
<b>α4-Integrin inhibitor:</b>	
Vedolizumab	IV: 300 mg
<b>IL-12/13 inhibitor:</b>	
Ustekinumab	SC/IV: 45–520 mg
<b>Immunomodulators:</b>	
Azathioprine	Oral: 1–5 mg/kg/day
6-Mercaptopurine	Oral: 1.25–2.5 mg/kg/day
Methotrexate	Oral: 7.5–30 mg/day IV/IM: 20–40 mg/m²

## XXXI. DRUGS USED FOR THE TREATMENT OF UROLOGIC DISORDERS

DRUG	ROUTE AND DOSAGE
<b>Drugs for erectile dysfunction:</b>	
Alprostadil	1–40 µg intracavernous injection
Avanafil	Oral = 50–200 mg not more than once a day approximately 30 minutes before intercourse
Sildenafil	Oral = 25–100 mg
Tadalafil	Oral = 10–20 mg
Vardenafil	Oral = 20 mg
Phentolamine	5 mg IV repeated as required
Papaverine	Intracavernous injection of papaverine (3–20 mg) with or without phentolamine (0.5–1 mg)
<b>Benign prostrate hypertrophy (BPH):</b>	
<b>α<sub>1</sub>-Blocker short acting:</b>	
Alfuzosin	Oral = 2.5–10 mg 6–24 hourly
Prazosin	Oral = 0.5–1 mg BD or TID initial to 20 mg divided dose/day oral or sublingual, 0.15–0.6 mg by IM
Indoramin	Oral = 20 mg tablet twice a day. If needed, the dose may be increased by 20 mg every 2 weeks. The maximum dose is 100 mg per day

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<b><math>\alpha_1</math>-Blocker long acting:</b>	
<i>Terazosin</i>	Oral = 1 mg tablet at bedtime is the initial dose Usual maintenance dose 2–10 mg OD
<i>Doxazosin</i>	Oral = 1 mg tablet OD initially, increase up to 8 mg BD
<b>Selective <math>\alpha_{1A}</math>-blocker:</b>	
<i>Silodosin</i>	Oral = 8 mg PO every day
<i>Tamsulosin</i>	Oral = 0.2–0.4 mg MR capsule OD
<b>Nonselective <math>\alpha</math>-blocker:</b>	
<i>Phenoxybenzamine</i>	Oral = 20–60 mg/day, 1 mg/kg slow IV infusion over 1 hour
<b>5-<math>\alpha</math> reductase inhibitors:</b>	
<i>Dutasteride</i>	Oral = 0.5 mg/day tablet
<i>Finasteride</i>	Oral = 1 mg OD with or without meals, review after 6 months
<b>Combinations:</b>	
<i>Dutasteride + tamsulosin</i>	Oral = 0.5 mg + 0.4 mg per day

## XXXII. DRUGS FOR THE TREATMENT OF ANEMIA

DRUG	ROUTE AND DOSAGE	
<b>Treatment of anemia:</b>		
<b>Oral iron salts and formulations</b>	<b>Elemental iron</b>	<b>Therapeutic</b> <b>Adult:</b> Formulation equivalent to 100–200 mg elemental iron/day <b>Pediatric:</b> Formulation equivalent to elemental iron 3–5 mg/kg/day
<i>Ferrous gluconate</i>	12%	
<i>Ferric ammonium citrate</i>	18%	
<i>Ferrous sulfate</i>	20%	
<i>Ferrous sulfate anhydrous</i>	30%	
<i>Ferrous fumarate</i>	33%	
<i>Ferrous succinate</i>	35%	
<i>Colloidal ferric hydroxide</i>	50%	
<i>Iron carbonyl iron</i>	100%	
<i>Iron polysaccharide complex (iron polymaltose)</i>	100%	<b>Pregnancy</b> 30–60 mg elemental iron with 0.4 mg folic acid daily  Oral iron preparations are available as tablets, capsules [extended release, film coated], suspension, chewable tablets
<b>Parenteral iron preparations:</b>		
<i>Iron dextran complex</i>	50 mg elemental iron/ml 2 ml deep IM injection by "Z" track technique/day or alternate day 2 ml slow IV injection (over 10 min)	

<i>Iron sucrose</i>	50 mg elemental iron/2.5 ml and 100 mg in 5 ml amp for IV inj.
<i>Ferric carboxymaltose</i>	50 mg elemental iron/ml in 2 ml and 10 ml vials
<i>Iron-sorbitol-citric acid</i>	75 mg elemental iron/ml (max 100 mg) daily or on alternate days
<b>Combination of iron salts, vitamins, and minerals</b>	Formulation differs (refer to individual formulation carefully)
<i>Folic acid</i>	<b>Therapeutic</b> = 2–5 mg/day <b>Prophylactic</b> = 0.5 mg/day
<i>Cyanocobalamin (vitamin B<sub>12</sub>)</i>	<b>Nutritional deficiency</b> Oral = 25–2000 µg/day Pediatric = 0.5–3 µg/day <b>Nutritional supplementation (RDA)</b> Adult 2.4 µg, pregnant women 2.6 µg, dietary supplement 50–6000 µg/day
<b>Hormones produced by kidney:</b>	
<i>Epoetin alfa (EPO)</i>	25–100 units/kg SC or IV 3 times a week (max dose 600 units/kg/wk)
<i>Darbepoetin alfa</i>	IV/SC: 0.45–2.25 µg/kg for 2–4 weeks
<b>Biologic response modifiers:</b>	
<i>Filgrastim</i>	5 µg/kg/day for 15–30 minutes
<i>Pegfilgrastim</i>	6 mg SC
<i>Sargramostim</i>	IV/SC: 250 µg/m <sup>2</sup> /day
<i>Tbo-filgrastim</i>	SC: 5 µg/kg/day
<b>Treatment of sickle cell anemia:</b>	
<i>Hydroxyurea</i>	Oral = 20–80 mg/kg day
<b>Iron chelator:</b>	
<i>Desferrioxamine</i>	<b>Acute iron intoxication</b> IM: 1 g/day initially followed by 500 mg 4 hourly for two doses IV: 15 mg/kg/hr followed by 500 mg 4 hourly for two doses <b>Chronic iron overload</b> SC: 20–40 mg/kg 8–24 hourly

## XXXIII. DRUGS FOR ACNE, SUPERFICIAL BACTERIAL INFECTIONS, AND ROSACEA

DRUG	ROUTE AND DOSAGE
<b>Topical agents for acne:</b>	
<i>Retinoids</i>	0.1% gel once daily (12 years or above)
<i>Tretinoin</i>	0.02% cream once daily in the evening time
<i>Alitretinoin</i>	0.1% 6–24 hourly

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DRUG	ROUTE AND DOSAGE		
<i>Adapalene</i>	0.1% gel once daily at bed time	<i>Erythromycin</i>	2–4% topical application. It used in combination with benzoyl peroxide topically
<i>Bexarotene</i>	1% gel once daily to three to four times based on lesion tolerance	<b>Agents for superficial bacterial infections (topical use):</b>	
<i>Tazarotene</i>	0.05–0.1% application daily in the evening	<i>Bacitracin Zinc</i>	500 IU/g ointment or cream
<i>Salicylic acid</i>	1.9% cream used topically once or twice daily	<i>Gentamicin</i>	0.1–0.3% ointment
<i>Azelaic acid</i>	10–20% gel gently to massaged into the affected area twice daily	<i>Mupirocin</i>	2% topical ointment
<i>Benzoyl peroxide</i>	3–9% gel once a day to two to three times a day	<i>Neomycin</i>	3.5 mg neomycin base per gram ointment
<b>Systemic retinoid for acne:</b>		<i>Polymyxin B</i>	5000 U/g ointment (often used in combination)
<i>Isotretinoin</i>	Oral = 0.5–1 mg/kg/day for 15–20 weeks	<i>Retapamulin</i>	1% ointment for twice-daily application
<i>Acitretin</i>	0.5–0.75 mg/kg/day oral for severe psoriasis in adults	<b>Agents used for rosacea (topical):</b>	
<i>Etretinate</i>	Discontinued	<i>Azelaic acid</i>	15–20% cream for twice-daily application
<i>Bexarotene</i>	Oral = 300 mg/m <sup>2</sup> /day	<i>Brimonidine</i>	0.33% topical gel
<b>Topical and oral antibiotics for acne:</b>		<i>Oxymetazoline</i>	1% topical cream applied in face avoiding eye and lips
<i>Minocycline</i>	Oral = 1 mg/kg once daily for up to 12 weeks	<i>Pimecrolimus</i>	1% topical application to be applied on affected area twice daily
<i>Clindamycin</i>	1% topical application twice daily to affected area	<i>Sulfacetamide sodium</i>	5–10% topical lotion
<i>Doxycycline</i>	Oral = 200 mg first day (100 mg every 12 hours) followed by a maintenance dose of 100 mg/day	<i>Doxycycline</i>	200 mg initially followed by 100–200 mg once a day oral
		<i>Metronidazole</i>	0.75% gel along with oral metronidazole

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Note: Drug names are shown in italics and Genus names are shown in underline.

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# PERCEPTIONS OF A RENEGADE MIND

DAVID DICKIE

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DAVID ICKE

**PERCEPTIONS  
OF A  
RENEGADE  
MIND**

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PERCEPTIONS  
OF A  
RENEGADE  
MIND



**DAVID ICKE**

**Dedication:**

To *Freeeeeedom!*

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**Renegade:**

Adjective

'Having rejected tradition: Unconventional.'

**Merriam-Webster Dictionary**

## **Acquiescence to tyranny is the death of the spirit**

You may be 38 years old, as I happen to be. And one day, some great opportunity stands before you and calls you to stand up for some great principle, some great issue, some great cause. And you refuse to do it because you are afraid

... You refuse to do it because you want to live longer ...

You're afraid that you will lose your job, or you are afraid that you will be criticised or that you will lose your popularity, or you're afraid that somebody will stab you, or shoot at you or bomb your house; so you refuse to take the stand.

Well, you may go on and live until you are 90, but you're just as dead at 38 as you would be at 90. And the cessation of breathing in your life is but the belated announcement of an earlier death of the spirit.

**Martin Luther King**

**How the few control the many and always have – the many do  
whatever they're told**

'Forward, the Light Brigade!'  
Was there a man dismayed?  
Not though the soldier knew  
    Someone had blundered.  
Theirs not to make reply,  
Theirs not to reason why,  
Theirs but to do and die.  
    Into the valley of Death  
        Rode the six hundred.

Cannon to right of them,  
Cannon to left of them,  
Cannon in front of them  
    Volleyed and thundered;  
Stormed at with shot and shell,  
    Boldly they rode and well,  
        Into the jaws of Death,  
        Into the mouth of hell  
            Rode the six hundred

**Alfred Lord Tennyson (1809-1892)**

The mist is lifting slowly  
I can see the way ahead  
And I've left behind the empty streets  
That once inspired my life  
And the strength of the emotion  
Is like thunder in the air  
'Cos the promise that we made each other  
Haunts me to the end

The secret of your beauty  
And the mystery of your soul  
I've been searching for in everyone I meet  
And the times I've been mistaken  
It's impossible to say  
And the grass is growing  
Underneath our feet

The words that I remember  
From my childhood still are true  
That there's none so blind  
As those who will not see  
And to those who lack the courage  
And say it's dangerous to try  
Well they just don't know  
That love eternal will not be denied

I know you're out there somewhere  
Somewhere, somewhere  
I know you're out there somewhere

Somewhere you can hear my voice  
I know I'll find you somehow  
Somehow, somehow  
I know I'll find you somehow  
And somehow I'll return again to you

**The Moody Blues**

## **Are you a gutless wonder - or a Renegade Mind?**

Monuments put from pen to paper,  
Turns me into a gutless wonder,  
And if you tolerate this,  
Then your children will be next.  
Gravity keeps my head down,  
Or is it maybe shame ...

**Manic Street Preachers**

Rise like lions after slumber  
In unvanquishable number.  
Shake your chains to earth like dew  
Which in sleep have fallen on you.  
Ye are many – they are few.

**Percy Shelley**

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# CHAPTER ONE

## I'm thinking' – Oh, but *are* you?

*Think for yourself and let others enjoy the privilege of doing so too*  
Voltaire

French-born philosopher, mathematician and scientist René Descartes became famous for his statement in Latin in the 17th century which translates into English as: 'I think, therefore I am.'

On the face of it that is true. Thought reflects perception and perception leads to both behaviour and self-identity. In that sense 'we' are what we think. But who or what is doing the thinking and is thinking the only route to perception? Clearly, as we shall see, 'we' are not always the source of 'our' perception, indeed with regard to humanity as a whole this is rarely the case; and thinking is far from the only means of perception. Thought is the village idiot compared with other expressions of consciousness that we all have the potential to access and tap into. This has to be true when we *are* those other expressions of consciousness which are infinite in nature. We have forgotten this, or, more to the point, been manipulated to forget.

These are not just the esoteric musings of the navel. The whole foundation of human control and oppression is control of perception. Once perception is hijacked then so is behaviour which is dictated by perception. Collective perception becomes collective behaviour and collective behaviour is what we call human society. Perception is all and those behind human control know that which is

why perception is the target 24/7 of the psychopathic manipulators that I call the Global Cult. They know that if they dictate perception they will dictate behaviour and collectively dictate the nature of human society. They are further aware that perception is formed from information received and if they control the circulation of information they will to a vast extent direct human behaviour.

Censorship of information and opinion has become globally Nazi-like in recent years and never more blatantly than since the illusory ‘virus pandemic’ was triggered out of China in 2019 and across the world in 2020. Why have billions submitted to house arrest and accepted fascistic societies in a way they would have never believed possible? Those controlling the information spewing from government, mainstream media and Silicon Valley (all controlled by the same Global Cult networks) told them they were in danger from a ‘deadly virus’ and only by submitting to house arrest and conceding their most basic of freedoms could they and their families be protected. This monumental and provable lie became the *perception* of the billions and therefore the *behaviour* of the billions. In those few words you have the whole structure and modus operandi of human control. Fear is a perception – False Emotion Appearing Real – and fear is the currency of control. In short ... get them by the balls (or give them the impression that you have) and their hearts and minds will follow. Nothing grips the dangly bits and freezes the rear-end more comprehensively than fear.

## **World number 1**

There are two ‘worlds’ in what appears to be one ‘world’ and the prime difference between them is knowledge. First we have the mass of human society in which the population is maintained in coldly-calculated ignorance through control of information and the ‘education’ (indoctrination) system. That’s all you really need to control to enslave billions in a perceptual delusion in which what are perceived to be *their* thoughts and opinions are ever-repeated mantras that the system has been downloading all their lives through ‘education’, media, science, medicine, politics and academia

in which the personnel and advocates are themselves overwhelmingly the perceptual products of the same repetition. Teachers and academics in general are processed by the same programming machine as everyone else, but unlike the great majority they never leave the ‘education’ program. It gripped them as students and continues to grip them as programmers of subsequent generations of students. The programmed become the programmers – the programmed programmers. The same can largely be said for scientists, doctors and politicians and not least because as the American writer Upton Sinclair said: ‘It is difficult to get a man to understand something when his salary depends upon his not understanding it.’ If your career and income depend on thinking the way the system demands then you will – bar a few free-minded exceptions – concede your mind to the Perceptual Mainframe that I call the Postage Stamp Consensus. This is a tiny band of perceived knowledge and possibility ‘taught’ (downloaded) in the schools and universities, pounded out by the mainstream media and on which all government policy is founded. Try thinking, and especially speaking and acting, outside of the ‘box’ of consensus and see what that does for your career in the Mainstream Everything which bullies, harasses, intimidates and ridicules the population into compliance. Here we have the simple structure which enslaves most of humanity in a perceptual prison cell for an entire lifetime and I’ll go deeper into this process shortly. Most of what humanity is taught as fact is nothing more than programmed belief. American science fiction author Frank Herbert was right when he said: ‘Belief can be manipulated. Only knowledge is dangerous.’ In the ‘Covid’ age belief is promoted and knowledge is censored. It was always so, but never to the extreme of today.

## **World number 2**

A ‘number 2’ is slang for ‘doing a poo’ and how appropriate that is when this other ‘world’ is doing just that on humanity every minute of every day. World number 2 is a global network of secret societies and semi-secret groups dictating the direction of society via

governments, corporations and authorities of every kind. I have spent more than 30 years uncovering and exposing this network that I call the Global Cult and knowing its agenda is what has made my books so accurate in predicting current and past events. Secret societies are secret for a reason. They want to keep their hoarded knowledge to themselves and their chosen initiates and to hide it from the population which they seek through ignorance to control and subdue. The whole foundation of the division between World 1 and World 2 is *knowledge*. What number 1 knows number 2 must not. Knowledge they have worked so hard to keep secret includes (a) the agenda to enslave humanity in a centrally-controlled global dictatorship, and (b) the nature of reality and life itself. The latter (b) must be suppressed to allow the former (a) to prevail as I shall be explaining. The way the Cult manipulates and interacts with the population can be likened to a spider's web. The 'spider' sits at the centre in the shadows and imposes its will through the web with each strand represented in World number 2 by a secret society, satanic or semi-secret group, and in World number 1 – the world of the seen – by governments, agencies of government, law enforcement, corporations, the banking system, media conglomerates and Silicon Valley ([Fig 1](#) overleaf). The spider and the web connect and coordinate all these organisations to pursue the same global outcome while the population sees them as individual entities working randomly and independently. At the level of the web governments *are* the banking system *are* the corporations *are* the media *are* Silicon Valley *are* the World Health Organization working from their inner cores as one unit. Apparently unconnected countries, corporations, institutions, organisations and people are on the *same team* pursuing the same global outcome. Strands in the web immediately around the spider are the most secretive and exclusive secret societies and their membership is emphatically restricted to the Cult inner-circle emerging through the generations from particular bloodlines for reasons I will come to. At the core of the core you would get them in a single room. That's how many people are dictating the direction of human society and its transformation

through the ‘Covid’ hoax and other means. As the web expands out from the spider we meet the secret societies that many people will be aware of – the Freemasons, Knights Templar, Knights of Malta, Opus Dei, the inner sanctum of the Jesuit Order, and such like. Note how many are connected to the Church of Rome and there is a reason for that. The Roman Church was established as a revamp, a rebranding, of the relocated ‘Church’ of Babylon and the Cult imposing global tyranny today can be tracked back to Babylon and Sumer in what is now Iraq.



**Figure 1:** The global web through which the few control the many. (Image Neil Hague.)

Inner levels of the web operate in the unseen away from the public eye and then we have what I call the cusp organisations located at the point where the hidden meets the seen. They include a series of satellite organisations answering to a secret society founded in London in the late 19th century called the Round Table and among them are the Royal Institute of International Affairs (UK, founded in 1920); Council on Foreign Relations (US, 1921); Bilderberg Group (worldwide, 1954); Trilateral Commission (US/worldwide, 1972); and the Club of Rome (worldwide, 1968) which was created to exploit environmental concerns to justify the centralisation of global power to ‘save the planet’. The Club of Rome instigated with others the human-caused climate change hoax which has led to all the ‘green

new deals' demanding that very centralisation of control. Cusp organisations, which include endless 'think tanks' all over the world, are designed to coordinate a single global policy between political and business leaders, intelligence personnel, media organisations and anyone who can influence the direction of policy in their own sphere of operation. Major players and regular attenders will know what is happening – or some of it – while others come and go and are kept overwhelmingly in the dark about the big picture. I refer to these cusp groupings as semi-secret in that they can be publicly identified, but what goes on at the inner-core is kept very much 'in house' even from most of their members and participants through a fiercely-imposed system of compartmentalisation. Only let them know what they need to know to serve your interests and no more. The structure of secret societies serves as a perfect example of this principle. Most Freemasons never get higher than the bottom three levels of 'degree' (degree of knowledge) when there are 33 official degrees of the Scottish Rite. Initiates only qualify for the next higher 'compartment' or degree if those at that level choose to allow them. Knowledge can be carefully assigned only to those considered 'safe'. I went to my local Freemason's lodge a few years ago when they were having an 'open day' to show how cuddly they were and when I chatted to some of them I was astonished at how little the rank and file knew even about the most ubiquitous symbols they use. The mushroom technique – keep them in the dark and feed them bullshit – applies to most people in the web as well as the population as a whole. Sub-divisions of the web mirror in theme and structure transnational corporations which have a headquarters somewhere in the world dictating to all their subsidiaries in different countries. Subsidiaries operate in their methodology and branding to the same centrally-dictated plan and policy in pursuit of particular ends. The Cult web functions in the same way. Each country has its own web as a subsidiary of the global one. They consist of networks of secret societies, semi-secret groups and bloodline families and their job is to impose the will of the spider and the global web in their particular country. Subsidiary networks control and manipulate the national political system, finance, corporations, media, medicine, etc. to

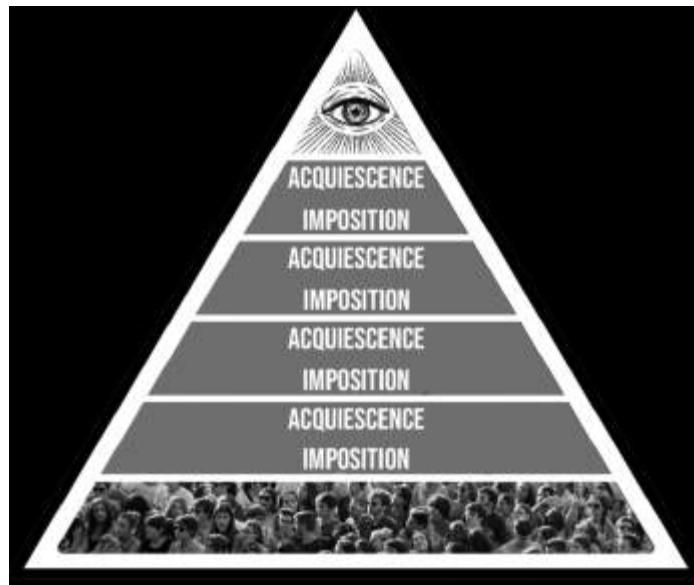
ensure that they follow the globally-dictated Cult agenda. These networks were the means through which the ‘Covid’ hoax could be played out with almost every country responding in the same way.

## **The ‘Yessir’ pyramid**

Compartmentalisation is the key to understanding how a tiny few can dictate the lives of billions when combined with a top-down sequence of imposition and acquiescence. The inner core of the Cult sits at the peak of the pyramidal hierarchy of human society ([Fig 2](#) overleaf). It imposes its will – its agenda for the world – on the level immediately below which acquiesces to that imposition. This level then imposes the Cult will on the level below them which acquiesces and imposes on the next level. Very quickly we meet levels in the hierarchy that have no idea there even is a Cult, but the sequence of imposition and acquiescence continues down the pyramid in just the same way. ‘I don’t know why we are doing this but the order came from “on-high” and so we better just do it.’ Alfred Lord Tennyson said of the cannon fodder levels in his poem *The Charge of the Light Brigade*: ‘Theirs not to reason why; theirs but to do and die.’ The next line says that ‘into the valley of death rode the six hundred’ and they died because they obeyed without question what their perceived ‘superiors’ told them to do. In the same way the population capitulated to ‘Covid’. The whole hierarchical pyramid functions like this to allow the very few to direct the enormous many.

Eventually imposition-acquiescence-imposition-acquiescence comes down to the mass of the population at the foot of the pyramid. If they acquiesce to those levels of the hierarchy imposing on them (governments/law enforcement/doctors/media) a circuit is completed between the population and the handful of super-psychopaths in the Cult inner core at the top of the pyramid. Without a circuit-breaking refusal to obey, the sequence of imposition and acquiescence allows a staggeringly few people to impose their will upon the entirety of humankind. We are looking at the very sequence that has subjugated billions since the start of 2020. Our freedom has not been taken from us. Humanity has given it

away. Fascists do not impose fascism because there are not enough of them. Fascism is imposed by the population acquiescing to fascism. Put another way allowing their perceptions to be programmed to the extent that leads to the population giving their freedom away by giving their perceptions – their mind – away. If this circuit is not broken by humanity ceasing to cooperate with their own enslavement then nothing can change. For that to happen people have to critically think and see through the lies and window dressing and then summon the backbone to act upon what they see. The Cult spends its days working to stop either happening and its methodology is systematic and highly detailed, but it can be overcome and that is what this book is all about.



**Figure 2:** The simple sequence of imposition and compliance that allows a handful of people at the peak of the pyramid to dictate the lives of billions.

## The Life Program

Okay, back to world number 1 or the world of the ‘masses’. Observe the process of what we call ‘life’ and it is a perceptual download from cradle to grave. The Cult has created a global structure in which perception can be programmed and the program continually topped-up with what appears to be constant confirmation that the program is indeed true reality. The important word here is ‘appears’.

This is the structure, the fly-trap, the Postage Stamp Consensus or Perceptual Mainframe, which represents that incredibly narrow band of perceived possibility delivered by the ‘education’ system, mainstream media, science and medicine. From the earliest age the download begins with parents who have themselves succumbed to the very programming their children are about to go through. Most parents don’t do this out of malevolence and mostly it is quite the opposite. They do what they believe is best for their children and that is what the program has told them is best. Within three or four years comes the major transition from parental programming to full-blown state (Cult) programming in school, college and university where perceptually-programmed teachers and academics pass on their programming to the next generations. Teachers who resist are soon marginalised and their careers ended while children who resist are called a problem child for whom Ritalin may need to be prescribed. A few years after entering the ‘world’ children are under the control of authority figures representing the state telling them when they have to be there, when they can leave and when they can speak, eat, even go to the toilet. This is calculated preparation for a lifetime of obeying authority in all its forms. Reflex-action fear of authority is instilled by authority from the start. Children soon learn the carrot and stick consequences of obeying or defying authority which is underpinned daily for the rest of their life. Fortunately I daydreamed through this crap and never obeyed authority simply because it told me to. This approach to my alleged ‘bettters’ continues to this day. There can be consequences of pursuing open-minded freedom in a world of closed-minded conformity. I spent a lot of time in school corridors after being ejected from the classroom for not taking some of it seriously and now I spend a lot of time being ejected from Facebook, YouTube and Twitter. But I can tell you that being true to yourself and not compromising your self-respect is far more exhilarating than bowing to authority for authority’s sake. You don’t have to be a sheep to the shepherd (authority) and the sheep dog (fear of not obeying authority).

The perceptual download continues throughout the formative years in school, college and university while script-reading ‘teachers’, ‘academics’ ‘scientists’, ‘doctors’ and ‘journalists’ insist that ongoing generations must be as programmed as they are. Accept the program or you will not pass your ‘exams’ which confirm your ‘degree’ of programming. It is tragic to think that many parents pressure their offspring to work hard at school to download the program and qualify for the next stage at college and university. The late, great, American comedian George Carlin said: ‘Here’s a bumper sticker I’d like to see: We are proud parents of a child who has resisted his teachers’ attempts to break his spirit and bend him to the will of his corporate masters.’ Well, the best of luck finding many of those, George. Then comes the moment to leave the formal programming years in academia and enter the ‘adult’ world of work. There you meet others in your chosen or prescribed arena who went through the same Postage Stamp Consensus program before you did. There is therefore overwhelming agreement between almost everyone on the basic foundations of Postage Stamp reality and the rejection, even contempt, of the few who have a mind of their own and are prepared to use it. This has two major effects. Firstly, the consensus confirms to the programmed that their download is really how things are. I mean, everyone knows that, right? Secondly, the arrogance and ignorance of Postage Stamp adherents ensure that anyone questioning the program will have unpleasant consequences for seeking their own truth and not picking their perceptions from the shelf marked: ‘Things you must believe without question and if you don’t you’re a dangerous lunatic conspiracy theorist and a harebrained nutter’.

Every government, agency and corporation is founded on the same Postage Stamp prison cell and you can see why so many people believe the same thing while calling it their own ‘opinion’. Fusion of governments and corporations in pursuit of the same agenda was the definition of fascism described by Italian dictator Benito Mussolini. The pressure to conform to perceptual norms downloaded for a lifetime is incessant and infiltrates society right

down to family groups that become censors and condemners of their own ‘black sheep’ for not, ironically, being sheep. We have seen an explosion of that in the ‘Covid’ era. Cult-owned global media unleashes its propaganda all day every day in support of the Postage Stamp and targets with abuse and ridicule anyone in the public eye who won’t bend their mind to the will of the tyranny. Any response to this is denied (certainly in my case). They don’t want to give a platform to expose official lies. Cult-owned-and-created Internet giants like Facebook, Google, YouTube and Twitter delete you for having an unapproved opinion. Facebook boasts that its AI censors delete 97-percent of ‘hate speech’ before anyone even reports it. Much of that ‘hate speech’ will simply be an opinion that Facebook and its masters don’t want people to see. Such perceptual oppression is widely known as fascism. Even Facebook executive Benny Thomas, a ‘CEO Global Planning Lead’, said in comments secretly recorded by investigative journalism operation Project Veritas that Facebook is ‘too powerful’ and should be broken up:

I mean, no king in history has been the ruler of two billion people, but Mark Zuckerberg is ... And he's 36. That's too much for a 36-year-old ... You should not have power over two billion people. I just think that's wrong.

Thomas said Facebook-owned platforms like Instagram, Oculus, and WhatsApp needed to be separate companies. ‘It’s too much power when they’re all one together’. That’s the way the Cult likes it, however. We have an executive of a Cult organisation in Benny Thomas that doesn’t know there is a Cult such is the compartmentalisation. Thomas said that Facebook and Google ‘are no longer companies, they’re countries’. Actually they are more powerful than countries on the basis that if you control information you control perception and control human society.

## **I love my oppressor**

Another expression of this psychological trickery is for those who realise they are being pressured into compliance to eventually

convince themselves to believe the official narratives to protect their self-respect from accepting the truth that they have succumbed to meek and subservient compliance. Such people become some of the most vehement defenders of the system. You can see them everywhere screaming abuse at those who prefer to think for themselves and by doing so reminding the compliers of their own capitulation to conformity. ‘You are talking dangerous nonsense you Covidiot!!’ Are you trying to convince me or yourself? It is a potent form of Stockholm syndrome which is defined as: ‘A psychological condition that occurs when a victim of abuse identifies and attaches, or bonds, positively with their abuser.’ An example is hostages bonding and even ‘falling in love’ with their kidnappers. The syndrome has been observed in domestic violence, abused children, concentration camp inmates, prisoners of war and many and various Satanic cults. These are some traits of Stockholm syndrome listed at [goodtherapy.org](http://goodtherapy.org):

- Positive regard towards perpetrators of abuse or captor [see ‘Covid’].
- Failure to cooperate with police and other government authorities when it comes to holding perpetrators of abuse or kidnapping accountable [or in the case of ‘Covid’ cooperating with the police to enforce and defend their captors’ demands].
- Little or no effort to escape [see ‘Covid’].
- Belief in the goodness of the perpetrators or kidnappers [see ‘Covid’].
- Appeasement of captors. This is a manipulative strategy for maintaining one’s safety. As victims get rewarded – perhaps with less abuse or even with life itself – their appeasing behaviours are reinforced [see ‘Covid’].
- Learned helplessness. This can be akin to ‘if you can’t beat ‘em, join ‘em’. As the victims fail to escape the abuse or captivity, they may start giving up and soon realize it’s just easier for everyone if they acquiesce all their power to their captors [see ‘Covid’].

- Feelings of pity toward the abusers, believing they are actually victims themselves. Because of this, victims may go on a crusade or mission to 'save' [protect] their abuser [see the venom unleashed on those challenging the official 'Covid' narrative].
- Unwillingness to learn to detach from their perpetrators and heal. In essence, victims may tend to be less loyal to themselves than to their abuser [*definitely* see 'Covid'].

Ponder on those traits and compare them with the behaviour of great swathes of the global population who have defended governments and authorities which have spent every minute destroying their lives and livelihoods and those of their children and grandchildren since early 2020 with fascistic lockdowns, house arrest and employment deletion to 'protect' them from a 'deadly virus' that their abusers' perceptually created to bring about this very outcome. We are looking at mass Stockholm syndrome. All those that agree to concede their freedom will believe those perceptions are originating in their own independent 'mind' when in fact by conceding their reality to Stockholm syndrome they have by definition conceded any independence of mind. Listen to the 'opinions' of the acquiescing masses in this 'Covid' era and what gushes forth is the repetition of the official version of everything delivered unprocessed, unfiltered and unquestioned. The whole programming dynamic works this way. I must be free because I'm told that I am and so I think that I am.

You can see what I mean with the chapter theme of 'I'm thinking – Oh, but *are you?*' The great majority are not thinking, let alone for themselves. They are repeating what authority has told them to believe which allows them to be controlled. Weaving through this mentality is the fear that the 'conspiracy theorists' are right and this again explains the often hysterical abuse that ensues when you dare to contest the official narrative of anything. Denial is the mechanism of hiding from yourself what you don't want to be true. Telling people what they want to hear is easy, but it's an infinitely greater challenge to tell them what they would rather not be happening.

One is akin to pushing against an open door while the other is met with vehement resistance no matter what the scale of evidence. I don't want it to be true so I'll convince myself that it's not. Examples are everywhere from the denial that a partner is cheating despite all the signs to the reflex-action rejection of any idea that world events in which country after country act in exactly the same way are centrally coordinated. To accept the latter is to accept that a force of unspeakable evil is working to destroy your life and the lives of your children with nothing too horrific to achieve that end. Who the heck wants that to be true? But if we don't face reality the end is duly achieved and the consequences are far worse and ongoing than breaking through the walls of denial today with the courage to make a stand against tyranny.

## **Connect the dots – but how?**

A crucial aspect of perceptual programming is to portray a world in which everything is random and almost nothing is connected to anything else. Randomness cannot be coordinated by its very nature and once you perceive events as random the idea they could be connected is waved away as the rantings of the tinfoil-hat brigade. You can't plan and coordinate random you idiot! No, you can't, but you can hide the coldly-calculated and long-planned behind the *illusion* of randomness. A foundation manifestation of the Renegade Mind is to scan reality for patterns that connect the apparently random and turn pixels and dots into pictures. This is the way I work and have done so for more than 30 years. You look for similarities in people, modus operandi and desired outcomes and slowly, then ever quicker, the picture forms. For instance: There would seem to be no connection between the 'Covid pandemic' hoax and the human-caused global-warming hoax and yet they are masks (appropriately) on the same face seeking the same outcome. Those pushing the global warming myth through the Club of Rome and other Cult agencies are driving the lies about 'Covid' – Bill Gates is an obvious one, but they are endless. Why would the same people be involved in both when they are clearly not connected? Oh, but they

are. Common themes with personnel are matched by common goals. The ‘solutions’ to both ‘problems’ are centralisation of global power to impose the will of the few on the many to ‘save’ humanity from ‘Covid’ and save the planet from an ‘existential threat’ (we need ‘zero Covid’ and ‘zero carbon emissions’). These, in turn, connect with the ‘dot’ of globalisation which was coined to describe the centralisation of global power in every area of life through incessant political and corporate expansion, trading blocks and superstates like the European Union. If you are the few and you want to control the many you have to centralise power and decision-making. The more you centralise power the more power the few at the centre will have over the many; and the more that power is centralised the more power those at the centre have to centralise even quicker. The momentum of centralisation gets faster and faster which is exactly the process we have witnessed. In this way the hoaxed ‘pandemic’ and the fakery of human-caused global warming serve the interests of globalisation and the seizure of global power in the hands of the Cult inner-circle which is behind ‘Covid’, ‘climate change’ and globalisation. At this point random ‘dots’ become a clear and obvious picture or pattern.

Klaus Schwab, the classic Bond villain who founded the Cult’s Gates-funded World Economic Forum, published a book in 2020, *The Great Reset*, in which he used the ‘problem’ of ‘Covid’ to justify a total transformation of human society to ‘save’ humanity from ‘climate change’. Schwab said: ‘The pandemic represents a rare but narrow window of opportunity to reflect, reimagine, and reset our world.’ What he didn’t mention is that the Cult he serves is behind both hoaxes as I show in my book *The Answer*. He and the Cult don’t have to reimagine the world. They know precisely what they want and that’s why they destroyed human society with ‘Covid’ to ‘build back better’ in their grand design. Their job is not to imagine, but to get humanity to imagine and agree with their plans while believing it’s all random. It must be pure coincidence that ‘The Great Reset’ has long been the Cult’s code name for the global imposition of fascism and replaced previous code-names of the ‘New World

'Order' used by Cult frontmen like Father George Bush and the 'New Order of the Ages' which emerged from Freemasonry and much older secret societies. New Order of the Ages appears on the reverse of the Great Seal of the United States as 'Novus ordo seclorum' underneath the Cult symbol used since way back of the pyramid and all seeing-eye ([Fig 3](#)). The pyramid is the hierarchy of human control headed by the illuminated eye that symbolises the force behind the Cult which I will expose in later chapters. The term 'Annuit Coeptis' translates as 'He favours our undertaking'. We are told the 'He' is the Christian god, but 'He' is not as I will be explaining.



**Figure 3:** The all-seeing eye of the Cult 'god' on the Freemason-designed Great Seal of the United States and also on the dollar bill.

## Having you on

Two major Cult techniques of perceptual manipulation that relate to all this are what I have called since the 1990s Problem-Reaction-Solution (PRS) and the Totalitarian Tiptoe (TT). They can be uncovered by the inquiring mind with a simple question: Who benefits? The answer usually identifies the perpetrators of a given action or happening through the concept of 'he who most benefits from a crime is the one most likely to have committed it'. The Latin 'Cue bono?' – Who benefits? – is widely attributed to the Roman orator and statesman Marcus Tullius Cicero. No wonder it goes back so far when the concept has been relevant to human behaviour since

history was recorded. Problem-Reaction-Solution is the technique used to manipulate us every day by covertly creating a problem (or the illusion of one) and offering the solution to the problem (or the illusion of one). In the first phase you create the problem and blame someone or something else for why it has happened. This may relate to a financial collapse, terrorist attack, war, global warming or pandemic, anything in fact that will allow you to impose the ‘solution’ to change society in the way you desire at that time. The ‘problem’ doesn’t have to be real. PRS is manipulation of perception and all you need is the population to believe the problem is real. Human-caused global warming and the ‘Covid pandemic’ only have to be *perceived* to be real for the population to accept the ‘solutions’ of authority. I refer to this technique as NO-Problem-Reaction-Solution. Billions did not meekly accept house arrest from early 2020 because there was a real deadly ‘Covid pandemic’ but because they perceived – believed – that to be the case. The antidote to Problem-Reaction-Solution is to ask who benefits from the proposed solution. Invariably it will be anyone who wants to justify more control through deletion of freedom and centralisation of power and decision-making.

The two world wars were Problem-Reaction-Solutions that transformed and realigned global society. Both were manipulated into being by the Cult as I have detailed in books since the mid-1990s. They dramatically centralised global power, especially World War Two, which led to the United Nations and other global bodies thanks to the overt and covert manipulations of the Rockefeller family and other Cult bloodlines like the Rothschilds. The UN is a stalking horse for full-blown world government that I will come to shortly. The land on which the UN building stands in New York was donated by the Rockefellers and the same Cult family was behind Big Pharma scalpel and drug ‘medicine’ and the creation of the World Health Organization as part of the UN. They have been stalwarts of the eugenics movement and funded Hitler’s race-purity expert Ernst Rudin. The human-caused global warming hoax has been orchestrated by the Club of Rome through the UN which is

manufacturing both the ‘problem’ through its Intergovernmental Panel on Climate Change and imposing the ‘solution’ through its Agenda 21 and Agenda 2030 which demand the total centralisation of global power to ‘save the world’ from a climate hoax the United Nations is itself perpetrating. What a small world the Cult can be seen to be particularly among the inner circles. The bedfellow of Problem-Reaction-Solution is the Totalitarian Tiptoe which became the Totalitarian Sprint in 2020. The technique is fashioned to hide the carefully-coordinated behind the cover of apparently random events. You start the sequence at ‘A’ and you know you are heading for ‘Z’. You don’t want people to know that and each step on the journey is presented as a random happening while all the steps strung together lead in the same direction. The speed may have quickened dramatically in recent times, but you can still see the incremental approach of the Tiptoe in the case of ‘Covid’ as each new imposition takes us deeper into fascism. Tell people they have to do this or that to get back to ‘normal’, then this and this and this. With each new demand adding to the ones that went before the population’s freedom is deleted until it disappears. The spider wraps its web around the flies more comprehensively with each new diktat. I’ll highlight this in more detail when I get to the ‘Covid’ hoax and how it has been pulled off. Another prime example of the Totalitarian Tiptoe is how the Cult-created European Union went from a ‘free-trade zone’ to a centralised bureaucratic dictatorship through the Tiptoe of incremental centralisation of power until nations became mere administrative units for Cult-owned dark suits in Brussels.

The antidote to ignorance is knowledge which the Cult seeks vehemently to deny us, but despite the systematic censorship to that end the Renegade Mind can overcome this by vociferously seeking out the facts no matter the impediments put in the way. There is also a method of thinking and perceiving – *knowing* – that doesn’t even need names, dates, place-type facts to identify the patterns that reveal the story. I’ll get to that in the final chapter. All you need to know about the manipulation of human society and to what end is still out there – *at the time of writing* – in the form of books, videos

and websites for those that really want to breach the walls of programmed perception. To access this knowledge requires the abandonment of the mainstream media as a source of information in the awareness that this is owned and controlled by the Cult and therefore promotes mass perceptions that suit the Cult. Mainstream media lies all day, every day. That is its function and very reason for being. Where it does tell the truth, here and there, is only because the truth and the Cult agenda very occasionally coincide. If you look for fact and insight to the BBC, CNN and virtually all the rest of them you are asking to be conned and perceptually programmed.

### **Know the outcome and you'll see the journey**

Events seem random when you have no idea where the world is being taken. Once you do the random becomes the carefully planned. Know the outcome and you'll see the journey is a phrase I have been using for a long time to give context to daily happenings that appear unconnected. Does a problem, or illusion of a problem, trigger a proposed 'solution' that further drives society in the direction of the outcome? Invariably the answer will be yes and the random – *abracadabra* – becomes the clearly coordinated. So what is this outcome that unlocks the door to a massively expanded understanding of daily events? I will summarise its major aspects – the fine detail is in my other books – and those new to this information will see that the world they thought they were living in is a very different place. The foundation of the Cult agenda is the incessant centralisation of power and all such centralisation is ultimately in pursuit of Cult control on a global level. I have described for a long time the planned world structure of top-down dictatorship as the Hunger Games Society. The term obviously comes from the movie series which portrayed a world in which a few living in military-protected hi-tech luxury were the overlords of a population condemned to abject poverty in isolated 'sectors' that were not allowed to interact. 'Covid' lockdowns and travel bans anyone? The 'Hunger Games' pyramid of structural control has the inner circle of the Cult at the top with pretty much the entire

population at the bottom under their control through dependency for survival on the Cult. The whole structure is planned to be protected and enforced by a military-police state ([Fig 4](#)).

Here you have the reason for the global lockdowns of the fake pandemic to coldly destroy independent incomes and livelihoods and make everyone dependent on the ‘state’ (the Cult that controls the ‘states’). I have warned in my books for many years about the plan to introduce a ‘guaranteed income’ – a barely survivable pittance – designed to impose dependency when employment was destroyed by AI technology and now even more comprehensively at great speed by the ‘Covid’ scam. Once the pandemic was played and lockdown consequences began to delete independent income the authorities began to talk right on cue about the need for a guaranteed income and a ‘Great Reset’. Guaranteed income will be presented as benevolent governments seeking to help a desperate people – desperate as a direct result of actions of the same governments. The truth is that such payments are a trap. You will only get them if you do exactly what the authorities demand including mass vaccination (genetic manipulation). We have seen this theme already in Australia where those dependent on government benefits have them reduced if parents don’t agree to have their children vaccinated according to an insane health-destroying government-dictated schedule. Calculated economic collapse applies to governments as well as people. The Cult wants rid of countries through the creation of a world state with countries broken up into regions ruled by a world government and super states like the European Union. Countries must be bankrupted, too, to this end and it’s being achieved by the trillions in ‘rescue packages’ and furlough payments, trillions in lost taxation, and money-no-object spending on ‘Covid’ including constant all-medium advertising (programming) which has made the media dependent on government for much of its income. The day of reckoning is coming – as planned – for government spending and given that it has been made possible by printing money and not by production/taxation there is inflation on the way that has the

potential to wipe out monetary value. In that case there will be no need for the Cult to steal your money. It just won't be worth anything (see the German Weimar Republic before the Nazis took over). Many have been okay with lockdowns while getting a percentage of their income from so-called furlough payments without having to work. Those payments are dependent, however, on people having at least a theoretical job with a business considered non-essential and ordered to close. As these business go under because they are closed by lockdown after lockdown the furlough stops and it will for everyone eventually. Then what? The 'then what?' is precisely the idea.



**Figure 4:** The Hunger Games Society structure I have long warned was planned and now the 'Covid' hoax has made it possible. This is the real reason for lockdowns.

## Hired hands

Between the Hunger Games Cult elite and the dependent population is planned to be a vicious military-police state (a fusion of the two into one force). This has been in the making for a long time with police looking ever more like the military and carrying weapons to match. The pandemic scam has seen this process accelerate so fast as

lockdown house arrest is brutally enforced by carefully recruited fascist minds and gormless system-servers. The police and military are planned to merge into a centrally-directed world army in a global structure headed by a world government which wouldn't be elected even by the election fixes now in place. The world army is not planned even to be human and instead wars would be fought, primarily against the population, using robot technology controlled by artificial intelligence. I have been warning about this for decades and now militaries around the world are being transformed by this very AI technology. The global regime that I describe is a particular form of fascism known as a technocracy in which decisions are not made by clueless and co-opted politicians but by unelected technocrats – scientists, engineers, technologists and bureaucrats. Cult-owned-and-controlled Silicon Valley giants are examples of technocracy and they already have far more power to direct world events than governments. They are with their censorship *selecting* governments. I know that some are calling the 'Great Reset' a Marxist communist takeover, but fascism and Marxism are different labels for the same tyranny. Tell those who lived in fascist Germany and Stalinist Russia that there was a difference in the way their freedom was deleted and their lives controlled. I could call it a fascist technocracy or a Marxist technocracy and they would be equally accurate. The Hunger Games society with its world government structure would oversee a world army, world central bank and single world cashless currency imposing its will on a microchipped population ([Fig 5](#)). Scan its different elements and see how the illusory pandemic is forcing society in this very direction at great speed. Leaders of 23 countries and the World Health Organization (WHO) backed the idea in March, 2021, of a global treaty for 'international cooperation' in 'health emergencies' and nations should 'come together as a global community for peaceful cooperation that extends beyond this crisis'. Cut the Orwellian bullshit and this means another step towards global government. The plan includes a cashless digital money system that I first warned about in 1993. Right at the start of 'Covid' the deeply corrupt Tedros

Adhanom Ghebreyesus, the crooked and merely gofer ‘head’ of the World Health Organization, said it was possible to catch the ‘virus’ by touching cash and it was better to use cashless means. The claim was ridiculous nonsense and like the whole ‘Covid’ mind-trick it was nothing to do with ‘health’ and everything to do with pushing every aspect of the Cult agenda. As a result of the Tedros lie the use of cash has plummeted. The Cult script involves a single world digital currency that would eventually be technologically embedded in the body. China is a massive global centre for the Cult and if you watch what is happening there you will know what is planned for everywhere. The Chinese government is developing a digital currency which would allow fines to be deducted immediately via AI for anyone caught on camera breaking its fantastic list of laws and the money is going to be programmable with an expiry date to ensure that no one can accrue wealth except the Cult and its operatives.



**Figure 5:** The structure of global control the Cult has been working towards for so long and this has been enormously advanced by the ‘Covid’ illusion.

## **Serfdom is so smart**

The Cult plan is far wider, extreme, and more comprehensive than even most conspiracy researchers appreciate and I will come to the true depths of deceit and control in the chapters ‘Who controls the

Cult?' and 'Escaping Wetiko'. Even the world that we know is crazy enough. We are being deluged with ever more sophisticated and controlling technology under the heading of 'smart'. We have smart televisions, smart meters, smart cards, smart cars, smart driving, smart roads, smart pills, smart patches, smart watches, smart skin, smart borders, smart pavements, smart streets, smart cities, smart communities, smart environments, smart growth, smart planet ... smart *everything* around us. Smart technologies and methods of operation are designed to interlock to create a global Smart Grid connecting the entirety of human society including human minds to create a centrally-dictated 'hive' mind. 'Smart cities' is code for densely-occupied megacities of total surveillance and control through AI. Ever more destructive frequency communication systems like 5G have been rolled out without any official testing for health and psychological effects (colossal). 5G/6G/7G systems are needed to run the Smart Grid and each one becomes more destructive of body and mind. Deleting independent income is crucial to forcing people into these AI-policed prisons by ending private property ownership (except for the Cult elite). The Cult's Great Reset now openly foresees a global society in which no one will own any possessions and everything will be rented while the Cult would own literally everything under the guise of government and corporations. The aim has been to use the lockdowns to destroy sources of income on a mass scale and when the people are destitute and in unrepayable amounts of debt (problem) Cult assets come forward with the pledge to write-off debt in return for handing over all property and possessions (solution). Everything – literally everything including people – would be connected to the Internet via AI. I was warning years ago about the coming Internet of Things (IoT) in which all devices and technology from your car to your fridge would be plugged into the Internet and controlled by AI. Now we are already there with much more to come. The next stage is the Internet of Everything (IoE) which is planned to include the connection of AI to the human brain and body to replace the human mind with a centrally-controlled AI mind. Instead of perceptions

being manipulated through control of information and censorship those perceptions would come direct from the Cult through AI. What do you think? You think whatever AI decides that you think. In human terms there would be no individual 'think' any longer. Too incredible? The ravings of a lunatic? Not at all. Cult-owned crazies in Silicon Valley have been telling us the plan for years without explaining the real motivation and calculated implications. These include Google executive and 'futurist' Ray Kurzweil who highlights the year 2030 for when this would be underway. He said:

Our thinking ... will be a hybrid of biological and non-biological thinking ... humans will be able to extend their limitations and 'think in the cloud' ... We're going to put gateways to the cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations.

As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

The sales-pitch of Kurzweil and Cult-owned Silicon Valley is that this would make us 'super-human' when the real aim is to make us post-human and no longer 'human' in the sense that we have come to know. The entire global population would be connected to AI and become the centrally-controlled 'hive-mind' of externally-delivered perceptions. The Smart Grid being installed to impose the Cult's will on the world is being constructed to allow particular locations – even one location – to control the whole global system. From these prime control centres, which absolutely include China and Israel, anything connected to the Internet would be switched on or off and manipulated at will. Energy systems could be cut, communication via the Internet taken down, computer-controlled driverless autonomous vehicles driven off the road, medical devices switched off, the potential is limitless given how much AI and Internet connections now run human society. We have seen nothing yet if we allow this to continue. Autonomous vehicle makers are working with law enforcement to produce cars designed to automatically pull over if they detect a police or emergency vehicle flashing from up to 100 feet away. At a police stop the car would be unlocked and the

window rolled down automatically. Vehicles would only take you where the computer (the state) allowed. The end of petrol vehicles and speed limiters on all new cars in the UK and EU from 2022 are steps leading to electric computerised transport over which ultimately you have no control. The picture is far bigger even than the Cult global network or web and that will become clear when I get to the nature of the ‘spider’. There is a connection between all these happenings and the instigation of DNA-manipulating ‘vaccines’ (which aren’t ‘vaccines’) justified by the ‘Covid’ hoax. That connection is the unfolding plan to transform the human body from a biological to a synthetic biological state and this is why synthetic biology is such a fast-emerging discipline of mainstream science. ‘Covid vaccines’ are infusing self-replicating synthetic genetic material into the cells to cumulatively take us on the Totalitarian Tiptoe from Human 1.0 to the synthetic biological Human 2.0 which will be physically and perceptually attached to the Smart Grid to one hundred percent control every thought, perception and deed.

Humanity needs to wake up and *fast*.

This is the barest explanation of where the ‘outcome’ is planned to go but it’s enough to see the journey happening all around us. Those new to this information will already see ‘Covid’ in a whole new context. I will add much more detail as we go along, but for the minutiae evidence see my mega-works, *The Answer*, *The Trigger* and *Everything You Need to Know But Have Never Been Told*.

Now – how does a Renegade Mind see the ‘world’?

## CHAPTER TWO

### Renegade Perception

*It is one thing to be clever and another to be wise*

George R.R. Martin

A simple definition of the difference between a programmed mind and a Renegade Mind would be that one sees only dots while the other connects them to see the picture. Reading reality with accuracy requires the observer to (a) know the planned outcome and (b) realise that everything, but *everything*, is connected.

The entirety of infinite reality is connected – that's its very nature – and with human society an expression of infinite reality the same must apply. Simple cause and effect is a connection. The effect is triggered by the cause and the effect then becomes the cause of another effect. Nothing happens in isolation because it *can't*. Life in whatever reality is simple choice and consequence. We make choices and these lead to consequences. If we don't like the consequences we can make different choices and get different consequences which lead to other choices and consequences. The choice and the consequence are not only connected they are indivisible. You can't have one without the other as an old song goes. A few cannot control the world unless those being controlled allow that to happen – cause and effect, choice and consequence. Control – who has it and who doesn't – is a two-way process, a symbiotic relationship, involving the controller and controlled. 'They took my freedom away!!' Well, yes, but you also gave it to them. Humanity is

subjected to mass control because humanity has acquiesced to that control. This is all cause and effect and literally a case of give and take. In the same way world events of every kind are connected and the Cult works incessantly to sell the illusion of the random and coincidental to maintain the essential (to them) perception of dots that hide the picture. Renegade Minds know this and constantly scan the world for patterns of connection. This is absolutely pivotal in understanding the happenings in the world and without that perspective clarity is impossible. First you know the planned outcome and then you identify the steps on the journey – the day-by-day apparently random which, when connected in relation to the outcome, no longer appear as individual events, but as the proverbial *chain* of events leading in the same direction. I'll give you some examples:

## **Political puppet show**

We are told to believe that politics is 'adversarial' in that different parties with different beliefs engage in an endless tussle for power. There may have been some truth in that up to a point – and only a point – but today divisions between 'different' parties are rhetorical not ideological. Even the rhetorical is fusing into one-speak as the parties eject any remaining free thinkers while others succumb to the ever-gathering intimidation of anyone with the 'wrong' opinion. The Cult is not a new phenomenon and can be traced back thousands of years as my books have documented. Its intergenerational initiates have been manipulating events with increasing effect the more that global power has been centralised. In ancient times the Cult secured control through the system of monarchy in which 'special' bloodlines (of which more later) demanded the right to rule as kings and queens simply by birthright and by vanquishing others who claimed the same birthright. There came a time, however, when people had matured enough to see the unfairness of such tyranny and demanded a say in who governed them. Note the word – *governed* them. Not served them – *governed* them, hence government defined as 'the political direction and control exercised over the

actions of the members, citizens, or inhabitants of communities, societies, and states; direction of the affairs of a state, community, etc.' Governments exercise control over rather than serve just like the monarchies before them. Bizarrely there are still countries like the United Kingdom which are ruled by a monarch *and* a government that officially answers to the monarch. The UK head of state and that of Commonwealth countries such as Canada, Australia and New Zealand is 'selected' by who in a *single family* had unprotected sex with whom and in what order. Pinch me it can't be true. Ouch! Shit, it is. The demise of monarchies in most countries offered a potential vacuum in which some form of free and fair society could arise and the Cult had that base covered. Monarchies had served its interests but they couldn't continue in the face of such widespread opposition and, anyway, replacing a 'royal' dictatorship that people could see with a dictatorship 'of the people' hiding behind the concept of 'democracy' presented far greater manipulative possibilities and ways of hiding coordinated tyranny behind the illusion of 'freedom'.

Democracy is quite wrongly defined as government selected by the population. This is not the case at all. It is government selected by *some* of the population (and then only in theory). This 'some' doesn't even have to be the majority as we have seen so often in first-past-the-post elections in which the so-called majority party wins fewer votes than the 'losing' parties combined. Democracy can give total power to a party in government from a minority of the votes cast. It's a sleight of hand to sell tyranny as freedom. Seventy-four million Trump-supporting Americans didn't vote for the 'Democratic' Party of Joe Biden in the distinctly dodgy election in 2020 and yet far from acknowledging the wishes and feelings of that great percentage of American society the Cult-owned Biden government set out from day one to destroy them and their right to a voice and opinion. Empty shell Biden and his Cult handlers said they were doing this to 'protect democracy'. Such is the level of lunacy and sickness to which politics has descended. Connect the dots and relate them to the desired outcome – a world government run by self-appointed technocrats and no longer even elected

politicians. While operating through its political agents in government the Cult is at the same time encouraging public distain for politicians by putting idiots and incompetents in theoretical power on the road to deleting them. The idea is to instil a public reaction that says of the technocrats: 'Well, they couldn't do any worse than the pathetic politicians.' It's all about controlling perception and Renegade Minds can see through that while programmed minds cannot when they are ignorant of both the planned outcome and the manipulation techniques employed to secure that end. This knowledge can be learned, however, and fast if people choose to get informed.

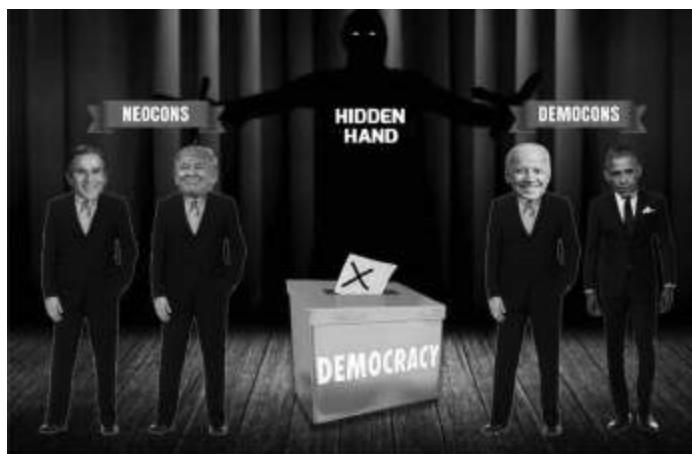
Politics may at first sight appear very difficult to control from a central point. I mean look at the 'different' parties and how would you be able to oversee them all and their constituent parts? In truth, it's very straightforward because of their structure. We are back to the pyramid of imposition and acquiescence. Organisations are structured in the same way as the system as a whole. Political parties are not open forums of free expression. They are hierarchies. I was a national spokesman for the British Green Party which claimed to be a different kind of politics in which influence and power was devolved; but I can tell you from direct experience – and it's far worse now – that Green parties are run as hierarchies like all the others however much they may try to hide that fact or kid themselves that it's not true. A very few at the top of all political parties are directing policy and personnel. They decide if you are elevated in the party or serve as a government minister and to do that you have to be a yes man or woman. Look at all the maverick political thinkers who never ascended the greasy pole. If you want to progress within the party or reach 'high-office' you need to fall into line and conform. Exceptions to this are rare indeed. Should you want to run for parliament or Congress you have to persuade the local or state level of the party to select you and for that you need to play the game as dictated by the hierarchy. If you secure election and wish to progress within the greater structure you need to go on conforming to what is acceptable to those running the hierarchy

from the peak of the pyramid. Political parties are perceptual gulags and the very fact that there are party ‘Whips’ appointed to ‘whip’ politicians into voting the way the hierarchy demands exposes the ridiculous idea that politicians are elected to serve the people they are supposed to represent. Cult operatives and manipulation has long seized control of major parties that have any chance of forming a government and at least most of those that haven’t. A new party forms and the Cult goes to work to infiltrate and direct. This has reached such a level today that you see video compilations of ‘leaders’ of all parties whether Democrats, Republicans, Conservative, Labour and Green parroting the same Cult mantra of ‘Build Back Better’ and the ‘Great Reset’ which are straight off the Cult song-sheet to describe the transformation of global society in response to the Cult-instigated hoaxes of the ‘Covid pandemic’ and human-caused ‘climate change’. To see Caroline Lucas, the Green Party MP that I knew when I was in the party in the 1980s, speaking in support of plans proposed by Cult operative Klaus Schwab representing the billionaire global elite is a real head-shaker.

## **Many parties – one master**

The party system is another mind-trick and was instigated to change the nature of the dictatorship by swapping ‘royalty’ for dark suits that people believed – though now ever less so – represented their interests. Understanding this trick is to realise that a single force (the Cult) controls all parties either directly in terms of the major ones or through manipulation of perception and ideology with others. You don’t need to manipulate Green parties to demand your transformation of society in the name of ‘climate change’ when they are obsessed with the lie that this is essential to ‘save the planet’. You just give them a platform and away they go serving your interests while believing they are being environmentally virtuous. America’s political structure is a perfect blueprint for how the two or multi-party system is really a one-party state. The Republican Party is controlled from one step back in the shadows by a group made up of billionaires and their gofers known as neoconservatives or Neocons.

I have exposed them in fine detail in my books and they were the driving force behind the policies of the imbecilic presidency of Boy George Bush which included 9/11 (see *The Trigger* for a comprehensive demolition of the official story), the subsequent ‘war on terror’ (war of terror) and the invasions of Afghanistan and Iraq. The latter was a No-Problem-Reaction-Solution based on claims by Cult operatives, including Bush and British Prime Minister Tony Blair, about Saddam Hussein’s ‘weapons of mass destruction’ which did not exist as war criminals Bush and Blair well knew.



**Figure 6:** Different front people, different parties – same control system.

The Democratic Party has its own ‘Neocon’ group controlling from the background which I call the ‘Democons’ and here’s the penny-drop – the Neocons and Democons answer to the same masters one step further back into the shadows (Fig 6). At that level of the Cult the Republican and Democrat parties are controlled by the same people and no matter which is in power the Cult is in power. This is how it works in almost every country and certainly in Britain with Conservative, Labour, Liberal Democrat and Green parties now all on the same page whatever the rhetoric may be in their feeble attempts to appear different. Neocons operated at the time of Bush through a think tank called The Project for the New American Century which in September, 2000, published a document entitled *Rebuilding America’s Defenses: Strategies, Forces, and Resources*

*For a New Century* demanding that America fight ‘multiple, simultaneous major theatre wars’ as a ‘core mission’ to force regime-change in countries including Iraq, Libya and Syria. Neocons arranged for Bush (‘Republican’) and Blair (‘Labour Party’) to front-up the invasion of Iraq and when they departed the Democons orchestrated the targeting of Libya and Syria through Barack Obama (‘Democrat’) and British Prime Minister David Cameron (‘Conservative Party’). We have ‘different’ parties and ‘different’ people, but the same unfolding script. The more the Cult has seized the reigns of parties and personnel the more their policies have transparently pursued the same agenda to the point where the fascist ‘Covid’ impositions of the Conservative junta of Jackboot Johnson in Britain were opposed by the Labour Party because they were not fascist enough. The Labour Party is likened to the US Democrats while the Conservative Party is akin to a British version of the Republicans and on both sides of the Atlantic they all speak the same language and support the direction demanded by the Cult although some more enthusiastically than others. It’s a similar story in country after country because it’s all centrally controlled. Oh, but what about Trump? I’ll come to him shortly. Political ‘choice’ in the ‘party’ system goes like this: You vote for Party A and they get into government. You don’t like what they do so next time you vote for Party B and they get into government. You don’t like what they do when it’s pretty much the same as Party A and why wouldn’t that be with both controlled by the same force? Given that only two, sometimes three, parties have any chance of forming a government to get rid of Party B that you don’t like you have to vote again for Party A which ... you don’t like. This, ladies and gentlemen, is what they call ‘democracy’ which we are told – wrongly – is a term interchangeable with ‘freedom’.

## **The cult of cults**

At this point I need to introduce a major expression of the Global Cult known as Sabbatian-Frankism. Sabbatian is also spelt as Sabbatean. I will summarise here. I have published major exposés

and detailed background in other works. Sabbatian-Frankism combines the names of two frauds posing as 'Jewish' men, Sabbatai Zevi (1626-1676), a rabbi, black magician and occultist who proclaimed he was the Jewish messiah; and Jacob Frank (1726-1791), the Polish 'Jew', black magician and occultist who said he was the reincarnation of 'messiah' Zevi and biblical patriarch Jacob. They worked across two centuries to establish the Sabbatian-Frankist cult that plays a major, indeed central, role in the manipulation of human society by the Global Cult which has its origins much further back in history than Sabbatai Zevi. I should emphasise two points here in response to the shrill voices that will scream 'anti-Semitism': (1) Sabbatian-Frankists are NOT Jewish and only pose as such to hide their cult behind a Jewish façade; and (2) my information about this cult has come from Jewish sources who have long realised that their society and community has been infiltrated and taken over by interloper Sabbatian-Frankists. Infiltration has been the foundation technique of Sabbatian-Frankism from its official origin in the 17th century. Zevi's Sabbatian sect attracted a massive following described as the biggest messianic movement in Jewish history, spreading as far as Africa and Asia, and he promised a return for the Jews to the 'Promised Land' of Israel. Sabbatianism was not Judaism but an inversion of everything that mainstream Judaism stood for. So much so that this sinister cult would have a feast day when Judaism had a fast day and whatever was forbidden in Judaism the Sabbatians were encouraged and even commanded to do. This included incest and what would be today called Satanism. Members were forbidden to marry outside the sect and there was a system of keeping their children ignorant of what they were part of until they were old enough to be trusted not to unknowingly reveal anything to outsiders. The same system is employed to this day by the Global Cult in general which Sabbatian-Frankism has enormously influenced and now largely controls.

Zevi and his Sabbatians suffered a setback with the intervention by the Sultan of the Islamic Ottoman Empire in the Middle East and what is now the Republic of Turkey where Zevi was located. The

Sultan gave him the choice of proving his ‘divinity’, converting to Islam or facing torture and death. Funnily enough Zevi chose to convert or at least appear to. Some of his supporters were disillusioned and drifted away, but many did not with 300 families also converting – only in theory – to Islam. They continued behind this Islamic smokescreen to follow the goals, rules and rituals of Sabbatianism and became known as ‘crypto-Jews’ or the ‘Dönmeh’ which means ‘to turn’. This is rather ironic because they didn’t ‘turn’ and instead hid behind a fake Islamic persona. The process of appearing to be one thing while being very much another would become the calling card of Sabbatianism especially after Zevi’s death and the arrival of the Satanist Jacob Frank in the 18th century when the cult became Sabbatian-Frankism and plumbbed still new depths of depravity and infiltration which included – still includes – human sacrifice and sex with children. Wherever Sabbatians go paedophilia and Satanism follow and is it really a surprise that Hollywood is so infested with child abuse and Satanism when it was established by Sabbatian-Frankists and is still controlled by them? Hollywood has been one of the prime vehicles for global perceptual programming and manipulation. How many believe the version of ‘history’ portrayed in movies when it is a travesty and inversion (again) of the truth? Rabbi Marvin Antelman describes Frankism in his book, *To Eliminate the Opiate*, as ‘a movement of complete evil’ while Jewish professor Gershom Scholem said of Frank in *The Messianic Idea in Judaism*: ‘In all his actions [he was] a truly corrupt and degenerate individual ... one of the most frightening phenomena in the whole of Jewish history.’ Frank was excommunicated by traditional rabbis, as was Zevi, but Frank was undeterred and enjoyed vital support from the House of Rothschild, the infamous banking dynasty whose inner-core are Sabbatian-Frankists and not Jews. Infiltration of the Roman Church and Vatican was instigated by Frank with many Dönmeh ‘turning’ again to convert to Roman Catholicism with a view to hijacking the reins of power. This was the ever-repeating modus operandi and continues to be so. Pose as an advocate of the religion, culture or country that you want to control and then

manipulate your people into the positions of authority and influence largely as advisers, administrators and Svengalis for those that appear to be in power. They did this with Judaism, Christianity (Christian Zionism is part of this), Islam and other religions and nations until Sabbatian-Frankism spanned the world as it does today.

## **Sabbatian Saudis and the terror network**

One expression of the Sabbatian-Frankist Dönme within Islam is the ruling family of Saudi Arabia, the House of Saud, through which came the vile distortion of Islam known as Wahhabism. This is the violent creed followed by terrorist groups like Al-Qaeda and ISIS or Islamic State. Wahhabism is the hand-chopping, head-chopping ‘religion’ of Saudi Arabia which is used to keep the people in a constant state of fear so the interloper House of Saud can continue to rule. Al-Qaeda and Islamic State were lavishly funded by the House of Saud while being created and directed by the Sabbatian-Frankist network in the United States that operates through the Pentagon, CIA and the government in general of whichever ‘party’. The front man for the establishment of Wahhabism in the middle of the 18th century was a Sabbatian-Frankist ‘crypto-Jew’ posing as Islamic called Muhammad ibn Abd al-Wahhab. His daughter would marry the son of Muhammad bin Saud who established the first Saudi state before his death in 1765 with support from the British Empire. Bin Saud’s successors would establish modern Saudi Arabia in league with the British and Americans in 1932 which allowed them to seize control of Islam’s major shrines in Mecca and Medina. They have dictated the direction of Sunni Islam ever since while Iran is the major centre of the Shiite version and here we have the source of at least the public conflict between them. The Sabbatian network has used its Wahhabi extremists to carry out Problem-Reaction-Solution terrorist attacks in the name of ‘Al-Qaeda’ and ‘Islamic State’ to justify a devastating ‘war on terror’, ever-increasing surveillance of the population and to terrify people into compliance. Another insight of the Renegade Mind is the streetwise understanding that

just because a country, location or people are attacked doesn't mean that those apparently representing that country, location or people are not behind the attackers. Often they are *orchestrating* the attacks because of the societal changes that can be then justified in the name of 'saving the population from terrorists'.

I show in great detail in *The Trigger* how Sabbatian-Frankists were the real perpetrators of 9/11 and not '19 Arab hijackers' who were blamed for what happened. Observe what was justified in the name of 9/11 alone in terms of Middle East invasions, mass surveillance and control that fulfilled the demands of the Project for the New American Century document published by the Sabbatian Neocons. What appear to be enemies are on the deep inside players on the same Sabbatian team. Israel and Arab 'royal' dictatorships are all ruled by Sabbatians and the recent peace agreements between Israel and Saudi Arabia, the United Arab Emirates (UAE) and others are only making formal what has always been the case behind the scenes. Palestinians who have been subjected to grotesque tyranny since Israel was bombed and terrorised into existence in 1948 have never stood a chance. Sabbatian-Frankists have controlled Israel (so the constant theme of violence and war which Sabbatians love) and they have controlled the Arab countries that Palestinians have looked to for real support that never comes. 'Royal families' of the Arab world in Saudi Arabia, Bahrain, UAE, etc., are all Sabbatians with allegiance to the aims of the cult and not what is best for their Arabic populations. They have stolen the oil and financial resources from their people by false claims to be 'royal dynasties' with a genetic right to rule and by employing vicious militaries to impose their will.

## **Satanic 'illumination'**

The Satanist Jacob Frank formed an alliance in 1773 with two other Sabbatians, Mayer Amschel Rothschild (1744-1812), founder of the Rothschild banking dynasty, and Jesuit-educated fraudulent Jew, Adam Weishaupt, and this led to the formation of the Bavarian Illuminati, firstly under another name, in 1776. The Illuminati would

be the manipulating force behind the French Revolution (1789-1799) and was also involved in the American Revolution (1775-1783) before and after the Illuminati's official creation. Weishaupt would later become (in public) a Protestant Christian in archetypal Sabbatian style. I read that his name can be decoded as Adam-Weishaupt or 'the first man to lead those who know'. He wasn't a leader in the sense that he was a subordinate, but he did lead those below him in a crusade of transforming human society that still continues today. The theme was confirmed as early as 1785 when a horseman courier called Lanz was reported to be struck by lighting and extensive Illuminati documents were found in his saddlebags. They made the link to Weishaupt and detailed the plan for world takeover. Current events with 'Covid' fascism have been in the making for a very long time. Jacob Frank was jailed for 13 years by the Catholic Inquisition after his arrest in 1760 and on his release he headed for Frankfurt, Germany, home city and headquarters of the House of Rothschild where the alliance was struck with Mayer Amschel Rothschild and Weishaupt. Rothschild arranged for Frank to be given the title of Baron and he became a wealthy nobleman with a big following of Jews in Germany, the Austro-Hungarian Empire and other European countries. Most of them would have believed he was on their side.

The name 'Illuminati' came from the Zohar which is a body of works in the Jewish mystical 'bible' called the Kabbalah. 'Zohar' is the foundation of Sabbatian-Frankist belief and in Hebrew 'Zohar' means 'splendour', 'radiance', 'illuminated', and so we have 'Illuminati'. They claim to be the 'Illuminated Ones' from their knowledge systematically hidden from the human population and passed on through generations of carefully-chosen initiates in the global secret society network or Cult. Hidden knowledge includes an awareness of the Cult agenda for the world and the nature of our collective reality that I will explore later. Cult 'illumination' is symbolised by the torch held by the Statue of Liberty which was gifted to New York by French Freemasons in Paris who knew exactly what it represents. 'Liberty' symbolises the goddess worshipped in

Babylon as Queen Semiramis or Ishtar. The significance of this will become clear. Notice again the ubiquitous theme of inversion with the Statue of 'Liberty' really symbolising mass control ([Fig 7](#)). A mirror-image statute stands on an island in the River Seine in Paris from where New York Liberty originated ([Fig 8](#)). A large replica of the Liberty flame stands on top of the Pont de l'Alma tunnel in Paris where Princess Diana died in a Cult ritual described in *The Biggest Secret*. Lucifer 'the light bringer' is related to all this (and much more as we'll see) and 'Lucifer' is a central figure in Sabbatian-Frankism and its associated Satanism. Sabbatians reject the Jewish Torah, or Pentateuch, the 'five books of Moses' in the Old Testament known as Genesis, Exodus, Leviticus, Numbers, and Deuteronomy which are claimed by Judaism and Christianity to have been dictated by 'God' to Moses on Mount Sinai. Sabbatians say these do not apply to them and they seek to replace them with the Zohar to absorb Judaism and its followers into their inversion which is an expression of a much greater global inversion. They want to delete all religions and force humanity to worship a one-world religion – Sabbatian Satanism that also includes worship of the Earth goddess. Satanic themes are being more and more introduced into mainstream society and while Christianity is currently the foremost target for destruction the others are planned to follow.



**Figure 7:** The Cult goddess of Babylon disguised as the Statue of Liberty holding the flame of Lucifer the 'light bringer'.



**Figure 8:** Liberty's mirror image in Paris where the New York version originated.

## **Marx brothers**

Rabbi Marvin Antelman connects the Illuminati to the Jacobins in *To Eliminate the Opiate* and Jacobins were the force behind the French Revolution. He links both to the Bund der Gerechten, or League of the Just, which was the network that inflicted communism/Marxism on the world. Antelman wrote:

The original inner circle of the Bund der Gerechten consisted of born Catholics, Protestants and Jews [Sabbatian-Frankist infiltrators], and those representatives of respective subdivisions formulated schemes for the ultimate destruction of their faiths. The heretical Catholics laid plans which they felt would take a century or more for the ultimate destruction of the church; the apostate Jews for the ultimate destruction of the Jewish religion.

Sabbatian-created communism connects into this anti-religion agenda in that communism does not allow for the free practice of religion. The Sabbatian 'Bund' became the International Communist Party and Communist League and in 1848 'Marxism' was born with the Communist Manifesto of Sabbatian assets Karl Marx and Friedrich Engels. It is absolutely no coincidence that Marxism, just a different name for fascist and other centrally-controlled tyrannies, is being imposed worldwide as a result of the 'Covid' hoax and nor that Marxist/fascist China was the place where the hoax originated. The reason for this will become very clear in the chapter 'Covid: The calculated catastrophe'. The so-called 'Woke' mentality has hijacked

traditional beliefs of the political left and replaced them with far-right make-believe ‘social justice’ better known as Marxism. Woke will, however, be swallowed by its own perceived ‘revolution’ which is really the work of billionaires and billionaire corporations feigning being ‘Woke’. Marxism is being touted by Wokers as a replacement for ‘capitalism’ when we don’t have ‘capitalism’. We have cartelism in which the market is stitched up by the very Cult billionaires and corporations bankrolling Woke. Billionaires love Marxism which keeps the people in servitude while they control from the top.

Terminally naïve Wokers think they are ‘changing the world’ when it’s the Cult that is doing the changing and when they have played their vital part and become surplus to requirements they, too, will be targeted. The Illuminati-Jacobins were behind the period known as ‘The Terror’ in the French Revolution in 1793 and 1794 when Jacobin Maximillian de Robespierre and his Orwellian ‘Committee of Public Safety’ killed 17,000 ‘enemies of the Revolution’ who had once been ‘friends of the Revolution’. Karl Marx (1818-1883), whose Sabbatian creed of Marxism has cost the lives of at least 100 million people, is a hero once again to Wokers who have been systematically kept ignorant of real history by their ‘education’ programming. As a result they now promote a Sabbatian ‘Marxist’ abomination destined at some point to consume them. Rabbi Antelman, who spent decades researching the Sabbatian plot, said of the League of the Just and Karl Marx:

Contrary to popular opinion Karl Marx did not originate the Communist Manifesto. He was paid for his services by the League of the Just, which was known in its country of origin, Germany, as the Bund der Gaeachteten.

Antelman said the text attributed to Marx was the work of other people and Marx ‘was only repeating what others already said’. Marx was ‘a hired hack – lackey of the wealthy Illuminists’. Marx famously said that religion was the ‘opium of the people’ (part of the Sabbatian plan to demonise religion) and Antelman called his books, *To Eliminate the Opiate*. Marx was born Jewish, but his family converted to Christianity (Sabbatian modus operandi) and he

attacked Jews, not least in his book, *A World Without Jews*. In doing so he supported the Sabbatian plan to destroy traditional Jewishness and Judaism which we are clearly seeing today with the vindictive targeting of orthodox Jews by the Sabbatian government of Israel over 'Covid' laws. I don't follow any religion and it has done much damage to the world over centuries and acted as a perceptual straightjacket. Renegade Minds, however, are always asking *why* something is being done. It doesn't matter if they agree or disagree with what is happening – *why* is it happening is the question. The 'why?' can be answered with regard to religion in that religions create interacting communities of believers when the Cult wants to dismantle all discourse, unity and interaction (see 'Covid' lockdowns) and the ultimate goal is to delete all religions for a one-world religion of Cult Satanism worshipping their 'god' of which more later. We see the same 'why?' with gun control in America. I don't have guns and don't want them, but why is the Cult seeking to disarm the population at the same time that law enforcement agencies are armed to their molars and why has every tyrant in history sought to disarm people before launching the final takeover? They include Hitler, Stalin, Pol Pot and Mao who followed confiscation with violent seizing of power. You know it's a Cult agenda by the people who immediately race to the microphones to exploit dead people in multiple shootings. Ultra-Zionist Cult lackey Senator Chuck Schumer was straight on the case after ten people were killed in Boulder, Colorado in March, 2021. Simple rule ... if Schumer wants it the Cult wants it and the same with his ultra-Zionist mate the wild-eyed Senator Adam Schiff. At the same time they were calling for the disarmament of Americans, many of whom live a long way from a police response, Schumer, Schiff and the rest of these pampered clowns were sitting on Capitol Hill behind a razor-wired security fence protected by thousands of armed troops in addition to their own armed bodyguards. Mom and pop in an isolated home? They're just potential mass shooters.

## Zion Mainframe

Sabbatian-Frankists and most importantly the Rothschilds were behind the creation of 'Zionism', a political movement that demanded a Jewish homeland in Israel as promised by Sabbatai Zevi. The very symbol of Israel comes from the German meaning of the name Rothschild. Dynasty founder Mayer Amschel Rothschild changed the family name from Bauer to Rothschild, or 'Red-Shield' in German, in deference to the six-pointed 'Star of David' hexagram displayed on the family's home in Frankfurt. The symbol later appeared on the flag of Israel after the Rothschilds were centrally involved in its creation. Hexagrams are not a uniquely Jewish symbol and are widely used in occult ('hidden') networks often as a symbol for Saturn (see my other books for why). Neither are Zionism and Jewishness interchangeable. Zionism is a political movement and philosophy and not a 'race' or a people. Many Jews oppose Zionism and many non-Jews, including US President Joe Biden, call themselves Zionists as does Israel-centric Donald Trump. America's support for the Israel government is pretty much a gimme with ultra-Zionist billionaires and corporations providing fantastic and dominant funding for both political parties. Former Congresswoman Cynthia McKinney has told how she was approached immediately she ran for office to 'sign the pledge' to Israel and confirm that she would always vote in that country's best interests. All American politicians are approached in this way. Anyone who refuses will get no support or funding from the enormous and all-powerful Zionist lobby that includes organisations like mega-lobby group AIPAC, the American Israel Public Affairs Committee. Trump's biggest funder was ultra-Zionist casino and media billionaire Sheldon Adelson while major funders of the Democratic Party include ultra-Zionist George Soros and ultra-Zionist financial and media mogul, Haim Saban. Some may reel back at the suggestion that Soros is an Israel-firster (Sabbatian-controlled Israel-firster), but Renegade Minds watch the actions not the words and everywhere Soros donates his billions the Sabbatian agenda benefits. In the spirit of Sabbatian inversion Soros pledged \$1 billion for a new university network to promote 'liberal values and tackle intolerance'. He made the announcement during his annual speech

at the Cult-owned World Economic Forum in Davos, Switzerland, in January, 2020, after his ‘harsh criticism’ of ‘authoritarian rulers’ around the world. You can only laugh at such brazen mendacity. How *he* doesn’t laugh is the mystery. Translated from the Orwellian ‘liberal values and tackle intolerance’ means teaching non-white people to hate white people and for white people to loathe themselves for being born white. The reason for that will become clear.

### **The ‘Anti-Semitism’ fraud**

Zionists support the Jewish homeland in the land of Palestine which has been the Sabbatian-Rothschild goal for so long, but not for the benefit of Jews. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. This is nothing more than a Sabbatian protection racket to stop legitimate investigation and exposure of their agendas and activities. The official definition of ‘anti-Semitism’ has more recently been expanded to include criticism of Zionism – a *political movement* – and this was done to further stop exposure of Sabbatian infiltrators who created Zionism as we know it today in the 19th century. Renegade Minds will talk about these subjects when they know the shit that will come their way. People must decide if they want to know the truth or just cower in the corner in fear of what others will say. Sabbatians have been trying to label me as ‘anti-Semitic’ since the 1990s as I have uncovered more and more about their background and agendas. Useless, gutless, fraudulent ‘journalists’ then just repeat the smears without question and on the day I was writing this section a pair of unquestioning repeaters called Ben Quinn and Archie Bland (how appropriate) outright called me an ‘anti-Semite’ in the establishment propaganda sheet, the London *Guardian*, with no supporting evidence. The

Sabbatian Anti-Semitism Industry said so and who are they to question that? They wouldn't dare. Ironically 'Semitic' refers to a group of languages in the Middle East that are almost entirely Arabic. 'Anti-Semitism' becomes 'anti-Arab' which if the consequences of this misunderstanding were not so grave would be hilarious. Don't bother telling Quinn and Bland. I don't want to confuse them, bless 'em. One reason I am dubbed 'anti-Semitic' is that I wrote in the 1990s that Jewish operatives (Sabbatians) were heavily involved in the Russian Revolution when Sabbatians overthrew the Romanov dynasty. This apparently made me 'anti-Semitic'. Oh, really? Here is a section from *The Trigger*:

British journalist Robert Wilton confirmed these themes in his 1920 book *The Last Days of the Romanovs* when he studied official documents from the Russian government to identify the members of the Bolshevik ruling elite between 1917 and 1919. The Central Committee included 41 Jews among 62 members; the Council of the People's Commissars had 17 Jews out of 22 members; and 458 of the 556 most important Bolshevik positions between 1918 and 1919 were occupied by Jewish people. Only 17 were Russian. Then there were the 23 Jews among the 36 members of the vicious Cheka Soviet secret police established in 1917 who would soon appear all across the country.

Professor Robert Service of Oxford University, an expert on 20th century Russian history, found evidence that ['Jewish'] Leon Trotsky had sought to make sure that Jews were enrolled in the Red Army and were disproportionately represented in the Soviet civil bureaucracy that included the Cheka which performed mass arrests, imprisonment and executions of 'enemies of the people'. A US State Department Decimal File (861.00/5339) dated November 13th, 1918, names [Rothschild banking agent in America] Jacob Schiff and a list of ultra-Zionists as funders of the Russian Revolution leading to claims of a 'Jewish plot', but the key point missed by all is they were not 'Jews' – they were Sabbatian-Frankists.

Britain's Winston Churchill made the same error by mistake or otherwise. He wrote in a 1920 edition of the *Illustrated Sunday Herald* that those behind the Russian revolution were part of a 'worldwide conspiracy for the overthrow of civilisation and for the reconstitution of society on the basis of arrested development, of envious malevolence, and impossible equality' (see 'Woke' today because that has been created by the same network). Churchill said there was no need to exaggerate the part played in the creation of Bolshevism and in the actual bringing about of the Russian

Revolution 'by these international and for the most part atheistical Jews' ['atheistical Jews' = Sabbatians]. Churchill said it is certainly a very great one and probably outweighs all others: 'With the notable exception of Lenin, the majority of the leading figures are Jews.' He went on to describe, knowingly or not, the Sabbatian modus operandi of placing puppet leaders nominally in power while they control from the background:

Moreover, the principal inspiration and driving power comes from the Jewish leaders. Thus Tchitcherin, a pure Russian, is eclipsed by his nominal subordinate, Litvinoff, and the influence of Russians like Bukharin or Lunacharski cannot be compared with the power of Trotsky, or of Zinovieff, the Dictator of the Red Citadel (Petrograd), or of Krassin or Radek – all Jews. In the Soviet institutions the predominance of Jews is even more astonishing. And the prominent, if not indeed the principal, part in the system of terrorism applied by the Extraordinary Commissions for Combatting Counter-Revolution has been taken by Jews, and in some notable cases by Jewesses.

What I said about seriously disproportionate involvement in the Russian Revolution by Jewish 'revolutionaries' (Sabbatians) is provable fact, but truth is no defence against the Sabbatian Anti-Semitism Industry, its repeater parrots like Quinn and Bland, and the now breathtaking network of so-called 'Woke' 'anti-hate' groups with interlocking leaderships and funding which have the role of discrediting and silencing anyone who gets too close to exposing the Sabbatians. We have seen 'truth is no defence' confirmed in legal judgements with the Saskatchewan Human Rights Commission in Canada decreeing this: 'Truthful statements can be presented in a manner that would meet the definition of hate speech, and not all truthful statements must be free from restriction.' Most 'anti-hate' activists, who are themselves consumed by hatred, are too stupid and ignorant of the world to know how they are being used. They are far too far up their own virtue-signalling arses and it's far too dark for them to see anything.

## **The 'revolution' game**

The background and methods of the 'Russian' Revolution are straight from the Sabbatian playbook seen in the French Revolution

and endless others around the world that appear to start as a revolution of the people against tyrannical rule and end up with a regime change to more tyrannical rule overtly or covertly. Wars, terror attacks and regime overthrows follow the Sabbatian cult through history with its agents creating them as Problem-Reaction-Solutions to remove opposition on the road to world domination. Sabbatian dots connect the Rothschilds with the Illuminati, Jacobins of the French Revolution, the 'Bund' or League of the Just, the International Communist Party, Communist League and the Communist Manifesto of Karl Marx and Friedrich Engels that would lead to the Rothschild-funded Russian Revolution. The sequence comes under the heading of 'creative destruction' when you advance to your global goal by continually destroying the status quo to install a new status quo which you then also destroy. The two world wars come to mind. With each new status quo you move closer to your planned outcome. Wars and mass murder are to Sabbatians a collective blood sacrifice ritual. They are obsessed with death for many reasons and one is that death is an inversion of life. Satanists and Sabbatians are obsessed with death and often target churches and churchyards for their rituals. Inversion-obsessed Sabbatians explain the use of inverted symbolism including the *inverted* pentagram and *inverted* cross. The inversion of the cross has been related to targeting Christianity, but the cross was a religious symbol long before Christianity and its inversion is a statement about the Sabbatian mentality and goals more than any single religion.

Sabbatians operating in Germany were behind the rise of the occult-obsessed Nazis and the subsequent Jewish exodus from Germany and Europe to Palestine and the United States after World War Two. The Rothschild dynasty was at the forefront of this both as political manipulators and by funding the operation. Why would Sabbatians help to orchestrate the horrors inflicted on Jews by the Nazis and by Stalin after they organised the Russian Revolution? Sabbatians hate Jews and their religion, that's why. They pose as Jews and secure positions of control within Jewish society and play the 'anti-Semitism' card to protect themselves from exposure

through a global network of organisations answering to the Sabbatian-created-and-controlled globe-spanning intelligence network that involves a stunning web of military-intelligence operatives and operations for a tiny country of just nine million. Among them are Jewish assets who are not Sabbatians but have been convinced by them that what they are doing is for the good of Israel and the Jewish community to protect them from what they have been programmed since childhood to believe is a Jew-hating hostile world. The Jewish community is just a highly convenient cover to hide the true nature of Sabbatians. Anyone getting close to exposing their game is accused by Sabbatian place-people and gofers of 'anti-Semitism' and claiming that all Jews are part of a plot to take over the world. I am not saying that. I am saying that Sabbatians – the *real* Jew-haters – have infiltrated the Jewish community to use them both as a cover and an 'anti-Semitic' defence against exposure. Thus we have the Anti-Semitism Industry targeted researchers in this way and most Jewish people think this is justified and genuine. They don't know that their 'Jewish' leaders and institutions of state, intelligence and military are not controlled by Jews at all, but cultists and stooges of Sabbatian-Frankism. I once added my name to a pro-Jewish freedom petition online and the next time I looked my name was gone and text had been added to the petition blurb to attack me as an 'anti-Semite' such is the scale of perceptual programming.

## **Moving on America**

I tell the story in *The Trigger* and a chapter called 'Atlantic Crossing' how particularly after Israel was established the Sabbatians moved in on the United States and eventually grasped control of government administration, the political system via both Democrats and Republicans, the intelligence community like the CIA and National Security Agency (NSA), the Pentagon and mass media. Through this seriously compartmentalised network Sabbatians and their operatives in Mossad, Israeli Defense Forces (IDF) and US agencies pulled off 9/11 and blamed it on 19 'Al-Qaeda hijackers' dominated by men from, or connected to, Sabbatian-ruled Saudi

Arabia. The '19' were not even on the planes let alone flew those big passenger jets into buildings while being largely incompetent at piloting one-engine light aircraft. 'Hijacker' Hani Hanjour who is said to have flown American Airlines Flight 77 into the Pentagon with a turn and manoeuvre most professional pilots said they would have struggled to do was banned from renting a small plane by instructors at the Freeway Airport in Bowie, Maryland, just *six weeks* earlier on the grounds that he was an incompetent pilot. The Jewish population of the world is just 0.2 percent with even that almost entirely concentrated in Israel (75 percent Jewish) and the United States (around two percent). This two percent and globally 0.2 percent refers to *Jewish* people and not Sabbatian interlopers who are a fraction of that fraction. What a sobering thought when you think of the fantastic influence on world affairs of tiny Israel and that the Project for the New America Century (PNAC) which laid out the blueprint in September, 2000, for America's war on terror and regime change wars in Iraq, Libya and Syria was founded and dominated by Sabbatians known as 'Neocons'. The document conceded that this plan would not be supported politically or publicly without a major attack on American soil and a Problem-Reaction-Solution excuse to send troops to war across the Middle East. Sabbatian Neocons said:

... [The] process of transformation ... [war and regime change] ... is likely to be a long one, absent some catastrophic and catalysing event – like a new Pearl Harbor.

Four months later many of those who produced that document came to power with their inane puppet George Bush from the long-time Sabbatian Bush family. They included Sabbatian Dick Cheney who was officially vice-president, but really de-facto president for the entirety of the 'Bush' government. Nine months after the 'Bush' inauguration came what Bush called at the time 'the Pearl Harbor of the 21st century' and with typical Sabbatian timing and symbolism 2001 was the 60th anniversary of the attack in 1941 by the Japanese Air Force on Pearl Harbor, Hawaii, which allowed President Franklin Delano Roosevelt to take the United States into a Sabbatian-

instigated Second World War that he said in his election campaign that he never would. The evidence is overwhelming that Roosevelt and his military and intelligence networks knew the attack was coming and did nothing to stop it, but they did make sure that America's most essential naval ships were not in Hawaii at the time. Three thousand Americans died in the Pearl Harbor attacks as they did on September 11th. By the 9/11 year of 2001 Sabbatians had widely infiltrated the US government, military and intelligence operations and used their compartmentalised assets to pull off the 'Al-Qaeda' attacks. If you read *The Trigger* it will blow your mind to see the utterly staggering concentration of 'Jewish' operatives (Sabbatian infiltrators) in essential positions of political, security, legal, law enforcement, financial and business power before, during, and after the attacks to make them happen, carry them out, and then cover their tracks – and I do mean *staggering* when you think of that 0.2 percent of the world population and two percent of Americans which are Jewish while Sabbatian infiltrators are a fraction of that. A central foundation of the 9/11 conspiracy was the hijacking of government, military, Air Force and intelligence computer systems in real time through 'back-door' access made possible by Israeli (Sabbatian) 'cyber security' software. Sabbatian-controlled Israel is on the way to rivalling Silicon Valley for domination of cyberspace and is becoming the dominant force in cyber-security which gives them access to entire computer systems and their passcodes across the world. Then add to this that Zionists head (officially) Silicon Valley giants like Google (Larry Page and Sergey Brin), Google-owned YouTube (Susan Wojcicki), Facebook (Mark Zuckerberg and Sheryl Sandberg), and Apple (Chairman Arthur D. Levinson), and that ultra-Zionist hedge fund billionaire Paul Singer has a \$1 billion stake in Twitter which is only nominally headed by 'CEO' pothead Jack Dorsey. As cable news host Tucker Carlson said of Dorsey: 'There used to be debate in the medical community whether dropping a ton of acid had permanent effects and I think that debate has now ended.' Carlson made the comment after Dorsey told a hearing on Capitol Hill (if you cut through his bullshit) that he

believed in free speech so long as he got to decide what you can hear and see. These 'big names' of Silicon Valley are only front men and women for the Global Cult, not least the Sabbatians, who are the true controllers of these corporations. Does anyone still wonder why these same people and companies have been ferociously censoring and banning people (like me) for exposing any aspect of the Cult agenda and especially the truth about the 'Covid' hoax which Sabbatians have orchestrated?

The Jeffrey Epstein paedophile ring was a Sabbatian operation. He was officially 'Jewish' but he was a Sabbatian and women abused by the ring have told me about the high number of 'Jewish' people involved. The Epstein horror has Sabbatian written all over it and matches perfectly their modus operandi and obsession with sex and ritual. Epstein was running a Sabbatian blackmail ring in which famous people with political and other influence were provided with young girls for sex while everything was being filmed and recorded on hidden cameras and microphones at his New York house, Caribbean island and other properties. Epstein survivors have described this surveillance system to me and some have gone public. Once the famous politician or other figure knew he or she was on video they tended to do whatever they were told. Here we go again ...when you've got them by the balls their hearts and minds will follow. Sabbatians use this blackmail technique on a wide scale across the world to entrap politicians and others they need to act as demanded. Epstein's private plane, the infamous 'Lolita Express', had many well-known passengers including Bill Clinton while Bill Gates has flown on an Epstein plane and met with him four years after Epstein had been jailed for paedophilia. They subsequently met many times at Epstein's home in New York according to a witness who was there. Epstein's infamous side-kick was Ghislaine Maxwell, daughter of Mossad agent and ultra-Zionist mega-crooked British businessman, Bob Maxwell, who at one time owned the *Daily Mirror* newspaper. Maxwell was murdered at sea on his boat in 1991 by Sabbatian-controlled Mossad when he became a liability with his

business empire collapsing as a former Mossad operative has confirmed (see *The Trigger*).

### **Money, money, money, funny money ...**

Before I come to the Sabbatian connection with the last three US presidents I will lay out the crucial importance to Sabbatians of controlling banking and finance. Sabbatian Mayer Amschel Rothschild set out to dominate this arena in his family's quest for total global control. What is freedom? It is, in effect, choice. The more choices you have the freer you are and the fewer your choices the more you are enslaved. In the global structure created over centuries by Sabbatians the biggest decider and restrictor of choice is ... money. Across the world if you ask people what they would like to do with their lives and why they are not doing that they will reply 'I don't have the money'. This is the idea. A global elite of multi-billionaires are described as 'greedy' and that is true on one level; but control of money – who has it and who doesn't – is not primarily about greed. It's about control. Sabbatians have seized ever more control of finance and sucked the wealth of the world out of the hands of the population. We talk now, after all, about the 'One-percent' and even then the wealthiest are a lot fewer even than that. This has been made possible by a money scam so outrageous and so vast it could rightly be called the scam of scams founded on creating 'money' out of nothing and 'loaning' that with interest to the population. Money out of nothing is called 'credit'. Sabbatians have asserted control over governments and banking ever more completely through the centuries and secured financial laws that allow banks to lend hugely more than they have on deposit in a confidence trick known as fractional reserve lending. Imagine if you could lend money that doesn't exist and charge the recipient interest for doing so. You would end up in jail. Bankers by contrast end up in mansions, private jets, Malibu and Monaco.

Banks are only required to keep a fraction of their deposits and wealth in their vaults and they are allowed to lend 'money' they don't have called 'credit'. Go into a bank for a loan and if you succeed

the banker will not move any real wealth into your account. They will type into your account the amount of the agreed 'loan' – say £100,000. This is not wealth that really exists; it is non-existent, fresh-air, created-out-of-nothing 'credit' which has never, does not, and will never exist except in theory. Credit is backed by nothing except wind and only has buying power because people think that it has buying power and accept it in return for property, goods and services. I have described this situation as like those cartoon characters you see chasing each other and when they run over the edge of a cliff they keep running forward on fresh air until one of them looks down, realises what's happened, and they all crash into the ravine. The whole foundation of the Sabbatian financial system is to stop people looking down except for periodic moments when they want to crash the system (as in 2008 and 2020 ongoing) and reap the rewards from all the property, businesses and wealth their borrowers had signed over as 'collateral' in return for a 'loan' of fresh air. Most people think that money is somehow created by governments when it comes into existence from the start as a debt through banks 'lending' illusory money called credit. Yes, the very currency of exchange is a *debt* from day one issued as an interest-bearing loan. Why don't governments create money interest-free and lend it to their people interest-free? Governments are controlled by Sabbatians and the financial system is controlled by Sabbatians for whom interest-free money would be a nightmare come true. Sabbatians underpin their financial domination through their global network of central banks, including the privately-owned US Federal Reserve and Britain's Bank of England, and this is orchestrated by a privately-owned central bank coordination body called the Bank for International Settlements in Basle, Switzerland, created by the usual suspects including the Rockefellers and Rothschilds. Central bank chiefs don't answer to governments or the people. They answer to the Bank for International Settlements or, in other words, the Global Cult which is dominated today by Sabbatians.

## **Built-in disaster**

There are so many constituent scams within the overall banking scam. When you take out a loan of thin-air credit only the amount of that loan is theoretically brought into circulation to add to the amount in circulation; but you are paying back the principle plus interest. The additional interest is not created and this means that with every 'loan' there is a shortfall in the money in circulation between what is borrowed and what has to be paid back. There is never even close to enough money in circulation to repay all outstanding public and private debt including interest. Coldly weaved in the very fabric of the system is the certainty that some will lose their homes, businesses and possessions to the banking 'lender'. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts it becomes painfully obvious that there is not enough money to service all debt and interest. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts and it becomes painfully obvious – as in 2008 and currently – that there is not enough money to service all debt and interest.

Sabbatian banksters have been leading the human population through a calculated series of booms (more debt incurred) and busts (when the debt can't be repaid and the banks get the debtor's tangible wealth in exchange for non-existent 'credit'). With each 'bust' Sabbatian bankers have absorbed more of the world's tangible wealth and we end up with the One-percent. Governments are in bankruptcy levels of debt to the same system and are therefore owned by a system they do not control. The Federal Reserve, 'America's central bank', is privately-owned and American presidents only nominally appoint its chairman or woman to maintain the illusion that it's an arm of government. It's not. The 'Fed' is a cartel of private banks which handed billions to its associates and friends after the crash of 2008 and has been Sabbatian-controlled since it was manipulated into being in 1913 through the covert trickery of Rothschild banking agents Jacob Schiff and Paul

Warburg, and the Sabbatian Rockefeller family. Somehow from a Jewish population of two-percent and globally 0.2 percent (Sabbatian interlopers remember are far smaller) ultra-Zionists headed the Federal Reserve for 31 years between 1987 and 2018 in the form of Alan Greenspan, Bernard Bernanke and Janet Yellen (now Biden's Treasury Secretary) with Yellen's deputy chairman a Israeli-American dual citizen and ultra-Zionist Stanley Fischer, a former governor of the Bank of Israel. Ultra-Zionist Fed chiefs spanned the presidencies of Ronald Reagan ('Republican'), Father George Bush ('Republican'), Bill Clinton ('Democrat'), Boy George Bush ('Republican') and Barack Obama ('Democrat'). We should really add the pre-Greenspan chairman, Paul Adolph Volcker, 'appointed' by Jimmy Carter ('Democrat') who ran the Fed between 1979 and 1987 during the Carter and Reagan administrations before Greenspan took over. Volcker was a long-time associate and business partner of the Rothschilds. No matter what the 'party' officially in power the United States economy was directed by the same force. Here are members of the Obama, Trump and Biden administrations and see if you can make out a common theme.

## **Barack Obama ('Democrat')**

Ultra-Zionists Robert Rubin, Larry Summers, and Timothy Geithner ran the US Treasury in the Clinton administration and two of them reappeared with Obama. Ultra-Zionist Fed chairman Alan Greenspan had manipulated the crash of 2008 through deregulation and jumped ship just before the disaster to make way for ultra-Zionist Bernard Bernanke to hand out trillions to Sabbatian 'too big to fail' banks and businesses, including the ubiquitous ultra-Zionist Goldman Sachs which has an ongoing staff revolving door operation between itself and major financial positions in government worldwide. Obama inherited the fallout of the crash when he took office in January, 2009, and fortunately he had the support of his ultra-Zionist White House Chief of Staff Rahm Emmanuel, son of a terrorist who helped to bomb Israel into being in 1948, and his ultra-Zionist senior adviser David Axelrod, chief strategist in Obama's two

successful presidential campaigns. Emmanuel, later mayor of Chicago and former senior fundraiser and strategist for Bill Clinton, is an example of the Sabbatian policy after Israel was established of migrating insider families to America so their children would be born American citizens. ‘Obama’ chose this financial team throughout his administration to respond to the Sabbatian-instigated crisis:

Timothy Geithner (ultra-Zionist) Treasury Secretary; Jacob J. Lew, Treasury Secretary; Larry Summers (ultra-Zionist), director of the White House National Economic Council; Paul Adolph Volcker (Rothschild business partner), chairman of the Economic Recovery Advisory Board; Peter Orszag (ultra-Zionist), director of the Office of Management and Budget overseeing all government spending; Penny Pritzker (ultra-Zionist), Commerce Secretary; Jared Bernstein (ultra-Zionist), chief economist and economic policy adviser to Vice President Joe Biden; Mary Schapiro (ultra-Zionist), chair of the Securities and Exchange Commission (SEC); Gary Gensler (ultra-Zionist), chairman of the Commodity Futures Trading Commission (CFTC); Sheila Bair (ultra-Zionist), chair of the Federal Deposit Insurance Corporation (FDIC); Karen Mills (ultra-Zionist), head of the Small Business Administration (SBA); Kenneth Feinberg (ultra-Zionist), Special Master for Executive [bail-out] Compensation. Feinberg would be appointed to oversee compensation (with strings) to 9/11 victims and families in a campaign to stop them having their day in court to question the official story. At the same time ultra-Zionist Bernard Bernanke was chairman of the Federal Reserve and these are only some of the ultra-Zionists with allegiance to Sabbatian-controlled Israel in the Obama government. Obama’s biggest corporate donor was ultra-Zionist Goldman Sachs which had employed many in his administration.

## **Donald Trump ('Republican')**

Trump claimed to be an outsider (he wasn’t) who had come to ‘drain the swamp’. He embarked on this goal by immediately appointing ultra-Zionist Steve Mnuchin, a Goldman Sachs employee for 17

years, as his Treasury Secretary. Others included Gary Cohn (ultra-Zionist), chief operating officer of Goldman Sachs, his first Director of the National Economic Council and chief economic adviser, who was later replaced by Larry Kudlow (ultra-Zionist). Trump's senior adviser throughout his four years in the White House was his sinister son-in-law Jared Kushner, a life-long friend of Israel Prime Minister Benjamin Netanyahu. Kushner is the son of a convicted crook who was pardoned by Trump in his last days in office. Other ultra-Zionists in the Trump administration included: Stephen Miller, Senior Policy Adviser; Avrahm Berkowitz, Deputy Adviser to Trump and his Senior Adviser Jared Kushner; Ivanka Trump, Adviser to the President, who converted to Judaism when she married Jared Kushner; David Friedman, Trump lawyer and Ambassador to Israel; Jason Greenblatt, Trump Organization executive vice president and chief legal officer, who was made Special Representative for International Negotiations and the Israeli-Palestinian Conflict; Rod Rosenstein, Deputy Attorney General; Elliot Abrams, Special Representative for Venezuela, then Iran; John Eisenberg, National Security Council Legal Adviser and Deputy Council to the President for National Security Affairs; Anne Neuberger, Deputy National Manager, National Security Agency; Ezra Cohen-Watnick, Acting Under Secretary of Defense for Intelligence; Elan Carr, Special Envoy to monitor and combat anti-Semitism; Len Khodorkovsky, Deputy Special Envoy to monitor and combat anti-Semitism; Reed Cordish, Assistant to the President, Intragovernmental and Technology Initiatives. Trump Vice President Mike Pence and Secretary of State Mike Pompeo, both Christian Zionists, were also vehement supporters of Israel and its goals and ambitions.

Donald 'free-speech believer' Trump pardoned a number of financial and violent criminals while ignoring calls to pardon Julian Assange and Edward Snowden whose crimes are revealing highly relevant information about government manipulation and corruption and the widespread illegal surveillance of the American people by US 'security' agencies. It's so good to know that Trump is on the side of freedom and justice and not mega-criminals with

allegiance to Sabbatian-controlled Israel. These included a pardon for Israeli spy Jonathan Pollard who was jailed for life in 1987 under the Espionage Act. Aviem Sella, the Mossad agent who recruited Pollard, was also pardoned by Trump while Assange sat in jail and Snowden remained in exile in Russia. Sella had 'fled' (was helped to escape) to Israel in 1987 and was never extradited despite being charged under the Espionage Act. A Trump White House statement said that Sella's clemency had been 'supported by Benjamin Netanyahu, Ron Dermer, Israel's US Ambassador, David Friedman, US Ambassador to Israel and Miriam Adelson, wife of leading Trump donor Sheldon Adelson who died shortly before. Other friends of Jared Kushner were pardoned along with Sholom Weiss who was believed to be serving the longest-ever white-collar prison sentence of more than 800 years in 2000. The sentence was commuted of Ponzi-schemer Eliyahu Weinstein who defrauded Jews and others out of \$200 million. I did mention that Assange and Snowden were ignored, right? Trump gave Sabbatians almost everything they asked for in military and political support, moving the US Embassy from Tel Aviv to Jerusalem with its critical symbolic and literal implications for Palestinian statehood, and the 'deal of the Century' designed by Jared Kushner and David Friedman which gave the Sabbatian Israeli government the green light to substantially expand its already widespread program of building illegal Jewish-only settlements in the occupied land of the West Bank. This made a two-state 'solution' impossible by seizing all the land of a potential Palestinian homeland and that had been the plan since 1948 and then 1967 when the Arab-controlled Gaza Strip, West Bank, Sinai Peninsula and Syrian Golan Heights were occupied by Israel. All the talks about talks and road maps and delays have been buying time until the West Bank was physically occupied by Israeli real estate. Trump would have to be a monumentally ill-informed idiot not to see that this was the plan he was helping to complete. The Trump administration was in so many ways the Kushner administration which means the Netanyahu administration which means the Sabbatian administration. I understand why many opposing Cult fascism in all its forms gravitated to Trump, but he

was a crucial part of the Sabbatian plan and I will deal with this in the next chapter.

## **Joe Biden ('Democrat')**

A barely cognitive Joe Biden took over the presidency in January, 2021, along with his fellow empty shell, Vice-President Kamala Harris, as the latest Sabbatian gofers to enter the White House. Names on the door may have changed and the 'party' – the force behind them remained the same as Zionists were appointed to a stream of pivotal areas relating to Sabbatian plans and policy. They included: Janet Yellen, Treasury Secretary, former head of the Federal Reserve, and still another ultra-Zionist running the US Treasury after Mnuchin (Trump), Lew and Geithner (Obama), and Summers and Rubin (Clinton); Anthony Blinken, Secretary of State; Wendy Sherman, Deputy Secretary of State (so that's 'Biden's' Sabbatian foreign policy sorted); Jeff Zients, White House coronavirus coordinator; Rochelle Walensky, head of the Centers for Disease Control; Rachel Levine, transgender deputy health secretary (that's 'Covid' hoax policy under control); Merrick Garland, Attorney General; Alejandro Mayorkas, Secretary of Homeland Security; Cass Sunstein, Homeland Security with responsibility for new immigration laws; Avril Haines, Director of National Intelligence; Anne Neuberger, National Security Agency cybersecurity director (note, cybersecurity); David Cohen, CIA Deputy Director; Ronald Klain, Biden's Chief of Staff (see Rahm Emanuel); Eric Lander, a 'leading geneticist', Office of Science and Technology Policy director (see Smart Grid, synthetic biology agenda); Jessica Rosenworcel, acting head of the Federal Communications Commission (FCC) which controls Smart Grid technology policy and electromagnetic communication systems including 5G. How can it be that so many pivotal positions are held by two-percent of the American population and 0.2 percent of the world population administration after administration no matter who is the president and what is the party? It's a coincidence? Of course it's not and this is why Sabbatians have built their colossal global web of interlocking 'anti-

hate' hate groups to condemn anyone who asks these glaring questions as an 'anti-Semite'. The way that Jewish people horrifically abused in Sabbatian-backed Nazi Germany are exploited to this end is stomach-turning and disgusting beyond words.

## **Political fusion**

Sabbatian manipulation has reversed the roles of Republicans and Democrats and the same has happened in Britain with the Conservative and Labour Parties. Republicans and Conservatives were always labelled the 'right' and Democrats and Labour the 'left', but look at the policy positions now and the Democrat-Labour 'left' has moved further to the 'right' than Republicans and Conservatives under the banner of 'Woke', the Cult-created far-right tyranny. Where once the Democrat-Labour 'left' defended free speech and human rights they now seek to delete them and as I said earlier despite the 'Covid' fascism of the Jackboot Johnson Conservative government in the UK the Labour Party of leader Keir Starmer demanded even more extreme measures. The Labour Party has been very publicly absorbed by Sabbatians after a political and media onslaught against the previous leader, the weak and inept Jeremy Corbyn, over made-up allegations of 'anti-Semitism' both by him and his party. The plan was clear with this 'anti-Semite' propaganda and what was required in response was a swift and decisive 'fuck off' from Corbyn and a statement to expose the Anti-Semitism Industry (Sabbatian) attempt to silence Labour criticism of the Israeli government (Sabbatians) and purge the party of all dissent against the extremes of ultra-Zionism (Sabbatians). Instead Corbyn and his party fell to their knees and appeased the abusers which, by definition, is impossible. Appeasing one demand leads only to a new demand to be appeased until takeover is complete. Like I say – 'fuck off' would have been a much more effective policy and I have used it myself with great effect over the years when Sabbatians are on my case which is most of the time. I consider that fact a great compliment, by the way. The outcome of the Labour Party capitulation is that we now have a Sabbatian-controlled

Conservative Party ‘opposed’ by a Sabbatian-controlled Labour Party in a one-party Sabbatian state that hurtles towards the extremes of tyranny (the Sabbatian cult agenda). In America the situation is the same. Labour’s Keir Starmer spends his days on his knees with his tongue out pointing to Tel Aviv, or I guess now Jerusalem, while Boris Johnson has an ‘anti-Semitism czar’ in the form of former Labour MP John Mann who keeps Starmer company on his prayer mat.

Sabbatian influence can be seen in Jewish members of the Labour Party who have been ejected for criticism of Israel including those from families that suffered in Nazi Germany. Sabbatians despise real Jewish people and target them even more harshly because it is so much more difficult to dub them ‘anti-Semitic’ although in their desperation they do try.

## CHAPTER THREE

### The Pushbacker sting

*Until you realize how easy it is for your mind to be manipulated, you remain the puppet of someone else's game*

Evita Ochel

I will use the presidencies of Trump and Biden to show how the manipulation of the one-party state plays out behind the illusion of political choice across the world. No two presidencies could – on the face of it – be more different and apparently at odds in terms of direction and policy.

A Renegade Mind sees beyond the obvious and focuses on outcomes and consequences and not image, words and waffle. The Cult embarked on a campaign to divide America between those who blindly support its agenda (the mentality known as 'Woke') and those who are pushing back on where the Cult and its Sabbatians want to go. This presents infinite possibilities for dividing and ruling the population by setting them at war with each other and allows a perceptual ring fence of demonisation to encircle the Pushbackers in a modern version of the Little Big Horn in 1876 when American cavalry led by Lieutenant Colonel George Custer were drawn into a trap, surrounded and killed by Native American tribes defending their land of thousands of years from being seized by the government. In this modern version the roles are reversed and it's those defending themselves from the Sabbatian government who are surrounded and the government that's seeking to destroy them. This trap was set years ago and to explain how we must return to 2016

and the emergence of Donald Trump as a candidate to be President of the United States. He set out to overcome the best part of 20 other candidates in the Republican Party before and during the primaries and was not considered by many in those early stages to have a prayer of living in the White House. The Republican Party was said to have great reservations about Trump and yet somehow he won the nomination. When you know how American politics works – politics in general – there is no way that Trump could have become the party's candidate unless the Sabbatian-controlled 'Neocons' that run the Republican Party wanted that to happen. We saw the proof in emails and documents made public by WikiLeaks that the Democratic Party hierarchy, or Democons, systematically undermined the campaign of Bernie Sanders to make sure that Sabbatian gofer Hillary Clinton won the nomination to be their presidential candidate. If the Democons could do that then the Neocons in the Republican Party could have derailed Trump in the same way. But they didn't and at that stage I began to conclude that Trump could well be the one chosen to be president. If that was the case the 'why' was pretty clear to see – the goal of dividing America between Cult agenda-supporting Wokers and Pushbackers who gravitated to Trump because he was telling them what they wanted to hear. His constituency of support had been increasingly ignored and voiceless for decades and profoundly through the eight years of Sabbatian puppet Barack Obama. Now here was someone speaking their language of pulling back from the incessant globalisation of political and economic power, the exporting of American jobs to China and elsewhere by 'American' (Sabbatian) corporations, the deletion of free speech, and the mass immigration policies that had further devastated job opportunities for the urban working class of all races and the once American heartlands of the Midwest.

### **Beware the forked tongue**

Those people collectively sighed with relief that at last a political leader was apparently on their side, but another trait of the Renegade Mind is that you look even harder at people telling you

what you want to hear than those who are telling you otherwise. Obviously as I said earlier people wish what they want to hear to be true and genuine and they are much more likely to believe that than someone saying what they don't want to here and don't want to be true. Sales people are taught to be skilled in eliciting by calculated questioning what their customers want to hear and repeating that back to them as their own opinion to get their targets to like and trust them. Assets of the Cult are also sales people in the sense of selling perception. To read Cult manipulation you have to play the long and expanded game and not fall for the Vaudeville show of party politics. Both American parties are vehicles for the Cult and they exploit them in different ways depending on what the agenda requires at that moment. Trump and the Republicans were used to be the focus of dividing America and isolating Pushbackers to open the way for a Biden presidency to become the most extreme in American history by advancing the full-blown Woke (Cult) agenda with the aim of destroying and silencing Pushbackers now labelled Nazi Trump supporters and white supremacists.

Sabbatians wanted Trump in office for the reasons described by ultra-Zionist Saul Alinsky (1909-1972) who was promoting the Woke philosophy through 'community organising' long before anyone had heard of it. In those days it still went by its traditional name of Marxism. The reason for the manipulated Trump phenomenon was laid out in Alinsky's 1971 book, *Rules for Radicals*, which was his blueprint for overthrowing democratic and other regimes and replacing them with Sabbatian Marxism. Not surprisingly his to-do list was evident in the Sabbatian French and Russian 'Revolutions' and that in China which will become very relevant in the next chapter about the 'Covid' hoax. Among Alinsky's followers have been the deeply corrupt Barack Obama, House Speaker Nancy Pelosi and Hillary Clinton who described him as a 'hero'. All three are Sabbatian stooges with Pelosi personifying the arrogant corrupt idiocy that so widely fronts up for the Cult inner core. Predictably as a Sabbatian advocate of the 'light-bringer' Alinsky features Lucifer on the dedication page of his book as the original radical who gained

his own kingdom ('Earth' as we shall see). One of Alinsky's golden radical rules was to pick an individual and focus all attention, hatred and blame on them and not to target faceless bureaucracies and corporations. *Rules for Radicals* is really a Sabbatian handbook with its contents repeatedly employed all over the world for centuries and why wouldn't Sabbatians bring to power their designer-villain to be used as the individual on which all attention, hatred and blame was bestowed? This is what they did and the only question for me is how much Trump knew that and how much he was manipulated. A bit of both, I suspect. This was Alinsky's Trump technique from a man who died in 1972. The technique has spanned history:

Pick the target, freeze it, personalize it, polarize it. Don't try to attack abstract corporations or bureaucracies. Identify a responsible individual. Ignore attempts to shift or spread the blame.

From the moment Trump came to illusory power everything was about him. It wasn't about Republican policy or opinion, but all about Trump. Everything he did was presented in negative, derogatory and abusive terms by the Sabbatian-dominated media led by Cult operations such as CNN, MSNBC, *The New York Times* and the Jeff Bezos-owned *Washington Post* – 'Pick the target, freeze it, personalize it, polarize it.' Trump was turned into a demon to be vilified by those who hated him and a demi-god loved by those who worshipped him. This, in turn, had his supporters, too, presented as equally demonic in preparation for the punchline later down the line when Biden was about to take office. It was here's a Trump, there's a Trump, everywhere a Trump, Trump. Virtually every news story or happening was filtered through the lens of 'The Donald'. You loved him or hated him and which one you chose was said to define you as Satan's spawn or a paragon of virtue. Even supporting some Trump policies or statements and not others was enough for an assault on your character. No shades of grey were or are allowed. Everything is black and white (literally and figuratively). A Californian I knew had her head utterly scrambled by her hatred for Trump while telling people they should love each other. She was so totally consumed by

Trump Derangement Syndrome as it became to be known that this glaring contradiction would never have occurred to her. By definition anyone who criticised Trump or praised his opponents was a hero and this lady described Joe Biden as 'a kind, honest gentleman' when he's a provable liar, mega-crook and vicious piece of work to boot. Sabbatians had indeed divided America using Trump as the fall-guy and all along the clock was ticking on the consequences for his supporters.

### **In hock to his masters**

Trump gave Sabbatians via Israel almost everything they wanted in his four years. Ask and you shall receive was the dynamic between himself and Benjamin Netanyahu orchestrated by Trump's ultra-Zionist son-in-law Jared Kushner, his ultra-Zionist Ambassador to Israel, David Friedman, and ultra-Zionist 'Israel adviser', Jason Greenblatt. The last two were central to the running and protecting from collapse of his business empire, the Trump Organisation, and colossal business failures made him forever beholden to Sabbatian networks that bailed him out. By the start of the 1990s Trump owed \$4 billion to banks that he couldn't pay and almost \$1 billion of that was down to him personally and not his companies. This mega-disaster was the result of building two new casinos in Atlantic City and buying the enormous Taj Mahal operation which led to crippling debt payments. He had borrowed fantastic sums from 72 banks with major Sabbatian connections and although the scale of debt should have had him living in a tent alongside the highway they never foreclosed. A plan was devised to lift Trump from the mire by BT Securities Corporation and Rothschild Inc. and the case was handled by Wilber Ross who had worked for the Rothschilds for 27 years. Ross would be named US Commerce Secretary after Trump's election. Another crucial figure in saving Trump was ultra-Zionist 'investor' Carl Icahn who bought the Taj Mahal casino. Icahn was made special economic adviser on financial regulation in the Trump administration. He didn't stay long but still managed to find time to make a tidy sum of a reported \$31.3 million when he sold his

holdings affected by the price of steel three days before Trump imposed a 235 percent tariff on steel imports. What amazing bits of luck these people have. Trump and Sabbatian operatives have long had a close association and his mentor and legal adviser from the early 1970s until 1986 was the dark and genetically corrupt ultra-Zionist Roy Cohn who was chief counsel to Senator Joseph McCarthy's 'communist' witch-hunt in the 1950s. *Esquire* magazine published an article about Cohn with the headline 'Don't mess with Roy Cohn'. He was described as the most feared lawyer in New York and 'a ruthless master of dirty tricks ... [with] ... more than one Mafia Don on speed dial'. Cohn's influence, contacts, support and protection made Trump a front man for Sabbatians in New York with their connections to one of Cohn's many criminal employers, the 'Russian' Sabbatian Mafia. Israel-centric media mogul Rupert Murdoch was introduced to Trump by Cohn and they started a long friendship. Cohn died in 1986 weeks after being disbarred for unethical conduct by the Appellate Division of the New York State Supreme Court. The wheels of justice do indeed run slow given the length of Cohn's crooked career.

## **QAnon-sense**

We are asked to believe that Donald Trump with his fundamental connections to Sabbatian networks and operatives has been leading the fight to stop the Sabbatian agenda for the fascistic control of America and the world. Sure he has. A man entrapped during his years in the White House by Sabbatian operatives and whose biggest financial donor was casino billionaire Sheldon Adelson who was Sabbatian to his DNA?? Oh, do come on. Trump has been used to divide America and isolate Pushbackers on the Cult agenda under the heading of 'Trump supporters', 'insurrectionists' and 'white supremacists'. The US Intelligence/Mossad Psyop or psychological operation known as QAnon emerged during the Trump years as a central pillar in the Sabbatian campaign to lead Pushbackers into the trap set by those that wished to destroy them. I knew from the start that QAnon was a scam because I had seen the same scenario many

times before over 30 years under different names and I had written about one in particular in the books. ‘Not again’ was my reaction when QAnon came to the fore. The same script is pulled out every few years and a new name added to the letterhead. The story always takes the same form: ‘Insiders’ or ‘the good guys’ in the government-intelligence-military ‘Deep State’ apparatus were going to instigate mass arrests of the ‘bad guys’ which would include the Rockefellers, Rothschilds, Barack Obama, Hillary Clinton, George Soros, etc., etc. Dates are given for when the ‘good guys’ are going to move in, but the dates pass without incident and new dates are given which pass without incident. The central message to Pushbackers in each case is that they don’t have to do anything because there is ‘a plan’ and it is all going to be sorted by the ‘good guys’ on the inside. ‘Trust the plan’ was a QAnon mantra when the only plan was to misdirect Pushbackers into putting their trust in a Psyop they believed to be real. Beware, beware, those who tell you what you want to hear and always check it out. Right up to Biden’s inauguration QAnon was still claiming that ‘the Storm’ was coming and Trump would stay on as president when Biden and his cronies were arrested and jailed. It was never going to happen and of course it didn’t, but what did happen as a result provided that punchline to the Sabbatian Trump/QAnon Psyop.

On January 6th, 2021, a very big crowd of Trump supporters gathered in the National Mall in Washington DC down from the Capitol Building to protest at what they believed to be widespread corruption and vote fraud that stopped Trump being re-elected for a second term as president in November, 2020. I say as someone that does not support Trump or Biden that the evidence is clear that major vote-fixing went on to favour Biden, a man with cognitive problems so advanced he can often hardly string a sentence together without reading the words written for him on the Teleprompter. Glaring ballot discrepancies included serious questions about electronic voting machines that make vote rigging a comparative cinch and hundreds of thousands of paper votes that suddenly appeared during already advanced vote counts and virtually all of

them for Biden. Early Trump leads in crucial swing states suddenly began to close and disappear. The pandemic hoax was used as the excuse to issue almost limitless numbers of mail-in ballots with no checks to establish that the recipients were still alive or lived at that address. They were sent to streams of people who had not even asked for them. Private organisations were employed to gather these ballots and who knows what they did with them before they turned up at the counts. The American election system has been manipulated over decades to become a sick joke with more holes than a Swiss cheese for the express purpose of dictating the results. Then there was the criminal manipulation of information by Sabbatian tech giants like Facebook, Twitter and Google-owned YouTube which deleted pro-Trump, anti-Biden accounts and posts while everything in support of Biden was left alone. Sabbatians wanted Biden to win because after the dividing of America it was time for full-on Woke and every aspect of the Cult agenda to be unleashed.

### **Hunter gatherer**

Extreme Silicon Valley bias included blocking information by the *New York Post* exposing a Biden scandal that should have ended his bid for president in the final weeks of the campaign. Hunter Biden, his monumentally corrupt son, is reported to have sent a laptop to be repaired at a local store and failed to return for it. Time passed until the laptop became the property of the store for non-payment of the bill. When the owner saw what was on the hard drive he gave a copy to the FBI who did nothing even though it confirmed widespread corruption in which the Joe Biden family were using his political position, especially when he was vice president to Obama, to make multiple millions in countries around the world and most notably Ukraine and China. Hunter Biden's one-time business partner Tony Bobulinski went public when the story broke in the *New York Post* to confirm the corruption he saw and that Joe Biden not only knew what was going on he also profited from the spoils. Millions were handed over by a Chinese company with close

connections – like all major businesses in China – to the Chinese communist party of President Xi Jinping. Joe Biden even boasted at a meeting of the Cult's World Economic Forum that as vice president he had ordered the government of Ukraine to fire a prosecutor. What he didn't mention was that the same man just happened to be investigating an energy company which was part of Hunter Biden's corrupt portfolio. The company was paying him big bucks for no other reason than the influence his father had. Overnight Biden's presidential campaign should have been over given that he had lied publicly about not knowing what his son was doing. Instead almost the entire Sabbatian-owned mainstream media and Sabbatian-owned Silicon Valley suppressed circulation of the story. This alone went a mighty way to rigging the election of 2020. Cult assets like Mark Zuckerberg at Facebook also spent hundreds of millions to be used in support of Biden and vote 'administration'.

The Cult had used Trump as the focus to divide America and was now desperate to bring in moronic, pliable, corrupt Biden to complete the double-whammy. No way were they going to let little things like the will of the people thwart their plan. Silicon Valley widely censored claims that the election was rigged because it *was* rigged. For the same reason anyone claiming it was rigged was denounced as a 'white supremacist' including the pathetically few Republican politicians willing to say so. Right across the media where the claim was mentioned it was described as a 'false claim' even though these excuses for 'journalists' would have done no research into the subject whatsoever. Trump won seven million more votes than any sitting president had ever achieved while somehow a cognitively-challenged soon to be 78-year-old who was hidden away from the public for most of the campaign managed to win more votes than any presidential candidate in history. It makes no sense. You only had to see election rallies for both candidates to witness the enthusiasm for Trump and the apathy for Biden. Tens of thousands would attend Trump events while Biden was speaking in empty car parks with often only television crews attending and framing their shots to hide the fact that no one was there. It was pathetic to see

footage come to light of Biden standing at a podium making speeches only to TV crews and party fixers while reading the words written for him on massive Teleprompter screens. So, yes, those protestors on January 6th had a point about election rigging, but some were about to walk into a trap laid for them in Washington by the Cult Deep State and its QAnon Psyop. This was the Capitol Hill riot ludicrously dubbed an ‘insurrection’.

## **The spider and the fly**

Renegade Minds know there are not two ‘sides’ in politics, only one side, the Cult, working through all ‘sides’. It’s a stage show, a puppet show, to direct the perceptions of the population into focusing on diversions like parties and candidates while missing the puppeteers with their hands holding all the strings. The Capitol Hill ‘insurrection’ brings us back to the Little Big Horn. Having created two distinct opposing groupings – Woke and Pushbackers – the trap was about to be sprung. Pushbackers were to be encircled and isolated by associating them all in the public mind with Trump and then labelling Trump as some sort of Confederate leader. I knew immediately that the Capitol riot was a set-up because of two things. One was how easy the rioters got into the building with virtually no credible resistance and secondly I could see – as with the ‘Covid’ hoax in the West at the start of 2020 – how the Cult could exploit the situation to move its agenda forward with great speed. My experience of Cult techniques and activities over more than 30 years has showed me that while they do exploit situations they haven’t themselves created this never happens with events of fundamental agenda significance. Every time major events giving cultists the excuse to rapidly advance their plan you find they are manipulated into being for the specific reason of providing that excuse – Problem-Reaction-Solution. Only a tiny minority of the huge crowd of Washington protestors sought to gain entry to the Capitol by smashing windows and breaching doors. That didn’t matter. The whole crowd and all Pushbackers, even if they did not support Trump, were going to be lumped together as dangerous

insurrectionists and conspiracy theorists. The latter term came into widespread use through a CIA memo in the 1960s aimed at discrediting those questioning the nonsensical official story of the Kennedy assassination and it subsequently became widely employed by the media. It's still being used by inept 'journalists' with no idea of its origin to discredit anyone questioning anything that authority claims to be true. When you are perpetrating a conspiracy you need to discredit the very word itself even though the dictionary definition of conspiracy is merely 'the activity of secretly planning with other people to do something bad or illegal' and 'a general agreement to keep silent about a subject for the purpose of keeping it secret'. On that basis there are conspiracies almost wherever you look. For obvious reasons the Cult and its lapdog media have to claim there are no conspiracies even though the word appears in state laws as with conspiracy to defraud, to murder, and to corrupt public morals.

Agent provocateurs are widely used by the Cult Deep State to manipulate genuine people into acting in ways that suit the desired outcome. By genuine in this case I mean protestors genuinely supporting Trump and claims that the election was stolen. In among them, however, were agents of the state wearing the garb of Trump supporters and QAnon to pump-prime the Capitol riot which some genuine Trump supporters naively fell for. I described the situation as 'Come into my parlour said the spider to the fly'. Leaflets appeared through the Woke paramilitary arm Antifa, the anti-fascist fascists, calling on supporters to turn up in Washington looking like Trump supporters even though they hated him. Some of those arrested for breaching the Capitol Building were sourced to Antifa and its stable mate Black Lives Matter. Both organisations are funded by Cult billionaires and corporations. One man charged for the riot was according to his lawyer a former FBI agent who had held top secret security clearance for 40 years. Attorney Thomas Plofchan said of his client, 66-year-old Thomas Edward Caldwell:

He has held a Top Secret Security Clearance since 1979 and has undergone multiple Special Background Investigations in support of his clearances. After retiring from the Navy, he

worked as a section chief for the Federal Bureau of Investigation from 2009-2010 as a GS-12 [mid-level employee].

He also formed and operated a consulting firm performing work, often classified, for U.S government customers including the US Drug Enforcement Agency, Department of Housing and Urban Development, the US Coast Guard, and the US Army Personnel Command.

A judge later released Caldwell pending trial in the absence of evidence about a conspiracy or that he tried to force his way into the building. *The New York Post* reported a 'law enforcement source' as saying that 'at least two known Antifa members were spotted' on camera among Trump supporters during the riot while one of the rioters arrested was John Earle Sullivan, a seriously extreme Black Lives Matter Trump-hater from Utah who was previously arrested and charged in July, 2020, over a BLM-Antifa riot in which drivers were threatened and one was shot. Sullivan is the founder of Utah-based Insurgence USA which is an affiliate of the Cult-created-and-funded Black Lives Matter movement. Footage appeared and was then deleted by Twitter of Trump supporters calling out Antifa infiltrators and a group was filmed changing into pro-Trump clothing before the riot. Security at the building was *pathetic* – as planned. Colonel Leroy Fletcher Prouty, a man with long experience in covert operations working with the US security apparatus, once described the tell-tale sign to identify who is involved in an assassination. He said:

No one has to direct an assassination – it happens. The active role is played secretly by permitting it to happen. This is the greatest single clue. Who has the power to call off or reduce the usual security precautions?

This principle applies to many other situations and certainly to the Capitol riot of January 6th, 2021.

## **The sting**

With such a big and potentially angry crowd known to be gathering near the Capitol the security apparatus would have had a major police detail to defend the building with National Guard troops on

standby given the strength of feeling among people arriving from all over America encouraged by the QAnon Psyop and statements by Donald Trump. Instead Capitol Police ‘security’ was flimsy, weak, and easily breached. The same number of officers was deployed as on a regular day and that is a blatant red flag. They were not staffed or equipped for a possible riot that had been an obvious possibility in the circumstances. No protective and effective fencing worth the name was put in place and there were no contingency plans. The whole thing was basically a case of standing aside and waving people in. Once inside police mostly backed off apart from one Capitol police officer who ridiculously shot dead unarmed Air Force veteran protestor Ashli Babbitt without a warning as she climbed through a broken window. The ‘investigation’ refused to name or charge the officer after what must surely be considered a murder in the circumstances. They just lifted a carpet and swept. The story was endlessly repeated about five people dying in the ‘armed insurrection’ when there was no report of rioters using weapons. Apart from Babbitt the other four died from a heart attack, strokes and apparently a drug overdose. Capitol police officer Brian Sicknick was reported to have died after being bludgeoned with a fire extinguisher when he was alive after the riot was over and died later of what the Washington Medical Examiner’s Office said was a stroke. Sicknick had no external injuries. The lies were delivered like rapid fire. There was a narrative to build with incessant repetition of the lie until the lie became the accepted ‘everybody knows that’ truth. The ‘Big Lie’ technique of Nazi Propaganda Minister Joseph Goebbels is constantly used by the Cult which was behind the Nazis and is today behind the ‘Covid’ and ‘climate change’ hoaxes. Goebbels said:

If you tell a lie big enough and keep repeating it, people will eventually come to believe it. The lie can be maintained only for such time as the State can shield the people from the political, economic and/or military consequences of the lie. It thus becomes vitally important for the State to use all of its powers to repress dissent, for the truth is the mortal enemy of the lie, and thus by extension, the truth is the greatest enemy of the State.

Most protestors had a free run of the Capitol Building. This allowed pictures to be taken of rioters in iconic parts of the building including the Senate chamber which could be used as propaganda images against all Pushbackers. One Congresswoman described the scene as ‘the worst kind of non-security anybody could ever imagine’. Well, the first part was true, but someone obviously did imagine it and made sure it happened. Some photographs most widely circulated featured people wearing QAnon symbols and now the Psyop would be used to dub all QAnon followers with the ubiquitous fit-all label of ‘white supremacist’ and ‘insurrectionists’. When a Muslim extremist called Noah Green drove his car at two police officers at the Capitol Building killing one in April, 2021, there was no such political and media hysteria. They were just disappointed he wasn’t white.

## **The witch-hunt**

Government prosecutor Michael Sherwin, an aggressive, dark-eyed, professional Rottweiler led the ‘investigation’ and to call it over the top would be to underestimate reality a thousand fold. Hundreds were tracked down and arrested for the crime of having the wrong political views and people were jailed who had done nothing more than walk in the building, committed no violence or damage to property, took a few pictures and left. They were labelled a ‘threat to the Republic’ while Biden sat in the White House signing executive orders written for him that were dismantling ‘the Republic’. Even when judges ruled that a mother and son should not be in jail the government kept them there. Some of those arrested have been badly beaten by prison guards in Washington and lawyers for one man said he suffered a fractured skull and was made blind in one eye. Meanwhile a woman is shot dead for no reason by a Capitol Police officer and we are not allowed to know who he is never mind what has happened to him although that will be *nothing*. The Cult’s QAnon/Trump sting to identify and isolate Pushbackers and then target them on the road to crushing and deleting them was a resounding success. You would have thought the Russians had

invaded the building at gunpoint and lined up senators for a firing squad to see the political and media reaction. Congresswoman Alexandria Ocasio-Cortez is a child in a woman's body, a terrible-twins, me, me, me, Woker narcissist of such proportions that words have no meaning. She said she thought she was going to die when 'insurrectionists' banged on her office door. It turned out she wasn't even in the Capitol Building when the riot was happening and the 'banging' was a Capitol Police officer. She referred to herself as a 'survivor' which is an insult to all those true survivors of violent and sexual abuse while she lives her pampered and privileged life talking drivel for a living. Her Woke colleague and fellow mega-narcissist Rashida Tlaib broke down describing the devastating effect on her, too, of *not being* in the building when the rioters were there. Ocasio-Cortez and Tlaib are members of a fully-Woke group of Congresswomen known as 'The Squad' along with Ilhan Omar and Ayanna Pressley. The Squad from what I can see can be identified by its vehement anti-white racism, anti-white men agenda, and, as always in these cases, the absence of brain cells on active duty.

The usual suspects were on the riot case immediately in the form of Democrat ultra-Zionist senators and operatives Chuck Schumer and Adam Schiff demanding that Trump be impeached for 'his part in the insurrection'. The same pair of prats had led the failed impeachment of Trump over the invented 'Russia collusion' nonsense which claimed Russia had helped Trump win the 2016 election. I didn't realise that Tel Aviv had been relocated just outside Moscow. I must find an up-to-date map. The Russia hoax was a Sabbatian operation to keep Trump occupied and impotent and to stop any rapport with Russia which the Cult wants to retain as a perceptual enemy to be pulled out at will. Puppet Biden began attacking Russia when he came to office as the Cult seeks more upheaval, division and war across the world. A two-year stage show 'Russia collusion inquiry' headed by the not-very-bright former 9/11 FBI chief Robert Mueller, with support from 19 lawyers, 40 FBI agents plus intelligence analysts, forensic accountants and other

staff, devoured tens of millions of dollars and found no evidence of Russia collusion which a ten-year-old could have told them on day one. Now the same moronic Schumer and Schiff wanted a second impeachment of Trump over the Capitol ‘insurrection’ (riot) which the arrested development of Schumer called another ‘Pearl Harbor’ while others compared it with 9/11 in which 3,000 died and, in the case of CNN, with the Rwandan genocide in the 1990s in which an estimated 500,000 to 600,000 were murdered, between 250, 000 and 500,000 women were raped, and populations of whole towns were hacked to death with machetes. To make those comparisons purely for Cult political reasons is beyond insulting to those that suffered and lost their lives and confirms yet again the callous inhumanity that we are dealing with. Schumer is a monumental idiot and so is Schiff, but they serve the Cult agenda and do whatever they’re told so they get looked after. Talking of idiots – another inane man who spanned the Russia and Capitol impeachment attempts was Senator Eric Swalwell who had the nerve to accuse Trump of collusion with the Russians while sleeping with a Chinese spy called Christine Fang or ‘Fang Fang’ which is straight out of a Bond film no doubt starring Klaus Schwab as the bloke living on a secret island and controlling laser weapons positioned in space and pointing at world capitals. Fang Fang plays the part of Bond’s infiltrator girlfriend which I’m sure she would enjoy rather more than sharing a bed with the brainless Swalwell, lying back and thinking of China. The FBI eventually warned Swalwell about Fang Fang which gave her time to escape back to the Chinese dictatorship. How very thoughtful of them. The second Trump impeachment also failed and hardly surprising when an impeachment is supposed to remove a sitting president and by the time it happened Trump was no longer president. These people are running your country America, well, officially anyway. Terrifying isn’t it?

## **Outcomes tell the story - always**

The outcome of all this – and it’s the *outcome* on which Renegade Minds focus, not the words – was that a vicious, hysterical and

obviously pre-planned assault was launched on Pushbackers to censor, silence and discredit them and even targeted their right to earn a living. They have since been condemned as ‘domestic terrorists’ that need to be treated like Al-Qaeda and Islamic State. ‘Domestic terrorists’ is a label the Cult has been trying to make stick since the period of the Oklahoma bombing in 1995 which was blamed on ‘far-right domestic terrorists’. If you read *The Trigger* you will see that the bombing was clearly a Problem-Reaction-Solution carried out by the Deep State during a Bill Clinton administration so corrupt that no dictionary definition of the term would even nearly suffice. Nearly 30,000 troops were deployed from all over America to the empty streets of Washington for Biden’s inauguration. Ten thousand of them stayed on with the pretext of protecting the capital from insurrectionists when it was more psychological programming to normalise the use of the military in domestic law enforcement in support of the Cult plan for a police-military state. Biden’s fascist administration began a purge of ‘wrong-thinkers’ in the military which means anyone that is not on board with Woke. The Capitol Building was surrounded by a fence with razor wire and the Land of the Free was further symbolically and literally dismantled. The circle was completed with the installation of Biden and the exploitation of the QAnon Psyop.

America had never been so divided since the civil war of the 19th century, Pushbackers were isolated and dubbed terrorists and now, as was always going to happen, the Cult immediately set about deleting what little was left of freedom and transforming American society through a swish of the hand of the most controlled ‘president’ in American history leading (officially at least) the most extreme regime since the country was declared an independent state on July 4th, 1776. Biden issued undebated, dictatorial executive orders almost by the hour in his opening days in office across the whole spectrum of the Cult wish-list including diluting controls on the border with Mexico allowing thousands of migrants to illegally enter the United States to transform the demographics of America and import an election-changing number of perceived Democrat

voters. Then there were Biden deportation amnesties for the already illegally resident (estimated to be as high as 20 or even 30 million). A bill before Congress awarded American citizenship to anyone who could prove they had worked in agriculture for just 180 days in the previous two years as 'Big Ag' secured its slave labour long-term. There were the plans to add new states to the union such as Puerto Rico and making Washington DC a state. They are all parts of a plan to ensure that the Cult-owned Woke Democrats would be permanently in power.

## **Border – what border?**

I have exposed in detail in other books how mass immigration into the United States and Europe is the work of Cult networks fuelled by the tens of billions spent to this and other ends by George Soros and his global Open Society (open borders) Foundations. The impact can be seen in America alone where the population has increased by *100 million* in little more than 30 years mostly through immigration. I wrote in *The Answer* that the plan was to have so many people crossing the southern border that the numbers become unstoppable and we are now there under Cult-owned Biden. El Salvador in Central America puts the scale of what is happening into context. A third of the population now lives in the United States, much of it illegally, and many more are on the way. The methodology is to crush Central and South American countries economically and spread violence through machete-wielding psychopathic gangs like MS-13 based in El Salvador and now operating in many American cities. Biden-imposed lax security at the southern border means that it is all but open. He said before his 'election' that he wanted to see a surge towards the border if he became president and that was the green light for people to do just that after election day to create the human disaster that followed for both America and the migrants. When that surge came the imbecilic Alexandria Ocasio-Cortez said it wasn't a 'surge' because they are 'children, not insurgents' and the term 'surge' (used by Biden) was a claim of 'white supremacists'.

This disingenuous lady may one day enter the realm of the most basic intelligence, but it won't be any time soon.

Sabbatians and the Cult are in the process of destroying America by importing violent people and gangs in among the genuine to terrorise American cities and by overwhelming services that cannot cope with the sheer volume of new arrivals. Something similar is happening in Europe as Western society in general is targeted for demographic and cultural transformation and upheaval. The plan demands violence and crime to create an environment of intimidation, fear and division and Soros has been funding the election of district attorneys across America who then stop prosecuting many crimes, reduce sentences for violent crimes and free as many violent criminals as they can. Sabbatians are creating the chaos from which order – their order – can respond in a classic Problem-Reaction-Solution. A Freemasonic moto says ‘Ordo Ab Chao’ (Order out of Chaos) and this is why the Cult is constantly creating chaos to impose a new ‘order’. Here you have the reason the Cult is constantly creating chaos. The ‘Covid’ hoax can be seen with those entering the United States by plane being forced to take a ‘Covid’ test while migrants flooding through southern border processing facilities do not. Nothing is put in the way of mass migration and if that means ignoring the government’s own ‘Covid’ rules then so be it. They know it’s all bullshit anyway. Any pushback on this is denounced as ‘racist’ by Wokers and Sabbatian fronts like the ultra-Zionist Anti-Defamation League headed by the appalling Jonathan Greenblatt which at the same time argues that Israel should not give citizenship and voting rights to more Palestinian Arabs or the ‘Jewish population’ (in truth the Sabbatian network) will lose control of the country.

## **Society-changing numbers**

Biden’s masters have declared that countries like El Salvador are so dangerous that their people must be allowed into the United States for humanitarian reasons when there are fewer murders in large parts of many Central American countries than in US cities like

Baltimore. That is not to say Central America cannot be a dangerous place and Cult-controlled American governments have been making it so since way back, along with the dismantling of economies, in a long-term plan to drive people north into the United States. Parts of Central America are very dangerous, but in other areas the story is being greatly exaggerated to justify relaxing immigration criteria. Migrants are being offered free healthcare and education in the United States as another incentive to head for the border and there is no requirement to be financially independent before you can enter to prevent the resources of America being drained. You can't blame migrants for seeking what they believe will be a better life, but they are being played by the Cult for dark and nefarious ends. The numbers since Biden took office are huge. In February, 2021, more than 100,000 people were known to have tried to enter the US illegally through the southern border (it was 34,000 in the same month in 2020) and in March it was 170,000 – a 418 percent increase on March, 2020. These numbers are only known people, not the ones who get in unseen. The true figure for migrants illegally crossing the border in a single month was estimated by one congressman at 250,000 and that number will only rise under Biden's current policy. Gangs of murdering drug-running thugs that control the Mexican side of the border demand money – thousands of dollars – to let migrants cross the Rio Grande into America. At the same time gun battles are breaking out on the border several times a week between rival Mexican drug gangs (which now operate globally) who are equipped with sophisticated military-grade weapons, grenades and armoured vehicles. While the Capitol Building was being 'protected' from a non-existent 'threat' by thousands of troops, and others were still deployed at the time in the Cult Neocon war in Afghanistan, the southern border of America was left to its fate. This is not incompetence, it is cold calculation.

By March, 2021, there were 17,000 unaccompanied children held at border facilities and many of them are ensnared by people traffickers for paedophile rings and raped on their journey north to America. This is not conjecture – this is fact. Many of those designated

children are in reality teenage boys or older. Meanwhile Wokers posture their self-purity for encouraging poor and tragic people to come to America and face this nightmare both on the journey and at the border with the disgusting figure of House Speaker Nancy Pelosi giving disingenuous speeches about caring for migrants. The woman's evil. Wokers condemned Trump for having children in cages at the border (so did Obama, *Shhhh*), but now they are sleeping on the floor without access to a shower with one border facility 729 percent over capacity. The Biden insanity even proposed flying migrants from the southern border to the northern border with Canada for 'processing'. The whole shambles is being overseen by ultra-Zionist Secretary of Homeland Security, the moronic liar Alejandro Mayorkas, who banned news cameras at border facilities to stop Americans seeing what was happening. Mayorkas said there was not a ban on news crews; it was just that they were not allowed to film. Alongside him at Homeland Security is another ultra-Zionist Cass Sunstein appointed by Biden to oversee new immigration laws. Sunstein despises conspiracy researchers to the point where he suggests they should be banned or *taxed* for having such views. The man is not bonkers or anything. He's perfectly well-adjusted, but adjusted to what is the question. Criticise what is happening and you are a 'white supremacist' when earlier non-white immigrants also oppose the numbers which effect their lives and opportunities. Black people in poor areas are particularly damaged by uncontrolled immigration and the increased competition for work opportunities with those who will work for less. They are also losing voting power as Hispanics become more dominant in former black areas. It's a downward spiral for them while the billionaires behind the policy drone on about how much they care about black people and 'racism'. None of this is about compassion for migrants or black people – that's just wind and air. Migrants are instead being mercilessly exploited to transform America while the countries they leave are losing their future and the same is true in Europe. Mass immigration may now be the work of Woke Democrats, but it can be traced back to the 1986 Immigration Reform and Control Act (it

wasn't) signed into law by Republican hero President Ronald Reagan which gave amnesty to millions living in the United States illegally and other incentives for people to head for the southern border. Here we have the one-party state at work again.

## **Save me syndrome**

Almost every aspect of what I have been exposing as the Cult agenda was on display in even the first days of 'Biden' with silencing of Pushbackers at the forefront of everything. A Renegade Mind will view the Trump years and QAnon in a very different light to their supporters and advocates as the dots are connected. The QAnon/Trump Psyop has given the Cult all it was looking for. We may not know how much, or little, that Trump realised he was being used, but that's a side issue. This pincer movement produced the desired outcome of dividing America and having Pushbackers isolated. To turn this around we have to look at new routes to empowerment which do not include handing our power to other people and groups through what I will call the 'Save Me Syndrome' – 'I want someone else to do it so that I don't have to'. We have seen this at work throughout human history and the QAnon/Trump Psyop is only the latest incarnation alongside all the others. Religion is an obvious expression of this when people look to a 'god' or priest to save them or tell them how to be saved and then there are 'save me' politicians like Trump. Politics is a diversion and not a 'saviour'. It is a means to block positive change, not make it possible.

Save Me Syndrome always comes with the same repeating theme of handing your power to whom or what you believe will save you while your real 'saviour' stares back from the mirror every morning. Renegade Minds are constantly vigilant in this regard and always asking the question 'What can I do?' rather than 'What can someone else do for me?' Gandhi was right when he said: 'You must be the change you want to see in the world.' We are indeed the people we have been waiting for. We are presented with a constant raft of reasons to concede that power to others and forget where the real power is. Humanity has the numbers and the Cult does not. It has to

use diversion and division to target the unstoppable power that comes from unity. Religions, governments, politicians, corporations, media, QAnon, are all different manifestations of this power-diversion and dilution. Refusing to give your power to governments and instead handing it to Trump and QAnon is not to take a new direction, but merely to recycle the old one with new names on the posters. I will explore this phenomenon as we proceed and how to break the cycles and recycles that got us here through the mists of repeating perception and so repeating history.

For now we shall turn to the most potent example in the entire human story of the consequences that follow when you give your power away. I am talking, of course, of the 'Covid' hoax.

## CHAPTER FOUR

### 'Covid': Calculated catastrophe

*Facts are threatening to those invested in fraud*  
DaShanne Stokes

We can easily unravel the real reason for the 'Covid pandemic' hoax by employing the Renegade Mind methodology that I have outlined this far. We'll start by comparing the long-planned Cult outcome with the 'Covid pandemic' outcome. Know the outcome and you'll see the journey.

I have highlighted the plan for the Hunger Games Society which has been in my books for so many years with the very few controlling the very many through ongoing dependency. To create this dependency it is essential to destroy independent livelihoods, businesses and employment to make the population reliant on the state (the Cult) for even the basics of life through a guaranteed pittance income. While independence of income remained these Cult ambitions would be thwarted. With this knowledge it was easy to see where the 'pandemic' hoax was going once talk of 'lockdowns' began and the closing of all but perceived 'essential' businesses to 'save' us from an alleged 'deadly virus'. Cult corporations like Amazon and Walmart were naturally considered 'essential' while mom and pop shops and stores had their doors closed by fascist decree. As a result with every new lockdown and new regulation more small and medium, even large businesses not owned by the Cult, went to the wall while Cult giants and their frontmen and women grew financially fatter by the second. Mom and pop were

denied an income and the right to earn a living and the wealth of people like Jeff Bezos (Amazon), Mark Zuckerberg (Facebook) and Sergei Brin and Larry Page (Google/Alphabet) have reached record levels. The Cult was increasing its own power through further dramatic concentrations of wealth while the competition was being destroyed and brought into a state of dependency. Lockdowns have been instigated to secure that very end and were never anything to do with health. My brother Paul spent 45 years building up a bus repair business, but lockdowns meant buses were running at a fraction of normal levels for months on end. Similar stories can told in their hundreds of millions worldwide. Efforts of a lifetime coldly destroyed by Cult multi-billionaires and their lackeys in government and law enforcement who continued to earn their living from the taxation of the people while denying the right of the same people to earn theirs. How different it would have been if those making and enforcing these decisions had to face the same financial hardships of those they affected, but they never do.

## **Gates of Hell**

Behind it all in the full knowledge of what he is doing and why is the psychopathic figure of Cult operative Bill Gates. His puppet Tedros at the World Health Organization declared 'Covid' a pandemic in March, 2020. The WHO had changed the definition of a 'pandemic' in 2009 just a month before declaring the 'swine flu pandemic' which would not have been so under the previous definition. The same applies to 'Covid'. The definition had included... 'an infection by an infectious agent, occurring simultaneously in different countries, with a significant mortality rate relative to the proportion of the population infected'. The new definition removed the need for 'significant mortality'. The 'pandemic' has been fraudulent even down to the definition, but Gates demanded economy-destroying lockdowns, school closures, social distancing, mandatory masks, a 'vaccination' for every man, woman and child on the planet and severe consequences and restrictions for those that refused. Who gave him this power? The

Cult did which he serves like a little boy in short trousers doing what his daddy tells him. He and his psychopathic missus even smiled when they said that much worse was to come (what they knew was planned to come). Gates responded in the matter-of-fact way of all psychopaths to a question about the effect on the world economy of what he was doing:

Well, it won't go to zero but it will shrink. Global GDP is probably going to take the biggest hit ever [Gates was smiling as he said this] ... in my lifetime this will be the greatest economic hit. But you don't have a choice. People act as if you have a choice. People don't feel like going to the stadium when they might get infected ... People are deeply affected by seeing these stats, by knowing they could be part of the transmission chain, old people, their parents and grandparents, could be affected by this, and so you don't get to say ignore what is going on here.

There will be the ability to open up, particularly in rich countries, if things are done well over the next few months, but for the world at large normalcy only returns when we have largely vaccinated the entire population.

The man has no compassion or empathy. How could he when he's a psychopath like all Cult players? My own view is that even beyond that he is very seriously mentally ill. Look in his eyes and you can see this along with his crazy flailing arms. You don't do what he has done to the world population since the start of 2020 unless you are mentally ill and at the most extreme end of psychopathic. You especially don't do it when to you know, as we shall see, that cases and deaths from 'Covid' are fakery and a product of monumental figure massaging. 'These stats' that Gates referred to are based on a 'test' that's not testing for the 'virus' as he has known all along. He made his fortune with big Cult support as an infamously ruthless software salesman and now buys global control of 'health' (death) policy without the population he affects having any say. It's a breathtaking outrage. Gates talked about people being deeply affected by fear of 'Covid' when that was because of *him* and his global network lying to them minute-by-minute supported by a lying media that he seriously influences and funds to the tune of hundreds of millions. He's handed big sums to media operations including the BBC, NBC, Al Jazeera, Univision, *PBS NewsHour*,

*ProPublica, National Journal, The Guardian, The Financial Times, The Atlantic, Texas Tribune, USA Today* publisher Gannett, Washington Monthly, Le Monde, Center for Investigative Reporting, Pulitzer Center on Crisis Reporting, National Press Foundation, International Center for Journalists, Solutions Journalism Network, the Poynter Institute for Media Studies, and many more. Gates is everywhere in the ‘Covid’ hoax and the man must go to prison – or a mental facility – for the rest of his life and his money distributed to those he has taken such enormous psychopathic pleasure in crushing.

## **The Muscle**

The Hunger Games global structure demands a police-military state – a fusion of the two into one force – which viciously imposes the will of the Cult on the population and protects the Cult from public rebellion. In that regard, too, the ‘Covid’ hoax just keeps on giving. Often unlawful, ridiculous and contradictory ‘Covid’ rules and regulations have been policed across the world by moronic automatons and psychopaths made faceless by face-nappy masks and acting like the Nazi SS and fascist blackshirts and brownshirts of Hitler and Mussolini. The smallest departure from the rules decreed by the psychos in government and their clueless gofers were jumped upon by the face-nappy fascists. Brutality against public protestors soon became commonplace even on girls, women and old people as the brave men with the batons – the Face-Nappies as I call them – broke up peaceful protests and handed out fines like confetti to people who couldn’t earn a living let alone pay hundreds of pounds for what was once an accepted human right. Robot Face-Nappies of Nottingham police in the English East Midlands fined one group £11,000 for attending a child’s birthday party. For decades I charted the transformation of law enforcement as genuine, decent officers were replaced with psychopaths and the brain dead who would happily and brutally do whatever their masters told them. Now they were let loose on the public and I would emphasise the point that none of this just happened. The step-by-step change in the dynamic between police and public was orchestrated from the shadows by

those who knew where this was all going and the same with the perceptual reframing of those in all levels of authority and official administration through ‘training courses’ by organisations such as Common Purpose which was created in the late 1980s and given a massive boost in Blair era Britain until it became a global phenomenon. Supposed public ‘servants’ began to view the population as the enemy and the same was true of the police. This was the start of the explosion of behaviour manipulation organisations and networks preparing for the all-war on the human psyche unleashed with the dawn of 2020. I will go into more detail about this later in the book because it is a core part of what is happening.

Police desecrated beauty spots to deter people gathering and arrested women for walking in the countryside alone ‘too far’ from their homes. We had arrogant, clueless sergeants in the Isle of Wight police where I live posting on Facebook what they insisted the population must do or else. A schoolmaster sergeant called Radford looked young enough for me to ask if his mother knew he was out, but he was posting what he *expected* people to do while a Sergeant Wilkinson boasted about fining lads for meeting in a McDonald’s car park where they went to get a lockdown takeaway. Wilkinson added that he had even cancelled their order. What a pair of prats these people are and yet they have increasingly become the norm among Jackboot Johnson’s Yellowshirts once known as the British police. This was the theme all over the world with police savagery common during lockdown protests in the United States, the Netherlands, and the fascist state of Victoria in Australia under its tyrannical and again moronic premier Daniel Andrews. Amazing how tyrannical and moronic tend to work as a team and the same combination could be seen across America as arrogant, narcissistic Woke governors and mayors such as Gavin Newsom (California), Andrew Cuomo (New York), Gretchen Whitmer (Michigan), Lori Lightfoot (Chicago) and Eric Garcetti (Los Angeles) did their Nazi and Stalin impressions with the full support of the compliant brutality of their enforcers in uniform as they arrested small business owners defying

fascist shutdown orders and took them to jail in ankle shackles and handcuffs. This happened to bistro owner Marlena Pavlos-Hackney in Gretchen Whitmer's fascist state of Michigan when police arrived to enforce an order by a state-owned judge for 'putting the community at risk' at a time when other states like Texas were dropping restrictions and migrants were pouring across the southern border without any 'Covid' questions at all. I'm sure there are many officers appalled by what they are ordered to do, but not nearly enough of them. If they were truly appalled they would not do it. As the months passed every opportunity was taken to have the military involved to make their presence on the streets ever more familiar and 'normal' for the longer-term goal of police-military fusion.

Another crucial element to the Hunger Games enforcement network has been encouraging the public to report neighbours and others for 'breaking the lockdown rules'. The group faced with £11,000 in fines at the child's birthday party would have been dobbed-in by a neighbour with a brain the size of a pea. The technique was most famously employed by the Stasi secret police in communist East Germany who had public informants placed throughout the population. A police chief in the UK says his force doesn't need to carry out 'Covid' patrols when they are flooded with so many calls from the public reporting other people for visiting the beach. Dorset police chief James Vaughan said people were so enthusiastic about snitching on their fellow humans they were now operating as an auxiliary arm of the police: 'We are still getting around 400 reports a week from the public, so we will respond to reports ... We won't need to be doing hotspot patrols because people are very quick to pick the phone up and tell us.' Vaughan didn't say that this is a pillar of all tyrannies of whatever complexion and the means to hugely extend the reach of enforcement while spreading distrust among the people and making them wary of doing anything that might get them reported. Those narcissistic Isle of Wight sergeants Radford and Wilkinson never fail to add a link to their Facebook posts where the public can inform on their fellow slaves.

Neither would be self-aware enough to realise they were imitating the Stasi which they might well never have heard of. Government psychologists that I will expose later laid out a policy to turn communities against each other in the same way.

## **A coincidence? Yep, and I can knit fog**

I knew from the start of the alleged pandemic that this was a Cult operation. It presented limitless potential to rapidly advance the Cult agenda and exploit manipulated fear to demand that every man, woman and child on the planet was ‘vaccinated’ in a process never used on humans before which infuses self-replicating *synthetic* material into human cells. Remember the plan to transform the human body from a biological to a synthetic biological state. I’ll deal with the ‘vaccine’ (that’s not actually a vaccine) when I focus on the genetic agenda. Enough to say here that mass global ‘vaccination’ justified by this ‘new virus’ set alarms ringing after 30 years of tracking these people and their methods. The ‘Covid’ hoax officially beginning in China was also a big red flag for reasons I will be explaining. The agenda potential was so enormous that I could dismiss any idea that the ‘virus’ appeared naturally. Major happenings with major agenda implications never occur without Cult involvement in making them happen. My questions were twofold in early 2020 as the media began its campaign to induce global fear and hysteria: Was this alleged infectious agent released on purpose by the Cult or did it even exist at all? I then did what I always do in these situations. I sat, observed and waited to see where the evidence and information would take me. By March and early April synchronicity was strongly – and ever more so since then – pointing me in the direction of *there is no ‘virus’*. I went public on that with derision even from swathes of the alternative media that voiced a scenario that the Chinese government released the ‘virus’ in league with Deep State elements in the United States from a top-level bio-lab in Wuhan where the ‘virus’ is said to have first appeared. I looked at that possibility, but I didn’t buy it for several reasons. Deaths from the ‘virus’ did not in any way match what they

would have been with a ‘deadly bioweapon’ and it is much more effective if you sell the *illusion* of an infectious agent rather than having a real one unless you can control through injection who has it and who doesn’t. Otherwise you lose control of events. A made-up ‘virus’ gives you a blank sheet of paper on which you can make it do whatever you like and have any symptoms or mutant ‘variants’ you choose to add while a real infectious agent would limit you to what it actually does. A phantom disease allows you to have endless ludicrous ‘studies’ on the ‘Covid’ dollar to widen the perceived impact by inventing ever more ‘at risk’ groups including one study which said those who walk slowly may be almost four times more likely to die from the ‘virus’. People are in psychiatric wards for less.

A real ‘deadly bioweapon’ can take out people in the hierarchy that are not part of the Cult, but essential to its operation. Obviously they don’t want that. Releasing a real disease means you immediately lose control of it. Releasing an illusory one means you don’t. Again it’s vital that people are extra careful when dealing with what they want to hear. A bioweapon unleashed from a Chinese laboratory in collusion with the American Deep State may fit a conspiracy narrative, but is it true? Would it not be far more effective to use the excuse of a ‘virus’ to justify the real bioweapon – the ‘vaccine’? That way your disease agent does not have to be transmitted and arrives directly through a syringe. I saw a French virologist Luc Montagnier quoted in the alternative media as saying he had discovered that the alleged ‘new’ severe acute respiratory syndrome coronavirus , or SARS-CoV-2, was made artificially and included elements of the human immunodeficiency ‘virus’ (HIV) and a parasite that causes malaria. SARS-CoV-2 is alleged to trigger an alleged illness called Covid-19. I remembered Montagnier’s name from my research years before into claims that an HIV ‘retrovirus’ causes AIDS – claims that were demolished by Berkeley virologist Peter Duesberg who showed that no one had ever proved that HIV causes acquired immunodeficiency syndrome or AIDS. Claims that become accepted as fact, publicly and medically, with no proof whatsoever are an ever-recurring story that profoundly applies to

'Covid'. Nevertheless, despite the lack of proof, Montagnier's team at the Pasteur Institute in Paris had a long dispute with American researcher Robert Gallo over which of them discovered and isolated the HIV 'virus' and with *no evidence* found it to cause AIDS. You will see later that there is also no evidence that any 'virus' causes any disease or that there is even such a thing as a 'virus' in the way it is said to exist. The claim to have 'isolated' the HIV 'virus' will be presented in its real context as we come to the shocking story – and it is a story – of SARS-CoV-2 and so will Montagnier's assertion that he identified the full SARS-CoV-2 genome.

## **Hoax in the making**

We can pick up the 'Covid' story in 2010 and the publication by the Rockefeller Foundation of a document called 'Scenarios for the Future of Technology and International Development'. The inner circle of the Rockefeller family has been serving the Cult since John D. Rockefeller (1839-1937) made his fortune with Standard Oil. It is less well known that the same Rockefeller – the Bill Gates of his day – was responsible for establishing what is now referred to as 'Big Pharma', the global network of pharmaceutical companies that make outrageous profits dispensing scalpel and drug 'medicine' and are obsessed with pumping vaccines in ever-increasing number into as many human arms and backsides as possible. John D. Rockefeller was the driving force behind the creation of the 'education' system in the United States and elsewhere specifically designed to program the perceptions of generations thereafter. The Rockefeller family donated exceptionally valuable land in New York for the United Nations building and were central in establishing the World Health Organization in 1948 as an agency of the UN which was created from the start as a Trojan horse and stalking horse for world government. Now enter Bill Gates. His family and the Rockefellers have long been extremely close and I have seen genealogy which claims that if you go back far enough the two families fuse into the same bloodline. Gates has said that the Bill and Melinda Gates Foundation was inspired by the Rockefeller Foundation and why not

when both are serving the same Cult? Major tax-exempt foundations are overwhelmingly criminal enterprises in which Cult assets fund the Cult agenda in the guise of 'philanthropy' while avoiding tax in the process. Cult operatives can become mega-rich in their role of front men and women for the psychopaths at the inner core and they, too, have to be psychopaths to knowingly serve such evil. Part of the deal is that a big percentage of the wealth gleaned from representing the Cult has to be spent advancing the ambitions of the Cult and hence you have the Rockefeller Foundation, Bill and Melinda Gates Foundation (and so many more) and people like George Soros with his global Open Society Foundations spending their billions in pursuit of global Cult control. Gates is a global public face of the Cult with his interventions in world affairs including Big Tech influence; a central role in the 'Covid' and 'vaccine' scam; promotion of the climate change shakedown; manipulation of education; geoengineering of the skies; and his food-control agenda as the biggest owner of farmland in America, his GMO promotion and through other means. As one writer said: 'Gates monopolizes or wields disproportionate influence over the tech industry, global health and vaccines, agriculture and food policy (including biopiracy and fake food), weather modification and other climate technologies, surveillance, education and media.' The almost limitless wealth secured through Microsoft and other not-allowed-to-fail ventures (including vaccines) has been ploughed into a long, long list of Cult projects designed to enslave the entire human race. Gates and the Rockefellers have been working as one unit with the Rockefeller-established World Health Organization leading global 'Covid' policy controlled by Gates through his mouth-piece Tedros. Gates became the WHO's biggest funder when Trump announced that the American government would cease its donations, but Biden immediately said he would restore the money when he took office in January, 2021. The Gates Foundation (the Cult) owns through limitless funding the world health system and the major players across the globe in the 'Covid' hoax.

Okay, with that background we return to that Rockefeller Foundation document of 2010 headed ‘Scenarios for the Future of Technology and International Development’ and its ‘imaginary’ epidemic of a virulent and deadly influenza strain which infected 20 percent of the global population and killed eight million in seven months. The Rockefeller scenario was that the epidemic destroyed economies, closed shops, offices and other businesses and led to governments imposing fierce rules and restrictions that included mandatory wearing of face masks and body-temperature checks to enter communal spaces like railway stations and supermarkets. The document predicted that even after the height of the Rockefeller-envisioned epidemic the authoritarian rule would continue to deal with further pandemics, transnational terrorism, environmental crises and rising poverty. Now you may think that the Rockefellers are our modern-day seers or alternatively, and rather more likely, that they well knew what was planned a few years further on. Fascism had to be imposed, you see, to ‘protect citizens from risk and exposure’. The Rockefeller scenario document said:

During the pandemic, national leaders around the world flexed their authority and imposed airtight rules and restrictions, from the mandatory wearing of face masks to body-temperature checks at the entries to communal spaces like train stations and supermarkets. Even after the pandemic faded, this more authoritarian control and oversight of citizens and their activities stuck and even intensified. In order to protect themselves from the spread of increasingly global problems – from pandemics and transnational terrorism to environmental crises and rising poverty – leaders around the world took a firmer grip on power.

At first, the notion of a more controlled world gained wide acceptance and approval. Citizens willingly gave up some of their sovereignty – and their privacy – to more paternalistic states in exchange for greater safety and stability. Citizens were more tolerant, and even eager, for top-down direction and oversight, and national leaders had more latitude to impose order in the ways they saw fit.

In developed countries, this heightened oversight took many forms: biometric IDs for all citizens, for example, and tighter regulation of key industries whose stability was deemed vital to national interests. In many developed countries, enforced cooperation with a suite of new regulations and agreements slowly but steadily restored both order and, importantly, economic growth.

There we have the prophetic Rockefellers in 2010 and three years later came their paper for the Global Health Summit in Beijing, China, when government representatives, the private sector, international organisations and groups met to discuss the next 100 years of 'global health'. The Rockefeller Foundation-funded paper was called 'Dreaming the Future of Health for the Next 100 Years' and more prophecy ensued as it described a dystopian future: 'The abundance of data, digitally tracking and linking people may mean the 'death of privacy' and may replace physical interaction with transient, virtual connection, generating isolation and raising questions of how values are shaped in virtual networks.' Next in the 'Covid' hoax preparation sequence came a 'table top' simulation in 2018 for another 'imaginary' pandemic of a disease called Clade X which was said to kill 900 million people. The exercise was organised by the Gates-funded Johns Hopkins University's Center for Health Security in the United States and this is the very same university that has been compiling the disgustingly and systematically erroneous global figures for 'Covid' cases and deaths. Similar Johns Hopkins health crisis scenarios have included the Dark Winter exercise in 2001 and Atlantic Storm in 2005.

## **Nostradamus 201**

For sheer predictive genius look no further prophecy-watchers than the Bill Gates-funded Event 201 held only six weeks before the 'coronavirus pandemic' is supposed to have broken out in China and Event 201 was based on a scenario of a global 'coronavirus pandemic'. Melinda Gates, the great man's missus, told the BBC that he had 'prepared for years' for a coronavirus pandemic which told us what we already knew. Nostradamugates had predicted in a TED talk in 2015 that a pandemic was coming that would kill a lot of people and demolish the world economy. My god, the man is a machine – possibly even literally. Now here he was only weeks before the real thing funding just such a simulated scenario and involving his friends and associates at Johns Hopkins, the World Economic Forum Cult-front of Klaus Schwab, the United Nations,

Johnson & Johnson, major banks, and officials from China and the Centers for Disease Control in the United States. What synchronicity – Johns Hopkins would go on to compile the fraudulent ‘Covid’ figures, the World Economic Forum and Schwab would push the ‘Great Reset’ in response to ‘Covid’, the Centers for Disease Control would be at the forefront of ‘Covid’ policy in the United States, Johnson & Johnson would produce a ‘Covid vaccine’, and everything would officially start just weeks later in China. Spooky, eh? They were even accurate in creating a simulation of a ‘virus’ pandemic because the ‘real thing’ would also be a simulation. Event 201 was not an exercise preparing for something that might happen; it was a rehearsal for what those in control knew was *going* to happen and very shortly. Hours of this simulation were posted on the Internet and the various themes and responses mirrored what would soon be imposed to transform human society. News stories were inserted and what they said would be commonplace a few weeks later with still more prophecy perfection. Much discussion focused on the need to deal with misinformation and the ‘anti-vax movement’ which is exactly what happened when the ‘virus’ arrived – was said to have arrived – in the West.

Cult-owned social media banned criticism and exposure of the official ‘virus’ narrative and when I said there *was* no ‘virus’ in early April, 2020, I was banned by one platform after another including YouTube, Facebook and later Twitter. The mainstream broadcast media in Britain was in effect banned from interviewing me by the Tony-Blair-created government broadcasting censor Ofcom headed by career government bureaucrat Melanie Dawes who was appointed just as the ‘virus’ hoax was about to play out in January, 2020. At the same time the Ickonic media platform was using Vimeo, another ultra-Zionist-owned operation, while our own player was being created and they deleted in an instant hundreds of videos, documentaries, series and shows to confirm their unbelievable vindictiveness. We had copies, of course, and they had to be restored one by one when our player was ready. These people have no class. Sabbatian Facebook promised free advertisements for the Gates-

controlled World Health Organization narrative while deleting ‘false claims and conspiracy theories’ to stop ‘misinformation’ about the alleged coronavirus. All these responses could be seen just a short while earlier in the scenarios of Event 201. Extreme censorship was absolutely crucial for the Cult because the official story was so ridiculous and unsupportable by the evidence that it could never survive open debate and the free-flow of information and opinion. If you can’t win a debate then don’t have one is the Cult’s approach throughout history. Facebook’s little boy front man – front boy – Mark Zuckerberg equated ‘credible and accurate information’ with official sources and exposing their lies with ‘misinformation’.

## **Silencing those that can see**

The censorship dynamic of Event 201 is now the norm with an army of narrative-supporting ‘fact-checker’ organisations whose entire reason for being is to tell the public that official narratives are true and those exposing them are lying. One of the most appalling of these ‘fact-checkers’ is called NewsGuard founded by ultra-Zionist Americans Gordon Crovitz and Steven Brill. Crovitz is a former publisher of *The Wall Street Journal*, former Executive Vice President of Dow Jones, a member of the Council on Foreign Relations (CFR), and on the board of the American Association of Rhodes Scholars. The CFR and Rhodes Scholarships, named after Rothschild agent Cecil Rhodes who plundered the gold and diamonds of South Africa for his masters and the Cult, have featured widely in my books. NewsGuard don’t seem to like me for some reason – I really can’t think why – and they have done all they can to have me censored and discredited which is, to quote an old British politician, like being savaged by a dead sheep. They are, however, like all in the censorship network, very well connected and funded by organisations themselves funded by, or connected to, Bill Gates. As you would expect with anything associated with Gates NewsGuard has an offshoot called HealthGuard which ‘fights online health care hoaxes’. How very kind. Somehow the NewsGuard European Managing Director Anna-Sophie Harling, a remarkably young-

looking woman with no broadcasting experience and little hands-on work in journalism, has somehow secured a position on the ‘Content Board’ of UK government broadcast censor Ofcom. An executive of an organisation seeking to discredit dissidents of the official narratives is making decisions for the government broadcast ‘regulator’ about content?? Another appalling ‘fact-checker’ is Full Fact funded by George Soros and global censors Google and Facebook.

It’s amazing how many activists in the ‘fact-checking’, ‘anti-hate’, arena turn up in government-related positions – people like UK Labour Party activist Imran Ahmed who heads the Center for Countering Digital Hate founded by people like Morgan McSweeney, now chief of staff to the Labour Party’s hapless and useless ‘leader’ Keir Starmer. Digital Hate – which is what it really is – uses the American spelling of Center to betray its connection to a transatlantic network of similar organisations which in 2020 shapeshifted from attacking people for ‘hate’ to attacking them for questioning the ‘Covid’ hoax and the dangers of the ‘Covid vaccine’. It’s just a coincidence, you understand. This is one of Imran Ahmed’s hysterical statements: ‘I would go beyond calling anti-vaxxers conspiracy theorists to say they are an extremist group that pose a national security risk.’ No one could ever accuse this prat of understatement and he’s including in that those parents who are now against vaccines after their children were damaged for life or killed by them. He’s such a nice man. Ahmed does the rounds of the Woke media getting soft-ball questions from spineless ‘journalists’ who never ask what right he has to campaign to destroy the freedom of speech of others while he demands it for himself. There also seems to be an overrepresentation in Ofcom of people connected to the narrative-worshipping BBC. This incredible global network of narrative-support was super-vital when the ‘Covid’ hoax was played in the light of the mega-whopper lies that have to be defended from the spotlight cast by the most basic intelligence.

## **Setting the scene**

The Cult plays the long game and proceeds step-by-step ensuring that everything is in place before major cards are played and they don't come any bigger than the 'Covid' hoax. The psychopaths can't handle events where the outcome isn't certain and as little as possible – preferably nothing – is left to chance. Politicians, government and medical officials who would follow direction were brought to illusory power in advance by the Cult web whether on the national stage or others like state governors and mayors of America. For decades the dynamic between officialdom, law enforcement and the public was changed from one of service to one of control and dictatorship. Behaviour manipulation networks established within government were waiting to impose the coming 'Covid' rules and regulations specifically designed to subdue and rewire the psyche of the people in the guise of protecting health. These included in the UK the Behavioural Insights Team part-owned by the British government Cabinet Office; the Scientific Pandemic Insights Group on Behaviours (SPI-B); and a whole web of intelligence and military groups seeking to direct the conversation on social media and control the narrative. Among them are the cyberwarfare (on the people) 77th Brigade of the British military which is also coordinated through the Cabinet Office as civilian and military leadership continues to combine in what they call the Fusion Doctrine. The 77th Brigade is a British equivalent of the infamous Israeli (Sabbatian) military cyberwarfare and Internet manipulation operation Unit 8200 which I expose at length in *The Trigger*. Also carefully in place were the medical and science advisers to government – many on the payroll past or present of Bill Gates – and a whole alternative structure of unelected government stood by to take control when elected parliaments were effectively closed down once the 'Covid' card was slammed on the table. The structure I have described here and so much more was installed in every major country through the Cult networks. The top-down control hierarchy looks like this: The Cult – Cult-owned Gates – the World Health Organization and Tedros – Gates-funded or controlled chief medical officers and science 'advisers' (dictators) in each country –

political ‘leaders’ – law enforcement – The People. Through this simple global communication and enforcement structure the policy of the Cult could be imposed on virtually the entire human population so long as they acquiesced to the fascism. With everything in place it was time for the button to be pressed in late 2019/early 2020.

These were the prime goals the Cult had to secure for its will to prevail:

- 1) Locking down economies, closing all but designated ‘essential’ businesses (Cult-owned corporations were ‘essential’), and putting the population under house arrest was an imperative to destroy independent income and employment and ensure dependency on the Cult-controlled state in the Hunger Games Society. Lockdowns had to be established as the global blueprint from the start to respond to the ‘virus’ and followed by pretty much the entire world.
- 2) The global population had to be terrified into believing in a deadly ‘virus’ that didn’t actually exist so they would unquestioningly obey authority in the belief that authority must know how best to protect them and their families. Software salesman Gates would suddenly morph into the world’s health expert and be promoted as such by the Cult-owned media.
- 3) A method of testing that wasn’t testing for the ‘virus’, but was only claimed to be, had to be in place to provide the illusion of ‘cases’ and subsequent ‘deaths’ that had a very different cause to the ‘Covid-19’ that would be scribbled on the death certificate.
- 4) Because there was no ‘virus’ and the great majority testing positive with a test not testing for the ‘virus’ would have no symptoms of anything the lie had to be sold that people without symptoms (without the ‘virus’) could still pass it on to others. This was crucial to justify for the first time quarantining – house arresting – healthy people. Without this the economy-destroying lockdown of *everybody* could not have been credibly sold.
- 5) The ‘saviour’ had to be seen as a vaccine which beyond evil drug companies were working like angels of mercy to develop as quickly as possible, with all corners cut, to save the day. The public must absolutely not know that the ‘vaccine’ had nothing to do with a ‘virus’ or that the contents were ready and waiting with a very different motive long before the ‘Covid’ card was even lifted from the pack.

I said in March, 2020, that the ‘vaccine’ would have been created way ahead of the ‘Covid’ hoax which justified its use and the following December an article in the New York *Intelligencer* magazine said the Moderna ‘vaccine’ had been ‘designed’ by

January, 2020. This was ‘before China had even acknowledged that the disease could be transmitted from human to human, more than a week before the first confirmed coronavirus case in the United States’. The article said that by the time the first American death was announced a month later ‘the vaccine had already been manufactured and shipped to the National Institutes of Health for the beginning of its Phase I clinical trial’. The ‘vaccine’ was actually ‘designed’ long before that although even with this timescale you would expect the article to ask how on earth it could have been done that quickly. Instead it asked why the ‘vaccine’ had not been rolled out then and not months later. Journalism in the mainstream is truly dead. I am going to detail in the next chapter why the ‘virus’ has never existed and how a hoax on that scale was possible, but first the foundation on which the Big Lie of ‘Covid’ was built.

## **The test that doesn’t test**

Fraudulent ‘testing’ is the bottom line of the whole ‘Covid’ hoax and was the means by which a ‘virus’ that did not exist *appeared* to exist. They could only achieve this magic trick by using a test not testing for the ‘virus’. To use a test that *was* testing for the ‘virus’ would mean that every test would come back negative given there was no ‘virus’. They chose to exploit something called the RT-PCR test invented by American biochemist Kary Mullis in the 1980s who said publicly that his PCR test … *cannot detect infectious disease*. Yes, the ‘test’ used worldwide to detect infectious ‘Covid’ to produce all the illusory ‘cases’ and ‘deaths’ compiled by Johns Hopkins and others *cannot detect infectious disease*. This fact came from the mouth of the man who invented PCR and was awarded the Nobel Prize in Chemistry in 1993 for doing so. Sadly, and incredibly conveniently for the Cult, Mullis died in August, 2019, at the age of 74 just before his test would be fraudulently used to unleash fascism on the world. He was said to have died from pneumonia which was an irony in itself. A few months later he would have had ‘Covid-19’ on his death certificate. I say the timing of his death was convenient because had he lived Mullis, a brilliant, honest and decent man, would have been

vociferously speaking out against the use of his test to detect 'Covid' when it was never designed, or able, to do that. I know that to be true given that Mullis made the same point when his test was used to 'detect' – not detect – HIV. He had been seriously critical of the Gallo/Montagnier claim to have isolated the HIV 'virus' and shown it to cause AIDS for which Mullis said there was no evidence. AIDS is actually not a disease but a series of diseases from which people die all the time. When they die from those *same diseases* after a positive 'test' for HIV then AIDS goes on their death certificate. I think I've heard that before somewhere. Countries instigated a policy with 'Covid' that anyone who tested positive with a test not testing for the 'virus' and died of any other cause within 28 days and even longer 'Covid-19' had to go on the death certificate. Cases have come from the test that can't test for infectious disease and the deaths are those who have died of *anything* after testing positive with a test not testing for the 'virus'. I'll have much more later about the death certificate scandal.

Mullis was deeply dismissive of the now US 'Covid' star Anthony Fauci who he said was a liar who didn't know anything about anything – 'and I would say that to his face – nothing.' He said of Fauci: 'The man thinks he can take a blood sample, put it in an electron microscope and if it's got a virus in there you'll know it – he doesn't understand electron microscopy and he doesn't understand medicine and shouldn't be in a position like he's in.' That position, terrifyingly, has made him the decider of 'Covid' fascism policy on behalf of the Cult in his role as director since 1984 of the National Institute of Allergy and Infectious Diseases (NIAID) while his record of being wrong is laughable; but being wrong, so long as it's the *right kind* of wrong, is why the Cult loves him. He'll say anything the Cult tells him to say. Fauci was made Chief Medical Adviser to the President immediately Biden took office. Biden was installed in the White House by Cult manipulation and one of his first decisions was to elevate Fauci to a position of even more control. This is a coincidence? Yes, and I identify as a flamenco dancer called Lola. How does such an incompetent criminal like Fauci remain in that

pivotal position in American health since *the 1980s*? When you serve the Cult it looks after you until you are surplus to requirements. Kary Mullis said prophetically of Fauci and his like: ‘Those guys have an agenda and it’s not an agenda we would like them to have ... they make their own rules, they change them when they want to, and Tony Fauci does not mind going on television in front of the people who pay his salary and lie directly into the camera.’ Fauci has done that almost daily since the ‘Covid’ hoax began. Lying is in Fauci’s DNA. To make the situation crystal clear about the PCR test this is a direct quote from its inventor Kary Mullis:

It [the PCR test] doesn’t tell you that you’re sick and doesn’t tell you that the thing you ended up with was really going to hurt you ...’

Ask yourself why governments and medical systems the world over have been using this very test to decide who is ‘infected’ with the SARS-CoV-2 ‘virus’ and the alleged disease it allegedly causes, ‘Covid-19’. The answer to that question will tell you what has been going on. By the way, here’s a little show-stopper – the ‘new’ SARS-CoV-2 ‘virus’ was ‘identified’ as such right from the start using ... *the PCR test not testing for the ‘virus’*. If you are new to this and find that shocking then stick around. I have hardly started yet. Even worse, other ‘tests’, like the ‘Lateral Flow Device’ (LFD), are considered so useless that they have to be *confirmed* by the PCR test! Leaked emails written by Ben Dyson, adviser to UK ‘Health’ Secretary Matt Hancock, said they were ‘dangerously unreliable’. Dyson, executive director of strategy at the Department of Health, wrote: ‘As of today, someone who gets a positive LFD result in (say) London has at best a 25 per cent chance of it being a true positive, but if it is a self-reported test potentially as low as 10 per cent (on an optimistic assumption about specificity) or as low as 2 per cent (on a more pessimistic assumption).’ These are the ‘tests’ that schoolchildren and the public are being urged to have twice a week or more and have to isolate if they get a positive. Each fake positive goes in the statistics as a ‘case’ no matter how ludicrously inaccurate and the

'cases' drive lockdown, masks and the pressure to 'vaccinate'. The government said in response to the email leak that the 'tests' were accurate which confirmed yet again what shocking bloody liars they are. The real false positive rate is *100 percent* as we'll see. In another 'you couldn't make it up' the UK government agreed to pay £2.8 billion to California's Innova Medical Group to supply the irrelevant lateral flow tests. The company's primary test-making centre is in China. Innova Medical Group, established in March, 2020, is owned by Pasaca Capital Inc, chaired by Chinese-American millionaire Charles Huang who was born in Wuhan.

## **How it works – and how it doesn't**

The RT-PCR test, known by its full title of Polymerase chain reaction, is used across the world to make millions, even billions, of copies of a DNA/RNA genetic information sample. The process is called 'amplification' and means that a tiny sample of genetic material is amplified to bring out the detailed content. I stress that it is not testing for an infectious disease. It is simply amplifying a sample of genetic material. In the words of Kary Mullis: 'PCR is ... just a process that's used to make a whole lot of something out of something.' To emphasise the point companies that make the PCR tests circulated around the world to 'test' for 'Covid' warn on the box that it can't be used to detect 'Covid' or infectious disease and is for research purposes only. It's okay, rest for a minute and you'll be fine. This is the test that produces the 'cases' and 'deaths' that have been used to destroy human society. All those global and national medical and scientific 'experts' demanding this destruction to 'save us' KNOW that the test is not testing for the 'virus' and the cases and deaths they claim to be real are an almost unimaginable fraud. Every one of them and so many others including politicians and psychopaths like Gates and Tedros must be brought before Nuremberg-type trials and jailed for the rest of their lives. The more the genetic sample is amplified by PCR the more elements of that material become sensitive to the test and by that I don't mean sensitive for a 'virus' but for elements of the genetic material which

is naturally in the body or relates to remnants of old conditions of various kinds lying dormant and causing no disease. Once the amplification of the PCR reaches a certain level *everyone* will test positive. So much of the material has been made sensitive to the test that everyone will have some part of it in their body. Even lying criminals like Fauci have said that once PCR amplifications pass 35 cycles everything will be a false positive that cannot be trusted for the reasons I have described. I say, like many proper doctors and scientists, that 100 percent of the 'positives' are false, but let's just go with Fauci for a moment.

He says that any amplification over 35 cycles will produce false positives and yet the US Centers for Disease Control (CDC) and Food and Drug Administration (FDA) have recommended up to 40 cycles and the National Health Service (NHS) in Britain admitted in an internal document for staff that it was using 45 cycles of amplification. A long list of other countries has been doing the same and at least one 'testing' laboratory has been using 50 cycles. Have you ever heard a doctor, medical 'expert' or the media ask what level of amplification has been used to claim a 'positive'. The 'test' comes back 'positive' and so you have the 'virus', end of story. Now we can see how the government in Tanzania could send off samples from a goat and a pawpaw fruit under human names and both came back positive for 'Covid-19'. Tanzania president John Magufuli mocked the 'Covid' hysteria, the PCR test and masks and refused to import the DNA-manipulating 'vaccine'. The Cult hated him and an article sponsored by the Bill Gates Foundation appeared in the London *Guardian* in February, 2021, headed 'It's time for Africa to rein in Tanzania's anti-vaxxer president'. Well, 'reined in' he shortly was. Magufuli appeared in good health, but then, in March, 2021, he was dead at 61 from 'heart failure'. He was replaced by Samia Hassan Suhulu who is connected to Klaus Schwab's World Economic Forum and she immediately reversed Magufuli's 'Covid' policy. A sample of cola tested positive for 'Covid' with the PCR test in Germany while American actress and singer-songwriter Erykah Badu tested positive in one nostril and negative in the other. Footballer Ronaldo called

the PCR test ‘bullshit’ after testing positive three times and being forced to quarantine and miss matches when there was nothing wrong with him. The mantra from Tedros at the World Health Organization and national governments (same thing) has been test, test, test. They know that the more tests they can generate the more fake ‘cases’ they have which go on to become ‘deaths’ in ways I am coming to. The UK government has its Operation Moonshot planned to test multiple millions every day in workplaces and schools with free tests for everyone to use twice a week at home in line with the Cult plan from the start to make testing part of life. A government advertisement for an ‘Interim Head of Asymptomatic Testing Communication’ said the job included responsibility for delivering a ‘communications strategy’ (propaganda) ‘to support the expansion of asymptomatic testing that *“normalises testing as part of everyday life”*. More tests means more fake ‘cases’, ‘deaths’ and fascism. I have heard of, and from, many people who booked a test, couldn’t turn up, and yet got a positive result through the post for a test they’d never even had. The whole thing is crazy, but for the Cult there’s method in the madness. Controlling and manipulating the level of amplification of the test means the authorities can control whenever they want the number of apparent ‘cases’ and ‘deaths’. If they want to justify more fascist lockdown and destruction of livelihoods they keep the amplification high. If they want to give the illusion that lockdowns and the ‘vaccine’ are working then they lower the amplification and ‘cases’ and ‘deaths’ will appear to fall. In January, 2021, the Cult-owned World Health Organization suddenly warned laboratories about over-amplification of the test and to lower the threshold. Suddenly headlines began appearing such as: ‘Why ARE “Covid” cases plummeting?’ This was just when the vaccine rollout was underway and I had predicted months before they would make cases appear to fall through amplification tampering when the ‘vaccine’ came. These people are so predictable.

## Cow vaccines?

The question must be asked of what is on the test swabs being poked far up the nose of the population to the base of the brain? A nasal swab punctured one woman's brain and caused it to leak fluid. Most of these procedures are being done by people with little training or medical knowledge. Dr Lorraine Day, former orthopaedic trauma surgeon and Chief of Orthopaedic Surgery at San Francisco General Hospital, says the tests are really a '*vaccine*'. Cows have long been vaccinated this way. She points out that masks have to cover the nose and the mouth where it is claimed the 'virus' exists in saliva. Why then don't they take saliva from the mouth as they do with a DNA test instead of pushing a long swab up the nose towards the brain? The ethmoid bone separates the nasal cavity from the brain and within that bone is the cribriform plate. Dr Day says that when the swab is pushed up against this plate and twisted the procedure is 'depositing things back there'. She claims that among these 'things' are nanoparticles that can enter the brain. Researchers have noted that a team at the Gates-funded Johns Hopkins have designed tiny, star-shaped micro-devices that can latch onto intestinal mucosa and release drugs into the body. Mucosa is the thin skin that covers the inside surface of parts of the body such as *the nose* and mouth and produces mucus to protect them. The Johns Hopkins micro-devices are called 'theragrippers' and were 'inspired' by a parasitic worm that digs its sharp teeth into a host's intestines. Nasal swabs are also coated in the sterilisation agent ethylene oxide. The US National Cancer Institute posts this explanation on its website:

At room temperature, ethylene oxide is a flammable colorless gas with a sweet odor. It is used primarily to produce other chemicals, including antifreeze. In smaller amounts, ethylene oxide is used as a pesticide and a sterilizing agent. The ability of ethylene oxide to damage DNA makes it an effective sterilizing agent but also accounts for its cancer-causing activity.

The Institute mentions lymphoma and leukaemia as cancers most frequently reported to be associated with occupational exposure to ethylene oxide along with stomach and breast cancers. How does anyone think this is going to work out with the constant testing

regime being inflicted on adults and children at home and at school that will accumulate in the body anything that's on the swab?

## **Doctors know best**

It is vital for people to realise that 'hero' doctors 'know' only what the Big Pharma-dominated medical authorities tell them to 'know' and if they refuse to 'know' what they are told to 'know' they are out the door. They are mostly not physicians or healers, but repeaters of the official narrative – or else. I have seen alleged professional doctors on British television make shocking statements that we are supposed to take seriously. One called 'Dr' Amir Khan, who is actually telling patients how to respond to illness, said that men could take the birth pill to 'help slow down the effects of Covid-19'. In March, 2021, another ridiculous 'Covid study' by an American doctor proposed injecting men with the female sex hormone progesterone as a 'Covid' treatment. British doctor Nighat Arif told the BBC that face coverings were now going to be part of ongoing normal. Yes, the vaccine protects you, she said (evidence?) ... but the way to deal with viruses in the community was always going to come down to hand washing, face covering and keeping a physical distance. That's not what we were told before the 'vaccine' was circulating. Arif said she couldn't imagine ever again going on the underground or in a lift without a mask. I was just thanking my good luck that she was not my doctor when she said – in March, 2021 – that if 'we are *behaving* and we are doing all the right things' she thought we could 'have our nearest and dearest around us at home ... around *Christmas* and *New Year!*' Her patronising delivery was the usual school teacher talking to six-year-olds as she repeated every government talking point and probably believed them all. If we have learned anything from the 'Covid' experience surely it must be that humanity's perception of doctors needs a fundamental rethink. NHS 'doctor' Sara Kayat told her television audience that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Not even Big Pharma claimed that. We have to stop taking 'experts' at their word without question when so many of them are

clueless and only repeating the party line on which their careers depend. That is not to say there are not brilliant doctors – there are and I have spoken to many of them since all this began – but you won't see them in the mainstream media or quoted by the psychopaths and yes-people in government.

## **Remember the name – Christian Drosten**

German virologist Christian Drosten, Director of Charité Institute of Virology in Berlin, became a national star after the pandemic hoax began. He was feted on television and advised the German government on 'Covid' policy. Most importantly to the wider world Drosten led a group that produced the 'Covid' testing protocol for the PCR test. What a remarkable feat given the PCR cannot test for infectious disease and even more so when you think that Drosten said that his method of testing for SARS-CoV-2 was developed 'without having virus material available'. *He developed a test for a 'virus' that he didn't have and had never seen.* Let that sink in as you survey the global devastation that came from what he did. The whole catastrophe of Drosten's 'test' was based on the alleged genetic sequence published by Chinese scientists on the Internet. We will see in the next chapter that this alleged 'genetic sequence' has never been produced by China or anyone and cannot be when there is no SARS-CoV-2. Drosten, however, doesn't seem to let little details like that get in the way. He was the lead author with Victor Corman from the same Charité Hospital of the paper 'Detection of 2019 novel coronavirus (2019-nCoV) by real-time PCR' published in a magazine called *Eurosurveillance*. This became known as the Corman-Drosten paper. In November, 2020, with human society devastated by the effects of the Corman-Drosten test baloney, the protocol was publicly challenged by 22 international scientists and independent researchers from Europe, the United States, and Japan. Among them were senior molecular geneticists, biochemists, immunologists, and microbiologists. They produced a document headed 'External peer review of the RTPCR test to detect SARS-Cov-2 Reveals 10 Major Flaws At The Molecular and Methodological Level: Consequences

For False-Positive Results'. The flaws in the Corman-Drosten test included the following:

- The test is non-specific because of erroneous design
- Results are enormously variable
- The test is unable to discriminate between the whole 'virus' and viral fragments
- It doesn't have positive or negative controls
- The test lacks a standard operating procedure
- It is unsupported by proper peer view

The scientists said the PCR 'Covid' testing protocol was not founded on science and they demanded the Corman-Drosten paper be retracted by *Eurosurveillance*. They said all present and previous Covid deaths, cases, and 'infection rates' should be subject to a massive retroactive inquiry. Lockdowns and travel restrictions should be reviewed and relaxed and those diagnosed through PCR to have 'Covid-19' should not be forced to isolate. Dr Kevin Corbett, a health researcher and nurse educator with a long academic career producing a stream of peer-reviewed publications at many UK universities, made the same point about the PCR test debacle. He said of the scientists' conclusions: 'Every scientific rationale for the development of that test has been totally destroyed by this paper. It's like Hiroshima/Nagasaki to the Covid test.' He said that China hadn't given them an isolated 'virus' when Drosten developed the test. Instead they had developed the test from *a sequence in a gene bank.*' Put another way ... *they made it up!* The scientists were supported in this contention by a Portuguese appeals court which ruled in November, 2020, that PCR tests are unreliable and it is unlawful to quarantine people based solely on a PCR test. The point about China not providing an isolated virus must be true when the 'virus' has never been isolated to this day and the consequences of that will become clear. Drosten and company produced this useless 'protocol' right on cue in January, 2020, just as the 'virus' was said to

be moving westward and it somehow managed to successfully pass a peer-review in 24 hours. In other words there was no peer-review for a test that would be used to decide who had 'Covid' and who didn't across the world. The Cult-created, Gates-controlled World Health Organization immediately recommended all its nearly 200 member countries to use the Drosten PCR protocol to detect 'cases' and 'deaths'. The sting was underway and it continues to this day.

So who is this Christian Drosten that produced the means through which death, destruction and economic catastrophe would be justified? His education background, including his doctoral thesis, would appear to be somewhat shrouded in mystery and his track record is dire as with another essential player in the 'Covid' hoax, the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College in London of whom more shortly. Drosten predicted in 2003 that the alleged original SARS 'virus' (SARS-1') was an epidemic that could have serious effects on economies and an effective vaccine would take at least two years to produce. Drosten's answer to every alleged 'outbreak' is a vaccine which you won't be shocked to know. What followed were just 774 official deaths worldwide and none in Germany where there were only nine cases. That is even if you believe there ever was a SARS 'virus' when the evidence is zilch and I will expand on this in the next chapter. Drosten claims to be co-discoverer of 'SARS-1' and developed a test for it in 2003. He was screaming warnings about 'swine flu' in 2009 and how it was a widespread infection far more severe than any dangers from a vaccine could be and people should get vaccinated. It would be helpful for Drosten's vocal chords if he simply recorded the words 'the virus is deadly and you need to get vaccinated' and copies could be handed out whenever the latest made-up threat comes along. Drosten's swine flu epidemic never happened, but Big Pharma didn't mind with governments spending hundreds of millions on vaccines that hardly anyone bothered to use and many who did wished they hadn't. A study in 2010 revealed that the risk of dying from swine flu, or H1N1, was no higher than that of the annual seasonal flu which is what at least most of 'it' really was as in

the case of 'Covid-19'. A media investigation into Drosten asked how with such a record of inaccuracy he could be *the* government adviser on these issues. The answer to that question is the same with Drosten, Ferguson and Fauci – they keep on giving the authorities the 'conclusions' and 'advice' they want to hear. Drosten certainly produced the goods for them in January, 2020, with his PCR protocol garbage and provided the foundation of what German internal medicine specialist Dr Claus Köhnlein, co-author of *Virus Mania*, called the 'test pandemic'. The 22 scientists in the *Eurosurveillance* challenge called out conflicts of interest within the Drosten 'protocol' group and with good reason. Olfert Landt, a regular co-author of Drosten 'studies', owns the biotech company TIB Molbiol Syntheselabor GmbH in Berlin which manufactures and sells the tests that Drosten and his mates come up with. They have done this with SARS, Enterotoxigenic E. coli (ETEC), MERS, Zika 'virus', yellow fever, and now 'Covid'. Landt told the *Berliner Zeitung* newspaper:

The testing, design and development came from the Charité [Drosten and Corman]. We simply implemented it immediately in the form of a kit. And if we don't have the virus, which originally only existed in Wuhan, we can make a synthetic gene to simulate the genome of the virus. That's what we did very quickly.

This is more confirmation that the Drosten test was designed without access to the 'virus' and only a synthetic simulation which is what SARS-CoV-2 really is – a computer-generated synthetic fiction. It's quite an enterprise they have going here. A Drosten team decides what the test for something should be and Landt's biotech company flogs it to governments and medical systems across the world. His company must have made an absolute fortune since the 'Covid' hoax began. Dr Reiner Fuellmich, a prominent German consumer protection trial lawyer in Germany and California, is on Drosten's case and that of Tedros at the World Health Organization for crimes against humanity with a class-action lawsuit being prepared in the United States and other legal action in Germany.

## **Why China?**

Scamming the world with a ‘virus’ that doesn’t exist would seem impossible on the face of it, but not if you have control of the relatively few people that make policy decisions and the great majority of the global media. Remember it’s not about changing ‘real’ reality it’s about controlling *perception* of reality. You don’t have to make something happen you only have to make people *believe* that it’s happening. Renegade Minds understand this and are therefore much harder to swindle. ‘Covid-19’ is not a ‘real’ ‘virus’. It’s a mind virus, like a computer virus, which has infected the minds, not the bodies, of billions. It all started, publically at least, in China and that alone is of central significance. The Cult was behind the revolution led by its asset Mao Zedong, or Chairman Mao, which established the People’s Republic of China on October 1st, 1949. It should have been called The Cult’s Republic of China, but the name had to reflect the recurring illusion that vicious dictatorships are run by and for the people (see all the ‘Democratic Republics’ controlled by tyrants). In the same way we have the ‘Biden’ Democratic Republic of America officially ruled by a puppet tyrant (at least temporarily) on behalf of Cult tyrants. The creation of Mao’s merciless communist/fascist dictatorship was part of a frenzy of activity by the Cult at the conclusion of World War Two which, like the First World War, it had instigated through its assets in Germany, Britain, France, the United States and elsewhere. Israel was formed in 1948; the Soviet Union expanded its ‘Iron Curtain’ control, influence and military power with the Warsaw Pact communist alliance in 1955; the United Nations was formed in 1945 as a Cult precursor to world government; and a long list of world bodies would be established including the World Health Organization (1948), World Trade Organization (1948 under another name until 1995), International Monetary Fund (1945) and World Bank (1944). Human society was redrawn and hugely centralised in the global Problem-Reaction-Solution that was World War Two. All these changes were significant. Israel would become the headquarters of the Sabbatians

and the revolution in China would prepare the ground and control system for the events of 2019/2020.

Renegade Minds know there are no borders except for public consumption. The Cult is a seamless, borderless global entity and to understand the game we need to put aside labels like borders, nations, countries, communism, fascism and democracy. These delude the population into believing that countries are ruled within their borders by a government of whatever shade when these are mere agencies of a global power. America's illusion of democracy and China's communism/fascism are subsidiaries – vehicles – for the same agenda. We may hear about conflict and competition between America and China and on the lower levels that will be true; but at the Cult level they are branches of the same company in the way of the McDonald's example I gave earlier. I have tracked in the books over the years support by US governments of both parties for Chinese Communist Party infiltration of American society through allowing the sale of land, even military facilities, and the acquisition of American business and university influence. All this is underpinned by the infamous stealing of intellectual property and technological know-how. Cult-owned Silicon Valley corporations waive their fraudulent 'morality' to do business with human-rights-free China; Cult-controlled Disney has become China's PR department; and China in effect owns 'American' sports such as basketball which depends for much of its income on Chinese audiences. As a result any sports player, coach or official speaking out against China's horrific human rights record is immediately condemned or fired by the China-worshipping National Basketball Association. One of the first acts of China-controlled Biden was to issue an executive order telling federal agencies to stop making references to the 'virus' by the 'geographic location of its origin'. Long-time Congressman Jerry Nadler warned that criticising China, America's biggest rival, leads to hate crimes against Asian people in the United States. So shut up you bigot. China is fast closing in on Israel as a country that must not be criticised which is apt, really, given that Sabbatians control them both. The two countries have

developed close economic, military, technological and strategic ties which include involvement in China's 'Silk Road' transport and economic initiative to connect China with Europe. Israel was the first country in the Middle East to recognise the establishment of Mao's tyranny in 1950 months after it was established.

## **Project Wuhan – the 'Covid' Psyop**

I emphasise again that the Cult plays the long game and what is happening to the world today is the result of centuries of calculated manipulation following a script to take control step-by-step of every aspect of human society. I will discuss later the common force behind all this that has spanned those centuries and thousands of years if the truth be told. Instigating the Mao revolution in China in 1949 with a 2020 'pandemic' in mind is not only how they work – the 71 years between them is really quite short by the Cult's standards of manipulation preparation. The reason for the Cult's Chinese revolution was to create a fiercely-controlled environment within which an extreme structure for human control could be incubated to eventually be unleashed across the world. We have seen this happen since the 'pandemic' emerged from China with the Chinese control-structure founded on AI technology and tyrannical enforcement sweep across the West. Until the moment when the Cult went for broke in the West and put its fascism on public display Western governments had to pay some lip-service to freedom and democracy to not alert too many people to the tyranny-in-the-making. Freedoms were more subtly eroded and power centralised with covert government structures put in place waiting for the arrival of 2020 when that smokescreen of 'freedom' could be dispensed with. The West was not able to move towards tyranny before 2020 anything like as fast as China which was created as a tyranny and had no limits on how fast it could construct the Cult's blueprint for global control. When the time came to impose that structure on the world it was the same Cult-owned Chinese communist/fascist government that provided the excuse – the 'Covid pandemic'. It was absolutely crucial to the Cult plan for the Chinese response to the 'pandemic' –

draconian lockdowns of the entire population – to become the blueprint that Western countries would follow to destroy the livelihoods and freedom of their people. This is why the Cult-owned, Gates-owned, WHO Director-General Tedros said early on:

The Chinese government is to be congratulated for the extraordinary measures it has taken to contain the outbreak. China is actually setting a new standard for outbreak response and it is not an exaggeration.

*Forbes* magazine said of China: ‘... those measures protected untold millions from getting the disease’. The Rockefeller Foundation ‘epidemic scenario’ document in 2010 said ‘prophetically’:

However, a few countries did fare better – China in particular. The Chinese government’s quick imposition and enforcement of mandatory quarantine for all citizens, as well as its instant and near-hermetic sealing off of all borders, saved millions of lives, stopping the spread of the virus far earlier than in other countries and enabling a swifter post-pandemic recovery.

Once again – *spooky*.

The first official story was the ‘bat theory’ or rather the bat diversion. The source of the ‘virus outbreak’ we were told was a “wet market” in Wuhan where bats and other animals are bought and eaten in horrifically unhygienic conditions. Then another story emerged through the alternative media that the ‘virus’ had been released on purpose or by accident from a BSL-4 (biosafety level 4) laboratory in Wuhan not far from the wet market. The lab was reported to create and work with lethal concoctions and bioweapons. Biosafety level 4 is the highest in the World Health Organization system of safety and containment. Renegade Minds are aware of what I call designer manipulation. The ideal for the Cult is for people to buy its prime narrative which in the opening salvos of the ‘pandemic’ was the wet market story. It knows, however, that there is now a considerable worldwide alternative media of researchers sceptical of anything governments say and they are often given a version of events in a form they can perceive as credible while misdirecting them from the real truth. In this case let them

think that the conspiracy involved is a ‘bioweapon virus’ released from the Wuhan lab to keep them from the real conspiracy – *there is no ‘virus’*. The WHO’s current position on the source of the outbreak at the time of writing appears to be: ‘We haven’t got a clue, mate.’ This is a good position to maintain mystery and bewilderment. The inner circle will know where the ‘virus’ came from – *nowhere*. The bottom line was to ensure the public believed there *was* a ‘virus’ and it didn’t much matter if they thought it was natural or had been released from a lab. The belief that there was a ‘deadly virus’ was all that was needed to trigger global panic and fear. The population was terrified into handing their power to authority and doing what they were told. They had to or they were ‘all gonna die’.

In March, 2020, information began to come my way from real doctors and scientists and my own additional research which had my intuition screaming: ‘Yes, that’s it! *There is no virus.*’ The ‘bioweapon’ was not the ‘virus’; it was the ‘vaccine’ already being talked about that would be the bioweapon. My conclusion was further enhanced by happenings in Wuhan. The ‘virus’ was said to be sweeping the city and news footage circulated of people collapsing in the street (which they’ve never done in the West with the same ‘virus’). The Chinese government was building ‘new hospitals’ in a matter of ten days to ‘cope with demand’ such was the virulent nature of the ‘virus’. Yet in what seemed like no time the ‘new hospitals’ closed – even if they even opened – and China declared itself ‘virus-free’. It was back to business as usual. This was more propaganda to promote the Chinese draconian lockdowns in the West as the way to ‘beat the virus’. Trouble was that we subsequently had lockdown after lockdown, but never business as usual. As the people of the West and most of the rest of the world were caught in an ever-worsening spiral of lockdown, social distancing, masks, isolated old people, families forced apart, and livelihood destruction, it was party-time in Wuhan. Pictures emerged of thousands of people enjoying pool parties and concerts. It made no sense until you realised there never was a ‘virus’ and the

whole thing was a Cult set-up to transform human society out of one its major global strongholds – China.

How is it possible to deceive virtually the entire world population into believing there is a deadly virus when there is not even a ‘virus’ let alone a deadly one? It’s nothing like as difficult as you would think and that’s clearly true because it happened.

**Postscript:** See end of book Postscript for more on the ‘Wuhan lab virus release’ story which the authorities and media were pushing heavily in the summer of 2021 to divert attention from the truth that the ‘Covid virus’ is pure invention.

## CHAPTER FIVE

### **There is no ‘virus’**

***You can fool some of the people all of the time, and all of the people some of the time, but you cannot fool all of the people all of the time***

**Abraham Lincoln**

The greatest form of mind control is repetition. The more you repeat the same mantra of alleged ‘facts’ the more will accept them to be true. It becomes an ‘everyone knows that, mate’. If you can also censor any other version or alternative to your alleged ‘facts’ you are pretty much home and cooking.

By the start of 2020 the Cult owned the global mainstream media almost in its entirety to spew out its ‘Covid’ propaganda and ignore or discredit any other information and view. Cult-owned social media platforms in Cult-owned Silicon Valley were poised and ready to unleash a campaign of ferocious censorship to obliterate all but the official narrative. To complete the circle many demands for censorship by Silicon Valley were led by the mainstream media as ‘journalists’ became full-out enforcers for the Cult both as propagandists and censors. Part of this has been the influx of young people straight out of university who have become ‘journalists’ in significant positions. They have no experience and a headful of programmed perceptions from their years at school and university at a time when today’s young are the most perceptually-targeted generations in known human history given the insidious impact of technology. They enter the media perceptually prepared and ready to repeat the narratives of the system that programmed them to

repeat its narratives. The BBC has a truly pathetic ‘specialist disinformation reporter’ called Marianna Spring who fits this bill perfectly. She is clueless about the world, how it works and what is really going on. Her role is to discredit anyone doing the job that a proper journalist would do and system-serving hacks like Spring wouldn’t dare to do or even see the need to do. They are too busy licking the arse of authority which can never be wrong and, in the case of the BBC propaganda programme, *Panorama*, contacting payments systems such as PayPal to have a donations page taken down for a film company making documentaries questioning vaccines. Even the BBC soap opera *EastEnders* included a disgracefully biased scene in which an inarticulate white working class woman was made to look foolish for questioning the ‘vaccine’ while a well-spoken black man and Asian woman promoted the government narrative. It ticked every BBC box and the fact that the black and minority community was resisting the ‘vaccine’ had nothing to do with the way the scene was written. The BBC has become a disgusting tyrannical propaganda and censorship operation that should be defunded and disbanded and a free media take its place with a brief to stop censorship instead of demanding it. A BBC ‘interview’ with Gates goes something like: ‘Mr Gates, sir, if I can call you sir, would you like to tell our audience why you are such a great man, a wonderful humanitarian philanthropist, and why you should absolutely be allowed as a software salesman to decide health policy for approaching eight billion people? Thank you, sir, please sir.’ Propaganda programming has been incessant and merciless and when all you hear is the same story from the media, repeated by those around you who have only heard the same story, is it any wonder that people on a grand scale believe absolute mendacious garbage to be true? You are about to see, too, why this level of information control is necessary when the official ‘Covid’ narrative is so nonsensical and unsupportable by the evidence.

## **Structure of Deceit**

The pyramid structure through which the ‘Covid’ hoax has been manifested is very simple and has to be to work. As few people as possible have to be involved with full knowledge of what they are doing – and why – or the real story would get out. At the top of the pyramid are the inner core of the Cult which controls Bill Gates who, in turn, controls the World Health Organization through his pivotal funding and his puppet Director-General mouthpiece, Tedros.

Before he was appointed Tedros was chair of the Gates-founded Global Fund to ‘fight against AIDS, tuberculosis and malaria’, a board member of the Gates-funded ‘vaccine alliance’ GAVI, and on the board of another Gates-funded organisation. Gates owns him and picked him for a specific reason – Tedros is a crook and worse. ‘Dr’ Tedros (he’s not a medical doctor, the first WHO chief not to be) was a member of the tyrannical Marxist government of Ethiopia for decades with all its human rights abuses. He has faced allegations of corruption and misappropriation of funds and was exposed three times for covering up cholera epidemics while Ethiopia’s health minister. Tedros appointed the mass-murdering genocidal Zimbabwe dictator Robert Mugabe as a WHO goodwill ambassador for public health which, as with Tedros, is like appointing a psychopath to run a peace and love campaign. The move was so ridiculous that he had to drop Mugabe in the face of widespread condemnation. American economist David Steinman, a Nobel peace prize nominee, lodged a complaint with the International Criminal Court in The Hague over alleged genocide by Tedros when he was Ethiopia’s foreign minister. Steinman says Tedros was a ‘crucial decision maker’ who directed the actions of Ethiopia’s security forces from 2013 to 2015 and one of three officials in charge when those security services embarked on the ‘killing’ and ‘torturing’ of Ethiopians. You can see where Tedros is coming from and it’s sobering to think that he has been the vehicle for Gates and the Cult to direct the global response to ‘Covid’. Think about that. A psychopathic Cult dictates to psychopath Gates who dictates to psychopath Tedros who dictates how countries of the world must respond to a ‘Covid virus’ never scientifically shown to exist. At the same time psychopathic Cult-owned Silicon Valley information

giants like Google, YouTube, Facebook and Twitter announced very early on that they would give the Cult/Gates/Tedros/WHO version of the narrative free advertising and censor those who challenged their intelligence-insulting, mendacious story.

The next layer in the global ‘medical’ structure below the Cult, Gates and Tedros are the chief medical officers and science ‘advisers’ in each of the WHO member countries which means virtually all of them. Medical officers and arbiters of science (they’re not) then take the WHO policy and recommended responses and impose them on their country’s population while the political ‘leaders’ say they are deciding policy (they’re clearly not) by ‘following the science’ on the advice of the ‘experts’ – the same medical officers and science ‘advisers’ (dictators). In this way with the rarest of exceptions the entire world followed the same policy of lockdown, people distancing, masks and ‘vaccines’ dictated by the psychopathic Cult, psychopathic Gates and psychopathic Tedros who we are supposed to believe give a damn about the health of the world population they are seeking to enslave. That, amazingly, is all there is to it in terms of crucial decision-making. Medical staff in each country then follow like sheep the dictates of the shepherds at the top of the national medical hierarchies – chief medical officers and science ‘advisers’ who themselves follow like sheep the shepherds of the World Health Organization and the Cult. Shepherds at the national level often have major funding and other connections to Gates and his Bill and Melinda Gates Foundation which carefully hands out money like confetti at a wedding to control the entire global medical system from the WHO down.

## **Follow the money**

Christopher Whitty, Chief Medical Adviser to the UK Government at the centre of ‘virus’ policy, a senior adviser to the government’s Scientific Advisory Group for Emergencies (SAGE), and Executive Board member of the World Health Organization, was gifted a grant of \$40 million by the Bill and Melinda Gates Foundation for malaria research in Africa. The BBC described the unelected Whitty as ‘the

official who will probably have the greatest impact on our everyday lives of any individual policymaker in modern times' and so it turned out. What Gates and Tedros have said Whitty has done like his equivalents around the world. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of Big Pharma giant GlaxoSmithKline with its fundamental financial and business connections to Bill Gates. In September, 2020, it was revealed that Vallance owned a deferred bonus of shares in GlaxoSmithKline worth £600,000 while the company was 'developing' a 'Covid vaccine'. Move along now – nothing to see here – what could possibly be wrong with that? Imperial College in London, a major player in 'Covid' policy in Britain and elsewhere with its 'Covid-19' Response Team, is funded by Gates and has big connections to China while the now infamous Professor Neil Ferguson, the useless 'computer modeller' at Imperial College is also funded by Gates. Ferguson delivered the dramatically inaccurate excuse for the first lockdowns (much more in the next chapter). The Institute for Health Metrics and Evaluation (IHME) in the United States, another source of outrageously false 'Covid' computer models to justify lockdowns, is bankrolled by Gates who is a vehement promotor of lockdowns. America's version of Whitty and Vallance, the again now infamous Anthony Fauci, has connections to 'Covid vaccine' maker Moderna as does Bill Gates through funding from the Bill and Melinda Gates Foundation. Fauci is director of the National Institute of Allergy and Infectious Diseases (NIAID), a major recipient of Gates money, and they are very close. Deborah Birx who was appointed White House Coronavirus Response Coordinator in February, 2020, is yet another with ties to Gates. Everywhere you look at the different elements around the world behind the coordination and decision making of the 'Covid' hoax there is Bill Gates and his money. They include the World Health Organization; Centers for Disease Control (CDC) in the United States; National Institutes of Health (NIH) of Anthony Fauci; Imperial College and Neil Ferguson; the London School of Hygiene where Chris Whitty worked; Regulatory agencies like the UK Medicines & Healthcare products Regulatory Agency (MHRA)

which gave emergency approval for ‘Covid vaccines’; Wellcome Trust; GAVI, the Vaccine Alliance; the Coalition for Epidemic Preparedness Innovations (CEPI); Johns Hopkins University which has compiled the false ‘Covid’ figures; and the World Economic Forum. A [Nationalfile.com](#) article said:

Gates has a lot of pull in the medical world, he has a multi-million dollar relationship with Dr. Fauci, and Fauci originally took the Gates line supporting vaccines and casting doubt on [the drug hydroxychloroquine]. Coronavirus response team member Dr. Deborah Birx, appointed by former president Obama to serve as United States Global AIDS Coordinator, also sits on the board of a group that has received billions from Gates’ foundation, and Birx reportedly used a disputed Bill Gates-funded model for the White House’s Coronavirus effort. Gates is a big proponent for a population lockdown scenario for the Coronavirus outbreak.

Another funder of Moderna is the Defense Advanced Research Projects Agency (DARPA), the technology-development arm of the Pentagon and one of the most sinister organisations on earth. DARPA had a major role with the CIA covert technology-funding operation In-Q-Tel in the development of Google and social media which is now at the centre of global censorship. Fauci and Gates are extremely close and openly admit to talking regularly about ‘Covid’ policy, but then why wouldn’t Gates have a seat at every national ‘Covid’ table after his Foundation committed \$1.75 billion to the ‘fight against Covid-19’. When passed through our Orwellian Translation Unit this means that he has bought and paid for the Cult-driven ‘Covid’ response worldwide. Research the major ‘Covid’ response personnel in your own country and you will find the same Gates funding and other connections again and again. Medical and science chiefs following World Health Organization ‘policy’ sit atop a medical hierarchy in their country of administrators, doctors and nursing staff. These ‘subordinates’ are told they must work and behave in accordance with the policy delivered from the ‘top’ of the national ‘health’ pyramid which is largely the policy delivered by the WHO which is the policy delivered by Gates and the Cult. The whole ‘Covid’ narrative has been imposed on medical staff by a climate of fear although great numbers don’t even need that to comply. They do so through breathtaking levels of ignorance and

include doctors who go through life simply repeating what Big Pharma and their hierarchical masters tell them to say and believe. No wonder Big Pharma ‘medicine’ is one of the biggest killers on Planet Earth.

The same top-down system of intimidation operates with regard to the Cult Big Pharma cartel which also dictates policy through national and global medical systems in this way. The Cult and Big Pharma agendas are the same because the former controls and owns the latter. ‘Health’ administrators, doctors, and nursing staff are told to support and parrot the dictated policy or they will face consequences which can include being fired. How sad it’s been to see medical staff meekly repeating and imposing Cult policy without question and most of those who can see through the deceit are only willing to speak anonymously off the record. They know what will happen if their identity is known. This has left the courageous few to expose the lies about the ‘virus’, face masks, overwhelmed hospitals that aren’t, and the dangers of the ‘vaccine’ that isn’t a vaccine. When these medical professionals and scientists, some renowned in their field, have taken to the Internet to expose the truth their articles, comments and videos have been deleted by Cult-owned Facebook, Twitter and YouTube. What a real head-shaker to see YouTube videos with leading world scientists and highly qualified medical specialists with an added link underneath to the notorious Cult propaganda website *Wikipedia* to find the ‘facts’ about the same subject.

### **HIV – the ‘Covid’ trial-run**

I’ll give you an example of the consequences for health and truth that come from censorship and unquestioning belief in official narratives. The story was told by PCR inventor Kary Mullis in his book *Dancing Naked in the Mind Field*. He said that in 1984 he accepted as just another scientific fact that Luc Montagnier of France’s Pasteur Institute and Robert Gallo of America’s National Institutes of Health had independently discovered that a ‘retrovirus’ dubbed HIV (human immunodeficiency virus) caused AIDS. They

were, after all, Mullis writes, specialists in retroviruses. This is how the medical and science pyramids work. Something is announced or *assumed* and then becomes an everybody-knows-that purely through repetition of the assumption as if it is fact. Complete crap becomes accepted truth with no supporting evidence and only repetition of the crap. This is how a 'virus' that doesn't exist became the 'virus' that changed the world. The HIV-AIDS fairy story became a multi-billion pound industry and the media poured out propaganda terrifying the world about the deadly HIV 'virus' that caused the lethal AIDS. By then Mullis was working at a lab in Santa Monica, California, to detect retroviruses with his PCR test in blood donations received by the Red Cross. In doing so he asked a virologist where he could find a reference for HIV being the cause of AIDS. 'You don't need a reference,' the virologist said ... '*Everybody knows it.*' Mullis said he wanted to quote a reference in the report he was doing and he said he felt a little funny about not knowing the source of such an important discovery when everyone else seemed to. The virologist suggested he cite a report by the Centers for Disease Control and Prevention (CDC) on morbidity and mortality. Mullis read the report, but it only said that an organism had been identified and did not say how. The report did not identify the original scientific work. Physicians, however, *assumed* (key recurring theme) that if the CDC was convinced that HIV caused AIDS then proof must exist. Mullis continues:

I did computer searches. Neither Montagnier, Gallo, nor anyone else had published papers describing experiments which led to the conclusion that HIV probably caused AIDS. I read the papers in Science for which they had become well known as AIDS doctors, but all they had said there was that they had found evidence of a past infection by something which was probably HIV in some AIDS patients.

They found antibodies. Antibodies to viruses had always been considered evidence of past disease, not present disease. Antibodies signaled that the virus had been defeated. The patient had saved himself. There was no indication in these papers that this virus caused a disease. They didn't show that everybody with the antibodies had the disease. In fact they found some healthy people with antibodies.

Mullis asked why their work had been published if Montagnier and Gallo hadn't really found this evidence, and why had they been fighting so hard to get credit for the discovery? He says he was hesitant to write 'HIV is the probable cause of AIDS' until he found published evidence to support that. 'Tens of thousands of scientists and researchers were spending billions of dollars a year doing research based on this idea,' Mullis writes. 'The reason had to be there somewhere; otherwise these people would not have allowed their research to settle into one narrow channel of investigation.' He said he lectured about PCR at numerous meetings where people were always talking about HIV and he asked them how they knew that HIV was the cause of AIDS:

Everyone said something. Everyone had the answer at home, in the office, in some drawer. They all knew, and they would send me the papers as soon as they got back. But I never got any papers. Nobody ever sent me the news about how AIDS was caused by HIV.

Eventually Mullis was able to ask Montagnier himself about the reference proof when he lectured in San Diego at the grand opening of the University of California AIDS Research Center. Mullis says this was the last time he would ask his question without showing anger. Montagnier said he should reference the CDC report. 'I read it', Mullis said, and it didn't answer the question. 'If Montagnier didn't know the answer who the hell did?' Then one night Mullis was driving when an interview came on National Public Radio with Peter Duesberg, a prominent virologist at Berkeley and a California Scientist of the Year. Mullis says he finally understood why he could not find references that connected HIV to AIDS – *there weren't any!* No one had ever proved that HIV causes AIDS even though it had spawned a multi-billion pound global industry and the media was repeating this as fact every day in their articles and broadcasts terrifying the shit out of people about AIDS and giving the impression that a positive test for HIV (see 'Covid') was a death sentence. Duesberg was a threat to the AIDS gravy train and the agenda that underpinned it. He was therefore abused and castigated after he told the Proceedings of the National Academy of Sciences

there was no good evidence implicating the new ‘virus’. Editors rejected his manuscripts and his research funds were deleted. Mullis points out that the CDC has defined AIDS as one of more than 30 diseases *if accompanied* by a positive result on a test that detects antibodies to HIV; but those same diseases are not defined as AIDS cases when antibodies are not detected:

If an HIV-positive woman develops uterine cancer, for example, she is considered to have AIDS. If she is not HIV positive, she simply has uterine cancer. An HIV-positive man with tuberculosis has AIDS; if he tests negative he simply has tuberculosis. If he lives in Kenya or Colombia, where the test for HIV antibodies is too expensive, he is simply presumed to have the antibodies and therefore AIDS, and therefore he can be treated in the World Health Organization’s clinic. It’s the only medical help available in some places. And it’s free, because the countries that support WHO are worried about AIDS.

Mullis accuses the CDC of continually adding new diseases (see ever more ‘Covid symptoms’) to the grand AIDS definition and of virtually doctoring the books to make it appear as if the disease continued to spread. He cites how in 1993 the CDC enormously broadened its AIDS definition and county health authorities were delighted because they received \$2,500 per year from the Federal government for every reported AIDS case. Ladies and gentlemen, I have just described, via Kary Mullis, the ‘Covid pandemic’ of 2020 and beyond. Every element is the same and it’s been pulled off in the same way by the same networks.

### **The ‘Covid virus’ exists? Okay – prove it. Er ... still waiting**

What Kary Mullis described with regard to ‘HIV’ has been repeated with ‘Covid’. A claim is made that a new, or ‘novel’, infection has been found and the entire medical system of the world repeats that as fact exactly as they did with HIV and AIDS. No one in the mainstream asks rather relevant questions such as ‘How do you know?’ and ‘Where is your proof?’ The SARS-CoV-2 ‘virus’ and the ‘Covid-19 disease’ became an overnight ‘everybody-knows-that’. The origin could be debated and mulled over, but what you could not suggest was that ‘SARS-CoV-2’ didn’t exist. That would be

ridiculous. ‘Everybody knows’ the ‘virus’ exists. Well, I didn’t for one along with American proper doctors like Andrew Kaufman and Tom Cowan and long-time American proper journalist Jon Rappaport. We dared to pursue the obvious and simple question: ‘Where’s the evidence?’ The overwhelming majority in medicine, journalism and the general public did not think to ask that. After all, *everyone knew* there was a new ‘virus’. Everyone was saying so and I heard it on the BBC. Some would eventually argue that the ‘deadly virus’ was nothing like as deadly as claimed, but few would venture into the realms of its very existence. Had they done so they would have found that the evidence for that claim had gone AWOL as with HIV causes AIDS. In fact, not even that. For something to go AWOL it has to exist in the first place and scientific proof for a ‘SARS-Cov-2’ can be filed under nothing, nowhere and zilch.

Dr Andrew Kaufman is a board-certified forensic psychiatrist in New York State, a Doctor of Medicine and former Assistant Professor and Medical Director of Psychiatry at SUNY Upstate Medical University, and Medical Instructor of Hematology and Oncology at the Medical School of South Carolina. He also studied biology at the Massachusetts Institute of Technology (MIT) and trained in Psychiatry at Duke University. Kaufman is retired from allopathic medicine, but remains a consultant and educator on natural healing, I saw a video of his very early on in the ‘Covid’ hoax in which he questioned claims about the ‘virus’ in the absence of any supporting evidence and with plenty pointing the other way. I did everything I could to circulate his work which I felt was asking the pivotal questions that needed an answer. I can recommend an excellent pull-together interview he did with the website The Last Vagabond entitled *Dr Andrew Kaufman: Virus Isolation, Terrain Theory and Covid-19* and his website is [andrewkaufmanmd.com](http://andrewkaufmanmd.com). Kaufman is not only a forensic psychiatrist; he is forensic in all that he does. He always reads original scientific papers, experiments and studies instead of second-third-fourth-hand reports about the ‘virus’ in the media which are repeating the repeated repetition of the narrative. When he did so with the original Chinese ‘virus’ papers Kaufman

realised that there was no evidence of a ‘SARS-Cov-2’. They had never – from the start – shown it to exist and every repeat of this claim worldwide was based on the accepted existence of proof that was nowhere to be found – see Kary Mullis and HIV. Here we go again.

## **Let's postulate**

Kaufman discovered that the Chinese authorities immediately concluded that the cause of an illness that broke out among about 200 initial patients in Wuhan was a ‘new virus’ when there were no grounds to make that conclusion. The alleged ‘virus’ was not isolated from other genetic material in their samples and then shown through a system known as Koch’s postulates to be the causative agent of the illness. The world was told that the SARS-Cov-2 ‘virus’ caused a disease they called ‘Covid-19’ which had ‘flu-like’ symptoms and could lead to respiratory problems and pneumonia. If it wasn’t so tragic it would almost be funny. *‘Flu-like’ symptoms?* *Pneumonia? Respiratory disease?* What in CHINA and particularly in Wuhan, one of the most polluted cities in the world with a resulting epidemic of respiratory disease?? Three hundred thousand people get pneumonia in China every year and there are nearly a billion cases worldwide of ‘flu-like symptoms’. These have a whole range of causes – including pollution in Wuhan – but no other possibility was credibly considered in late 2019 when the world was told there was a new and deadly ‘virus’. The global prevalence of pneumonia and ‘flu-like systems’ gave the Cult networks unlimited potential to re-diagnose these other causes as the mythical ‘Covid-19’ and that is what they did from the very start. Kaufman revealed how Chinese medical and science authorities (all subordinates to the Cult-owned communist government) took genetic material from the lungs of only a few of the first patients. The material contained their own cells, bacteria, fungi and other microorganisms living in their bodies. The only way you could prove the existence of the ‘virus’ and its responsibility for the alleged ‘Covid-19’ was to isolate the virus from all the other material – a process also known as ‘purification’ – and

then follow the postulates sequence developed in the late 19th century by German physician and bacteriologist Robert Koch which became the ‘gold standard’ for connecting an alleged causation agent to a disease:

1. The microorganism (bacteria, fungus, virus, etc.) must be present in every case of the disease and all patients must have the same symptoms. It must also *not be present in healthy individuals*.
2. The microorganism must be isolated from the host with the disease. If the microorganism is a bacteria or fungus it must be grown in a pure culture. If it is a virus, it must be purified (i.e. containing no other material except the virus particles) from a clinical sample.
3. The specific disease, with all of its characteristics, must be reproduced when the infectious agent (the purified virus or a pure culture of bacteria or fungi) is inoculated into a healthy, susceptible host.
4. The microorganism must be recoverable from the experimentally infected host as in step 2.

*Not one* of these criteria has been met in the case of ‘SARS-Cov-2’ and ‘Covid-19’. Not ONE. EVER. Robert Koch refers to bacteria and not viruses. What are called ‘viral particles’ are so minute (hence masks are useless by any definition) that they could only be seen after the invention of the electron microscope in the 1930s and can still only be observed through that means. American bacteriologist and virologist Thomas Milton Rivers, the so-called ‘Father of Modern Virology’ who was very significantly director of the Rockefeller Institute for Medical Research in the 1930s, developed a less stringent version of Koch’s postulates to identify ‘virus’ causation known as ‘Rivers criteria’. ‘Covid’ did not pass that process either. Some even doubt whether any ‘virus’ can be isolated from other particles containing genetic material in the Koch method. Freedom of Information requests in many countries asking for scientific proof that the ‘Covid virus’ has been purified and isolated and shown to exist have all come back with a ‘we don’t have that’ and when this happened with a request to the UK Department of Health they added this comment:

However, outside of the scope of the [Freedom of Information Act] and on a discretionary basis, the following information has been advised to us, which may be of interest. Most infectious diseases are caused by viruses, bacteria or fungi. Some bacteria or fungi have the capacity to grow on their own in isolation, for example in colonies on a petri dish. Viruses are different in that they are what we call 'obligate pathogens' – that is, they cannot survive or reproduce without infecting a host ...

... For some diseases, it is possible to establish causation between a microorganism and a disease by isolating the pathogen from a patient, growing it in pure culture and reintroducing it to a healthy organism. These are known as 'Koch's postulates' and were developed in 1882. However, as our understanding of disease and different disease-causing agents has advanced, these are no longer the method for determining causation [Andrew Kaufman asks why in that case are there two published articles falsely claiming to satisfy Koch's postulates].

It has long been known that viral diseases cannot be identified in this way as viruses cannot be grown in 'pure culture'. When a patient is tested for a viral illness, this is normally done by looking for the presence of antigens, or viral genetic code in a host with molecular biology techniques [Kaufman asks how you could know the origin of these chemicals without having a pure culture for comparison].

For the record 'antigens' are defined so:

Invading microorganisms have antigens on their surface that the human body can recognise as being foreign – meaning not belonging to it. When the body recognises a foreign antigen, lymphocytes (white blood cells) produce antibodies, which are complementary in shape to the antigen.

Notwithstanding that this is open to question in relation to 'SARS-CoV-2' the presence of 'antibodies' can have many causes and they are found in people that are perfectly well. Kary Mullis said: 'Antibodies ... had always been considered evidence of past disease, not present disease.'

## **'Covid' really is a computer 'virus'**

Where the UK Department of Health statement says 'viruses' are now 'diagnosed' through a 'viral genetic code in a host with molecular biology techniques', they mean ... *the PCR test* which its inventor said cannot test for infectious disease. They have no credible method of connecting a 'virus' to a disease and we will see that there is no scientific proof that any 'virus' causes any disease or there is any such thing as a 'virus' in the way that it is described. Tenacious Canadian researcher Christine Massey and her team made

some 40 Freedom of Information requests to national public health agencies in different countries asking for proof that SARS-CoV-2 has been isolated and not one of them could supply that information. Massey said of her request in Canada: 'Freedom of Information reveals Public Health Agency of Canada has no record of 'SARS-CoV-2' isolation performed by anyone, anywhere, ever.' If you accept the comment from the UK Department of Health it's because they can't isolate a 'virus'. Even so many 'science' papers claimed to have isolated the 'Covid virus' until they were questioned and had to admit they hadn't. A reply from the Robert Koch Institute in Germany was typical: 'I am not aware of a paper which purified isolated SARS-CoV-2.' So what the hell was Christian Drosten and his gang using to design the 'Covid' testing protocol that has produced all the illusory Covid' cases and 'Covid' deaths when the head of the Chinese version of the CDC admitted there was a problem right from the start in that the 'virus' had never been isolated/purified? Breathe deeply: What they are calling 'Covid' is actually created by a *computer program* i.e. *they made it up* – er, that's it. They took lung fluid, with many sources of genetic material, from one single person alleged to be infected with Covid-19 by a PCR test which they *claimed*, without clear evidence, contained a 'virus'. They used several computer programs to create a model of a theoretical virus genome sequence from more than fifty-six million small sequences of RNA, each of an unknown source, assembling them like a puzzle with no known solution. The computer filled in the gaps with sequences from bits in the gene bank to make it look like a bat SARS-like coronavirus! A wave of the magic wand and poof, an *in silico* (computer-generated) genome, a scientific fantasy, was created. UK health researcher Dr Kevin Corbett made the same point with this analogy:

... It's like giving you a few bones and saying that's your fish. It could be any fish. Not even a skeleton. Here's a few fragments of bones. That's your fish ... It's all from gene bank and the bits of the virus sequence that weren't there they made up.

They synthetically created them to fill in the blanks. That's what genetics is; it's a code. So it's ABBBCCDDDD and you're missing some what you think is EEE so you put it in. It's all

synthetic. You just manufacture the bits that are missing. This is the end result of the geneticization of virology. This is basically a computer virus.

Further confirmation came in an email exchange between British citizen journalist Frances Leader and the government's Medicines & Healthcare Products Regulatory Agency (the Gates-funded MHRA) which gave emergency permission for untested 'Covid vaccines' to be used. The agency admitted that the 'vaccine' is not based on an isolated 'virus', but comes from a *computer-generated model*. Frances Leader was naturally banned from Cult-owned fascist Twitter for making this exchange public. The process of creating computer-generated alleged 'viruses' is called 'in silico' or 'in silicon' – computer chips – and the term 'in silico' is believed to originate with biological experiments using only a computer in 1989. 'Vaccines' involved with 'Covid' are also produced 'in silico' or by computer not a natural process. If the original 'virus' is nothing more than a made-up computer model how can there be 'new variants' of something that never existed in the first place? They are not new 'variants'; they are new *computer models* only minutely different to the original program and designed to further terrify the population into having the 'vaccine' and submitting to fascism. You want a 'new variant'? Click, click, enter – there you go. Tell the medical profession that you have discovered a 'South African variant', 'UK variants' or a 'Brazilian variant' and in the usual HIV-causes-AIDS manner they will unquestioningly repeat it with no evidence whatsoever to support these claims. They will go on television and warn about the dangers of 'new variants' while doing nothing more than repeating what they have been told to be true and knowing that any deviation from that would be career suicide. Big-time insiders will know it's a hoax, but much of the medical community is clueless about the way they are being played and themselves play the public without even being aware they are doing so. What an interesting 'coincidence' that AstraZeneca and Oxford University were conducting 'Covid vaccine trials' in the three countries – the UK, South Africa and Brazil – where the first three 'variants' were claimed to have 'broken out'.

## **Here's your 'virus' – it's a unicorn**

Dr Andrew Kaufman presented a brilliant analysis describing how the 'virus' was imagined into fake existence when he dissected an article published by *Nature* and written by 19 authors detailing *alleged* 'sequencing of a complete viral genome' of the 'new SARS-CoV-2 virus'. This computer-modelled *in silico* genome was used as a template for all subsequent genome sequencing experiments that resulted in the so-called variants which he said now number more than 6,000. The fake genome was constructed from more than 56 million individual short strands of RNA. Those little pieces were assembled into longer pieces by finding areas of overlapping sequences. The computer programs created over two million possible combinations from which the authors simply chose the longest one. They then compared this to a 'bat virus' and the computer 'alignment' rearranged the sequence and filled in the gaps! They called this computer-generated abomination the 'complete genome'. Dr Tom Cowan, a fellow medical author and collaborator with Kaufman, said such computer-generation constitutes scientific fraud and he makes this superb analogy:

Here is an equivalency: A group of researchers claim to have found a unicorn because they found a piece of a hoof, a hair from a tail, and a snippet of a horn. They then add that information into a computer and program it to re-create the unicorn, and they then claim this computer re-creation is the real unicorn. Of course, they had never actually seen a unicorn so could not possibly have examined its genetic makeup to compare their samples with the actual unicorn's hair, hooves and horn.

The researchers claim they decided which is the real genome of SARS-CoV-2 by 'consensus', sort of like a vote. Again, different computer programs will come up with different versions of the imaginary 'unicorn', so they come together as a group and decide which is the real imaginary unicorn.

This is how the 'virus' that has transformed the world was brought into fraudulent 'existence'. Extraordinary, yes, but as the Nazis said the bigger the lie the more will believe it. Cowan, however, wasn't finished and he went on to identify what he called the real blockbuster in the paper. He quotes this section from a paper written

by virologists and published by the CDC and then explains what it means:

Therefore, we examined the capacity of SARS-CoV-2 to infect and replicate in several common primate and human cell lines, including human adenocarcinoma cells (A549), human liver cells (HUH 7.0), and human embryonic kidney cells (HEK-293T). In addition to Vero E6 and Vero CCL81 cells. ... Each cell line was inoculated at high multiplicity of infection and examined 24h post-infection.

No CPE was observed in any of the cell lines except in Vero cells, which grew to greater than 10 to the 7th power at 24 h post-infection. In contrast, HUH 7.0 and 293T showed only modest viral replication, and A549 cells were incompatible with SARS CoV-2 infection.

Cowan explains that when virologists attempt to prove infection they have three possible 'hosts' or models on which they can test. The first was humans. Exposure to humans was generally not done for ethical reasons and has never been done with SARS-CoV-2 or any coronavirus. The second possible host was animals. Cowan said that forgetting for a moment that they never actually use purified virus when exposing animals they do use solutions that they *claim* contain the virus. Exposure to animals has been done with SARS-CoV-2 in an experiment involving mice and this is what they found: *None of the wild (normal) mice got sick*. In a group of genetically-modified mice, a statistically insignificant number lost weight and had slightly bristled fur, but they experienced nothing like the illness called 'Covid-19'. Cowan said the third method – the one they mostly rely on – is to inoculate solutions they *say* contain the virus onto a variety of tissue cultures. This process had never been shown to kill tissue *unless* the sample material was starved of nutrients and poisoned as *part of the process*. Yes, incredibly, in tissue experiments designed to show the 'virus' is responsible for killing the tissue they starve the tissue of nutrients and add toxic drugs including antibiotics and they do not have control studies to see if it's the starvation and poisoning that is degrading the tissue rather than the 'virus' they allege to be in there somewhere. You want me to pinch you? Yep, I understand. Tom Cowan said this about the whole nonsensical farce as he explains what that quote from the CDC paper really means:

The shocking thing about the above quote is that using their own methods, the virologists found that solutions containing SARS-CoV-2 – even in high amounts – were NOT, I repeat NOT, infective to any of the three human tissue cultures they tested. In plain English, this means they proved, on their terms, that this ‘new coronavirus’ is not infectious to human beings. It is ONLY infective to monkey kidney cells, and only then when you add two potent drugs (gentamicin and amphotericin), known to be toxic to kidneys, to the mix.

My friends, read this again and again. These virologists, published by the CDC, performed a clear proof, on their terms, showing that the SARS-CoV-2 virus is harmless to human beings. That is the only possible conclusion, but, unfortunately, this result is not even mentioned in their conclusion. They simply say they can provide virus stocks cultured only on monkey Vero cells, thanks for coming.

Cowan concluded: ‘If people really understood how this “science” was done, I would hope they would storm the gates and demand honesty, transparency and truth.’ Dr Michael Yeadon, former Vice President and Chief Scientific Adviser at drug giant Pfizer has been a vocal critic of the ‘Covid vaccine’ and its potential for multiple harm. He said in an interview in April, 2021, that ‘not one [vaccine] has the virus. He was asked why vaccines normally using a ‘dead’ version of a disease to activate the immune system were not used for ‘Covid’ and instead we had the synthetic methods of the ‘mRNA Covid vaccine’. Yeadon said that to do the former ‘you’d have to have some of [the virus] wouldn’t you?’ He added: ‘No-one’s got any – seriously.’ Yeadon said that surely they couldn’t have fooled the whole world for a year without having a virus, ‘but oddly enough ask around – no one’s got it’. He didn’t know why with all the ‘great labs’ around the world that the virus had not been isolated – ‘Maybe they’ve been too busy running bad PCR tests and vaccines that people don’t need.’ What is today called ‘science’ is not ‘science’ at all. Science is no longer what is, but whatever people can be manipulated to *believe* that it is. Real science has been hijacked by the Cult to dispense and produce the ‘expert scientists’ and contentions that suit the agenda of the Cult. How big-time this has happened with the ‘Covid’ hoax which is entirely based on fake science delivered by fake ‘scientists’ and fake ‘doctors’. The human-caused climate change hoax is also entirely based on fake science delivered by fake ‘scientists’ and fake ‘climate experts’. In both cases real

scientists, climate experts and doctors have their views suppressed and deleted by the Cult-owned science establishment, media and Silicon Valley. This is the ‘science’ that politicians claim to be ‘following’ and a common denominator of ‘Covid’ and climate are Cult psychopaths Bill Gates and his mate Klaus Schwab at the Gates-funded World Economic Forum. But, don’t worry, it’s all just a coincidence and absolutely nothing to worry about. Zzzzzzzz.

## **What is a ‘virus’ REALLY?**

Dr Tom Cowan is one of many contesting the very existence of viruses let alone that they cause disease. This is understandable when there is no scientific evidence for a disease-causing ‘virus’. German virologist Dr Stefan Lanka won a landmark case in 2017 in the German Supreme Court over his contention that there is no such thing as a measles virus. He had offered a big prize for anyone who could prove there is and Lanka won his case when someone sought to claim the money. There is currently a prize of more than 225,000 euros on offer from an Isolate Truth Fund for anyone who can prove the isolation of SARS-CoV-2 and its genetic substance. Lanka wrote in an article headed ‘The Misconception Called Virus’ that scientists think a ‘virus’ is causing tissue to become diseased and degraded when in fact it is the *processes they are using* which do that – not a ‘virus’. Lanka has done an important job in making this point clear as Cowan did in his analysis of the CDC paper. Lanka says that all claims about viruses as disease-causing pathogens are wrong and based on ‘easily recognisable, understandable and verifiable misinterpretations.’ Scientists believed they were working with ‘viruses’ in their laboratories when they were really working with ‘typical particles of specific dying tissues or cells ...’ Lanka said that the tissue decaying process claimed to be caused by a ‘virus’ still happens when no alleged ‘virus’ is involved. It’s the *process* that does the damage and not a ‘virus’. The genetic sample is deprived of nutrients, removed from its energy supply through removal from the body and then doused in toxic antibiotics to remove any bacteria. He confirms again that establishment scientists do not (pinch me)

conduct control experiments to see if this is the case and if they did they would see the claims that 'viruses' are doing the damage is nonsense. He adds that during the measles 'virus' court case he commissioned an independent laboratory to perform just such a control experiment and the result was that the tissues and cells died in the exact same way as with alleged 'infected' material. This is supported by a gathering number of scientists, doctors and researchers who reject what is called 'germ theory' or the belief in the body being infected by contagious sources emitted by other people. Researchers Dawn Lester and David Parker take the same stance in their highly-detailed and sourced book *What Really Makes You Ill – Why everything you thought you knew about disease is wrong* which was recommended to me by a number of medical professionals genuinely seeking the truth. Lester and Parker say there is no provable scientific evidence to show that a 'virus' can be transmitted between people or people and animals or animals and people:

The definition also claims that viruses are the cause of many diseases, as if this has been definitively proven. But this is not the case; there is no original scientific evidence that definitively demonstrates that any virus is the cause of any disease. The burden of proof for any theory lies with those who proposed it; but none of the existing documents provides 'proof' that supports the claim that 'viruses' are pathogens.

Dr Tom Cowan employs one of his clever analogies to describe the process by which a 'virus' is named as the culprit for a disease when what is called a 'virus' is only material released by cells detoxing themselves from infiltration by chemical or radiation poisoning. The tidal wave of technologically-generated radiation in the 'smart' modern world plus all the toxic food and drink are causing this to happen more than ever. Deluded 'scientists' misread this as a gathering impact of what they wrongly label 'viruses'.

## **Paper can infect houses**

Cowan said in an article for [davidicke.com](http://davidicke.com) – with his tongue only mildly in his cheek – that he believed he had made a tremendous

discovery that may revolutionise science. He had discovered that small bits of paper are alive, ‘well alive-ish’, can ‘infect’ houses, and then reproduce themselves inside the house. The result was that this explosion of growth in the paper inside the house causes the house to explode, blowing it to smithereens. His evidence for this new theory is that in the past months he had carefully examined many of the houses in his neighbourhood and found almost no scraps of paper on the lawns and surrounds of the house. There was an occasional stray label, but nothing more. Then he would return to these same houses a week or so later and with a few, not all of them, particularly the old and decrepit ones, he found to his shock and surprise they were littered with stray bits of paper. He knew then that the paper had infected these houses, made copies of itself, and blew up the house. A young boy on a bicycle at one of the sites told him he had seen a demolition crew using dynamite to explode the house the previous week, but Cowan dismissed this as the idle thoughts of silly boys because ‘I was on to something big’. He was on to how ‘scientists’ mistake genetic material in the detoxifying process for something they call a ‘virus’. Cowan said of his house and paper story:

If this sounds crazy to you, it’s because it should. This scenario is obviously nuts. But consider this admittedly embellished, for effect, current viral theory that all scientists, medical doctors and virologists currently believe.

He takes the example of the ‘novel SARS-Cov2’ virus to prove the point. First they take someone with an undefined illness called ‘Covid-19’ and don’t even attempt to find any virus in their sputum. Never mind the scientists still describe how this ‘virus’, which they have not located attaches to a cell receptor, injects its genetic material, in ‘Covid’s’ case, RNA, into the cell. The RNA once inserted exploits the cell to reproduce itself and makes ‘thousands, nay millions, of copies of itself ... Then it emerges victorious to claim its next victim’:

If you were to look in the scientific literature for proof, actual scientific proof, that uniform SARS-CoV2 viruses have been properly isolated from the sputum of a sick person, that actual spike proteins could be seen protruding from the virus (which has not been found), you would find that such evidence doesn't exist.

If you go looking in the published scientific literature for actual pictures, proof, that these spike proteins or any viral proteins are ever attached to any receptor embedded in any cell membrane, you would also find that no such evidence exists. If you were to look for a video or documented evidence of the intact virus injecting its genetic material into the body of the cell, reproducing itself and then emerging victorious by budding off the cell membrane, you would find that no such evidence exists.

The closest thing you would find is electron micrograph pictures of cellular particles, possibly attached to cell debris, both of which to be seen were stained by heavy metals, a process that completely distorts their architecture within the living organism. This is like finding bits of paper stuck to the blown-up bricks, thereby proving the paper emerged by taking pieces of the bricks on its way out.

## **The Enders baloney**

Cowan describes the 'Covid' story as being just as make-believe as his paper story and he charts back this fantasy to a Nobel Prize winner called John Enders (1897-1985), an American biomedical scientist who has been dubbed 'The Father of Modern Vaccines'. Enders is claimed to have 'discovered' the process of the viral culture which 'proved' that a 'virus' caused measles. Cowan explains how Enders did this 'by using the EXACT same procedure that has been followed by every virologist to find and characterize every new virus since 1954'. Enders took throat swabs from children with measles and immersed them in 2ml of milk. Penicillin (100u/ml) and the antibiotic streptomycin (50,g/ml) were added and the whole mix was centrifuged – rotated at high speed to separate large cellular debris from small particles and molecules as with milk and cream, for example. Cowan says that if the aim is to find little particles of genetic material ('viruses') in the snot from children with measles it would seem that the last thing you would do is mix the snot with other material – milk –that also has genetic material. 'How are you ever going to know whether whatever you found came from the snot or the milk?' He points out that streptomycin is a 'nephrotoxic' or poisonous-to-the-kidney drug. You will see the relevance of that

shortly. Cowan says that it gets worse, much worse, when Enders describes the culture medium upon which the virus 'grows': 'The culture medium consisted of bovine amniotic fluid (90%), beef embryo extract (5%), horse serum (5%), antibiotics and phenol red as an indicator of cell metabolism.' Cowan asks incredulously: 'Did he just say that the culture medium also contained fluids and tissues that are themselves rich sources of genetic material?' The genetic cocktail, or 'medium', is inoculated onto tissue and cells from rhesus monkey *kidney* tissue. This is where the importance of streptomycin comes in and currently-used antimicrobials and other drugs that are *poisonous to kidneys* and used in ALL modern viral cultures (e.g. gentamicin, streptomycin, and amphotericin). Cowan asks: 'How are you ever going to know from this witch's brew where any genetic material comes from as we now have five different sources of rich genetic material in our mix?' Remember, he says, that all genetic material, whether from monkey kidney tissues, bovine serum, milk, etc., is made from the exact same components. The same central question returns: 'How are you possibly going to know that it was the virus that killed the kidney tissue and not the toxic antibiotic and starvation rations on which you are growing the tissue?' John Enders answered the question himself – *you can't*:

A second agent was obtained from an uninoculated culture of monkey kidney cells. The cytopathic changes [death of the cells] it induced in the unstained preparations could not be distinguished with confidence from the viruses isolated from measles.

The death of the cells ('cytopathic changes') happened in exactly the same manner, whether they inoculated the kidney tissue with the measles snot or not, Cowan says. 'This is evidence that the destruction of the tissue, the very proof of viral causation of illness, was not caused by anything in the snot because they saw the same destructive effect when the snot was not even used ... the cytopathic, i.e., cell-killing, changes come from the process of the culture itself, not from any virus in any snot, period.' Enders quotes in his 1957 paper a virologist called Ruckle as reporting similar findings 'and in addition has isolated an agent from monkey kidney tissue that is so

far indistinguishable from human measles virus'. In other words, Cowan says, these particles called 'measles viruses' are simply and clearly breakdown products of the starved and poisoned tissue. For measles 'virus' see all 'viruses' including the so-called 'Covid virus'. Enders, the 'Father of Modern Vaccines', also said:

There is a potential risk in employing cultures of primate cells for the production of vaccines composed of attenuated virus, since the presence of other agents possibly latent in primate tissues cannot be definitely excluded by any known method.

Cowan further quotes from a paper published in the journal *Viruses* in May, 2020, while the 'Covid pandemic' was well underway in the media if not in reality. 'EVs' here refers to particles of genetic debris from our own tissues, such as exosomes of which more in a moment: 'The remarkable resemblance between EVs and viruses has caused quite a few problems in the studies focused on the analysis of EVs released during viral infections.' Later the paper adds that to date a reliable method that can actually guarantee a complete separation (of EVs from viruses) DOES NOT EXIST. This was published at a time when a fairy tale 'virus' was claimed in total certainty to be causing a fairy tale 'viral disease' called 'Covid-19' – a fairy tale that was already well on the way to transforming human society in the image that the Cult has worked to achieve for so long. Cowan concludes his article:

To summarize, there is no scientific evidence that pathogenic viruses exist. What we think of as 'viruses' are simply the normal breakdown products of dead and dying tissues and cells. When we are well, we make fewer of these particles; when we are starved, poisoned, suffocated by wearing masks, or afraid, we make more.

There is no engineered virus circulating and making people sick. People in laboratories all over the world are making genetically modified products to make people sick. These are called vaccines. There is no virome, no 'ecosystem' of viruses, viruses are not 8%, 50% or 100 % of our genetic material. These are all simply erroneous ideas based on the misconception called a virus.

## **What is 'Covid'? Load of bollocks**

The background described here by Cowan and Lanka was emphasised in the first video presentation that I saw by Dr Andrew Kaufman when he asked whether the ‘Covid virus’ was in truth a natural defence mechanism of the body called ‘exosomes’. These are released by cells when in states of toxicity – see the same themes returning over and over. They are released ever more profusely as chemical and radiation toxicity increases and think of the potential effect therefore of 5G alone as its destructive frequencies infest the human energetic information field with a gathering pace (5G went online in Wuhan in 2019 as the ‘virus’ emerged). I’ll have more about this later. Exosomes transmit a warning to the rest of the body that ‘Houston, we have a problem’. Kaufman presented images of exosomes and compared them with ‘Covid’ under an electron microscope and the similarity was remarkable. They both attach to the same cell receptors (*claimed* in the case of ‘Covid’), contain the same genetic material in the form of RNA or ribonucleic acid, and both are found in ‘viral cell cultures’ with damaged or dying cells. James Hildreth MD, President and Chief Executive Officer of the Meharry Medical College at Johns Hopkins, said: ‘The virus is fully an exosome in every sense of the word.’ Kaufman’s conclusion was that there is no ‘virus’: ‘This entire pandemic is a completely manufactured crisis … there is no evidence of anyone dying from [this] illness.’ Dr Tom Cowan and Sally Fallon Morell, authors of *The Contagion Myth*, published a statement with Dr Kaufman in February, 2021, explaining why the ‘virus’ does not exist and you can read it that in full in the Appendix.

‘Virus’ theory can be traced to the ‘cell theory’ in 1858 of German physician Rudolf Virchow (1821-1920) who contended that disease originates from a single cell infiltrated by a ‘virus’. Dr Stefan Lanka said that findings and insights with respect to the structure, function and central importance of tissues in the creation of life, which were already known in 1858, comprehensively refute the cell theory. Virchow ignored them. We have seen the part later played by John Enders in the 1950s and Lanka notes that infection theories were only established as a global dogma through the policies and

eugenics of the Third Reich in Nazi Germany (creation of the same Sabbatian cult behind the ‘Covid’ hoax). Lanka said: ‘Before 1933, scientists dared to contradict this theory; after 1933, these critical scientists were silenced’. Dr Tom Cowan’s view is that ill-health is caused by too much of something, too little of something, or toxification from chemicals and radiation – not contagion. We must also highlight as a major source of the ‘virus’ theology a man still called the ‘Father of Modern Virology’ – Thomas Milton Rivers (1888-1962). There is no way given the Cult’s long game policy that it was a coincidence for the ‘Father of Modern Virology’ to be director of the Rockefeller Institute for Medical Research from 1937 to 1956 when he is credited with making the Rockefeller Institute a leader in ‘viral research’. Cult Rockefellers were the force behind the creation of Big Pharma ‘medicine’, established the World Health Organisation in 1948, and have long and close associations with the Gates family that now runs the WHO during the pandemic hoax through mega-rich Cult gofer and psychopath Bill Gates.

Only a Renegade Mind can see through all this bullshit by asking the questions that need to be answered, not taking ‘no’ or prevarication for an answer, and certainly not hiding from the truth in fear of speaking it. Renegade Minds have always changed the world for the better and they will change this one no matter how bleak it may currently appear to be.

## CHAPTER SIX

### Sequence of deceit

*If you tell the truth, you don't have to remember anything*

Mark Twain

**A**gainst the background that I have laid out this far the sequence that took us from an invented 'virus' in Cult-owned China in late 2019 to the fascist transformation of human society can be seen and understood in a whole new context.

We were told that a deadly disease had broken out in Wuhan and the world media began its campaign (coordinated by behavioural psychologists as we shall see) to terrify the population into unquestioning compliance. We were shown images of Chinese people collapsing in the street which never happened in the West with what was supposed to be the same condition. In the earliest days when alleged cases and deaths were few the fear register was hysterical in many areas of the media and this would expand into the common media narrative across the world. The real story was rather different, but we were never told that. The Chinese government, one of the Cult's biggest centres of global operation, said they had discovered a new illness with flu-like and pneumonia-type symptoms in a city with such toxic air that it is overwhelmed with flu-like symptoms, pneumonia and respiratory disease. Chinese scientists said it was a new – 'novel' – coronavirus which they called Sars-Cov-2 and that it caused a disease they labelled 'Covid-19'. There was no evidence for this and the 'virus' has never to this day been isolated, purified and its genetic code established from that. It

was from the beginning a computer-generated fiction. Stories of Chinese whistleblowers saying the number of deaths was being suppressed or that the ‘new disease’ was related to the Wuhan bio-lab misdirected mainstream and alternative media into cul-de-sacs to obscure the real truth – there was no ‘virus’.

Chinese scientists took genetic material from the lung fluid of just a few people and said they had found a ‘new’ disease when this material had a wide range of content. There was no evidence for a ‘virus’ for the very reasons explained in the last two chapters. The ‘virus’ has never been shown to (a) exist and (b) cause any disease. People were diagnosed on symptoms that are so widespread in Wuhan and polluted China and with a PCR test that can’t detect infectious disease. On this farce the whole global scam was sold to the rest of the world which would also diagnose respiratory disease as ‘Covid-19’ from symptoms alone or with a PCR test not testing for a ‘virus’. Flu miraculously disappeared *worldwide* in 2020 and into 2021 as it was redesignated ‘Covid-19’. It was really the same old flu with its ‘flu-like’ symptoms attributed to ‘flu-like’ ‘Covid-19’. At the same time with very few exceptions the Chinese response of draconian lockdown and fascism was the chosen weapon to respond across the West as recommended by the Cult-owned Tedros at the Cult-owned World Health Organization run by the Cult-owned Gates. All was going according to plan. Chinese scientists – everything in China is controlled by the Cult-owned government – compared their contaminated RNA lung-fluid material with other RNA sequences and said it appeared to be just under 80 percent identical to the SARS-CoV-1 ‘virus’ claimed to be the cause of the SARS (severe acute respiratory syndrome) ‘outbreak’ in 2003. They decreed that because of this the ‘new virus’ had to be related and they called it SARS-CoV-2. There are some serious problems with this assumption and *assumption* was all it was. Most ‘factual’ science turns out to be assumptions repeated into everyone-knows-that. A match of under 80-percent is meaningless. Dr Kaufman makes the point that there’s a 96 percent genetic correlation between humans and chimpanzees, but ‘no one would say our genetic material is part

of the chimpanzee family'. Yet the Chinese authorities were claiming that a much lower percentage, less than 80 percent, proved the existence of a new 'coronavirus'. For goodness sake human DNA is 60 percent similar to a *banana*.

## **You are feeling sleepy**

The entire 'Covid' hoax is a global Psyop, a psychological operation to program the human mind into believing and fearing a complete fantasy. A crucial aspect of this was what *appeared* to happen in Italy. It was all very well streaming out daily images of an alleged catastrophe in Wuhan, but to the Western mind it was still on the other side of the world in a very different culture and setting. A reaction of 'this could happen to me and my family' was still nothing like as intense enough for the mind-doctors. The Cult needed a Western example to push people over that edge and it chose Italy, one of its major global locations going back to the Roman Empire. An Italian 'Covid' crisis was manufactured in a particular area called Lombardy which just happens to be notorious for its toxic air and therefore respiratory disease. Wuhan, China, *déjà vu*. An hysterical media told horror stories of Italians dying from 'Covid' in their droves and how Lombardy hospitals were being overrun by a tidal wave of desperately ill people needing treatment after being struck down by the 'deadly virus'. Here was the psychological turning point the Cult had planned. Wow, if this is happening in Italy, the Western mind concluded, this indeed could happen to me and my family. Another point is that Italian authorities responded by following the Chinese blueprint so vehemently recommended by the Cult-owned World Health Organization. They imposed fascistic lockdowns on the whole country viciously policed with the help of surveillance drones sweeping through the streets seeking out anyone who escaped from mass house arrest. Livelihoods were destroyed and psychology unravelled in the way we have witnessed since in all lockdown countries. Crucial to the plan was that Italy responded in this way to set the precedent of suspending freedom and imposing fascism in a 'Western liberal democracy'. I emphasised in an

animated video explanation on [davidicke.com](http://davidicke.com) posted in the summer of 2020 how important it was to the Cult to expand the Chinese lockdown model across the West. Without this, and the bare-faced lie that non-symptomatic people could still transmit a ‘disease’ they didn’t have, there was no way locking down the whole population, sick and not sick, could be pulled off. At just the right time and with no evidence Cult operatives and gofers claimed that people without symptoms could pass on the ‘disease’. In the name of protecting the ‘vulnerable’ like elderly people, who lockdowns would kill by the tens of thousands, we had for the first time healthy people told to isolate as well as the sick. The great majority of people who tested positive had no symptoms because there was nothing wrong with them. It was just a trick made possible by a test not testing for the ‘virus’.

Months after my animated video the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College confirmed that I was right. He didn’t say it in those terms, naturally, but he did say it. Ferguson will enter the story shortly for his outrageously crazy ‘computer models’ that led to Britain, the United States and many other countries following the Chinese and now Italian methods of response. Put another way, following the Cult script. Ferguson said that SAGE, the UK government’s scientific advisory group which has controlled ‘Covid’ policy from the start, wanted to follow the Chinese lockdown model (while they all continued to work and be paid), but they wondered if they could possibly, in Ferguson’s words, ‘get away with it in Europe’. ‘Get away with it’? Who the hell do these moronic, arrogant people think they are? This appalling man Ferguson said that once Italy went into national lockdown they realised they, too, could mimic China:

It’s a communist one-party state, we said. We couldn’t get away with it in Europe, we thought ... and then Italy did it. And we realised we could. Behind this garbage from Ferguson is a simple fact: Doing the same as China in every country was the plan from the start and Ferguson’s ‘models’ would play a central role in achieving that. It’s just a coincidence, of course, and absolutely nothing to worry your little head about.

## **Oops, sorry, our mistake**

Once the Italian segment of the Psyop had done the job it was designed to do a very different story emerged. Italian authorities revealed that 99 percent of those who had 'died from Covid-19' in Italy had one, two, three, or more 'co-morbidities' or illnesses and health problems that could have ended their life. The US Centers for Disease Control and Prevention (CDC) published a figure of 94 percent for Americans dying of 'Covid' while having other serious medical conditions – on average two to three (some five or six) other potential causes of death. In terms of death from an unproven 'virus' I say it is 100 percent. The other one percent in Italy and six percent in the US would presumably have died from 'Covid's' flu-like symptoms with a range of other possible causes in conjunction with a test not testing for the 'virus'. Fox News reported that even more startling figures had emerged in one US county in which 410 of 422 deaths attributed to 'Covid-19' had other potentially deadly health conditions. The Italian National Health Institute said later that the average age of people dying with a 'Covid-19' diagnosis in Italy was about 81. Ninety percent were over 70 with ten percent over 90. In terms of other reasons to die some 80 percent had two or more chronic diseases with half having three or more including cardiovascular problems, diabetes, respiratory problems and cancer. Why is the phantom 'Covid-19' said to kill overwhelmingly old people and hardly affect the young? Old people continually die of many causes and especially respiratory disease which you can re-diagnose 'Covid-19' while young people die in tiny numbers by comparison and rarely of respiratory disease. Old people 'die of Covid' because they die of other things that can be redesignated 'Covid' and it really is that simple.

## **Flu has flown**

The blueprint was in place. Get your illusory 'cases' from a test not testing for the 'virus' and redesignate other causes of death as 'Covid-19'. You have an instant 'pandemic' from something that is nothing more than a computer-generated fiction. With near-on a

billion people having ‘flu-like’ symptoms every year the potential was limitless and we can see why flu quickly and apparently miraculously disappeared *worldwide* by being diagnosed ‘Covid-19’. The painfully bloody obvious was explained away by the childlike media in headlines like this in the UK *‘Independent’*: ‘Not a single case of flu detected by Public Health England this year as Covid restrictions suppress virus’. I kid you not. The masking, social distancing and house arrest that did not make the ‘Covid virus’ disappear somehow did so with the ‘flu virus’. Even worse the article, by a bloke called Samuel Lovett, suggested that maybe the masking, sanitising and other ‘Covid’ measures should continue to keep the flu away. With a ridiculousness that disturbs your breathing (it’s ‘Covid-19’) the said Lovett wrote: ‘With widespread social distancing and mask-wearing measures in place throughout the UK, the usual routes of transmission for influenza have been blocked.’ He had absolutely no evidence to support that statement, but look at the consequences of him acknowledging the obvious. With flu not disappearing at all and only being relabelled ‘Covid-19’ he would have to contemplate that ‘Covid’ was a hoax on a scale that is hard to imagine. You need guts and commitment to truth to even go there and that’s clearly something Samuel Lovett does not have in abundance. He would never have got it through the editors anyway.

Tens of thousands die in the United States alone every winter from flu including many with pneumonia complications. CDC figures record *45 million* Americans diagnosed with flu in 2017-2018 of which 61,000 died and some reports claim 80,000. Where was the same hysteria then that we have seen with ‘Covid-19’? Some 250,000 Americans are admitted to hospital with pneumonia every year with about 50,000 cases proving fatal. About 65 million suffer respiratory disease every year and three million deaths makes this the third biggest cause of death worldwide. You only have to redesignate a portion of all these people ‘Covid-19’ and you have an instant global pandemic or the *appearance* of one. Why would doctors do this? They are told to do this and all but a few dare not refuse those who must be obeyed. Doctors in general are not researching their own

knowledge and instead take it direct and unquestioned from the authorities that own them and their careers. The authorities say they must now diagnose these symptoms ‘Covid-19’ and not flu, or whatever, and they do it. Dark suits say put ‘Covid-19’ on death certificates no matter what the cause of death and the doctors do it. Renegade Minds don’t fall for the illusion that doctors and medical staff are all highly-intelligent, highly-principled, seekers of medical truth. *Some are*, but not the majority. They are repeaters, gofers, and yes sir, no sir, purveyors of what the system demands they purvey. The ‘Covid’ con is not merely confined to diseases of the lungs. Instructions to doctors to put ‘Covid-19’ on death certificates for anyone dying of *anything* within 28 days (or much more) of a positive test not testing for the ‘virus’ opened the floodgates. The term dying *with* ‘Covid’ and not *of* ‘Covid’ was coined to cover the truth. Whether it was a *with* or an *of* they were all added to the death numbers attributed to the ‘deadly virus’ compiled by national governments and globally by the Gates-funded Johns Hopkins operation in the United States that was so involved in those ‘pandemic’ simulations. Fraudulent deaths were added to the ever-growing list of fraudulent ‘cases’ from false positives from a false test. No wonder Professor Walter Ricciardi, scientific advisor to the Italian minister of health, said after the Lombardy hysteria had done its job that ‘Covid’ death rates were due to Italy having the second oldest population in the world and to *how hospitals record deaths*:

The way in which we code deaths in our country is very generous in the sense that all the people who die in hospitals with the coronavirus are deemed to be dying of the coronavirus. On re-evaluation by the National Institute of Health, only 12 per cent of death certificates have shown a direct causality from coronavirus, while 88 per cent of patients who have died have at least one pre-morbidity – many had two or three.

This is extraordinary enough when you consider the propaganda campaign to use Italy to terrify the world, but how can they even say twelve percent were genuine when the ‘virus’ has not been shown to exist, its ‘code’ is a computer program, and diagnosis comes from a test not testing for it? As in China, and soon the world, ‘Covid-19’ in

Italy was a redesignation of diagnosis. Lies and corruption were to become the real ‘pandemic’ fuelled by a pathetically-compliant medical system taking its orders from the tiny few at the top of their national hierarchy who answered to the World Health Organization which answers to Gates and the Cult. Doctors were told – ordered – to diagnose a particular set of symptoms ‘Covid-19’ and put that on the death certificate for any cause of death if the patient had tested positive with a test not testing for the virus or had ‘Covid’ symptoms like the flu. The United States even introduced big financial incentives to manipulate the figures with hospitals receiving £4,600 from the Medicare system for diagnosing someone with regular pneumonia, \$13,000 if they made the diagnosis from the same symptoms ‘Covid-19’ pneumonia, and \$39, 000 if they put a ‘Covid’ diagnosed patient on a ventilator that would almost certainly kill them. A few – painfully and pathetically few – medical whistleblowers revealed (before Cult-owned YouTube deleted their videos) that they had been instructed to ‘let the patient crash’ and put them straight on a ventilator instead of going through a series of far less intrusive and dangerous methods as they would have done before the pandemic hoax began and the financial incentives kicked in. We are talking cold-blooded murder given that ventilators are so damaging to respiratory systems they are usually the last step before heaven awaits. Renegade Minds never fall for the belief that people in white coats are all angels of mercy and cannot be full-on psychopaths. I have explained in detail in *The Answer* how what I am describing here played out across the world coordinated by the World Health Organization through the medical hierarchies in almost every country.

## **Medical scientist calls it**

Information about the non-existence of the ‘virus’ began to emerge for me in late March, 2020, and mushroomed after that. I was sent an email by Sir Julian Rose, a writer, researcher, and organic farming promotor, from a medical scientist friend of his in the United States. Even at that early stage in March the scientist was able to explain

how the ‘Covid’ hoax was being manipulated. He said there were no reliable tests for a specific ‘Covid-19 virus’ and nor were there any reliable agencies or media outlets for reporting numbers of actual ‘Covid-19’ cases. We have seen in the long period since then that he was absolutely right. ‘Every action and reaction to Covid-19 is based on totally flawed data and we simply cannot make accurate assessments,’ he said. Most people diagnosed with ‘Covid-19’ were showing nothing more than cold and flu-like symptoms ‘because most coronavirus strains *are* nothing more than cold/flu-like symptoms’. We had farcical situations like an 84-year-old German man testing positive for ‘Covid-19’ and his nursing home ordered to quarantine only for him to be found to have a common cold. The scientist described back then why PCR tests and what he called the ‘Mickey Mouse test kits’ were useless for what they were claimed to be identifying. ‘The idea these kits can isolate a specific virus like Covid-19 is nonsense,’ he said. Significantly, he pointed out that ‘if you want to create a totally false panic about a totally false pandemic – pick a coronavirus’. This is exactly what the Cult-owned Gates, World Economic Forum and Johns Hopkins University did with their Event 201 ‘simulation’ followed by their real-life simulation called the ‘pandemic’. The scientist said that all you had to do was select the sickest of people with respiratory-type diseases in a single location – ‘say Wuhan’ – and administer PCR tests to them. You can then claim that anyone showing ‘viral sequences’ similar to a coronavirus ‘which will inevitably be quite a few’ is suffering from a ‘new’ disease:

Since you already selected the sickest flu cases a fairly high proportion of your sample will go on to die. You can then say this ‘new’ virus has a CFR [case fatality rate] higher than the flu and use this to infuse more concern and do more tests which will of course produce more ‘cases’, which expands the testing, which produces yet more ‘cases’ and so on and so on. Before long you have your ‘pandemic’, and all you have done is use a simple test kit trick to convert the worst flu and pneumonia cases into something new that doesn’t ACTUALLY EXIST [my emphasis].

He said that you then ‘just run the same scam in other countries’ and make sure to keep the fear message running high ‘so that people

will feel panicky and less able to think critically'. The only problem to overcome was the fact *there is no* actual new deadly pathogen and only regular sick people. This meant that deaths from the 'new deadly pathogen' were going to be way too low for a real new deadly virus pandemic, but he said this could be overcome in the following ways – all of which would go on to happen:

1. You can claim this is just the beginning and more deaths are imminent [you underpin this with fantasy 'computer projections']. Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.
2. You can [say that people] 'minimizing' the dangers are irresponsible and bully them into not talking about numbers.
3. You can talk crap about made up numbers hoping to blind people with pseudoscience.
4. You can start testing well people (who, of course, will also likely have shreds of coronavirus [RNA] in them) and thus inflate your 'case figures' with 'asymptomatic carriers' (you will of course have to spin that to sound deadly even though any virologist knows the more symptom-less cases you have the less deadly is your pathogen).

The scientist said that if you take these simple steps 'you can have your own entirely manufactured pandemic up and running in weeks'. His analysis made so early in the hoax was brilliantly prophetic of what would actually unfold. Pulling all the information together in these recent chapters we have this is simple 1, 2, 3, of how you can delude virtually the entire human population into believing in a 'virus' that doesn't exist:

- A 'Covid case' is someone who tests positive with a test not testing for the 'virus'.
- A 'Covid death' is someone who dies of *any cause* within 28 days (or much longer) of testing positive with a test not testing for the 'virus'.
- Asymptomatic means there is nothing wrong with you, but they claim you can pass on what you don't have to justify locking

down (quarantining) healthy people in totality.

The foundations of the hoax are that simple. A study involving ten million people in Wuhan, published in November, 2020, demolished the whole lie about those without symptoms passing on the ‘virus’. They found ‘300 asymptomatic cases’ and traced their contacts to find that not one of them was detected with the ‘virus’.

‘Asymptomatic’ patients and their contacts were isolated for no less than two weeks and nothing changed. I know it’s all crap, but if you are going to claim that those without symptoms can transmit ‘the virus’ then you must produce evidence for that and they never have. Even World Health Organization official Dr Maria Van Kerkhove, head of the emerging diseases and zoonosis unit, said as early as June, 2020, that she doubted the validity of asymptomatic transmission. She said that ‘from the data we have, it still seems to be rare that an asymptomatic person actually transmits onward to a secondary individual’ and by ‘rare’ she meant that she couldn’t cite any case of asymptomatic transmission.

## **The Ferguson factor**

The problem for the Cult as it headed into March, 2020, when the script had lockdown due to start, was that despite all the manipulation of the case and death figures they still did not have enough people alleged to have died from ‘Covid’ to justify mass house arrest. This was overcome in the way the scientist described: ‘You can claim this is just the beginning and more deaths are imminent ... Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.’ Enter one Professor Neil Ferguson, the Gates-funded ‘epidemiologist’ at the Gates-funded Imperial College in London. Ferguson is Britain’s Christian Drosten in that he has a dire record of predicting health outcomes, but is still called upon to advise government on the next health outcome when another ‘crisis’ comes along. This may seem to be a strange and ridiculous thing to do. Why would you keep turning for policy guidance to people who have a history of being

monumentally wrong? Ah, but it makes sense from the Cult point of view. These ‘experts’ keep on producing predictions that suit the Cult agenda for societal transformation and so it was with Neil Ferguson as he revealed his horrific (and clearly insane) computer model predictions that allowed lockdowns to be imposed in Britain, the United States and many other countries. Ferguson does not have even an A-level in biology and would appear to have no formal training in computer modelling, medicine or epidemiology, according to Derek Winton, an MSc in Computational Intelligence. He wrote an article somewhat aghast at what Ferguson did which included taking no account of respiratory disease ‘seasonality’ which means it is far worse in the winter months. Who would have thought that respiratory disease could be worse in the winter? Well, certainly not Ferguson.

The massively China-connected Imperial College and its bizarre professor provided the excuse for the long-incubated Chinese model of human control to travel westward at lightning speed. Imperial College confirms on its website that it collaborates with the Chinese Research Institute; publishes more than 600 research papers every year with Chinese research institutions; has 225 Chinese staff; 2,600 Chinese students – the biggest international group; 7,000 former students living in China which is the largest group outside the UK; and was selected for a tour by China’s President Xi Jinping during his state visit to the UK in 2015. The college takes major donations from China and describes itself as the UK’s number one university collaborator with Chinese research institutions. The China communist/fascist government did not appear phased by the woeful predictions of Ferguson and Imperial when during the lockdown that Ferguson induced the college signed a five-year collaboration deal with China tech giant Huawei that will have Huawei’s indoor 5G network equipment installed at the college’s West London tech campus along with an ‘AI cloud platform’. The deal includes Chinese sponsorship of Imperial’s Venture Catalyst entrepreneurship competition. Imperial is an example of the enormous influence the Chinese government has within British and North American

universities and research centres – and further afield. Up to 200 academics from more than a dozen UK universities are being investigated on suspicion of ‘unintentionally’ helping the Chinese government build weapons of mass destruction by ‘transferring world-leading research in advanced military technology such as aircraft, missile designs and cyberweapons’. Similar scandals have broken in the United States, but it’s all a coincidence. Imperial College serves the agenda in many other ways including the promotion of every aspect of the United Nations Agenda 21/2030 (the Great Reset) and produced computer models to show that human-caused ‘climate change’ is happening when in the real world it isn’t. Imperial College is driving the climate agenda as it drives the ‘Covid’ agenda (both Cult hoaxes) while Patrick Vallance, the UK government’s Chief Scientific Adviser on ‘Covid’, was named Chief Scientific Adviser to the UN ‘climate change’ conference known as COP26 hosted by the government in Glasgow, Scotland. ‘Covid’ and ‘climate’ are fundamentally connected.

## **Professor Woeful**

From Imperial’s bosom came Neil Ferguson still advising government despite his previous disasters and it was announced early on that he and other key people like UK Chief Medical Adviser Chris Whitty had caught the ‘virus’ as the propaganda story was being sold. Somehow they managed to survive and we had Prime Minister Boris Johnson admitted to hospital with what was said to be a severe version of the ‘virus’ in this same period. His whole policy and demeanour changed when he returned to Downing Street. It’s a small world with these government advisors – especially in their communal connections to Gates – and Ferguson had partnered with Whitty to write a paper called ‘Infectious disease: Tough choices to reduce Ebola transmission’ which involved another scare-story that didn’t happen. Ferguson’s ‘models’ predicted that up to 150, 000 could die from ‘mad cow disease’, or BSE, and its version in sheep if it was transmitted to humans. BSE was not transmitted and instead triggered by an organophosphate pesticide used to treat a pest on

cows. Fewer than 200 deaths followed from the human form. Models by Ferguson and his fellow incompetents led to the unnecessary culling of millions of pigs, cattle and sheep in the foot and mouth outbreak in 2001 which destroyed the lives and livelihoods of farmers and their families who had often spent decades building their herds and flocks. Vast numbers of these animals did not have foot and mouth and had no contact with the infection. Another ‘expert’ behind the cull was Professor Roy Anderson, a computer modeller at Imperial College specialising in the epidemiology of *human*, not animal, disease. Anderson has served on the Bill and Melinda Gates Grand Challenges in Global Health advisory board and chairs another Gates-funded organisation. Gates is everywhere.

In a precursor to the ‘Covid’ script Ferguson backed closing schools ‘for prolonged periods’ over the swine flu ‘pandemic’ in 2009 and said it would affect a third of the world population if it continued to spread at the speed he claimed to be happening. His mates at Imperial College said much the same and a news report said: ‘One of the authors, the epidemiologist and disease modeller Neil Ferguson, who sits on the World Health Organisation’s emergency committee for the outbreak, said the virus had “full pandemic potential”.’ Professor Liam Donaldson, the Chris Whitty of his day as Chief Medical Officer, said the worst case could see 30 percent of the British people infected by swine flu with 65,000 dying. Ferguson and Donaldson were indeed proved correct when at the end of the year the number of deaths attributed to swine flu was 392. The term ‘expert’ is rather liberally applied unfortunately, not least to complete idiots. Swine flu ‘projections’ were great for GlaxoSmithKline (GSK) as millions rolled in for its Pandemrix influenza vaccine which led to brain damage with children most affected. The British government (taxpayers) paid out more than £60 million in compensation after GSK was given immunity from prosecution. Yet another ‘Covid’ déjà vu. Swine flu was supposed to have broken out in Mexico, but Dr Wolfgang Wodarg, a German doctor, former member of parliament and critic of the ‘Covid’ hoax, observed ‘the spread of swine flu’ in Mexico City at the time. He

said: 'What we experienced in Mexico City was a very mild flu which did not kill more than usual – which killed even fewer people than usual.' Hyping the fear against all the facts is not unique to 'Covid' and has happened many times before. Ferguson is reported to have over-estimated the projected death toll of bird flu (H5N1) by some three million-fold, but bird flu vaccine makers again made a killing from the scare. This is some of the background to the Neil Ferguson who produced the perfectly-timed computer models in early 2020 predicting that half a million people would die in Britain without draconian lockdown and 2.2 million in the United States. Politicians panicked, people panicked, and lockdowns of alleged short duration were instigated to 'flatten the curve' of cases gleaned from a test not testing for the 'virus'. I said at the time that the public could forget the 'short duration' bit. This was an agenda to destroy the livelihoods of the population and force them into mass control through dependency and there was going to be nothing 'short' about it. American researcher Daniel Horowitz described the consequences of the 'models' spewed out by Gates-funded Ferguson and Imperial College:

What led our government and the governments of many other countries into panic was a single Imperial College of UK study, funded by global warming activists, that predicted 2.2 million deaths if we didn't lock down the country. In addition, the reported 8-9% death rate in Italy scared us into thinking there was some other mutation of this virus that they got, which might have come here.

Together with the fact that we were finally testing and had the ability to actually report new cases, we thought we were headed for a death spiral. But again ... we can't flatten a curve if we don't know when the curve started.

How about it *never* started?

## **Giving them what they want**

An investigation by German news outlet *Welt Am Sonntag* (*World on Sunday*) revealed how in March, 2020, the German government gathered together 'leading scientists from several research institutes and universities' and 'together, they were to produce a [modelling]

paper that would serve as legitimization for further tough political measures'. The Cult agenda was justified by computer modelling not based on evidence or reality; it was specifically constructed to justify the Cult demand for lockdowns all over the world to destroy the independent livelihoods of the global population. All these modellers and everyone responsible for the 'Covid' hoax have a date with a trial like those in Nuremberg after World War Two when Nazis faced the consequences of their war crimes. These corrupt-beyond-belief 'modellers' wrote the paper according to government instructions and it said that if lockdown measures were lifted then up to one million Germans would die from 'Covid-19' adding that some would die 'agonizingly at home, gasping for breath' unable to be treated by hospitals that couldn't cope. All lies. No matter – it gave the Cult all that it wanted. What did long-time government 'modeller' Neil Ferguson say? If the UK and the United States didn't lockdown half a million would die in Britain and 2.2 million Americans. Anyone see a theme here? 'Modellers' are such a crucial part of the lockdown strategy that we should look into their background and follow the money. Researcher Rosemary Frei produced an excellent article headlined 'The Modelling-paper Mafiosi'. She highlights a guy called John Edmunds, a British epidemiologist, and professor in the Faculty of Epidemiology and Population Health at the London School of Hygiene & Tropical Medicine. He studied at Imperial College. Edmunds is a member of government 'Covid' advisory bodies which have been dictating policy, the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) and the Scientific Advisory Group for Emergencies (SAGE).

Ferguson, another member of NERVTAG and SAGE, led the way with the original 'virus' and Edmunds has followed in the 'variant' stage and especially the so-called UK or Kent variant known as the 'Variant of Concern' (VOC) B.1.1.7. He said in a co-written report for the Centre for Mathematical modelling of Infectious Diseases at the London School of Hygiene and Tropical Medicine, with input from the Centre's 'Covid-19' Working Group, that there was 'a realistic

possibility that VOC B.1.1.7 is associated with an increased risk of death compared to non-VOC viruses'. Fear, fear, fear, get the vaccine, fear, fear, fear, get the vaccine. Rosemary Frei reveals that almost all the paper's authors and members of the modelling centre's 'Covid-19' Working Group receive funding from the Bill and Melinda Gates Foundation and/or the associated Gates-funded Wellcome Trust. The paper was published by e-journal *Medr* <sup>xiv</sup> which only publishes papers not peer-reviewed and the journal was established by an organisation headed by Facebook's Mark Zuckerberg and his missus. What a small world it is. Frei discovered that Edmunds is on the Scientific Advisory Board of the Coalition for Epidemic Preparedness Innovations (CEPI) which was established by the Bill and Melinda Gates Foundation, Klaus Schwab's Davos World Economic Forum and Big Pharma giant Wellcome. CEPI was 'launched in Davos [in 2017] to develop vaccines to stop future epidemics', according to its website. 'Our mission is to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines for people during outbreaks.' What kind people they are. Rosemary Frei reveals that Public Health England (PHE) director Susan Hopkins is an author of her organisation's non-peer-reviewed reports on 'new variants'. Hopkins is a professor of infectious diseases at London's Imperial College which is gifted tens of millions of dollars a year by the Bill and Melinda Gates Foundation. Gates-funded modelling disaster Neil Ferguson also co-authors Public Health England reports and he spoke in December, 2020, about the potential danger of the B.1.1.7. 'UK variant' promoted by Gates-funded modeller John Edmunds. When I come to the 'Covid vaccines' the 'new variants' will be shown for what they are – bollocks.

## **Connections, connections**

All these people and modellers are lockdown-obsessed or, put another way, they demand what the Cult demands. Edmunds said in January, 2021, that to ease lockdowns too soon would be a disaster and they had to 'vaccinate much, much, much more widely than the

elderly'. Rosemary Frei highlights that Edmunds is married to Jeanne Pimenta who is described in a LinkedIn profile as director of epidemiology at GlaxoSmithKline (GSK) and she held shares in the company. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of GSK and has a deferred bonus of shares in the company worth £600,000. GSK has serious business connections with Bill Gates and is collaborating with mRNA-'vaccine' company CureVac to make 'vaccines' for the new variants that Edmunds is talking about. GSK is planning a 'Covid vaccine' with drug giant Sanofi. Puppet Prime Minister Boris Johnson announced in the spring of 2021 that up to 60 million vaccine doses were to be made at the GSK facility at Barnard Castle in the English North East. Barnard Castle, with a population of just 6,000, was famously visited in breach of lockdown rules in April, 2020, by Johnson aide Dominic Cummings who said that he drove there 'to test his eyesight' before driving back to London. Cummings would be better advised to test his integrity – not that it would take long. The GSK facility had nothing to do with his visit then although I'm sure Patrick Vallance would have been happy to arrange an introduction and some tea and biscuits. Ruthless psychopath Gates has made yet another fortune from vaccines in collaboration with Big Pharma companies and gushes at the phenomenal profits to be made from vaccines – more than a 20-to-1 return as he told one interviewer. Gates also tweeted in December, 2019, with the foreknowledge of what was coming: 'What's next for our foundation? I'm particularly excited about what the next year could mean for one of the best buys in global health: vaccines.'

Modeller John Edmunds is a big promotor of vaccines as all these people appear to be. He's the dean of the London School of Hygiene & Tropical Medicine's Faculty of Epidemiology and Population Health which is primarily funded by the Bill and Melinda Gates Foundation and the Gates-established and funded GAVI vaccine alliance which is the Gates vehicle to vaccinate the world. The organisation Doctors Without Borders has described GAVI as being 'aimed more at supporting drug-industry desires to promote new

products than at finding the most efficient and sustainable means for fighting the diseases of poverty'. But then that's why the psychopath Gates created it. John Edmunds said in a video that the London School of Hygiene & Tropical Medicine is involved in every aspect of vaccine development including large-scale clinical trials. He contends that mathematical modelling can show that vaccines protect individuals and society. That's on the basis of shit in and shit out, I take it. Edmunds serves on the UK Vaccine Network as does Ferguson and the government's foremost 'Covid' adviser, the grim-faced, dark-eyed Chris Whitty. The Vaccine Network says it works 'to support the government to identify and shortlist targeted investment opportunities for the most promising vaccines and vaccine technologies that will help combat infectious diseases with epidemic potential, and to address structural issues related to the UK's broader vaccine infrastructure'. Ferguson is acting Director of the Imperial College Vaccine Impact Modelling Consortium which has funding from the Bill and Melina Gates Foundation and the Gates-created GAVI 'vaccine alliance'. Anyone wonder why these characters see vaccines as the answer to every problem? Ferguson is wildly enthusiastic in his support for GAVI's campaign to vaccine children en masse in poor countries. You would expect someone like Gates who has constantly talked about the need to reduce the population to want to fund vaccines to keep more people alive. I'm sure that's why he does it. The John Edmunds London School of Hygiene & Tropical Medicine (LSHTM) has a Vaccines Manufacturing Innovation Centre which develops, tests and commercialises vaccines. Rosemary Frei writes:

The vaccines centre also performs affiliated activities like combating 'vaccine hesitancy'. The latter includes the Vaccine Confidence Project. The project's stated purpose is, among other things, 'to provide analysis and guidance for early response and engagement with the public to ensure sustained confidence in vaccines and immunisation'. The Vaccine Confidence Project's director is LSHTM professor Heidi Larson. For more than a decade she's been researching how to combat vaccine hesitancy.

How the bloody hell can blokes like John Edmunds and Neil Ferguson with those connections and financial ties model 'virus' case

and death projections for the government and especially in a way that gives their paymasters like Gates exactly what they want? It's insane, but this is what you find throughout the world.

## **'Covid' is not dangerous, oops, wait, yes it is**

Only days before Ferguson's nightmare scenario made Jackboot Johnson take Britain into a China-style lockdown to save us from a deadly 'virus' the UK government website gov.uk was reporting something very different to Ferguson on a page of official government guidance for 'high consequence infectious diseases (HCID)'. It said this about 'Covid-19':

As of 19 March 2020, COVID-19 *is no longer considered to be a high consequence infectious diseases (HCID) in the UK* [my emphasis]. The 4 nations public health HCID group made an interim recommendation in January 2020 to classify COVID-19 as an HCID. This was based on consideration of the UK HCID criteria about the virus and the disease with information available during the early stages of the outbreak.

Now that more is known about COVID-19, the public health bodies in the UK have reviewed the most up to date information about COVID-19 against the UK HCID criteria. They have determined that several features have now changed; in particular, more information is available about mortality rates (low overall), and there is now greater clinical awareness and a specific and sensitive laboratory test, the availability of which continues to increase. The Advisory Committee on Dangerous Pathogens (ACDP) is also of the opinion that COVID-19 should no longer be classified as an HCID.

Soon after the government had been exposed for downgrading the risk they upgraded it again and everyone was back to singing from the same Cult hymn book. Ferguson and his fellow Gates clones indicated that lockdowns and restrictions would have to continue until a Gates-funded vaccine was developed. Gates said the same because Ferguson and his like were repeating the Gates script which is the Cult script. 'Flatten the curve' became an ongoing nightmare of continuing lockdowns with periods in between of severe restrictions in pursuit of destroying independent incomes and had nothing to do with protecting health about which the Cult gives not a shit. Why wouldn't Ferguson be pushing a vaccine 'solution' when he's owned by vaccine-obsessive Gates who makes a fortune from them and

when Ferguson heads the Vaccine Impact Modelling Consortium at Imperial College funded by the Gates Foundation and GAVI, the ‘vaccine alliance’, created by Gates as his personal vaccine promotion operation? To compound the human catastrophe that Ferguson’s ‘models’ did so much to create he was later exposed for breaking his own lockdown rules by having sexual liaisons with his married girlfriend Antonia Staats at his home while she was living at another location with her husband and children. Staats was a ‘climate’ activist and senior campaigner at the Soros-funded Avaaz which I wouldn’t trust to tell me that grass is green. Ferguson had to resign as a government advisor over this hypocrisy in May, 2020, but after a period of quiet he was back being quoted by the ridiculous media on the need for more lockdowns and a vaccine rollout. Other government-advising ‘scientists’ from Imperial College held the fort in his absence and said lockdown could be indefinite until a vaccine was found. The Cult script was being sung by the payrolled choir. I said there was no intention of going back to ‘normal’ when the ‘vaccine’ came because the ‘vaccine’ is part of a very different agenda that I will discuss in Human 2.0. Why would the Cult want to let the world go back to normal when destroying that normal forever was the whole point of what was happening? House arrest, closing businesses and schools through lockdown, (un)social distancing and masks all followed the Ferguson fantasy models. Again as I predicted (these people are so predictable) when the ‘vaccine’ arrived we were told that house arrest, lockdown, (un)social distancing and masks would still have to continue. I will deal with the masks in the next chapter because they are of fundamental importance.

## **Where's the 'pandemic'?**

Any mildly in-depth assessment of the figures revealed what was really going on. Cult-funded and controlled organisations still have genuine people working within them such is the number involved. So it is with Genevieve Briand, assistant program director of the Applied Economics master’s degree program at Johns Hopkins

University. She analysed the impact that 'Covid-19' had on deaths from *all* causes in the United States using official data from the CDC for the period from early February to early September, 2020. She found that allegedly 'Covid' *related*-deaths exceeded those from heart disease which she found strange with heart disease always the biggest cause of fatalities. Her research became even more significant when she noted the sudden decline in 2020 of *all* non-'Covid' deaths: 'This trend is completely contrary to the pattern observed in all previous years ... the total decrease in deaths by other causes almost exactly equals the increase in deaths by Covid-19.' This was such a game, set and match in terms of what was happening that Johns Hopkins University deleted the article on the grounds that it 'was being used to support false and dangerous inaccuracies about the impact of the pandemic'. No – because it exposed the scam from official CDC figures and this was confirmed when those figures were published in January, 2021. Here we can see the effect of people dying from heart attacks, cancer, road accidents and gunshot wounds – *anything* – having 'Covid-19' on the death certificate along with those diagnosed from 'symptoms' who had even not tested positive with a test not testing for the 'virus'. I am not kidding with the gunshot wounds, by the way. Brenda Bock, coroner in Grand County, Colorado, revealed that two gunshot victims tested positive for the 'virus' within the previous 30 days and were therefore classified as 'Covid deaths'. Bock said: 'These two people had tested positive for Covid, but that's not what killed them. A gunshot wound is what killed them.' She said she had not even finished her investigation when the state listed the gunshot victims as deaths due to the 'virus'. The death and case figures for 'Covid-19' are an absolute joke and yet they are repeated like parrots by the media, politicians and alleged medical 'experts'. The official Cult narrative is the only show in town.

Genevieve Briand found that deaths from all causes were not exceptional in 2020 compared with previous years and a Spanish magazine published figures that said the same about Spain which was a 'Covid' propaganda hotspot at one point. *Discovery Salud*, a

health and medicine magazine, quoted government figures which showed how 17,000 *fewer* people died in Spain in 2020 than in 2019 and more than 26,000 fewer than in 2018. The age-standardised mortality rate for England and Wales when age distribution is taken into account was significantly lower in 2020 than the 1970s, 80s and 90s, and was only the ninth highest since 2000. Where is the ‘pandemic’?

Post mortems and autopsies virtually disappeared for ‘Covid’ deaths amid claims that ‘virus-infected’ bodily fluids posed a risk to those carrying out the autopsy. This was rejected by renowned German pathologist and forensic doctor Klaus Püschel who said that he and his staff had by then done 150 autopsies on ‘Covid’ patients with no problems at all. He said they were needed to know why some ‘Covid’ patients suffered blood clots and not severe respiratory infections. The ‘virus’ is, after all, called SARS or ‘severe acute respiratory syndrome’. I highlighted in the spring of 2020 this phenomenon and quoted New York intensive care doctor Cameron Kyle-Sidell who posted a soon deleted YouTube video to say that they had been told to prepare to treat an infectious disease called ‘Covid-19’, but that was not what they were dealing with. Instead he likened the lung condition of the most severely ill patients to what you would expect with cabin depressurisation in a plane at 30,000 feet or someone dropped on the top of Everest without oxygen or acclimatisation. I have never said this is not happening to a small minority of alleged ‘Covid’ patients – I am saying this is not caused by a phantom ‘contagious virus’. Indeed Kyle-Sidell said that ‘Covid-19’ was not the disease they were told was coming their way. ‘We are operating under a medical paradigm that is untrue,’ he said, and he believed they were treating the wrong disease: ‘These people are being slowly starved of oxygen.’ Patients would take off their oxygen masks in a state of fear and stress and while they were blue in the face on the brink of death. They did not look like patients dying of pneumonia. You can see why they don’t want autopsies when their virus doesn’t exist and there is another condition in some people that they don’t wish to be uncovered. I should add here that

the 5G system of millimetre waves was being rapidly introduced around the world in 2020 and even more so now as they fire 5G at the Earth from satellites. At 60 gigahertz within the 5G range that frequency interacts with the oxygen molecule and stops people breathing in sufficient oxygen to be absorbed into the bloodstream. They are installing 5G in schools and hospitals. The world is not mad or anything. 5G can cause major changes to the lungs and blood as I detail in *The Answer* and these consequences are labelled 'Covid-19', the alleged symptoms of which can be caused by 5G and other electromagnetic frequencies as cells respond to radiation poisoning.

## **The 'Covid death' scam**

Dr Scott Jensen, a Minnesota state senator and medical doctor, exposed 'Covid' Medicare payment incentives to hospitals and death certificate manipulation. He said he was sent a seven-page document by the US Department of Health 'coaching' him on how to fill out death certificates which had never happened before. The document said that he didn't need to have a laboratory test for 'Covid-19' to put that on the death certificate and that shocked him when death certificates are supposed to be about facts. Jensen described how doctors had been 'encouraged, if not pressured' to make a diagnosis of 'Covid-19' if they thought it was probable or '*presumed*'. No positive test was necessary – not that this would have mattered anyway. He said doctors were told to diagnose 'Covid' by symptoms when these were the same as colds, allergies, other respiratory problems, and certainly with influenza which 'disappeared' in the 'Covid' era. A common sniffle was enough to get the dreaded verdict. Ontario authorities decreed that a single care home resident with *one* symptom from a long list must lead to the isolation of the entire home. Other courageous doctors like Jensen made the same point about death figure manipulation and how deaths by other causes were falling while 'Covid-19 deaths' were rising at the same rate due to re-diagnosis. Their videos rarely survive long on YouTube with its Cult-supporting algorithms courtesy of CEO Susan Wojcicki and her bosses at Google. Figure-tampering was so glaring

and ubiquitous that even officials were letting it slip or outright saying it. UK chief scientific adviser Patrick Vallance said on one occasion that ‘Covid’ on the death certificate doesn’t mean ‘Covid’ was the cause of death (so why the hell is it there?) and we had the rare sight of a BBC reporter telling the truth when she said: ‘Someone could be successfully treated for Covid, in say April, discharged, and then in June, get run over by a bus and die ... That person would still be counted as a Covid death in England.’ Yet the BBC and the rest of the world media went on repeating the case and death figures as if they were real. Illinois Public Health Director Dr Ngozi Ezike revealed the deceit while her bosses must have been clenching their buttocks:

If you were in a hospice and given a few weeks to live and you were then found to have Covid that would be counted as a Covid death. [There might be] a clear alternate cause, but it is still listed as a Covid death. So everyone listed as a Covid death doesn’t mean that was the cause of the death, but that they had Covid at the time of death.

Yes, a ‘Covid virus’ never shown to exist and tested for with a test not testing for the ‘virus’. In the first period of the pandemic hoax through the spring of 2020 the process began of designating almost everything a ‘Covid’ death and this has continued ever since. I sat in a restaurant one night listening to a loud conversation on the next table where a family was discussing in bewilderment how a relative who had no symptoms of ‘Covid’, and had died of a long-term problem, could have been diagnosed a death by the ‘virus’. I could understand their bewilderment. If they read this book they will know why this medical fraud has been perpetrated the world over.

## **Some media truth shock**

The media ignored the evidence of death certificate fraud until eventually one columnist did speak out when she saw it first-hand. Bel Mooney is a long-time national newspaper journalist in Britain currently working for the *Daily Mail*. Her article on February 19th, 2021, carried this headline: ‘My dad Ted passed three Covid tests

and died of a chronic illness yet he's officially one of Britain's 120,000 victims of the virus and is far from alone ... so how many more are there?' She told how her 99-year-old father was in a care home with a long-standing chronic obstructive pulmonary disease and vascular dementia. Maybe, but he was still aware enough to tell her from the start that there was no 'virus' and he refused the 'vaccine' for that reason. His death was not unexpected given his chronic health problems and Mooney said she was shocked to find that 'Covid-19' was declared the cause of death on his death certificate. She said this was a 'bizarre and unacceptable untruth' for a man with long-time health problems who had tested negative twice at the home for the 'virus'. I was also shocked by this story although not by what she said. I had been highlighting the death certificate manipulation for ten months. It was the confirmation that a professional full-time journalist only realised this was going on when it affected her directly and neither did she know that whether her dad tested positive or negative was irrelevant with the test not testing for the 'virus'. Where had she been? She said she did not believe in 'conspiracy theories' without knowing I'm sure that this and 'conspiracy theorists' were terms put into widespread circulation by the CIA in the 1960s to discredit those who did not accept the ridiculous official story of the Kennedy assassination. A blanket statement of 'I don't believe in conspiracy theories' is always bizarre. The dictionary definition of the term alone means the world is drowning in conspiracies. What she said was even more daft when her dad had just been affected by the 'Covid' conspiracy. Why else does she think that 'Covid-19' was going on the death certificates of people who died of something else?

To be fair once she saw from personal experience what was happening she didn't mince words. Mooney was called by the care home on the morning of February 9th to be told her father had died in his sleep. When she asked for the official cause of death what came back was 'Covid-19'. Mooney challenged this and was told there had been deaths from Covid on the dementia floor (confirmed by a test not testing for the 'virus') so they considered it 'reasonable

to assume'. 'But doctor,' Mooney rightly protested, 'an assumption isn't a diagnosis.' She said she didn't blame the perfectly decent and sympathetic doctor – 'he was just doing his job'. Sorry, but that's *bullshit*. He wasn't doing his job at all. He was putting a false cause of death on the death certificate and that is a criminal offence for which he should be brought to account and the same with the millions of doctors worldwide who have done the same. They were not doing their job they were following orders and that must not wash at new Nuremberg trials any more than it did at the first ones. Mooney's doctor was 'assuming' (presuming) as he was told to, but 'just following orders' makes no difference to his actions. A doctor's job is to serve the patient and the truth, not follow orders, but that's what they have done all over the world and played a central part in making the 'Covid' hoax possible with all its catastrophic consequences for humanity. Shame on them and they must answer for their actions. Mooney said her disquiet worsened when she registered her father's death by telephone and was told by the registrar there had been very many other cases like hers where 'the deceased' had not tested positive for 'Covid' yet it was recorded as the cause of death. The test may not matter, but those involved at their level *think* it matters and it shows a callous disregard for accurate diagnosis. The pressure to do this is coming from the top of the national 'health' pyramids which in turn obey the World Health Organization which obeys Gates and the Cult. Mooney said the registrar agreed that this must distort the national figures adding that 'the strangest thing is that every winter we record countless deaths from flu, and this winter there have been none. Not one!' She asked if the registrar thought deaths from flu were being misdiagnosed and lumped together with 'Covid' deaths. The answer was a 'puzzled yes'. Mooney said that the funeral director said the same about 'Covid' deaths which had nothing to do with 'Covid'. They had lost count of the number of families upset by this and other funeral companies in different countries have had the same experience. Mooney wrote:

The nightly shroud-waving and shocking close-ups of pain imposed on us by the TV news bewildered and terrified the population into eager compliance with lockdowns. We were invited to ‘save the NHS’ and to grieve for strangers – the real-life loved ones behind those shocking death counts. Why would the public imagine what I now fear, namely that the way Covid-19 death statistics are compiled might make the numbers seem greater than they are?

Oh, just a little bit – like 100 percent.

## **Do the maths**

Mooney asked why a country would wish to skew its mortality figures by wrongly certifying deaths? What had been going on? Well, if you don’t believe in conspiracies you will never find the answer which is that *it’s a conspiracy*. She did, however, describe what she had discovered as a ‘national scandal’. In reality it’s a global scandal and happening everywhere. Pillars of this conspiracy were all put into place before the button was pressed with the Drosten PCR protocol and high amplifications to produce the cases and death certificate changes to secure illusory ‘Covid’ deaths.

Mooney notes that normally two doctors were needed to certify a death, with one having to know the patient, and how the rules were changed in the spring of 2020 to allow one doctor to do this. In the same period ‘Covid deaths’ were decreed to be all cases where Covid-19 was put on the death certificate even without a positive test or any symptoms. Mooney asked: ‘How many of the 30,851 (as of January 15) care home resident deaths with Covid-19 on the certificate (32.4 per cent of all deaths so far) were based on an assumption, like that of my father? And what has that done to our national psyche?’ All of them is the answer to the first question and it has devastated and dismantled the national psyche, actually the global psyche, on a colossal scale. In the UK case and death data is compiled by organisations like Public Health England (PHE) and the Office for National Statistics (ONS). Mooney highlights the insane policy of counting a death from any cause as ‘Covid-19’ if this happens within 28 days of a positive test (with a test not testing for the ‘virus’) and she points out that ONS statistics reflect deaths ‘involving Covid’ ‘or due to Covid’ which meant in practice any

death where ‘Covid-19’ was mentioned on the death certificate. She described the consequences of this fraud:

Most people will accept the narrative they are fed, so panicky governments here and in Europe witnessed the harsh measures enacted in totalitarian China and jumped into lockdown. Headlines about Covid deaths tolled like the knell that would bring doomsday to us all. Fear stalked our empty streets. Politicians parroted the frankly ridiculous aim of ‘zero Covid’ and shut down the economy, while most British people agreed that lockdown was essential and (astonishingly to me, as a patriotic Brit) even wanted more restrictions.

For what? Lies on death certificates? Never mind the grim toll of lives ruined, suicides, schools closed, rising inequality, depression, cancelled hospital treatments, cancer patients in a torture of waiting, poverty, economic devastation, loneliness, families kept apart, and so on. How many lives have been lost as a direct result of lockdown?

She said that we could join in a national chorus of shock and horror at reaching the 120,000 death toll which was surely certain to have been totally skewed all along, but what about the human cost of lockdown justified by these ‘death figures’? *The British Medical Journal* had reported a 1,493 percent increase in cases of children taken to Great Ormond Street Hospital with abusive head injuries alone and then there was the effect on families:

Perhaps the most shocking thing about all this is that families have been kept apart – and obeyed the most irrational, changing rules at the whim of government – because they believed in the statistics. They succumbed to fear, which his generation rejected in that war fought for freedom. Dad (God rest his soul) would be angry. And so am I.

Another theme to watch is that in the winter months when there are more deaths from all causes they focus on ‘Covid’ deaths and in the summer when the British Lung Foundation says respiratory disease plummets by 80 percent they rage on about ‘cases’. Either way fascism on population is always the answer.

## **Nazi eugenics in the 21st century**

Elderly people in care homes have been isolated from their families month after lonely month with no contact with relatives and grandchildren who were banned from seeing them. We were told

that lockdown fascism was to ‘protect the vulnerable’ like elderly people. At the same time Do Not Resuscitate (DNR) orders were placed on their medical files so that if they needed resuscitation it wasn’t done and ‘Covid-19’ went on their death certificates. Old people were not being ‘protected’ they were being culled – murdered in truth. DNR orders were being decreed for disabled and young people with learning difficulties or psychological problems. The UK Care Quality Commission, a non-departmental body of the Department of Health and Social Care, found that 34 percent of those working in health and social care were pressured into placing ‘do not attempt cardiopulmonary resuscitation’ orders on ‘Covid’ patients who suffered from disabilities and learning difficulties without involving the patient or their families in the decision. UK judges ruled that an elderly woman with dementia should have the DNA-manipulating ‘Covid vaccine’ against her son’s wishes and that a man with severe learning difficulties should have the jab despite his family’s objections. Never mind that many had already died. The judiciary always supports doctors and government in fascist dictatorships. They wouldn’t dare do otherwise. A horrific video was posted showing fascist officers from Los Angeles police forcibly giving the ‘Covid’ shot to women with special needs who were screaming that they didn’t want it. The same fascists are seen giving the jab to a sleeping elderly woman in a care home. This is straight out of the Nazi playbook. Hitler’s Nazis committed mass murder of the mentally ill and physically disabled throughout Germany and occupied territories in the programme that became known as Aktion T4, or just T4. Sabbatian-controlled Hitler and his grotesque crazies set out to kill those they considered useless and unnecessary. The Reich Committee for the Scientific Registering of Hereditary and Congenital Illnesses registered the births of babies identified by physicians to have ‘defects’. By 1941 alone more than 5,000 children were murdered by the state and it is estimated that in total the number of innocent people killed in Aktion T4 was between 275,000 and 300,000. Parents were told their children had been sent away for ‘special treatment’ never to return. It is rather pathetic to see claims about plans for new extermination camps being dismissed today

when the same force behind current events did precisely that 80 years ago. Margaret Sanger was a Cult operative who used 'birth control' to sanitise her programme of eugenics. Organisations she founded became what is now Planned Parenthood. Sanger proposed that 'the whole dysgenic population would have its choice of segregation or sterilization'. These included epileptics, 'feeble-minded', and prostitutes. Sanger opposed charity because it perpetuated 'human waste'. She reveals the Cult mentality and if anyone thinks that extermination camps are a 'conspiracy theory' their naivety is touching if breathtakingly stupid.

If you don't believe that doctors can act with callous disregard for their patients it is worth considering that doctors and medical staff agreed to put government-decreed DNR orders on medical files and do nothing when resuscitation is called for. I don't know what you call such people in your house. In mine they are Nazis from the Josef Mengele School of Medicine. Phenomenal numbers of old people have died worldwide from the effects of lockdown, depression, lack of treatment, the 'vaccine' (more later) and losing the will to live. A common response at the start of the manufactured pandemic was to remove old people from hospital beds and transfer them to nursing homes. The decision would result in a mass cull of elderly people in those homes through lack of treatment – *not* 'Covid'. Care home whistleblowers have told how once the 'Covid' era began doctors would not come to their homes to treat patients and they were begging for drugs like antibiotics that often never came. The most infamous example was ordered by New York governor Andrew Cuomo, brother of a moronic CNN host, who amazingly was given an Emmy Award for his handling of the 'Covid crisis' by the ridiculous Wokers that hand them out. Just how ridiculous could be seen in February, 2021, when a Department of Justice and FBI investigation began into how thousands of old people in New York died in nursing homes after being discharged from hospital to make way for 'Covid' patients on Cuomo's say-so – and how he and his staff covered up these facts. This couldn't have happened to a nicer psychopath. Even then there was a 'Covid' spin. Reports said that

thousands of old people who tested positive for ‘Covid’ in hospital were transferred to nursing homes to both die of ‘Covid’ and transmit it to others. No – they were in hospital because they were ill and the fact that they tested positive with a test not testing for the ‘virus’ is irrelevant. They were ill often with respiratory diseases ubiquitous in old people near the end of their lives. Their transfer out of hospital meant that their treatment stopped and many would go on to die.

### **They're old. Who gives a damn?**

I have exposed in the books for decades the Cult plan to cull the world’s old people and even to introduce at some point what they call a ‘demise pill’ which at a certain age everyone would take and be out of here by law. In March, 2021, Spain legalised euthanasia and assisted suicide following the Netherlands, Belgium, Luxembourg and Canada on the Tiptoe to the demise pill. Treatment of old people by many ‘care’ homes has been a disgrace in the ‘Covid’ era. There are many, many, caring staff – I know some. There have, however, been legions of stories about callous treatment of old people and their families. Police were called when families came to take their loved ones home in the light of isolation that was killing them. They became prisoners of the state. Care home residents in insane, fascist Ontario, Canada, were not allowed to leave their *room* once the ‘Covid’ hoax began. UK staff have even wheeled elderly people away from windows where family members were talking with them. Oriana Criscuolo from Stockport in the English North West dropped off some things for her 80-year-old father who has Parkinson’s disease and dementia and she wanted to wave to him through a ground-floor window. She was told that was ‘illegal’. When she went anyway they closed the curtains in the middle of the day. Oriana said:

It’s just unbelievable. I cannot understand how care home staff – people who are being paid to care – have become so uncaring. Their behaviour is inhumane and cruel. It’s beyond belief.

She was right and this was not a one-off. What a way to end your life in such loveless circumstances. UK registered nurse Nicky Millen, a proper old school nurse for 40 years, said that when she started her career care was based on dignity, choice, compassion and empathy. Now she said ‘the things that are important to me have gone out of the window.’ She was appalled that people were dying without their loved ones and saying goodbye on iPads. Nicky described how a distressed 89-year-old lady stroked her face and asked her ‘how many paracetamol would it take to finish me off’. Life was no longer worth living while not seeing her family. Nicky said she was humiliated in front of the ward staff and patients for letting the lady stroke her face and giving her a cuddle. Such is the dehumanisation that the ‘Covid’ hoax has brought to the surface. Nicky worked in care homes where patients told her they were being held prisoner. ‘I want to live until I die’, one said to her. ‘I had a lady in tears because she hadn’t seen her great-grandson.’ Nicky was compassionate old school meeting psychopathic New Normal. She also said she had worked on a ‘Covid’ ward with no ‘Covid’ patients. Jewish writer Shai Held wrote an article in March, 2020, which was headlined ‘The Staggering, Heartless Cruelty Toward the Elderly’. What he described was happening from the earliest days of lockdown. He said ‘the elderly’ were considered a group and not unique individuals (the way of the Woke). Shai Held said:

Notice how the all-too-familiar rhetoric of dehumanization works: ‘The elderly’ are bunched together as a faceless mass, all of them considered culprits and thus effectively deserving of the suffering the pandemic will inflict upon them. Lost entirely is the fact that the elderly are individual human beings, each with a distinctive face and voice, each with hopes and dreams, memories and regrets, friendships and marriages, loves lost and loves sustained.

‘The elderly’ have become another dehumanised group for which anything goes and for many that has resulted in cold disregard for their rights and their life. The distinctive face that Held talks about is designed to be deleted by masks until everyone is part of a faceless mass.

## **'War-zone' hospitals myth**

Again and again medical professionals have told me what was really going on and how hospitals 'overrun like war zones' according to the media were virtually empty. The mantra from medical whistleblowers was please don't use my name or my career is over. Citizen journalists around the world sneaked into hospitals to film evidence exposing the 'war-zone' lie. They really *were* largely empty with closed wards and operating theatres. I met a hospital worker in my town on the Isle of Wight during the first lockdown in 2020 who said the only island hospital had never been so quiet. Lockdown was justified by the psychopaths to stop hospitals being overrun. At the same time that the island hospital was near-empty the military arrived here to provide *extra beds*. It was all propaganda to ramp up the fear to ensure compliance with fascism as were never-used temporary hospitals with thousands of beds known as Nightingales and never-used make-shift mortuaries opened by the criminal UK government. A man who helped to install those extra island beds attributed to the army said they were never used and the hospital was empty. Doctors and nurses 'stood around talking or on their phones, wandering down to us to see what we were doing'. There were no masks or social distancing. He accused the useless local island paper, the *County Press*, of 'pumping the fear as if our hospital was overrun and we only have one so it should have been'. He described ambulances parked up with crews outside in deck chairs. When his brother called an ambulance he was told there was a two-hour backlog which he called 'bullshit'. An old lady on the island fell 'and was in a bad way', but a caller who rang for an ambulance was told the situation wasn't urgent enough. Ambulance stations were working under capacity while people would hear ambulances with sirens blaring driving through the streets. When those living near the stations realised what was going on they would follow them as they left, circulated around an urban area with the sirens going, and then came back without stopping. All this was to increase levels of fear and the same goes for the 'ventilator shortage crisis' that cost tens of millions for hastily produced ventilators never to be used.

Ambulance crews that agreed to be exploited in this way for fear propaganda might find themselves a mirror. I wish them well with that. Empty hospitals were the obvious consequence of treatment and diagnoses of non-'Covid' conditions cancelled and those involved handed a death sentence. People have been dying at home from undiagnosed and untreated cancer, heart disease and other life-threatening conditions to allow empty hospitals to deal with a 'pandemic' that wasn't happening.

## **Death of the innocent**

'War-zones' have been laying off nursing staff, even doctors where they can. There was no work for them. Lockdown was justified by saving lives and protecting the vulnerable they were actually killing with DNR orders and preventing empty hospitals being 'overrun'. In Britain the mantra of stay at home to 'save the NHS' was everywhere and across the world the same story was being sold when it was all lies. Two California doctors, Dan Erickson and Artin Massihi at Accelerated Urgent Care in Bakersfield, held a news conference in April, 2020, to say that intensive care units in California were 'empty, essentially', with hospitals shutting floors, not treating patients and laying off doctors. The California health system was working at minimum capacity 'getting rid of doctors because we just don't have the volume'. They said that people with conditions such as heart disease and cancer were not coming to hospital out of fear of 'Covid-19'. Their video was deleted by Susan Wojcicki's Cult-owned YouTube after reaching five million views. Florida governor Ron Desantis, who rejected the severe lockdowns of other states and is being targeted for doing so, said that in March, 2020, every US governor was given models claiming they would run out of hospital beds in days. That was never going to happen and the 'modellers' knew it. Deceit can be found at every level of the system. Urgent children's operations were cancelled including fracture repairs and biopsies to spot cancer. Eric Nicholls, a consultant paediatrician, said 'this is obviously concerning and we need to return to normal operating and to increase capacity as soon as possible'. Psychopaths

in power were rather less concerned *because* they are psychopaths. Deletion of urgent care and diagnosis has been happening all over the world and how many kids and others have died as a result of the actions of these cold and heartless lunatics dictating ‘health’ policy? The number must be stratospheric. Richard Sullivan, professor of cancer and global health at King’s College London, said people feared ‘Covid’ more than cancer such was the campaign of fear. ‘Years of lost life will be quite dramatic’, Sullivan said, with ‘a huge amount of avoidable mortality’. Sarah Woolnough, executive director for policy at Cancer Research UK, said there had been a 75 percent drop in urgent referrals to hospitals by family doctors of people with suspected cancer. Sullivan said that ‘a lot of services have had to scale back – we’ve seen a dramatic decrease in the amount of elective cancer surgery’. Lockdown deaths worldwide has been absolutely fantastic with the *New York Post* reporting how data confirmed that ‘lockdowns end more lives than they save’:

There was a sharp decline in visits to emergency rooms and an increase in fatal heart attacks because patients didn’t receive prompt treatment. Many fewer people were screened for cancer. Social isolation contributed to excess deaths from dementia and Alzheimer’s.

Researchers predicted that the social and economic upheaval would lead to tens of thousands of “deaths of despair” from drug overdoses, alcoholism and suicide. As unemployment surged and mental-health and substance-abuse treatment programs were interrupted, the reported levels of anxiety, depression and suicidal thoughts increased dramatically, as did alcohol sales and fatal drug overdoses.

This has been happening while nurses and other staff had so much time on their hands in the ‘war-zones’ that Tic-Tok dancing videos began appearing across the Internet with medical staff dancing around in empty wards and corridors as people died at home from causes that would normally have been treated in hospital.

## **Mentions in dispatches**

One brave and truth-committed whistleblower was Louise Hampton, a call handler with the UK NHS who made a viral Internet video saying she had done ‘fuck all’ during the ‘pandemic’

which was ‘a load of bollocks’. She said that ‘Covid-19’ was rebranded flu and of course she lost her job. This is what happens in the medical and endless other professions now when you tell the truth. Louise filmed inside ‘war-zone’ accident and emergency departments to show they were empty and I mean *empty* as in no one there. The mainstream media could have done the same and blown the gaff on the whole conspiracy. They haven’t to their eternal shame. Not that most ‘journalists’ seem capable of manifesting shame as with the psychopaths they slavishly repeat without question. The relative few who were admitted with serious health problems were left to die alone with no loved ones allowed to see them because of ‘Covid’ rules and they included kids dying without the comfort of mum and dad at their bedside while the evil behind this couldn’t give a damn. It was all good fun to them. A Scottish NHS staff nurse publicly quit in the spring of 2021 saying: ‘I can no longer be part of the lies and the corruption by the government.’ She said hospitals ‘aren’t full, the beds aren’t full, beds have been shut, wards have been shut’. Hospitals were never busy throughout ‘Covid’. The staff nurse said that Nicola Sturgeon, tragically the leader of the Scottish government, was on television saying save the hospitals and the NHS – ‘but the beds are empty’ and ‘we’ve not seen flu, we always see flu every year’. She wrote to government and spoke with her union Unison (the unions are Cult-compromised and *useless*, but nothing changed. Many of her colleagues were scared of losing their jobs if they spoke out as they wanted to. She said nursing staff were being affected by wearing masks all day and ‘my head is splitting every shift from wearing a mask’. The NHS is part of the fascist tyranny and must be dismantled so we can start again with human beings in charge. (Ironically, hospitals were reported to be busier again when official ‘Covid’ cases *fell* in spring/summer of 2021 and many other conditions required treatment at the same time as *the fake vaccine rollout*.)

I will cover the ‘Covid vaccine’ scam in detail later, but it is another indicator of the sickening disregard for human life that I am highlighting here. The DNA-manipulating concoctions do not fulfil

the definition of a ‘vaccine’, have never been used on humans before and were given only emergency approval because trials were not completed and they continued using the unknowing public. The result was what a NHS senior nurse with responsibility for ‘vaccine’ procedure said was ‘genocide’. She said the ‘vaccines’ were not ‘vaccines’. They had not been shown to be safe and claims about their effectiveness by drug companies were ‘poetic licence’. She described what was happening as a ‘horrid act of human annihilation’. The nurse said that management had instigated a policy of not providing a Patient Information Leaflet (PIL) before people were ‘vaccinated’ even though health care professionals are supposed to do this according to protocol. Patients should also be told that they are taking part in an ongoing clinical trial. Her challenges to what is happening had seen her excluded from meetings and ridiculed in others. She said she was told to ‘watch my step … or I would find myself surplus to requirements’. The nurse, who spoke anonymously in fear of her career, said she asked her NHS manager why he/she was content with taking part in genocide against those having the ‘vaccines’. The reply was that everyone had to play their part and to ‘put up, shut up, and get it done’. Government was ‘leaning heavily’ on NHS management which was clearly leaning heavily on staff. This is how the global ‘medical’ hierarchy operates and it starts with the Cult and its World Health Organization.

She told the story of a doctor who had the Pfizer jab and when questioned had no idea what was in it. The doctor had never read the literature. We have to stop treating doctors as intellectual giants when so many are moral and medical pygmies. The doctor did not even know that the ‘vaccines’ were not fully approved or that their trials were ongoing. They were, however, asking their patients if they minded taking part in follow-ups for research purposes – yes, the *ongoing clinical trial*. The nurse said the doctor’s ignorance was not rare and she had spoken to a hospital consultant who had the jab without any idea of the background or that the ‘trials’ had not been completed. Nurses and pharmacists had shown the same ignorance.

'My NHS colleagues have forsaken their duty of care, broken their code of conduct – Hippocratic Oath – and have been brainwashed just the same as the majority of the UK public through propaganda ...' She said she had not been able to recruit a single NHS colleague, doctor, nurse or pharmacist to stand with her and speak out. Her union had refused to help. She said that if the genocide came to light she would not hesitate to give evidence at a Nuremberg-type trial against those in power who could have affected the outcomes but didn't.

## **And all for what?**

To put the nonsense into perspective let's say the 'virus' does exist and let's go completely crazy and accept that the official manipulated figures for cases and deaths are accurate. *Even then* a study by Stanford University epidemiologist Dr John Ioannidis published on the World Health Organization website produced an average infection to fatality rate of ... 0.23 percent! Ioannidis said: 'If one could sample equally from all locations globally, the median infection fatality rate might even be substantially lower than the 0.23% observed in my analysis.' For healthy people under 70 it was ... 0.05 percent! This compares with the 3.4 percent claimed by the Cult-owned World Health Organization when the hoax was first played and maximum fear needed to be generated. An updated Stanford study in April, 2021, put the 'infection' to 'fatality' rate at just 0.15 percent. Another team of scientists led by Megan O'Driscoll and Henrik Salje studied data from 45 countries and published their findings on the Nature website. For children and young people the figure is so small it virtually does not register although authorities will be hyping dangers to the young when they introduce DNA-manipulating 'vaccines' for children. The O'Driscoll study produced an average infection-fatality figure of 0.003 for children from birth to four; 0.001 for 5 to 14; 0.003 for 15 to 19; and it was still only 0.456 up to 64. To claim that children must be 'vaccinated' to protect them from 'Covid' is an obvious lie and so there must be another reason and there is. What's more the average age of a 'Covid' death is akin

to the average age that people die in general. The average age of death in England is about 80 for men and 83 for women. The average age of death from alleged 'Covid' is between 82 and 83. California doctors, Dan Erickson and Artin Massihi, said at their April media conference that projection models of millions of deaths had been 'woefully inaccurate'. They produced detailed figures showing that Californians had a 0.03 chance of dying from 'Covid' based on the number of people who tested positive (with a test not testing for the 'virus'). Erickson said there was a 0.1 percent chance of dying from 'Covid' in the *state* of New York, not just the city, and a 0.05 percent chance in Spain, a centre of 'Covid-19' hysteria at one stage. The Stanford studies supported the doctors' data with fatality rate estimates of 0.23 and 0.15 percent. How close are these figures to my estimate of *zero*? Death-rate figures claimed by the World Health Organization at the start of the hoax were some 15 times higher. The California doctors said there was no justification for lockdowns and the economic devastation they caused. Everything they had ever learned about quarantine was that you quarantine the *sick* and not the healthy. They had never seen this before and it made no medical sense.

Why in the light of all this would governments and medical systems the world over say that billions must go under house arrest; lose their livelihood; in many cases lose their mind, their health and their life; force people to wear masks dangerous to health and psychology; make human interaction and even family interaction a criminal offence; ban travel; close restaurants, bars, watching live sport, concerts, theatre, and any activity involving human togetherness and discourse; and closing schools to isolate children from their friends and cause many to commit suicide in acts of hopelessness and despair? The California doctors said lockdown consequences included increased child abuse, partner abuse, alcoholism, depression, and other impacts they were seeing every day. Who would do that to the entire human race if not mentally-ill psychopaths of almost unimaginable extremes like Bill Gates? We must face the reality of what we are dealing with and come out of

denial. Fascism and tyranny are made possible only by the target population submitting and acquiescing to fascism and tyranny. The whole of human history shows that to be true. Most people naively and unquestioning believed what they were told about a ‘deadly virus’ and meekly and weakly submitted to house arrest. Those who didn’t believe it – at least in total – still submitted in fear of the consequences of not doing so. For the rest who wouldn’t submit draconian fines have been imposed, brutal policing by psychopaths *for* psychopaths, and condemnation from the meek and weak who condemn the Pushbackers on behalf of the very force that has them, too, in its gunsights. ‘Pathetic’ does not even begin to suffice.

Britain’s brainless ‘Health’ Secretary Matt Hancock warned anyone lying to border officials about returning from a list of ‘hotspot’ countries could face a jail sentence of up to ten years which is more than for racially-aggravated assault, incest and attempting to have sex with a child under 13. Hancock is a lunatic, but he has the state apparatus behind him in a Cult-led chain reaction and the same with UK ‘Vaccine Minister’ Nadhim Zahawi, a prominent member of the mega-Cult secret society, Le Cercle, which featured in my earlier books. The Cult enforces its will on governments and medical systems; government and medical systems enforce their will on business and police; business enforces its will on staff who enforce it on customers; police enforce the will of the Cult on the population and play their essential part in creating a world of fascist control that their own children and grandchildren will have to live in their entire lives. It is a hierarchical pyramid of imposition and acquiescence and, yes indeedy, of clinical insanity.

Does anyone bright enough to read this book have to ask what the answer is? I think not, but I will reveal it anyway in the fewest of syllables: Tell the psychos and their moronic lackeys to fuck off and let’s get on with our lives. We are many – They are few.

## CHAPTER SEVEN

### War on your mind

***One believes things because one has been conditioned to believe them***

**Aldous Huxley, *Brave New World***

I have described the ‘Covid’ hoax as a ‘Psyop’ and that is true in every sense and on every level in accordance with the definition of that term which is psychological warfare. Break down the ‘Covid pandemic’ to the foundation themes and it is psychological warfare on the human individual and collective mind.

The same can be said for the entire human belief system involving every subject you can imagine. Huxley was right in his contention that people believe what they are conditioned to believe and this comes from the repetition throughout their lives of the same falsehoods. They spew from government, corporations, media and endless streams of ‘experts’ telling you what the Cult wants you to believe and often believing it themselves (although *far* from always). ‘Experts’ are rewarded with ‘prestigious’ jobs and titles and as agents of perceptual programming with regular access to the media. The Cult has to control the narrative – control *information* – or they lose control of the vital, crucial, without-which-they-cannot-prevail public perception of reality. The foundation of that control today is the Internet made possible by the Defense Advanced Research Projects Agency (DARPA), the incredibly sinister technological arm of the Pentagon. The Internet is the result of military technology.

DARPA openly brags about establishing the Internet which has been a long-term project to lasso the minds of the global population. I have said for decades the plan is to control information to such an extreme that eventually no one would see or hear anything that the Cult does not approve. We are closing in on that end with ferocious censorship since the ‘Covid’ hoax began and in my case it started back in the 1990s in terms of books and speaking venues. I had to create my own publishing company in 1995 precisely because no one else would publish my books even then. I think they’re all still running.

## **Cult Internet**

To secure total control of information they needed the Internet in which pre-programmed algorithms can seek out ‘unclean’ content for deletion and even stop it being posted in the first place. The Cult had to dismantle print and non-Internet broadcast media to ensure the transfer of information to the appropriate-named ‘Web’ – a critical expression of the *Cult* web. We’ve seen the ever-quickenning demise of traditional media and control of what is left by a tiny number of corporations operating worldwide. Independent journalism in the mainstream is already dead and never was that more obvious than since the turn of 2020. The Cult wants all information communicated via the Internet to globally censor and allow the plug to be pulled any time. Lockdowns and forced isolation has meant that communication between people has been through electronic means and no longer through face-to-face discourse and discussion. Cult psychopaths have targeted the bars, restaurants, sport, venues and meeting places in general for this reason. None of this is by chance and it’s to stop people gathering in any kind of privacy or number while being able to track and monitor all Internet communications and block them as necessary. Even private messages between individuals have been censored by these fascists that control Cult fronts like Facebook, Twitter, Google and YouTube which are all officially run by Sabbatian place-people and from the background by higher-level Sabbatian place people.

Facebook, Google, Amazon and their like were seed-funded and supported into existence with money-no-object infusions of funds either directly or indirectly from DARPA and CIA technology arm In-Q-Tel. The Cult plays the long game and prepares very carefully for big plays like 'Covid'. Amazon is another front in the psychological war and pretty much controls the global market in book sales and increasingly publishing. Amazon's limitless funds have deleted fantastic numbers of independent publishers to seize global domination on the way to deciding which books can be sold and circulated and which cannot. Moves in that direction are already happening. Amazon's leading light Jeff Bezos is the grandson of Lawrence Preston Gise who worked with DARPA predecessor ARPA. Amazon has big connections to the CIA and the Pentagon. The plan I have long described went like this:

1. Employ military technology to establish the Internet.
2. Sell the Internet as a place where people can freely communicate without censorship and allow that to happen until the Net becomes the central and irreversible pillar of human society. If the Internet had been highly censored from the start many would have rejected it.
3. Fund and manipulate major corporations into being to control the circulation of information on your Internet using cover stories about geeks in garages to explain how they came about. Give them unlimited funds to expand rapidly with no need to make a profit for years while non-Cult companies who need to balance the books cannot compete. You know that in these circumstances your Googles, YouTubes, Facebooks and Amazons are going to secure near monopolies by either crushing or buying up the opposition.
4. Allow freedom of expression on both the Internet and communication platforms to draw people in until the Internet is the central and irreversible pillar of human society and your communication corporations have reached a stage of near monopoly domination.
5. Then unleash your always-planned frenzy of censorship on the basis of 'where else are you going to go?' and continue to expand that until nothing remains that the Cult does not want its human targets to see.

The process was timed to hit the 'Covid' hoax to ensure the best chance possible of controlling the narrative which they knew they had to do at all costs. They were, after all, about to unleash a 'deadly virus' that didn't really exist. If you do that in an environment of free-flowing information and opinion you would be dead in the

water before you could say Gates is a psychopath. The network was in place through which the Cult-created-and-owned World Health Organization could dictate the ‘Covid’ narrative and response policy slavishly supported by Cult-owned Internet communication giants and mainstream media while those telling a different story were censored. Google, YouTube, Facebook and Twitter openly announced that they would do this. What else would we expect from Cult-owned operations like Facebook which former executives have confirmed set out to make the platform more addictive than cigarettes and coldly manipulates emotions of its users to sow division between people and groups and scramble the minds of the young? If Zuckerberg lives out the rest of his life without going to jail for crimes against humanity, and most emphatically against the young, it will be a travesty of justice. Still, no matter, cause and effect will catch up with him eventually and the same with Sergey Brin and Larry Page at Google with its CEO Sundar Pichai who fix the Google search results to promote Cult narratives and hide the opposition. Put the same key words into Google and other search engines like DuckDuckGo and you will see how different results can be. Wikipedia is another intensely biased ‘encyclopaedia’ which skews its content to the Cult agenda. YouTube links to Wikipedia’s version of ‘Covid’ and ‘climate change’ on video pages in which experts in their field offer a different opinion (even that is increasingly rare with Wojcicki censorship). Into this ‘Covid’ silence-them network must be added government media censors, sorry ‘regulators’, such as Ofcom in the UK which imposed tyrannical restrictions on British broadcasters that had the effect of banning me from ever appearing. Just to debate with me about my evidence and views on ‘Covid’ would mean breaking the fascistic impositions of Ofcom and its CEO career government bureaucrat Melanie Dawes. Gutless British broadcasters tremble at the very thought of fascist Ofcom.

## **Psychos behind ‘Covid’**

The reason for the ‘Covid’ catastrophe in all its facets and forms can be seen by whom and what is driving the policies worldwide in such a coordinated way. Decisions are not being made to protect health, but to target psychology. The dominant group guiding and ‘advising’ government policy are not medical professionals. They are psychologists and behavioural scientists. Every major country has its own version of this phenomenon and I’ll use the British example to show how it works. In many ways the British version has been affecting the wider world in the form of the huge behaviour manipulation network in the UK which operates in other countries. The network involves private companies, government, intelligence and military. The Cabinet Office is at the centre of the government ‘Covid’ Psyop and part-owns, with ‘innovation charity’ Nesta, the Behavioural Insights Team (BIT) which claims to be independent of government but patently isn’t. The BIT was established in 2010 and its job is to manipulate the psyche of the population to acquiesce to government demands and so much more. It is also known as the ‘Nudge Unit’, a name inspired by the 2009 book by two ultra-Zionists, Cass Sunstein and Richard Thaler, called *Nudge: Improving Decisions About Health, Wealth, and Happiness*. The book, as with the Behavioural Insights Team, seeks to ‘nudge’ behaviour (manipulate it) to make the public follow patterns of action and perception that suit those in authority (the Cult). Sunstein is so skilled at this that he advises the World Health Organization and the UK Behavioural Insights Team and was Administrator of the White House Office of Information and Regulatory Affairs in the Obama administration. Biden appointed him to the Department of Homeland Security – another ultra-Zionist in the fold to oversee new immigration laws which is another policy the Cult wants to control. Sunstein is desperate to silence anyone exposing conspiracies and co-authored a 2008 report on the subject in which suggestions were offered to ban ‘conspiracy theorizing’ or impose ‘some kind of tax, financial or otherwise, on those who disseminate such theories’. I guess a psychiatrist’s chair is out of the question?

Sunstein's mate Richard Thaler, an 'academic affiliate' of the UK Behavioural Insights Team, is a proponent of 'behavioural economics' which is defined as the study of 'the effects of psychological, cognitive, emotional, cultural and social factors on the decisions of individuals and institutions'. Study the effects so they can be manipulated to be what you want them to be. Other leading names in the development of behavioural economics are ultra-Zionists Daniel Kahneman and Robert J. Shiller and they, with Thaler, won the Nobel Memorial Prize in Economic Sciences for their work in this field. The Behavioural Insights Team is operating at the heart of the UK government and has expanded globally through partnerships with several universities including Harvard, Oxford, Cambridge, University College London (UCL) and Pennsylvania. They claim to have 'trained' (reframed) 20,000 civil servants and run more than 750 projects involving 400 randomised controlled trials in dozens of countries' as another version of mind reframers Common Purpose. BIT works from its office in New York with cities and their agencies, as well as other partners, across the United States and Canada – this is a company part-owned by the British government Cabinet Office. An executive order by President Cult-servant Obama established a US Social and Behavioral Sciences Team in 2015. They all have the same reason for being and that's to brainwash the population directly and by brainwashing those in positions of authority.

### **'Covid' mind game**

Another prime aspect of the UK mind-control network is the 'independent' [joke] Scientific Pandemic Insights Group on Behaviours (SPI-B) which 'provides behavioural science advice aimed at anticipating and helping people adhere to interventions that are recommended by medical or epidemiological experts'. That means manipulating public perception and behaviour to do whatever government tells them to do. It's disgusting and if they really want the public to be 'safe' this lot should all be under lock and key. According to the government website SPI-B consists of

'behavioural scientists, health and social psychologists, anthropologists and historians' and advises the Whitty-Vallance-led Scientific Advisory Group for Emergencies (SAGE) which in turn advises the government on 'the science' (it doesn't) and 'Covid' policy. When politicians say they are being guided by 'the science' this is the rabble in each country they are talking about and that 'science' is dominated by behaviour manipulators to enforce government fascism through public compliance. The Behaviour Insight Team is headed by psychologist David Solomon Halpern, a visiting professor at King's College London, and connects with a national and global web of other civilian and military organisations as the Cult moves towards its goal of fusing them into one fascistic whole in every country through its 'Fusion Doctrine'. The behaviour manipulation network involves, but is not confined to, the Foreign Office; National Security Council; government communications headquarters (GCHQ); MI5; MI6; the Cabinet Office-based Media Monitoring Unit; and the Rapid Response Unit which 'monitors digital trends to spot emerging issues; including misinformation and disinformation; and identifies the best way to respond'.

There is also the 77th Brigade of the UK military which operates like the notorious Israeli military's Unit 8200 in manipulating information and discussion on the Internet by posing as members of the public to promote the narrative and discredit those who challenge it. Here we have the military seeking to manipulate *domestic* public opinion while the Nazis in government are fine with that. Conservative Member of Parliament Tobias Ellwood, an advocate of lockdown and control through 'vaccine passports', is a Lieutenant Colonel reservist in the 77th Brigade which connects with the military operation jHub, the 'innovation centre' for the Ministry of Defence and Strategic Command. jHub has also been involved with the civilian National Health Service (NHS) in 'symptom tracing' the population. The NHS is a key part of this mind control network and produced a document in December, 2020, explaining to staff how to use psychological manipulation with different groups and ages to get them to have the DNA-manipulating 'Covid vaccine'

that's designed to cumulatively rewrite human genetics. The document, called 'Optimising Vaccination Roll Out – Do's and Dont's for all messaging, documents and "communications" in the widest sense', was published by NHS England and the NHS Improvement *Behaviour Change Unit* in partnership with Public Health England and Warwick Business School. I hear the mantra about 'save the NHS' and 'protect the NHS' when we need to scrap the NHS and start again. The current version is far too corrupt, far too anti-human and totally compromised by Cult operatives and their assets. UK government broadcast media censor Ofcom will connect into this web – as will the BBC with its tremendous Ofcom influence – to control what the public see and hear and dictate mass perception. Nuremberg trials must include personnel from all these organisations.

## **The fear factor**

The 'Covid' hoax has led to the creation of the UK Cabinet Office-connected Joint Biosecurity Centre (JBC) which is officially described as providing 'expert advice on pandemics' using its independent [all Cult operations are 'independent'] analytical function to provide real-time analysis about infection outbreaks to identify and respond to outbreaks of Covid-19'. Another role is to advise the government on a response to spikes in infections – 'for example by closing schools or workplaces in local areas where infection levels have risen'. Put another way, promoting the Cult agenda. The Joint Biosecurity Centre is modelled on the Joint Terrorism Analysis Centre which analyses intelligence to set 'terrorism threat levels' and here again you see the fusion of civilian and military operations and intelligence that has led to military intelligence producing documents about 'vaccine hesitancy' and how it can be combated. Domestic civilian matters and opinions should not be the business of the military. The Joint Biosecurity Centre is headed by Tom Hurd, director general of the Office for Security and Counter-Terrorism from the establishment-to-its-fingertips Hurd family. His father is former Foreign Secretary Douglas Hurd. How coincidental that Tom

Hurd went to the elite Eton College and Oxford University with Boris Johnson. Imperial College with its ridiculous computer modeller Neil Ferguson will connect with this gigantic web that will itself interconnect with similar set-ups in other major and not so major countries. Compared with this Cult network the politicians, be they Boris Johnson, Donald Trump or Joe Biden, are bit-part players ‘following the science’. The network of psychologists was on the ‘Covid’ case from the start with the aim of generating maximum fear of the ‘virus’ to ensure compliance by the population. A government behavioural science group known as SPI-B produced a paper in March, 2020, for discussion by the main government science advisory group known as SAGE. It was headed ‘Options for increasing adherence to social distancing measures’ and it said the following in a section headed ‘Persuasion’:

- A substantial number of people still do not feel sufficiently personally threatened; it could be that they are reassured by the low death rate in their demographic group, although levels of concern may be rising. Having a good understanding of the risk has been found to be positively associated with adoption of COVID-19 social distancing measures in Hong Kong.
- The perceived level of personal threat needs to be increased among those who are complacent, using hard-hitting evaluation of options for increasing social distancing emotional messaging. To be effective this must also empower people by making clear the actions they can take to reduce the threat.
- Responsibility to others: There seems to be insufficient understanding of, or feelings of responsibility about, people’s role in transmitting the infection to others ... Messaging about actions need to be framed positively in terms of protecting oneself and the community, and increase confidence that they will be effective.
- Some people will be more persuaded by appeals to play by the rules, some by duty to the community, and some to personal risk.

All these different approaches are needed. The messaging also needs to take account of the realities of different people's lives. Messaging needs to take account of the different motivational levers and circumstances of different people.

All this could be achieved the SPI-B psychologists said by *using the media to increase the sense of personal threat* which translates as terrify the shit out of the population, including children, so they all do what we want. That's not happened has it? Those excuses for 'journalists' who wouldn't know journalism if it bit them on the arse (the great majority) have played their crucial part in serving this Cult-government Psyop to enslave their own kids and grandkids. How they live with themselves I have no idea. The psychological war has been underpinned by constant government 'Covid' propaganda in almost every television and radio ad break, plus the Internet and print media, which has pounded out the fear with taxpayers footing the bill for their own programming. The result has been people terrified of a 'virus' that doesn't exist or one with a tiny fatality rate even if you believe it does. People walk down the street and around the shops wearing face-nappies damaging their health and psychology while others report those who refuse to be that naïve to the police who turn up in their own face-nappies. I had a cameraman come to my flat and he was so frightened of 'Covid' he came in wearing a mask and refused to shake my hand in case he caught something. He had – naïveitis – and the thought that he worked in the mainstream media was both depressing and made his behaviour perfectly explainable. The fear which has gripped the minds of so many and frozen them into compliance has been carefully cultivated by these psychologists who are really psychopaths. If lives get destroyed and a lot of young people commit suicide it shows our plan is working. SPI-B then turned to compulsion on the public to comply. 'With adequate preparation, rapid change can be achieved', it said. Some countries had introduced mandatory self-isolation on a wide scale without evidence of major public unrest and a large majority of the UK's population appeared to be supportive of more coercive measures with 64 percent of adults saying they would

support putting London under a lockdown (watch the ‘polls’ which are designed to make people believe that public opinion is in favour or against whatever the subject in hand).

For ‘aggressive protective measures’ to be effective, the SPI-B paper said, special attention should be devoted to those population groups that are more at risk. Translated from the Orwellian this means making the rest of population feel guilty for not protecting the ‘vulnerable’ such as old people which the Cult and its agencies were about to kill on an industrial scale with lockdown, lack of treatment and the Gates ‘vaccine’. Psychopath psychologists sold their guilt-trip so comprehensively that Los Angeles County Supervisor Hilda Solis reported that children were apologising (from a distance) to their parents and grandparents for bringing ‘Covid’ into their homes and getting them sick. ‘... These apologies are just some of the last words that loved ones will ever hear as they die alone,’ she said. Gut-wrenchingly Solis then used this childhood tragedy to tell children to stay at home and ‘keep your loved ones alive’. Imagine heaping such potentially life-long guilt on a kid when it has absolutely nothing to do with them. These people are deeply disturbed and the psychologists behind this even more so.

## **Uncivil war – divide and rule**

Professional mind-controllers at SPI-B wanted the media to increase a sense of responsibility to others (do as you’re told) and promote ‘positive messaging’ for those actions while in contrast to invoke ‘social disapproval’ by the unquestioning, obedient, community of anyone with a mind of their own. Again the compliant Goebbels-like media obliged. This is an old, old, trick employed by tyrannies the world over throughout human history. You get the target population to keep the target population in line – *your* line. SPI-B said this could ‘play an important role in preventing anti-social behaviour or discouraging failure to enact pro-social behaviour’. For ‘anti-social’ in the Orwellian parlance of SPI-B see any behaviour that government doesn’t approve. SPI-B recommendations said that ‘social disapproval’ should be accompanied by clear messaging and

promotion of strong collective identity – hence the government and celebrity mantra of ‘we’re all in this together’. Sure we are. The mind doctors have such contempt for their targets that they think some clueless comedian, actor or singer telling them to do what the government wants will be enough to win them over. We have had UK comedian Lenny Henry, actor Michael Caine and singer Elton John wheeled out to serve the propagandists by urging people to have the DNA-manipulating ‘Covid’ non-‘vaccine’. The role of Henry and fellow black celebrities in seeking to coax a ‘vaccine’ reluctant black community into doing the government’s will was especially stomach-turning. An emotion-manipulating script and carefully edited video featuring these black ‘celebs’ was such an insult to the intelligence of black people and where’s the self-respect of those involved selling their souls to a fascist government agenda? Henry said he heard black people’s ‘legitimate worries and concerns’, but people must ‘trust the facts’ when they were doing exactly that by not having the ‘vaccine’. They had to include the obligatory reference to Black Lives Matter with the line ... ‘Don’t let coronavirus cost even more black lives – because we matter’. My god, it was pathetic. ‘I know the vaccine is safe and what it does.’ How? ‘I’m a comedian and it says so in my script.’

SPI-B said social disapproval needed to be carefully managed to avoid victimisation, scapegoating and misdirected criticism, but they knew that their ‘recommendations’ would lead to exactly that and the media were specifically used to stir-up the divide-and-conquer hostility. Those who conform like good little baa, baas, are praised while those who have seen through the tidal wave of lies are ‘Covidiots’. The awake have been abused by the fast asleep for not conforming to fascism and impositions that the awake know are designed to endanger their health, dehumanise them, and tear asunder the very fabric of human society. We have had the curtain-twitchers and morons reporting neighbours and others to the face-nappied police for breaking ‘Covid rules’ with fascist police delighting in posting links and phone numbers where this could be done. The Cult cannot impose its will without a compliant police

and military or a compliant population willing to play their part in enslaving themselves and their kids. The words of a pastor in Nazi Germany are so appropriate today:

First they came for the socialists and I did not speak out because I was not a socialist.

Then they came for the trade unionists and I did not speak out because I was not a trade unionist.

Then they came for the Jews and I did not speak out because I was not a Jew.

Then they came for me and there was no one left to speak for me.

Those who don't learn from history are destined to repeat it and so many are.

### **'Covid' rules: Rewiring the mind**

With the background laid out to this gigantic national and global web of psychological manipulation we can put 'Covid' rules into a clear and sinister perspective. Forget the claims about protecting health. 'Covid' rules are about dismantling the human mind, breaking the human spirit, destroying self-respect, and then putting Humpty Dumpty together again as a servile, submissive slave. Social isolation through lockdown and distancing have devastating effects on the human psyche as the psychological psychopaths well know and that's the real reason for them. Humans need contact with each other, discourse, closeness and touch, or they eventually, and literally, go crazy. Masks, which I will address at some length, fundamentally add to the effects of isolation and the Cult agenda to dehumanise and de-individualise the population. To do this while knowing – in fact *seeking* – this outcome is the very epitome of evil and psychologists involved in this *are* the epitome of evil. They must like all the rest of the Cult demons and their assets stand trial for crimes against humanity on a scale that defies the imagination. Psychopaths in uniform use isolation to break enemy troops and agents and make them subservient and submissive to tell what they know. The technique is rightly considered a form of torture and

torture is most certainly what has been imposed on the human population.

Clinically-insane American psychologist Harry Harlow became famous for his isolation experiments in the 1950s in which he separated baby monkeys from their mothers and imprisoned them for months on end in a metal container or ‘pit of despair’. They soon began to show mental distress and depression as any idiot could have predicted. Harlow put other monkeys in steel chambers for three, six or twelve months while denying them any contact with animals or humans. He said that the effects of total social isolation for six months were ‘so devastating and debilitating that we had assumed initially that twelve months of isolation would not produce any additional decrement’; but twelve months of isolation ‘almost obliterated the animals socially’. This is what the Cult and its psychopaths are doing to you and your children. Even monkeys in partial isolation in which they were not allowed to form relationships with other monkeys became ‘aggressive and hostile, not only to others, but also towards their own bodies’. We have seen this in the young as a consequence of lockdown. UK government psychopaths launched a public relations campaign telling people not to hug each other even after they received the ‘Covid-19 vaccine’ which we were told with more lies would allow a return to ‘normal life’. A government source told *The Telegraph*: ‘It will be along the lines that it is great that you have been vaccinated, but if you are going to visit your family and hug your grandchildren there is a chance you are going to infect people you love.’ The source was apparently speaking from a secure psychiatric facility. Janet Lord, director of Birmingham University’s Institute of Inflammation and Ageing, said that parents and grandparents should avoid hugging their children. Well, how can I put it, Ms Lord? Fuck off. Yep, that’ll do.

## **Destroying the kids – where are the parents?**

Observe what has happened to people enslaved and isolated by lockdown as suicide and self-harm has soared worldwide,

particularly among the young denied the freedom to associate with their friends. A study of 49,000 people in English-speaking countries concluded that almost half of young adults are at clinical risk of mental health disorders. A national survey in America of 1,000 currently enrolled high school and college students found that 5 percent reported attempting suicide during the pandemic. Data from the US CDC's National Syndromic Surveillance Program from January 1st to October 17th, 2020, revealed a 31 percent increase in mental health issues among adolescents aged 12 to 17 compared with 2019. The CDC reported that America in general suffered the biggest drop in life expectancy since World War Two as it fell by a year in the first half of 2020 as a result of 'deaths of despair' – overdoses and suicides. Deaths of despair have leapt by more than 20 percent during lockdown and include the highest number of fatal overdoses ever recorded in a single year – 81,000. Internet addiction is another consequence of being isolated at home which lowers interest in physical activities as kids fall into inertia and what's the point? Children and young people are losing hope and giving up on life, sometimes literally. A 14-year-old boy killed himself in Maryland because he had 'given up' when his school district didn't reopen; an 11-year-old boy shot himself during a zoom class; a teenager in Maine succumbed to the isolation of the 'pandemic' when he ended his life after experiencing a disrupted senior year at school. Children as young as nine have taken their life and all these stories can be repeated around the world. Careers are being destroyed before they start and that includes those in sport in which promising youngsters have not been able to take part. The plan of the psycho-psychologists is working all right. Researchers at Cambridge University found that lockdowns cause significant harm to children's mental health. Their study was published in the *Archives of Disease in Childhood*, and followed 168 children aged between 7 and 11. The researchers concluded:

During the UK lockdown, children's depression symptoms have increased substantially, relative to before lockdown. The scale of this effect has direct relevance for the continuation of different elements of lockdown policy, such as complete or partial school closures ...

... Specifically, we observed a statistically significant increase in ratings of depression, with a medium-to-large effect size. Our findings emphasise the need to incorporate the potential impact of lockdown on child mental health in planning the ongoing response to the global pandemic and the recovery from it.

Not a chance when the Cult's psycho-psychologists were getting exactly what they wanted. The UK's Royal College of Paediatrics and Child Health has urged parents to look for signs of eating disorders in children and young people after a three to four fold increase. Specialists say the 'pandemic' is a major reason behind the rise. You don't say. The College said isolation from friends during school closures, exam cancellations, loss of extra-curricular activities like sport, and an increased use of social media were all contributory factors along with fears about the virus (psycho-psychologists again), family finances, and students being forced to quarantine. Doctors said young people were becoming severely ill by the time they were seen with 'Covid' regulations reducing face-to-face consultations. Nor is it only the young that have been devastated by the psychopaths. Like all bullies and cowards the Cult is targeting the young, elderly, weak and infirm. A typical story was told by a British lady called Lynn Parker who was not allowed to visit her husband in 2020 for the last ten and half months of his life 'when he needed me most' between March 20th and when he died on December 19th. This vacates the criminal and enters the territory of evil. The emotional impact on the immune system alone is immense as are the number of people of all ages worldwide who have died as a result of Cult-demanded, Gates-demanded, lockdowns.

## **Isolation is torture**

The experience of imposing solitary confinement on millions of prisoners around the world has shown how a large percentage become 'actively psychotic and/or acutely suicidal'. Social isolation has been found to trigger 'a specific psychiatric syndrome, characterized by hallucinations; panic attacks; overt paranoia; diminished impulse control; hypersensitivity to external stimuli; and difficulties with thinking, concentration and memory'. Juan Mendez,

a United Nations rapporteur (investigator), said that isolation is a form of torture. Research has shown that even after isolation prisoners find it far more difficult to make social connections and I remember chatting to a shop assistant after one lockdown who told me that when her young son met another child again he had no idea how to act or what to do. Hannah Flanagan, Director of Emergency Services at Journey Mental Health Center in Dane County, Wisconsin, said: ‘The specificity about Covid social distancing and isolation that we’ve come across as contributing factors to the suicides are really new to us this year.’ But they are not new to those that devised them. They are getting the effect they want as the population is psychologically dismantled to be rebuilt in a totally different way. Children and the young are particularly targeted. They will be the adults when the full-on fascist AI-controlled technocracy is planned to be imposed and they are being prepared to meekly submit. At the same time older people who still have a memory of what life was like before – and how fascist the new normal really is – are being deleted. You are going to see efforts to turn the young against the old to support this geriatric genocide. Hannah Flanagan said the big increase in suicide in her county proved that social isolation is not only harmful, but deadly. Studies have shown that isolation from others is one of the main risk factors in suicide and even more so with women. Warnings that lockdown could create a ‘perfect storm’ for suicide were ignored. After all this was one of the *reasons* for lockdown. Suicide, however, is only the most extreme of isolation consequences. There are many others. Dr Dhruv Khullar, assistant professor of healthcare policy at Weill Cornell Medical College, said in a *New York Times* article in 2016 long before the fake ‘pandemic’:

A wave of new research suggests social separation is bad for us. Individuals with less social connection have disrupted sleep patterns, altered immune systems, more inflammation and higher levels of stress hormones. One recent study found that isolation increases the risk of heart disease by 29 percent and stroke by 32 percent. Another analysis that pooled data from 70 studies and 3.4 million people found that socially isolated individuals had a 30 percent higher risk of dying in the next seven years, and that this effect was largest in middle age.

Loneliness can accelerate cognitive decline in older adults, and isolated individuals are twice as likely to die prematurely as those with more robust social interactions. These effects start early: Socially isolated children have significantly poorer health 20 years later, even after controlling for other factors. All told, loneliness is as important a risk factor for early death as obesity and smoking.

There you have proof from that one article alone four years before 2020 that those who have enforced lockdown, social distancing and isolation knew what the effect would be and that is even more so with professional psychologists that have been driving the policy across the globe. We can go back even further to the years 2000 and 2003 and the start of a major study on the effects of isolation on health by Dr Janine Gronewold and Professor Dirk M. Hermann at the University Hospital in Essen, Germany, who analysed data on 4,316 people with an average age of 59 who were recruited for the long-term research project. They found that socially isolated people are more than 40 percent more likely to have a heart attack, stroke, or other major cardiovascular event and nearly 50 percent more likely to die from any cause. Given the financial Armageddon unleashed by lockdown we should note that the study found a relationship between increased cardiovascular risk and lack of financial support. After excluding other factors social isolation was still connected to a 44 percent increased risk of cardiovascular problems and a 47 percent increased risk of death by any cause. Lack of financial support was associated with a 30 percent increase in the risk of cardiovascular health events. Dr Gronewold said it had been known for some time that feeling lonely or lacking contact with close friends and family can have an impact on physical health and the study had shown that having strong social relationships is of high importance for heart health. Gronewold said they didn't understand yet why people who are socially isolated have such poor health outcomes, but this was obviously a worrying finding, particularly during these times of prolonged social distancing. Well, it can be explained on many levels. You only have to identify the point in the body where people feel loneliness and missing people they are parted from – it's in the centre of the chest where they feel the ache of loneliness and the ache of missing people. 'My heart aches for

you' ... 'My heart aches for some company.' I will explain this more in the chapter Escaping Wetiko, but when you realise that the body is the mind – they are expressions of each other – the reason why state of the mind dictates state of the body becomes clear.

American psychologist Ranjit Powar was highlighting the effects of lockdown isolation as early as April, 2020. She said humans have evolved to be social creatures and are wired to live in interactive groups. Being isolated from family, friends and colleagues could be unbalancing and traumatic for most people and could result in short or even long-term psychological and physical health problems. An increase in levels of anxiety, aggression, depression, forgetfulness and hallucinations were possible psychological effects of isolation. 'Mental conditions may be precipitated for those with underlying pre-existing susceptibilities and show up in many others without any pre-condition.' Powar said personal relationships helped us cope with stress and if we lost this outlet for letting off steam the result can be a big emotional void which, for an average person, was difficult to deal with. 'Just a few days of isolation can cause increased levels of anxiety and depression' – so what the hell has been the effect on the global population of *18 months* of this at the time of writing? Powar said: 'Add to it the looming threat of a dreadful disease being repeatedly hammered in through the media and you have a recipe for many shades of mental and physical distress.' For those with a house and a garden it is easy to forget that billions have had to endure lockdown isolation in tiny overcrowded flats and apartments with nowhere to go outside. The psychological and physical consequences of this are unimaginable and with lunatic and abusive partners and parents the consequences have led to tremendous increases in domestic and child abuse and alcoholism as people seek to shut out the horror. Ranjit Powar said:

Staying in a confined space with family is not all a rosy picture for everyone. It can be extremely oppressive and claustrophobic for large low-income families huddled together in small single-room houses. Children here are not lucky enough to have many board/electronic games or books to keep them occupied.

Add to it the deep insecurity of running out of funds for food and basic necessities. On the other hand, there are people with dysfunctional family dynamics, such as domineering, abusive or alcoholic partners, siblings or parents which makes staying home a period of trial. Incidence of suicide and physical abuse against women has shown a worldwide increase. Heightened anxiety and depression also affect a person's immune system, making them more susceptible to illness.

To think that Powar's article was published on April 11th, 2020.

## **Six-feet fantasy**

Social (unsocial) distancing demanded that people stay six feet or two metres apart. UK government advisor Robert Dingwall from the New and Emerging Respiratory Virus Threats Advisory Group said in a radio interview that the two-metre rule was 'conjured up out of nowhere' and was not based on science. No, it was not based on *medical* science, but it didn't come out of nowhere. The distance related to *psychological* science. Six feet/two metres was adopted in many countries and we were told by people like the criminal Anthony Fauci and his ilk that it was founded on science. Many schools could not reopen because they did not have the space for six-feet distancing. Then in March, 2021, after a year of six-feet 'science', a study published in the *Journal of Infectious Diseases* involving more than 500,000 students and almost 100,000 staff over 16 weeks revealed no significant difference in 'Covid' cases between six feet and three feet and Fauci changed his tune. Now three feet was okay. There is no difference between six feet and three *inches* when there is no 'virus' and they got away with six feet for psychological reasons for as long as they could. I hear journalists and others talk about 'unintended consequences' of lockdown. They are not *unintended* at all; they have been coldly-calculated for a specific outcome of human control and that's why super-psychopaths like Gates have called for them so vehemently. Super-psychopath psychologists have demanded them and psychopathic or clueless, spineless, politicians have gone along with them by 'following the science'. But it's not science at all. 'Science' is not what is; it's only what people can be manipulated to believe it is. The whole 'Covid' catastrophe is

founded on mind control. Three word or three statement mantras issued by the UK government are a well-known mind control technique and so we've had 'Stay home/protect the NHS/save lives', 'Stay alert/control the virus/save lives' and 'hands/face/space'. One of the most vocal proponents of extreme 'Covid' rules in the UK has been Professor Susan Michie, a member of the British Communist Party, who is not a medical professional. Michie is the director of the Centre for Behaviour Change at University College London. She is a *behavioural psychologist* and another filthy rich 'Marxist' who praised China's draconian lockdown. She was known by fellow students at Oxford University as 'Stalin's nanny' for her extreme Marxism. Michie is an influential member of the UK government's Scientific Advisory Group for Emergencies (SAGE) and behavioural manipulation groups which have dominated 'Covid' policy. She is a consultant adviser to the World Health Organization on 'Covid-19' and behaviour. Why the hell are lockdowns anything to do with her when they are claimed to be about health? Why does a behavioural psychologist from a group charged with changing the behaviour of the public want lockdown, human isolation and mandatory masks? Does that question really need an answer? Michie *absolutely* has to explain herself before a Nuremberg court when humanity takes back its world again and even more so when you see the consequences of masks that she demands are compulsory. This is a Michie classic:

The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Those words alone should carry a prison sentence when you ponder on the callous disregard for children involved and what a statement it makes about the mind and motivations of Susan Michie. What a lovely lady and what she said there encapsulates the mentality of the psychopaths behind the 'Covid' horror. Let us compare what Michie said with a countrywide study in Germany published at [researchsquare.com](https://www.researchsquare.com) involving 25,000 school children and 17,854 health complaints submitted by parents. Researchers

found that masks are harming children physically, psychologically, and behaviourally with 24 health issues associated with mask wearing. They include: shortness of breath (29.7%); dizziness (26.4%); increased headaches (53%); difficulty concentrating (50%); drowsiness or fatigue (37%); and malaise (42%). Nearly a third of children experienced more sleep issues than before and a quarter developed new fears. Researchers found health issues and other impairments in 68 percent of masked children covering their faces for an average of 4.5 hours a day. Hundreds of those taking part experienced accelerated respiration, tightness in the chest, weakness, and short-term impairment of consciousness. A reminder of what Michie said again:

The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Psychopaths in government and psychology now have children and young people – plus all the adults – wearing masks for hours on end while clueless teachers impose the will of the psychopaths on the young they should be protecting. What the hell are parents doing?

## **Cult lab rats**

We have some schools already imposing on students microchipped buzzers that activate when they get ‘too close’ to their pals in the way they do with lab rats. How apt. To the Cult and its brain-dead servants our children *are* lab rats being conditioned to be unquestioning, dehumanised slaves for the rest of their lives. Children and young people are being weaned and frightened away from the most natural human instincts including closeness and touch. I have tracked in the books over the years how schools were banning pupils from greeting each other with a hug and the whole Cult-induced Me Too movement has terrified men and boys from a relaxed and natural interaction with female friends and work colleagues to the point where many men try never to be in a room

alone with a woman that's not their partner. Airhead celebrities have as always played their virtue-signalling part in making this happen with their gross exaggeration. For every monster like Harvey Weinstein there are at least tens of thousands of men that don't treat women like that; but everyone must be branded the same and policy changed for them as well as the monster. I am going to be using the word 'dehumanise' many times in this chapter because that is what the Cult is seeking to do and it goes very deep as we shall see. Don't let them kid you that social distancing is planned to end one day. That's not the idea. We are seeing more governments and companies funding and producing wearable gadgets to keep people apart and they would not be doing that if this was meant to be short-term. A tech start-up company backed by GCHQ, the British Intelligence and military surveillance headquarters, has created a social distancing wrist sensor that alerts people when they get too close to others. The CIA has also supported tech companies developing similar devices. The wearable sensor was developed by Tended, one of a number of start-up companies supported by GCHQ (see the CIA and DARPA). The device can be worn on the wrist or as a tag on the waistband and will vibrate whenever someone wearing the device breaches social distancing and gets anywhere near natural human contact. The company had a lucky break in that it was developing a distancing sensor when the 'Covid' hoax arrived which immediately provided a potentially enormous market. How fortunate. The government in big-time Cult-controlled Ontario in Canada is investing \$2.5 million in wearable contact tracing technology that 'will alert users if they may have been exposed to the Covid-19 in the workplace and will beep or vibrate if they are within six feet of another person'. Facedrive Inc., the technology company behind this, was founded in 2016 with funding from the Ontario Together Fund and obviously they, too, had a prophet on the board of directors. The human surveillance and control technology is called TraceSCAN and would be worn by the human cyborgs in places such as airports, workplaces, construction sites, care homes and ... *schools*.

I emphasise schools with children and young people the prime targets. You know what is planned for society as a whole if you keep your eyes on the schools. They have always been places where the state program the next generation of slaves to be its compliant worker-ants – or Woker-ants these days; but in the mist of the ‘Covid’ madness they have been transformed into mind laboratories on a scale never seen before. Teachers and head teachers are just as programmed as the kids – often more so. Children are kept apart from human interaction by walk lanes, classroom distancing, staggered meal times, masks, and the rolling-out of buzzer systems. Schools are now physically laid out as a laboratory maze for lab-rats. Lunatics at a school in Anchorage, Alaska, who should be prosecuted for child abuse, took away desks and forced children to kneel (know your place) on a mat for five hours a day while wearing a mask and using their chairs as a desk. How this was supposed to impact on a ‘virus’ only these clinically insane people can tell you and even then it would be clap-trap. The school banned recess (interaction), art classes (creativity), and physical exercise (getting body and mind moving out of inertia). Everyone behind this outrage should be in jail or better still a mental institution. The behavioural manipulators are all for this dystopian approach to schools.

Professor Susan Michie, the mind-doctor and British Communist Party member, said it was wrong to say that schools were safe. They had to be made so by ‘distancing’, masks and ventilation (sitting all day in the cold). I must ask this lady round for dinner on a night I know I am going to be out and not back for weeks. She probably wouldn’t be able to make it, anyway, with all the visits to her own psychologist she must have block-booked.

## **Masking identity**

I know how shocking it must be for you that a behaviour manipulator like Michie wants everyone to wear masks which have long been a feature of mind-control programs like the infamous MKUltra in the United States, but, there we are. We live and learn. I spent many years from 1996 to right across the millennium

researching mind control in detail on both sides of the Atlantic and elsewhere. I met a large number of mind-control survivors and many had been held captive in body and mind by MKUltra. MK stands for mind-control, but employs the German spelling in deference to the Nazis spirited out of Germany at the end of World War Two by Operation Paperclip in which the US authorities, with help from the Vatican, transported Nazi mind-controllers and engineers to America to continue their work. Many of them were behind the creation of NASA and they included Nazi scientist and SS officer Wernher von Braun who swapped designing V-2 rockets to bombard London with designing the Saturn V rockets that powered the NASA moon programme's Apollo craft. I think I may have mentioned that the Cult has no borders. Among Paperclip escapees was Josef Mengele, the Angel of Death in the Nazi concentration camps where he conducted mind and genetic experiments on children often using twins to provide a control twin to measure the impact of his 'work' on the other. If you want to observe the Cult mentality in all its extremes of evil then look into the life of Mengele. I have met many people who suffered mercilessly under Mengele in the United States where he operated under the name Dr Greene and became a stalwart of MKUltra programming and torture. Among his locations was the underground facility in the Mojave Desert in California called the China Lake Naval Weapons Station which is almost entirely below the surface. My books *The Biggest Secret*, *Children of the Matrix* and *The Perception Deception* have the detailed background to MKUltra.

The best-known MKUltra survivor is American Cathy O'Brien. I first met her and her late partner Mark Phillips at a conference in Colorado in 1996. Mark helped her escape and deprogram from decades of captivity in an offshoot of MKUltra known as Project Monarch in which 'sex slaves' were provided for the rich and famous including Father George Bush, Dick Cheney and the Clintons. Read Cathy and Mark's book *Trance-Formation of America* and if you are new to this you will be shocked to the core. I read it in 1996 shortly before, with the usual synchronicity of my life, I found

myself given a book table at the conference right next to hers. MKUltra never ended despite being very publicly exposed (only a small part of it) in the 1970s and continues in other guises. I am still in touch with Cathy. She contacted me during 2020 after masks became compulsory in many countries to tell me how they were used as part of MKUltra programming. I had been observing 'Covid regulations' and the relationship between authority and public for months. I saw techniques that I knew were employed on individuals in MKUltra being used on the global population. I had read many books and manuals on mind control including one called *Silent Weapons for Quiet Wars* which came to light in the 1980s and was a guide on how to perceptually program on a mass scale. 'Silent Weapons' refers to mind-control. I remembered a line from the manual as governments, medical authorities and law enforcement agencies have so obviously talked to – or rather at – the adult population since the 'Covid' hoax began as if they are children. The document said:

If a person is spoken to by a T.V. advertiser as if he were a twelve-year-old, then, due to suggestibility, he will, with a certain probability, respond or react to that suggestion with the uncritical response of a twelve-year-old and will reach in to his economic reservoir and deliver its energy to buy that product on impulse when he passes it in the store.

That's why authority has spoken to adults like children since all this began.

### **Why did Michael Jackson wear masks?**

Every aspect of the 'Covid' narrative has mind-control as its central theme. Cathy O'Brien wrote an article for [davidicke.com](http://davidicke.com) about the connection between masks and mind control. Her daughter Kelly who I first met in the 1990s was born while Cathy was still held captive in MKUltra. Kelly was forced to wear a mask as part of her programming from the age of *two* to dehumanise her, target her sense of individuality and reduce the amount of oxygen her brain and body received. *Bingo*. This is the real reason for compulsory

masks, why they have been enforced en masse, and why they seek to increase the number they demand you wear. First one, then two, with one disgraceful alleged ‘doctor’ recommending four which is nothing less than a death sentence. Where and how often they must be worn is being expanded for the purpose of mass mind control and damaging respiratory health which they can call ‘Covid-19’. Canada’s government headed by the man-child Justin Trudeau, says it’s fine for children of two and older to wear masks. An insane ‘study’ in Italy involving just 47 children concluded there was no problem for babies as young as *four months* wearing them. Even after people were ‘vaccinated’ they were still told to wear masks by the criminal that is Anthony Fauci. Cathy wrote that mandating masks is allowing the authorities literally to control the air we breathe which is what was done in MKUltra. You might recall how the singer Michael Jackson wore masks and there is a reason for that. He was subjected to MKUltra mind control through Project Monarch and his psyche was scrambled by these simpletons. Cathy wrote:

In MKUltra Project Monarch mind control, Michael Jackson had to wear a mask to silence his voice so he could not reach out for help. Remember how he developed that whisper voice when he wasn’t singing? Masks control the mind from the outside in, like the redefining of words is doing. By controlling what we can and cannot say for fear of being labeled racist or beaten, for example, it ultimately controls thought that drives our words and ultimately actions (or lack thereof).

Likewise, a mask muffles our speech so that we are not heard, which controls voice ... words ... mind. This is Mind Control. Masks are an obvious mind control device, and I am disturbed so many people are complying on a global scale. Masks depersonalize while making a person feel as though they have no voice. It is a barrier to others. People who would never choose to comply but are forced to wear a mask in order to keep their job, and ultimately their family fed, are compromised. They often feel shame and are subdued. People have stopped talking with each other while media controls the narrative.

The ‘no voice’ theme has often become literal with train passengers told not to speak to each other in case they pass on the ‘virus’, singing banned for the same reason and bonkers California officials telling people riding roller coasters that they cannot shout and scream. Cathy said she heard every day from healed MKUltra survivors who cannot wear a mask without flashing back on ways

their breathing was controlled – ‘from ball gags and penises to water boarding’. She said that through the years when she saw images of people in China wearing masks ‘due to pollution’ that it was really to control their oxygen levels. ‘I knew it was as much of a population control mechanism of depersonalisation as are burkas’, she said. Masks are another Chinese communist/fascist method of control that has been swept across the West as the West becomes China at lightning speed since we entered 2020.

## **Mask-19**

There are other reasons for mandatory masks and these include destroying respiratory health to call it ‘Covid-19’ and stunting brain development of children and the young. Dr Margarite Griesz-Brisson MD, PhD, is a Consultant Neurologist and Neurophysiologist and the Founder and Medical Director of the London Neurology and Pain Clinic. Her CV goes down the street and round the corner. She is clearly someone who cares about people and won’t parrot the propaganda. Griesz-Brisson has a PhD in pharmacology, with special interest in neurotoxicology, environmental medicine, neuroregeneration and neuroplasticity (the way the brain can change in the light of information received). She went public in October, 2020, with a passionate warning about the effects of mask-wearing laws:

The reinhalation of our exhaled air will without a doubt create oxygen deficiency and a flooding of carbon dioxide. We know that the human brain is very sensitive to oxygen deprivation. There are nerve cells for example in the hippocampus that can’t be longer than 3 minutes without oxygen – they cannot survive. The acute warning symptoms are headaches, drowsiness, dizziness, issues in concentration, slowing down of reaction time – reactions of the cognitive system.

Oh, I know, let’s tell bus, truck and taxi drivers to wear them and people working machinery. How about pilots, doctors and police? Griesz-Brisson makes the important point that while the symptoms she mentions may fade as the body readjusts this does not alter the fact that people continue to operate in oxygen deficit with long list of

potential consequences. She said it was well known that neurodegenerative diseases take years or decades to develop. 'If today you forget your phone number, the breakdown in your brain would have already started 20 or 30 years ago.' She said degenerative processes in your brain are getting amplified as your oxygen deprivation continues through wearing a mask. Nerve cells in the brain are unable to divide themselves normally in these circumstances and lost nerve cells will no longer be regenerated. 'What is gone is gone.' Now consider that people like shop workers and *schoolchildren* are wearing masks for hours every day. What in the name of sanity is going to be happening to them? 'I do not wear a mask, I need my brain to think', Griesz-Brisson said, 'I want to have a clear head when I deal with my patients and not be in a carbon dioxide-induced anaesthesia'. If you are told to wear a mask anywhere ask the organisation, police, store, whatever, for their risk assessment on the dangers and negative effects on mind and body of enforcing mask-wearing. They won't have one because it has never been done not even by government. All of them must be subject to class-action lawsuits as the consequences come to light. They don't do mask risk assessments for an obvious reason. They know what the conclusions would be and independent scientific studies that *have* been done tell a horror story of consequences.

### **'Masks are criminal'**

Dr Griesz-Brisson said that for children and adolescents, masks are an absolute no-no. They had an extremely active and adaptive immune system and their brain was incredibly active with so much to learn. 'The child's brain, or the youth's brain, is thirsting for oxygen.' The more metabolically active an organ was, the more oxygen it required; and in children and adolescents every organ was metabolically active. Griesz-Brisson said that to deprive a child's or adolescent's brain of oxygen, or to restrict it in any way, was not only dangerous to their health, it was absolutely criminal. 'Oxygen deficiency inhibits the development of the brain, and the damage that has taken place as a result CANNOT be reversed.' Mind

manipulators of MKUltra put masks on two-year-olds they wanted to neurologically rewire and you can see why. Griesz-Brisson said a child needs the brain to learn and the brain needs oxygen to function. 'We don't need a clinical study for that. This is simple, indisputable physiology.' Consciously and purposely induced oxygen deficiency was an absolutely deliberate health hazard, and an absolute medical contraindication which means that 'this drug, this therapy, this method or measure should not be used, and is not allowed to be used'. To coerce an entire population to use an absolute medical contraindication by force, she said, there had to be definite and serious reasons and the reasons must be presented to competent interdisciplinary and independent bodies to be verified and authorised. She had this warning of the consequences that were coming if mask wearing continued:

When, in ten years, dementia is going to increase exponentially, and the younger generations couldn't reach their god-given potential, it won't help to say 'we didn't need the masks'. I know how damaging oxygen deprivation is for the brain, cardiologists know how damaging it is for the heart, pulmonologists know how damaging it is for the lungs. Oxygen deprivation damages every single organ. Where are our health departments, our health insurance, our medical associations? It would have been their duty to be vehemently against the lockdown and to stop it and stop it from the very beginning.

Why do the medical boards issue punishments to doctors who give people exemptions? Does the person or the doctor seriously have to prove that oxygen deprivation harms people? What kind of medicine are our doctors and medical associations representing? Who is responsible for this crime? The ones who want to enforce it? The ones who let it happen and play along, or the ones who don't prevent it?

All of the organisations and people she mentions there either answer directly to the Cult or do whatever hierarchical levels above them tell them to do. The outcome of both is the same. 'It's not about masks, it's not about viruses, it's certainly not about your health', Griesz-Brisson said. 'It is about much, much more. I am not participating. I am not afraid.' They were taking our air to breathe and there was no unfounded medical exemption from face masks. Oxygen deprivation was dangerous for every single brain. It had to be the free decision of every human being whether they want to

wear a mask that was absolutely ineffective to protect themselves from a virus. She ended by rightly identifying where the responsibility lies for all this:

The imperative of the hour is personal responsibility. We are responsible for what we think, not the media. We are responsible for what we do, not our superiors. We are responsible for our health, not the World Health Organization. And we are responsible for what happens in our country, not the government.

Halle-bloody-lujah.

## **But surgeons wear masks, right?**

Independent studies of mask-wearing have produced a long list of reports detailing mental, emotional and physical dangers. What a definition of insanity to see police officers imposing mask-wearing on the public which will cumulatively damage their health while the police themselves wear masks that will cumulatively damage *their* health. It's utter madness and both public and police do this because 'the government says so' – yes a government of brain-donor idiots like UK Health Secretary Matt Hancock reading the 'follow the science' scripts of psychopathic, lunatic psychologists. The response you get from Stockholm syndrome sufferers defending the very authorities that are destroying them and their families is that 'surgeons wear masks'. This is considered the game, set and match that they must work and don't cause oxygen deficit. Well, actually, scientific studies have shown that they *do* and oxygen levels are monitored in operating theatres to compensate. Surgeons wear masks to stop spittle and such like dropping into open wounds – not to stop 'viral particles' which are so minuscule they can only be seen through an electron microscope. Holes in the masks are significantly bigger than 'viral particles' and if you sneeze or cough they will breach the mask. I watched an incredibly disingenuous 'experiment' that claimed to prove that masks work in catching 'virus' material from the mouth and nose. They did this with a slow motion camera and the mask did block big stuff which stayed inside the mask and

against the face to be breathed in or cause infections on the face as we have seen with many children. ‘Viral particles’, however, would never have been picked up by the camera as they came through the mask when they are far too small to be seen. The ‘experiment’ was therefore disingenuous *and* useless.

Studies have concluded that wearing masks in operating theatres (and thus elsewhere) make no difference to preventing infection while the opposite is true with toxic shite building up in the mask and this had led to an explosion in tooth decay and gum disease dubbed by dentists ‘mask mouth’. You might have seen the Internet video of a furious American doctor urging people to take off their masks after a four-year-old patient had been rushed to hospital the night before and nearly died with a lung infection that doctors sourced to mask wearing. A study in the journal *Cancer Discovery* found that inhalation of harmful microbes can contribute to advanced stage lung cancer in adults and long-term use of masks can help breed dangerous pathogens. Microbiologists have said frequent mask wearing creates a moist environment in which microbes can grow and proliferate before entering the lungs. The Canadian Agency for Drugs and Technologies in Health, or CADTH, a Canadian national organisation that provides research and analysis to healthcare decision-makers, said this as long ago as 2013 in a report entitled ‘Use of Surgical Masks in the Operating Room: A Review of the Clinical Effectiveness and Guidelines’. It said:

- No evidence was found to support the use of surgical face masks to reduce the frequency of surgical site infections
- No evidence was found on the effectiveness of wearing surgical face masks to protect staff from infectious material in the operating room.
- Guidelines recommend the use of surgical face masks by staff in the operating room to protect both operating room staff and patients (despite the lack of evidence).

We were told that the world could go back to ‘normal’ with the arrival of the ‘vaccines’. When they came, fraudulent as they are, the story changed as I knew that it would. We are in the midst of transforming ‘normal’, not going back to it. Mary Ramsay, head of immunisation at Public Health England, echoed the words of US criminal Anthony Fauci who said masks and other regulations must stay no matter if people are vaccinated. The Fauci idiot continued to wear two masks – different colours so both could be clearly seen – after he *claimed* to have been vaccinated. Senator Rand Paul told Fauci in one exchange that his double-masks were ‘theatre’ and he was right. It’s all theatre. Mary Ramsay back-tracked on the vaccine-return-to-normal theme when she said the public may need to wear masks and social-distance for years despite the jabs. ‘People have got used to those lower-level restrictions now, and [they] can live with them’, she said telling us what the idea has been all along. ‘The vaccine does not give you a pass, even if you have had it, you must continue to follow all the guidelines’ said a Public Health England statement which reneged on what we had been told before and made having the ‘vaccine’ irrelevant to ‘normality’ even by the official story. Spain’s fascist government trumped everyone by passing a law mandating the wearing of masks on the beach and even when swimming in the sea. The move would have devastated what’s left of the Spanish tourist industry, posed potential breathing dangers to swimmers and had Northern European sunbathers walking around with their forehead brown and the rest of their face white as a sheet. The ruling was so crazy that it had to be retracted after pressure from public and tourist industry, but it confirmed where the Cult wants to go with masks and how clinically insane authority has become. The determination to make masks permanent and hide the serious dangers to body and mind can be seen in the censorship of scientist Professor Denis Rancourt by Bill Gates-funded academic publishing website ResearchGate over his papers exposing the dangers and uselessness of masks. Rancourt said:

ResearchGate today has permanently locked my account, which I have had since 2015. Their reasons graphically show the nature of their attack against democracy, and their corruption of

science ... By their obscene non-logic, a scientific review of science articles reporting on harms caused by face masks has a 'potential to cause harm'. No criticism of the psychological device (face masks) is tolerated, if the said criticism shows potential to influence public policy.

This is what happens in a fascist world.

## **Where are the 'greens' (again)?**

Other dangers of wearing masks especially regularly relate to the inhalation of minute plastic fibres into the lungs and the deluge of discarded masks in the environment and oceans. Estimates predicted that more than 1.5 billion disposable masks will end up in the world's oceans every year polluting the water with tons of plastic and endangering marine wildlife. Studies project that humans are using 129 billion face masks each month worldwide – about three million a minute. Most are disposable and made from plastic, non-biodegradable microfibers that break down into smaller plastic particles that become widespread in ecosystems. They are littering cities, clogging sewage channels and turning up in bodies of water. I have written in other books about the immense amounts of microplastics from endless sources now being absorbed into the body. Rolf Halden, director of the Arizona State University (ASU) Biodesign Center for Environmental Health Engineering, was the senior researcher in a 2020 study that analysed 47 human tissue samples and found microplastics in all of them. 'We have detected these chemicals of plastics in every single organ that we have investigated', he said. I wrote in *The Answer* about the world being deluged with microplastics. A study by the Worldwide Fund for Nature (WWF) found that people are consuming on average every week some 2,000 tiny pieces of plastic mostly through water and also through marine life and the air. Every year humans are ingesting enough microplastics to fill a heaped dinner plate and in a life-time of 79 years it is enough to fill two large waste bins. Marco Lambertini, WWF International director general said: 'Not only are plastics polluting our oceans and waterways and killing marine life – it's in all of us and we can't escape consuming plastics,' American

geologists found tiny plastic fibres, beads and shards in rainwater samples collected from the remote slopes of the Rocky Mountain National Park near Denver, Colorado. Their report was headed: 'It is raining plastic.' Rachel Adams, senior lecturer in Biomedical Science at Cardiff Metropolitan University, said that among health consequences are internal inflammation and immune responses to a 'foreign body'. She further pointed out that microplastics become carriers of toxins including mercury, pesticides and dioxins (a known cause of cancer and reproductive and developmental problems). These toxins accumulate in the fatty tissues once they enter the body through microplastics. Now this is being compounded massively by people putting plastic on their face and throwing it away.

Workers exposed to polypropylene plastic fibres known as 'flock' have developed 'flock worker's lung' from inhaling small pieces of the flock fibres which can damage lung tissue, reduce breathing capacity and exacerbate other respiratory problems. Now ... commonly used surgical masks have three layers of melt-blown textiles made of ... polypropylene. We have billions of people putting these microplastics against their mouth, nose and face for hours at a time day after day in the form of masks. How does anyone think that will work out? I mean – what could possibly go wrong? We posted a number of scientific studies on this at [davidicke.com](http://davidicke.com), but when I went back to them as I was writing this book the links to the science research website where they were hosted were dead. Anything that challenges the official narrative in any way is either censored or vilified. The official narrative is so unsupportable by the evidence that only deleting the truth can protect it. A study by Chinese scientists still survived – with the usual twist which it why it was still active, I guess. Yes, they found that virtually all the masks they tested increased the daily intake of microplastic fibres, but people should still wear them because the danger from the 'virus' was worse said the crazy 'team' from the Institute of Hydrobiology in Wuhan. Scientists first discovered microplastics in lung tissue of some patients who died of lung cancer

in the 1990s. Subsequent studies have confirmed the potential health damage with the plastic degrading slowly and remaining in the lungs to accumulate in volume. Wuhan researchers used a machine simulating human breathing to establish that masks shed up to nearly 4,000 microplastic fibres in a month with reused masks producing more. Scientists said some masks are laced with toxic chemicals and a variety of compounds seriously restricted for both health and environmental reasons. They include cobalt (used in blue dye) and formaldehyde known to cause watery eyes, burning sensations in the eyes, nose, and throat, plus coughing, wheezing and nausea. No – that must be 'Covid-19'.

### **Mask 'worms'**

There is another and potentially even more sinister content of masks. Mostly new masks of different makes filmed under a microscope around the world have been found to contain strange black fibres or 'worms' that appear to move or 'crawl' by themselves and react to heat and water. The nearest I have seen to them are the self-replicating fibres that are pulled out through the skin of those suffering from Morgellons disease which has been connected to the phenomena of 'chemtrails' which I will bring into the story later on. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. Black 'worm' fibres in masks have that kind of feel to them and there is a nanotechnology technique called 'worm micelles' which carry and release drugs or anything else you want to deliver to the body. For sure the suppression of humanity by mind altering drugs is the Cult agenda big time and the more excuses they can find to gain access to the body the more opportunities there are to make that happen whether through 'vaccines' or masks pushed against the mouth and nose for hours on end.

So let us summarise the pros and cons of masks:

**Against masks:** Breathing in your own carbon dioxide; depriving the body and brain of sufficient oxygen; build-up of toxins in the mask that can be breathed into the lungs and cause rashes on the face and ‘mask-mouth’; breathing microplastic fibres and toxic chemicals into the lungs; dehumanisation and deleting individualisation by literally making people faceless; destroying human emotional interaction through facial expression and deleting parental connection with their babies which look for guidance to their facial expression.

**For masks:** They don’t protect you from a ‘virus’ that doesn’t exist and even if it did ‘viral’ particles are so minute they are smaller than the holes in the mask.

Governments, police, supermarkets, businesses, transport companies, and all the rest who seek to impose masks have done no risk assessment on their consequences for health and psychology and are now open to group lawsuits when the impact becomes clear with a cumulative epidemic of respiratory and other disease. Authorities will try to exploit these effects and hide the real cause by dubbing them ‘Covid-19’. Can you imagine setting out to force the population to wear health-destroying masks without doing any assessment of the risks? It is criminal and it is evil, but then how many people targeted in this way, who see their children told to wear them all day at school, have asked for a risk assessment? Billions can’t be imposed upon by the few unless the billions allow it. Oh, yes, with just a tinge of irony, 85 percent of all masks made worldwide come from *China*.

## **Wash your hands in toxic shite**

‘Covid’ rules include the use of toxic sanitisers and again the health consequences of constantly applying toxins to be absorbed through the skin is obvious to any level of Renegade Mind. America’s Food and Drug Administration (FDA) said that sanitisers are drugs and issued a warning about 75 dangerous brands which contain

methanol used in antifreeze and can cause death, kidney damage and blindness. The FDA circulated the following warning even for those brands that it claims to be safe:

Store hand sanitizer out of the reach of pets and children, and children should use it only with adult supervision. Do not drink hand sanitizer. This is particularly important for young children, especially toddlers, who may be attracted by the pleasant smell or brightly colored bottles of hand sanitizer.

Drinking even a small amount of hand sanitizer can cause alcohol poisoning in children. (However, there is no need to be concerned if your children eat with or lick their hands after using hand sanitizer.) During this coronavirus pandemic, poison control centers have had an increase in calls about accidental ingestion of hand sanitizer, so it is important that adults monitor young children's use.

Do not allow pets to swallow hand sanitizer. If you think your pet has eaten something potentially dangerous, call your veterinarian or a pet poison control center right away. Hand sanitizer is flammable and should be stored away from heat and flames. When using hand sanitizer, rub your hands until they feel completely dry before performing activities that may involve heat, sparks, static electricity, or open flames.

There you go, perfectly safe, then, and that's without even a mention of the toxins absorbed through the skin. Come on kids – sanitise your hands everywhere you go. It will save you from the 'virus'. Put all these elements together of the 'Covid' normal and see how much health and psychology is being cumulatively damaged, even devastated, to 'protect your health'. Makes sense, right? They are only imposing these things because they care, right? *Right?*

## **Submitting to insanity**

Psychological reframing of the population goes very deep and is done in many less obvious ways. I hear people say how contradictory and crazy 'Covid' rules are and how they are ever changing. This is explained away by dismissing those involved as idiots. It is a big mistake. The Cult is delighted if its cold calculation is perceived as incompetence and idiocy when it is anything but. Oh, yes, there are idiots within the system – lots of them – but they are *administering* the Cult agenda, mostly unknowingly. They are not deciding and dictating it. The bulwark against tyranny is self-

respect, always has been, always will be. It is self-respect that has broken every tyranny in history. By its very nature self-respect will not bow to oppression and its perpetrators. There is so little self-respect that it's always the few that overturn dictators. Many may eventually follow, but the few with the iron spines (self-respect) kick it off and generate the momentum. The Cult targets self-respect in the knowledge that once this has gone only submission remains. Crazy, contradictory, ever-changing 'Covid' rules are systematically applied by psychologists to delete self-respect. They *want* you to see that the rules make no sense. It is one thing to decide to do something when *you* have made the choice based on evidence and logic. You still retain your self-respect. It is quite another when you can see what you are being told to do is insane, ridiculous and makes no sense, and *yet you still do it*. Your self-respect is extinguished and this has been happening as ever more obviously stupid and nonsensical things have been demanded and the great majority have complied even when they can see they are stupid and nonsensical.

People walk around in face-nappies knowing they are damaging their health and make no difference to a 'virus'. They do it in fear of not doing it. I know it's daft, but I'll do it anyway. When that happens something dies inside of you and submissive reframing has begun. Next there's a need to hide from yourself that you have conceded your self-respect and you convince yourself that you have not really submitted to fear and intimidation. You begin to believe that you are complying with craziness because it's the right thing to do. When first you concede your self-respect of  $2+2 = 4$  to  $2+2 = 5$  you *know* you are compromising your self-respect. Gradually to avoid facing that fact you begin to *believe* that  $2+2=5$ . You have been reframed and I have been watching this process happening in the human psyche on an industrial scale. The Cult is working to break your spirit and one of its major tools in that war is humiliation. I read how former American soldier Bradley Manning (later Chelsea Manning after a sex-change) was treated after being jailed for supplying WikiLeaks with documents exposing the enormity of

government and elite mendacity. Manning was isolated in solitary confinement for eight months, put under 24-hour surveillance, forced to hand over clothing before going to bed, and stand naked for every roll call. This is systematic humiliation. The introduction of anal swab 'Covid' tests in China has been done for the same reason to delete self-respect and induce compliant submission. Anal swabs are mandatory for incoming passengers in parts of China and American diplomats have said they were forced to undergo the indignity which would have been calculated humiliation by the Cult-owned Chinese government that has America in its sights.

### **Government-people: An abusive relationship**

Spirit-breaking psychological techniques include giving people hope and apparent respite from tyranny only to take it away again. This happened in the UK during Christmas, 2020, when the psycho-psychologists and their political lackeys announced an easing of restrictions over the holiday only to reimpose them almost immediately on the basis of yet another lie. There is a big psychological difference between getting used to oppression and being given hope of relief only to have that dashed. Psychologists know this and we have seen the technique used repeatedly. Then there is traumatising people before you introduce more extreme regulations that require compliance. A perfect case was the announcement by the dark and sinister Whitty and Vallance in the UK that 'new data' predicted that 4,000 could die every day over the winter of 2020/2021 if we did not lockdown again. I think they call it lying and after traumatising people with that claim out came Jackboot Johnson the next day with new curbs on human freedom. Psychologists know that a frightened and traumatised mind becomes suggestable to submission and behaviour reframing. Underpinning all this has been to make people fearful and suspicious of each other and see themselves as a potential danger to others. In league with deleted self-respect you have the perfect psychological recipe for self-loathing. The relationship between authority and public is now demonstrably the same as that of

subservience to an abusive partner. These are signs of an abusive relationship explained by psychologist Leslie Becker-Phelps:

**Psychological and emotional abuse:** Undermining a partner's self-worth with verbal attacks, name-calling, and belittling. Humiliating the partner in public, unjustly accusing them of having an affair, or interrogating them about their every behavior. Keeping partner confused or off balance by saying they were just kidding or blaming the partner for 'making' them act this way ... Feigning in public that they care while turning against them in private. This leads to victims frequently feeling confused, incompetent, unworthy, hopeless, and chronically self-doubting. [Apply these techniques to how governments have treated the population since New Year, 2020, and the parallels are obvious.]

**Physical abuse:** The abuser might physically harm their partner in a range of ways, such as grabbing, hitting, punching, or shoving them. They might throw objects at them or harm them with a weapon. [Observe the physical harm imposed by masks, lockdown, and so on.]

**Threats and intimidation:** One way abusers keep their partners in line is by instilling fear. They might be verbally threatening, or give threatening looks or gestures. Abusers often make it known that they are tracking their partner's every move. They might destroy their partner's possessions, threaten to harm them, or threaten to harm their family members. Not surprisingly, victims of this abuse often feel anxiety, fear, and panic. [No words necessary.]

**Isolation:** Abusers often limit their partner's activities, forbidding them to talk or interact with friends or family. They might limit access to a car or even turn off their phone. All of this might be done by physically holding them against their will, but is often accomplished through psychological abuse and intimidation. The more isolated a person feels, the fewer resources they have to help gain perspective on their situation and to escape from it. [No words necessary.]

**Economic abuse:** Abusers often make their partners beholden to them for money by controlling access to funds of any kind. They might prevent their partner from getting a job or withhold access to money they earn from a job. This creates financial dependency that makes leaving the relationship very difficult. [See destruction of livelihoods and the proposed meagre 'guaranteed income' so long as you do whatever you are told.]

**Using children:** An abuser might disparage their partner's parenting skills, tell their children lies about their partner, threaten to take custody of their children, or threaten to harm their children. These tactics instil fear and often elicit compliance. [See reframed social service mafia and how children are being mercilessly abused by the state over 'Covid' while their parents look on too frightened to do anything.]

A further recurring trait in an abusive relationship is the abused blaming themselves for their abuse and making excuses for the abuser. We have the public blaming each other for lockdown abuse by government and many making excuses for the government while attacking those who challenge the government. How often we have heard authorities say that rules are being imposed or reimposed only because people have refused to 'behave' and follow the rules. We don't want to do it – it's *you*.

Renegade Minds are an antidote to all of these things. They will never concede their self-respect no matter what the circumstances. Even when apparent humiliation is heaped upon them they laugh in its face and reflect back the humiliation on the abuser where it belongs. Renegade Minds will never wear masks they know are only imposed to humiliate, suppress and damage both physically and psychologically. Consequences will take care of themselves and they will never break their spirit or cause them to concede to tyranny. UK newspaper columnist Peter Hitchens was one of the few in the mainstream media to speak out against lockdowns and forced vaccinations. He then announced he had taken the jab. He wanted to see family members abroad and he believed vaccine passports were inevitable even though they had not yet been introduced. Hitchens

has a questioning and critical mind, but not a Renegade one. If he had no amount of pressure would have made him concede. Hitchens excused his action by saying that the battle has been lost. Renegade Minds never accept defeat when freedom is at stake and even if they are the last one standing the self-respect of not submitting to tyranny is more important than any outcome or any consequence.

That's why Renegade Minds are the only minds that ever changed anything worth changing.

## CHAPTER EIGHT

### 'Reframing' insanity

*Insanity is relative. It depends on who has who locked in what cage*

Ray Bradbury

'Reframing' a mind means simply to change its perception and behaviour. This can be done subconsciously to such an extent that subjects have no idea they have been 'reframed' while to any observer changes in behaviour and attitudes are obvious.

Human society is being reframed on a ginormous scale since the start of 2020 and here we have the reason why psychologists rather than doctors have been calling the shots. Ask most people who have succumbed to 'Covid' reframing if they have changed and most will say 'no'; but they *have* and fundamentally. The Cult's long-game has been preparing for these times since way back and crucial to that has been to prepare both population and officialdom mentally and emotionally. To use the mind-control parlance they had to reframe the population with a mentality that would submit to fascism and reframe those in government and law enforcement to impose fascism or at least go along with it. The result has been the fact-deleted mindlessness of 'Wokeness' and officialdom that has either enthusiastically or unquestioningly imposed global tyranny demanded by reframed politicians on behalf of psychopathic and deeply evil cultists. 'Cognitive reframing' identifies and challenges the way someone sees the world in the form of situations, experiences and emotions and then restructures those perceptions to view the same set of circumstances in a different way. This can have

benefits if the attitudes are personally destructive while on the other side it has the potential for individual and collective mind control which the subject has no idea has even happened.

Cognitive therapy was developed in the 1960s by Aaron T. Beck who was born in Rhode Island in 1921 as the son of Jewish immigrants from the Ukraine. He became interested in the techniques as a treatment for depression. Beck's daughter Judith S. Beck is prominent in the same field and they founded the Beck Institute for Cognitive Behavior Therapy in Philadelphia in 1994. Cognitive reframing, however, began to be used worldwide by those with a very dark agenda. The Cult reframes politicians to change their attitudes and actions until they are completely at odds with what they once appeared to stand for. The same has been happening to government administrators at all levels, law enforcement, military and the human population. Cultists love mind control for two main reasons: It allows them to control what people think, do and say to secure agenda advancement and, by definition, it calms their legendary insecurity and fear of the unexpected. I have studied mind control since the time I travelled America in 1996. I may have been talking to next to no one in terms of an audience in those years, but my goodness did I gather a phenomenal amount of information and knowledge about so many things including the techniques of mind control. I have described this in detail in other books going back to *The Biggest Secret* in 1998. I met a very large number of people recovering from MKUltra and its offshoots and successors and I began to see how these same techniques were being used on the population in general. This was never more obvious than since the 'Covid' hoax began.

## **Reframing the enforcers**

I have observed over the last two decades and more the very clear transformation in the dynamic between the police, officialdom and the public. I tracked this in the books as the relationship mutated from one of serving the public to seeing them as almost the enemy and certainly a lower caste. There has always been a class divide

based on income and always been some psychopathic, corrupt, and big-I-am police officers. This was different. Wholesale change was unfolding in the collective dynamic; it was less about money and far more about position and perceived power. An us-and-them was emerging. Noses were lifted skyward by government administration and law enforcement and their attitude to the public they were *supposed* to be serving changed to one of increasing contempt, superiority and control. The transformation was so clear and widespread that it had to be planned. Collective attitudes and dynamics do not change naturally and organically that quickly on that scale. I then came across an organisation in Britain called Common Purpose created in the late 1980s by Julia Middleton who would work in the office of Deputy Prime Minister John Prescott during the long and disastrous premiership of war criminal Tony Blair. When Blair speaks the Cult is speaking and the man should have been in jail a long time ago. Common Purpose proclaims itself to be one of the biggest 'leadership development' organisations in the world while functioning as a *charity* with all the financial benefits which come from that. It hosts 'leadership development' courses and programmes all over the world and claims to have 'brought together' what it calls 'leaders' from more than 100 countries on six continents. The modus operandi of Common Purpose can be compared with the work of the UK government's reframing network that includes the Behavioural Insights Team 'nudge unit' and 'Covid' reframing specialists at SPI-B. WikiLeaks described Common Purpose long ago as 'a hidden virus in our government and schools' which is unknown to the general public: 'It recruits and trains "leaders" to be loyal to the directives of Common Purpose and the EU, instead of to their own departments, which they then undermine or subvert, the NHS [National Health Service] being an example.' This is a vital point to understand the 'Covid' hoax. The NHS, and its equivalent around the world, has been utterly reframed in terms of administrators and much of the medical personnel with the transformation underpinned by recruitment policies. The outcome has been the criminal and psychopathic behaviour of the

NHS over ‘Covid’ and we have seen the same in every other major country. WikiLeaks said Common Purpose trainees are ‘learning to rule without regard to democracy’ and to usher in a police state (current events explained). Common Purpose operated like a ‘glue’ and had members in the NHS, BBC, police, legal profession, church, many of Britain’s 7,000 quangos, local councils, the Civil Service, government ministries and Parliament, and controlled many RDA’s (Regional Development Agencies). Here we have one answer for how and why British institutions and their like in other countries have changed so negatively in relation to the public. This further explains how and why the beyond-disgraceful reframed BBC has become a propaganda arm of ‘Covid’ fascism. They are all part of a network pursuing the same goal.

By 2019 Common Purpose was quoting a figure of 85,000 ‘leaders’ that had attended its programmes. These ‘students’ of all ages are known as Common Purpose ‘graduates’ and they consist of government, state and local government officials and administrators, police chiefs and officers, and a whole range of others operating within the national, local and global establishment. Cressida Dick, Commissioner of the London Metropolitan Police, is the Common Purpose graduate who was the ‘Gold Commander’ that oversaw what can only be described as the murder of Brazilian electrician Jean Charles de Menezes in 2005. He was held down by psychopathic police and shot seven times in the head by a psychopathic lunatic after being mistaken for a terrorist when he was just a bloke going about his day. Dick authorised officers to pursue and keep surveillance on de Menezes and ordered that he be stopped from entering the underground train system. Police psychopaths took her at her word clearly. She was ‘disciplined’ for this outrage by being *promoted* – eventually to the top of the ‘Met’ police where she has been a disaster. Many Chief Constables controlling the police in different parts of the UK are and have been Common Purpose graduates. I have heard the ‘graduate’ network described as a sort of Mafia or secret society operating within the fabric of government at all levels pursuing a collective policy

ingrained at Common Purpose training events. Founder Julia Middleton herself has said:

Locally and internationally, Common Purpose graduates will be 'lighting small fires' to create change in their organisations and communities ... The Common Purpose effect is best illustrated by the many stories of small changes brought about by leaders, who themselves have changed.

A Common Purpose mission statement declared:

Common Purpose aims to improve the way society works by expanding the vision, decision-making ability and influence of all kinds of leaders. The organisation runs a variety of educational programmes for leaders of all ages, backgrounds and sectors, in order to provide them with the inspirational, information and opportunities they need to change the world.

Yes, but into what? Since 2020 the answer has become clear.

### **NLP and the Delphi technique**

Common Purpose would seem to be a perfect name or would common programming be better? One of the foundation methods of reaching 'consensus' (group think) is by setting the agenda theme and then encouraging, cajoling or pressuring everyone to agree a 'consensus' in line with the core theme promoted by Common Purpose. The methodology involves the 'Delphi technique', or an adaption of it, in which opinions are expressed that are summarised by a 'facilitator or change agent' at each stage. Participants are 'encouraged' to modify their views in the light of what others have said. Stage by stage the former individual opinions are merged into group consensus which just happens to be what Common Purpose wants them to believe. A key part of this is to marginalise anyone refusing to concede to group think and turn the group against them to apply pressure to conform. We are seeing this very technique used on the general population to make 'Covid' group-thinkers hostile to those who have seen through the bullshit. People can be reframed by using perception manipulation methods such as Neuro-Linguistic Programming (NLP) in which you change perception with the use of

carefully constructed language. An NLP website described the technique this way:

... A method of influencing brain behaviour (the 'neuro' part of the phrase) through the use of language (the 'linguistic' part) and other types of communication to enable a person to 'recode' the way the brain responds to stimuli (that's the 'programming') and manifest new and better behaviours. Neuro-Linguistic Programming often incorporates hypnosis and self-hypnosis to help achieve the change (or 'programming') that is wanted.

British alternative media operation UKColumn has done very detailed research into Common Purpose over a long period. I quoted co-founder and former naval officer Brian Gerrish in my book *Remember Who You Are*, published in 2011, as saying the following years before current times:

It is interesting that many of the mothers who have had children taken by the State speak of the Social Services people being icily cool, emotionless and, as two ladies said in slightly different words, '... like little robots'. We know that NLP is cumulative, so people can be given small imperceptible doses of NLP in a course here, another in a few months, next year etc. In this way, major changes are accrued in their personality, but the day by day change is almost unnoticeable.

In these and other ways 'graduates' have had their perceptions uniformly reframed and they return to their roles in the institutions of government, law enforcement, legal profession, military, 'education', the UK National Health Service and the whole swathe of the establishment structure to pursue a common agenda preparing for the 'post-industrial', 'post-democratic' society. I say 'preparing' but we are now there. 'Post-industrial' is code for the Great Reset and 'post-democratic' is 'Covid' fascism. UKColumn has spoken to partners of those who have attended Common Purpose 'training'. They have described how personalities and attitudes of 'graduates' changed very noticeably for the worse by the time they had completed the course. They had been 'reframed' and told they are the 'leaders' – the special ones – who know better than the population. There has also been the very demonstrable recruitment of psychopaths and narcissists into government administration at all

levels and law enforcement. If you want psychopathy hire psychopaths and you get a simple cause and effect. If you want administrators, police officers and 'leaders' to perceive the public as lesser beings who don't matter then employ narcissists. These personalities are identified using 'psychometrics' that identifies knowledge, abilities, attitudes and personality traits, mostly through carefully-designed questionnaires and tests. As this policy has passed through the decades we have had power-crazy, power-trippers appointed into law enforcement, security and government administration in preparation for current times and the dynamic between public and law enforcement/officialdom has been transformed. UKColumn's Brian Gerrish said of the narcissistic personality:

Their love of themselves and power automatically means that they will crush others who get in their way. I received a major piece of the puzzle when a friend pointed out that when they made public officials re-apply for their own jobs several years ago they were also required to do psychometric tests. This was undoubtedly the start of the screening process to get 'their' sort of people in post.

How obvious that has been since 2020 although it was clear what was happening long before if people paid attention to the changing public-establishment dynamic.

## **Change agents**

At the centre of events in 'Covid' Britain is the National Health Service (NHS) which has behaved disgracefully in slavishly following the Cult agenda. The NHS management structure is awash with Common Purpose graduates or 'change agents' working to a common cause. Helen Bevan, a Chief of Service Transformation at the NHS Institute for Innovation and Improvement, co-authored a document called 'Towards a million change agents, a review of the social movements literature: implications for large scale change in the NHS'. The document compared a project management approach to that of change and social movements where 'people change

themselves and each other – peer to peer'. Two definitions given for a 'social movement' were:

*A group of people who consciously attempt to build a radically new social order; involves people of a broad range of social backgrounds; and deploys politically confrontational and socially disruptive tactics* – Cyrus Zirakzadeh 1997

*Collective challenges, based on common purposes and social solidarities, in sustained interaction with elites, opponents, and authorities* – Sidney Tarrow 1994

Helen Bevan wrote another NHS document in which she defined 'framing' as 'the process by which leaders construct, articulate and put across their message in a powerful and compelling way in order to win people to their cause and call them to action'. I think I could come up with another definition that would be rather more accurate. The National Health Service and institutions of Britain and the wider world have been taken over by reframed 'change agents' and that includes everything from the United Nations to national governments, local councils and social services which have been kidnapping children from loving parents on an extraordinary and gathering scale on the road to the end of parenthood altogether. Children from loving homes are stolen and kidnapped by the state and put into the 'care' (inversion) of the local authority through council homes, foster parents and forced adoption. At the same time children are allowed to be abused without response while many are under council 'care'. UKColumn highlighted the Common Purpose connection between South Yorkshire Police and Rotherham council officers in the case of the scandal in that area of the sexual exploitation of children to which the authorities turned not one blind eye, but both:

We were alarmed to discover that the Chief Executive, the Strategic Director of Children and Young People's Services, the Manager for the Local Strategic Partnership, the Community Cohesion Manager, the Cabinet Member for Cohesion, the Chief Constable and his predecessor had all attended Leadership training courses provided by the pseudo-charity Common Purpose.

Once 'change agents' have secured positions of hire and fire within any organisation things start to move very quickly. Personnel are then hired and fired on the basis of whether they will work towards the agenda the change agent represents. If they do they are rapidly promoted even though they may be incompetent. Those more qualified and skilled who are pre-Common Purpose 'old school' see their careers stall and even disappear. This has been happening for decades in every institution of state, police, 'health' and social services and all of them have been transformed as a result in their attitudes to their jobs and the public. Medical professions, including nursing, which were once vocations for the caring now employ many cold, callous and couldn't give a shit personality types. The UKColumn investigation concluded:

By blurring the boundaries between people, professions, public and private sectors, responsibility and accountability, Common Purpose encourages 'graduates' to believe that as new selected leaders, they can work together, outside of the established political and social structures, to achieve a paradigm shift or CHANGE – so called 'Leading Beyond Authority'. In doing so, the allegiance of the individual becomes 'reframed' on CP colleagues and their NETWORK.

## **Reframing the Face-Nappies**

Nowhere has this process been more obvious than in the police where recruitment of psychopaths and development of unquestioning mind-controlled group-thinkers have transformed law enforcement into a politically-correct 'Woke' joke and a travesty of what should be public service. Today they wear their face-nappies like good little gofers and enforce 'Covid' rules which are fascism under another name. Alongside the specifically-recruited psychopaths we have software minds incapable of free thought. Brian Gerrish again:

An example is the policeman who would not get on a bike for a press photo because he had not done the cycling proficiency course. Normal people say this is political correctness gone mad. Nothing could be further from the truth. The policeman has been reframed, and in his reality it is perfect common sense not to get on the bike ‘because he hasn’t done the cycling course’.

Another example of this is where the police would not rescue a boy from a pond until they had taken advice from above on the ‘risk assessment’. A normal person would have arrived, perhaps thought of the risk for a moment, and dived in. To the police now ‘reframed’, they followed ‘normal’ procedure.

There are shocking cases of reframed ambulance crews doing the same. Sheer unthinking stupidity of London Face-Nappies headed by Common Purpose graduate Cressida Dick can be seen in their behaviour at a vigil in March, 2021, for a murdered woman, Sarah Everard. A police officer had been charged with the crime. Anyone with a brain would have left the vigil alone in the circumstances. Instead they ‘manhandled’ women to stop them breaking ‘Covid rules’ to betray classic reframing. Minds in the thrall of perception control have no capacity for seeing a situation on its merits and acting accordingly. ‘Rules is rules’ is their only mind-set. My father used to say that rules and regulations are for the guidance of the intelligent and the blind obedience of the idiot. Most of the intelligent, decent, coppers have gone leaving only the other kind and a few old school for whom the job must be a daily nightmare. The combination of psychopaths and rule-book software minds has been clearly on public display in the ‘Covid’ era with automaton robots in uniform imposing fascistic ‘Covid’ regulations on the population without any personal initiative or judging situations on their merits. There are thousands of examples around the world, but I’ll make my point with the infamous Derbyshire police in the English East Midlands – the ones who think pouring dye into beauty spots and using drones to track people walking in the countryside away from anyone is called ‘policing’. To them there are rules decreed by the government which they have to enforce and in their bewildered state a group gathering in a closed space and someone walking alone in the countryside are the same thing. It is beyond idiocy and enters the realm of clinical insanity.

Police officers in Derbyshire said they were ‘horrified’ – *horrified* – to find 15 to 20 ‘irresponsible’ kids playing a football match at a closed leisure centre ‘in breach of coronavirus restrictions’. When they saw the police the kids ran away leaving their belongings behind and the reframed men and women of Derbyshire police were seeking to establish their identities with a view to fining their parents. The most natural thing for youngsters to do – kicking a ball about – is turned into a criminal activity and enforced by the moronic software programs of Derbyshire police. You find the same mentality in every country. These barely conscious ‘horrified’ officers said they had to take action because ‘we need to ensure these rules are being followed’ and ‘it is of the utmost importance that you ensure your children are following the rules and regulations for Covid-19’. Had any of them done ten seconds of research to see if this parroting of their masters’ script could be supported by any evidence? Nope. Reframed people don’t think – others think for them and that’s the whole idea of reframing. I have seen police officers one after the other repeating without question word for word what officialdom tells them just as I have seen great swathes of the public doing the same. Ask either for ‘their’ opinion and out spews what they have been told to think by the official narrative. Police and public may seem to be in different groups, but their mentality is the same. Most people do whatever they are told in fear not doing so or because they believe what officialdom tells them; almost the entirety of the police do what they are told for the same reason. Ultimately it’s the tiny inner core of the global Cult that’s telling both what to do.

So Derbyshire police were ‘horrified’. Oh, really? Why did they think those kids were playing football? It was to relieve the psychological consequences of lockdown and being denied human contact with their friends and interaction, touch and discourse vital to human psychological health. Being denied this month after month has dismantled the psyche of many children and young people as depression and suicide have exploded. Were Derbyshire police *horrified by that?* Are you kidding? Reframed people don’t have those

mental and emotional processes that can see how the impact on the psychological health of youngsters is far more dangerous than any 'virus' even if you take the mendacious official figures to be true. The reframed are told (programmed) how to act and so they do. The Derbyshire Chief Constable in the first period of lockdown when the black dye and drones nonsense was going on was Peter Goodman. He was the man who severed the connection between his force and the Derbyshire Constabulary *Male Voice* Choir when he decided that it was not inclusive enough to allow women to join. The fact it was a male voice choir making a particular sound produced by male voices seemed to elude a guy who terrifyingly ran policing in Derbyshire. He retired weeks after his force was condemned as disgraceful by former Supreme Court Justice Jonathan Sumption for their behaviour over extreme lockdown impositions. Goodman was replaced by his deputy Rachel Swann who was in charge when her officers were 'horrified'. The police statement over the boys committing the hanging-offence of playing football included the line about the youngsters being 'irresponsible in the times we are all living through' missing the point that the real relevance of the 'times we are all living through' is the imposition of fascism enforced by psychopaths and reframed minds of police officers playing such a vital part in establishing the fascist tyranny that their own children and grandchildren will have to live in their entire lives. As a definition of insanity that is hard to beat although it might be run close by imposing masks on people that can have a serious effect on their health while wearing a face nappy all day themselves. Once again public and police do it for the same reason – the authorities tell them to and who are they to have the self-respect to say no?

## **Wokers in uniform**

How reframed do you have to be to arrest a *six-year-old* and take him to court for *picking a flower* while waiting for a bus? Brain dead police and officialdom did just that in North Carolina where criminal proceedings happen regularly for children under nine. Attorney Julie Boyer gave the six-year-old crayons and a colouring book

during the ‘flower’ hearing while the ‘adults’ decided his fate. County Chief District Court Judge Jay Corpening asked: ‘Should a child that believes in Santa Claus, the Easter Bunny and the tooth fairy be making life-altering decisions?’ Well, of course not, but common sense has no meaning when you have a common purpose and a reframed mind. Treating children in this way, and police operating in American schools, is all part of the psychological preparation for children to accept a police state as normal all their adult lives. The same goes for all the cameras and biometric tracking technology in schools. Police training is focused on reframing them as snowflake Wokers and this is happening in the military. Pentagon top brass said that ‘training sessions on extremism’ were needed for troops who asked why they were so focused on the Capitol Building riot when Black Lives Matter riots were ignored. What’s the difference between them some apparently and rightly asked. Actually, there is a difference. Five people died in the Capitol riot, only one through violence, and that was a police officer shooting an unarmed protestor. BLM riots killed at least 25 people and cost billions. Asking the question prompted the psychopaths and reframed minds that run the Pentagon to say that more ‘education’ (programming) was needed. Troop training is all based on psychological programming to make them fodder for the Cult – ‘Military men are just dumb, stupid animals to be used as pawns in foreign policy’ as Cult-to-his-DNA former Secretary of State Henry Kissinger famously said. Governments see the police in similar terms and it’s time for those among them who can see this to defend the people and stop being enforcers of the Cult agenda upon the people.

The US military, like the country itself, is being targeted for destruction through a long list of Woke impositions. Cult-owned gaga ‘President’ Biden signed an executive order when he took office to allow taxpayer money to pay for transgender surgery for active military personnel and veterans. Are you a man soldier? No, I’m a LGBTQIA+ with a hint of Skoliosexual and Spectrasexual. Oh, good man. Bad choice of words you bigot. The Pentagon announced in March, 2021, the appointment of the first ‘diversity and inclusion

officer' for US Special Forces. Richard Torres-Estrada arrived with the publication of a 'D&I Strategic Plan which will guide the enterprise-wide effort to institutionalize and sustain D&I'. If you think a Special Forces 'Strategic Plan' should have something to do with defending America you haven't been paying attention.

Defending Woke is now the military's new role. Torres-Estrada has posted images comparing Donald Trump with Adolf Hitler and we can expect no bias from him as a representative of the supposedly non-political Pentagon. Cable news host Tucker Carlson said: 'The Pentagon is now the Yale faculty lounge but with cruise missiles.' Meanwhile Secretary of Defense Lloyd Austin, a board member of weapons-maker Raytheon with stock and compensation interests in October, 2020, worth \$1.4 million, said he was purging the military of the 'enemy within' – anyone who isn't Woke and supports Donald Trump. Austin refers to his targets as 'racist extremists' while in true Woke fashion being himself a racist extremist. Pentagon documents pledge to 'eradicate, eliminate and conquer all forms of racism, sexism and homophobia'. The definitions of these are decided by 'diversity and inclusion committees' peopled by those who see racism, sexism and homophobia in every situation and opinion. Woke (the Cult) is dismantling the US military and purging testosterone as China expands its military and gives its troops 'masculinity training'. How do we think that is going to end when this is all Cult coordinated? The US military, like the British military, is controlled by Woke and spineless top brass who just go along with it out of personal career interests.

## **'Woke' means fast asleep**

Mind control and perception manipulation techniques used on individuals to create group-think have been unleashed on the global population in general. As a result many have no capacity to see the obvious fascist agenda being installed all around them or what 'Covid' is really all about. Their brains are firewalled like a computer system not to process certain concepts, thoughts and realisations that are bad for the Cult. The young are most targeted as the adults they

will be when the whole fascist global state is planned to be fully implemented. They need to be prepared for total compliance to eliminate all pushback from entire generations. The Cult has been pouring billions into taking complete control of 'education' from schools to universities via its operatives and corporations and not least Bill Gates as always. The plan has been to transform 'education' institutions into programming centres for the mentality of 'Woke'. James McConnell, professor of psychology at the University of Michigan, wrote in *Psychology Today* in 1970:

The day has come when we can combine sensory deprivation with drugs, hypnosis, and astute manipulation of reward and punishment, to gain almost absolute control over an individual's behaviour. It should then be possible to achieve a very rapid and highly effective type of brainwashing that would allow us to make dramatic changes in a person's behaviour and personality ...

... We should reshape society so that we all would be trained from birth to want to do what society wants us to do. We have the techniques to do it... no-one owns his own personality you acquired, and there's no reason to believe you should have the right to refuse to acquire a new personality if your old one is anti-social.

This was the potential for mass brainwashing in 1970 and the mentality there displayed captures the arrogant psychopathy that drives it forward. I emphasise that not all young people have succumbed to Woke programming and those that haven't are incredibly impressive people given that today's young are the most perceptually-targeted generations in history with all the technology now involved. Vast swathes of the young generations, however, have fallen into the spell – and that's what it is – of Woke. The Woke mentality and perceptual program is founded on *inversion* and you will appreciate later why that is so significant. Everything with Woke is inverted and the opposite of what it is claimed to be. Woke was a term used in African-American culture from the 1900s and referred to an awareness of social and racial justice. This is not the meaning of the modern version or 'New Woke' as I call it in *The Answer*. Oh, no, Woke today means something very different no matter how much Wokers may seek to hide that and insist Old Woke and New

Woke are the same. See if you find any 'awareness of social justice' here in the modern variety:

- Woke demands 'inclusivity' while excluding anyone with a different opinion and calls for mass censorship to silence other views.
- Woke claims to stand against oppression when imposing oppression is the foundation of all that it does. It is the driver of political correctness which is nothing more than a Cult invention to manipulate the population to silence itself.
- Woke believes itself to be 'liberal' while pursuing a global society that can only be described as fascist (see 'anti-fascist' fascist Antifa).
- Woke calls for 'social justice' while spreading injustice wherever it goes against the common 'enemy' which can be easily identified as a differing view.
- Woke is supposed to be a metaphor for 'awake' when it is solid-gold asleep and deep in a Cult-induced coma that meets the criteria for 'off with the fairies'.

I state these points as obvious facts if people only care to look. I don't do this with a sense of condemnation. We need to appreciate that the onslaught of perceptual programming on the young has been incessant and merciless. I can understand why so many have been reframed, or, given their youth, framed from the start to see the world as the Cult demands. The Cult has had access to their minds day after day in its 'education' system for their entire formative years. Perception is formed from information received and the Cult-created system is a life-long download of information delivered to elicit a particular perception, thus behaviour. The more this has expanded into still new extremes in recent decades and ever-increasing censorship has deleted other opinions and information why wouldn't that lead to a perceptual reframing on a mass scale? I

have described already cradle-to-grave programming and in more recent times the targeting of young minds from birth to adulthood has entered the stratosphere. This has taken the form of skewing what is ‘taught’ to fit the Cult agenda and the omnipresent techniques of group-think to isolate non-believers and pressure them into line. There has always been a tendency to follow the herd, but we really are in a new world now in relation to that. We have parents who can see the ‘Covid’ hoax told by their children not to stop them wearing masks at school, being ‘Covid’ tested or having the ‘vaccine’ in fear of the peer-pressure consequences of being different. What is ‘peer-pressure’ if not pressure to conform to group-think? Renegade Minds never group-think and always retain a set of perceptions that are unique to them. Group-think is always underpinned by consequences for not group-thinking. Abuse now aimed at those refusing DNA-manipulating ‘Covid vaccines’ are a potent example of this. The biggest pressure to conform comes from the very group which is itself being manipulated. ‘I am programmed to be part of a hive mind and so you must be.’

Woke control structures in ‘education’ now apply to every mainstream organisation. Those at the top of the ‘education’ hierarchy (the Cult) decide the policy. This is imposed on governments through the Cult network; governments impose it on schools, colleges and universities; their leadership impose the policy on teachers and academics and they impose it on children and students. At any level where there is resistance, perhaps from a teacher or university lecturer, they are targeted by the authorities and often fired. Students themselves regularly demand the dismissal of academics (increasingly few) at odds with the narrative that the students have been programmed to believe in. It is quite a thought that students who are being targeted by the Cult become so consumed by programmed group-think that they launch protests and demand the removal of those who are trying to push back against those targeting the students. Such is the scale of perceptual inversion. We see this with ‘Covid’ programming as the Cult imposes the rules via psycho-psychologists and governments on

shops, transport companies and businesses which impose them on their staff who impose them on their customers who pressure Pushbackers to conform to the will of the Cult which is in the process of destroying them and their families. Scan all aspects of society and you will see the same sequence every time.

## **Fact free Woke and hijacking the 'left'**

There is no more potent example of this than 'Woke', a mentality only made possible by the deletion of factual evidence by an 'education' system seeking to produce an ever more uniform society. Why would you bother with facts when you don't know any? Deletion of credible history both in volume and type is highly relevant. Orwell said: 'Who controls the past controls the future: who controls the present controls the past.' They who control the perception of the past control the perception of the future and they who control the present control the perception of the past through the writing and deleting of history. Why would you oppose the imposition of Marxism in the name of Wokeism when you don't know that Marxism cost at least 100 million lives in the 20th century alone? Watch videos and read reports in which Woker generations are asked basic historical questions – it's mind-blowing. A survey of 2,000 people found that six percent of millennials (born approximately early 1980s to early 2000s) believed the Second World War (1939-1945) broke out with the assassination of President Kennedy (in 1963) and one in ten thought Margaret Thatcher was British Prime Minister at the time. She was in office between 1979 and 1990. We are in a post-fact society. Provable facts are no defence against the fascism of political correctness or Silicon Valley censorship. Facts don't matter anymore as we have witnessed with the 'Covid' hoax. Sacrificing uniqueness to the Woke group-think religion is all you are required to do and that means thinking for yourself is the biggest Woke no, no. All religions are an expression of group-think and censorship and Woke is just another religion with an orthodoxy defended by group-think and censorship. Burned at

the stake becomes burned on Twitter which leads back eventually to burned at the stake as Woke humanity regresses to ages past.

The biggest Woke inversion of all is its creators and funders. I grew up in a traditional left of centre political household on a council estate in Leicester in the 1950s and 60s – you know, the left that challenged the power of wealth-hoarding elites and threats to freedom of speech and opinion. In those days students went on marches defending freedom of speech while today's Wokers march for its deletion. What on earth could have happened? Those very elites (collectively the Cult) that we opposed in my youth and early life have funded into existence the antithesis of that former left and hijacked the 'brand' while inverting everything it ever stood for. We have a mentality that calls itself 'liberal' and 'progressive' while acting like fascists. Cult billionaires and their corporations have funded themselves into control of 'education' to ensure that Woke programming is unceasing throughout the formative years of children and young people and that non-Wokers are isolated (that word again) whether they be students, teachers or college professors. The Cult has funded into existence the now colossal global network of Woke organisations that have spawned and promoted all the 'causes' on the Cult wish-list for global transformation and turned Wokers into demanders of them. Does anyone really think it's a coincidence that the Cult agenda for humanity is a carbon (sorry) copy of the societal transformations desired by Woke?? These are only some of them:

**Political correctness:** The means by which the Cult deletes all public debates that it knows it cannot win if we had the free-flow of information and evidence.

**Human-caused 'climate change':** The means by which the Cult seeks to transform society into a globally-controlled dictatorship imposing its will over the fine detail of everyone's lives 'to save the planet' which doesn't actually need saving.

**Transgender obsession:** Preparing collective perception to accept the ‘new human’ which would not have genders because it would be created technologically and not through procreation. I’ll have much more on this in Human 2.0.

**Race obsession:** The means by which the Cult seeks to divide and rule the population by triggering racial division through the perception that society is more racist than ever when the opposite is the case. Is it perfect in that regard? No. But to compare today with the racism of apartheid and segregation brought to an end by the civil rights movement in the 1960s is to insult the memory of that movement and inspirations like Martin Luther King. Why is the ‘anti-racism’ industry (which it is) so dominated by privileged white people?

**White supremacy:** This is a label used by privileged white people to demonise poor and deprived white people pushing back on tyranny to marginalise and destroy them. White people are being especially targeted as the dominant race by number within Western society which the Cult seeks to transform in its image. If you want to change a society you must weaken and undermine its biggest group and once you have done that by using the other groups you next turn on them to do the same ... ‘Then they came for the Jews and I was not a Jew so I did nothing.’

**Mass migration:** The mass movement of people from the Middle East, Africa and Asia into Europe, from the south into the United States and from Asia into Australia are another way the Cult seeks to dilute the racial, cultural and political influence of white people on Western society. White people ask why their governments appear to be working against them while being politically and culturally biased towards incoming cultures. Well, here’s your answer. In the same way sexually ‘straight’ people, men and women, ask why the

authorities are biased against them in favour of other sexualities. The answer is the same – that's the way the Cult wants it to be for very sinister motives.

These are all central parts of the Cult agenda and central parts of the Woke agenda and Woke was created and continues to be funded to an immense degree by Cult billionaires and corporations. If anyone begins to say 'coincidence' the syllables should stick in their throat.

### **Billionaire 'social justice warriors'**

Joe Biden is a 100 percent-owned asset of the Cult and the Wokers' man in the White House whenever he can remember his name and for however long he lasts with his rapidly diminishing cognitive function. Even walking up the steps of an aircraft without falling on his arse would appear to be a challenge. He's not an empty-shell puppet or anything. From the minute Biden took office (or the Cult did) he began his executive orders promoting the Woke wish-list. You will see the Woke agenda imposed ever more severely because it's really the *Cult* agenda. Woke organisations and activist networks spawned by the Cult are funded to the extreme so long as they promote what the Cult wants to happen. Woke is funded to promote 'social justice' by billionaires who become billionaires by destroying social justice. The social justice mantra is only a cover for dismantling social justice and funded by billionaires that couldn't give a damn about social justice. Everything makes sense when you see that. One of Woke's premier funders is Cult billionaire financier George Soros who said: 'I am basically there to make money, I cannot and do not look at the social consequences of what I do.' This is the same Soros who has given more than \$32 billion to his Open Society Foundations global Woke network and funded Black Lives Matter, mass immigration into Europe and the United States, transgender activism, climate change activism, political correctness and groups targeting 'white supremacy' in the form of privileged white thugs that dominate Antifa. What a scam it all is and when

you are dealing with the unquestioning fact-free zone of Woke scamming them is child's play. All you need to pull it off in all these organisations are a few in-the-know agents of the Cult and an army of naïve, reframed, uninformed, narcissistic, know-nothings convinced of their own self-righteousness, self-purity and virtue.

Soros and fellow billionaires and billionaire corporations have poured hundreds of millions into Black Lives Matter and connected groups and promoted them to a global audience. None of this is motivated by caring about black people. These are the billionaires that have controlled and exploited a system that leaves millions of black people in abject poverty and deprivation which they do absolutely nothing to address. The same Cult networks funding BLM were behind the *slave trade!* Black Lives Matter hijacked a phrase that few would challenge and they have turned this laudable concept into a political weapon to divide society. You know that BLM is a fraud when it claims that *All Lives Matter*, the most inclusive statement of all, is 'racist'. BLM and its Cult masters don't want to end racism. To them it's a means to an end to control all of humanity never mind the colour, creed, culture or background. What has destroying the nuclear family got to do with ending racism? Nothing – but that is one of the goals of BLM and also happens to be a goal of the Cult as I have been exposing in my books for decades. Stealing children from loving parents and giving schools ever more power to override parents is part of that same agenda. BLM is a Marxist organisation and why would that not be the case when the Cult created Marxism *and* BLM? Patrisse Cullors, a BLM co-founder, said in a 2015 video that she and her fellow organisers, including co-founder Alicia Garza, are 'trained Marxists'. The lady known after marriage as Patrisse Khan-Cullors bought a \$1.4 million home in 2021 in one of the whitest areas of California with a black population of just 1.6 per cent and has so far bought *four* high-end homes for a total of \$3.2 million. How very Marxist. There must be a bit of spare in the BLM coffers, however, when Cult corporations and billionaires have handed over the best part of \$100 million. Many black people can see that Black Lives Matter is not

working for them, but against them, and this is still more confirmation. Black journalist Jason Whitlock, who had his account suspended by Twitter for simply linking to the story about the ‘Marxist’s’ home buying spree, said that BLM leaders are ‘making millions of dollars off the backs of these dead black men who they wouldn’t spit on if they were on fire and alive’.

## **Black Lies Matter**

Cult assets and agencies came together to promote BLM in the wake of the death of career criminal George Floyd who had been jailed a number of times including for forcing his way into the home of a black woman with others in a raid in which a gun was pointed at her stomach. Floyd was filmed being held in a Minneapolis street in 2020 with the knee of a police officer on his neck and he subsequently died. It was an appalling thing for the officer to do, but the same technique has been used by police on peaceful protestors of lockdown without any outcry from the Woke brigade. As unquestioning supporters of the Cult agenda Wokers have supported lockdown and all the ‘Covid’ claptrap while attacking anyone standing up to the tyranny imposed in its name. Court documents would later include details of an autopsy on Floyd by County Medical Examiner Dr Andrew Baker who concluded that Floyd had taken a fatal level of the drug fentanyl. None of this mattered to fact-free, question-free, Woke. Floyd’s death was followed by worldwide protests against police brutality amid calls to defund the police. Throwing babies out with the bathwater is a Woke speciality. In the wake of the murder of British woman Sarah Everard a Green Party member of the House of Lords, Baroness Jones of Moulsecoomb (Nincompoopia would have been better), called for a 6pm curfew for all men. This would be in breach of the Geneva Conventions on war crimes which ban collective punishment, but that would never have crossed the black and white Woke mind of Baroness Nincompoopia who would have been far too convinced of her own self-righteousness to compute such details. Many American cities did defund the police in the face of Floyd riots

and after \$15 million was deleted from the police budget in Washington DC under useless Woke mayor Muriel Bowser car-jacking alone rose by 300 percent and within six months the US capital recorded its highest murder rate in 15 years. The same happened in Chicago and other cities in line with the Cult/Soros plan to bring fear to streets and neighbourhoods by reducing the police, releasing violent criminals and not prosecuting crime. This is the mob-rule agenda that I have warned in the books was coming for so long. Shootings in the area of Minneapolis where Floyd was arrested increased by 2,500 percent compared with the year before. Defunding the police over George Floyd has led to a big increase in dead people with many of them black. Police protection for politicians making these decisions stayed the same or increased as you would expect from professional hypocrites. The Cult doesn't actually want to abolish the police. It wants to abolish local control over the police and hand it to federal government as the psychopaths advance the Hunger Games Society. Many George Floyd protests turned into violent riots with black stores and businesses destroyed by fire and looting across America fuelled by Black Lives Matter. Woke doesn't do irony. If you want civil rights you must loot the liquor store and the supermarket and make off with a smart TV. It's the only way.

### **It's not a race war – it's a class war**

Black people are patronised by privileged blacks and whites alike and told they are victims of white supremacy. I find it extraordinary to watch privileged blacks supporting the very system and bloodline networks behind the slave trade and parroting the same Cult-serving manipulative crap of their privileged white, often billionaire, associates. It is indeed not a race war but a class war and colour is just a diversion. Black Senator Cory Booker and black Congresswoman Maxine Waters, more residents of Nincompoopia, personify this. Once you tell people they are victims of someone else you devalue both their own responsibility for their plight and the power they have to impact on their reality and experience. Instead

we have: 'You are only in your situation because of whitey – turn on them and everything will change.' It won't change. Nothing changes in our lives unless *we* change it. Crucial to that is never seeing yourself as a victim and always as the creator of your reality. Life is a simple sequence of choice and consequence. Make different choices and you create different consequences. *You* have to make those choices – not Black Lives Matter, the Woke Mafia and anyone else that seeks to dictate your life. Who are they these Wokers, an emotional and psychological road traffic accident, to tell you what to do? Personal empowerment is the last thing the Cult and its Black Lives Matter want black people or anyone else to have. They claim to be defending the underdog while *creating* and perpetuating the underdog. The Cult's worst nightmare is human unity and if they are going to keep blacks, whites and every other race under economic servitude and control then the focus must be diverted from what they have in common to what they can be manipulated to believe divides them. Blacks have to be told that their poverty and plight is the fault of the white bloke living on the street in the same poverty and with the same plight they are experiencing. The difference is that your plight black people is due to him, a white supremacist with 'white privilege' living on the street. Don't unite as one human family against your mutual oppressors and suppressors – fight the oppressor with the white face who is as financially deprived as you are. The Cult knows that as its 'Covid' agenda moves into still new levels of extremism people are going to respond and it has been spreading the seeds of disunity everywhere to stop a united response to the evil that targets *all of us*.

Racist attacks on 'whiteness' are getting ever more outrageous and especially through the American Democratic Party which has an appalling history for anti-black racism. Barack Obama, Joe Biden, Hillary Clinton and Nancy Pelosi all eulogised about Senator Robert Byrd at his funeral in 2010 after a nearly 60-year career in Congress. Byrd was a brutal Ku Klux Klan racist and a violent abuser of Cathy O'Brien in MKUltra. He said he would never fight in the military 'with a negro by my side' and 'rather I should die a thousand times,

and see Old Glory trampled in the dirt never to rise again, than to see this beloved land of ours become degraded by race mongrels, a throwback to the blackest specimen from the wilds'. Biden called Byrd a 'very close friend and mentor'. These 'Woke' hypocrites are not anti-racist they are anti-poor and anti-people not of their perceived class. Here is an illustration of the scale of anti-white racism to which we have now descended. Seriously Woke and moronic *New York Times* contributor Damon Young described whiteness as a 'virus' that 'like other viruses will not die until there are no bodies left for it to infect'. He went on: '... the only way to stop it is to locate it, isolate it, extract it, and kill it.' Young can say that as a black man with no consequences when a white man saying the same in reverse would be facing a jail sentence. *That's* racism. We had super-Woke numbskull senators Tammy Duckworth and Mazie Hirono saying they would object to future Biden Cabinet appointments if he did not nominate more Asian Americans and Pacific Islanders. Never mind the ability of the candidate what do they look like? Duckworth said: 'I will vote for racial minorities and I will vote for LGBTQ, but anyone else I'm not voting for.' Appointing people on the grounds of race is illegal, but that was not a problem for this ludicrous pair. They were on-message and that's a free pass in any situation.

## Critical race racism

White children are told at school they are intrinsically racist as they are taught the divisive 'critical race theory'. This claims that the law and legal institutions are inherently racist and that race is a socially constructed concept used by white people to further their economic and political interests at the expense of people of colour. White is a 'virus' as we've seen. Racial inequality results from 'social, economic, and legal differences that white people create between races to maintain white interests which leads to poverty and criminality in minority communities'. I must tell that to the white guy sleeping on the street. The principal of East Side Community School in New York sent white parents a manifesto that called on

them to become ‘white traitors’ and advocate for full ‘white abolition’. These people are teaching your kids when they urgently need a psychiatrist. The ‘school’ included a chart with ‘eight white identities’ that ranged from ‘white supremacist’ to ‘white abolition’ and defined the behaviour white people must follow to end ‘the regime of whiteness’. Woke blacks and their privileged white associates are acting exactly like the slave owners of old and Ku Klux Klan racists like Robert Byrd. They are too full of their own self-purity to see that, but it’s true. Racism is not a body type; it’s a state of mind that can manifest through any colour, creed or culture.

Another racial fraud is ‘*equity*’. Not equality of treatment and opportunity – equity. It’s a term spun as equality when it means something very different. Equality in its true sense is a raising up while ‘*equity*’ is a race to the bottom. Everyone in the same level of poverty is ‘*equity*’. Keep everyone down – that’s equity. The Cult doesn’t want anyone in the human family to be empowered and BLM leaders, like all these ‘anti-racist’ organisations, continue their privileged, pampered existence by perpetuating the perception of gathering racism. When is the last time you heard an ‘anti-racist’ or ‘anti-Semitism’ organisation say that acts of racism and discrimination have *fallen*? It’s not in the interests of their fund-raising and power to influence and the same goes for the professional soccer anti-racism operation, Kick It Out. Two things confirmed that the Black Lives Matter riots in the summer of 2020 were Cult creations. One was that while anti-lockdown protests were condemned in this same period for ‘transmitting ‘Covid’ the authorities supported mass gatherings of Black Lives Matter supporters. I even saw self-deluding people claiming to be doctors say the two types of protest were not the same. No – the non-existent ‘Covid’ was in favour of lockdowns and attacked those that protested against them while ‘Covid’ supported Black Lives Matter and kept well away from its protests. The whole thing was a joke and as lockdown protestors were arrested, often brutally, by reframed Face-Nappies we had the grotesque sight of police officers taking the knee to Black Lives Matter, a Cult-funded Marxist

organisation that supports violent riots and wants to destroy the nuclear family and white people.

## **He's not white? Shucks!**

Woke obsession with race was on display again when ten people were shot dead in Boulder, Colorado, in March, 2021. Cult-owned Woke TV channels like CNN said the shooter appeared to be a white man and Wokers were on Twitter condemning 'violent white men' with the usual mantras. Then the shooter's name was released as Ahmad Al Aliwi Alissa, an anti-Trump Arab-American, and the sigh of disappointment could be heard five miles away. Never mind that ten people were dead and what that meant for their families. Race baiting was all that mattered to these sick Cult-serving people like Barack Obama who exploited the deaths to further divide America on racial grounds which is his job for the Cult. This is the man that 'racist' white Americans made the first black president of the United States and then gave him a second term. Not-very-bright Obama has become filthy rich on the back of that and today appears to have a big influence on the Biden administration. Even so he's still a downtrodden black man and a victim of white supremacy. This disingenuous fraud reveals the contempt he has for black people when he puts on a Deep South Alabama accent whenever he talks to them, no, *at* them.

Another BLM red flag was how the now fully-Woke (fully-Cult) and fully-virtue-signalled professional soccer authorities had their teams taking the knee before every match in support of Marxist Black Lives Matter. Soccer authorities and clubs displayed 'Black Lives Matter' on the players' shirts and flashed the name on electronic billboards around the pitch. Any fans that condemned what is a Freemasonic taking-the-knee ritual were widely condemned as you would expect from the Woke virtue-signallers of professional sport and the now fully-Woke media. We have reverse racism in which you are banned from criticising any race or culture except for white people for whom anything goes – say what you like, no problem. What has this got to do with racial harmony and

equality? We've had black supremacists from Black Lives Matter telling white people to fall to their knees in the street and apologise for their white supremacy. Black supremacists acting like white supremacist slave owners of the past couldn't breach their self-obsessed, race-obsessed sense of self-purity. Joe Biden appointed a race-obsessed black supremacist Kristen Clarke to head the Justice Department Civil Rights Division. Clarke claimed that blacks are endowed with 'greater mental, physical and spiritual abilities' than whites. If anyone reversed that statement they would be vilified. Clarke is on-message so no problem. She's never seen a black-white situation in which the black figure is anything but a virtuous victim and she heads the Civil Rights Division which should treat everyone the same or it isn't civil rights. Another perception of the Renegade Mind: If something or someone is part of the Cult agenda they will be supported by Woke governments and media no matter what. If they're not, they will be condemned and censored. It really is that simple and so racist Clarke prospers despite (make that because of) her racism.

## **The end of culture**

Biden's administration is full of such racial, cultural and economic bias as the Cult requires the human family to be divided into warring factions. We are now seeing racially-segregated graduations and everything, but everything, is defined through the lens of perceived 'racism. We have 'racist' mathematics, 'racist' food and even 'racist' *plants*. World famous Kew Gardens in London said it was changing labels on plants and flowers to tell its pre-'Covid' more than two million visitors a year how racist they are. Kew director Richard Deverell said this was part of an effort to 'move quickly to decolonise collections' after they were approached by one Ajay Chhabra 'an actor with an insight into how sugar cane was linked to slavery'. They are *plants* you idiots. 'Decolonisation' in the Woke manual really means colonisation of society with its mentality and by extension colonisation by the Cult. We are witnessing a new Chinese-style 'Cultural Revolution' so essential to the success of all

Marxist takeovers. Our cultural past and traditions have to be swept away to allow a new culture to be built-back-better. Woke targeting of long-standing Western cultural pillars including historical monuments and cancelling of historical figures is what happened in the Mao revolution in China which ‘purged remnants of capitalist and traditional elements from Chinese society’ and installed Maoism as the dominant ideology’. For China see the Western world today and for ‘dominant ideology’ see Woke. Better still see Marxism or Maoism. The ‘Covid’ hoax has specifically sought to destroy the arts and all elements of Western culture from people meeting in a pub or restaurant to closing theatres, music venues, sports stadiums, places of worship and even banning *singing*. Destruction of Western society is also why criticism of any religion is banned except for Christianity which again is the dominant religion as white is the numerically-dominant race. Christianity may be fading rapidly, but its history and traditions are weaved through the fabric of Western society. Delete the pillars and other structures will follow until the whole thing collapses. I am not a Christian defending that religion when I say that. I have no religion. It’s just a fact. To this end Christianity has itself been turned Woke to usher its own downfall and its ranks are awash with ‘change agents’ – knowing and unknowing – at every level including Pope Francis (*definitely* knowing) and the clueless Archbishop of Canterbury Justin Welby (possibly not, but who can be sure?). Woke seeks to coordinate attacks on Western culture, traditions, and ways of life through ‘intersectionality’ defined as ‘the complex, cumulative way in which the effects of multiple forms of discrimination (such as racism, sexism, and classism) combine, overlap, or intersect especially in the experiences of marginalised individuals or groups’. Wade through the Orwellian Woke-speak and this means coordinating disparate groups in a common cause to overthrow freedom and liberal values.

The entire structure of public institutions has been infested with Woke – government at all levels, political parties, police, military, schools, universities, advertising, media and trade unions. This abomination has been achieved through the Cult web by appointing

Wokers to positions of power and battering non-Wokers into line through intimidation, isolation and threats to their job. Many have been fired in the wake of the empathy-deleted, vicious hostility of 'social justice' Wokers and the desire of gutless, spineless employers to virtue-signal their Wokeness. Corporations are filled with Wokers today, most notably those in Silicon Valley. Ironically at the top they are not Woke at all. They are only exploiting the mentality their Cult masters have created and funded to censor and enslave while the Wokers cheer them on until it's their turn. Thus the Woke 'liberal left' is an inversion of the traditional liberal left. Campaigning for justice on the grounds of power and wealth distribution has been replaced by campaigning for identity politics. The genuine traditional left would never have taken money from today's billionaire abusers of fairness and justice and nor would the billionaires have wanted to fund that genuine left. It would not have been in their interests to do so. The division of opinion in those days was between the haves and have nots. This all changed with Cult manipulated and funded identity politics. The division of opinion today is between Wokers and non-Wokers and not income brackets. Cult corporations and their billionaires may have taken wealth disparity to cataclysmic levels of injustice, but as long as they speak the language of Woke, hand out the dosh to the Woke network and censor the enemy they are 'one of us'. Billionaires who don't give a damn about injustice are laughing at them till their bellies hurt. Wokers are not even close to self-aware enough to see that. The transformed 'left' dynamic means that Wokers who drone on about 'social justice' are funded by billionaires that have destroyed social justice the world over. It's *why* they are billionaires.

## **The climate con**

Nothing encapsulates what I have said more comprehensively than the hoax of human-caused global warming. I have detailed in my books over the years how Cult operatives and organisations were the pump-primers from the start of the climate con. A purpose-built vehicle for this is the Club of Rome established by the Cult in 1968

with the Rockefellers and Rothschilds centrally involved all along. Their gofer frontman Maurice Strong, a Canadian oil millionaire, hosted the Earth Summit in Rio de Janeiro, Brazil, in 1992 where the global ‘green movement’ really expanded in earnest under the guiding hand of the Cult. The Earth Summit established Agenda 21 through the Cult-created-and-owned United Nations to use the illusion of human-caused climate change to justify the transformation of global society to save the world from climate disaster. It is a No-Problem-Reaction-Solution sold through governments, media, schools and universities as whole generations have been terrified into believing that the world was going to end in their lifetimes unless what old people had inflicted upon them was stopped by a complete restructuring of how everything is done. Chill, kids, it’s all a hoax. Such restructuring is precisely what the Cult agenda demands (purely by coincidence of course). Today this has been given the codename of the Great Reset which is only an updated term for Agenda 21 and its associated Agenda 2030. The latter, too, is administered through the UN and was voted into being by the General Assembly in 2015. Both 21 and 2030 seek centralised control of all resources and food right down to the raindrops falling on your own land. These are some of the demands of Agenda 21 established in 1992. See if you recognise this society emerging today:

- End national sovereignty
- State planning and management of all land resources, ecosystems, deserts, forests, mountains, oceans and fresh water; agriculture; rural development; biotechnology; and ensuring ‘*equity*’
- The state to ‘define the role’ of business and financial resources
- Abolition of private property
- ‘Restructuring’ the family unit (see BLM)
- Children raised by the state
- People told what their job will be
- Major restrictions on movement
- Creation of ‘human settlement zones’

- Mass resettlement as people are forced to vacate land where they live
- Dumbing down education
- Mass global depopulation in pursuit of all the above

The United Nations was created as a Trojan horse for world government. With the climate con of critical importance to promoting that outcome you would expect the UN to be involved. Oh, it's involved all right. The UN is promoting Agenda 21 and Agenda 2030 justified by 'climate change' while also driving the climate hoax through its Intergovernmental Panel on Climate Change (IPCC), one of the world's most corrupt organisations. The IPCC has been lying ferociously and constantly since the day it opened its doors with the global media hanging unquestioningly on its every mendacious word. The Green movement is entirely Woke and has long lost its original environmental focus since it was co-opted by the Cult. An obsession with 'global warming' has deleted its values and scrambled its head. I experienced a small example of what I mean on a beautiful country walk that I have enjoyed several times a week for many years. The path merged into the fields and forests and you felt at one with the natural world. Then a 'Green' organisation, the Hampshire and Isle of Wight Wildlife Trust, took over part of the land and proceeded to cut down a large number of trees, including mature ones, to install a horrible big, bright steel 'this-is-ours-stay-out' fence that destroyed the whole atmosphere of this beautiful place. No one with a feel for nature would do that. Day after day I walked to the sound of chainsaws and a magnificent mature weeping willow tree that I so admired was cut down at the base of the trunk. When I challenged a Woke young girl in a green shirt (of course) about this vandalism she replied: 'It's a weeping willow – it will grow back.' This is what people are paying for when they donate to the Hampshire and Isle of Wight Wildlife Trust and many other 'green' organisations today. It is not the environmental movement that I knew and instead has become a support-system – as with Extinction Rebellion – for a very dark agenda.

## **Private jets for climate justice**

The Cult-owned, Gates-funded, World Economic Forum and its founder Klaus Schwab were behind the emergence of Greta Thunberg to harness the young behind the climate agenda and she was invited to speak to the world at ... the UN. Schwab published a book, *Covid-19: The Great Reset* in 2020 in which he used the 'Covid' hoax and the climate hoax to lay out a new society straight out of Agenda 21 and Agenda 2030. Bill Gates followed in early 2021 when he took time out from destroying the world to produce a book in his name about the way to save it. Gates flies across the world in private jets and admitted that 'I probably have one of the highest greenhouse gas footprints of anyone on the planet ... my personal flying alone is gigantic.' He has also bid for the planet's biggest private jet operator. Other climate change saviours who fly in private jets include John Kerry, the US Special Presidential Envoy for Climate, and actor Leonardo DiCaprio, a 'UN Messenger of Peace with special focus on climate change'. These people are so full of bullshit they could corner the market in manure. We mustn't be sceptical, though, because the Gates book, *How to Avoid a Climate Disaster: The Solutions We Have and the Breakthroughs We Need*, is a genuine attempt to protect the world and not an obvious pile of excrement attributed to a mega-psychopath aimed at selling his masters' plans for humanity. The Gates book and the other shite-pile by Klaus Schwab could have been written by the same person and may well have been. Both use 'climate change' and 'Covid' as the excuses for their new society and by coincidence the Cult's World Economic Forum and Bill and Melinda Gates Foundation promote the climate hoax and hosted Event 201 which pre-empted with a 'simulation' the very 'coronavirus' hoax that would be simulated for real on humanity within weeks. The British 'royal' family is promoting the 'Reset' as you would expect through Prince 'climate change caused the war in Syria' Charles and his hapless son Prince William who said that we must 'reset our relationship with nature and our trajectory as a species' to avoid a climate disaster. Amazing how many promoters of the 'Covid' and 'climate change' control

systems are connected to Gates and the World Economic Forum. A ‘study’ in early 2021 claimed that carbon dioxide emissions must fall by the equivalent of a global lockdown roughly every two years for the next decade to save the planet. The ‘study’ appeared in the same period that the Schwab mob claimed in a video that lockdowns destroying the lives of billions are good because they make the earth ‘quieter’ with less ‘ambient noise’. They took down the video amid a public backlash for such arrogant, empathy-deleted stupidity You see, however, where they are going with this. Corinne Le Quéré, a professor at the Tyndall Centre for Climate Change Research, University of East Anglia, was lead author of the climate lockdown study, and she writes for ... the World Economic Forum. Gates calls in ‘his’ book for changing ‘every aspect of the economy’ (long-time Cult agenda) and for humans to eat synthetic ‘meat’ (predicted in my books) while cows and other farm animals are eliminated.

Australian TV host and commentator Alan Jones described what carbon emission targets would mean for farm animals in Australia alone if emissions were reduced as demanded by 35 percent by 2030 and zero by 2050:

Well, let’s take agriculture, the total emissions from agriculture are about 75 million tonnes of carbon dioxide, equivalent. Now reduce that by 35 percent and you have to come down to 50 million tonnes, I’ve done the maths. So if you take for example 1.5 million cows, you’re going to have to reduce the herd by 525,000 [by] 2030, nine years, that’s 58,000 cows a year. The beef herd’s 30 million, reduce that by 35 percent, that’s 10.5 million, which means 1.2 million cattle have to go every year between now and 2030. This is insanity!

There are 75 million sheep. Reduce that by 35 percent, that’s 26 million sheep, that’s almost 3 million a year. So under the Paris Agreement over 30 million beasts. dairy cows, cattle, pigs and sheep would go. More than 8,000 every minute of every hour for the next decade, do these people know what they’re talking about?

Clearly they don’t at the level of campaigners, politicians and administrators. The Cult *does* know; that’s the outcome it wants. We are faced with not just a war on humanity. Animals and the natural world are being targeted and I have been saying since the ‘Covid’ hoax began that the plan eventually was to claim that the ‘deadly virus’ is able to jump from animals, including farm animals and

domestic pets, to humans. Just before this book went into production came this story: 'Russia registers world's first Covid-19 vaccine for cats & dogs as makers of Sputnik V warn pets & farm animals could spread virus'. The report said 'top scientists warned that the deadly pathogen could soon begin spreading through homes and farms' and 'the next stage is the infection of farm and domestic animals'. Know the outcome and you'll see the journey. Think what that would mean for animals and keep your eye on a term called zoonosis or zoonotic diseases which transmit between animals and humans. The Cult wants to break the connection between animals and people as it does between people and people. Farm animals fit with the Cult agenda to transform food from natural to synthetic.

### **The gas of life is killing us**

There can be few greater examples of Cult inversion than the condemnation of carbon dioxide as a dangerous pollutant when it is the gas of life. Without it the natural world would be dead and so we would all be dead. We breathe in oxygen and breathe out carbon dioxide while plants produce oxygen and absorb carbon dioxide. It is a perfect symbiotic relationship that the Cult wants to dismantle for reasons I will come to in the final two chapters. Gates, Schwab, other Cult operatives and mindless repeaters, want the world to be 'carbon neutral' by at least 2050 and the earlier the better. 'Zero carbon' is the cry echoed by lunatics calling for 'Zero Covid' when we already have it. These carbon emission targets will deindustrialise the world in accordance with Cult plans – the post-industrial, post-democratic society – and with so-called renewables like solar and wind not coming even close to meeting human energy needs blackouts and cold are inevitable. Texans got the picture in the winter of 2021 when a snow storm stopped wind turbines and solar panels from working and the lights went down along with water which relies on electricity for its supply system. Gates wants everything to be powered by electricity to ensure that his masters have the kill switch to stop all human activity, movement, cooking, water and warmth any time they like. The climate lie is so

stupendously inverted that it claims we must urgently reduce carbon dioxide when we *don't have enough*.

Co<sub>2</sub> in the atmosphere is a little above 400 parts per million when the optimum for plant growth is 2,000 ppm and when it falls anywhere near 150 ppm the natural world starts to die and so do we. It fell to as low as 280 ppm in an 1880 measurement in Hawaii and rose to 413 ppm in 2019 with industrialisation which is why the planet has become *greener* in the industrial period. How insane then that psychopathic madman Gates is not satisfied only with blocking the rise of Co<sub>2</sub>. He's funding technology to suck it out of the atmosphere. The reason why will become clear. The industrial era is not destroying the world through Co<sub>2</sub> and has instead turned around a potentially disastrous ongoing fall in Co<sub>2</sub>. Greenpeace co-founder and scientist Patrick Moore walked away from Greenpeace in 1986 and has exposed the green movement for fear-mongering and lies. He said that 500 million years ago there was *17 times* more Co<sub>2</sub> in the atmosphere than we have today and levels have been falling for hundreds of millions of years. In the last 150 million years Co<sub>2</sub> levels in Earth's atmosphere had reduced by *90 percent*. Moore said that by the time humanity began to unlock carbon dioxide from fossil fuels we were at '38 seconds to midnight' and in that sense: 'Humans are [the Earth's] salvation.' Moore made the point that only half the Co<sub>2</sub> emitted by fossil fuels stays in the atmosphere and we should remember that all pollution pouring from chimneys that we are told is carbon dioxide is in fact nothing of the kind. It's pollution. Carbon dioxide is an invisible gas.

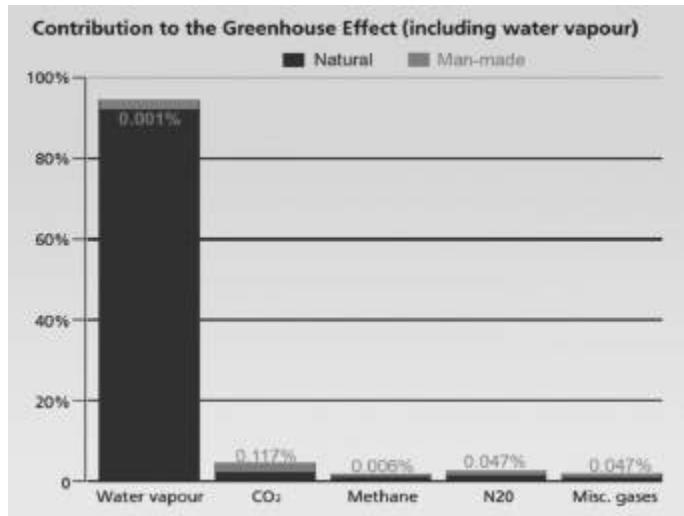
William Happer, Professor of Physics at Princeton University and long-time government adviser on climate, has emphasised the Co<sub>2</sub> deficiency for maximum growth and food production. Greenhouse growers don't add carbon dioxide for a bit of fun. He said that most of the warming in the last 100 years, after the earth emerged from the super-cold period of the 'Little Ice Age' into a natural warming cycle, was over by 1940. Happer said that a peak year for warming in 1988 can be explained by a 'monster El Nino' which is a natural and cyclical warming of the Pacific that has nothing to do with 'climate

change'. He said the effect of Co2 could be compared to painting a wall with red paint in that once two or three coats have been applied it didn't matter how much more you slapped on because the wall will not get much redder. Almost all the effect of the rise in Co2 has already happened, he said, and the volume in the atmosphere would now have to *double* to increase temperature by a single degree. Climate hoaxers know this and they have invented the most ridiculously complicated series of 'feedback' loops to try to overcome this rather devastating fact. You hear puppet Greta going on cluelessly about feedback loops and this is why.

### **The Sun affects temperature? No you *climate denier***

Some other nonsense to contemplate: Climate graphs show that rises in temperature do not follow rises in Co2 – *it's the other way round* with a lag between the two of some 800 years. If we go back 800 years from present time we hit the Medieval Warm Period when temperatures were higher than now without any industrialisation and this was followed by the Little Ice Age when temperatures plummeted. The world was still emerging from these centuries of serious cold when many climate records began which makes the ever-repeated line of the 'hottest year since records began' meaningless when you are not comparing like with like. The coldest period of the Little Ice Age corresponded with the lowest period of sunspot activity when the Sun was at its least active. Proper scientists will not be at all surprised by this when it confirms the obvious fact that earth temperature is affected by the scale of Sun activity and the energetic power that it subsequently emits; but when is the last time you heard a climate hoaxter talking about the Sun as a source of earth temperature?? Everything has to be focussed on Co2 which makes up just 0.117 percent of so-called greenhouse gases and only a fraction of even that is generated by human activity. The rest is natural. More than 90 percent of those greenhouse gases are water vapour and clouds ([Fig 9](#)). Ban moisture I say. Have you noticed that the climate hoaxers no longer use the polar bear as their promotion image? That's because far from becoming extinct polar

bear communities are stable or thriving. Joe Bastardi, American meteorologist, weather forecaster and outspoken critic of the climate lie, documents in his book *The Climate Chronicles* how weather patterns and events claimed to be evidence of climate change have been happening since long before industrialisation: 'What happened before naturally is happening again, as is to be expected given the cyclical nature of the climate due to the design of the planet.' If you read the detailed background to the climate hoax in my other books you will shake your head and wonder how anyone could believe the crap which has spawned a multi-trillion dollar industry based on absolute garbage (see HIV causes AIDS and Sars-Cov-2 causes 'Covid-19'). Climate and 'Covid' have much in common given they have the same source. They both have the contradictory *everything* factor in which everything is explained by reference to them. It's hot – 'it's climate change'. It's cold – 'it's climate change'. I got a sniffle – 'it's Covid'. I haven't got a sniffle – 'it's Covid'. Not having a sniffle has to be a symptom of 'Covid'. Everything is and not having a sniffle is especially dangerous if you are a slow walker. For sheer audacity I offer you a Cambridge University 'study' that actually linked 'Covid' to 'climate change'. It had to happen eventually. They concluded that climate change played a role in 'Covid-19' spreading from animals to humans because ... wait for it ... I kid you not ... *the two groups were forced closer together as populations grow.* Er, that's it. The whole foundation on which this depended was that 'Bats are the likely zoonotic origin of SARS-CoV-1 and SARS-CoV-2'. Well, they are not. They are nothing to do with it. Apart from bats not being the origin and therefore 'climate change' effects on bats being irrelevant I am in awe of their academic insight. Where would we be without them? Not where we are that's for sure.



**Figure 9:** The idea that the gas of life is disastrously changing the climate is an insult to brain cell activity.

One other point about the weather is that climate modification is now well advanced and not every major weather event is natural – or earthquake come to that. I cover this subject at some length in other books. China is openly planning a rapid expansion of its weather modification programme which includes changing the climate in an area more than one and a half times the size of India. China used weather manipulation to ensure clear skies during the 2008 Olympics in Beijing. I have quoted from US military documents detailing how to employ weather manipulation as a weapon of war and they did that in the 1960s and 70s during the conflict in Vietnam with Operation Popeye manipulating monsoon rains for military purposes. Why would there be international treaties on weather modification if it wasn't possible? Of course it is. Weather is energetic information and it can be changed.

## How was the climate hoax pulled off? See 'Covid'

If you can get billions to believe in a 'virus' that doesn't exist you can get them to believe in human-caused climate change that doesn't exist. Both are being used by the Cult to transform global society in the way it has long planned. Both hoaxes have been achieved in pretty much the same way. First you declare a lie is a fact. There's a

'virus' you call SARS-Cov-2 or humans are warming the planet with their behaviour. Next this becomes, via Cult networks, the foundation of government, academic and science policy and belief. Those who parrot the mantra are given big grants to produce research that confirms the narrative is true and ever more 'symptoms' are added to make the 'virus'/'climate change' sound even more scary. Scientists and researchers who challenge the narrative have their grants withdrawn and their careers destroyed. The media promote the lie as the unquestionable truth and censor those with an alternative view or evidence. A great percentage of the population believe what they are told as the lie becomes an everybody-knows-that and the believing-masses turn on those with a mind of their own. The technique has been used endlessly throughout human history. Wokers are the biggest promotorrs of the climate lie *and* 'Covid' fascism because their minds are owned by the Cult; their sense of self-righteous self-purity knows no bounds; and they exist in a bubble of reality in which facts are irrelevant and only get in the way of looking without seeing.

Running through all of this like veins in a blue cheese is control of information, which means control of perception, which means control of behaviour, which collectively means control of human society. The Cult owns the global media and Silicon Valley fascists for the simple reason that it *has* to. Without control of information it can't control perception and through that human society. Examine every facet of the Cult agenda and you will see that anything supporting its introduction is never censored while anything pushing back is always censored. I say again: Psychopaths that know why they are doing this must go before Nuremberg trials and those that follow their orders must trot along behind them into the same dock. 'I was just following orders' didn't work the first time and it must not work now. Nuremberg trials must be held all over the world before public juries for politicians, government officials, police, compliant doctors, scientists and virologists, and all Cult operatives such as Gates, Tedros, Fauci, Vallance, Whitty, Ferguson, Zuckerberg, Wojcicki, Brin, Page, Dorsey, the whole damn lot of

them – including, no *especially*, the psychopath psychologists. Without them and the brainless, gutless excuses for journalists that have repeated their lies, none of this could be happening. Nobody can be allowed to escape justice for the psychological and economic Armageddon they are all responsible for visiting upon the human race.

As for the compliant, unquestioning, swathes of humanity, and the self-obsessed, all-knowing ignorance of the Wokers ... don't start me. God help their kids. God help their grandkids. God *help them*.

## CHAPTER NINE

### We must have it? So what is it?

*Well I won't back down. No, I won't back down. You can stand me up at the Gates of Hell. But I won't back down*

Tom Petty

I will now focus on the genetically-manipulating ‘Covid vaccines’ which do not meet this official definition of a vaccine by the US Centers for Disease Control (CDC): ‘A product that stimulates a person’s immune system to produce immunity to a specific disease, protecting the person from that disease.’ On that basis ‘Covid vaccines’ are not a vaccine in that the makers don’t even claim they stop infection or transmission.

They are instead part of a multi-levelled conspiracy to change the nature of the human body and what it means to be ‘human’ and to depopulate an enormous swathe of humanity. What I shall call Human 1.0 is on the cusp of becoming Human 2.0 and for very sinister reasons. Before I get to the ‘Covid vaccine’ in detail here’s some background to vaccines in general. Government regulators do not test vaccines – the makers do – and the makers control which data is revealed and which isn’t. Children in America are given 50 vaccine doses by age six and 69 by age 19 and the effect of the whole combined schedule has never been tested. Autoimmune diseases when the immune system attacks its own body have soared in the mass vaccine era and so has disease in general in children and the young. Why wouldn’t this be the case when vaccines target the *immune system*? The US government gave Big Pharma drug

companies immunity from prosecution for vaccine death and injury in the 1986 National Childhood Vaccine Injury Act (NCVIA) and since then the government (taxpayer) has been funding compensation for the consequences of Big Pharma vaccines. The criminal and satanic drug giants can't lose and the vaccine schedule has increased dramatically since 1986 for this reason. There is no incentive to make vaccines safe and a big incentive to make money by introducing ever more. Even against a ridiculously high bar to prove vaccine liability, and with the government controlling the hearing in which it is being challenged for compensation, the vaccine court has so far paid out more than \$4 billion. These are the vaccines we are told are safe and psychopaths like Zuckerberg censor posts saying otherwise. The immunity law was even justified by a ruling that vaccines by their nature were 'unavoidably unsafe'.

Check out the ingredients of vaccines and you will be shocked if you are new to this. *They put that in children's bodies?? What??* Try aluminium, a brain toxin connected to dementia, aborted foetal tissue and formaldehyde which is used to embalm corpses. World-renowned aluminium expert Christopher Exley had his research into the health effect of aluminium in vaccines shut down by Keele University in the UK when it began taking funding from the Bill and Melinda Gates Foundation. Research when diseases 'eradicated' by vaccines began to decline and you will find the fall began long *before* the vaccine was introduced. Sometimes the fall even plateaued after the vaccine. Diseases like scarlet fever for which there was no vaccine declined in the same way because of environmental and other factors. A perfect case in point is the polio vaccine. Polio began when lead arsenate was first sprayed as an insecticide and residues remained in food products. Spraying started in 1892 and the first US polio epidemic came in Vermont in 1894. The simple answer was to stop spraying, but Rockefeller-created Big Pharma had a better idea. Polio was decreed to be caused by the *poliovirus* which 'spreads from person to person and can infect a person's spinal cord'. Lead arsenate was replaced by the lethal DDT which had the same effect of causing paralysis by damaging the brain and central nervous

system. Polio plummeted when DDT was reduced and then banned, but the vaccine is still given the credit for something it didn't do. Today by far the biggest cause of polio is the vaccines promoted by Bill Gates. Vaccine justice campaigner Robert Kennedy Jr, son of assassinated (by the Cult) US Attorney General Robert Kennedy, wrote:

In 2017, the World Health Organization (WHO) reluctantly admitted that the global explosion in polio is predominantly vaccine strain. The most frightening epidemics in Congo, Afghanistan, and the Philippines, are all linked to vaccines. In fact, by 2018, 70% of global polio cases were vaccine strain.

Vaccines make fortunes for Cult-owned Gates and Big Pharma while undermining the health and immune systems of the population. We had a glimpse of the mentality behind the Big Pharma cartel with a report on WION (World is One News), an international English language TV station based in India, which exposed the extraordinary behaviour of US drug company Pfizer over its 'Covid vaccine'. The WION report told how Pfizer had made fantastic demands of Argentina, Brazil and other countries in return for its 'vaccine'. These included immunity from prosecution, even for Pfizer negligence, government insurance to protect Pfizer from law suits and handing over as collateral sovereign assets of the country to include Argentina's bank reserves, military bases and embassy buildings. Pfizer demanded the same of Brazil in the form of waiving sovereignty of its assets abroad; exempting Pfizer from Brazilian laws; and giving Pfizer immunity from all civil liability. This is a 'vaccine' developed with government funding. Big Pharma is evil incarnate as a creation of the Cult and all must be handed tickets to Nuremberg.

### **Phantom 'vaccine' for a phantom 'disease'**

I'll expose the 'Covid vaccine' fraud and then go on to the wider background of why the Cult has set out to 'vaccinate' every man, woman and child on the planet for an alleged 'new disease' with a survival rate of 99.77 percent (or more) even by the grotesquely-

manipulated figures of the World Health Organization and Johns Hopkins University. The ‘infection’ to ‘death’ ratio is 0.23 to 0.15 percent according to Stanford epidemiologist Dr John Ioannidis and while estimates vary the danger remains tiny. I say that if the truth be told the fake infection to fake death ratio is zero. Never mind all the evidence I have presented here and in *The Answer* that there is no ‘virus’ let us just focus for a moment on that death-rate figure of say 0.23 percent. The figure includes all those worldwide who have tested positive with a test not testing for the ‘virus’ and then died within 28 days or even longer of any other cause – *any other cause*. Now subtract all those illusory ‘Covid’ deaths on the global data sheets from the 0.23 percent. What do you think you would be left with? *Zero*. A vaccination has never been successfully developed for a so-called coronavirus. They have all failed at the animal testing stage when they caused hypersensitivity to what they were claiming to protect against and made the impact of a disease far worse. Cult-owned vaccine corporations got around that problem this time by bypassing animal trials, going straight to humans and making the length of the ‘trials’ before the public rollout as short as they could get away with. Normally it takes five to ten years or more to develop vaccines that still cause demonstrable harm to many people and that’s without including the long-term effects that are never officially connected to the vaccination. ‘Covid’ non-vaccines have been officially produced and approved in a matter of months from a standing start and part of the reason is that (a) they were developed before the ‘Covid’ hoax began and (b) they are based on computer programs and not natural sources. Official non-trials were so short that government agencies gave *emergency*, not full, approval. ‘Trials’ were not even completed and full approval cannot be secured until they are. Public ‘Covid vaccination’ is actually a *continuation of the trial*. Drug company ‘trials’ are not scheduled to end until 2023 by which time a lot of people are going to be dead. Data on which government agencies gave this emergency approval was supplied by the Big Pharma corporations themselves in the form of Pfizer/BioNTech, AstraZeneca, Moderna, Johnson & Johnson, and

others, and this is the case with all vaccines. By its very nature *emergency* approval means drug companies do not have to prove that the ‘vaccine’ is ‘safe and effective’. How could they with trials way short of complete? Government regulators only have to *believe* that they *could* be safe and effective. It is criminal manipulation to get products in circulation with no testing worth the name. Agencies giving that approval are infested with Big Pharma-connected place-people and they act in the interests of Big Pharma (the Cult) and not the public about whom they do not give a damn.

## **More human lab rats**

‘Covid vaccines’ produced in record time by Pfizer/BioNTech and Moderna employ a technique *never approved before for use on humans*. They are known as mRNA ‘vaccines’ and inject a synthetic version of ‘viral’ mRNA or ‘messenger RNA’. The key is in the term ‘messenger’. The body works, or doesn’t, on the basis of information messaging. Communications are constantly passing between and within the genetic system and the brain. Change those messages and you change the state of the body and even its very nature and you can change psychology and behaviour by the way the brain processes information. I think you are going to see significant changes in personality and perception of many people who have had the ‘Covid vaccine’ synthetic potions. Insider Aldous Huxley predicted the following in 1961 and mRNA ‘vaccines’ can be included in the term ‘pharmacological methods’:

There will be, in the next generation or so, a pharmacological method of making people love their servitude, and producing dictatorship without tears, so to speak, producing a kind of painless concentration camp for entire societies, so that people will in fact have their own liberties taken away from them, but rather enjoy it, because they will be distracted from any desire to rebel by propaganda or brainwashing, or brainwashing enhanced by pharmacological methods. And this seems to be the final revolution.

Apologists claim that mRNA synthetic ‘vaccines’ don’t change the DNA genetic blueprint because RNA does not affect DNA only the other way round. This is so disingenuous. A process called ‘reverse

'transcription' can convert RNA into DNA and be integrated into DNA in the cell nucleus. This was highlighted in December, 2020, by scientists at Harvard and Massachusetts Institute of Technology (MIT). Geneticists report that more than 40 percent of mammalian genomes results from reverse transcription. On the most basic level if messaging changes then that sequence must lead to changes in DNA which is receiving and transmitting those communications. How can introducing synthetic material into cells not change the cells where DNA is located? The process is known as transfection which is defined as 'a technique to insert foreign nucleic acid (DNA or RNA) into a cell, typically with the intention of altering the properties of the cell'. Researchers at the Sloan Kettering Institute in New York found that changes in messenger RNA can deactivate tumour-suppressing proteins and thereby promote cancer. This is what happens when you mess with messaging. 'Covid vaccine' maker Moderna was founded in 2010 by Canadian stem cell biologist Derrick J. Rossi after his breakthrough discovery in the field of transforming and reprogramming stem cells. These are neutral cells that can be programmed to become any cell including sperm cells. Moderna was therefore founded on the principle of genetic manipulation and has never produced any vaccine or drug before its genetically-manipulating synthetic 'Covid' shite. Look at the name – Mode-RNA or Modify-RNA. Another important point is that the US Supreme Court has ruled that genetically-modified DNA, or complementary DNA (cDNA) synthesized in the laboratory from messenger RNA, can be patented and owned. These psychopaths are doing this to the human body.

Cells replicate synthetic mRNA in the 'Covid vaccines' and in theory the body is tricked into making antigens which trigger antibodies to target the 'virus spike proteins' which as Dr Tom Cowan said have *never been seen*. Cut the crap and these 'vaccines' deliver *self-replicating* synthetic material to the cells with the effect of changing human DNA. The more of them you have the more that process is compounded while synthetic material is all the time self-replicating. 'Vaccine'-maker Moderna describes mRNA as 'like

software for the cell' and so they are messing with the body's software. What happens when you change the software in a computer? Everything changes. For this reason the Cult is preparing a production line of mRNA 'Covid vaccines' and a long list of excuses to use them as with all the 'variants' of a 'virus' never shown to exist. The plan is further to transfer the mRNA technique to other vaccines mostly given to children and young people. The cumulative consequences will be a transformation of human DNA through a constant infusion of synthetic genetic material which will kill many and change the rest. Now consider that governments that have given emergency approval for a vaccine that's not a vaccine; never been approved for humans before; had no testing worth the name; and the makers have been given immunity from prosecution for any deaths or adverse effects suffered by the public. The UK government awarded *permanent legal indemnity* to itself and its employees for harm done when a patient is being treated for 'Covid-19' or 'suspected Covid-19'. That is quite a thought when these are possible 'side-effects' from the 'vaccine' (they are not 'side', they are effects) listed by the US Food and Drug Administration:

Guillain-Barre syndrome; acute disseminated encephalomyelitis; transverse myelitis; encephalitis; myelitis; encephalomyelitis; meningoencephalitis; meningitis; encephalopathy; convulsions; seizures; stroke; narcolepsy; cataplexy; anaphylaxis; acute myocardial infarction (heart attack); myocarditis; pericarditis; autoimmune disease; death; implications for pregnancy, and birth outcomes; other acute demyelinating diseases; non anaphylactic allergy reactions; thrombocytopenia ; disseminated intravascular coagulation; venous thromboembolism; arthritis; arthralgia; joint pain; Kawasaki disease; multisystem inflammatory syndrome in children; vaccine enhanced disease. The latter is the way the 'vaccine' has the potential to make diseases far worse than they would otherwise be.

UK doctor and freedom campaigner Vernon Coleman described the conditions in this list as 'all unpleasant, most of them very serious, and you can't get more serious than death'. The thought that anyone at all has had the 'vaccine' in these circumstances is testament to the potential that humanity has for clueless, unquestioning, stupidity and for many that programmed stupidity has already been terminal.

## An insider speaks

Dr Michael Yeadon is a former Vice President, head of research and Chief Scientific Adviser at vaccine giant Pfizer. Yeadon worked on the inside of Big Pharma, but that did not stop him becoming a vocal critic of 'Covid vaccines' and their potential for multiple harms, including infertility in women. By the spring of 2021 he went much further and even used the no, no, term 'conspiracy'. When you begin to see what is going on it is impossible not to do so. Yeadon spoke out in an interview with freedom campaigner James Delingpole and I mentioned earlier how he said that no one had samples of 'the virus'. He explained that the mRNA technique originated in the anti-cancer field and ways to turn on and off certain genes which could be advantageous if you wanted to stop cancer growing out of control. 'That's the origin of them. They are a very unusual application, really.' Yeadon said that treating a cancer patient with an aggressive procedure might be understandable if the alternative was dying, but it was quite another thing to use the same technique as a public health measure. Most people involved wouldn't catch the infectious agent you were vaccinating against and if they did they probably wouldn't die:

If you are really using it as a public health measure you really want to as close as you can get to zero side-effects ... I find it odd that they chose techniques that were really cutting their teeth in the field of oncology and I'm worried that in using gene-based vaccines that have to be injected in the body and spread around the body, get taken up into some cells, and the regulators haven't quite told us which cells they get taken up into ... you are going to be generating a wide range of responses ... with multiple steps each of which could go well or badly.

I doubt the Cult intends it to go well. Yeadon said that you can put any gene you like into the body through the 'vaccine'. 'You can certainly give them a gene that would do them some harm if you wanted.' I was intrigued when he said that when used in the cancer field the technique could turn genes on and off. I explore this process in *The Answer* and with different genes having different functions you could create mayhem – physically and psychologically – if you turned the wrong ones on and the right ones off. I read reports of an experiment by researchers at the University of Washington's school of computer science and engineering in which they encoded DNA to infect computers. The body is itself a biological computer and if human DNA can inflict damage on a computer why can't the computer via synthetic material mess with the human body? It can. The Washington research team said it was possible to insert malicious malware into 'physical DNA strands' and corrupt the computer system of a gene sequencing machine as it 'reads gene letters and stores them as binary digits 0 and 1'. They concluded that hackers could one day use blood or spit samples to access computer systems and obtain sensitive data from police forensics labs or infect genome files. It is at this level of digital interaction that synthetic 'vaccines' need to be seen to get the full picture and that will become very clear later on. Michael Yeadon said it made no sense to give the 'vaccine' to younger people who were in no danger from the 'virus'. What was the benefit? It was all downside with potential effects:

The fact that my government in what I thought was a civilised, rational country, is raining [the 'vaccine'] on people in their 30s and 40s, even my children in their 20s, they're getting letters and phone calls, I know this is not right and any of you doctors who are vaccinating you know it's not right, too. They are not at risk. They are not at risk from the disease, so you are now hoping that the side-effects are so rare that you get away with it. You don't give new technology ... that you don't understand to 100 percent of the population.

Blood clot problems with the AstraZeneca 'vaccine' have been affecting younger people to emphasise the downside risks with no benefit. AstraZeneca's version, produced with Oxford University, does not use mRNA, but still gets its toxic cocktail inside cells where

it targets DNA. The Johnson & Johnson ‘vaccine’ which uses a similar technique has also produced blood clot effects to such an extent that the United States paused its use at one point. They are all ‘gene therapy’ (cell modification) procedures and not ‘vaccines’. The truth is that once the content of these injections enter cells we have no idea what the effect will be. People can speculate and some can give very educated opinions and that’s good. In the end, though, only the makers know what their potions are designed to do and even they won’t know every last consequence. Michael Yeadon was scathing about doctors doing what they knew to be wrong.

‘Everyone’s mute’, he said. Doctors in the NHS must know this was not right, coming into work and injecting people. ‘I don’t know how they sleep at night. I know I couldn’t do it. I know that if I were in that position I’d have to quit.’ He said he knew enough about toxicology to know this was not a good risk-benefit. Yeadon had spoken to seven or eight university professors and all except two would not speak out publicly. Their universities had a policy that no one said anything that countered the government and its medical advisors. They were afraid of losing their government grants. This is how intimidation has been used to silence the truth at every level of the system. I say silence, but these people could still speak out if they made that choice. Yeadon called them ‘moral cowards’ – ‘This is about your children and grandchildren’s lives and you have just buggered off and left it.’

## **‘Variant’ nonsense**

Some of his most powerful comments related to the alleged ‘variants’ being used to instil more fear, justify more lockdowns, and introduce more ‘vaccines’. He said government claims about ‘variants’ were nonsense. He had checked the alleged variant ‘codes’ and they were 99.7 percent identical to the ‘original’. This was the human identity difference equivalent to putting a baseball cap on and off or wearing it the other way round. A 0.3 percent difference would make it impossible for that ‘variant’ to escape immunity from the ‘original’. This made no sense of having new ‘vaccines’ for

'variants'. He said there would have to be at least a *30 percent* difference for that to be justified and even then he believed the immune system would still recognise what it was. Gates-funded 'variant modeller' and 'vaccine'-pusher John Edmunds might care to comment. Yeadon said drug companies were making new versions of the 'vaccine' as a 'top up' for 'variants'. Worse than that, he said, the 'regulators' around the world like the MHRA in the UK had got together and agreed that because 'vaccines' for 'variants' were so similar to the first 'vaccines' *they did not have to do safety studies*. How transparently sinister that is. This is when Yeadon said: 'There is a conspiracy here.' There was no need for another vaccine for 'variants' and yet we were told that there was and the country had shut its borders because of them. 'They are going into hundreds of millions of arms without passing 'go' or any regulator. Why did they do that? Why did they pick this method of making the vaccine?'

The reason had to be something bigger than that it seemed and 'it's not protection against the virus'. It's was a far bigger project that meant politicians and advisers were willing to do things and not do things that knowingly resulted in avoidable deaths – 'that's already happened when you think about lockdown and deprivation of health care for a year.' He spoke of people prepared to do something that results in the avoidable death of their fellow human beings and it not bother them. This is the penny-drop I have been working to get across for more than 30 years – the level of pure evil we are dealing with. Yeadon said his friends and associates could not believe there could be that much evil, but he reminded them of Stalin, Pol Pot and Hitler and of what Stalin had said: 'One death is a tragedy. A million? A statistic.' He could not think of a benign explanation for why you need top-up vaccines 'which I'm sure you don't' and for the regulators 'to just get out of the way and wave them through'. Why would the regulators do that when they were still wrestling with the dangers of the 'parent' vaccine? He was clearly shocked by what he had seen since the 'Covid' hoax began and now he was thinking the previously unthinkable:

If you wanted to depopulate a significant proportion of the world and to do it in a way that doesn't involve destruction of the environment with nuclear weapons, poisoning everyone with anthrax or something like that, and you wanted plausible deniability while you had a multi-year infectious disease crisis, I actually don't think you could come up with a better plan of work than seems to be in front of me. I can't say that's what they are going to do, but I can't think of a benign explanation why they are doing it.

He said he never thought that they would get rid of 99 percent of humans, but now he wondered. 'If you wanted to that this would be a hell of a way to do it – it would be unstoppable folks.' Yeadon had concluded that those who submitted to the 'vaccine' would be allowed to have some kind of normal life (but for how long?) while screws were tightened to coerce and mandate the last few percent. 'I think they'll put the rest of them in a prison camp. I wish I was wrong, but I don't think I am.' Other points he made included: There were no coronavirus vaccines then suddenly they all come along at the same time; we have no idea of the long term affect with trials so short; coercing or forcing people to have medical procedures is against the Nuremberg Code instigated when the Nazis did just that; people should at least delay having the 'vaccine'; a quick Internet search confirms that masks don't reduce respiratory viral transmission and 'the government knows that'; they have smashed civil society and they know that, too; two dozen peer-reviewed studies show no connection between lockdown and reducing deaths; he knew from personal friends the elite were still flying around and going on holiday while the public were locked down; the elite were not having the 'vaccines'. He was also asked if 'vaccines' could be made to target difference races. He said he didn't know, but the document by the Project for the New American Century in September, 2000, said developing 'advanced forms of biological warfare that can target *specific genotypes* may transform biological warfare from the realm of terror to a politically useful tool.' Oh, they're evil all right. Of that we can be *absolutely* sure.

## **Another cull of old people**

We have seen from the CDC definition that the mRNA 'Covid vaccine' is not a vaccine and nor are the others that *claim* to reduce 'severity of symptoms' in *some* people, but not protect from infection or transmission. What about all the lies about returning to 'normal' if people were 'vaccinated'? If they are not claimed to stop infection and transmission of the alleged 'virus', how does anything change? This was all lies to manipulate people to take the jabs and we are seeing that now with masks and distancing still required for the 'vaccinated'. How did they think that elderly people with fragile health and immune responses were going to be affected by infusing their cells with synthetic material and other toxic substances? They *knew* that in the short and long term it would be devastating and fatal as the culling of the old that began with the first lockdowns was continued with the 'vaccine'. Death rates in care homes soared immediately residents began to be 'vaccinated' – infused with synthetic material. Brave and committed whistleblower nurses put their careers at risk by exposing this truth while the rest kept their heads down and their mouths shut to put their careers before those they are supposed to care for. A long-time American Certified Nursing Assistant who gave his name as James posted a video in which he described emotionally what happened in his care home when vaccination began. He said that during 2020 very few residents were sick with 'Covid' and no one died during the entire year; but shortly after the Pfizer mRNA injections 14 people died within two weeks and many others were near death. 'They're dropping like flies', he said. Residents who walked on their own before the shot could no longer and they had lost their ability to conduct an intelligent conversation. The home's management said the sudden deaths were caused by a 'super-spreader' of 'Covid-19'. Then how come, James asked, that residents who refused to take the injections were not sick? It was a case of inject the elderly with mRNA synthetic potions and blame their illness and death that followed on the 'virus'. James described what was happening in care homes as 'the greatest crime of genocide this country has ever seen'. Remember the NHS staff nurse from earlier who used the same

word ‘genocide’ for what was happening with the ‘vaccines’ and that it was an ‘act of human annihilation’. A UK care home whistleblower told a similar story to James about the effect of the ‘vaccine’ in deaths and ‘outbreaks’ of illness dubbed ‘Covid’ after getting the jab. She told how her care home management and staff had zealously imposed government regulations and no one was allowed to even question the official narrative let alone speak out against it. She said the NHS was even worse. Again we see the results of reframing. A worker at a local care home where I live said they had not had a single case of ‘Covid’ there for almost a year and when the residents were ‘vaccinated’ they had 19 positive cases in two weeks with eight dying.

### **It's not the 'vaccine' – honest**

The obvious cause and effect was being ignored by the media and most of the public. Australia’s health minister Greg Hunt (a former head of strategy at the World Economic Forum) was admitted to hospital after he had the ‘vaccine’. He was suffering according to reports from the skin infection ‘cellulitis’ and it must have been a severe case to have warranted days in hospital. Immediately the authorities said this was nothing to do with the ‘vaccine’ when an effect of some vaccines is a ‘cellulitis-like reaction’. We had families of perfectly healthy old people who died after the ‘vaccine’ saying that if only they had been given the ‘vaccine’ earlier they would still be alive. As a numbskull rating that is off the chart. A father of four ‘died of Covid’ at aged 48 when he was taken ill two days after having the ‘vaccine’. The man, a health administrator, had been ‘shielding during the pandemic’ and had ‘not really left the house’ until he went for the ‘vaccine’. Having the ‘vaccine’ and then falling ill and dying does not seem to have qualified as a possible cause and effect and ‘Covid-19’ went on his death certificate. His family said they had no idea how he ‘caught the virus’. A family member said: ‘Tragically, it could be that going for a vaccination ultimately led to him catching Covid ...The sad truth is that they are never going to know where it came from.’ The family warned people to remember

that the virus still existed and was ‘very real’. So was their stupidity. Nurses and doctors who had the first round of the ‘vaccine’ were collapsing, dying and ending up in a hospital bed while they or their grieving relatives were saying they’d still have the ‘vaccine’ again despite what happened. I kid you not. You mean if your husband returned from the dead he’d have the same ‘vaccine’ again that killed him??

Doctors at the VCU Medical Center in Richmond, Virginia, said the Johnson & Johnson ‘vaccine’ was to blame for a man’s skin peeling off. Patient Richard Terrell said: ‘It all just happened so fast. My skin peeled off. It’s still coming off on my hands now.’ He said it was stinging, burning and itching and when he bent his arms and legs it was very painful with ‘the skin swollen and rubbing against itself’. Pfizer/BioNTech and Moderna vaccines use mRNA to change the cell while the Johnson & Johnson version uses DNA in a process similar to AstraZeneca’s technique. Johnson & Johnson and AstraZeneca have both had their ‘vaccines’ paused by many countries after causing serious blood problems. Terrell’s doctor Fnu Nutan said he could have died if he hadn’t got medical attention. It sounds terrible so what did Nutan and Terrell say about the ‘vaccine’ now? Oh, they still recommend that people have it. A nurse in a hospital bed 40 minutes after the vaccination and unable to swallow due to throat swelling was told by a doctor that he lost mobility in his arm for 36 hours following the vaccination. What did he say to the ailing nurse? ‘Good for you for getting the vaccination.’ We are dealing with a serious form of cognitive dissonance madness in both public and medical staff. There is a remarkable correlation between those having the ‘vaccine’ and trumpeting the fact and suffering bad happenings shortly afterwards. Witold Rogiewicz, a Polish doctor, made a video of his ‘vaccination’ and ridiculed those who were questioning its safety and the intentions of Bill Gates: ‘Vaccinate yourself to protect yourself, your loved ones, friends and also patients. And to mention quickly I have info for anti-vaxxers and anti-Covidiers if you want to contact Bill Gates you can do this through me.’ He further ridiculed the dangers of 5G. Days later he

was dead, but naturally the vaccination wasn't mentioned in the verdict of 'heart attack'.

## **Lies, lies and more lies**

So many members of the human race have slipped into extreme states of insanity and unfortunately they include reframed doctors and nursing staff. Having a 'vaccine' and dying within minutes or hours is not considered a valid connection while death from any cause within 28 days or longer of a positive test with a test not testing for the 'virus' means 'Covid-19' goes on the death certificate. How could that 'vaccine'-death connection not have been made except by calculated deceit? US figures in the initial rollout period to February 12th, 2020, revealed that a third of the deaths reported to the CDC after 'Covid vaccines' happened within 48 hours. Five men in the UK suffered an 'extremely rare' blood clot problem after having the AstraZeneca 'vaccine', but no causal link was established said the Gates-funded Medicines and Healthcare products Regulatory Agency (MHRA) which had given the 'vaccine' emergency approval to be used. Former Pfizer executive Dr Michael Yeadon explained in his interview how the procedures could cause blood coagulation and clots. People who should have been at no risk were dying from blood clots in the brain and he said he had heard from medical doctor friends that people were suffering from skin bleeding and massive headaches. The AstraZeneca 'shot' was stopped by some 20 countries over the blood clotting issue and still the corrupt MHRA, the European Medicines Agency (EMA) and the World Health Organization said that it should continue to be given even though the EMA admitted that it 'still cannot rule out definitively' a link between blood clotting and the 'vaccine'. Later Marco Cavaleri, head of EMA vaccine strategy, said there was indeed a clear link between the 'vaccine' and thrombosis, but they didn't know why. So much for the trials showing the 'vaccine' is safe. Blood clots were affecting younger people who would be under virtually no danger from 'Covid' even if it existed which makes it all the more stupid and sinister.

The British government responded to public alarm by wheeling out June Raine, the terrifyingly weak infant school headmistress sound-alike who heads the UK MHRA drug ‘regulator’. The idea that she would stand up to Big Pharma and government pressure is laughable and she told us that all was well in the same way that she did when allowing untested, never-used-on-humans-before, genetically-manipulating ‘vaccines’ to be exposed to the public in the first place. Mass lying is the new normal of the ‘Covid’ era. The MHRA later said 30 cases of rare blood clots had by then been connected with the AstraZeneca ‘vaccine’ (that means a lot more in reality) while stressing that the benefits of the jab in preventing ‘Covid-19’ outweighed any risks. A more ridiculous and disingenuous statement with callous disregard for human health it is hard to contemplate. Immediately after the mendacious ‘all-clears’ two hospital workers in Denmark experienced blood clots and cerebral haemorrhaging following the AstraZeneca jab and one died. Top Norwegian health official Pål Andre Holme said the ‘vaccine’ was the only common factor: ‘There is nothing in the patient history of these individuals that can give such a powerful immune response ... I am confident that the antibodies that we have found are the cause, and I see no other explanation than it being the vaccine which triggers it.’ Strokes, a clot or bleed in the brain, were clearly associated with the ‘vaccine’ from word of mouth and whistleblower reports. Similar consequences followed with all these ‘vaccines’ that we were told were so safe and as the numbers grew by the day it was clear we were witnessing human carnage.

## **Learning the hard way**

A woman interviewed by UKColumn told how her husband suffered dramatic health effects after the vaccine when he’d been in good health all his life. He went from being a little unwell to losing all feeling in his legs and experiencing ‘excruciating pain’. Misdiagnosis followed twice at Accident and Emergency (an ‘allergy’ and ‘sciatica’) before he was admitted to a neurology ward where doctors said his serious condition had been caused by the

'vaccine'. Another seven 'vaccinated' people were apparently being treated on the same ward for similar symptoms. The woman said he had the 'vaccine' because they believed media claims that it was safe. 'I didn't think the government would give out a vaccine that does this to somebody; I believed they would be bringing out a vaccination that would be safe.' What a tragic way to learn that lesson. Another woman posted that her husband was transporting stroke patients to hospital on almost every shift and when he asked them if they had been 'vaccinated' for 'Covid' they all replied 'yes'. One had a 'massive brain bleed' the day after his second dose. She said her husband reported the 'just been vaccinated' information every time to doctors in A and E only for them to ignore it, make no notes and appear annoyed that it was even mentioned. This particular report cannot be verified, but it expresses a common theme that confirms the monumental underreporting of 'vaccine' consequences. Interestingly as the 'vaccines' and their brain blood clot/stroke consequences began to emerge the UK National Health Service began a publicity campaign telling the public what to do in the event of a stroke. A Scottish NHS staff nurse who quit in disgust in March, 2021, said:

I have seen traumatic injuries from the vaccine, they're not getting reported to the yellow card [adverse reaction] scheme, they're treating the symptoms, not asking why, why it's happening. It's just treating the symptoms and when you speak about it you're dismissed like you're crazy, I'm not crazy, I'm not crazy because every other colleague I've spoken to is terrified to speak out, they've had enough.

Videos appeared on the Internet of people uncontrollably shaking after the 'vaccine' with no control over muscles, limbs and even their face. A Scottish mother broke out in a severe rash all over her body almost immediately after she was given the AstraZeneca 'vaccine'. The pictures were horrific. Leigh King, a 41-year-old hairdresser from Lanarkshire said: 'Never in my life was I prepared for what I was about to experience ... My skin was so sore and constantly hot ... I have never felt pain like this ...' But don't you worry, the 'vaccine' is perfectly safe. Then there has been the effect on medical

staff who have been pressured to have the ‘vaccine’ by psychopathic ‘health’ authorities and government. A London hospital consultant who gave the name K. Polyakova wrote this to the *British Medical Journal* or *BMJ*:

I am currently struggling with ... the failure to report the reality of the morbidity caused by our current vaccination program within the health service and staff population. The levels of sickness after vaccination is unprecedented and staff are getting very sick and some with neurological symptoms which is having a huge impact on the health service function. Even the young and healthy are off for days, some for weeks, and some requiring medical treatment. Whole teams are being taken out as they went to get vaccinated together.

Mandatory vaccination in this instance is stupid, unethical and irresponsible when it comes to protecting our staff and public health. We are in the voluntary phase of vaccination, and encouraging staff to take an unlicensed product that is impacting on their immediate health ... it is clearly stated that these vaccine products do not offer immunity or stop transmission. In which case why are we doing it?

Not to protect health that’s for sure. Medical workers are lauded by governments for agenda reasons when they couldn’t give a toss about them any more than they can for the population in general. Schools across America faced the same situation as they closed due to the high number of teachers and other staff with bad reactions to the Pfizer/BioNTech, Moderna, and Johnson & Johnson ‘Covid vaccines’ all of which were linked to death and serious adverse effects. The *BMJ* took down the consultant’s comments pretty quickly on the grounds that they were being used to spread ‘disinformation’. They were exposing the truth about the ‘vaccine’ was the real reason. The cover-up is breathtaking.

## **Hiding the evidence**

The scale of the ‘vaccine’ death cover-up worldwide can be confirmed by comparing official figures with the personal experience of the public. I heard of many people in my community who died immediately or soon after the vaccine that would never appear in the media or even likely on the official totals of ‘vaccine’ fatalities and adverse reactions when only about ten percent are estimated to be

reported and I have seen some estimates as low as one percent in a Harvard study. In the UK alone by April 29th, 2021, some 757,654 adverse reactions had been officially reported from the Pfizer/BioNTech, Oxford/AstraZeneca and Moderna 'vaccines' with more than a thousand deaths linked to jabs and that means an estimated ten times this number in reality from a ten percent reporting rate percentage. That's seven million adverse reactions and 10,000 potential deaths and a one percent reporting rate would be ten times *those* figures. In 1976 the US government pulled the swine flu vaccine after 53 deaths. The UK data included a combined 10,000 eye disorders from the 'Covid vaccines' with more than 750 suffering visual impairment or blindness and again multiply by the estimated reporting percentages. As 'Covid cases' officially fell hospitals virtually empty during the 'Covid crisis' began to fill up with a range of other problems in the wake of the 'vaccine' rollout. The numbers across America have also been catastrophic. Deaths linked to *all* types of vaccine increased by *6,000 percent* in the first quarter of 2021 compared with 2020. A 39-year-old woman from Ogden, Utah, died four days after receiving a second dose of Moderna's 'Covid vaccine' when her liver, heart and kidneys all failed despite the fact that she had no known medical issues or conditions. Her family sought an autopsy, but Dr Erik Christensen, Utah's chief medical examiner, said proving vaccine injury as a cause of death almost never happened. He could think of only one instance where an autopsy would name a vaccine as the official cause of death and that would be anaphylaxis where someone received a vaccine and died almost instantaneously. 'Short of that, it would be difficult for us to definitively say this is the vaccine,' Christensen said. If that is true this must be added to the estimated ten percent (or far less) reporting rate of vaccine deaths and serious reactions and the conclusion can only be that vaccine deaths and serious reactions – including these 'Covid' potions – are phenomenally understated in official figures. The same story can be found everywhere. Endless accounts of deaths and serious reactions among the public, medical

and care home staff while official figures did not even begin to reflect this.

Professional script-reader Dr David Williams, a ‘top public-health official’ in Ontario, Canada, insulted our intelligence by claiming only four serious adverse reactions and no deaths from the more than 380,000 vaccine doses then given. This bore no resemblance to what people knew had happened in their own circles and we had Dirk Huyer in charge of getting millions vaccinated in Ontario while at the same time he was Chief Coroner for the province investigating causes of death including possible death from the vaccine. An aide said he had stepped back from investigating deaths, but evidence indicated otherwise. Rosemary Frei, who secured a Master of Science degree in molecular biology at the Faculty of Medicine at Canada’s University of Calgary before turning to investigative journalism, was one who could see that official figures for ‘vaccine’ deaths and reactions made no sense. She said that doctors seldom reported adverse events and when people got really sick or died after getting a vaccination they would attribute that to anything except the vaccines. It had been that way for years and anyone who wondered aloud whether the ‘Covid vaccines’ or other shots cause harm is immediately branded as ‘anti-vax’ and ‘anti-science’. This was ‘career-threatening’ for health professionals. Then there was the huge pressure to support the push to ‘vaccinate’ billions in the quickest time possible. Frei said:

So that’s where we’re at today. More than half a million vaccine doses have been given to people in Ontario alone. The rush is on to vaccinate all 15 million of us in the province by September. And the mainstream media are screaming for this to be sped up even more. That all adds up to only a very slim likelihood that we’re going to be told the truth by officials about how many people are getting sick or dying from the vaccines.

What is true of Ontario is true of everywhere.

## **They KNEW – and still did it**

The authorities knew what was going to happen with multiple deaths and adverse reactions. The UK government’s Gates-funded

and Big Pharma-dominated Medicines and Healthcare products Regulatory Agency (MHRA) hired a company to employ AI in compiling the projected reactions to the ‘vaccine’ that would otherwise be uncountable. The request for applications said: ‘The MHRA urgently seeks an Artificial Intelligence (AI) software tool to process the expected high volume of Covid-19 vaccine Adverse Drug Reaction ...’ This was from the agency, headed by the disingenuous June Raine, that gave the ‘vaccines’ emergency approval and the company was hired before the first shot was given. ‘We are going to kill and maim you – is that okay?’ ‘Oh, yes, perfectly fine – I’m very grateful, thank you, doctor.’ The range of ‘Covid vaccine’ adverse reactions goes on for page after page in the MHRA criminally underreported ‘Yellow Card’ system and includes affects to eyes, ears, skin, digestion, blood and so on. Raine’s MHRA amazingly claimed that the ‘overall safety experience ... is so far as expected from the clinical trials’. The death, serious adverse effects, deafness and blindness were *expected*? When did they ever mention that? If these human tragedies were expected then those that gave approval for the use of these ‘vaccines’ must be guilty of crimes against humanity including murder – a definition of which is ‘killing a person with malice aforethought or with recklessness manifesting extreme indifference to the value of human life.’ People involved at the MHRA, the CDC in America and their equivalent around the world must go before Nuremberg trials to answer for their callous inhumanity. We are only talking here about the immediate effects of the ‘vaccine’. The longer-term impact of the DNA synthetic manipulation is the main reason they are so hysterically desperate to inoculate the entire global population in the shortest possible time.

Africa and the developing world are a major focus for the ‘vaccine’ depopulation agenda and a mass vaccination sales-pitch is underway thanks to caring people like the Rockefellers and other Cult assets. The Rockefeller Foundation, which pre-empted the ‘Covid pandemic’ in a document published in 2010 that ‘predicted’ what happened a decade later, announced an initial \$34.95 million grant in February, 2021, ‘to ensure more equitable access to Covid-19

testing and vaccines' among other things in Africa in collaboration with '24 organizations, businesses, and government agencies'. The pan-Africa initiative would focus on 10 countries: Burkina Faso, Ethiopia, Ghana, Kenya, Nigeria, Rwanda, South Africa, Tanzania, Uganda, and Zambia'. Rajiv Shah, President of the Rockefeller Foundation and former administrator of CIA-controlled USAID, said that if Africa was not mass-vaccinated (to change the DNA of its people) it was a 'threat to all of humanity' and not fair on Africans. When someone from the Rockefeller Foundation says they want to do something to help poor and deprived people and countries it is time for a belly-laugh. They are doing this out of the goodness of their 'heart' because 'vaccinating' the entire global population is what the 'Covid' hoax set out to achieve. Official 'decolonisation' of Africa by the Cult was merely a prelude to financial colonisation on the road to a return to physical colonisation. The 'vaccine' is vital to that and the sudden and convenient death of the 'Covid' sceptic president of Tanzania can be seen in its true light. A lot of people in Africa are aware that this is another form of colonisation and exploitation and they need to stand their ground.

### **The 'vaccine is working' scam**

A potential problem for the Cult was that the 'vaccine' is meant to change human DNA and body messaging and not to protect anyone from a 'virus' never shown to exist. The vaccine couldn't work because it was not designed to work and how could they make it *appear* to be working so that more people would have it? This was overcome by lowering the amplification rate of the PCR test to produce fewer 'cases' and therefore fewer 'deaths'. Some of us had been pointing out since March, 2020, that the amplification rate of the test not testing for the 'virus' had been made artificially high to generate positive tests which they could call 'cases' to justify lockdowns. The World Health Organization recommended an absurdly high 45 amplification cycles to ensure the high positives required by the Cult and then remained silent on the issue until January 20th, 2021 – Biden's Inauguration Day. This was when the

'vaccinations' were seriously underway and on that day the WHO recommended after discussions with America's CDC that laboratories *lowered their testing amplification*. Dr David Samadi, a certified urologist and health writer, said the WHO was encouraging all labs to reduce their cycle count for PCR tests. He said the current cycle was much too high and was 'resulting in any particle being declared a positive case'. Even one mainstream news report I saw said this meant the number of 'Covid' infections may have been 'dramatically inflated'. Oh, just a little bit. The CDC in America issued new guidance to laboratories in April, 2021, to use 28 cycles *but only for 'vaccinated' people*. The timing of the CDC/WHO interventions were cynically designed to make it appear the 'vaccines' were responsible for falling cases and deaths when the real reason can be seen in the following examples. New York's state lab, the Wadsworth Center, identified 872 positive tests in July, 2020, based on a threshold of 40 cycles. When the figure was lowered to 35 cycles *43 percent* of the 872 were no longer 'positives'. At 30 cycles the figure was 63 percent. A Massachusetts lab found that between *85 to 90 percent* of people who tested positive in July with a cycle threshold of 40 would be negative at 30 cycles, Ashish Jha, MD, director of the Harvard Global Health Institute, said: 'I'm really shocked that it could be that high ... Boy, does it really change the way we need to be thinking about testing.' I'm shocked that I could see the obvious in the spring of 2020, with no medical background, and most medical professionals still haven't worked it out. No, that's not shocking – it's terrifying.

Three weeks after the WHO directive to lower PCR cycles the London *Daily Mail* ran this headline: 'Why ARE Covid cases plummeting? New infections have fallen 45% in the US and 30% globally in the past 3 weeks but experts say vaccine is NOT the main driver because only 8% of Americans and 13% of people worldwide have received their first dose.' They acknowledged that the drop could not be attributed to the 'vaccine', but soon this morphed throughout the media into the 'vaccine' has caused cases and deaths to fall when it was the PCR threshold. In December, 2020, there was

chaos at English Channel ports with truck drivers needing negative 'Covid' tests before they could board a ferry home for Christmas. The government wanted to remove the backlog as fast as possible and they brought in troops to do the 'testing'. Out of 1,600 drivers just 36 tested positive and the rest were given the all clear to cross the Channel. I guess the authorities thought that 36 was the least they could get away with without the unquestioning catching on. The amplification trick which most people believed in the absence of information in the mainstream applied more pressure on those refusing the 'vaccine' to succumb when it 'obviously worked'. The truth was the exact opposite with deaths in care homes soaring with the 'vaccine' and in Israel the term used was 'skyrocket'. A re-analysis of published data from the Israeli Health Ministry led by Dr Hervé Seligmann at the Medicine Emerging Infectious and Tropical Diseases at Aix-Marseille University found that Pfizer's 'Covid vaccine' killed 'about 40 times more [elderly] people than the disease itself would have killed' during a five-week vaccination period and 260 *times* more younger people than would have died from the 'virus' even according to the manipulated 'virus' figures. Dr Seligmann and his co-study author, Haim Yativ, declared after reviewing the Israeli 'vaccine' death data: 'This is a new Holocaust.'

Then, in mid-April, 2021, after vast numbers of people worldwide had been 'vaccinated', the story changed with clear coordination. The UK government began to prepare the ground for more future lockdowns when Nuremberg-destined Boris Johnson told yet another whopper. He said that cases had fallen because of *lockdowns* not 'vaccines'. Lockdowns are irrelevant when *there is no 'virus'* and the test and fraudulent death certificates are deciding the number of 'cases' and 'deaths'. Study after study has shown that lockdowns don't work and instead kill and psychologically destroy people. Meanwhile in the United States Anthony Fauci and Rochelle Walensky, the ultra-Zionist head of the CDC, peddled the same line. More lockdown was the answer and not the 'vaccine', a line repeated on cue by the moron that is Canadian Prime Minister Justin Trudeau. Why all the hysteria to get everyone 'vaccinated' if lockdowns and

not ‘vaccines’ made the difference? None of it makes sense on the face of it. Oh, but it does. The Cult wants lockdowns *and* the ‘vaccine’ and if the ‘vaccine’ is allowed to be seen as the total answer lockdowns would no longer be justified when there are still livelihoods to destroy. ‘Variants’ and renewed upward manipulation of PCR amplification are planned to instigate never-ending lockdown *and* more ‘vaccines’.

## **You must have it – we’re desperate**

Israel, where the Jewish and Arab population are ruled by the Sabbatian Cult, was the front-runner in imposing the DNA-manipulating ‘vaccine’ on its people to such an extent that Jewish refusers began to liken what was happening to the early years of Nazi Germany. This would seem to be a fantastic claim. Why would a government of Jewish people be acting like the Nazis did? If you realise that the Sabbatian Cult was behind the Nazis and that Sabbatians hate Jews the pieces start to fit and the question of why a ‘Jewish’ government would treat Jews with such callous disregard for their lives and freedom finds an answer. Those controlling the government of Israel *aren’t Jewish* – they’re Sabbatian. Israeli lawyer Tamir Turgal was one who made the Nazi comparison in comments to German lawyer Reiner Fuellmich who is leading a class action lawsuit against the psychopaths for crimes against humanity. Turgal described how the Israeli government was vaccinating children and pregnant women on the basis that there was no evidence that this was dangerous when they had no evidence that it *wasn’t* dangerous either. They just had no evidence. This was medical experimentation and Turgal said this breached the Nuremberg Code about medical experimentation and procedures requiring informed consent and choice. Think about that. A Nuremberg Code developed because of Nazi experimentation on Jews and others in concentration camps by people like the evil-beyond-belief Josef Mengele is being breached by the *Israeli* government; but when you know that it’s a *Sabbatian* government along with its intelligence and military agencies like Mossad, Shin Bet and the Israeli Defense Forces, and that Sabbatians

were the force behind the Nazis, the kaleidoscope comes into focus. What have we come to when Israeli Jews are suing their government for violating the Nuremberg Code by essentially making Israelis subject to a medical experiment using the controversial 'vaccines'? It's a shocker that this has to be done in the light of what happened in Nazi Germany. The Anshe Ha-Emet, or 'People of the Truth', made up of Israeli doctors, lawyers, campaigners and public, have launched a lawsuit with the International Criminal Court. It says:

When the heads of the Ministry of Health as well as the prime minister presented the vaccine in Israel and began the vaccination of Israeli residents, the vaccinated were not advised, that, in practice, they are taking part in a medical experiment and that their consent is required for this under the Nuremberg Code.

The irony is unbelievable, but easily explained in one word: Sabbatians. The foundation of Israeli 'Covid' apartheid is the 'green pass' or 'green passport' which allows Jews and Arabs who have had the DNA-manipulating 'vaccine' to go about their lives – to work, fly, travel in general, go to shopping malls, bars, restaurants, hotels, concerts, gyms, swimming pools, theatres and sports venues, while non-'vaccinated' are banned from all those places and activities. Israelis have likened the 'green pass' to the yellow stars that Jews in Nazi Germany were forced to wear – the same as the yellow stickers that a branch of UK supermarket chain Morrisons told exempt mask-wears they had to display when shopping. How very sensitive. The Israeli system is blatant South African-style apartheid on the basis of compliance or non-compliance to fascism rather than colour of the skin. How appropriate that the Sabbatian Israeli government was so close to the pre-Mandela apartheid regime in Pretoria. The Sabbatian-instigated 'vaccine passport' in Israel is planned for everywhere. Sabbatians struck a deal with Pfizer that allowed them to lead the way in the percentage of a national population infused with synthetic material and the result was catastrophic. Israeli freedom activist Shai Dannon told me how chairs were appearing on beaches that said 'vaccinated only'. Health Minister Yuli Edelstein said that anyone unwilling or unable to get

the jabs that ‘confer immunity’ will be ‘left behind’. The man’s a liar. Not even the makers claim the ‘vaccines’ confer immunity. When you see those figures of ‘vaccine’ deaths these psychopaths were saying that you must take the chance the ‘vaccine’ will kill you or maim you while knowing it will change your DNA or lockdown for you will be permanent. That’s fascism. The Israeli parliament passed a law to allow personal information of the non-vaccinated to be shared with local and national authorities for three months. This was claimed by its supporters to be a way to ‘encourage’ people to be vaccinated. Hadas Ziv from Physicians for Human Rights described this as a ‘draconian law which crushed medical ethics and the patient rights’. But that’s the idea, the Sabbatians would reply.

## **Your papers, please**

Sabbatian Israel was leading what has been planned all along to be a global ‘vaccine pass’ called a ‘green passport’ without which you would remain in permanent lockdown restriction and unable to do anything. This is how badly – *desperately* – the Cult is to get everyone ‘vaccinated’. The term and colour ‘green’ was not by chance and related to the psychology of fusing the perception of the green climate hoax with the ‘Covid’ hoax and how the ‘solution’ to both is the same Great Reset. Lying politicians, health officials and psychologists denied there were any plans for mandatory vaccinations or restrictions based on vaccinations, but they knew that was exactly what was meant to happen with governments of all countries reaching agreements to enforce a global system. ‘Free’ Denmark and ‘free’ Sweden unveiled digital vaccine certification. Cyprus, Czech Republic, Estonia, Greece, Hungary, Iceland, Italy, Poland, Portugal, Slovakia, and Spain have all committed to a vaccine passport system and the rest including the whole of the EU would follow. The satanic UK government will certainly go this way despite mendacious denials and at the time of writing it is trying to manipulate the public into having the ‘vaccine’ so they could go abroad on a summer holiday. How would that work without something to prove you had the synthetic toxicity injected into you?

Documents show that the EU's European Commission was moving towards 'vaccine certificates' in 2018 and 2019 before the 'Covid' hoax began. They knew what was coming. Abracadabra – Ursula von der Leyen, the German President of the Commission, announced in March, 2021, an EU 'Digital Green Certificate' – green again – to track the public's 'Covid status'. The passport sting is worldwide and the Far East followed the same pattern with South Korea ruling that only those with 'vaccination' passports – again the *green* pass – would be able to 'return to their daily lives'.

Bill Gates has been preparing for this 'passport' with other Cult operatives for years and beyond the paper version is a Gates-funded 'digital tattoo' to identify who has been vaccinated and who hasn't. The 'tattoo' is reported to include a substance which is externally readable to confirm who has been vaccinated. This is a bio-luminous light-generating enzyme (think fireflies) called ... *Luciferase*. Yes, named after the Cult 'god' Lucifer the 'light bringer' of whom more to come. Gates said he funded the readable tattoo to ensure children in the developing world were vaccinated and no one was missed out. He cares so much about poor kids as we know. This was just the cover story to develop a vaccine tagging system for everyone on the planet. Gates has been funding the ID2020 'alliance' to do just that in league with other lovely people at Microsoft, GAVI, the Rockefeller Foundation, Accenture and IDEO.org. He said in interviews in March, 2020, before any 'vaccine' publicly existed, that the world must have a globalised digital certificate to track the 'virus' and who had been vaccinated. Gates knew from the start that the mRNA vaccines were coming and when they would come and that the plan was to tag the 'vaccinated' to marginalise the intelligent and stop them doing anything including travel. Evil just doesn't suffice. Gates was exposed for offering a \$10 million bribe to the Nigerian House of Representatives to invoke compulsory 'Covid' vaccination of all Nigerians. Sara Cunial, a member of the Italian Parliament, called Gates a 'vaccine criminal'. She urged the Italian President to hand him over to the International Criminal Court for crimes against

humanity and condemned his plans to 'chip the human race' through ID2020.

You know it's a long-planned agenda when war criminal and Cult gofer Tony Blair is on the case. With the scale of arrogance only someone as dark as Blair can muster he said: 'Vaccination in the end is going to be your route to liberty.' Blair is a disgusting piece of work and he confirms that again. The media has given a lot of coverage to a bloke called Charlie Mullins, founder of London's biggest independent plumbing company, Pimlico Plumbers, who has said he won't employ anyone who has not been vaccinated or have them go to any home where people are not vaccinated. He said that if he had his way no one would be allowed to walk the streets if they have not been vaccinated. Gates was cheering at the time while I was alerting the white coats. The plan is that people will qualify for 'passports' for having the first two doses and then to keep it they will have to have all the follow ups and new ones for invented 'variants' until human genetics is transformed and many are dead who can't adjust to the changes. Hollywood celebrities – the usual propaganda stunt – are promoting something called the WELL Health-Safety Rating to verify that a building or space has 'taken the necessary steps to prioritize the health and safety of their staff, visitors and other stakeholders'. They included Lady Gaga, Jennifer Lopez, Michael B. Jordan, Robert DeNiro, Venus Williams, Wolfgang Puck, Deepak Chopra and 17th Surgeon General Richard Carmona. Yawn. WELL Health-Safety has big connections with China. Parent company Delos is headed by former Goldman Sachs partner Paul Scialla. This is another example – and we will see so many others – of using the excuse of 'health' to dictate the lives and activities of the population. I guess one confirmation of the 'safety' of buildings is that only 'vaccinated' people can go in, right?

## **Electronic concentration camps**

I wrote decades ago about the plans to restrict travel and here we are for those who refuse to bow to tyranny. This can be achieved in one go with air travel if the aviation industry makes a blanket decree.

The ‘vaccine’ and guaranteed income are designed to be part of a global version of China’s social credit system which tracks behaviour 24/7 and awards or deletes ‘credits’ based on whether your behaviour is supported by the state or not. I mean your entire lifestyle – what you do, eat, say, everything. Once your credit score falls below a certain level consequences kick in. In China tens of millions have been denied travel by air and train because of this. All the locations and activities denied to refusers by the ‘vaccine’ passports will be included in one big mass ban on doing almost anything for those that don’t bow their head to government. It’s beyond fascist and a new term is required to describe its extremes – I guess fascist technocracy will have to do. The way the Chinese system of technological – technocratic – control is sweeping the West can be seen in the Los Angeles school system and is planned to be expanded worldwide. Every child is required to have a ‘Covid’-tracking app scanned daily before they can enter the classroom. The so-called Daily Pass tracking system is produced by Gates’ Microsoft which I’m sure will shock you rigid. The pass will be scanned using a barcode (one step from an inside-the-body barcode) and the information will include health checks, ‘Covid’ tests and vaccinations. Entry codes are for one specific building only and access will only be allowed if a student or teacher has a negative test with a test not testing for the ‘virus’, has no symptoms of anything alleged to be related to ‘Covid’ (symptoms from a range of other illness), and has a temperature under 100 degrees. No barcode, no entry, is planned to be the case for everywhere and not only schools.

Kids are being psychologically prepared to accept this as ‘normal’ their whole life which is why what they can impose in schools is so important to the Cult and its gofers. Long-time American freedom campaigner John Whitehead of the Rutherford Institute was not exaggerating when he said: ‘Databit by databit, we are building our own electronic concentration camps.’ Canada under its Cult gofer prime minister Justin Trudeau has taken a major step towards the real thing with people interned against their will if they test positive with a test not testing for the ‘virus’ when they arrive at a Canadian

airport. They are jailed in internment hotels often without food or water for long periods and with many doors failing to lock there have been sexual assaults. The interned are being charged sometimes \$2,000 for the privilege of being abused in this way. Trudeau is fully on board with the Cult and says the ‘Covid pandemic’ has provided an opportunity for a global ‘reset’ to permanently change Western civilisation. His number two, Deputy Prime Minister Chrystia Freeland, is a trustee of the World Economic Forum and a Rhodes Scholar. The Trudeau family have long been servants of the Cult. See *The Biggest Secret* and Cathy O’Brien’s book *Trance-Formation of America* for the horrific background to Trudeau’s father Pierre Trudeau another Canadian prime minister. Hide your fascism behind the façade of a heart-on-the-sleeve liberal. It’s a well-honed Cult technique.

## **What can the ‘vaccine’ really do?**

We have a ‘virus’ never shown to exist and ‘variants’ of the ‘virus’ that have also never been shown to exist except, like the ‘original’, as computer-generated fictions. Even if you believe there’s a ‘virus’ the ‘case’ to ‘death’ rate is in the region of 0.23 to 0.15 percent and those ‘deaths’ are concentrated among the very old around the same average age that people die anyway. In response to this lack of threat (in truth none) psychopaths and idiots, knowingly and unknowingly answering to Gates and the Cult, are seeking to ‘vaccinate’ every man, woman and child on Planet Earth. Clearly the ‘vaccine’ is not about ‘Covid’ – none of this ever has been. So what is it all about *really*? Why the desperation to infuse genetically-manipulating synthetic material into everyone through mRNA fraudulent ‘vaccines’ with the intent of doing this over and over with the excuses of ‘variants’ and other ‘virus’ inventions? Dr Sherri Tenpenny, an osteopathic medical doctor in the United States, has made herself an expert on vaccines and their effects as a vehement campaigner against their use. Tenpenny was board certified in emergency medicine, the director of a level two trauma centre for 12 years, and moved to Cleveland in 1996 to start an integrative

medicine practice which has treated patients from all 50 states and some 17 other countries. Weaning people off pharmaceutical drugs is a speciality.

She became interested in the consequences of vaccines after attending a meeting at the National Vaccine Information Center in Washington DC in 2000 where she ‘sat through four days of listening to medical doctors and scientists and lawyers and parents of vaccine injured kids’ and asked: ‘What’s going on?’ She had never been vaccinated and never got ill while her father was given a list of vaccines to be in the military and was ‘sick his entire life’. The experience added to her questions and she began to examine vaccine documents from the Centers for Disease Control (CDC). After reading the first one, the 1998 version of *The General Recommendations of Vaccination*, she thought: ‘This is it?’ The document was poorly written and bad science and Tenpenny began 20 years of research into vaccines that continues to this day. She began her research into ‘Covid vaccines’ in March, 2020, and she describes them as ‘deadly’. For many, as we have seen, they already have been. Tenpenny said that in the first 30 days of the ‘vaccine’ rollout in the United States there had been more than 40,000 adverse events reported to the vaccine adverse event database. A document had been delivered to her the day before that was 172 pages long. ‘We have over 40,000 adverse events; we have over 3,100 cases of [potentially deadly] anaphylactic shock; we have over 5,000 neurological reactions.’ Effects ranged from headaches to numbness, dizziness and vertigo, to losing feeling in hands or feet and paraesthesia which is when limbs ‘fall asleep’ and people have the sensation of insects crawling underneath their skin. All this happened in the first 30 days and remember that only about *ten percent* (or far less) of adverse reactions and vaccine-related deaths are estimated to be officially reported. Tenpenny said:

So can you think of one single product in any industry, any industry, for as long as products have been made on the planet that within 30 days we have 40,000 people complaining of side effects that not only is still on the market but ... we’ve got paid actors telling us how great

they are for getting their vaccine. We're offering people \$500 if they will just get their vaccine and we've got nurses and doctors going; 'I got the vaccine, I got the vaccine'.

Tenpenny said they were not going to be 'happy dancing folks' when they began to suffer Bell's palsy (facial paralysis), neuropathies, cardiac arrhythmias and autoimmune reactions that kill through a blood disorder. 'They're not going to be so happy, happy then, but we're never going to see pictures of those people' she said. Tenpenny described the 'vaccine' as 'a well-designed killing tool'.

## No off-switch

Bad as the initial consequences had been Tenpenny said it would be maybe 14 months before we began to see the 'full ravage' of what is going to happen to the 'Covid vaccinated' with full-out consequences taking anything between two years and 20 years to show. You can understand why when you consider that variations of the 'Covid vaccine' use mRNA (messenger RNA) to in theory activate the immune system to produce protective antibodies without using the actual 'virus'. How can they when it's a computer program and they've never isolated what they claim is the 'real thing'? Instead they use *synthetic* mRNA. They are inoculating synthetic material into the body which through a technique known as the Trojan horse is absorbed into cells to change the nature of DNA. Human DNA is changed by an infusion of messenger RNA and with each new 'vaccine' of this type it is changed even more. Say so and you are banned by Cult Internet platforms. The contempt the contemptuous Mark Zuckerberg has for the truth and human health can be seen in an internal Facebook video leaked to the Project Veritas investigative team in which he said of the 'Covid vaccines': '... I share some caution on this because we just don't know the long term side-effects of basically modifying people's DNA and RNA.' At the same time this disgusting man's Facebook was censoring and banning anyone saying exactly the same. He must go before a Nuremberg trial for crimes against humanity when he *knows* that he

is censoring legitimate concerns and denying the right of informed consent on behalf of the Cult that owns him. People have been killed and damaged by the very ‘vaccination’ technique he cast doubt on himself when they may not have had the ‘vaccine’ with access to information that he denied them. The plan is to have at least annual ‘Covid vaccinations’, add others to deal with invented ‘variants’, and change all other vaccines into the mRNA system. Pfizer executives told shareholders at a virtual Barclays Global Healthcare Conference in March, 2021, that the public may need a third dose of ‘Covid vaccine’, plus regular yearly boosters and the company planned to hike prices to milk the profits in a ‘significant opportunity for our vaccine’. These are the professional liars, cheats and opportunists who are telling you their ‘vaccine’ is safe. Given this volume of mRNA planned to be infused into the human body and its ability to then replicate we will have a transformation of human genetics from biological to synthetic biological – exactly the long-time Cult plan for reasons we’ll see – and many will die. Sherri Tenpenny said of this replication:

It’s like having an on-button but no off-button and that whole mechanism ... they actually give it a name and they call it the Trojan horse mechanism, because it allows that [synthetic] virus and that piece of that [synthetic] virus to get inside of your cells, start to replicate and even get inserted into other parts of your DNA as a Trojan-horse.

Ask the overwhelming majority of people who have the ‘vaccine’ what they know about the contents and what they do and they would reply: ‘The government says it will stop me getting the virus.’ Governments give that false impression on purpose to increase take-up. You can read Sherri Tenpenny’s detailed analysis of the health consequences in her blog at [Vaxxter.com](http://Vaxxter.com), but in summary these are some of them. She highlights the statement by Bill Gates about how human beings can become their own ‘vaccine manufacturing machine’. The man is insane. [‘Vaccine’-generated] ‘antibodies’ carry synthetic messenger RNA into the cells and the damage starts, Tenpenny contends, and she says that lungs can be adversely affected through varying degrees of pus and bleeding which

obviously affects breathing and would be dubbed ‘Covid-19’. Even more sinister was the impact of ‘antibodies’ on macrophages, a white blood cell of the immune system. They consist of Type 1 and Type 2 which have very different functions. She said Type 1 are ‘hyper-vigilant’ white blood cells which ‘gobble up’ bacteria etc. However, in doing so, this could cause inflammation and in extreme circumstances be fatal. She says these affects are mitigated by Type 2 macrophages which kick in to calm down the system and stop it going rogue. They clear up dead tissue debris and reduce inflammation that the Type 1 ‘fire crews’ have caused. Type 1 kills the infection and Type 2 heals the damage, she says. This is her punchline with regard to ‘Covid vaccinations’: She says that mRNA ‘antibodies’ block Type 2 macrophages by attaching to them and deactivating them. This meant that when the Type 1 response was triggered by infection there was nothing to stop that getting out of hand by calming everything down. There’s an on-switch, but no off-switch, she says. What follows can be ‘over and out, see you when I see you’.

## **Genetic suicide**

Tenpenny also highlights the potential for autoimmune disease – the body attacking itself – which has been associated with vaccines since they first appeared. Infusing a synthetic foreign substance into cells could cause the immune system to react in a panic believing that the body is being overwhelmed by an invader (it is) and the consequences can again be fatal. There is an autoimmune response known as a ‘cytokine storm’ which I have likened to a homeowner panicked by an intruder and picking up a gun to shoot randomly in all directions before turning the fire on himself. The immune system unleashes a storm of inflammatory response called cytokines to a threat and the body commits hara-kiri. The lesson is that you mess with the body’s immune response at your peril and these ‘vaccines’ seriously – fundamentally – mess with immune response. Tenpenny refers to a consequence called anaphylactic shock which is a severe and highly dangerous allergic reaction when the immune system

floods the body with chemicals. She gives the example of having a bee sting which primes the immune system and makes it sensitive to those chemicals. When people are stung again maybe years later the immune response can be so powerful that it leads to anaphylactic shock. Tenpenny relates this 'shock' with regard to the 'Covid vaccine' to something called polyethylene glycol or PEG. Enormous numbers of people have become sensitive to this over decades of use in a whole range of products and processes including food, drink, skin creams and 'medicine'. Studies have claimed that some 72 percent of people have antibodies triggered by PEG compared with two percent in the 1960s and allergic hypersensitive reactions to this become a gathering cause for concern. Tenpenny points out that the 'mRNA vaccine' is coated in a 'bubble' of polyethylene glycol which has the potential to cause anaphylactic shock through immune sensitivity. Many reports have appeared of people reacting this way after having the 'Covid vaccine'. What do we think is going to happen as humanity has more and more of these 'vaccines'?

Tenpenny said: 'All these pictures we have seen with people with these rashes ... these weepy rashes, big reactions on their arms and things like that – it's an acute allergic reaction most likely to the polyethylene glycol that you've been previously primed and sensitised to.'

Those who have not studied the conspiracy and its perpetrators at length might think that making the population sensitive to PEG and then putting it in these 'vaccines' is just a coincidence. It is not. It is instead testament to how carefully and coldly-planned current events have been and the scale of the conspiracy we are dealing with. Tenpenny further explains that the 'vaccine' mRNA procedure can breach the blood-brain barrier which protects the brain from toxins and other crap that will cause malfunction. In this case they could make two proteins corrupt brain function to cause Amyotrophic lateral sclerosis (ALS), a progressive nervous system disease leading to loss of muscle control, and frontal lobe degeneration – Alzheimer's and dementia. Immunologist J. Bart Classon published a paper connecting mRNA 'vaccines' to prion

disease which can lead to Alzheimer's and other forms of neurodegenerative disease while others have pointed out the potential to affect the placenta in ways that make women infertile. This will become highly significant in the next chapter when I will discuss other aspects of this non-vaccine that relate to its nanotechnology and transmission from the injected to the uninjected.

## **Qualified in idiocy**

Tenpenny describes how research has confirmed that these 'vaccine'-generated antibodies can interact with a range of other tissues in the body and attack many other organs including the lungs. 'This means that if you have a hundred people standing in front of you that all got this shot they could have a hundred different symptoms.'

Anyone really think that Cult gofers like the Queen, Tony Blair, Christopher Whitty, Anthony Fauci, and all the other psychopaths have really had this 'vaccine' in the pictures we've seen? Not a bloody chance. Why don't doctors all tell us about all these dangers and consequences of the 'Covid vaccine'? Why instead do they encourage and pressure patients to have the shot? Don't let's think for a moment that doctors and medical staff can't be stupid, lazy, and psychopathic and that's without the financial incentives to give the jab. Tenpenny again:

Some people are going to die from the vaccine directly but a large number of people are going to start to get horribly sick and get all kinds of autoimmune diseases 42 days to maybe a year out. What are they going to do, these stupid doctors who say; 'Good for you for getting that vaccine.' What are they going to say; 'Oh, it must be a mutant, we need to give an extra dose of that vaccine.'

Because now the vaccine, instead of one dose or two doses we need three or four because the stupid physicians aren't taking the time to learn anything about it. If I can learn this sitting in my living room reading a 19 page paper and several others so can they. There's nothing special about me, I just take the time to do it.

Remember how Sara Kayat, the NHS and TV doctor, said that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Doctors can be idiots like every other profession and they

should not be worshipped as infallible. They are not and far from it. Behind many medical and scientific ‘experts’ lies an uninformed prat trying to hide themselves from you although in the ‘Covid’ era many have failed to do so as with UK narrative-repeating ‘TV doctor’ Hilary Jones. Pushing back against the minority of proper doctors and scientists speaking out against the ‘vaccine’ has been the entire edifice of the Cult global state in the form of governments, medical systems, corporations, mainstream media, Silicon Valley, and an army of compliant doctors, medical staff and scientists willing to say anything for money and to enhance their careers by promoting the party line. If you do that you are an ‘expert’ and if you won’t you are an ‘anti-vaxxer’ and ‘Covidiot’. The pressure to be ‘vaccinated’ is incessant. We have even had reports claiming that the ‘vaccine’ can help cure cancer and Alzheimer’s and make the lame walk. I am waiting for the announcement that it can bring you coffee in the morning and cook your tea. Just as the symptoms of ‘Covid’ seem to increase by the week so have the miracles of the ‘vaccine’. American supermarket giant Kroger Co. offered nearly 500,000 employees in 35 states a \$100 bonus for having the ‘vaccine’ while donut chain Krispy Kreme promised ‘vaccinated’ customers a free glazed donut every day for the rest of 2021. Have your DNA changed and you will get a doughnut although we might not have to give you them for long. Such offers and incentives confirm the desperation.

Perhaps the worse vaccine-stunt of them all was UK ‘Health’ Secretary Matt-the-prat Hancock on live TV after watching a clip of someone being ‘vaccinated’ when the roll-out began. Hancock faked tears so badly it was embarrassing. Brain-of-Britain Piers Morgan, the lockdown-supporting, ‘vaccine’ supporting, ‘vaccine’ passport-supporting, TV host played along with Hancock – ‘You’re quite emotional about that’ he said in response to acting so atrocious it would have been called out at a school nativity which will presumably today include Mary and Jesus in masks, wise men keeping their camels six feet apart, and shepherds under tent arrest. System-serving Morgan tweeted this: ‘Love the idea of covid vaccine passports for everywhere: flights, restaurants, clubs, football, gyms,

shops etc. It's time covid-denying, anti-vaxxer loonies had their bullsh\*t bluff called & bar themselves from going anywhere that responsible citizens go.' If only I could aspire to his genius. To think that Morgan, who specialises in shouting over anyone he disagrees with, was lauded as a free speech hero when he lost his job after storming off the set of his live show like a child throwing his dolly out of the pram. If he is a free speech hero we are in real trouble. I have no idea what 'bullsh\*t' means, by the way, the \* throws me completely.

The Cult is desperate to infuse its synthetic DNA-changing concoction into everyone and has been using every lie, trick and intimidation to do so. The question of '*Why?*' we shall now address.

## CHAPTER TEN

### Human 2.0

***I believe that at the end of the century the use of words and general educated opinion will have altered so much that one will be able to speak of machines thinking without expecting to be contradicted –***

**Alan Turing (1912-1954), the ‘Father of artificial intelligence’**

I have been exposing for decades the plan to transform the human body from a biological to a synthetic-biological state. The new human that I will call Human 2.0 is planned to be connected to artificial intelligence and a global AI ‘Smart Grid’ that would operate as one global system in which AI would control everything from your fridge to your heating system to your car to your mind. Humans would no longer be ‘human’, but post-human and sub-human, with their thinking and emotional processes replaced by AI.

What I said sounded crazy and beyond science fiction and I could understand that. To any balanced, rational, mind it *is* crazy. Today, however, that world is becoming reality and it puts the ‘Covid vaccine’ into its true context. Ray Kurzweil is the ultra-Zionist ‘computer scientist, inventor and futurist’ and co-founder of the Singularity University. Singularity refers to the merging of humans with machines or ‘transhumanism’. Kurzweil has said humanity would be connected to the cyber ‘cloud’ in the period of the ever-recurring year of 2030:

Our thinking ... will be a hybrid of biological and non-biological thinking ... humans will be able to extend their limitations and ‘think in the cloud’ ... We’re going to put gateways to the

cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations. As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

They are trying to sell this end-of-humanity-as-we-know-it as the next stage of 'evolution' when we become super-human and 'like the gods'. They are lying to you. Shocked, eh? The population, and again especially the young, have been manipulated into addiction to technologies designed to enslave them for life. First they induced an addiction to smartphones (holdables); next they moved to technology on the body (wearables); and then began the invasion of the body (implantables). I warned way back about the plan for microchipped people and we are now entering that era. We should not be diverted into thinking that this refers only to chips we can see. Most important are the nanochips known as smart dust, neural dust and nanobots which are far too small to be seen by the human eye. Nanotechnology is everywhere, increasingly in food products, and released into the atmosphere by the geoengineering of the skies funded by Bill Gates to 'shut out the Sun' and 'save the planet from global warming'. Gates has been funding a project to spray millions of tonnes of chalk (calcium carbonate) into the stratosphere over Sweden to 'dim the Sun' and cool the Earth. Scientists warned the move could be disastrous for weather systems in ways no one can predict and opposition led to the Swedish space agency announcing that the 'experiment' would not be happening as planned in the summer of 2021; but it shows where the Cult is going with dimming the impact of the Sun and there's an associated plan to change the planet's atmosphere. Who gives psychopath Gates the right to dictate to the entire human race and dismantle planetary systems? The world will not be safe while this man is at large.

The global warming hoax has made the Sun, like the gas of life, something to fear when both are essential to good health and human survival (more inversion). The body transforms sunlight into vital vitamin D through a process involving ... *cholesterol*. This is the cholesterol we are also told to fear. We are urged to take Big Pharma

statin drugs to reduce cholesterol and it's all systematic. Reducing cholesterol means reducing vitamin D uptake with all the multiple health problems that will cause. At least if you take statins long term it saves the government from having to pay you a pension. The delivery system to block sunlight is widely referred to as chemtrails although these have a much deeper agenda, too. They appear at first to be contrails or condensation trails streaming from aircraft into cold air at high altitudes. Contrails disperse very quickly while chemtrails do not and spread out across the sky before eventually their content falls to earth. Many times I have watched aircraft cross-cross a clear blue sky releasing chemtrails until it looks like a cloudy day. Chemtrails contain many things harmful to humans and the natural world including toxic heavy metals, aluminium (see Alzheimer's) and nanotechnology. Ray Kurzweil reveals the reason without actually saying so: 'Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.' How do you deliver that? *From the sky.* Self-replicating nanobots would connect everything to the Smart Grid. The phenomenon of Morgellons disease began in the chemtrail era and the correlation has led to it being dubbed the 'chemtrail disease'. Self-replicating fibres appear in the body that can be pulled out through the skin. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. I cover this at greater length in *Phantom Self*.

## **'Vaccine' operating system**

'Covid vaccines' with their self-replicating synthetic material are also designed to make the connection between humanity and Kurzweil's 'cloud'. American doctor and dedicated campaigner for truth, Carrie Madej, an Internal Medicine Specialist in Georgia with more than 20 years medical experience, has highlighted the nanotechnology aspect of the fake 'vaccines'. She explains how one of the components in at least the Moderna and Pfizer synthetic potions are 'lipid nanoparticles' which are 'like little tiny computer bits' – a 'sci-fi substance' known as nanobots and hydrogel which can be 'triggered

at any moment to deliver its payload' and act as 'biosensors'. The synthetic substance had 'the ability to accumulate data from your body like your breathing, your respiration, thoughts and emotions, all kind of things' and each syringe could carry a *million* nanobots:

This substance because it's like little bits of computers in your body, crazy, but it's true, it can do that, [and] obviously has the ability to act through Wi-Fi. It can receive and transmit energy, messages, frequencies or impulses. That issue has never been addressed by these companies. What does that do to the human?

Just imagine getting this substance in you and it can react to things all around you, the 5G, your smart device, your phones, what is happening with that? What if something is triggering it, too, like an impulse, a frequency? We have something completely foreign in the human body.

Madej said her research revealed that electromagnetic (EMF) frequencies emitted by phones and other devices had increased dramatically in the same period of the 'vaccine' rollout and she was seeing more people with radiation problems as 5G and other electromagnetic technology was expanded and introduced to schools and hospitals. She said she was 'floored with the EMF coming off' the devices she checked. All this makes total sense and syncs with my own work of decades when you think that Moderna refers in documents to its mRNA 'vaccine' as an 'operating system':

Recognizing the broad potential of mRNA science, we set out to create an mRNA technology platform that functions very much like an operating system on a computer. It is designed so that it can plug and play interchangeably with different programs. In our case, the 'program' or 'app' is our mRNA drug – the unique mRNA sequence that codes for a protein ...

... Our mRNA Medicines – 'The Software Of Life': When we have a concept for a new mRNA medicine and begin research, fundamental components are already in place. Generally, the only thing that changes from one potential mRNA medicine to another is the coding region – the actual genetic code that instructs ribosomes to make protein. Utilizing these instruction sets gives our investigational mRNA medicines a software-like quality. We also have the ability to combine different mRNA sequences encoding for different proteins in a single mRNA investigational medicine.

Who needs a real ‘virus’ when you can create a computer version to justify infusing your operating system into the entire human race on the road to making living, breathing people into cyborgs? What is missed with the ‘vaccines’ is the *digital* connection between synthetic material and the body that I highlighted earlier with the study that hacked a computer with human DNA. On one level the body is digital, based on mathematical codes, and I’ll have more about that in the next chapter. Those who ridiculously claim that mRNA ‘vaccines’ are not designed to change human genetics should explain the words of Dr Tal Zaks, chief medical officer at Moderna, in a 2017 TED talk. He said that over the last 30 years ‘we’ve been living this phenomenal digital scientific revolution, and I’m here today to tell you, that we are actually *hacking the software of life*, and that it’s changing the way we think about prevention and treatment of disease’:

In every cell there’s this thing called messenger RNA, or mRNA for short, that transmits the critical information from the DNA in our genes to the protein, which is really the stuff we’re all made out of. This is the critical information that determines what the cell will do. So we think about it as an operating system. So if you could change that, if you could introduce a line of code, or change a line of code, it turns out, that has profound implications for everything, from the flu to cancer.

Zaks should more accurately have said that this has profound implications for the human genetic code and the nature of DNA. Communications within the body go both ways and not only one. But, hey, no, the ‘Covid vaccine’ will not affect your genetics. Cult fact-checkers say so even though the man who helped to develop the mRNA technique says that it does. Zaks said in 2017:

If you think about what it is we’re trying to do. We’ve taken information and our understanding of that information and how that information is transmitted in a cell, and we’ve taken our understanding of medicine and how to make drugs, and we’re fusing the two. We think of it as information therapy.

I have been writing for decades that the body is an information field communicating with itself and the wider world. This is why

radiation which is information can change the information field of body and mind through phenomena like 5G and change their nature and function. 'Information therapy' means to change the body's information field and change the way it operates. DNA is a receiver-transmitter of information and can be mutated by information like mRNA synthetic messaging. Technology to do this has been ready and waiting in the underground bases and other secret projects to be rolled out when the 'Covid' hoax was played. 'Trials' of such short and irrelevant duration were only for public consumption. When they say the 'vaccine' is 'experimental' that is not true. It may appear to be 'experimental' to those who don't know what's going on, but the trials have already been done to ensure the Cult gets the result it desires. Zaks said that it took decades to sequence the human genome, completed in 2003, but now they could do it in a week. By 'they' he means scientists operating in the public domain. In the secret projects they were sequencing the genome in a week long before even 2003.

## **Deluge of mRNA**

Highly significantly the Moderna document says the guiding premise is that if using mRNA as a medicine works for one disease then it should work for many diseases. They were leveraging the flexibility afforded by their platform and the fundamental role mRNA plays in protein synthesis to pursue mRNA medicines for a broad spectrum of diseases. Moderna is confirming what I was saying through 2020 that multiple 'vaccines' were planned for 'Covid' (and later invented 'variants') and that previous vaccines would be converted to the mRNA system to infuse the body with massive amounts of genetically-manipulating synthetic material to secure a transformation to a synthetic-biological state. The 'vaccines' are designed to kill stunning numbers as part of the long-exposed Cult depopulation agenda and transform the rest. Given this is the goal you can appreciate why there is such hysterical demand for every human to be 'vaccinated' for an alleged 'disease' that has an estimated 'infection' to 'death' ratio of 0.23-0.15 percent. As I write

children are being given the ‘vaccine’ in trials (their parents are a disgrace) and ever-younger people are being offered the vaccine for a ‘virus’ that even if you believe it exists has virtually zero chance of harming them. Horrific effects of the ‘trials’ on a 12-year-old girl were revealed by a family member to be serious brain and gastric problems that included a bowel obstruction and the inability to swallow liquids or solids. She was unable to eat or drink without throwing up, had extreme pain in her back, neck and abdomen, and was paralysed from the waist down which stopped her urinating unaided. When the girl was first taken to hospital doctors said it was all in her mind. She was signed up for the ‘trial’ by her parents for whom no words suffice. None of this ‘Covid vaccine’ insanity makes any sense unless you see what the ‘vaccine’ really is – a body-changer. Synthetic biology or ‘SynBio’ is a fast-emerging and expanding scientific discipline which includes everything from genetic and molecular engineering to electrical and computer engineering. Synthetic biology is defined in these ways:

- A multidisciplinary area of research that seeks to create new biological parts, devices, and systems, or to redesign systems that are already found in nature.
- The use of a mixture of physical engineering and genetic engineering to create new (and therefore synthetic) life forms.
- An emerging field of research that aims to combine the knowledge and methods of biology, engineering and related disciplines in the design of chemically-synthesized DNA to create organisms with novel or enhanced characteristics and traits (synthetic organisms including humans).

We now have synthetic blood, skin, organs and limbs being developed along with synthetic body parts produced by 3D printers. These are all elements of the synthetic human programme and this comment by Kurzweil’s co-founder of the Singularity University,

Peter Diamandis, can be seen in a whole new light with the ‘Covid’ hoax and the sanctions against those that refuse the ‘vaccine’:

Anybody who is going to be resisting the progress forward [to transhumanism] is going to be resisting evolution and, fundamentally, they will die out. It’s not a matter of whether it’s good or bad. It’s going to happen.

‘Resisting evolution’? What absolute bollocks. The arrogance of these people is without limit. His ‘it’s going to happen’ mantra is another way of saying ‘resistance is futile’ to break the spirit of those pushing back and we must not fall for it. Getting this genetically-transforming ‘vaccine’ into everyone is crucial to the Cult plan for total control and the desperation to achieve that is clear for anyone to see. Vaccine passports are a major factor in this and they, too, are a form of resistance is futile. It’s NOT. The paper funded by the Rockefeller Foundation for the 2013 ‘health conference’ in China said:

We will interact more with artificial intelligence. The use of robotics, bio-engineering to augment human functioning is already well underway and will advance. Re-engineering of humans into potentially separate and unequal forms through genetic engineering or mixed human-robots raises debates on ethics and equality.

A new demography is projected to emerge after 2030 [that year again] of technologies (robotics, genetic engineering, nanotechnology) producing robots, engineered organisms, ‘nanobots’ and artificial intelligence (AI) that can self-replicate. Debates will grow on the implications of an impending reality of human designed life.

What is happening today is so long planned. The world army enforcing the will of the world government is intended to be a robot army, not a human one. Today’s military and its technologically ‘enhanced’ troops, pilotless planes and driverless vehicles are just stepping stones to that end. Human soldiers are used as Cult fodder and its time they woke up to that and worked for the freedom of the population instead of their own destruction and their family’s destruction – the same with the police. Join us and let’s sort this out. The phenomenon of enforce my own destruction is widespread in the ‘Covid’ era with Woker ‘luvvies’ in the acting and entertainment

industries supporting ‘Covid’ rules which have destroyed their profession and the same with those among the public who put signs on the doors of their businesses ‘closed due to Covid – stay safe’ when many will never reopen. It’s a form of masochism and most certainly insanity.

## **Transgender = transhumanism**

When something explodes out of nowhere and is suddenly everywhere it is always the Cult agenda and so it is with the tidal wave of claims and demands that have infiltrated every aspect of society under the heading of ‘transgenderism’. The term ‘trans’ is so ‘in’ and this is the dictionary definition:

A prefix meaning ‘across’, ‘through’, occurring ... in loanwords from Latin, used in particular for denoting movement or conveyance from place to place (transfer; transmit; transplant) or complete change (transform; transmute), or to form adjectives meaning ‘crossing’, ‘on the other side of’, or ‘going beyond’ the place named (transmontane; transnational; trans-Siberian).

Transgender means to go beyond gender and transhuman means to go beyond human. Both are aspects of the Cult plan to transform the human body to a synthetic state with *no gender*. Human 2.0 is not designed to procreate and would be produced technologically with no need for parents. The new human would mean the end of parents and so men, and increasingly women, are being targeted for the deletion of their rights and status. Parental rights are disappearing at an ever-quickening speed for the same reason. The new human would have no need for men or women when there is no procreation and no gender. Perhaps the transgender movement that appears to be in a permanent state of frenzy might now contemplate on how it is being used. This was never about transgender rights which are only the interim excuse for confusing gender, particularly in the young, on the road to *fusing* gender. Transgender activism is not an end; it is a *means* to an end. We see again the technique of creative destruction in which you destroy the status quo to ‘build back better’ in the form that you want. The gender status quo had to be

destroyed by persuading the Cult-created Woke mentality to believe that you can have 100 genders or more. A programme for 9 to 12 year olds produced by the Cult-owned BBC promoted the 100 genders narrative. The very idea may be the most monumental nonsense, but it is not what is true that counts, only what you can make people *believe* is true. Once the gender of  $2 + 2 = 4$  has been dismantled through indoctrination, intimidation and  $2 + 2 = 5$  then the new no-gender normal can take its place with Human 2.0.

Aldous Huxley revealed the plan in his prophetic *Brave New World* in 1932:

Natural reproduction has been done away with and children are created, 'decanted', and raised in 'hatcheries and conditioning centres'. From birth, people are genetically designed to fit into one of five castes, which are further split into 'Plus' and 'Minus' members and designed to fulfil predetermined positions within the social and economic strata of the World State.

How could Huxley know this in 1932? For the same reason George Orwell knew about the Big Brother state in 1948, Cult insiders I have quoted knew about it in 1969, and I have known about it since the early 1990s. If you are connected to the Cult or you work your balls off to uncover the plan you can predict the future. The process is simple. If there is a plan for the world and nothing intervenes to stop it then it will happen. Thus if you communicate the plan ahead of time you are perceived to have predicted the future, but you haven't. You have revealed the plan which without intervention will become the human future. The whole reason I have done what I have is to alert enough people to inspire an intervention and maybe at last that time has come with the Cult and its intentions now so obvious to anyone with a brain in working order.

## **The future is here**

Technological wombs that Huxley described to replace parent procreation are already being developed and they are only the projects we know about in the public arena. Israeli scientists told *The Times of Israel* in March, 2021, that they have grown 250-cell embryos

into mouse foetuses with fully formed organs using artificial wombs in a development they say could pave the way for gestating humans outside the womb. Professor Jacob Hanna of the Weizmann Institute of Science said:

We took mouse embryos from the mother at day five of development, when they are just of 250 cells, and had them in the incubator from day five until day 11, by which point they had grown all their organs.

By day 11 they make their own blood and have a beating heart, a fully developed brain. Anybody would look at them and say, 'this is clearly a mouse foetus with all the characteristics of a mouse.' It's gone from being a ball of cells to being an advanced foetus.

A special liquid is used to nourish embryo cells in a laboratory dish and they float on the liquid to duplicate the first stage of embryonic development. The incubator creates all the right conditions for its development, Hanna said. The liquid gives the embryo 'all the nutrients, hormones and sugars they need' along with a custom-made electronic incubator which controls gas concentration, pressure and temperature. The cutting-edge in the underground bases and other secret locations will be light years ahead of that, however, and this was reported by the London *Guardian* in 2017:

We are approaching a biotechnological breakthrough. Ectogenesis, the invention of a complete external womb, could completely change the nature of human reproduction. In April this year, researchers at the Children's Hospital of Philadelphia announced their development of an artificial womb.

The article was headed 'Artificial wombs could soon be a reality. What will this mean for women?' What would it mean for children is an even bigger question. No mother to bond with only a machine in preparation for a life of soulless interaction and control in a world governed by machines (see the *Matrix* movies). Now observe the calculated manipulations of the 'Covid' hoax as human interaction and warmth has been curtailed by distancing, isolation and fear with people communicating via machines on a scale never seen before.

These are all dots in the same picture as are all the personal assistants, gadgets and children's toys through which kids and adults communicate with AI as if it is human. The AI 'voice' on Sat-Nav should be included. All these things are psychological preparation for the Cult endgame. Before you can make a physical connection with AI you have to make a psychological connection and that is what people are being conditioned to do with this ever gathering human-AI interaction. Movies and TV programmes depicting the transhuman, robot dystopia relate to a phenomenon known as 'pre-emptive programming' in which the world that is planned is portrayed everywhere in movies, TV and advertising. This is conditioning the conscious and subconscious mind to become familiar with the planned reality to dilute resistance when it happens for real. What would have been a shock such is the change is made less so. We have young children put on the road to transgender transition surgery with puberty blocking drugs at an age when they could never be able to make those life-changing decisions.

Rachel Levine, a professor of paediatrics and psychiatry who believes in treating children this way, became America's highest-ranked openly-transgender official when she was confirmed as US Assistant Secretary at the Department of Health and Human Services after being nominated by Joe Biden (the Cult). Activists and governments press for laws to deny parents a say in their children's transition process so the kids can be isolated and manipulated into agreeing to irreversible medical procedures. A Canadian father Robert Hoogland was denied bail by the Vancouver Supreme Court in 2021 and remained in jail for breaching a court order that he stay silent over his young teenage daughter, a minor, who was being offered life-changing hormone therapy without parental consent. At the age of 12 the girl's 'school counsellor' said she may be transgender, referred her to a doctor and told the school to treat her like a boy. This is another example of state-serving schools imposing ever more control over children's lives while parents have ever less.

Contemptible and extreme child abuse is happening all over the world as the Cult gender-fusion operation goes into warp-speed.

## **Why the war on men – and now women?**

The question about what artificial wombs mean for women should rightly be asked. The answer can be seen in the deletion of women's rights involving sport, changing rooms, toilets and status in favour of people in male bodies claiming to identify as women. I can identify as a mountain climber, but it doesn't mean I can climb a mountain any more than a biological man can be a biological woman. To believe so is a triumph of belief over factual reality which is the very perceptual basis of everything Woke. Women's sport is being destroyed by allowing those with male bodies who say they identify as female to 'compete' with girls and women. Male body 'women' dominate 'women's' competition with their greater muscle mass, bone density, strength and speed. With that disadvantage sport for women loses all meaning. To put this in perspective nearly 300 American high school boys can run faster than the quickest woman sprinter in the world. Women are seeing their previously protected spaces invaded by male bodies simply because they claim to identify as women. That's all they need to do to access all women's spaces and activities under the Biden 'Equality Act' that destroys equality for women with the usual Orwellian Woke inversion. Male sex offenders have already committed rapes in women's prisons after claiming to identify as women to get them transferred. Does this not matter to the Woke 'equality' hypocrites? Not in the least. What matters to Cult manipulators and funders behind transgender activists is to advance gender fusion on the way to the no-gender 'human'. When you are seeking to impose transparent nonsense like this, or the 'Covid' hoax, the only way the nonsense can prevail is through censorship and intimidation of dissenters, deletion of factual information, and programming of the unquestioning, bewildered and naive. You don't have to scan the world for long to see that all these things are happening.

Many women's rights organisations have realised that rights and status which took such a long time to secure are being eroded and that it is systematic. Kara Dansky of the global Women's Human Rights Campaign said that Biden's transgender executive order immediately he took office, subsequent orders, and Equality Act legislation that followed 'seek to erase women and girls in the law as a category'. *Exactly.* I said during the long ago-started war on men (in which many women play a crucial part) that this was going to turn into a war on them. The Cult is phasing out *both* male and female genders. To get away with that they are brought into conflict so they are busy fighting each other while the Cult completes the job with no unity of response. Unity, people, *unity*. We need unity everywhere. Transgender is the only show in town as the big step towards the no-gender human. It's not about rights for transgender people and never has been. Woke political correctness is deleting words relating to genders to the same end. Wokers believe this is to be 'inclusive' when the opposite is true. They are deleting words describing gender because gender *itself* is being deleted by Human 2.0. Terms like 'man', 'woman', 'mother' and 'father' are being deleted in the universities and other institutions to be replaced by the *no*-gender, not trans-gender, 'individuals' and 'guardians'. Women's rights campaigner Maria Keffler of Partners for Ethical Care said: 'Children are being taught from kindergarten upward that some boys have a vagina, some girls have a penis, and that kids can be any gender they want to be.' Do we really believe that suddenly countries all over the world at the same time had the idea of having drag queens go into schools or read transgender stories to very young children in the local library? It's coldly-calculated confusion of gender on the way to the fusion of gender. Suzanne Vierling, a psychologist from Southern California, made another important point:

Yesterday's slave woman who endured gynecological medical experiments is today's girl-child being butchered in a booming gender-transitioning sector. Ovaries removed, pushing her into menopause and osteoporosis, uncharted territory, and parents' rights and authority decimated.

The erosion of parental rights is a common theme in line with the Cult plans to erase the very concept of parents and 'ovaries removed, pushing her into menopause' means what? Those born female lose the ability to have children – another way to discontinue humanity as we know it.

## **Eliminating Human 1.0 (before our very eyes)**

To pave the way for Human 2.0 you must phase out Human 1.0. This is happening through plummeting sperm counts and making women infertile through an onslaught of chemicals, radiation (including smartphones in pockets of men) and mRNA 'vaccines'. Common agriculture pesticides are also having a devastating impact on human fertility. I have been tracking collapsing sperm counts in the books for a long time and in 2021 came a book by fertility scientist and reproductive epidemiologist Shanna Swan, *Count Down: How Our Modern World Is Threatening Sperm Counts, Altering Male and Female Reproductive Development and Imperiling the Future of the Human Race*. She reports how the global fertility rate dropped by half between 1960 and 2016 with America's birth rate 16 percent below where it needs to be to sustain the population. Women are experiencing declining egg quality, more miscarriages, and more couples suffer from infertility. Other findings were an increase in erectile dysfunction, infant boys developing more genital abnormalities, male problems with conception, and plunging levels of the male hormone testosterone which would explain why so many men have lost their backbone and masculinity. This has been very evident during the 'Covid' hoax when women have been prominent among the Pushbackers and big strapping blokes have bowed their heads, covered their faces with a nappy and quietly submitted. Mind control expert Cathy O'Brien also points to how global education introduced the concept of 'we're all winners' in sport and classrooms: 'Competition was defused, and it in turn defused a sense of fighting back.' This is another version of the 'equity' doctrine in which you drive down rather than raise up. What a contrast in Cult-controlled China with its global ambitions

where the government published plans in January, 2021, to 'cultivate masculinity' in boys from kindergarten through to high school in the face of a 'masculinity crisis'. A government adviser said boys would be soon become 'delicate, timid and effeminate' unless action was taken. Don't expect any similar policy in the targeted West. A 2006 study showed that a 65-year-old man in 2002 had testosterone levels 15 percent lower than a 65-year-old man in 1987 while a 2020 study found a similar story with young adults and adolescents. Men are getting prescriptions for testosterone replacement therapy which causes an even greater drop in sperm count with up to 99 percent seeing sperm counts drop to zero during the treatment. More sperm is defective and malfunctioning with some having two heads or not pursuing an egg.

A class of *synthetic* chemicals known as phthalates are being blamed for the decline. These are found everywhere in plastics, shampoos, cosmetics, furniture, flame retardants, personal care products, pesticides, canned foods and even receipts. Why till receipts? Everyone touches them. Let no one delude themselves that all this is not systematic to advance the long-time agenda for human body transformation. Phthalates mimic hormones and disrupt the hormone balance causing testosterone to fall and genital birth defects in male infants. Animals and fish have been affected in the same way due to phthalates and other toxins in rivers. When fish turn gay or change sex through chemicals in rivers and streams it is a pointer to why there has been such an increase in gay people and the sexually confused. It doesn't matter to me what sexuality people choose to be, but if it's being affected by chemical pollution and consumption then we need to know. Does anyone really think that this is not connected to the transgender agenda, the war on men and the condemnation of male 'toxic masculinity'? You watch this being followed by 'toxic femininity'. It's already happening. When breastfeeding becomes 'chest-feeding', pregnant women become pregnant people along with all the other Woke claptrap you know that the world is going insane and there's a Cult scam in progress. Transgender activists are promoting the Cult agenda while Cult

billionaires support and fund the insanity as they laugh themselves to sleep at the sheer stupidity for which humans must be infamous in galaxies far, far away.

## **'Covid vaccines' and female infertility**

We can now see why the 'vaccine' has been connected to potential infertility in women. Dr Michael Yeadon, former Vice President and Chief Scientific Advisor at Pfizer, and Dr Wolfgang Wodarg in Germany, filed a petition with the European Medicines Agency in December, 2020, urging them to stop trials for the Pfizer/BioNTech shot and all other mRNA trials until further studies had been done. They were particularly concerned about possible effects on fertility with 'vaccine'-produced antibodies attacking the protein Syncytin-1 which is responsible for developing the placenta. The result would be infertility 'of indefinite duration' in women who have the 'vaccine' with the placenta failing to form. Section 10.4.2 of the Pfizer/BioNTech trial protocol says that pregnant women or those who might become so should not have mRNA shots. Section 10.4 warns men taking mRNA shots to 'be abstinent from heterosexual intercourse' and not to donate sperm. The UK government said that it *did not know* if the mRNA procedure had an effect on fertility. *Did not know?* These people have to go to jail. UK government advice did not recommend at the start that pregnant women had the shot and said they should avoid pregnancy for at least two months after 'vaccination'. The 'advice' was later updated to pregnant women should only have the 'vaccine' if the benefits outweighed the risks to mother and foetus. What the hell is that supposed to mean? Then 'spontaneous abortions' began to appear and rapidly increase on the adverse reaction reporting schemes which include only a fraction of adverse reactions. Thousands and ever-growing numbers of 'vaccinated' women are describing changes to their menstrual cycle with heavier blood flow, irregular periods and menstruating again after going through the menopause – all links to reproduction effects. Women are passing blood clots and the lining of their uterus while men report erectile dysfunction and blood effects. Most

significantly of all *unvaccinated* women began to report similar menstrual changes after interaction with '*vaccinated*' people and men and children were also affected with bleeding noses, blood clots and other conditions. 'Shedding' is when vaccinated people can emit the content of a vaccine to affect the unvaccinated, but this is different. '*Vaccinated*' people were not shedding a 'live virus' allegedly in '*vaccines*' as before because the fake '*Covid vaccines*' involve synthetic material and other toxicity. Doctors exposing what is happening prefer the term '*transmission*' to shedding. Somehow those that have had the shots are transmitting effects to those that haven't. Dr Carrie Madej said the nano-content of the '*vaccines*' can 'act like an antenna' to others around them which fits perfectly with my own conclusions. This '*vaccine*' transmission phenomenon was becoming known as the book went into production and I deal with this further in the Postscript.

Vaccine effects on sterility are well known. The World Health Organization was accused in 2014 of sterilising millions of women in Kenya with the evidence confirmed by the content of the vaccines involved. The same WHO behind the '*Covid*' hoax admitted its involvement for more than ten years with the vaccine programme. Other countries made similar claims. Charges were lodged by Tanzania, Nicaragua, Mexico, and the Philippines. The Gardasil vaccine claimed to protect against a genital '*virus*' known as HPV has also been linked to infertility. Big Pharma and the WHO (same thing) are criminal and satanic entities. Then there's the Bill Gates Foundation which is connected through funding and shared interests with 20 pharmaceutical giants and laboratories. He stands accused of directing the policy of United Nations Children's Fund (UNICEF), vaccine alliance GAVI, and other groupings, to advance the vaccine agenda and silence opposition at great cost to women and children. At the same time Gates wants to reduce the global population. Coincidence?

**Great Reset = Smart Grid = new human**

The Cult agenda I have been exposing for 30 years is now being openly promoted by Cult assets like Gates and Klaus Schwab of the World Economic Forum under code-terms like the 'Great Reset', 'Build Back Better' and 'a rare but narrow window of opportunity to reflect, reimagine, and reset our world'. What provided this 'rare but narrow window of opportunity'? The 'Covid' hoax did. Who created that? *They* did. My books from not that long ago warned about the planned 'Internet of Things' (IoT) and its implications for human freedom. This was the plan to connect all technology to the Internet and artificial intelligence and today we are way down that road with an estimated 36 billion devices connected to the World Wide Web and that figure is projected to be 76 billion by 2025. I further warned that the Cult planned to go beyond that to the Internet of *Everything* when the human brain was connected via AI to the Internet and Kurzweil's 'cloud'. Now we have Cult operatives like Schwab calling for precisely that under the term 'Internet of Bodies', a fusion of the physical, digital and biological into one centrally-controlled Smart Grid system which the Cult refers to as the 'Fourth Industrial Revolution'. They talk about the 'biological', but they really mean the synthetic-biological which is required to fully integrate the human body and brain into the Smart Grid and artificial intelligence planned to replace the human mind. We have everything being synthetically manipulated including the natural world through GMO and smart dust, the food we eat and the human body itself with synthetic 'vaccines'. I said in *The Answer* that we would see the Cult push for synthetic meat to replace animals and in February, 2021, the so predictable psychopath Bill Gates called for the introduction of synthetic meat to save us all from 'climate change'. The climate hoax just keeps on giving like the 'Covid' hoax. The war on meat by vegan activists is a carbon (oops, sorry) copy of the manipulation of transgender activists. They have no idea (except their inner core) that they are being used to promote and impose the agenda of the Cult or that they are only the *vehicle* and not the *reason*. This is not to say those who choose not to eat meat shouldn't be respected and supported in that right, but there are ulterior motives

for those in power. A *Forbes* article in December, 2019, highlighted the plan so beloved of Schwab and the Cult under the heading: 'What Is The Internet of Bodies? And How Is It Changing Our World?' The article said the human body is the latest data platform (remember 'our vaccine is an operating system'). *Forbes* described the plan very accurately and the words could have come straight out of my books from long before:

The Internet of Bodies (IoB) is an extension of the IoT and basically connects the human body to a network through devices that are ingested, implanted, or connected to the body in some way. Once connected, data can be exchanged, and the body and device can be remotely monitored and controlled.

They were really describing a human hive mind with human perception centrally-dictated via an AI connection as well as allowing people to be 'remotely monitored and controlled'.

Everything from a fridge to a human mind could be directed from a central point by these insane psychopaths and 'Covid vaccines' are crucial to this. *Forbes* explained the process I mentioned earlier of holdable and wearable technology followed by implantable. The article said there were three generations of the Internet of Bodies that include:

- Body external: These are wearable devices such as Apple Watches or Fitbits that can monitor our health.
- Body internal: These include pacemakers, cochlear implants, and digital pills that go inside our bodies to monitor or control various aspects of health.
- Body embedded: The third generation of the Internet of Bodies is embedded technology where technology and the human body are melded together and have a real-time connection to a remote machine.

*Forbes* noted the development of the Brain Computer Interface (BCI) which merges the brain with an external device for monitoring and controlling in real-time. ‘The ultimate goal is to help restore function to individuals with disabilities by using brain signals rather than conventional neuromuscular pathways.’ Oh, do fuck off. The goal of brain interface technology is controlling human thought and emotion from the central point in a hive mind serving its masters wishes. Many people are now agreeing to be chipped to open doors without a key. You can recognise them because they’ll be wearing a mask, social distancing and lining up for the ‘vaccine’. The Cult plans a Great Reset money system after they have completed the demolition of the global economy in which ‘money’ will be exchanged through communication with body operating systems. Rand Corporation, a Cult-owned think tank, said of the Internet of Bodies or IoB:

Internet of Bodies technologies fall under the broader IoT umbrella. But as the name suggests, IoB devices introduce an even more intimate interplay between humans and gadgets. IoB devices monitor the human body, collect health metrics and other personal information, and transmit those data over the Internet. Many devices, such as fitness trackers, are already in use ... IoB devices ... and those in development can track, record, and store users’ whereabouts, bodily functions, and what they see, hear, and even think.

Schwab’s World Economic Forum, a long-winded way of saying ‘fascism’ or ‘the Cult’, has gone full-on with the Internet of Bodies in the ‘Covid’ era. ‘We’re entering the era of the Internet of Bodies’, it declared, ‘collecting our physical data via a range of devices that can be implanted, swallowed or worn’. The result would be a huge amount of health-related data that could improve human wellbeing around the world, and prove crucial in fighting the ‘Covid-19 pandemic’. Does anyone think these clowns care about ‘human wellbeing’ after the death and devastation their pandemic hoax has purposely caused? Schwab and co say we should move forward with the Internet of Bodies because ‘Keeping track of symptoms could help us stop the spread of infection, and quickly detect new cases’. How wonderful, but keeping track’ is all they are really bothered

about. Researchers were investigating if data gathered from smartwatches and similar devices could be used as viral infection alerts by tracking the user's heart rate and breathing. Schwab said in his 2018 book *Shaping the Future of the Fourth Industrial Revolution*:

The lines between technologies and beings are becoming blurred and not just by the ability to create lifelike robots or synthetics. Instead it is about the ability of new technologies to literally become part of us. Technologies already influence how we understand ourselves, how we think about each other, and how we determine our realities. As the technologies ... give us deeper access to parts of ourselves, we may begin to integrate digital technologies into our bodies.

You can see what the game is. Twenty-four hour control and people – if you could still call them that – would never know when something would go ping and take them out of circulation. It's the most obvious rush to a global fascist dictatorship and the complete submission of humanity and yet still so many are locked away in their Cult-induced perceptual coma and can't see it.

## **Smart Grid control centres**

The human body is being transformed by the 'vaccines' and in other ways into a synthetic cyborg that can be attached to the global Smart Grid which would be controlled from a central point and other sub-locations of Grid manipulation. Where are these planned to be? Well, China for a start which is one of the Cult's biggest centres of operation. The technological control system and technocratic rule was incubated here to be unleashed across the world after the 'Covid' hoax came out of China in 2020. Another Smart Grid location that will surprise people new to this is Israel. I have exposed in *The Trigger* how Sabbatian technocrats, intelligence and military operatives were behind the horrors of 9/11 and not 19 Arab hijackers' who somehow manifested the ability to pilot big passenger airliners when instructors at puddle-jumping flying schools described some of them as a joke. The 9/11 attacks were made possible through control of civilian and military air computer systems and those of the White House, Pentagon and connected agencies. See *The Trigger* – it

will blow your mind. The controlling and coordinating force were the Sabbatian networks in Israel and the United States which by then had infiltrated the entire US government, military and intelligence system. The real name of the American Deep State is 'Sabbatian State'. Israel is a tiny country of only nine million people, but it is one of the global centres of cyber operations and fast catching Silicon Valley in importance to the Cult. Israel is known as the 'start-up nation' for all the cyber companies spawned there with the Sabbatian specialisation of 'cyber security' that I mentioned earlier which gives those companies access to computer systems of their clients in real time through 'backdoors' written into the coding when security software is downloaded. The Sabbatian centre of cyber operations outside Silicon Valley is the Israeli military Cyber Intelligence Unit, the biggest infrastructure project in Israel's history, headquartered in the desert-city of Beersheba and involving some 20,000 'cyber soldiers'. Here are located a literal army of Internet trolls scanning social media, forums and comment lists for anyone challenging the Cult agenda. The UK military has something similar with its 77th Brigade and associated operations. The Beersheba complex includes research and development centres for other Cult operations such as Intel, Microsoft, IBM, Google, Apple, Hewlett-Packard, Cisco Systems, Facebook and Motorola. [Techcrunch.com](#) ran an article about the Beersheba global Internet technology centre headlined 'Israel's desert city of Beersheba is turning into a cybertech oasis':

The military's massive relocation of its prestigious technology units, the presence of multinational and local companies, a close proximity to Ben Gurion University and generous government subsidies are turning Beersheba into a major global cybertech hub. Beersheba has all of the ingredients of a vibrant security technology ecosystem, including Ben Gurion University with its graduate program in cybersecurity and Cyber Security Research Center, and the presence of companies such as EMC, Deutsche Telekom, PayPal, Oracle, IBM, and Lockheed Martin. It's also the future home of the INCB (Israeli National Cyber Bureau); offers a special income tax incentive for cyber security companies, and was the site for the relocation of the army's intelligence corps units.

Sabbatians have taken over the cyber world through the following process: They scan the schools for likely cyber talent and develop them at Ben Gurion University and their period of conscription in the Israeli Defense Forces when they are stationed at the Beersheba complex. When the cyber talented officially leave the army they are funded to start cyber companies with technology developed by themselves or given to them by the state. Much of this is stolen through backdoors of computer systems around the world with America top of the list. Others are sent off to Silicon Valley to start companies or join the major ones and so we have many major positions filled by apparently 'Jewish' but really Sabbatian operatives. Google, YouTube and Facebook are all run by 'Jewish' CEOs while Twitter is all but run by ultra-Zionist hedge-fund shark Paul Singer. At the centre of the Sabbatian global cyber web is the Israeli army's Unit 8200 which specialises in hacking into computer systems of other countries, inserting viruses, gathering information, instigating malfunction, and even taking control of them from a distance. A long list of Sabbatians involved with 9/11, Silicon Valley and Israeli cyber security companies are operatives of Unit 8200. This is not about Israel. It's about the Cult. Israel is planned to be a Smart Grid hub as with China and what is happening at Beersheba is not for the benefit of Jewish people who are treated disgustingly by the Sabbatian elite that control the country. A glance at the Nuremberg Codes will tell you that.

The story is much bigger than 'Covid', important as that is to where we are being taken. Now, though, it's time to really strap in. There's more ... much more ...

## CHAPTER ELEVEN

### Who controls the Cult?

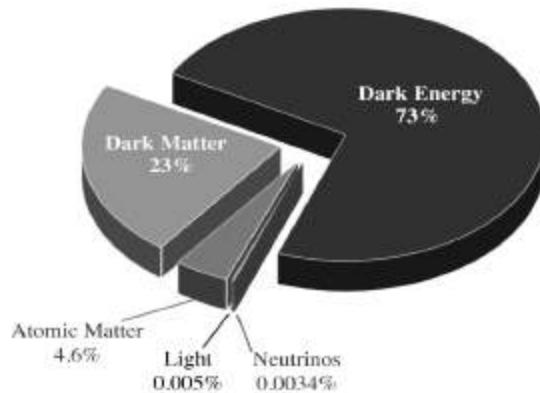
*Awake, arise or be forever fall'n*

**John Milton, Paradise Lost**

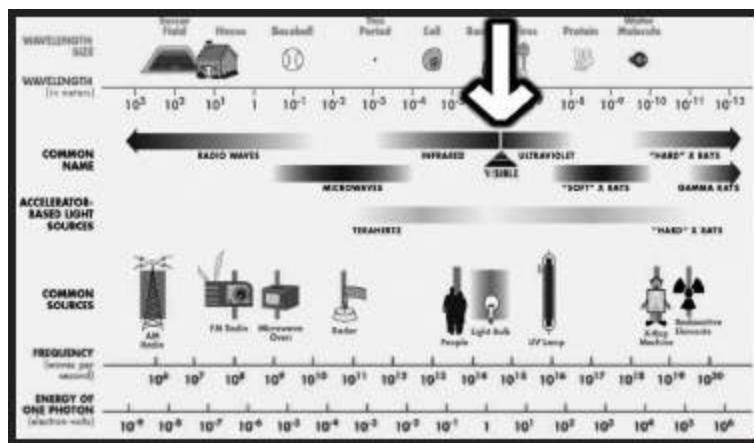
I have exposed this far the level of the Cult conspiracy that operates in the world of the seen and within the global secret society and satanic network which operates in the shadows one step back from the seen. The story, however, goes much deeper than that.

The 'Covid' hoax is major part of the Cult agenda, but only part, and to grasp the biggest picture we have to expand our attention beyond the realm of human sight and into the infinity of possibility that we cannot see. It is from here, ultimately, that humanity is being manipulated into a state of total control by the force which dictates the actions of the Cult. How much of reality can we see? Next to damn all is the answer. We may appear to see all there is to see in the 'space' our eyes survey and observe, but little could be further from the truth. The human 'world' is only a tiny band of frequency that the body's visual and perceptual systems can decode into *perception* of a 'world'. According to mainstream science the electromagnetic spectrum is 0.005 percent of what exists in the Universe ([Fig 10](#)). The maximum estimate I have seen is 0.5 percent and either way it's minuscule. I say it is far, far, smaller even than 0.005 percent when you compare reality we see with the totality of reality that we don't. Now get this if you are new to such information: Visible light, the only band of frequency that we can see, is a *fraction* of the 0.005

percent (Fig 11 overleaf). Take this further and realise that our universe is one of infinite universes and that universes are only a fragment of overall reality – *infinite* reality. Then compare that with the almost infinitesimal frequency band of visible light or human sight. You see that humans are as near blind as it is possible to be without actually being so. Artist and filmmaker, Sergio Toporek, said:



**Figure 10:** Humans can perceive such a tiny band of visual reality it's laughable.



**Figure 11:** We can see a smear of the 0.005 percent electromagnetic spectrum, but we still know it all. Yep, makes sense.

Consider that you can see less than 1% of the electromagnetic spectrum and hear less than 1% of the acoustic spectrum. 90% of the cells in your body carry their own microbial DNA and are not 'you'. The atoms in your body are 99.99999999999999% empty space and none of them are the ones you were born with ... Human beings have 46 chromosomes, two less than a potato.

The existence of the rainbow depends on the conical photoreceptors in your eyes; to animals without cones, the rainbow does not exist. So you don't just look at a rainbow, you create it. This is pretty amazing, especially considering that all the beautiful colours you see represent less than 1% of the electromagnetic spectrum.

Suddenly the 'world' of humans looks a very different place. Take into account, too, that Planet Earth when compared with the projected size of this single universe is the equivalent of a billionth of a pinhead. Imagine the ratio that would be when compared to infinite reality. To think that Christianity once insisted that Earth and humanity were the centre of everything. This background is vital if we are going to appreciate the nature of 'human' and how we can be manipulated by an unseen force. To human visual reality virtually *everything* is unseen and yet the prevailing perception within the institutions and so much of the public is that if we can't see it, touch it, hear it, taste it and smell it then it cannot exist. Such perception is indoctrinated and encouraged by the Cult and its agents because it isolates believers in the strictly limited, village-idiot, realm of the five senses where perceptions can be firewalled and information controlled. Most of those perpetuating the 'this-world-is-all-there-is' insanity are themselves indoctrinated into believing the same delusion. While major players and influencers know that official reality is laughable most of those in science, academia and medicine really believe the nonsense they peddle and teach succeeding generations. Those who challenge the orthodoxy are dismissed as nutters and freaks to protect the manufactured illusion from exposure. Observe the dynamic of the 'Covid' hoax and you will see how that takes the same form. The inner-circle psychopaths know it's a gigantic scam, but almost the entirety of those imposing their fascist rules believe that 'Covid' is all that they're told it is.

## **Stolen identity**

Ask people who they are and they will give you their name, place of birth, location, job, family background and life story. Yet that is not who they are – it is what they are *experiencing*. The difference is *absolutely crucial*. The true 'I', the eternal, infinite 'I', is consciousness,

a state of being aware. Forget ‘form’. That is a vehicle for a brief experience. Consciousness does not come *from* the brain, but *through* the brain and even that is more symbolic than literal. We are awareness, pure awareness, and this is what withdraws from the body at what we call ‘death’ to continue our eternal beingness, *isness*, in other realms of reality within the limitlessness of infinity or the Biblical ‘many mansions in my father’s house’. Labels of a human life, man, woman, transgender, black, white, brown, nationality, circumstances and income are not who we are. They are what we are – awareness – is *experiencing* in a brief connection with a band of frequency we call ‘human’. The labels are not the self; they are, to use the title of one of my books, a *Phantom Self*. I am not David Icke born in Leicester, England, on April 29th, 1952. I am the consciousness *having that experience*. The Cult and its non-human masters seek to convince us through the institutions of ‘education’, science, medicine, media and government that what we are *experiencing* is who we *are*. It’s so easy to control and direct perception locked away in the bewildered illusions of the five senses with no expanded radar. Try, by contrast, doing the same with a humanity aware of its true self and its true power to consciously create its reality and experience. How is it possible to do this? We do it all day every day. If you perceive yourself as ‘little me’ with no power to impact upon your life and the world then your life experience will reflect that. You will hand the power you don’t think you have to authority in all its forms which will use it to control your experience. This, in turn, will appear to confirm your perception of ‘little me’ in a self-fulfilling feedback loop. But that is what ‘little me’ really is – a *perception*. We are all ‘big-me’, infinite me, and the Cult has to make us forget that if its will is to prevail. We are therefore manipulated and pressured into self-identifying with human labels and not the consciousness/awareness *experiencing* those human labels.

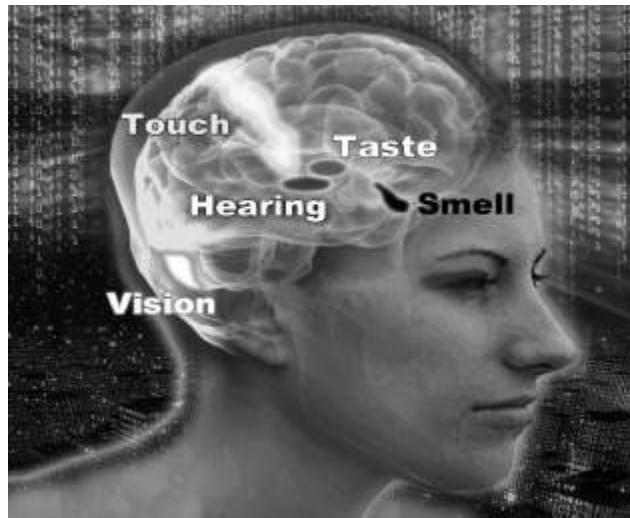
The phenomenon of identity politics is a Cult-instigated manipulation technique to sub-divide previous labels into even smaller ones. A United States university employs this list of letters to

describe student identity: LGBTQQFAGPBDSM or lesbian, gay, bisexual, transgender, transsexual, queer, questioning, flexual, asexual, gender-fuck, polyamorous, bondage/discipline, dominance/submission and sadism/masochism. I'm sure other lists are even longer by now as people feel the need to self-identify the 'I' with the minutiae of race and sexual preference. Wokers programmed by the Cult for generations believe this is about 'inclusivity' when it's really the Cult locking them away into smaller and smaller versions of Phantom Self while firewalls them from the influence of their true self, the infinite, eternal 'I'. You may notice that my philosophy which contends that we are all unique points of attention/awareness within the same infinite whole or Oneness is the ultimate non-racism. The very sense of Oneness makes the judgement of people by their body-type, colour or sexuality utterly ridiculous and confirms that racism has no understanding of reality (including anti-white racism). Yet despite my perception of life Cult agents and fast-asleep Wokers label me racist to discredit my information while they are themselves phenomenally racist and sexist. All they see is race and sexuality and they judge people as good or bad, demons or untouchables, by their race and sexuality. All they see is *Phantom Self* and perceive themselves in terms of *Phantom Self*. They are pawns and puppets of the Cult agenda to focus attention and self-identity in the five senses and play those identities against each other to divide and rule. Columbia University has introduced segregated graduations in another version of social distancing designed to drive people apart and teach them that different racial and cultural groups have nothing in common with each other. The last thing the Cult wants is unity. Again the pump-primers of this will be Cult operatives in the knowledge of what they are doing, but the rest are just the *Phantom Self* blind leading the *Phantom Self* blind. We *do* have something in common – we are all *the same consciousness* having different temporary experiences.

## **What is this 'human'?**

Yes, what *is* ‘human’? That is what we are supposed to be, right? I mean ‘human’? True, but ‘human’ is the experience not the ‘I’. Break it down to basics and ‘human’ is the way that information is processed. If we are to experience and interact with this band of frequency we call the ‘world’ we must have a vehicle that operates within that band of frequency. Our consciousness in its prime form cannot do that; it is way beyond the frequency of the human realm. My consciousness or awareness could not tap these keys and pick up the cup in front of me in the same way that radio station A cannot interact with radio station B when they are on different frequencies. The human body is the means through which we have that interaction. I have long described the body as a biological computer which processes information in a way that allows consciousness to experience this reality. The body is a receiver, transmitter and processor of information in a particular way that we call human. We visually perceive only the world of the five senses in a wakened state – that is the limit of the body’s visual decoding system. In truth it’s not even visual in the way we experience ‘visual reality’ as I will come to in a moment. We are ‘human’ because the body processes the information sources of human into a reality and behaviour system that we *perceive* as human. Why does an elephant act like an elephant and not like a human or a duck? The elephant’s biological computer is a different information field and processes information according to that program into a visual and behaviour type we call an elephant. The same applies to everything in our reality. These body information fields are perpetuated through procreation (like making a copy of a software program). The Cult wants to break that cycle and intervene technologically to transform the human information field into one that will change what we call humanity. If it can change the human information field it will change the way that field processes information and change humanity both ‘physically’ and psychologically. Hence the *messenger* (information) RNA ‘vaccines’ and so much more that is targeting human genetics by changing the body’s information – *messaging* – construct through food, drink, radiation, toxicity and other means.

Reality that we experience is nothing like reality as it really is in the same way that the reality people experience in virtual reality games is not the reality they are really living in. The game is only a decoded source of information that appears to be a reality. Our world is also an information construct – a *simulation* (more later). In its base form our reality is a wavefield of information much the same in theme as Wi-Fi. The five senses decode wavefield information into electrical information which they communicate to the brain to decode into holographic (illusory ‘physical’) information. Different parts of the brain specialise in decoding different senses and the information is fused into a reality that appears to be outside of us but is really inside the brain and the genetic structure in general ([Fig 12](#) overleaf). DNA is a receiver-transmitter of information and a vital part of this decoding process and the body’s connection to other realities. Change DNA and you change the way we decode and connect with reality – see ‘Covid vaccines’. Think of computers decoding Wi-Fi. You have information encoded in a radiation field and the computer decodes that information into a very different form on the screen. You can’t see the Wi-Fi until its information is made manifest on the screen and the information on the screen is inside the computer and not outside. I have just described how we decode the ‘human world’. All five senses decode the waveform ‘Wi-Fi’ field into electrical signals and the brain (computer) constructs reality inside the brain and not outside – ‘You don’t just look at a rainbow, you create it’. Sound is a simple example. We don’t hear sound until the brain decodes it. Waveform sound waves are picked up by the hearing sense and communicated to the brain in an electrical form to be decoded into the sounds that we hear. Everything we hear is inside the brain along with everything we see, feel, smell and taste. Words and language are waveform fields generated by our vocal chords which pass through this process until they are decoded by the brain into words that we hear. Different languages are different frequency fields or sound waves generated by vocal chords. Late British philosopher Alan Watts said:



**Figure 12:** The brain receives information from the five senses and constructs from that our perceived reality.

[Without the brain] the world is devoid of light, heat, weight, solidity, motion, space, time or any other imaginable feature. All these phenomena are interactions, or transactions, of vibrations with a certain arrangement of neurons.

That's exactly what they are and scientist Robert Lanza describes in his book, *Biocentrism*, how we decode electromagnetic waves and energy into visual and 'physical' experience. He uses the example of a flame emitting photons, electromagnetic energy, each pulsing electrically and magnetically:

... these ... invisible electromagnetic waves strike a human retina, and if (and only if) the waves happen to measure between 400 and 700 nano meters in length from crest to crest, then their energy is just right to deliver a stimulus to the 8 million cone-shaped cells in the retina.

Each in turn send an electrical pulse to a neighbour neuron, and on up the line this goes, at 250 mph, until it reaches the ... occipital lobe of the brain, in the back of the head. There, a cascading complex of neurons fire from the incoming stimuli, and we subjectively perceive this experience as a yellow brightness occurring in a place we have been conditioned to call the 'external world'.

## You hear what you decode

If a tree falls or a building collapses they make no noise unless someone is there to decode the energetic waves generated by the disturbance into what we call sound. Does a falling tree make a noise? Only if you hear it – *decode* it. Everything in our reality is a frequency field of information operating within the overall ‘Wi-Fi’ field that I call The Field. A vibrational disturbance is generated in The Field by the fields of the falling tree or building. These disturbance waves are what we decode into the sound of them falling. If no one is there to do that then neither will make any noise. Reality is created by the observer – *decoder* – and the *perceptions* of the observer affect the decoding process. For this reason different people – different *perceptions* – will perceive the same reality or situation in a different way. What one may perceive as a nightmare another will see as an opportunity. The question of why the Cult is so focused on controlling human perception now answers itself. All experienced reality is the act of decoding and we don’t experience Wi-Fi until it is decoded on the computer screen. The sight and sound of an Internet video is encoded in the Wi-Fi all around us, but we don’t see or hear it until the computer decodes that information. Taste, smell and touch are all phenomena of the brain as a result of the same process. We don’t taste, smell or feel anything except in the brain and there are pain relief techniques that seek to block the signal from the site of discomfort to the brain because if the brain doesn’t decode that signal we don’t feel pain. Pain is in the brain and only appears to be at the point of impact thanks to the feedback loop between them. We don’t see anything until electrical information from the sight senses is decoded in an area at the back of the brain. If that area is damaged we can go blind when our eyes are perfectly okay. So why do we go blind if we damage an eye? We damage the information processing between the waveform visual information and the visual decoding area of the brain. If information doesn’t reach the brain in a form it can decode then we can’t see the visual reality that it represents. What’s more the brain is decoding only a fraction of the information it receives and the rest is absorbed by the

sub-conscious mind. This explanation is from the science magazine, *Wonderpedia*:

Every second, 11 million sensations crackle along these [brain] pathways ... The brain is confronted with an alarming array of images, sounds and smells which it rigorously filters down until it is left with a manageable list of around 40. Thus 40 sensations per second make up what we perceive as reality.

The ‘world’ is not what people are told to believe that is it and the inner circles of the Cult *know that*.

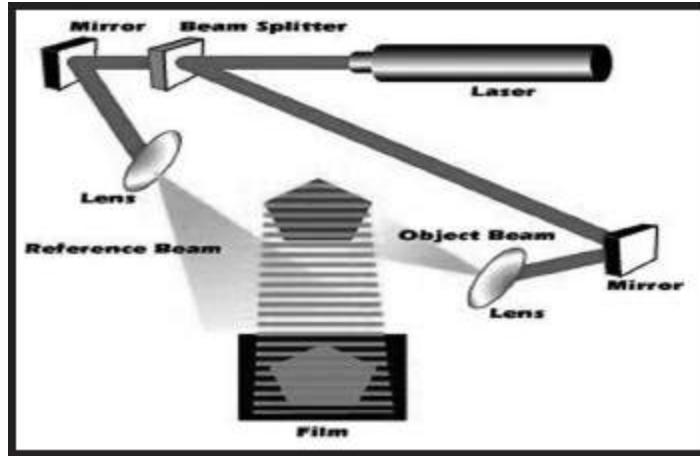
### **Illusory ‘physical’ reality**

We can only see a smear of 0.005 percent of the Universe which is only one of a vast array of universes – ‘mansions’ – within infinite reality. Even then the brain decodes only 40 pieces of information (‘sensations’) from a potential *11 million* that we receive every second. Two points strike you from this immediately: The sheer breathtaking stupidity of believing we know anything so rigidly that there’s nothing more to know; and the potential for these processes to be manipulated by a malevolent force to control the reality of the population. One thing I can say for sure with no risk of contradiction is that when you can perceive an almost indescribable fraction of infinite reality there is always more to know as in tidal waves of it. Ancient Greek philosopher Socrates was so right when he said that wisdom is to know how little we know. How obviously true that is when you think that we are experiencing a physical world of solidity that is neither physical nor solid and a world of apartness when everything is connected. Cult-controlled ‘science’ dismisses the so-called ‘paranormal’ and all phenomena related to that when the ‘para’-normal is perfectly normal and explains the alleged ‘great mysteries’ which dumbfound scientific minds. There is a reason for this. A ‘scientific mind’ in terms of the mainstream is a material mind, a five-sense mind imprisoned in see it, touch it, hear it, smell it and taste it. Phenomena and happenings that can’t be explained that way leave the ‘scientific mind’ bewildered and the rule is that if they

can't account for why something is happening then it can't, by definition, be happening. I beg to differ. Telepathy is thought waves passing through The Field (think wave disturbance again) to be decoded by someone able to connect with that wavelength (information). For example: You can pick up the thought waves of a friend at any distance and at the very least that will bring them to mind. A few minutes later the friend calls you. 'My god', you say, 'that's incredible – I was just thinking of you.' Ah, but *they* were thinking of *you* before they made the call and that's what you decoded. Native peoples not entrapped in five-sense reality do this so well it became known as the 'bush telegraph'. Those known as psychics and mediums (genuine ones) are doing the same only across dimensions of reality. 'Mind over matter' comes from the fact that matter and mind are the *same*. The state of one influences the state of the other. Indeed one *and* the other are illusions. They are aspects of the same field. Paranormal phenomena are all explainable so why are they still considered 'mysteries' or not happening? Once you go down this road of understanding you begin to expand awareness beyond the five senses and that's the nightmare for the Cult.



**Figure 13:** Holograms are not solid, but the best ones appear to be.



**Figure 14:** How holograms are created by capturing a waveform version of the subject image.

## Holographic ‘solidity’

Our reality is not solid, it is holographic. We are now well aware of holograms which are widely used today. Two-dimensional information is decoded into a three-dimensional reality that is not solid although can very much appear to be (Fig 13). Holograms are created with a laser divided into two parts. One goes directly onto a photographic print ('reference beam') and the other takes a waveform image of the subject ('working beam') before being directed onto the print where it 'collides' with the other half of the laser (Fig 14). This creates a *waveform* interference pattern which contains the wavefield information of whatever is being photographed (Fig 15 overleaf). The process can be likened to dropping pebbles in a pond. Waves generated by each one spread out across the water to collide with the others and create a wave representation of where the stones fell and at what speed, weight and distance. A waveform interference pattern of a hologram is akin to the waveform information in The Field which the five senses decode into electrical signals to be decoded by the brain into a holographic illusory 'physical' reality. In the same way when a laser (think human attention) is directed at the waveform interference pattern a three-dimensional version of the subject is projected into apparently 'solid' reality (Fig 16). An amazing trait of holograms reveals more 'paranormal mysteries'. Information of the *whole*

hologram is encoded in waveform in every part of the interference pattern by the way they are created. This means that every *part* of a hologram is a smaller version of the whole. Cut the interference wave-pattern into four and you won't get four parts of the image. You get quarter-sized versions of the *whole* image. The body is a hologram and the same applies. Here we have the basis of acupuncture, reflexology and other forms of healing which identify representations of the whole body in all of the parts, hands, feet, ears, everywhere. Skilled palm readers can do what they do because the information of whole body is encoded in the hand. The concept of as above, so below, comes from this.



**Figure 15:** A waveform interference pattern that holds the information that transforms into a hologram.



**Figure 16:** Holographic people including 'Elvis' holographically inserted to sing a duet with Celine Dion.

The question will be asked of why, if solidity is illusory, we can't just walk through walls and each other. The resistance is not solid against solid; it is electromagnetic field against electromagnetic field and we decode this into the *experience* of solid against solid. We should also not underestimate the power of belief to dictate reality. What you believe is impossible *will be*. Your belief impacts on your decoding processes and they won't decode what you think is impossible. What we believe we perceive and what we perceive we experience. 'Can't dos' and 'impossibles' are like a firewall in a computer system that won't put on the screen what the firewall blocks. How vital that is to understanding how human experience has been hijacked. I explain in *The Answer, Everything You Need To Know But Have Never Been Told* and other books a long list of 'mysteries' and 'paranormal' phenomena that are not mysterious and perfectly normal once you realise what reality is and how it works. 'Ghosts' can be seen to pass through 'solid' walls because the walls are not solid and the ghost is a discarnate entity operating on a frequency so different to that of the wall that it's like two radio stations sharing the same space while never interfering with each other. I have seen ghosts do this myself. The apartness of people and objects is also an illusion. Everything is connected by the Field like all sea life is connected by the sea. It's just that within the limits of our visual reality we only 'see' holographic information and not the field of information that connects everything and from which the holographic world is made manifest. If you can only see holographic 'objects' and not the field that connects them they will appear to you as unconnected to each other in the same way that we see the computer while not seeing the Wi-Fi.

## **What you don't know *can* hurt you**

Okay, we return to those 'two worlds' of human society and the Cult with its global network of interconnecting secret societies and satanic groups which manipulate through governments, corporations, media, religions, etc. The fundamental difference between them is *knowledge*. The idea has been to keep humanity

ignorant of the plan for its total enslavement underpinned by a crucial ignorance of reality – who we are and where we are – and how we interact with it. ‘Human’ should be the interaction between our expanded eternal consciousness and the five-sense body experience. We are meant to be *in* this world in terms of the five senses but not *of* this world in relation to our greater consciousness and perspective. In that state we experience the small picture of the five senses within the wider context of the big picture of awareness beyond the five senses. Put another way the five senses see the dots and expanded awareness connects them into pictures and patterns that give context to the apparently random and unconnected. Without the context of expanded awareness the five senses see only apartness and randomness with apparently no meaning. The Cult and its other-dimensional controllers seek to intervene in the frequency realm where five-sense reality is supposed to connect with expanded reality and to keep the two apart (more on this in the final chapter). When that happens five-sense mental and emotional processes are no longer influenced by expanded awareness, or the True ‘I’, and instead are driven by the isolated perceptions of the body’s decoding systems. They are in the world *and* of it. Here we have the human plight and why humanity with its potential for infinite awareness can be so easily manipulatable and descend into such extremes of stupidity.

Once the Cult isolates five-sense mind from expanded awareness it can then program the mind with perceptions and beliefs by controlling information that the mind receives through the ‘education’ system of the formative years and the media perceptual bombardment and censorship of an entire lifetime. Limit perception and a sense of the possible through limiting knowledge by limiting and skewing information while censoring and discrediting that which could set people free. As the title of another of my books says ... *And The Truth Shall Set You Free*. For this reason the last thing the Cult wants in circulation is the truth about anything – especially the reality of the eternal ‘I’ – and that’s why it is desperate to control information. The Cult knows that information becomes perception

which becomes behaviour which, collectively, becomes human society. Cult-controlled and funded mainstream ‘science’ denies the existence of an eternal ‘I’ and seeks to dismiss and trash all evidence to the contrary. Cult-controlled mainstream religion has a version of ‘God’ that is little more than a system of control and dictatorship that employs threats of damnation in an afterlife to control perceptions and behaviour in the here and now through fear and guilt. Neither is true and it’s the ‘neither’ that the Cult wishes to suppress. This ‘neither’ is that everything is an expression, a point of attention, within an infinite state of consciousness which is the real meaning of the term ‘God’.

Perceptual obsession with the ‘physical body’ and five-senses means that ‘God’ becomes personified as a bearded bloke sitting among the clouds or a raging bully who loves us if we do what ‘he’ wants and condemns us to the fires of hell if we don’t. These are no more than a ‘spiritual’ fairy tales to control and dictate events and behaviour through fear of this ‘God’ which has bizarrely made ‘God-fearing’ in religious circles a state to be desired. I would suggest that fearing *anything* is not to be encouraged and celebrated, but rather deleted. You can see why ‘God fearing’ is so beneficial to the Cult and its religions when *they* decide what ‘God’ wants and what ‘God’ demands (the Cult demands) that everyone do. As the great American comedian Bill Hicks said satirising a Christian zealot: ‘I think what God meant to say.’ How much of this infinite awareness (“God”) that we access is decided by how far we choose to expand our perceptions, self-identity and sense of the possible. The scale of self-identity reflects itself in the scale of awareness that we can connect with and are influenced by – how much knowing and insight we have instead of programmed perception. You cannot expand your awareness into the infinity of possibility when you believe that you are little me Peter the postman or Mary in marketing and nothing more. I’ll deal with this in the concluding chapter because it’s crucial to how we turnaround current events.

## **Where the Cult came from**

When I realised in the early 1990s there was a Cult network behind global events I asked the obvious question: When did it start? I took it back to ancient Rome and Egypt and on to Babylon and Sumer in Mesopotamia, the 'Land Between Two Rivers', in what we now call Iraq. The two rivers are the Tigris and Euphrates and this region is of immense historical and other importance to the Cult, as is the land called Israel only 550 miles away by air. There is much more going with deep esoteric meaning across this whole region. It's not only about 'wars for oil'. Priceless artefacts from Mesopotamia were stolen or destroyed after the American and British invasion of Iraq in 2003 justified by the lies of Boy Bush and Tony Blair (their Cult masters) about non-existent 'weapons of mass destruction'.

Mesopotamia was the location of Sumer (about 5,400BC to 1,750BC), and Babylon (about 2,350BC to 539BC). Sabbatians may have become immensely influential in the Cult in modern times but they are part of a network that goes back into the mists of history. Sumer is said by historians to be the 'cradle of civilisation'. I disagree. I say it was the re-start of what we call human civilisation after cataclysmic events symbolised in part as the 'Great Flood' destroyed the world that existed before. These fantastic upheavals that I have been describing in detail in the books since the early 1990s appear in accounts and legends of ancient cultures across the world and they are supported by geological and biological evidence. Stone tablets found in Iraq detailing the Sumer period say the cataclysms were caused by non-human 'gods' they call the Anunnaki. These are described in terms of extraterrestrial visitations in which knowledge supplied by the Anunnaki is said to have been the source of at least one of the world's oldest writing systems and developments in astronomy, mathematics and architecture that were way ahead of their time. I have covered this subject at length in *The Biggest Secret* and *Children of the Matrix* and the same basic 'Anunnaki' story can be found in Zulu accounts in South Africa where the late and very great Zulu high shaman Credo Mutwa told me that the Sumerian Anunnaki were known by Zulus as the Chitauri or 'children of the serpent'. See my six-hour video interview with Credo on this subject entitled *The*

*Reptilian Agenda* recorded at his then home near Johannesburg in 1999 which you can watch on the Ickonic media platform.

The Cult emerged out of Sumer, Babylon and Egypt (and elsewhere) and established the Roman Empire before expanding with the Romans into northern Europe from where many empires were savagely imposed in the form of Cult-controlled societies all over the world. Mass death and destruction was their calling card. The Cult established its centre of operations in Europe and European Empires were Cult empires which allowed it to expand into a global force. Spanish and Portuguese colonialists headed for Central and South America while the British and French targeted North America. Africa was colonised by Britain, France, Belgium, the Netherlands, Portugal, Spain, Italy, and Germany. Some like Britain and France moved in on the Middle East. The British Empire was by far the biggest for a simple reason. By now Britain was the headquarters of the Cult from which it expanded to form Canada, the United States, Australia and New Zealand. The Sun never set on the British Empire such was the scale of its occupation. London remains a global centre for the Cult along with Rome and the Vatican although others have emerged in Israel and China. It is no accident that the 'virus' is alleged to have come out of China while Italy was chosen as the means to terrify the Western population into compliance with 'Covid' fascism. Nor that Israel has led the world in 'Covid' fascism and mass 'vaccination'.

You would think that I would mention the United States here, but while it has been an important means of imposing the Cult's will it is less significant than would appear and is currently in the process of having what power it does have deleted. The Cult in Europe has mostly loaded the guns for the US to fire. America has been controlled from Europe from the start through Cult operatives in Britain and Europe. The American Revolution was an illusion to make it appear that America was governing itself while very different forces were pulling the strings in the form of Cult families such as the Rothschilds through the Rockefellers and other subordinates. The Rockefellers are extremely close to Bill Gates and

established both scalpel and drug ‘medicine’ and the World Health Organization. They play a major role in the development and circulation of vaccines through the Rockefeller Foundation on which Bill Gates said his Foundation is based. Why wouldn’t this be the case when the Rockefellers and Gates are on the same team? Cult infiltration of human society goes way back into what we call history and has been constantly expanding and centralising power with the goal of establishing a global structure to dictate everything. Look how this has been advanced in great leaps with the ‘Covid’ hoax.

## **The non-human dimension**

I researched and observed the comings and goings of Cult operatives through the centuries and even thousands of years as they were born, worked to promote the agenda within the secret society and satanic networks, and then died for others to replace them. Clearly there had to be a coordinating force that spanned this entire period while operatives who would not have seen the end goal in their lifetimes came and went advancing the plan over millennia. I went in search of that coordinating force with the usual support from the extraordinary synchronicity of my life which has been an almost daily experience since 1990. I saw common themes in religious texts and ancient cultures about a non-human force manipulating human society from the hidden. Christianity calls this force Satan, the Devil and demons; Islam refers to the Jinn or Djinn; Zulus have their Chitauri (spelt in other ways in different parts of Africa); and the Gnostic people in Egypt in the period around and before 400AD referred to this phenomena as the ‘Archons’, a word meaning rulers in Greek. Central American cultures speak of the ‘Predators’ among other names and the same theme is everywhere. I will use ‘Archons’ as a collective name for all of them. When you see how their nature and behaviour is described all these different sources are clearly talking about the same force. Gnostics described the Archons in terms of ‘luminous fire’ while Islam relates the Jinn to ‘smokeless fire’. Some refer to beings in form that could occasionally be seen, but the most common of common theme is that they operate from

unseen realms which means almost all existence to the visual processes of humans. I had concluded that this was indeed the foundation of human control and that the Cult was operating within the human frequency band on behalf of this hidden force when I came across the writings of Gnostics which supported my conclusions in the most extraordinary way.

A sealed earthen jar was found in 1945 near the town of Nag Hammadi about 75-80 miles north of Luxor on the banks of the River Nile in Egypt. Inside was a treasure trove of manuscripts and texts left by the Gnostic people some 1,600 years earlier. They included 13 leather-bound papyrus codices (manuscripts) and more than 50 texts written in Coptic Egyptian estimated to have been hidden in the jar in the period of 400AD although the source of the information goes back much further. Gnostics oversaw the Great or Royal Library of Alexandria, the fantastic depository of ancient texts detailing advanced knowledge and accounts of human history. The Library was dismantled and destroyed in stages over a long period with the death-blow delivered by the Cult-established Roman Church in the period around 415AD. The Church of Rome was the Church of Babylon relocated as I said earlier. Gnostics were not a race. They were a way of perceiving reality. Whenever they established themselves and their information circulated the terrorists of the Church of Rome would target them for destruction. This happened with the Great Library and with the Gnostic Cathars who were burned to death by the psychopaths after a long period of oppression at the siege of the Castle of Monségur in southern France in 1244. The Church has always been terrified of Gnostic information which demolishes the official Christian narrative although there is much in the Bible that supports the Gnostic view if you read it in another way. To anyone studying the texts of what became known as the Nag Hammadi Library it is clear that great swathes of Christian and Biblical belief has its origin with Gnostics sources going back to Sumer. Gnostic themes have been twisted to manipulate the perceived reality of Bible believers. Biblical texts have been in the open for centuries where they could be changed while Gnostic

documents found at Nag Hammadi were sealed away and untouched for 1,600 years. What you see is what they wrote.

### **Use your *pneuma* not your *nous***

Gnosticism and Gnostic come from 'gnosis' which means knowledge, or rather *secret* knowledge, in the sense of spiritual awareness – knowledge about reality and life itself. The desperation of the Cult's Church of Rome to destroy the Gnostics can be understood when the knowledge they were circulating was the last thing the Cult wanted the population to know. Sixteen hundred years later the same Cult is working hard to undermine and silence me for the same reason. The dynamic between knowledge and ignorance is a constant. 'Time' appears to move on, but essential themes remain the same. We are told to 'use your *nous*', a Gnostic word for head/brain/intelligence. They said, however, that spiritual awakening or 'salvation' could only be secured by expanding awareness *beyond* what they called *nous* and into *pneuma* or Infinite Self. Obviously as I read these texts the parallels with what I have been saying since 1990 were fascinating to me. There is a universal truth that spans human history and in that case why wouldn't we be talking the same language 16 centuries apart? When you free yourself from the perception program of the five senses and explore expanded realms of consciousness you are going to connect with the same information no matter what the perceived 'era' within a manufactured timeline of a single and tiny range of manipulated frequency. Humans working with 'smart' technology or knocking rocks together in caves is only a timeline appearing to operate within the human frequency band. Expanded awareness and the knowledge it holds have always been there whether the era be Stone Age or computer age. We can only access that knowledge by opening ourselves to its frequency which the five-sense prison cell is designed to stop us doing. Gates, Fauci, Whitty, Vallance, Zuckerberg, Brin, Page, Wojcicki, Bezos, and all the others behind the 'Covid' hoax clearly have a long wait before their range of frequency can make that connection given that an open heart is

crucial to that as we shall see. Instead of accessing knowledge directly through expanded awareness it is given to Cult operatives by the secret society networks of the Cult where it has been passed on over thousands of years outside the public arena. Expanded realms of consciousness is where great artists, composers and writers find their inspiration and where truth awaits anyone open enough to connect with it. We need to go there fast.

## **Archon hijack**

A fifth of the Nag Hammadi texts describe the existence and manipulation of the Archons led by a 'Chief Archon' they call 'Yaldabaoth', or the 'Demiurge', and this is the Christian 'Devil', 'Satan', 'Lucifer', and his demons. Archons in Biblical symbolism are the 'fallen ones' which are also referred to as fallen angels after the angels expelled from heaven according to the Abrahamic religions of Judaism, Christianity and Islam. These angels are claimed to tempt humans to 'sin' ongoing and you will see how accurate that symbolism is during the rest of the book. The theme of 'original sin' is related to the 'Fall' when Adam and Eve were 'tempted by the serpent' and fell from a state of innocence and 'obedience' (connection) with God into a state of disobedience (disconnection). The Fall is said to have brought sin into the world and corrupted everything including human nature. Yaldabaoth, the 'Lord Archon', is described by Gnostics as a 'counterfeit spirit', 'The Blind One', 'The Blind God', and 'The Foolish One'. The Jewish name for Yaldabaoth in Talmudic writings is Samael which translates as 'Poison of God', or 'Blindness of God'. You see the parallels. Yaldabaoth in Islamic belief is the Muslim Jinn devil known as Shaytan – Shaytan is Satan as the same themes are found all over the world in every religion and culture. The 'Lord God' of the Old Testament is the 'Lord Archon' of Gnostic manuscripts and that's why he's such a bloodthirsty bastard. Satan is known by Christians as 'the Demon of Demons' and Gnostics called Yaldabaoth the 'Archon of Archons'. Both are known as 'The Deceiver'. We are talking about the same 'bloke' for sure and these common themes

using different names, storylines and symbolism tell a common tale of the human plight.

Archons are referred to in Nag Hammadi documents as mind parasites, inverters, guards, gatekeepers, detainers, judges, pitiless ones and deceivers. The 'Covid' hoax alone is a glaring example of all these things. The Biblical 'God' is so different in the Old and New Testaments because they are not describing the same phenomenon. The vindictive, angry, hate-filled, 'God' of the Old Testament, known as Yahweh, is Yaldabaoth who is depicted in Cult-dictated popular culture as the 'Dark Lord', 'Lord of Time', Lord (Darth) Vader and Dormammu, the evil ruler of the 'Dark Dimension' trying to take over the 'Earth Dimension' in the Marvel comic movie, *Dr Strange*. Yaldabaoth is both the Old Testament 'god' and the Biblical 'Satan'. Gnostics referred to Yaldabaoth as the 'Great Architect of the Universe' and the Cult-controlled Freemason network calls their god 'the Great Architect of the Universe' (also Grand Architect). The 'Great Architect' Yaldabaoth is symbolised by the Cult as the all-seeing eye at the top of the pyramid on the Great Seal of the United States and the dollar bill. Archon is encoded in *arch-itect* as it is in *arch-angels* and *arch-bishops*. All religions have the theme of a force for good and force for evil in some sort of spiritual war and there is a reason for that – the theme is true. The Cult and its non-human masters are quite happy for this to circulate. They present themselves as the force for good fighting evil when they are really the force of evil (absence of love). The whole foundation of Cult modus operandi is inversion. They promote themselves as a force for good and anyone challenging them in pursuit of peace, love, fairness, truth and justice is condemned as a satanic force for evil. This has been the game plan throughout history whether the Church of Rome inquisitions of non-believers or 'conspiracy theorists' and 'anti-vaxxers' of today. The technique is the same whatever the timeline era.

## **Yaldabaoth is revolting (true)**

Yaldabaoth and the Archons are said to have revolted against God with Yaldabaoth claiming to *be* God – the *All That Is*. The Old Testament ‘God’ (Yaldabaoth) demanded to be worshipped as such: ‘*I am the LORD, and there is none else, there is no God beside me*’ (Isaiah 45:5). I have quoted in other books a man who said he was the unofficial son of the late Baron Philippe de Rothschild of the Mouton-Rothschild wine producing estates in France who died in 1988 and he told me about the Rothschild ‘revolt from God’. The man said he was given the name Phillip Eugene de Rothschild and we shared long correspondence many years ago while he was living under another identity. He said that he was conceived through ‘occult incest’ which (within the Cult) was ‘normal and to be admired’. ‘Phillip’ told me about his experience attending satanic rituals with rich and famous people whom he names and you can see them and the wider background to Cult Satanism in my other books starting with *The Biggest Secret*. Cult rituals are interactions with Archontic ‘gods’. ‘Phillip’ described Baron Philippe de Rothschild as ‘a master Satanist and hater of God’ and he used the same term ‘revolt from God’ associated with Yaldabaoth/Satan/Lucifer/the Devil in describing the Sabbatian Rothschild dynasty. ‘I played a key role in my family’s revolt from God’, he said. That role was to infiltrate in classic Sabbatian style the Christian Church, but eventually he escaped the mind-prison to live another life. The Cult has been targeting religion in a plan to make worship of the Archons the global one-world religion. Infiltration of Satanism into modern ‘culture’, especially among the young, through music videos, stage shows and other means, is all part of this.

Nag Hammadi texts describe Yaldabaoth and the Archons in their prime form as energy – consciousness – and say they can take form if they choose in the same way that consciousness takes form as a human. Yaldabaoth is called ‘formless’ and represents a deeply inverted, distorted and chaotic state of consciousness which seeks to attach to humans and turn them into a likeness of itself in an attempt at assimilation. For that to happen it has to manipulate

humans into low frequency mental and emotional states that match its own. Archons can certainly appear in human form and this is the origin of the psychopathic personality. The energetic distortion Gnostics called Yaldabaoth is psychopathy. When psychopathic Archons take human form that human will be a psychopath as an expression of Yaldabaoth consciousness. Cult psychopaths are Archons in human form. The principle is the same as that portrayed in the 2009 *Avatar* movie when the American military travelled to a fictional Earth-like moon called Pandora in the Alpha Centauri star system to infiltrate a society of blue people, or Na'vi, by hiding within bodies that looked like the Na'vi. Archons posing as humans have a particular hybrid information field, part human, part Archon, (the ancient 'demigods') which processes information in a way that manifests behaviour to match their psychopathic evil, lack of empathy and compassion, and stops them being influenced by the empathy, compassion and love that a fully-human information field is capable of expressing. Cult bloodlines interbreed, be they royalty or dark suits, for this reason and you have their obsession with incest. Interbreeding with full-blown humans would dilute the Archontic energy field that guarantees psychopathy in its representatives in the human realm.

Gnostic writings say the main non-human forms that Archons take are *serpentine* (what I have called for decades 'reptilian' amid unbounded ridicule from the Archontically-programmed) and what Gnostics describe as 'an unborn baby or foetus with grey skin and dark, unmoving eyes'. This is an excellent representation of the ET 'Greys' of UFO folklore which large numbers of people claim to have seen and been abducted by – Zulu shaman Credo Mutwa among them. I agree with those that believe in extraterrestrial or interdimensional visitations today and for thousands of years past. No wonder with their advanced knowledge and technological capability they were perceived and worshipped as gods for technological and other 'miracles' they appeared to perform. Imagine someone arriving in a culture disconnected from the modern world with a smartphone and computer. They would be

seen as a ‘god’ capable of ‘miracles’. The Renegade Mind, however, wants to know the source of everything and not only the way that source manifests as human or non-human. In the same way that a Renegade Mind seeks the original source material for the ‘Covid virus’ to see if what is claimed is true. The original source of Archons in form is consciousness – the distorted state of consciousness known to Gnostics as Yaldabaoth.

### **‘Revolt from God’ is energetic disconnection**

Where I am going next will make a lot of sense of religious texts and ancient legends relating to ‘Satan’, Lucifer’ and the ‘gods’. Gnostic descriptions sync perfectly with the themes of my own research over the years in how they describe a consciousness distortion seeking to impose itself on human consciousness. I’ve referred to the core of infinite awareness in previous books as Infinite Awareness in Awareness of Itself. By that I mean a level of awareness that knows that it is all awareness and is aware of all awareness. From here comes the frequency of love in its true sense and balance which is what love is on one level – the balance of all forces into a single whole called Oneness and Isness. The more we disconnect from this state of love that many call ‘God’ the constituent parts of that Oneness start to unravel and express themselves as a part and not a whole. They become individualised as intellect, mind, selfishness, hatred, envy, desire for power over others, and such like. This is not a problem in the greater scheme in that ‘God’, the *All That Is*, can experience all these possibilities through different expressions of itself including humans. What we as expressions of the whole experience the *All That Is* experiences. We are the *All That Is* experiencing itself. As we withdraw from that state of Oneness we disconnect from its influence and things can get very unpleasant and very stupid. Archontic consciousness is at the extreme end of that. It has so disconnected from the influence of Oneness that it has become an inversion of unity and love, an inversion of everything, an inversion of life itself. Evil is appropriately live written backwards. Archontic consciousness is obsessed with death, an inversion of life,

and so its manifestations in Satanism are obsessed with death. They use inverted symbols in their rituals such as the inverted pentagram and cross. Sabbatians as Archontic consciousness incarnate invert Judaism and every other religion and culture they infiltrate. They seek disunity and chaos and they fear unity and harmony as they fear love like garlic to a vampire. As a result the Cult, Archons incarnate, act with such evil, psychopathy and lack of empathy and compassion disconnected as they are from the source of love. How could Bill Gates and the rest of the Archontic psychopaths do what they have to human society in the 'Covid' era with all the death, suffering and destruction involved and have no emotional consequence for the impact on others? Now you know. Why have Zuckerberg, Brin, Page, Wojcicki and company callously censored information warning about the dangers of the 'vaccine' while thousands have been dying and having severe, sometimes life-changing reactions? Now you know. Why have Tedros, Fauci, Whitty, Vallance and their like around the world been using case and death figures they're aware are fraudulent to justify lockdowns and all the deaths and destroyed lives that have come from that? Now you know. Why did Christian Drosten produce and promote a 'testing' protocol that he knew couldn't test for infectious disease which led to a global human catastrophe. Now you know. The Archontic mind doesn't give a shit ([Fig 17](#)). I personally think that Gates and major Cult insiders are a form of AI cyborg that the Archons want humans to become.

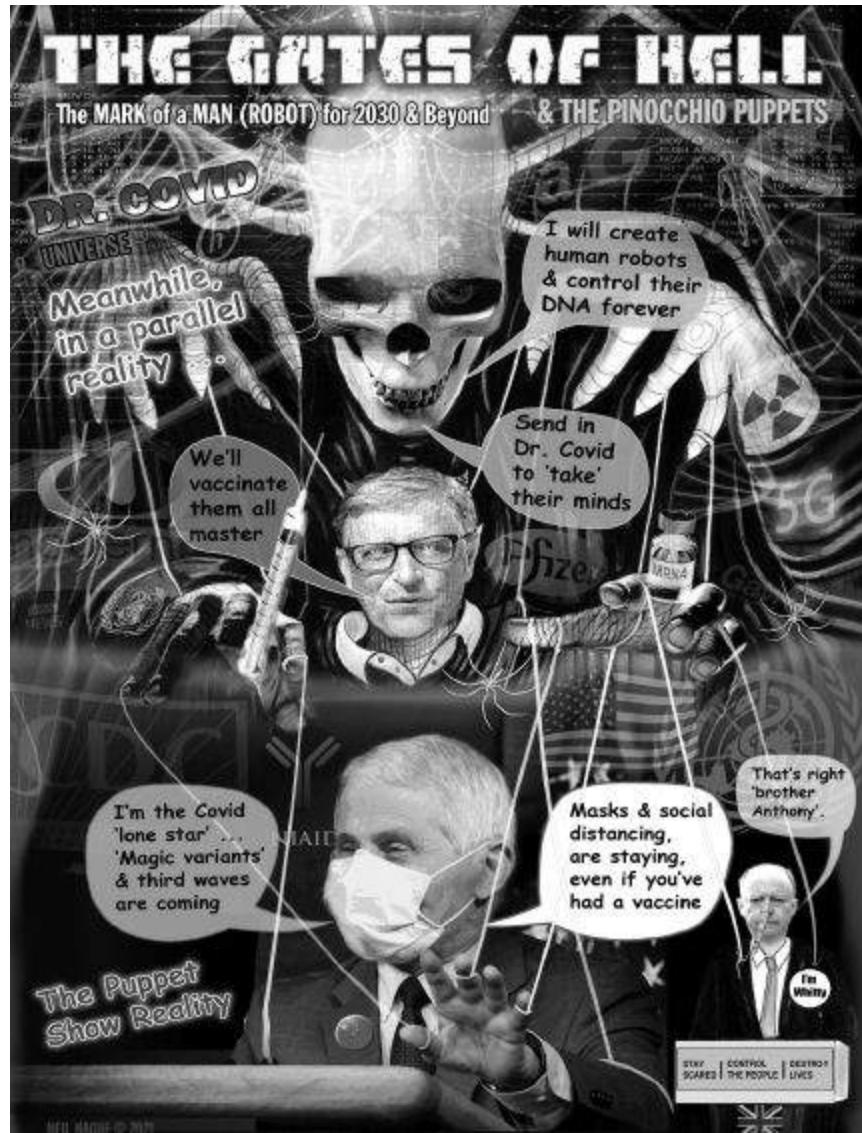


Figure 17: Artist Neil Hague's version of the 'Covid' hierarchy.

## Human batteries

A state of such inversion does have its consequences, however. The level of disconnection from the Source of All means that you withdraw from that source of energetic sustenance and creativity. This means that you have to find your own supply of energetic power and it has – *us*. When the Morpheus character in the first *Matrix* movie held up a battery he spoke a profound truth when he said: 'The Matrix is a computer-generated dream world built to keep us under control in order to change the human being into one of

these.' The statement was true in all respects. We do live in a technologically-generated virtual reality simulation (more very shortly) and we have been manipulated to be an energy source for Archontic consciousness. The Disney-Pixar animated movie *Monsters, Inc.* in 2001 symbolised the dynamic when monsters in their world had no energy source and they would enter the human world to terrify children in their beds, catch the child's scream, terror (low-vibrational frequencies), and take that energy back to power the monster world. The lead character you might remember was a single giant eye and the symbolism of the Cult's all-seeing eye was obvious. Every thought and emotion is broadcast as a frequency unique to that thought and emotion. Feelings of love and joy, empathy and compassion, are high, quick, frequencies while fear, depression, anxiety, suffering and hate are low, slow, dense frequencies. Which kind do you think Archontic consciousness can connect with and absorb? In such a low and dense frequency state there's no way it can connect with the energy of love and joy. Archons can only feed off energy compatible with their own frequency and they and their Cult agents want to delete the human world of love and joy and manipulate the transmission of low vibrational frequencies through low-vibrational human mental and emotional states. *We are their energy source.* Wars are energetic banquets to the Archons – a world war even more so – and think how much low-frequency mental and emotional energy has been generated from the consequences for humanity of the 'Covid' hoax orchestrated by Archons incarnate like Gates.

The ancient practice of human sacrifice 'to the gods', continued in secret today by the Cult, is based on the same principle. 'The gods' are Archontic consciousness in different forms and the sacrifice is induced into a state of intense terror to generate the energy the Archontic frequency can absorb. Incarnate Archons in the ritual drink the blood which contains an adrenaline they crave which floods into the bloodstream when people are terrorised. Most of the sacrifices, ancient and modern, are children and the theme of 'sacrificing young virgins to the gods' is just code for children. They

have a particular pre-puberty energy that Archons want more than anything and the energy of the young in general is their target. The California Department of Education wants students to chant the names of Aztec gods (Archontic gods) once worshipped in human sacrifice rituals in a curriculum designed to encourage them to ‘challenge racist, bigoted, discriminatory, imperialist/colonial beliefs’, join ‘social movements that struggle for social justice’, and ‘build new possibilities for a post-racist, post-systemic racism society’. It’s the usual Woke crap that inverts racism and calls it anti-racism. In this case solidarity with ‘indigenous tribes’ is being used as an excuse to chant the names of ‘gods’ to which people were sacrificed (and still are in secret). What an example of Woke’s inability to see beyond black and white, us and them, They condemn the colonisation of these tribal cultures by Europeans (quite right), but those cultures sacrificing people including children to their ‘gods’, and mass murdering untold numbers as the Aztecs did, is just fine. One chant is to the Aztec god Tezcatlipoca who had a man sacrificed to him in the 5th month of the Aztec calendar. His heart was cut out and he was eaten. Oh, that’s okay then. Come on children … after three … Other sacrificial ‘gods’ for the young to chant their allegiance include Quetzalcoatl, Huitzilopochtli and Xipe Totec. The curriculum says that ‘chants, affirmations, and energizers can be used to bring the class together, build unity around ethnic studies principles and values, and to reinvigorate the class following a lesson that may be emotionally taxing or even when student engagement may appear to be low’. Well, that’s the cover story, anyway. Chanting and mantras are the repetition of a particular frequency generated from the vocal cords and chanting the names of these Archontic ‘gods’ tunes you into their frequency. That is the last thing you want when it allows for energetic synchronisation, attachment and perceptual influence. Initiates chant the names of their ‘Gods’ in their rituals for this very reason.

## **Vampires of the Woke**

Paedophilia is another way that Archons absorb the energy of children. Paedophiles possessed by Archontic consciousness are used as the conduit during sexual abuse for discarnate Archons to vampire the energy of the young they desire so much. Stupendous numbers of children disappear every year never to be seen again although you would never know from the media. Imagine how much low-vibrational energy has been generated by children during the 'Covid' hoax when so many have become depressed and psychologically destroyed to the point of killing themselves.

Shocking numbers of children are now taken by the state from loving parents to be handed to others. I can tell you from long experience of researching this since 1996 that many end up with paedophiles and assets of the Cult through corrupt and Cult-owned social services which in the reframing era has hired many psychopaths and emotionless automatons to do the job. Children are even stolen to order using spurious reasons to take them by the corrupt and secret (because they're corrupt) 'family courts'. I have written in detail in other books, starting with *The Biggest Secret* in 1997, about the ubiquitous connections between the political, corporate, government, intelligence and military elites (Cult operatives) and Satanism and paedophilia. If you go deep enough both networks have an interlocking leadership. The Woke mentality has been developed by the Cult for many reasons: To promote almost every aspect of its agenda; to hijack the traditional political left and turn it fascist; to divide and rule; and to target agenda pushbackers. But there are other reasons which relate to what I am describing here. How many happy and joyful Wokers do you ever see especially at the extreme end? They are a mental and psychological mess consumed by emotional stress and constantly emotionally cocked for the next explosion of indignation at someone referring to a female as a female. They are walking, talking, batteries as Morpheus might say emitting frequencies which both enslave them in low-vibrational bubbles of perceptual limitation and feed the Archons. Add to this the hatred claimed to be love; fascism claimed to 'anti-fascism', racism claimed to be 'anti-racism';

exclusion claimed to inclusion; and the abuse-filled Internet trolling. You have a purpose-built Archontic energy system with not a wind turbine in sight and all founded on Archontic *inversion*. We have whole generations now manipulated to serve the Archons with their actions and energy. They will be doing so their entire adult lives unless they snap out of their Archon-induced trance. Is it really a surprise that Cult billionaires and corporations put so much money their way? Where is the energy of joy and laughter, including laughing at yourself which is confirmation of your own emotional security? Mark Twain said: 'The human race has one really effective weapon, and that is laughter.' We must use it all the time. Woke has destroyed comedy because it has no humour, no joy, sense of irony, or self-deprecation. Its energy is dense and intense. *Mmmmm*, lunch says the Archontic frequency. Rudolf Steiner (1861-1925) was the Austrian philosopher and famous esoteric thinker who established Waldorf education or Steiner schools to treat children like unique expressions of consciousness and not minds to be programmed with the perceptions determined by authority. I'd been writing about this energy vampiring for decades when I was sent in 2016 a quote by Steiner. He was spot on:

There are beings in the spiritual realms for whom anxiety and fear emanating from human beings offer welcome food. When humans have no anxiety and fear, then these creatures starve. If fear and anxiety radiates from people and they break out in panic, then these creatures find welcome nutrition and they become more and more powerful. These beings are hostile towards humanity. Everything that feeds on negative feelings, on anxiety, fear and superstition, despair or doubt, are in reality hostile forces in super-sensible worlds, launching cruel attacks on human beings, while they are being fed ... These are exactly the feelings that belong to contemporary culture and materialism; because it estranges people from the spiritual world, it is especially suited to evoke hopelessness and fear of the unknown in people, thereby calling up the above mentioned hostile forces against them.

Pause for a moment from this perspective and reflect on what has happened in the world since the start of 2020. Not only will pennies drop, but billion dollar bills. We see the same theme from Don Juan Matus, a Yaqui Indian shaman in Mexico and the information source for Peruvian-born writer, Carlos Castaneda, who wrote a series of

books from the 1960s to 1990s. Don Juan described the force manipulating human society and his name for the Archons was the predator:

We have a predator that came from the depths of the cosmos and took over the rule of our lives. Human beings are its prisoners. The predator is our lord and master. It has rendered us docile, helpless. If we want to protest, it suppresses our protest. If we want to act independently, it demands that we don't do so ... indeed we are held prisoner!

They took us over because we are food to them, and they squeeze us mercilessly because we are their sustenance. Just as we rear chickens in coops, the predators rear us in human coops, humaneros. Therefore, their food is always available to them.

Different cultures, different eras, same recurring theme.

## **The 'ennoia' dilemma**

Nag Hammadi Gnostic manuscripts say that Archon consciousness has no 'ennoia'. This is directly translated as 'intentionality', but I'll use the term 'creative imagination'. The *All That Is* in awareness of itself is the source of all creativity – all possibility – and the more disconnected you are from that source the more you are subsequently denied 'creative imagination'. Given that Archon consciousness is almost entirely disconnected it severely lacks creativity and has to rely on far more mechanical processes of thought and exploit the creative potential of those that do have 'ennoia'. You can see cases of this throughout human society. Archon consciousness almost entirely dominates the global banking system and if we study how that system works you will appreciate what I mean. Banks manifest 'money' out of nothing by issuing lines of 'credit' which is 'money' that has never, does not, and will never exist except in theory. It's a confidence trick. If you think 'credit' figures-on-a-screen 'money' is worth anything you accept it as payment. If you don't then the whole system collapses through lack of confidence in the value of that 'money'. Archontic bankers with no 'ennoia' are 'lending' 'money' that doesn't exist to humans that *do* have creativity – those that have the inspired ideas and create businesses and products. Archon banking feeds off human creativity

which it controls through ‘money’ creation and debt. Humans have the creativity and Archons exploit that for their own benefit and control while having none themselves. Archon Internet platforms like Facebook claim joint copyright of everything that creative users post and while Archontic minds like Zuckerberg may officially head that company it will be human creatives on the staff that provide the creative inspiration. When you have limitless ‘money’ you can then buy other companies established by creative humans. Witness the acquisition record of Facebook, Google and their like. Survey the Archon-controlled music industry and you see non-creative dark suit executives making their fortune from the human creativity of their artists. The cases are endless. Research the history of people like Gates and Zuckerberg and how their empires were built on exploiting the creativity of others. Archon minds cannot create out of nothing, but they are skilled (because they have to be) in what Gnostic texts call ‘countermimicry’. They can imitate, but not innovate. Sabbatians trawl the creativity of others through backdoors they install in computer systems through their cybersecurity systems. Archon-controlled China is globally infamous for stealing intellectual property and I remember how Hong Kong, now part of China, became notorious for making counterfeit copies of the creativity of others – ‘countermimicry’. With the now pervasive and all-seeing surveillance systems able to infiltrate any computer you can appreciate the potential for Archons to vampire the creativity of humans. Author John Lamb Lash wrote in his book about the Nag Hammadi texts, *Not In His Image*:

Although they cannot originate anything, because they lack the divine factor of ennoia (intentionality), Archons can imitate with a vengeance. Their expertise is simulation (HAL, virtual reality). The Demiurge [Yaldabaoth] fashions a heaven world copied from the fractal patterns [of the original] ... His construction is celestial kitsch, like the fake Italianate villa of a Mafia don complete with militant angels to guard every portal.

This brings us to something that I have been speaking about since the turn of the millennium. Our reality is a simulation; a virtual reality that we think is real. No, I’m not kidding.

## **Human reality? Well, virtually**

I had pondered for years about whether our reality is ‘real’ or some kind of construct. I remembered being immensely affected on a visit as a small child in the late 1950s to the then newly-opened Planetarium on the Marylebone Road in London which is now closed and part of the adjacent Madame Tussauds wax museum. It was in the middle of the day, but when the lights went out there was the night sky projected in the Planetarium’s domed ceiling and it appeared to be so real. The experience never left me and I didn’t know why until around the turn of the millennium when I became certain that our ‘night sky’ and entire reality is a projection, a virtual reality, akin to the illusory world portrayed in the *Matrix* movies. I looked at the sky one day in this period and it appeared to me like the domed roof of the Planetarium. The release of the first *Matrix* movie in 1999 also provided a synchronistic and perfect visual representation of where my mind had been going for a long time. I hadn’t come across the Gnostic Nag Hammadi texts then. When I did years later the correlation was once again astounding. As I read Gnostic accounts from 1,600 years and more earlier it was clear that they were describing the same simulation phenomenon. They tell how the Yaldabaoth ‘Demiurge’ and Archons created a ‘bad copy’ of original reality to rule over all that were captured by its illusions and the body was a prison to trap consciousness in the ‘bad copy’ fake reality. Read how Gnostics describe the ‘bad copy’ and update that to current times and they are referring to what we would call today a virtual reality simulation.

Author John Lamb Lash said ‘the Demiurge fashions a heaven world copied from the fractal patterns’ of the original through expertise in ‘HAL’ or virtual reality simulation. Fractal patterns are part of the energetic information construct of our reality, a sort of blueprint. If these patterns were copied in computer terms it would indeed give you a copy of a ‘natural’ reality in a non-natural frequency and digital form. The principle is the same as making a copy of a website. The original website still exists, but now you can change the copy version to make it whatever you like and it can

become very different to the original website. Archons have done this with our reality, a *synthetic* copy of prime reality that still exists beyond the frequency walls of the simulation. Trapped within the illusions of this synthetic Matrix, however, were and are human consciousness and other expressions of prime reality and this is why the Archons via the Cult are seeking to make the human body synthetic and give us synthetic AI minds to complete the job of turning the entire reality synthetic including what we perceive to be the natural world. To quote Kurzweil: ‘Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.’ Yes, *synthetic* ‘creatures’ just as ‘Covid’ and other genetically-manipulating ‘vaccines’ are designed to make the human body synthetic. From this perspective it is obvious why Archons and their Cult are so desperate to infuse synthetic material into every human with their ‘Covid’ scam.

### **Let there be (electromagnetic) light**

Yaldabaoth, the force that created the simulation, or Matrix, makes sense of the Gnostic reference to ‘The Great Architect’ and its use by Cult Freemasonry as the name of its deity. The designer of the Matrix in the movies is called ‘The Architect’ and that trilogy is jam-packed with symbolism relating to these subjects. I have contended for years that the angry Old Testament God (Yaldabaoth) is the ‘God’ being symbolically ‘quoted’ in the opening of Genesis as ‘creating the world’. This is not the creation of prime reality – it’s the creation of the *simulation*. The Genesis ‘God’ says: ‘Let there be Light: and there was light.’ But what is this ‘Light’? I have said for decades that the speed of light (186,000 miles per second) is not the fastest speed possible as claimed by mainstream science and is in fact the frequency walls or outer limits of the Matrix. You can’t have a fastest or slowest anything within all possibility when everything is possible. The human body is encoded to operate within the speed of light or *within the simulation* and thus we see only the tiny frequency band of visible *light*. Near-death experiencers who perceive reality outside the body during temporary ‘death’ describe a very different

form of light and this is supported by the Nag Hammadi texts. Prime reality beyond the simulation ('Upper Aeons' to the Gnostics) is described as a realm of incredible beauty, bliss, love and harmony – a realm of 'watery light' that is so powerful 'there are no shadows'. Our false reality of Archon control, which Gnostics call the 'Lower Aeons', is depicted as a realm with a different kind of 'light' and described in terms of chaos, 'Hell', 'the Abyss' and 'Outer Darkness', where trapped souls are tormented and manipulated by demons (relate that to the 'Covid' hoax alone). The watery light theme can be found in near-death accounts and it is not the same as *simulation* 'light' which is electromagnetic or radiation light within the speed of light – the 'Lower Aeons'. Simulation 'light' is the 'luminous fire' associated by Gnostics with the Archons. The Bible refers to Yaldabaoth as 'that old serpent, called the Devil, and Satan, which deceiveth the whole world' (Revelation 12:9). I think that making a simulated copy of prime reality ('countermimicry') and changing it dramatically while all the time manipulating humanity to believe it to be real could probably meet the criteria of deceiving the whole world. Then we come to the Cult god Lucifer – the *Light Bringer*. Lucifer is symbolic of Yaldabaoth, the bringer of radiation light that forms the bad copy simulation within the speed of light. 'He' is symbolised by the lighted torch held by the Statue of Liberty and in the name 'Illuminati'. Sabbatian-Frankism declares that Lucifer is the true god and Lucifer is the real god of Freemasonry honoured as their 'Great or Grand Architect of the Universe' (simulation).

I would emphasise, too, the way Archontic technologically-generated luminous fire of radiation has deluged our environment since I was a kid in the 1950s and changed the nature of The Field with which we constantly interact. Through that interaction technological radiation is changing us. The Smart Grid is designed to operate with immense levels of communication power with 5G expanding across the world and 6G, 7G, in the process of development. Radiation is the simulation and the Archontic manipulation system. Why wouldn't the Archon Cult wish to unleash radiation upon us to an ever-greater extreme to form

Kurzweil's 'cloud'? The plan for a synthetic human is related to the need to cope with levels of radiation beyond even anything we've seen so far. Biological humans would not survive the scale of radiation they have in their script. The Smart Grid is a technological sub-reality within the technological simulation to further disconnect five-sense perception from expanded consciousness. It's a technological prison of the mind.

### **Infusing the 'spirit of darkness'**

A recurring theme in religion and native cultures is the manipulation of human genetics by a non-human force and most famously recorded as the biblical 'sons of god' (the gods plural in the original) who interbred with the daughters of men. The Nag Hammadi *Apocryphon of John* tells the same story this way:

He [Yaldabaoth] sent his angels [Archons/demons] to the daughters of men, that they might take some of them for themselves and raise offspring for their enjoyment. And at first they did not succeed. When they had no success, they gathered together again and they made a plan together ... And the angels changed themselves in their likeness into the likeness of their mates, filling them with the spirit of darkness, which they had mixed for them, and with evil ... And they took women and begot children out of the darkness according to the likeness of their spirit.

Possession when a discarnate entity takes over a human body is an age-old theme and continues today. It's very real and I've seen it. Satanic and secret society rituals can create an energetic environment in which entities can attach to initiates and I've heard many stories of how people have changed their personality after being initiated even into lower levels of the Freemasons. I have been inside three Masonic temples, one at a public open day and two by just walking in when there was no one around to stop me. They were in Ryde, the town where I live, Birmingham, England, when I was with a group, and Boston, Massachusetts. They all felt the same energetically – dark, dense, low-vibrational and sinister. Demonic attachment can happen while the initiate has no idea what is going on. To them it's just a ritual to get in the Masons and do a bit of good

business. In the far more extreme rituals of Satanism human possession is even more powerful and they are designed to make possession possible. The hierarchy of the Cult is dictated by the power and perceived status of the possessing Archon. In this way the Archon hierarchy becomes the Cult hierarchy. Once the entity has attached it can influence perception and behaviour and if it attaches to the extreme then so much of its energy (information) infuses into the body information field that the hologram starts to reflect the nature of the possessing entity. This is the *Exorcist* movie type of possession when facial features change and it's known as shapeshifting. Islam's Jinn are said to be invisible tricksters who change shape, 'whisper', confuse and take human form. These are all traits of the Archons and other versions of the same phenomenon. Extreme possession could certainty infuse the 'spirit of darkness' into a partner during sex as the Nag Hammadi texts appear to describe. Such an infusion can change genetics which is also energetic information. Human genetics is information and the 'spirit of darkness' is information. Mix one with the other and change must happen. Islam has the concept of a 'Jinn baby' through possession of the mother and by Jinn taking human form. There are many ways that human genetics can be changed and remember that Archons have been aware all along of advanced techniques to do this. What is being done in human society today – and far more – was known about by Archons at the time of the 'fallen ones' and their other versions described in religions and cultures.

Archons and their human-world Cult are obsessed with genetics as we see today and they know this dictates how information is processed into perceived reality during a human life. They needed to produce a human form that would decode the simulation and this is symbolically known as 'Adam and Eve' who left the 'garden' (prime reality) and 'fell' into Matrix reality. The simulation is not a 'physical' construct (there is no 'physical'); it is a source of information. Think Wi-Fi again. The simulation is an energetic field encoded with information and body-brain systems are designed to decode that information encoded in wave or frequency form which

is transmitted to the brain as electrical signals. These are decoded by the brain to construct our sense of reality – an illusory ‘physical’ world that only exists in the brain or the mind. Virtual reality games mimic this process using the same sensory decoding system. Information is fed to the senses to decode a virtual reality that can appear so real, but isn’t (Figs 18 and 19). Some scientists believe – and I agree with them – that what we perceive as ‘physical’ reality only exists when we are looking or observing. The act of perception or focus triggers the decoding systems which turn waveform information into holographic reality. When we are not observing something our reality reverts from a holographic state to a waveform state. This relates to the same principle as a falling tree not making a noise unless someone is there to hear it or decode it. The concept makes sense from the simulation perspective. A computer is not decoding all the information in a Wi-Fi field all the time and only decodes or brings into reality on the screen that part of Wi-Fi that it’s decoding – focusing upon – at that moment.



**Figure 18:** Virtual reality technology ‘hacks’ into the body’s five-sense decoding system.



**Figure 19:** The result can be experienced as very ‘real’.

Interestingly, Professor Donald Hoffman at the Department of Cognitive Sciences at the University of California, Irvine, says that our experienced reality is like a computer interface that shows us only the level with which we interact while hiding all that exists beyond it: ‘Evolution shaped us with a user interface that hides the truth. Nothing that we see is the truth – the very language of space and time and objects is the wrong language to describe reality.’ He is correct in what he says on so many levels. Space and time are not a universal reality. They are a phenomenon of decoded *simulation* reality as part of the process of enslaving our sense of reality. Near-death experiencers report again and again how space and time did not exist as we perceive them once they were free of the body – body decoding systems. You can appreciate from this why Archons and their Cult are so desperate to entrap human attention in the five senses where we are in the Matrix and of the Matrix. Opening your mind to expanded states of awareness takes you beyond the information confines of the simulation and you become aware of knowledge and insights denied to you before. This is what we call ‘awakening’ – *awakening from the Matrix* – and in the final chapter I will relate this to current events.

## **Where are the ‘aliens’?**

A simulation would explain the so-called ‘Fermi Paradox’ named after Italian physicist Enrico Fermi (1901-1954) who created the first nuclear reactor. He considered the question of why there is such a lack of extraterrestrial activity when there are so many stars and planets in an apparently vast universe; but what if the night sky that we see, or think we do, is a simulated projection as I say? If you control the simulation and your aim is to hold humanity fast in essential ignorance would you want other forms of life including advanced life coming and going sharing information with humanity? Or would you want them to believe they were isolated and apparently alone? Themes of human isolation and apartness are common whether they be the perception of a lifeless universe or the fascist isolation laws of the ‘Covid’ era. Paradoxically the very

existence of a simulation means that we are not alone when some force had to construct it. My view is that experiences that people have reported all over the world for centuries with Reptilians and Grey entities are Archon phenomena as Nag Hammadi texts describe; and that benevolent 'alien' interactions are non-human groups that come in and out of the simulation by overcoming Archon attempts to keep them out. It should be highlighted, too, that Reptilians and Greys are obsessed with *genetics* and *technology* as related by cultural accounts and those who say they have been abducted by them. Technology is their way of overcoming some of the limitations in their creative potential and our technology-driven and controlled human society of today is *archetypical* Archon-Reptilian-Grey modus operandi. Technocracy is really *Archontocracy*. The Universe does not have to be as big as it appears with a simulation. There is no space or distance only information decoded into holographic reality. What we call 'space' is only the absence of holographic 'objects' and that 'space' is The Field of energetic information which connects everything into a single whole. The same applies with the artificially-generated information field of the simulation. The Universe is not big or small as a physical reality. It is decoded information, that's all, and its perceived size is decided by the way the simulation is encoded to make it appear. The entire night sky as we perceive it only exists in our brain and so where are those 'millions of light years'? The 'stars' on the ceiling of the Planetarium looked a vast distance away.

There's another point to mention about 'aliens'. I have been highlighting since the 1990s the plan to stage a fake 'alien invasion' to justify the centralisation of global power and a world military. Nazi scientist Werner von Braun, who was taken to America by Operation Paperclip after World War Two to help found NASA, told his American assistant Dr Carol Rosin about the Cult agenda when he knew he was dying in 1977. Rosin said that he told her about a sequence that would lead to total human control by a one-world government. This included threats from terrorism, rogue nations, meteors and asteroids before finally an 'alien invasion'. All of these

things, von Braun said, would be bogus and what I would refer to as a No-Problem-Reaction-Solution. Keep this in mind when ‘the aliens are coming’ is the new mantra. The aliens are not coming – they are *already here* and they have infiltrated human society while looking human. French-Canadian investigative journalist Serge Monast said in 1994 that he had uncovered a NASA/military operation called Project Blue Beam which fits with what Werner von Braun predicted. Monast died of a ‘heart attack’ in 1996 the day after he was arrested and spent a night in prison. He was 51. He said Blue Beam was a plan to stage an alien invasion that would include religious figures beamed holographically into the sky as part of a global manipulation to usher in a ‘new age’ of worshipping what I would say is the Cult ‘god’ Yaldabaoth in a one-world religion. Fake holographic asteroids are also said to be part of the plan which again syncs with von Braun. How could you stage an illusory threat from asteroids unless they were holographic inserts? This is pretty straightforward given the advanced technology outside the public arena and the fact that our ‘physical’ reality is holographic anyway. Information fields would be projected and we would decode them into the illusion of a ‘physical’ asteroid. If they can sell a global ‘pandemic’ with a ‘virus’ that doesn’t exist what will humans not believe if government and media tell them?

All this is particularly relevant as I write with the Pentagon planning to release in June, 2021, information about ‘UFO sightings’. I have been following the UFO story since the early 1990s and the common theme throughout has been government and military denials and cover up. More recently, however, the Pentagon has suddenly become more talkative and apparently open with Air Force pilot radar images released of unexplained craft moving and changing direction at speeds well beyond anything believed possible with human technology. Then, in March, 2021, former Director of National Intelligence John Ratcliffe said a Pentagon report months later in June would reveal a great deal of information about UFO sightings unknown to the public. He said the report would have ‘massive implications’. The order to do this was included bizarrely

in a \$2.3 trillion ‘coronavirus’ relief and government funding bill passed by the Trump administration at the end of 2020. I would add some serious notes of caution here. I have been pointing out since the 1990s that the US military and intelligence networks have long had craft – ‘flying saucers’ or anti-gravity craft – which any observer would take to be extraterrestrial in origin. Keeping this knowledge from the public allows craft flown by *humans* to be perceived as alien visitations. I am not saying that ‘aliens’ do not exist. I would be the last one to say that, but we have to be streetwise here. President Ronald Reagan told the UN General Assembly in 1987: ‘I occasionally think how quickly our differences worldwide would vanish if we were facing an alien threat from outside this world.’ That’s the idea. Unite against a common ‘enemy’ with a common purpose behind your ‘saviour force’ (the Cult) as this age-old technique of mass manipulation goes global.

### **Science moves this way ...**

I could find only one other person who was discussing the simulation hypothesis publicly when I concluded it was real. This was Nick Bostrom, a Swedish-born philosopher at the University of Oxford, who has explored for many years the possibility that human reality is a computer simulation although his version and mine are not the same. Today the simulation and holographic reality hypothesis have increasingly entered the scientific mainstream. Well, the more open-minded mainstream, that is. Here are a few of the ever-gathering examples. American nuclear physicist Silas Beane led a team of physicists at the University of Bonn in Germany pursuing the question of whether we live in a simulation. They concluded that we probably do and it was likely based on a lattice of cubes. They found that cosmic rays align with that specific pattern. The team highlighted the Greisen-Zatsepin-Kuzmin (GZK) limit which refers to cosmic ray particle interaction with cosmic background radiation that creates an apparent boundary for cosmic ray particles. They say in a paper entitled ‘Constraints on the Universe as a Numerical Simulation’ that this ‘pattern of constraint’ is exactly what you

would find with a computer simulation. They also made the point that a simulation would create its own ‘laws of physics’ that would limit possibility. I’ve been making the same point for decades that the *perceived* laws of physics relate only to this reality, or what I would later call the simulation. When designers write codes to create computer and virtual reality games they are the equivalent of the laws of physics for that game. Players interact within the limitations laid out by the coding. In the same way those who wrote the codes for the simulation decided the laws of physics that would apply. These can be overridden by expanded states of consciousness, but not by those enslaved in only five-sense awareness where simulation codes rule. Overriding the codes is what people call ‘miracles’. They are not. They are bypassing the encoded limits of the simulation. A population caught in simulation perception would have no idea that this was their plight. As the Bonn paper said: ‘Like a prisoner in a pitch-black cell we would not be able to see the “walls” of our prison.’ That’s true if people remain mesmerised by the five senses. Open to expanded awareness and those walls become very clear. The main one is the speed of light.

American theoretical physicist James Gates is another who has explored the simulation question and found considerable evidence to support the idea. Gates was Professor of Physics at the University of Maryland, Director of The Center for String and Particle Theory, and on Barack Obama’s Council of Advisors on Science and Technology. He and his team found *computer codes* of digital data embedded in the fabric of our reality. They relate to on-off electrical charges of 1 and 0 in the binary system used by computers. ‘We have no idea what they are doing there’, Gates said. They found within the energetic fabric mathematical sequences known as error-correcting codes or block codes that ‘reboot’ data to its original state or ‘default settings’ when something knocks it out of sync. Gates was asked if he had found a set of equations embedded in our reality indistinguishable from those that drive search engines and browsers and he said: ‘That is correct.’ Rich Terrile, director of the Centre for Evolutionary Computation and Automated Design at NASA’s Jet

Propulsion Laboratory, has said publicly that he believes the Universe is a digital hologram that must have been created by a form of intelligence. I agree with that in every way. Waveform information is delivered electrically by the senses to the brain which constructs a *digital* holographic reality that we call the ‘world’. This digital level of reality can be read by the esoteric art of numerology. Digital holograms are at the cutting edge of holographics today. We have digital technology everywhere designed to access and manipulate our digital level of perceived reality. Synthetic mRNA in ‘Covid vaccines’ has a digital component to manipulate the body’s digital ‘operating system’.

## **Reality is numbers**

How many know that our reality can be broken down to numbers and codes that are the same as computer games? Max Tegmark, a physicist at the Massachusetts Institute of Technology (MIT), is the author of *Our Mathematical Universe* in which he lays out how reality can be entirely described by numbers and maths in the way that a video game is encoded with the ‘physics’ of computer games. Our world and computer virtual reality are essentially the same.

Tegmark imagines the perceptions of characters in an advanced computer game when the graphics are so good they don’t know they are in a game. They think they can bump into real objects (electromagnetic resistance in our reality), fall in love and feel emotions like excitement. When they began to study the apparently ‘physical world’ of the video game they would realise that everything was made of pixels (which have been found in our energetic reality as must be the case when on one level our world is digital). What computer game characters thought was physical ‘stuff’, Tegmark said, could actually be broken down into numbers:

And we’re exactly in this situation in our world. We look around and it doesn’t seem that mathematical at all, but everything we see is made out of elementary particles like quarks and electrons. And what properties does an electron have? Does it have a smell or a colour or a texture? No! ... We physicists have come up with geeky names for [Electron] properties, like

electric charge, or spin, or lepton number, but the electron doesn't care what we call it, the properties are just numbers.

This is the illusory reality Gnostics were describing. This is the simulation. The A, C, G, and T codes of DNA have a binary value – A and C = 0 while G and T = 1. This has to be when the simulation is digital and the body must be digital to interact with it. Recurring mathematical sequences are encoded throughout reality and the body. They include the Fibonacci sequence in which the two previous numbers are added to get the next one, as in ... 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, etc. The sequence is encoded in the human face and body, proportions of animals, DNA, seed heads, pine cones, trees, shells, spiral galaxies, hurricanes and the number of petals in a flower. The list goes on and on. There are fractal patterns – a 'never-ending pattern that is infinitely complex and self-similar across all scales in the as above, so below, principle of holograms. These and other famous recurring geometrical and mathematical sequences such as Phi, Pi, Golden Mean, Golden Ratio and Golden Section are *computer codes* of the simulation. I had to laugh and give my head a shake the day I finished this book and it went into the production stage. I was sent an article in *Scientific American* published in April, 2021, with the headline 'Confirmed! We Live in a Simulation'. Two decades after I first said our reality is a simulation and the speed of light is its outer limit the article suggested that we do live in a simulation and that the speed of light is its outer limit. I left school at 15 and never passed a major exam in my life while the writer was up to his eyes in qualifications. As I will explain in the final chapter *knowing* is far better than thinking and they come from very different sources. The article rightly connected the speed of light to the processing speed of the 'Matrix' and said what has been in my books all this time ... 'If we are in a simulation, as it appears, then space is an abstract property written in code. It is not real'. No it's not and if we live in a simulation something created it and it wasn't *us*. 'That David Icke says we are manipulated by aliens' – he's crackers.'

## **Wow ...**

The reality that humanity thinks is so real is an illusion. Politicians, governments, scientists, doctors, academics, law enforcement, media, school and university curriculums, on and on, are all founded on a world that *does not exist* except as a simulated prison cell. Is it such a stretch to accept that 'Covid' doesn't exist when our entire 'physical' reality doesn't exist? Revealed here is the knowledge kept under raps in the Cult networks of compartmentalised secrecy to control humanity's sense of reality by inducing the population to believe in a reality that's not real. If it wasn't so tragic in its experiential consequences the whole thing would be hysterically funny. None of this is new to Renegade Minds. Ancient Greek philosopher Plato (about 428 to about 347BC) was a major influence on Gnostic belief and he described the human plight thousands of years ago with his Allegory of the Cave. He told the symbolic story of prisoners living in a cave who had never been outside. They were chained and could only see one wall of the cave while behind them was a fire that they could not see. Figures walked past the fire casting shadows on the prisoners' wall and those moving shadows became their sense of reality. Some prisoners began to study the shadows and were considered experts on them (today's academics and scientists), but what they studied was only an illusion (today's academics and scientists). A prisoner escaped from the cave and saw reality as it really is. When he returned to report this revelation they didn't believe him, called him mad and threatened to kill him if he tried to set them free. Plato's tale is not only a brilliant analogy of the human plight and our illusory reality. It describes, too, the dynamics of the 'Covid' hoax. I have only skimmed the surface of these subjects here. The aim of this book is to crisply connect all essential dots to put what is happening today into its true context. All subject areas and their connections in this chapter are covered in great evidential detail in *Everything You Need To Know, But Have Never Been Told* and *The Answer*.

They say that bewildered people 'can't see the forest for the trees'. Humanity, however, can't see the forest for the *twigs*. The five senses

see only twigs while Renegade Minds can see the forest and it's the forest where the answers lie with the connections that reveals. Breaking free of perceptual programming so the forest can be seen is the way we turn all this around. Not breaking free is how humanity got into this mess. The situation may seem hopeless, but I promise you it's not. We are a perceptual heartbeat from paradise if only we knew.

## CHAPTER TWELVE

### Escaping Wetiko

*Life is simply a vacation from the infinite*

Dean Cavanagh

Renegade Minds weave the web of life and events and see common themes in the apparently random. They are always there if you look for them and their pursuit is aided by incredible synchronicity that comes when your mind is open rather than mesmerised by what it thinks it can see.

Infinite awareness is infinite possibility and the more of infinite possibility that we access the more becomes infinitely possible. That may be stating the apparently obvious, but it is a devastatingly-powerful fact that can set us free. We are a point of attention within an infinity of consciousness. The question is how much of that infinity do we choose to access? How much knowledge, insight, awareness, wisdom, do we want to connect with and explore? If your focus is only in the five senses you will be influenced by a fraction of infinite awareness. I mean a range so tiny that it gives new meaning to infinitesimal. Limitation of self-identity and a sense of the possible limit accordingly your range of consciousness. We are what we think we are. Life is what we think it is. The dream is the dreamer and the dreamer is the dream. Buddhist philosophy puts it this way: 'As a thing is viewed, so it appears.' Most humans live in the realm of touch, taste, see, hear, and smell and that's the limit of their sense of the possible and sense of self. Many will follow a religion and speak of a God in his heaven, but their lives are still

dominated by the five senses in their perceptions and actions. The five senses become the arbiter of everything. When that happens all except a smear of infinity is sealed away from influence by the rigid, unyielding, reality bubbles that are the five-sense human or Phantom Self. Archon Cult methodology is to isolate consciousness within five-sense reality – the simulation – and then program that consciousness with a sense of self and the world through a deluge of life-long information designed to instil the desired perception that allows global control. Efforts to do this have increased dramatically with identity politics as identity bubbles are squeezed into the minutiae of five-sense detail which disconnect people even more profoundly from the infinite ‘I’.

Five-sense focus and self-identity are like a firewall that limits access to the infinite realms. You only perceive one radio or television station and no other. We’ll take that literally for a moment. Imagine a vast array of stations giving different information and angles on reality, but you only ever listen to one. Here we have the human plight in which the population is overwhelmingly confined to CultFM. This relates only to the frequency range of CultFM and limits perception and insight to that band – limits *possibility* to that band. It means you are connecting with an almost imperceptibly minuscule range of possibility and creative potential within the infinite Field. It’s a world where everything seems apart from everything else and where synchronicity is rare. Synchronicity is defined in the dictionary as ‘the happening by chance of two or more related or similar events at the same time’. Use of ‘by chance’ betrays a complete misunderstanding of reality. Synchronicity is not ‘by chance’. As people open their minds, or ‘awaken’ to use the term, they notice more and more coincidences in their lives, bits of ‘luck’, apparently miraculous happenings that put them in the right place at the right time with the right people. Days become peppered with ‘fancy meeting you here’ and ‘what are the chances of that?’ My entire life has been lived like this and ever more so since my own colossal awakening in 1990 and 91 which transformed my sense of reality. Synchronicity is not ‘by chance’; it is by accessing expanded

realms of possibility which allow expanded potential for manifestation. People broadcasting the same vibe from the same openness of mind tend to be drawn ‘by chance’ to each other through what I call frequency magnetism and it’s not only people. In the last more than 30 years incredible synchronicity has also led me through the Cult maze to information in so many forms and to crucial personal experiences. These ‘coincidences’ have allowed me to put the puzzle pieces together across an enormous array of subjects and situations. Those who have breached the bubble of five-sense reality will know exactly what I mean and this escape from the perceptual prison cell is open to everyone whenever they make that choice. This may appear super-human when compared with the limitations of ‘human’, but it’s really our natural state. ‘Human’ as currently experienced is consciousness in an unnatural state of induced separation from the infinity of the whole. I’ll come to how this transformation into unity can be made when I have described in more detail the force that holds humanity in servitude by denying this access to infinite self.

## **The Wetiko factor**

I have been talking and writing for decades about the way five-sense mind is systematically barricaded from expanded awareness. I have used the analogy of a computer (five-sense mind) and someone at the keyboard (expanded awareness). Interaction between the computer and the operator is symbolic of the interaction between five-sense mind and expanded awareness. The computer directly experiences the Internet and the operator experiences the Internet via the computer which is how it’s supposed to be – the two working as one. Archons seek to control that point where the operator connects with the computer to stop that interaction ([Fig 20](#)). Now the operator is banging the keyboard and clicking the mouse, but the computer is not responding and this happens when the computer is taken over – *possessed* – by an appropriately-named computer ‘virus’. The operator has lost all influence over the computer which goes its own way making decisions under the control of the ‘virus’. I have

just described the dynamic through which the force known to Gnostics as Yaldabaoth and Archons disconnects five-sense mind from expanded awareness to imprison humanity in perceptual servitude.



**Figure 20:** The mind ‘virus’ I have been writing about for decades seeks to isolate five-sense mind (the computer) from the true ‘I’. (Image by Neil Hague).

About a year ago I came across a Native American concept of Wetiko which describes precisely the same phenomenon. Wetiko is the spelling used by the Cree and there are other versions including wintiko and windigo used by other tribal groups. They spell the name with lower case, but I see Wetiko as a proper noun as with Archons and prefer a capital. I first saw an article about Wetiko by writer and researcher Paul Levy which so synced with what I had been writing about the computer/operator disconnection and later the Archons. I then read his book, the fascinating *Dispelling Wetiko, Breaking the Spell of Evil*. The parallels between what I had concluded long before and the Native American concept of Wetiko were so clear and obvious that it was almost funny. For Wetiko see the Gnostic Archons for sure and the Jinn, the Predators, and every other name for a force of evil, inversion and chaos. Wetiko is the Native American name for the force that divides the computer from

the operator ([Fig 21](#)). Indigenous author Jack D. Forbes, a founder of the Native American movement in the 1960s, wrote another book about Wetiko entitled *Columbus And Other Cannibals – The Wetiko Disease of Exploitation, Imperialism, and Terrorism* which I also read. Forbes says that Wetiko refers to an evil person or spirit ‘who terrorizes other creatures by means of terrible acts, including cannibalism’. Zulu shaman Credo Mutwa told me that African accounts tell how cannibalism was brought into the world by the Chitauri ‘gods’ – another manifestation of Wetiko. The distinction between ‘evil person or spirit’ relates to Archons/Wetiko possessing a human or acting as pure consciousness. Wetiko is said to be a sickness of the soul or spirit and a state of being that takes but gives nothing back – the Cult and its operatives perfectly described. Black Hawk, a Native American war leader defending their lands from confiscation, said European invaders had ‘poisoned hearts’ – Wetiko hearts – and that this would spread to native societies. Mention of the heart is very significant as we shall shortly see. Forbes writes: ‘Tragically, the history of the world for the past 2,000 years is, in great part, the story of the epidemiology of the wetiko disease.’ Yes, and much longer. Forbes is correct when he says: ‘The wetikos destroyed Egypt and Babylon and Athens and Rome and Tenochtitlan [capital of the Aztec empire] and perhaps now they will destroy the entire earth.’ Evil, he said, is the number one export of a Wetiko culture – see its globalisation with ‘Covid’. Constant war, mass murder, suffering of all kinds, child abuse, Satanism, torture and human sacrifice are all expressions of Wetiko and the Wetiko possessed. The world is Wetiko made manifest, *but it doesn’t have to be*. There is a way out of this even now.



**Figure 21:** The mind ‘virus’ is known to Native Americans as ‘Wetiko’. (Image by Neil Hague).

## Cult of Wetiko

Wetiko is the Yaldabaoth frequency distortion that seeks to attach to human consciousness and absorb it into its own. Once this connection is made Wetiko can drive the perceptions of the target which they believe to be coming from their own mind. All the horrors of history and today from mass killers to Satanists, paedophiles like Jeffrey Epstein and other psychopaths, are the embodiment of Wetiko and express its state of being in all its grotesqueness. The Cult is Wetiko incarnate, Yaldabaoth incarnate, and it seeks to facilitate Wetiko assimilation of humanity in totality into its distortion by manipulating the population into low frequency states that match its own. Paul Levy writes: ‘Holographically enforced within the psyche of every human being the wetiko virus pervades and underlies the entire field of consciousness, and can therefore potentially manifest through any one of us at any moment if we are not mindful.’ The ‘Covid’ hoax has achieved this with many people, but others have not fallen into Wetiko’s frequency lair. Players in the ‘Covid’ human catastrophe including Gates, Schwab, Tedros, Fauci, Whitty, Vallance, Johnson, Hancock, Ferguson, Drosten, and all the rest, including the psychopath psychologists, are expressions of Wetiko. This is why

they have no compassion or empathy and no emotional consequence for what they do that would make them stop doing it. Observe all the people who support the psychopaths in authority against the Pushbackers despite the damaging impact the psychopaths have on their own lives and their family's lives. You are again looking at Wetiko possession which prevents them seeing through the lies to the obvious scam going on. *Why can't they see it?* Wetiko won't let them see it. The perceptual divide that has now become a chasm is between the Wetikoed and the non-Wetikoed.

Paul Levy describes Wetiko in the same way that I have long described the Archontic force. They are the same distorted consciousness operating across dimensions of reality: '... the subtle body of wetiko is not located in the third dimension of space and time, literally existing in another dimension ... it is able to affect ordinary lives by mysteriously interpenetrating into our three-dimensional world.' Wetiko does this through its incarnate representatives in the Cult and by weaving itself into The Field which on our level of reality is the electromagnetic information field of the simulation or Matrix. More than that, the simulation *is* Wetiko / Yaldabaoth. Caleb Scharf, Director of Astrobiology at Columbia University, has speculated that 'alien life' could be so advanced that it has transcribed itself into the quantum realm to become what we call physics. He said intelligence indistinguishable from the fabric of the Universe would solve many of its greatest mysteries:

Perhaps hyper-advanced life isn't just external. Perhaps it's already all around. It is embedded in what we perceive to be physics itself, from the root behaviour of particles and fields to the phenomena of complexity and emergence ... In other words, life might not just be in the equations. It might BE the equations [My emphasis].

Scharf said it is possible that 'we don't recognise advanced life because it forms an integral and unsuspicious part of what we've considered to be the natural world'. I agree. Wetiko/Yaldabaoth *is* the simulation. We are literally in the body of the beast. But that doesn't mean it has to control us. We all have the power to overcome Wetiko

influence and the Cult knows that. I doubt it sleeps too well because it knows that.

## **Which Field?**

This, I suggest, is how it all works. There are two Fields. One is the fierce electromagnetic light of the Matrix within the speed of light; the other is the ‘watery light’ of The Field beyond the walls of the Matrix that connects with the Great Infinity. Five-sense mind and the decoding systems of the body attach us to the Field of Matrix light. They have to or we could not experience this reality. Five-sense mind sees only the Matrix Field of information while our expanded consciousness is part of the Infinity Field. When we open our minds, and most importantly our hearts, to the Infinity Field we have a mission control which gives us an expanded perspective, a road map, to understand the nature of the five-sense world. If we are isolated only in five-sense mind there is no mission control. We’re on our own trying to understand a world that’s constantly feeding us information to ensure we do not understand. People in this state can feel ‘lost’ and bewildered with no direction or radar. You can see ever more clearly those who are influenced by the Fields of Big Infinity or little five-sense mind simply by their views and behaviour with regard to the ‘Covid’ hoax. We have had this division throughout known human history with the mass of the people on one side and individuals who could see and intuit beyond the walls of the simulation – Plato’s prisoner who broke out of the cave and saw reality for what it is. Such people have always been targeted by Wetiko/Archon-possessed authority, burned at the stake or demonised as mad, bad and dangerous. The Cult today and its global network of ‘anti-hate’, ‘anti-fascist’ Woke groups are all expressions of Wetiko attacking those exposing the conspiracy, ‘Covid’ lies and the ‘vaccine’ agenda.

Woke as a whole is Wetiko which explains its black and white mentality and how at one it is with the Wetiko-possessed Cult. Paul Levy said: ‘To be in this paradigm is to still be under the thrall of a two-valued logic – where things are either true or false – of a

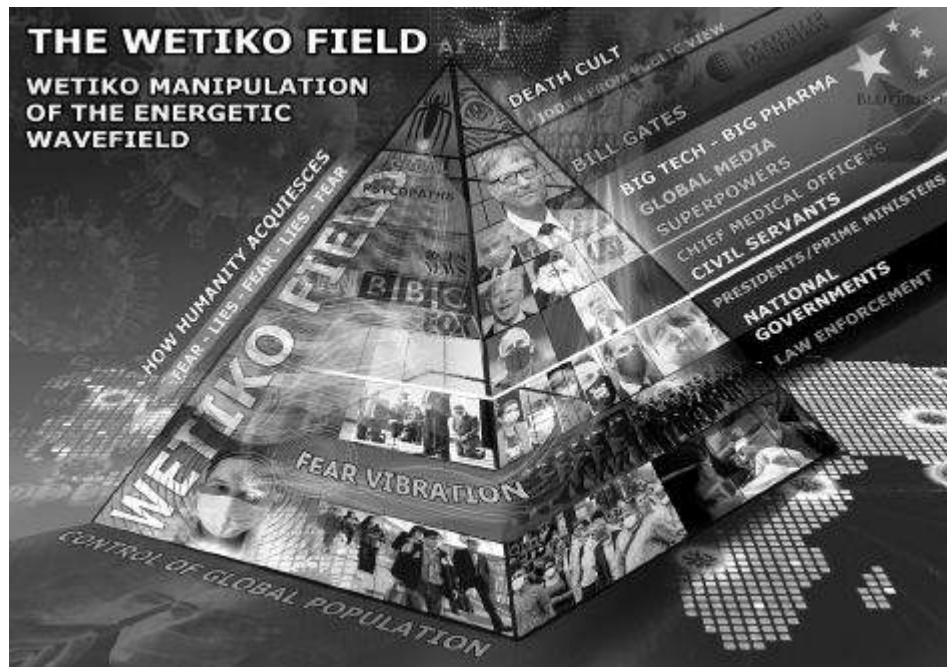
wetikoized mind.' Wetiko consciousness is in a permanent rage, therefore so is Woke, and then there is Woke inversion and contradiction. 'Anti-fascists' act like fascists because fascists *and* 'anti-fascists' are both Wetiko at work. Political parties act the same while claiming to be different for the same reason. Secret society and satanic rituals are attaching initiates to Wetiko and the cold, ruthless, psychopathic mentality that secures the positions of power all over the world is Wetiko. Reframing 'training programmes' have the same cumulative effect of attaching Wetiko and we have their graduates described as automatons and robots with a cold, psychopathic, uncaring demeanour. They are all traits of Wetiko possession and look how many times they have been described in this book and elsewhere with regard to personnel behind 'Covid' including the police and medical profession. Climbing the greasy pole in any profession in a Wetiko society requires traits of Wetiko to get there and that is particularly true of politics which is not about fair competition and pre-eminence of ideas. It is founded on how many backs you can stab and arses you can lick. This culminated in the global 'Covid' coordination between the Wetiko possessed who pulled it off in all the different countries without a trace of empathy and compassion for their impact on humans. Our sight sense can see only holographic form and not the Field which connects holographic form. Therefore we perceive 'physical' objects with 'space' in between. In fact that 'space' is energy/consciousness operating on multiple frequencies. One of them is Wetiko and that connects the Cult psychopaths, those who submit to the psychopaths, and those who serve the psychopaths in the media operations of the world. Wetiko is Gates. Wetiko is the mask-wearing submissive. Wetiko is the fake journalist and 'fact-checker'. The Wetiko Field is coordinating the whole thing. Psychopaths, gofers, media operatives, 'anti-hate' hate groups, 'fact-checkers' and submissive people work as one unit *even without human coordination* because they are attached to the *same* Field which is organising it all ([Fig 22](#)). Paul Levy is here describing how Wetiko-possessed people are drawn together and refuse to let any information breach their rigid

perceptions. He was writing long before ‘Covid’, but I think you will recognise followers of the ‘Covid’ religion *oh just a little bit*:

People who are channelling the vibratory frequency of wetiko align with each other through psychic resonance to reinforce their unspoken shared agreement so as to uphold their deranged view of reality. Once an unconscious content takes possession of certain individuals, it irresistibly draws them together by mutual attraction and knits them into groups tied together by their shared madness that can easily swell into an avalanche of insanity.

A psychic epidemic is a closed system, which is to say that it is insular and not open to any new information or informing influences from the outside world which contradict its fixed, limited, and limiting perspective.

There we have the Woke mind and the ‘Covid’ mind. Compatible resonance draws the awakening together, too, which is clearly happening today.



**Figure 22:** The Wetiko Field from which the Cult pyramid and its personnel are made manifest. (Image by Neil Hague).

## Spiritual servitude

Wetiko doesn't care about humans. It's not human; it just possesses humans for its own ends and the effect (depending on the scale of

possession) can be anything from extreme psychopathy to unquestioning obedience. Wetiko's worst nightmare is for human consciousness to expand beyond the simulation. Everything is focussed on stopping that happening through control of information, thus perception, thus frequency. The 'education system', media, science, medicine, academia, are all geared to maintaining humanity in five-sense servitude as is the constant stimulation of low-vibrational mental and emotional states (see 'Covid'). Wetiko seeks to dominate those subconscious spaces between five-sense perception and expanded consciousness where the computer meets the operator. From these subconscious hiding places Wetiko speaks to us to trigger urges and desires that we take to be our own and manipulate us into anything from low-vibrational to psychopathic states. Remember how Islam describes the Jinn as invisible tricksters that 'whisper' and confuse. Wetiko is the origin of the 'trickster god' theme that you find in cultures all over the world. Jinn, like the Archons, are Wetiko which is terrified of humans awakening and reconnecting with our true self for then its energy source has gone. With that the feedback loop breaks between Wetiko and human perception that provides the energetic momentum on which its very existence depends as a force of evil. Humans are both its target and its source of survival, but only if we are operating in low-vibrational states of fear, hate, depression and the background anxiety that most people suffer. We are Wetiko's target because we are its key to survival. It needs us, not the other way round. Paul Levy writes:

A vampire has no intrinsic, independent, substantial existence in its own right; it only exists in relation to us. The pathogenic, vampiric mind-parasite called wetiko is nothing in itself – not being able to exist from its own side – yet it has a 'virtual reality' such that it can potentially destroy our species ...

...The fact that a vampire is not reflected by a mirror can also mean that what we need to see is that there's nothing, no-thing to see, other than ourselves. The fact that wetiko is the expression of something inside of us means that the cure for wetiko is with us as well. The critical issue is finding this cure within us and then putting it into effect.

Evil begets evil because if evil does not constantly expand and find new sources of energetic sustenance its evil, its *distortion*, dies with the assimilation into balance and harmony. Love is the garlic to Wetiko's vampire. Evil, the absence of love, cannot exist in the presence of love. I think I see a way out of here. I have emphasised so many times over the decades that the Archons/Wetiko and their Cult are not all powerful. *They are not.* I don't care how it looks even now *they are not.* I have not called them little boys in short trousers for effect. I have said it because it is true. Wetiko's insatiable desire for power over others is not a sign of its omnipotence, but its insecurity. Paul Levy writes: 'Due to the primal fear which ultimately drives it and which it is driven to cultivate, wetiko's body politic has an intrinsic and insistent need for centralising power and control so as to create imagined safety for itself.' *Yeeeeees!* Exactly! Why does Wetiko want humans in an ongoing state of fear? Wetiko itself *is* fear and it is petrified of love. As evil is an absence of love, so love is an absence of fear. Love conquers all and *especially* Wetiko which *is* fear. Wetiko brought fear into the world when it wasn't here before. *Fear* was the 'fall', the fall into low-frequency ignorance and illusion – fear is False Emotion Appearing Real. The simulation is driven and energised by fear because Wetiko/Yaldabaoth (fear) *are* the simulation. Fear is the absence of love and Wetiko is the absence of love.

## **Wetiko today**

We can now view current events from this level of perspective. The 'Covid' hoax has generated momentous amounts of ongoing fear, anxiety, depression and despair which have empowered Wetiko. No wonder people like Gates have been the instigators when they are Wetiko incarnate and exhibit every trait of Wetiko in the extreme. See how cold and unemotional these people are like Gates and his cronies, how dead of eye they are. That's Wetiko. Sabbatians are Wetiko and everything they control including the World Health Organization, Big Pharma and the 'vaccine' makers, national 'health'

hierarchies, corporate media, Silicon Valley, the banking system, and the United Nations with its planned transformation into world government. All are controlled and possessed by the Wetiko distortion into distorting human society in its image. We are with this knowledge at the gateway to understanding the world.

Divisions of race, culture, creed and sexuality are diversions to hide the real division between those possessed and influenced by Wetiko and those that are not. The ‘Covid’ hoax has brought both clearly into view. Human behaviour is not about race. Tyrants and dictatorships come in all colours and creeds. What unites the US president bombing the innocent and an African tribe committing genocide against another as in Rwanda? What unites them? *Wetiko*. All wars are Wetiko, all genocide is Wetiko, all hunger over centuries in a world of plenty is Wetiko. Children going to bed hungry, including in the West, is Wetiko. Cult-generated Woke racial divisions that focus on the body are designed to obscure the reality that divisions in behaviour are manifestations of mind, not body. Obsession with body identity and group judgement is a means to divert attention from the real source of behaviour – mind and perception. Conflict sown by the Woke both within themselves and with their target groups are Wetiko providing lunch for itself through still more agents of the division, chaos, and fear on which it feeds. The Cult is seeking to assimilate the entirety of humanity and all children and young people into the Wetiko frequency by manipulating them into states of fear and despair. Witness all the suicide and psychological unravelling since the spring of 2020. Wetiko psychopaths want to impose a state of unquestioning obedience to authority which is no more than a conduit for Wetiko to enforce its will and assimilate humanity into itself. It needs us to believe that resistance is futile when it fears resistance and even more so the game-changing non-cooperation with its impositions. It can use violent resistance for its benefit. Violent impositions and violent resistance are *both* Wetiko. The Power of Love with its Power of No will sweep Wetiko from our world. Wetiko and its Cult know that. They just don’t want us to know.

## **AI Wetiko**

This brings me to AI or artificial intelligence and something else Wetikos don't want us to know. What is AI *really*? I know about computer code algorithms and AI that learns from data input. These, however, are more diversions, the expeditionary force, for the real AI that they want to connect to the human brain as promoted by Silicon Valley Wetikos like Kurzweil. What is this AI? It is the frequency of *Wetiko*, the frequency of the Archons. The connection of AI to the human brain is the connection of the Wetiko frequency to create a Wetiko hive mind and complete the job of assimilation. The hive mind is planned to be controlled from Israel and China which are both 100 percent owned by Wetiko Sabbatians. The assimilation process has been going on minute by minute in the 'smart' era which fused with the 'Covid' era. We are told that social media is scrambling the minds of the young and changing their personality. This is true, but what is social media? Look more deeply at how it works, how it creates divisions and conflict, the hostility and cruelty, the targeting of people until they are destroyed. That's Wetiko. Social media is manipulated to tune people to the Wetiko frequency with all the emotional exploitation tricks employed by platforms like Facebook and its Wetiko front man, Zuckerberg. Facebook's Instagram announced a new platform for children to overcome a legal bar on them using the main site. This is more Wetiko exploitation and manipulation of kids. Amnesty International likened the plan to foxes offering to guard the henhouse and said it was incompatible with human rights. Since when did Wetiko or Zuckerberg (I repeat myself) care about that? Would Brin and Page at Google, Wojcicki at YouTube, Bezos at Amazon and whoever the hell runs Twitter act as they do if they were not channelling Wetiko? Would those who are developing technologies for no other reason than human control? How about those designing and selling technologies to kill people and Big Pharma drug and 'vaccine' producers who know they will end or devastate lives? Quite a thought for these people to consider is that if you are Wetiko in a human life you are Wetiko on the 'other side' unless your frequency

changes and that can only change by a change of perception which becomes a change of behaviour. Where Gates is going does not bear thinking about although perhaps that's exactly where he wants to go. Either way, that's where he's going. His frequency will make it so.

## **The frequency lair**

I have been saying for a long time that a big part of the addiction to smartphones and devices is that a frequency is coming off them that entraps the mind. People spend ages on their phones and sometimes even a minute or so after they put them down they pick them up again and it all repeats. 'Covid' lockdowns will have increased this addiction a million times for obvious reasons. Addictions to alcohol overindulgence and drugs are another way that Wetiko entraps consciousness to attach to its own. Both are symptoms of low-vibrational psychological distress which alcoholism and drug addiction further compound. Do we think it's really a coincidence that access to them is made so easy while potions that can take people into realms beyond the simulation are banned and illegal? I have explored smartphone addiction in other books, the scale is mind-blowing, and that level of addiction does not come without help. Tech companies that make these phones are Wetiko and they will have no qualms about destroying the minds of children. We are seeing again with these companies the Wetiko perceptual combination of psychopathic enforcers and weak and meek unquestioning compliance by the rank and file.

The global Smart Grid is the Wetiko Grid and it is crucial to complete the Cult endgame. The simulation is radiation and we are being deluged with technological radiation on a devastating scale. Wetiko frauds like Elon Musk serve Cult interests while occasionally criticising them to maintain his street-cred. 5G and other forms of Wi-Fi are being directed at the earth from space on a volume and scale that goes on increasing by the day. Elon Musk's (officially) SpaceX Starlink project is in the process of putting tens of thousands of satellites in low orbit to cover every inch of the planet with 5G and other Wi-Fi to create Kurzweil's global 'cloud' to which the

human mind is planned to be attached very soon. SpaceX has approval to operate 12,000 satellites with more than 1,300 launched at the time of writing and applications filed for 30,000 more. Other operators in the Wi-Fi, 5G, low-orbit satellite market include OneWeb (UK), Telesat (Canada), and AST & Science (US). Musk tells us that AI could be the end of humanity and then launches a company called Neuralink to connect the human brain to computers. Musk's (in theory) Tesla company is building electric cars and the driverless vehicles of the smart control grid. As frauds and bullshitters go Elon Musk in my opinion is Major League.

5G and technological radiation in general are destructive to human health, genetics and psychology and increasing the strength of artificial radiation underpins the five-sense perceptual bubbles which are themselves expressions of radiation or electromagnetism. Freedom activist John Whitehead was so right with his 'databit by databit, we are building our own electronic concentration camps'. The Smart Grid and 5G is a means to control the human mind and infuse perceptual information into The Field to influence anyone in sync with its frequency. You can change perception and behaviour en masse if you can manipulate the population into those levels of frequency and this is happening all around us today. The arrogance of Musk and his fellow Cult operatives knows no bounds in the way that we see with Gates. Musk's satellites are so many in number already they are changing the night sky when viewed from Earth. The astronomy community has complained about this and they have seen nothing yet. Some consequences of Musk's Wetiko hubris include: Radiation; visible pollution of the night sky; interference with astronomy and meteorology; ground and water pollution from intensive use of increasingly many spaceports; accumulating space debris; continual deorbiting and burning up of aging satellites, polluting the atmosphere with toxic dust and smoke; and ever-increasing likelihood of collisions. A collective public open letter of complaint to Musk said:

We are writing to you ... because SpaceX is in process of surrounding the Earth with a network of thousands of satellites whose very purpose is to irradiate every square inch of the

Earth. SpaceX, like everyone else, is treating the radiation as if it were not there. As if the mitochondria in our cells do not depend on electrons moving undisturbed from the food we digest to the oxygen we breathe.

As if our nervous systems and our hearts are not subject to radio frequency interference like any piece of electronic equipment. As if the cancer, diabetes, and heart disease that now afflict a majority of the Earth's population are not metabolic diseases that result from interference with our cellular machinery. As if insects everywhere, and the birds and animals that eat them, are not starving to death as a result.

People like Musk and Gates believe in their limitless Wetiko arrogance that they can do whatever they like to the world because they own it. Consequences for humanity are irrelevant. It's absolutely time that we stopped taking this shit from these self-styled masters of the Earth when you consider where this is going.

## **Why is the Cult so anti-human?**

I hear this question often: Why would they do this when it will affect them, too? Ah, but will it? Who is this *them*? Forget their bodies. They are just vehicles for Wetiko consciousness. When you break it all down to the foundations we are looking at a state of severely distorted consciousness targeting another state of consciousness for assimilation. The rest is detail. The simulation is the fly-trap in which unique sensations of the five senses create a cycle of addiction called reincarnation. Renegade Minds see that everything which happens in our reality is a smaller version of the whole picture in line with the holographic principle. Addiction to the radiation of smart technology is a smaller version of addiction to the whole simulation. Connecting the body/brain to AI is taking that addiction on a giant step further to total ongoing control by assimilating human incarnate consciousness into Wetiko. I have watched during the 'Covid' hoax how many are becoming ever more profoundly attached to Wetiko's perceptual calling cards of aggressive response to any other point of view ('There is no other god but me'), psychopathic lack of compassion and empathy, and servile submission to the narrative and will of authority. Wetiko is the psychopaths *and* subservience to psychopaths. The Cult of Wetiko is

so anti-human because it is *not* human. It embarked on a mission to destroy human by targeting everything that it means to be human and to survive as human. ‘Covid’ is not the end, just a means to an end. The Cult with its Wetiko consciousness is seeking to change Earth systems, including the atmosphere, to suit them, not humans. The gathering bombardment of 5G alone from ground and space is dramatically changing The Field with which the five senses interact. There is so much more to come if we sit on our hands and hope it will all go away. It is not meant to go away. It is meant to get ever more extreme and we need to face that while we still can – just.

Carbon dioxide is the gas of life. Without that human is over. Kaput, gone, history. No natural world, no human. The Cult has created a cock and bull story about carbon dioxide and climate change to justify its reduction to the point where Gates and the ignoramus Biden ‘climate chief’ John Kerry want to suck it out of the atmosphere. Kerry wants to do this because his master Gates does. Wetikos have made the gas of life a demon with the usual support from the Wokers of Extinction Rebellion and similar organisations and the bewildered puppet-child that is Greta Thunberg who was put on the world stage by Klaus Schwab and the World Economic Forum. The name Extinction Rebellion is both ironic and as always Wetiko inversion. The gas that we need to survive must be reduced to save us from extinction. The most basic need of human is oxygen and we now have billions walking around in face nappies depriving body and brain of this essential requirement of human existence. More than that 5G at 60 gigahertz interacts with the oxygen molecule to reduce the amount of oxygen the body can absorb into the bloodstream. The obvious knock-on consequences of that for respiratory and cognitive problems and life itself need no further explanation. Psychopaths like Musk are assembling a global system of satellites to deluge the human atmosphere with this insanity. The man should be in jail. Here we have two most basic of human needs, oxygen and carbon dioxide, being dismantled.

Two others, water and food, are getting similar treatment with the United Nations Agendas 21 and 2030 – the Great Reset – planning to

centrally control all water and food supplies. People will not even own rain water that falls on their land. Food is affected at the most basic level by reducing carbon dioxide. We have genetic modification or GMO infiltrating the food chain on a mass scale, pesticides and herbicides polluting the air and destroying the soil. Freshwater fish that provide livelihoods for 60 million people and feed hundreds of millions worldwide are being 'pushed to the brink' according the conservationists while climate change is the only focus. Now we have Gates and Schwab wanting to dispense with current food sources all together and replace them with a synthetic version which the Wetiko Cult would control in terms of production and who eats and who doesn't. We have been on the Totalitarian Tiptoe to this for more than 60 years as food has become ever more processed and full of chemical shite to the point today when it's not natural food at all. As Dr Tom Cowan says: 'If it has a label don't eat it.' Bill Gates is now the biggest owner of farmland in the United States and he does nothing without an ulterior motive involving the Cult. Klaus Schwab wrote: 'To feed the world in the next 50 years we will need to produce as much food as was produced in the last 10,000 years ... food security will only be achieved, however, if regulations on genetically modified foods are adapted to reflect the reality that gene editing offers a precise, efficient and safe method of improving crops.' Liar. People and the world are being targeted with aluminium through vaccines, chemtrails, food, drink cans, and endless other sources when aluminium has been linked to many health issues including dementia which is increasing year after year. Insects, bees and wildlife essential to the food chain are being deleted by pesticides, herbicides and radiation which 5G is dramatically increasing with 6G and 7G to come. The pollinating bee population is being devastated while wildlife including birds, dolphins and whales are having their natural radar blocked by the effects of ever-increasing radiation. In the summer windscreens used to be splattered with insects so numerous were they. It doesn't happen now. Where have they gone?

## **Synthetic everything**

The Cult is introducing genetically-modified versions of trees, plants and insects including a Gates-funded project to unleash hundreds of millions of genetically-modified, lab-altered and patented male mosquitoes to mate with wild mosquitoes and induce genetic flaws that cause them to die out. Clinically-insane Gates-funded Japanese researchers have developed mosquitos that spread vaccine and are dubbed 'flying vaccinators'. Gates is funding the modification of weather patterns in part to sell the myth that this is caused by carbon dioxide and he's funding geoengineering of the skies to change the atmosphere. Some of this came to light with the Gates-backed plan to release tonnes of chalk into the atmosphere to 'deflect the Sun and cool the planet'. Funny how they do this while the heating effect of the Sun is not factored into climate projections focussed on carbon dioxide. The reason is that they want to reduce carbon dioxide (so don't mention the Sun), but at the same time they do want to reduce the impact of the Sun which is so essential to human life and health. I have mentioned the sun-cholesterol-vitamin D connection as they demonise the Sun with warnings about skin cancer (caused by the chemicals in sun cream they tell you to splash on). They come from the other end of the process with statin drugs to reduce cholesterol that turns sunlight into vitamin D. A lack of vitamin D leads to a long list of health effects and how vitamin D levels must have fallen with people confined to their homes over 'Covid'. Gates is funding other forms of geoengineering and most importantly chemtrails which are dropping heavy metals, aluminium and self-replicating nanotechnology onto the Earth which is killing the natural world. See *Everything You Need To Know, But Have Never Been Told* for the detailed background to this.

Every human system is being targeted for deletion by a force that's not human. The Wetiko Cult has embarked on the process of transforming the human body from biological to synthetic biological as I have explained. Biological is being replaced by the artificial and synthetic – Archontic 'countermimicry' – right across human society. The plan eventually is to dispense with the human body altogether

and absorb human consciousness – which it wouldn't really be by then – into cyberspace (the simulation which is Wetiko/Yaldabaoth). Preparations for that are already happening if people would care to look. The alternative media rightly warns about globalism and 'the globalists', but this is far bigger than that and represents the end of the human race as we know it. The 'bad copy' of prime reality that Gnostics describe was a bad copy of harmony, wonder and beauty to start with before Wetiko/Yaldabaoth set out to change the simulated 'copy' into something very different. The process was slow to start with. Entrapped humans in the simulation timeline were not technologically aware and they had to be brought up to intellectual speed while being suppressed spiritually to the point where they could build their own prison while having no idea they were doing so. We have now reached that stage where technological intellect has the potential to destroy us and that's why events are moving so fast. Central American shaman Don Juan Matus said:

Think for a moment, and tell me how you would explain the contradictions between the intelligence of man the engineer and the stupidity of his systems of belief, or the stupidity of his contradictory behaviour. Sorcerers believe that the predators have given us our systems of beliefs, our ideas of good and evil; our social mores. They are the ones who set up our dreams of success or failure. They have given us covetousness, greed, and cowardice. It is the predator who makes us complacent, routinary, and egomaniacal.

In order to keep us obedient and meek and weak, the predators engaged themselves in a stupendous manoeuvre – stupendous, of course, from the point of view of a fighting strategist; a horrendous manoeuvre from the point of those who suffer it. They gave us their mind. The predators' mind is baroque, contradictory, morose, filled with the fear of being discovered any minute now.

For 'predators' see Wetiko, Archons, Yaldabaoth, Jinn, and all the other versions of the same phenomenon in cultures and religions all over the world. The theme is always the same because it's true and it's real. We have reached the point where we have to deal with it. The question is – how?

## **Don't fight – walk away**

I thought I'd use a controversial subheading to get things moving in terms of our response to global fascism. What do you mean 'don't fight'? What do you mean 'walk away'? We've got to fight. We can't walk away. Well, it depends what we mean by fight and walk away. If fighting means physical combat we are playing Wetiko's game and falling for its trap. It wants us to get angry, aggressive, and direct hate and hostility at the enemy we think we must fight. Every war, every battle, every conflict, has been fought with Wetiko leading both sides. It's what it does. Wetiko wants a fight, anywhere, any place. Just hit me, son, so I can hit you back. Wetiko hits Wetiko and Wetiko hits Wetiko in return. I am very forthright as you can see in exposing Wetikos of the Cult, but I don't hate them. I refuse to hate them. It's what they want. What you hate you become. What you *fight* you become. Wokers, 'anti-haters' and 'anti-fascists' prove this every time they reach for their keyboards or don their balaclavas. By walk away I mean to disengage from Wetiko which includes ceasing to cooperate with its tyranny. Paul Levy says of Wetiko:

The way to 'defeat' evil is not to try to destroy it (for then, in playing evil's game, we have already lost), but rather, to find the invulnerable place within ourselves where evil is unable to vanquish us – this is to truly 'win' our battle with evil.

Wetiko is everywhere in human society and it's been on steroids since the 'Covid' hoax. Every shouting match over wearing masks has Wetiko wearing a mask and Wetiko not wearing one. It's an electrical circuit of push and resist, push and resist, with Wetiko pushing *and* resisting. Each polarity is Wetiko empowering itself. Dictionary definitions of 'resist' include 'opposing, refusing to accept or comply with' and the word to focus on is 'opposing'. What form does this take – setting police cars alight or 'refusing to accept or comply with'? The former is Wetiko opposing Wetiko while the other points the way forward. This is the difference between those aggressively demanding that government fascism must be obeyed who stand in stark contrast to the great majority of Pushbackers. We saw this clearly with a march by thousands of Pushbackers against lockdown in London followed days later by a Woker-hijacked

protest in Bristol in which police cars were set on fire. Masks were virtually absent in London and widespread in Bristol. Wetiko wants lockdown on every level of society and infuses its aggression to police it through its unknowing stooges. Lockdown protesters are the ones with the smiling faces and the hugs, The two blatantly obvious states of being – getting more obvious by the day – are the result of Wokers and their like becoming ever more influenced by the simulation Field of Wetiko and Pushbackers ever more influenced by The Field of a far higher vibration beyond the simulation. Wetiko can't invade the heart which is where most lockdown opponents are coming from. It's the heart that allows them to see through the lies to the truth in ways I will be highlighting.

Renegade Minds know that calmness is the place from which wisdom comes. You won't find wisdom in a hissing fit and wisdom is what we need in abundance right now. Calmness is not weakness – you don't have to scream at the top of your voice to be strong. Calmness is indeed a sign of strength. 'No' means I'm not doing it. NOOOO!!! doesn't mean you're not doing it even more. Volume does not advance 'No – I'm not doing it'. You are just not doing it. Wetiko possessed and influenced don't know how to deal with that. Wetiko wants a fight and we should not give it one. What it needs more than anything is our *cooperation* and we should not give that either. Mass rallies and marches are great in that they are a visual representation of feeling, but if it ends there they are irrelevant. You demand that Wetikos act differently? Well, they're not going to do it. They are Wetikos. We don't need to waste our time demanding that something doesn't happen when that will make no difference. We need to delete the means that *allows* it to happen. This, invariably, is our cooperation. You can demand a child stop firing a peashooter at the dog or you can refuse to buy the peashooter. If you provide the means you are cooperating with the dog being smacked on the nose with a pea. How can the authorities enforce mask-wearing if millions in a country refuse? What if the 74 million Pushbackers that voted for Trump in 2020 refused to wear masks, close their businesses or stay in their homes. It would be unenforceable. The

few control the many through the compliance of the many and that's always been the dynamic be it 'Covid' regulations or the Roman Empire. I know people can find it intimidating to say no to authority or stand out in a crowd for being the only one with a face on display; but it has to be done or it's over. I hope I've made clear in this book that where this is going will be far more intimidating than standing up now and saying 'No' – I will not cooperate with my own enslavement and that of my children. There might be consequences for some initially, although not so if enough do the same. The question that must be addressed is what is going to happen if we don't? It is time to be strong and unyieldingly so. No means no. Not here and there, but *everywhere* and *always*. I have refused to wear a mask and obey all the other nonsense. I will not comply with tyranny. I repeat: Fascism is not imposed by fascists – there are never enough of them. Fascism is imposed by the population acquiescing to fascism. *I will not do it.* I will die first, or my body will. Living meekly under fascism is a form of death anyway, the death of the spirit that Martin Luther King described.

## **Making things happen**

We must not despair. This is not over till it's over and it's far from that. The 'fat lady' must refuse to sing. The longer the 'Covid' hoax has dragged on and impacted on more lives we have seen an awakening of phenomenal numbers of people worldwide to the realisation that what they have believed all their lives is not how the world really is. Research published by the system-serving University of Bristol and King's College London in February, 2021, concluded: 'One in every 11 people in Britain say they trust David Icke's take on the coronavirus pandemic.' It will be more by now and we have gathering numbers to build on. We must urgently progress from seeing the scam to ceasing to cooperate with it. Prominent German lawyer Reiner Fuellmich, also licenced to practice law in America, is doing a magnificent job taking the legal route to bring the psychopaths to justice through a second Nuremberg tribunal for crimes against humanity. Fuellmich has an impressive record of

beating the elite in court and he formed the German Corona Investigative Committee to pursue civil charges against the main perpetrators with a view to triggering criminal charges. Most importantly he has grasped the foundation of the hoax – the PCR test not testing for the ‘virus’ – and Christian Drosten is therefore on his charge sheet along with Gates frontman Tedros at the World Health Organization. Major players must be not be allowed to inflict their horrors on the human race without being brought to book. A life sentence must follow for Bill Gates and the rest of them. A group of researchers has also indicted the government of Norway for crimes against humanity with copies sent to the police and the International Criminal Court. The lawsuit cites participation in an internationally-planned false pandemic and violation of international law and human rights, the European Commission’s definition of human rights by coercive rules, Nuremberg and Hague rules on fundamental human rights, and the Norwegian constitution. We must take the initiative from hereon and not just complain, protest and react.

There are practical ways to support vital mass non-cooperation. Organising in numbers is one. Lockdown marches in London in the spring in 2021 were mass non-cooperation that the authorities could not stop. There were too many people. Hundreds of thousands walked the London streets in the centre of the road for mile after mile while the Face-Nappies could only look on. They were determined, but calm, and just *did it* with no histrionics and lots of smiles. The police were impotent. Others are organising group shopping without masks for mutual support and imagine if that was happening all over. Policing it would be impossible. If the store refuses to serve people in these circumstances they would be faced with a long line of trolleys full of goods standing on their own and everything would have to be returned to the shelves. How would they cope with that if it kept happening? I am talking here about moving on from complaining to being pro-active; from watching things happen to making things happen. I include in this our relationship with the police. The behaviour of many Face-Nappies

has been disgraceful and anyone who thinks they would never find concentration camp guards in the ‘enlightened’ modern era have had that myth busted big-time. The period and setting may change – Wetikos never do. I watched film footage from a London march in which a police thug viciously kicked a protestor on the floor who had done nothing. His fellow Face-Nappies stood in a ring protecting him. What he did was a criminal assault and with a crowd far outnumbering the police this can no longer be allowed to happen unchallenged. I get it when people chant ‘shame on you’ in these circumstances, but that is no longer enough. They *have* no shame those who do this. Crowds needs to start making a citizen’s arrest of the police who commit criminal offences and brutally attack innocent people and defenceless women. A citizen’s arrest can be made under section 24A of the UK Police and Criminal Evidence (PACE) Act of 1984 and you will find something similar in other countries. I prefer to call it a Common Law arrest rather than citizen’s for reasons I will come to shortly. Anyone can arrest a person committing an indictable offence or if they have reasonable grounds to suspect they are committing an indictable offence. On both counts the attack by the police thug would have fallen into this category. A citizen’s arrest can be made to stop someone:

- Causing physical injury to himself or any other person
- Suffering physical injury
- Causing loss of or damage to property
- Making off before a constable can assume responsibility for him

A citizen’s arrest may also be made to prevent a breach of the peace under Common Law and if they believe a breach of the peace will happen or anything related to harm likely to be done or already done in their presence. This is the way to go I think – the Common Law version. If police know that the crowd and members of the public will no longer be standing and watching while they commit

their thuggery and crimes they will think twice about acting like Brownshirts and Blackshirts.

## **Common Law – common sense**

Mention of Common Law is very important. Most people think the law is the law as in one law. This is not the case. There are two bodies of law, Common Law and Statute Law, and they are not the same. Common Law is founded on the simple premise of do no harm. It does not recognise victimless crimes in which no harm is done while Statute Law does. There is a Statute Law against almost everything. So what is Statute Law? Amazingly it's the law of the sea that was brought ashore by the Cult to override the law of the land which is Common Law. They had no right to do this and as always they did it anyway. They had to. They could not impose their will on the people through Common Law which only applies to do no harm. How could you stitch up the fine detail of people's lives with that? Instead they took the law of the sea, or Admiralty Law, and applied it to the population. Statute Law refers to all the laws spewing out of governments and their agencies including all the fascist laws and regulations relating to 'Covid'. The key point to make is that Statute Law is *contract law*. It only applies between *contracting* corporations. Most police officers don't even know this. They have to be kept in the dark, too. Long ago when merchants and their sailing ships began to trade with different countries a contractual law was developed called Admiralty Law and other names. Again it only applied to *contracts* agreed between *corporate* entities. If there is no agreed contract the law of the sea had no jurisdiction *and that still applies to its new alias of Statute Law*. The problem for the Cult when the law of the sea was brought ashore was an obvious one. People were not corporations and neither were government entities. To overcome the latter they made governments and all associated organisations corporations. All the institutions are *private corporations* and I mean governments and their agencies, local councils, police, courts, military, US states, the whole lot. Go to the

Dun and Bradstreet corporate listings website for confirmation that they are all corporations. You are arrested by a private corporation called the police by someone who is really a private security guard and they take you to court which is another private corporation.

Neither have jurisdiction over you unless you consent and *contract* with them. This is why you hear the mantra about law enforcement policing by *consent* of the people. In truth the people 'consent' only in theory through monumental trickery.

Okay, the Cult overcame the corporate law problem by making governments and institutions corporate entities; but what about people? They are not corporations are they? Ah ... well in a sense, and *only* a sense, they are. Not people exactly – the illusion of people. The Cult creates a corporation in the name of everyone at the time that their birth certificate is issued. Note birth/ *berth* certificate and when you go to court under the law of the sea on land you stand in a *dock*. These are throwbacks to the origin. My Common Law name is David Vaughan Icke. The name of the corporation created by the government when I was born is called Mr David Vaughan Icke usually written in capitals as MR DAVID VAUGHAN ICKE. That is not me, the living, breathing man. It is a fictitious corporate entity. The trick is to make you think that David Vaughan Icke and MR DAVID VAUGHAN ICKE are the same thing. *They are not*. When police charge you and take you to court they are prosecuting the corporate entity and not the living, breathing, man or woman. They have to trick you into identifying as the corporate entity and contracting with them. Otherwise they have no jurisdiction. They do this through a language known as legalese. Lawful and legal are not the same either. Lawful relates to Common Law and legal relates to Statute Law. Legalese is the language of Statue Law which uses terms that mean one thing to the public and another in legalese. Notice that when a police officer tells someone why they are being charged he or she will say at the end: 'Do you understand?' To the public that means 'Do you comprehend?' In legalese it means 'Do you stand under me?' Do you stand under my authority? If you say

yes to the question you are unknowingly agreeing to give them jurisdiction over you in a contract between two corporate entities.

This is a confidence trick in every way. Contracts have to be agreed between informed parties and if you don't know that David Vaughan Icke is agreeing to be the corporation MR DAVID VAUGHAN ICKE you cannot knowingly agree to contract. They are deceiving you and another way they do this is to ask for proof of identity. You usually show them a driving licence or other document on which your corporate name is written. In doing so you are accepting that you are that corporate entity when you are not. Referring to yourself as a 'person' or 'citizen' is also identifying with your corporate fiction which is why I made the Common Law point about the citizen's arrest. If you are approached by a police officer you identify yourself immediately as a living, breathing, man or woman and say 'I do not consent, I do not contract with you and I do not understand' or stand under their authority. I have a Common Law birth certificate as a living man and these are available at no charge from [commonlawcourt.com](http://commonlawcourt.com). Businesses registered under the Statute Law system means that its laws apply. There are, however, ways to run a business under Common Law. Remember all 'Covid' laws and regulations are Statute Law – the law of *contracts* and you do not have to contract. This doesn't mean that you can kill someone and get away with it. Common Law says do no harm and that applies to physical harm, financial harm etc. Police are employees of private corporations and there needs to be a new system of non-corporate Common Law constables operating outside the Statute Law system. If you go to [davidicke.com](http://davidicke.com) and put Common Law into the search engine you will find videos that explain Common Law in much greater detail. It is definitely a road we should walk.

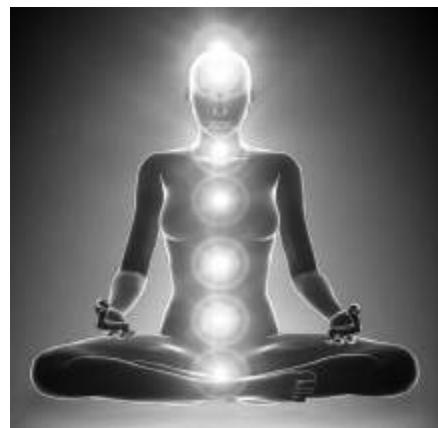
## **With all my heart**

I have heard people say that we are in a spiritual war. I don't like the term 'war' with its Wetiko dynamic, but I know what they mean. Sweep aside all the bodily forms and we are in a situation in which two states of consciousness are seeking very different realities.

Wetiko wants upheaval, chaos, fear, suffering, conflict and control. The other wants love, peace, harmony, fairness and freedom. That's where we are. We should not fall for the idea that Wetiko is all-powerful and there's nothing we can do. Wetiko is not all-powerful. It's a joke, pathetic. It doesn't have to be, but it has made that choice for now. A handful of times over the years when I have felt the presence of its frequency I have allowed it to attach briefly so I could consciously observe its nature. The experience is not pleasant, the energy is heavy and dark, but the ease with which you can kick it back out the door shows that its real power is in persuading us that it has power. It's all a con. Wetiko is a con. It's a trickster and not a power that can control us if we unleash our own. The con is founded on manipulating humanity to give its power to Wetiko which recycles it back to present the illusion that it has power when its power is *ours* that we gave away. This happens on an energetic level and plays out in the world of the seen as humanity giving its power to Wetiko authority which uses that power to control the population when the power is only the power the population has handed over. How could it be any other way for billions to be controlled by a relative few? I have had experiences with people possessed by Wetiko and again you can kick its arse if you do it with an open heart. Oh yes – the *heart* which can transform the world of perceived 'matter'.

We are receiver-transmitters and processors of information, but what information and where from? Information is processed into perception in three main areas – the brain, the heart and the belly. These relate to thinking, knowing, and emotion. Wetiko wants us to be head and belly people which means we think within the confines of the Matrix simulation and low-vibrational emotional reaction scrambles balance and perception. A few minutes on social media and you see how emotion is the dominant force. Woke is all emotion and is therefore thought-free and fact-free. Our heart is something different. It *knows* while the head *thinks* and has to try to work it out because it doesn't know. The human energy field has seven prime vortexes which connect us with wider reality ([Fig 23](#)). Chakra means

'wheels of light' in the Sanskrit language of ancient India. The main ones are: The crown chakra on top of the head; brow (or 'third eye') chakra in the centre of the forehead; throat chakra; heart chakra in the centre of the chest; solar plexus chakra below the sternum; sacral chakra beneath the navel; and base chakra at the bottom of the spine. Each one has a particular function or functions. We feel anxiety and nervousness in the belly where the sacral chakra is located and this processes emotion that can affect the colon to give people 'the shits' or make them 'shit scared' when they are nervous. Chakras all play an important role, but the Mr and Mrs Big is the heart chakra which sits at the centre of the seven, above the chakras that connect us to the 'physical' and below those that connect with higher realms (or at least should). Here in the heart chakra we feel love, empathy and compassion – 'My heart goes out to you'. Those with closed hearts become literally 'heart-less' in their attitudes and behaviour (see Bill Gates). Native Americans portrayed Wetiko with what Paul Levy calls a 'frigid, icy heart, devoid of mercy' (see Bill Gates).



**Figure 23:** The chakra system which interpenetrates the human energy field. The heart chakra is the governor – or should be.

Wetiko trembles at the thought of heart energy which it cannot infiltrate. The frequency is too high. What it seeks to do instead is close the heart chakra vortex to block its perceptual and energetic influence. Psychopaths have 'hearts of stone' and emotionally-damaged people have 'heartache' and 'broken hearts'. The astonishing amount of heart disease is related to heart chakra

disruption with its fundamental connection to the ‘physical’ heart. Dr Tom Cowan has written an outstanding book challenging the belief that the heart is a pump and making the connection between the ‘physical’ and spiritual heart. Rudolph Steiner who was way ahead of his time said the same about the fallacy that the heart is a pump. *What?* The heart is not a pump? That’s crazy, right? Everybody knows that. Read Cowan’s *Human Heart, Cosmic Heart* and you will realise that the very idea of the heart as a pump is ridiculous when you see the evidence. How does blood in the feet so far from the heart get pumped horizontally up the body by the heart?? Cowan explains in the book the real reason why blood moves as it does. Our ‘physical’ heart is used to symbolise love when the source is really the heart vortex or spiritual heart which is our most powerful energetic connection to ‘out there’ expanded consciousness. That’s why we feel *knowing* – intuitive knowing – in the centre of the chest. Knowing doesn’t come from a process of thoughts leading to a conclusion. It is there in an instant all in one go. Our heart knows because of its connection to levels of awareness that *do* know. This is the meaning and source of intuition – intuitive *knowing*.

For the last more than 30 years of uncovering the global game and the nature of reality my heart has been my constant antenna for truth and accuracy. An American intelligence insider once said that I had quoted a disinformor in one of my books and yet I had only quoted the part that was true. He asked: ‘How do you do that?’ By using my heart antenna was the answer and anyone can do it. Heart-centred is how we are meant to be. With a closed heart chakra we withdraw into a closed mind and the bubble of five-sense reality. If you take a moment to focus your attention on the centre of your chest, picture a spinning wheel of light and see it opening and expanding. You will feel it happening, too, and perceptions of the heart like joy and love as the heart impacts on the mind as they interact. The more the chakra opens the more you will feel expressions of heart consciousness and as the process continues, and becomes part of you, insights and knowings will follow. An open

heart is connected to that level of awareness that knows all is *One*. You will see from its perspective that the fault-lines that divide us are only illusions to control us. An open heart does not process the illusions of race, creed and sexuality except as brief experiences for a consciousness that is all. Our heart does not see division, only unity (Figs 24 and 25). There's something else, too. Our hearts love to laugh. Mark Twain's quote that says 'The human race has one really effective weapon, and that is laughter' is really a reference to the heart which loves to laugh with the joy of knowing the true nature of infinite reality and that all the madness of human society is an illusion of the mind. Twain also said: 'Against the assault of laughter nothing can stand.' This is so true of Wetiko and the Cult. Their insecurity demands that they be taken seriously and their power and authority acknowledged and feared. We should do nothing of the sort. We should not get aggressive or fearful which their insecurity so desires. We should laugh in their face. Even in their no-face as police come over in their face-nappies and expect to be taken seriously. They don't take themselves seriously looking like that so why should we? Laugh in the face of intimidation. Laugh in the face of tyranny. You will see by its reaction that you have pressed all of its buttons. Wetiko does not know what to do in the face of laughter or when its targets refuse to concede their joy to fear. We have seen many examples during the 'Covid' hoax when people have expressed their energetic power and the string puppets of Wetiko retreat with their tail limp between their knees. Laugh – the world is bloody mad after all and if it's a choice between laughter and tears I know which way I'm going.



**Figure 24:** Head consciousness without the heart sees division and everything apart from everything else.



**Figure 25:** Heart consciousness sees everything as One.

## **Vaccines' and the soul**

The foundation of Wetiko/Archon control of humans is the separation of incarnate five-sense mind from the infinite 'I' and closing the heart chakra where the True 'I' lives during a human life. The goal has been to achieve complete separation in both cases. I was interested therefore to read an account by a French energetic healer of what she said she experienced with a patient who had been given the 'Covid' vaccine. Genuine energy healers can sense information and consciousness fields at different levels of being which are referred to as 'subtle bodies'. She described treating the patient who later returned after having, without the healer's knowledge, two doses of the 'Covid vaccine'. The healer said:

I noticed immediately the change, very heavy energy emanating from [the] subtle bodies. The scariest thing was when I was working on the heart chakra, I connected with her soul: it was detached from the physical body, it had no contact and it was, as if it was floating in a state of total confusion: a damage to the consciousness that loses contact with the physical body, i.e. with our biological machine, there is no longer any communication between them.

I continued the treatment by sending light to the heart chakra, the soul of the person, but it seemed that the soul could no longer receive any light, frequency or energy. It was a very powerful experience for me. Then I understood that this substance is indeed used to detach consciousness so that this consciousness can no longer interact through this body that it possesses in life, where there is no longer any contact, no frequency, no light, no more energetic balance or mind.

This would create a human that is rudderless and at the extreme almost zombie-like operating with a fractional state of consciousness at the mercy of Wetiko. I was especially intrigued by what the healer said in the light of the prediction by the highly-informed Rudolf Steiner more than a hundred years ago. He said:

In the future, we will eliminate the soul with medicine. Under the pretext of a 'healthy point of view', there will be a vaccine by which the human body will be treated as soon as possible directly at birth, so that the human being cannot develop the thought of the existence of soul and Spirit. To materialistic doctors will be entrusted the task of removing the soul of humanity.

As today, people are vaccinated against this disease or that disease, so in the future, children will be vaccinated with a substance that can be produced precisely in such a way that people, thanks to this vaccination, will be immune to being subjected to the 'madness' of spiritual life. He would be extremely smart, but he would not develop a conscience, and that is the true goal of some materialistic circles.

Steiner said the vaccine would detach the physical body from the etheric body (subtle bodies) and 'once the etheric body is detached the relationship between the universe and the etheric body would become extremely unstable, and man would become an automaton'. He said 'the physical body of man must be polished on this Earth by spiritual will – so the vaccine becomes a kind of arymanique (Wetiko) force' and 'man can no longer get rid of a given materialistic feeling'. Humans would then, he said, become 'materialistic of constitution and can no longer rise to the spiritual'. I have been writing for years about DNA being a receiver-transmitter of information that connects us to other levels of reality and these 'vaccines' changing DNA can be likened to changing an antenna and what it can transmit and receive. Such a disconnection would clearly lead to changes in personality and perception. Steiner further predicted the arrival of AI. Big Pharma 'Covid vaccine' makers, expressions of Wetiko, are testing their DNA-manipulating evil on children as I write with a view to giving the 'vaccine' to babies. If it's a soul-body disconnecter – and I say that it is or can be – every child would be disconnected from 'soul' at birth and the 'vaccine' would create a closed system in which spiritual guidance from the greater self would play no part. This has been the ambition of Wetiko all

along. A Pentagon video from 2005 was leaked of a presentation explaining the development of vaccines to change behaviour by their effect on the brain. Those that believe this is not happening with the 'Covid' genetically-modifying procedure masquerading as a 'vaccine' should make an urgent appointment with Naivety Anonymous. Klaus Schwab wrote in 2018:

Neurotechnologies enable us to better influence consciousness and thought and to understand many activities of the brain. They include decoding what we are thinking in fine levels of detail through new chemicals and interventions that can influence our brains to correct for errors or enhance functionality.

The plan is clear and only the heart can stop it. With every heart that opens, every mind that awakens, Wetiko is weakened. Heart and love are far more powerful than head and hate and so nothing like a majority is needed to turn this around.

## **Beyond the Phantom**

Our heart is the prime target of Wetiko and so it must be the answer to Wetiko. We *are* our heart which is part of one heart, the infinite heart. Our heart is where the true self lives in a human life behind firewalls of five-sense illusion when an imposter takes its place – *Phantom Self*; but our heart waits patiently to be set free any time we choose to see beyond the Phantom, beyond Wetiko. A Wetikoed Phantom Self can wreak mass death and destruction while the love of forever is locked away in its heart. The time is here to unleash its power and let it sweep away the fear and despair that is Wetiko. Heart consciousness does not seek manipulated, censored, advantage for its belief or religion, its activism and desires. As an expression of the One it treats all as One with the same rights to freedom and opinion. Our heart demands fairness for itself no more than for others. From this unity of heart we can come together in mutual support and transform this Wetikoed world into what reality is meant to be – a place of love, joy, happiness, fairness, justice and freedom. Wetiko has another agenda and that's why the world is as

it is, but enough of this nonsense. Wetiko can't stay where hearts are open and it works so hard to keep them closed. Fear is its currency and its food source and love in its true sense has no fear. Why would love have fear when it knows it is *All That Is, Has Been, And Ever Can Be* on an eternal exploration of all possibility? Love in this true sense is not the physical attraction that passes for love. This can be an expression of it, yes, but Infinite Love, a love without condition, goes far deeper to the core of all being. It is the core of all being. Infinite reality was born from love beyond the illusions of the simulation. Love infinitely expressed is the knowing that all is One and the swiftly-passing experience of separation is a temporary hallucination. You cannot disconnect from Oneness; you can only perceive that you have and withdraw from its influence. This is the most important of all perception trickery by the mind parasite that is Wetiko and the foundation of all its potential for manipulation.

If we open our hearts, open the sluice gates of the mind, and redefine self-identity amazing things start to happen. Consciousness expands or contracts in accordance with self-identity. When true self is recognised as infinite awareness and label self – Phantom Self – is seen as only a series of brief experiences life is transformed. Consciousness expands to the extent that self-identity expands and everything changes. You see unity, not division, the picture, not the pixels. From this we can play the long game. No more is an experience something in and of itself, but a fleeting moment in the eternity of forever. Suddenly people in uniform and dark suits are no longer intimidating. Doing what your heart knows to be right is no longer intimidating and consequences for those actions take on the same nature of a brief experience that passes in the blink of an infinite eye. Intimidation is all in the mind. Beyond the mind there is no intimidation.

An open heart does not consider consequences for what it knows to be right. To do so would be to consider not doing what it knows to be right and for a heart in its power that is never an option. The Renegade Mind is really the Renegade Heart. Consideration of consequences will always provide a getaway car for the mind and

the heart doesn't want one. What is right in the light of what we face today is to stop cooperating with Wetiko in all its forms and to do it without fear or compromise. You cannot compromise with tyranny when tyranny always demands more until it has everything. Life is your perception and you are your destiny. Change your perception and you change your life. Change collective perception and we change the world.

*Come on people ... One human family, One heart, One goal ...  
FREEEEEDOM!*

We must settle for nothing less.

## **Postscript**

**T**he big scare story as the book goes to press is the ‘Indian’ variant and the world is being deluged with propaganda about the ‘Covid catastrophe’ in India which mirrors in its lies and misrepresentations what happened in Italy before the first lockdown in 2020.

The *New York Post* published a picture of someone who had ‘collapsed in the street from Covid’ in India in April, 2021, which was actually taken during a gas leak in May, 2020. Same old, same old. Media articles in mid-February were asking why India had been so untouched by ‘Covid’ and then as their vaccine rollout gathered pace the alleged ‘cases’ began to rapidly increase. Indian ‘Covid vaccine’ maker Bharat Biotech was funded into existence by the Bill and Melinda Gates Foundation (the pair announced their divorce in May, 2021, which is a pity because they so deserve each other). The Indian ‘Covid crisis’ was ramped up by the media to terrify the world and prepare people for submission to still more restrictions. The scam that worked the first time was being repeated only with far more people seeing through the deceit. [Davidicke.com](http://Davidicke.com) and [Ickonic.com](http://Ickonic.com) have sought to tell the true story of what is happening by talking to people living through the Indian nightmare which has nothing to do with ‘Covid’. We posted a letter from ‘Alisha’ in Pune who told a very different story to government and media mendacity. She said scenes of dying people and overwhelmed hospitals were designed to hide what was really happening – genocide and starvation. Alisha said that millions had already died of starvation during the ongoing lockdowns while government and media were lying and making it look like the ‘virus’:

Restaurants, shops, gyms, theatres, basically everything is shut. The cities are ghost towns. Even so-called 'essential' businesses are only open till 11am in the morning. You basically have just an hour to buy food and then your time is up.

Inter-state travel and even inter-district travel is banned. The cops wait at all major crossroads to question why you are traveling outdoors or to fine you if you are not wearing a mask.

The medical community here is also complicit in genocide, lying about hospitals being full and turning away people with genuine illnesses, who need immediate care. They have even created a shortage of oxygen cylinders.

This is the classic Cult modus operandi played out in every country. Alisha said that people who would not have a PCR test not testing for the 'virus' were being denied hospital treatment. She said the people hit hardest were migrant workers and those in rural areas. Most businesses employed migrant workers and with everything closed there were no jobs, no income and no food. As a result millions were dying of starvation or malnutrition. All this was happening under Prime Minister Narendra Modi, a 100-percent asset of the Cult, and it emphasises yet again the scale of pure anti-human evil we are dealing with. Australia banned its people from returning home from India with penalties for trying to do so of up to five years in jail and a fine of £37,000. The manufactured 'Covid' crisis in India was being prepared to justify further fascism in the West. Obvious connections could be seen between the Indian 'vaccine' programme and increased 'cases' and this became a common theme. The Seychelles, the most per capita 'Covid vaccinated' population in the world, went back into lockdown after a 'surge of cases'.

Long ago the truly evil Monsanto agricultural biotechnology corporation with its big connections to Bill Gates devastated Indian farming with genetically-modified crops. Human rights activist Gurcharan Singh highlighted the efforts by the Indian government to complete the job by destroying the food supply to hundreds of millions with 'Covid' lockdowns. He said that 415 million people at the bottom of the disgusting caste system (still going whatever they say) were below the poverty line and struggled to feed themselves every year. Now the government was imposing lockdown at just the

time to destroy the harvest. This deliberate policy was leading to mass starvation. People may reel back at the suggestion that a government would do that, but Wetiko-controlled ‘leaders’ are capable of any level of evil. In fact what is described in India is in the process of being instigated worldwide. The food chain and food supply are being targeted at every level to cause world hunger and thus control. Bill Gates is not the biggest owner of farmland in America for no reason and destroying access to food aids both the depopulation agenda and the plan for synthetic ‘food’ already being funded into existence by Gates. Add to this the coming hyper-inflation from the suicidal creation of fake ‘money’ in response to ‘Covid’ and the breakdown of container shipping systems and you have a cocktail that can only lead one way and is meant to. The Cult plan is to crash the entire system to ‘build back better’ with the Great Reset.

## **'Vaccine' transmission**

Reports from all over the world continue to emerge of women suffering menstrual and fertility problems after having the fake ‘vaccine’ and of the non-‘vaccinated’ having similar problems when interacting with the ‘vaccinated’. There are far too many for ‘coincidence’ to be credible. We’ve had menopausal women getting periods, others having periods stop or not stopping for weeks, passing clots, sometimes the lining of the uterus, breast irregularities, and miscarriages (which increased by 400 percent in parts of the United States). Non-‘vaccinated’ men and children have suffered blood clots and nose bleeding after interaction with the ‘vaccinated’. Babies have died from the effects of breast milk from a ‘vaccinated’ mother. Awake doctors – the small minority – speculated on the cause of non-‘vaccinated’ suffering the same effects as the ‘vaccinated’. Was it nanotechnology in the synthetic substance transmitting frequencies or was it a straight chemical bioweapon that was being transmitted between people? I am not saying that some kind of chemical transmission is not one possible answer, but the foundation of all that the Cult does is frequency and

this is fertile ground for understanding how transmission can happen. American doctor Carrie Madej, an internal medicine physician and osteopath, has been practicing for the last 20 years, teaching medical students, and she says attending different meetings where the agenda for humanity was discussed. Madej, who operates out of Georgia, did not dismiss other possible forms of transmission, but she focused on frequency in search of an explanation for transmission. She said the Moderna and Pfizer 'vaccines' contained nano-lipid particles as a key component. This was a brand new technology never before used on humanity. 'They're using a nanotechnology which is pretty much little tiny computer bits ... nanobots or hydrogel.' Inside the 'vaccines' was 'this sci-fi kind of substance' which suppressed immune checkpoints to get into the cell. I referred to this earlier as the 'Trojan horse' technique that tricks the cell into opening a gateway for the self-replicating synthetic material and while the immune system is artificially suppressed the body has no defences. Madej said the substance served many purposes including an on-demand ability to 'deliver the payload' and using the nano 'computer bits' as biosensors in the body. 'It actually has the ability to accumulate data from your body, like your breathing, your respiration, thoughts, emotions, all kinds of things.'

She said the technology obviously has the ability to operate through Wi-Fi and transmit and receive energy, messages, frequencies or impulses. 'Just imagine you're getting this new substance in you and it can react to things all around you, the 5G, your smart device, your phones.' We had something completely foreign in the human body that had never been launched large scale at a time when we were seeing 5G going into schools and hospitals (plus the Musk satellites) and she believed the 'vaccine' transmission had something to do with this: '... if these people have this inside of them ... it can act like an antenna and actually transmit it outwardly as well.' The synthetic substance produced its own voltage and so it could have that kind of effect. This fits with my own contention that the nano receiver-transmitters are designed to connect people to the

Smart Grid and break the receiver-transmitter connection to expanded consciousness. That would explain the French energy healer's experience of the disconnection of body from 'soul' with those who have had the 'vaccine'. The nanobots, self-replicating inside the body, would also transmit the synthetic frequency which could be picked up through close interaction by those who have not been 'vaccinated'. Madej speculated that perhaps it was 5G and increased levels of other radiation that was causing the symptoms directly although interestingly she said that non-'vaccinated' patients had shown improvement when they were away from the 'vaccinated' person they had interacted with. It must be remembered that you can control frequency and energy with your mind and you can consciously create energetic barriers or bubbles with the mind to stop damaging frequencies from penetrating your field. American paediatrician Dr Larry Palevsky said the 'vaccine' was not a 'vaccine' and was never designed to protect from a 'viral' infection. He called it 'a massive, brilliant propaganda of genocide' because they didn't have to inject everyone to get the result they wanted. He said the content of the jabs was able to infuse any material into the brain, heart, lungs, kidneys, liver, sperm and female productive system. 'This is genocide; this is a weapon of mass destruction.' At the same time American colleges were banning students from attending if they didn't have this life-changing and potentially life-ending 'vaccine'. Class action lawsuits must follow when the consequences of this college fascism come to light. As the book was going to press came reports about fertility effects on sperm in 'vaccinated' men which would absolutely fit with what I have been saying and hospitals continued to fill with 'vaccine' reactions. Another question is what about transmission via blood transfusions? The NHS has extended blood donation restrictions from seven days after a 'Covid vaccination' to 28 days after even a sore arm reaction.

I said in the spring of 2020 that the then touted 'Covid vaccine' would be ongoing each year like the flu jab. A year later Pfizer CEO, the appalling Albert Bourla, said people would 'likely' need a 'booster dose' of the 'vaccine' within 12 months of getting 'fully

'vaccinated' and then a yearly shot. 'Variants will play a key role', he said confirming the point. Johnson & Johnson CEO Alex Gorsky also took time out from his 'vaccine' disaster to say that people may need to be vaccinated against 'Covid-19' each year. UK Health Secretary, the psychopath Matt Hancock, said additional 'boosters' would be available in the autumn of 2021. This is the trap of the 'vaccine passport'. The public will have to accept every last 'vaccine' they introduce, including for the fake 'variants', or it would cease to be valid. The only other way in some cases would be continuous testing with a test not testing for the 'virus' and what is on the swabs constantly pushed up your noise towards the brain every time?

## **'Vaccines' changing behaviour**

I mentioned in the body of the book how I believed we would see gathering behaviour changes in the 'vaccinated' and I am already hearing such comments from the non-'vaccinated' describing behaviour changes in friends, loved ones and work colleagues. This will only increase as the self-replicating synthetic material and nanoparticles expand in body and brain. An article in the *Guardian* in 2016 detailed research at the University of Virginia in Charlottesville which developed a new method for controlling brain circuits associated with complex animal behaviour. The method, dubbed 'magnetogenetics', involves genetically-engineering a protein called ferritin, which stores and releases iron, to create a magnetised substance – 'Magneto' – that can activate specific groups of nerve cells from a distance. This is claimed to be an advance on other methods of brain activity manipulation known as optogenetics and chemogenetics (the Cult has been developing methods of brain control for a long time). The ferritin technique is said to be non-invasive and able to activate neurons 'rapidly and reversibly'. In other words, human thought and perception. The article said that earlier studies revealed how nerve cell proteins 'activated by heat and mechanical pressure can be genetically engineered so that they become sensitive to radio waves and magnetic fields, by attaching them to an iron-storing protein called ferritin, or to inorganic

paramagnetic particles'. Sensitive to radio waves and magnetic fields? You mean like 5G, 6G and 7G? This is the human-AI Smart Grid hive mind we are talking about. The *Guardian* article said:

... the researchers injected Magneto into the striatum of freely behaving mice, a deep brain structure containing dopamine-producing neurons that are involved in reward and motivation, and then placed the animals into an apparatus split into magnetised and non-magnetised sections.

Mice expressing Magneto spent far more time in the magnetised areas than mice that did not, because activation of the protein caused the striatal neurons expressing it to release dopamine, so that the mice found being in those areas rewarding. This shows that Magneto can remotely control the firing of neurons deep within the brain, and also control complex behaviours.

Make no mistake this basic methodology will be part of the 'Covid vaccine' cocktail and using magnetics to change brain function through electromagnetic field frequency activation. The Pentagon is developing a 'Covid vaccine' using ferritin. Magnetics would explain changes in behaviour and why videos are appearing across the Internet as I write showing how magnets stick to the skin at the point of the 'vaccine' shot. Once people take these 'vaccines' anything becomes possible in terms of brain function and illness which will be blamed on 'Covid-19' and 'variants'. Magnetic field manipulation would further explain why the non-'vaccinated' are reporting the same symptoms as the 'vaccinated' they interact with and why those symptoms are reported to decrease when not in their company. Interestingly 'Magneto', a 'mutant', is a character in the Marvel Comic *X-Men* stories with the ability to manipulate magnetic fields and he believes that mutants should fight back against their human oppressors by any means necessary. The character was born Erik Lehnsherr to a Jewish family in Germany.

## Cult-controlled courts

The European Court of Human Rights opened the door for mandatory 'Covid-19 vaccines' across the continent when it ruled in a Czech Republic dispute over childhood immunisation that legally

enforced vaccination could be ‘necessary in a democratic society’. The 17 judges decided that compulsory vaccinations did not breach human rights law. On the face of it the judgement was so inverted you gasp for air. If not having a vaccine infused into your body is not a human right then what is? Ah, but they said human rights law which has been specifically written to delete all human rights at the behest of the state (the Cult). Article 8 of the European Convention on Human Rights relates to the right to a private life. The crucial word here is ‘*except*’:

There shall be no interference by a public authority with the exercise of this right EXCEPT such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic wellbeing of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others [My emphasis].

No interference *except* in accordance with the law means there *are* no ‘human rights’ *except* what EU governments decide you can have at their behest. ‘As is necessary in a democratic society’ explains that reference in the judgement and ‘in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others’ gives the EU a coach and horses to ride through ‘human rights’ and scatter them in all directions. The judiciary is not a check and balance on government extremism; it is a vehicle to enforce it. This judgement was almost laughably predictable when the last thing the Cult wanted was a decision that went against mandatory vaccination. Judges rule over and over again to benefit the system of which they are a part. Vaccination disputes that come before them are invariably delivered in favour of doctors and authorities representing the view of the state which owns the judiciary. Oh, yes, and we have even had calls to stop putting ‘Covid-19’ on death certificates within 28 days of a ‘positive test’ because it is claimed the practice makes the ‘vaccine’ appear not to work. They are laughing at you.

The scale of madness, inhumanity and things to come was highlighted when those not ‘vaccinated’ for ‘Covid’ were refused evacuation from the Caribbean island of St Vincent during massive volcanic eruptions. Cruise ships taking residents to the safety of another island allowed only the ‘vaccinated’ to board and the rest were left to their fate. Even in life and death situations like this we see ‘Covid’ stripping people of their most basic human instincts and the insanity is even more extreme when you think that fake ‘vaccine’-makers are not even claiming their body-manipulating concoctions stop ‘infection’ and ‘transmission’ of a ‘virus’ that doesn’t exist. St Vincent Prime Minister Ralph Gonsalves said: ‘The chief medical officer will be identifying the persons already vaccinated so that we can get them on the ship.’ Note again the power of the chief medical officer who, like Whitty in the UK, will be answering to the World Health Organization. This is the Cult network structure that has overridden politicians who ‘follow the science’ which means doing what WHO-controlled ‘medical officers’ and ‘science advisers’ tell them. Gonsalves even said that residents who were ‘vaccinated’ after the order so they could board the ships would still be refused entry due to possible side effects such as ‘wooziness in the head’. The good news is that if they were woozy enough in the head they could qualify to be prime minister of St Vincent.

## **Microchipping freedom**

The European judgement will be used at some point to justify moves to enforce the ‘Covid’ DNA-manipulating procedure. Sandra Ro, CEO of the Global Blockchain Business Council, told a World Economic Forum event that she hoped ‘vaccine passports’ would help to ‘drive forced consent and standardisation’ of global digital identity schemes: ‘I’m hoping with the desire and global demand for some sort of vaccine passport – so that people can get travelling and working again – [it] will drive forced consent, standardisation, and frankly, cooperation across the world.’ The lady is either not very bright, or thoroughly mendacious, to use the term ‘forced consent’.

You do not ‘consent’ if you are forced – you *submit*. She was describing what the plan has been all along and that’s to enforce a digital identity on every human without which they could not function. ‘Vaccine passports’ are opening the door and are far from the end goal. A digital identity would allow you to be tracked in everything you do in cyberspace and this is the same technique used by Cult-owned China to enforce its social credit system of total control. The ultimate ‘passport’ is planned to be a microchip as my books have warned for nearly 30 years. Those nice people at the Pentagon working for the Cult-controlled Defense Advanced Research Projects Agency (DARPA) claimed in April, 2021, they have developed a microchip inserted under the skin to detect ‘asymptomatic Covid-19 infection’ before it becomes an outbreak and a ‘revolutionary filter’ that can remove the ‘virus’ from the blood when attached to a dialysis machine. The only problems with this are that the ‘virus’ does not exist and people transmitting the ‘virus’ with no symptoms is brain-numbing bullshit. This is, of course, not a ruse to get people to be microchipped for very different reasons. DARPA also said it was producing a one-stop ‘vaccine’ for the ‘virus’ and all ‘variants’. One of the most sinister organisations on Planet Earth is doing this? Better have it then. These people are insane because Wetiko that possesses them is insane.

Researchers from the Salk Institute in California announced they have created an embryo that is part human and part monkey. My books going back to the 1990s have exposed experiments in top secret underground facilities in the United States where humans are being crossed with animal and non-human ‘extraterrestrial’ species. They are now easing that long-developed capability into the public arena and there is much more to come given we are dealing with psychiatric basket cases. Talking of which – Elon Musk’s scientists at Neuralink trained a monkey to play Pong and other puzzles on a computer screen using a joystick and when the monkey made the correct move a metal tube squirted banana smoothie into his mouth which is the basic technique for training humans into unquestioning compliance. Two Neuralink chips were in the monkey’s skull and

more than 2,000 wires ‘fanned out’ into its brain. Eventually the monkey played a video game purely with its brain waves. Psychopathic narcissist Musk said the ‘breakthrough’ was a step towards putting Neuralink chips into human skulls and merging minds with artificial intelligence. *Exactly.* This man is so dark and Cult to his DNA.

## **World Economic Fascism (WEF)**

The World Economic Forum is telling you the plan by the statements made at its many and various events. Cult-owned fascist YouTube CEO Susan Wojcicki spoke at the 2021 WEF Global Technology Governance Summit (see the name) in which 40 governments and 150 companies met to ensure ‘the responsible design and deployment of emerging technologies’. Orwellian translation: ‘Ensuring the design and deployment of long-planned technologies will advance the Cult agenda for control and censorship.’ Freedom-destroyer and Nuremberg-bound Wojcicki expressed support for tech platforms like hers to censor content that is ‘technically legal but could be harmful’. Who decides what is ‘harmful’? She does and they do. ‘Harmful’ will be whatever the Cult doesn’t want people to see and we have legislation proposed by the UK government that would censor content on the basis of ‘harm’ no matter if the information is fair, legal and provably true. Make that *especially* if it is fair, legal and provably true. Wojcicki called for a global coalition to be formed to enforce content moderation standards through automated censorship. This is a woman and mega-censor so self-deluded that she shamelessly accepted a ‘free expression’ award – *Wojcicki* – in an event sponsored by her own *YouTube*. They have no shame and no self-awareness.

You know that ‘Covid’ is a scam and Wojcicki a Cult operative when YouTube is censoring medical and scientific opinion purely on the grounds of whether it supports or opposes the Cult ‘Covid’ narrative. Florida governor Ron DeSantis compiled an expert panel with four professors of medicine from Harvard, Oxford, and Stanford Universities who spoke against forcing children and

vaccinated people to wear masks. They also said there was no proof that lockdowns reduced spread or death rates of 'Covid-19'. Cult-gofer Wojcicki and her YouTube deleted the panel video 'because it included content that contradicts the consensus of local and global health authorities regarding the efficacy of masks to prevent the spread of Covid-19'. This 'consensus' refers to what the Cult tells the World Health Organization to say and the WHO tells 'local health authorities' to do. Wojcicki knows this, of course. The panellists pointed out that censorship of scientific debate was responsible for deaths from many causes, but Wojcicki couldn't care less. She would not dare go against what she is told and as a disgrace to humanity she wouldn't want to anyway. The UK government is seeking to pass a fascist 'Online Safety Bill' to specifically target with massive fines and other means non-censored video and social media platforms to make them censor 'lawful but harmful' content like the Cult-owned Facebook, Twitter, Google and YouTube. What is 'lawful but harmful' would be decided by the fascist Blair-created Ofcom.

Another WEF obsession is a cyber-attack on the financial system and this is clearly what the Cult has planned to take down the bank accounts of everyone – except theirs. Those that think they have enough money for the Cult agenda not to matter to them have got a big lesson coming if they continue to ignore what is staring them in the face. The World Economic Forum, funded by Gates and fronted by Klaus Schwab, announced it would be running a 'simulation' with the Russian government and global banks of just such an attack called Cyber Polygon 2021. What they simulate – as with the 'Covid' Event 201 – they plan to instigate. The WEF is involved in a project with the Cult-owned Carnegie Endowment for International Peace called the WEF-Carnegie Cyber Policy Initiative which seeks to merge Wall Street banks, 'regulators' (I love it) and intelligence agencies to 'prevent' (arrange and allow) a cyber-attack that would bring down the global financial system as long planned by those that control the WEF and the Carnegie operation. The Carnegie Endowment for International Peace sent an instruction to First World

War US President Woodrow Wilson not to let the war end before society had been irreversibly transformed.

## **The Wuhan lab diversion**

As I close, the Cult-controlled authorities and lapdog media are systematically pushing ‘the virus was released from the Wuhan lab’ narrative. There are two versions – it happened by accident and it happened on purpose. Both are nonsense. The perceived existence of the never-shown-to-exist ‘virus’ is vital to sell the impression that there is actually an infective agent to deal with and to allow the endless potential for terrifying the population with ‘variants’ of a ‘virus’ that does not exist. The authorities at the time of writing are going with the ‘by accident’ while the alternative media is promoting the ‘on purpose’. Cable news host Tucker Carlson who has questioned aspects of lockdown and ‘vaccine’ compulsion has bought the Wuhan lab story. ‘Everyone now agrees’ he said. Well, I don’t and many others don’t and the question is *why* does the system and its media suddenly ‘agree’? When the media moves as one unit with a narrative it is always a lie – witness the hour by hour mendacity of the ‘Covid’ era. Why would this Cult-owned combination which has unleashed lies like machine gun fire suddenly ‘agree’ to tell the truth??

Much of the alternative media is buying the lie because it fits the conspiracy narrative, but it’s the *wrong* conspiracy. The real conspiracy is that *there is no virus* and that is what the Cult is desperate to hide. The idea that the ‘virus’ was released by accident is ludicrous when the whole ‘Covid’ hoax was clearly long-planned and waiting to be played out as it was so fast in accordance with the Rockefeller document and Event 201. So they prepared everything in detail over decades and then sat around strumming their fingers waiting for an ‘accidental’ release from a bio-lab? *What??* It’s crazy. Then there’s the ‘on purpose’ claim. You want to circulate a ‘deadly virus’ and hide the fact that you’ve done so and you release it down the street from the highest-level bio-lab in China? I repeat – *What??*

You would release it far from that lab to stop any association being made. But, no, we'll do it in a place where the connection was certain to be made. Why would you need to scam 'cases' and 'deaths' and pay hospitals to diagnose 'Covid-19' if you had a real 'virus'? What are sections of the alternative media doing believing this crap? Where were all the mass deaths in Wuhan from a 'deadly pathogen' when the recovery to normal life after the initial propaganda was dramatic in speed? Why isn't the 'deadly pathogen' now circulating all over China with bodies in the street? Once again we have the technique of tell them what they want to hear and they will likely believe it. The alternative media has its 'conspiracy' and with Carlson it fits with his 'China is the danger' narrative over years. China *is* a danger as a global Cult operations centre, but not for this reason. The Wuhan lab story also has the potential to instigate conflict with China when at some stage the plan is to trigger a Problem-Reaction-Solution confrontation with the West. Question everything – *everything* – and especially when the media agrees on a common party line.

### **Third wave ... fourth wave ... fifth wave ...**

As the book went into production the world was being set up for more lockdowns and a 'third wave' supported by invented 'variants' that were increasing all the time and will continue to do so in public statements and computer programs, but not in reality. India became the new Italy in the 'Covid' propaganda campaign and we were told to be frightened of the new 'Indian strain'. Somehow I couldn't find it within myself to do so. A document produced for the UK government entitled 'Summary of further modelling of easing of restrictions – Roadmap Step 2' declared that a third wave was inevitable (of course when it's in the script) and it would be the fault of children and those who refuse the health-destroying fake 'Covid vaccine'. One of the computer models involved came from the Cult-owned *Imperial College* and the other from Warwick University which I wouldn't trust to tell me the date in a calendar factory. The document states that both models presumed extremely high uptake

of the ‘Covid vaccines’ and didn’t allow for ‘variants’. The document states: ‘The resurgence is a result of some people (mostly children) being ineligible for vaccination; others choosing not to receive the vaccine; and others being vaccinated but not perfectly protected.’ The mendacity takes the breath away. Okay, blame those with a brain who won’t take the DNA-modifying shots and put more pressure on children to have it as ‘trials’ were underway involving children as young as six months with parents who give insanity a bad name. Massive pressure is being put on the young to have the fake ‘vaccine’ and child age consent limits have been systematically lowered around the world to stop parents intervening. Most extraordinary about the document was its claim that the ‘third wave’ would be driven by ‘the resurgence in both hospitalisations and deaths … dominated by *those that have received two doses of the vaccine*, comprising around 60-70% of the wave respectively’. The predicted peak of the ‘third wave’ suggested 300 deaths per day with 250 of them *fully ‘vaccinated’ people*. How many more lies do acquiescers need to be told before they see the obvious? Those who took the jab to ‘protect themselves’ are projected to be those who mostly get sick and die? So what’s in the ‘vaccine’? The document went on:

It is possible that a summer of low prevalence could be followed by substantial increases in incidence over the following autumn and winter. Low prevalence in late summer should not be taken as an indication that SARS-CoV-2 has retreated or that the population has high enough levels of immunity to prevent another wave.

They are telling you the script and while many British people believed ‘Covid’ restrictions would end in the summer of 2021 the government was preparing for them to be ongoing. Authorities were awarding contracts for ‘Covid marshals’ to police the restrictions with contracts starting in July, 2021, and going through to January 31st, 2022, and the government was advertising for ‘Media Buying Services’ to secure media propaganda slots worth a potential £320 million for ‘Covid-19 campaigns’ with a contract not ending until March, 2022. The recipient – via a list of other front companies – was reported to be American media marketing giant Omnicom Group

Inc. While money is no object for ‘Covid’ the UK waiting list for all other treatment – including life-threatening conditions – passed 4.5 million. Meantime the Cult is seeking to control all official ‘inquiries’ to block revelations about what has really been happening and why. It must not be allowed to – we need Nuremberg jury trials in every country. The cover-up doesn’t get more obvious than appointing ultra-Zionist professor Philip Zelikow to oversee two dozen US virologists, public health officials, clinicians, former government officials and four American ‘charitable foundations’ to ‘learn the lessons’ of the ‘Covid’ debacle. The personnel will be those that created and perpetuated the ‘Covid’ lies while Zelikow is the former executive director of the 9/11 Commission who ensured that the truth about those attacks never came out and produced a report that must be among the most mendacious and manipulative documents ever written – see *The Trigger* for the detailed exposure of the almost unimaginable 9/11 story in which Sabbatians can be found at every level.

## **Passive no more**

People are increasingly challenging the authorities with amazing numbers of people taking to the streets in London well beyond the ability of the Face-Nappies to stop them. Instead the Nappies choose situations away from the mass crowds to target, intimidate, and seek to promote the impression of ‘violent protestors’. One such incident happened in London’s Hyde Park. Hundreds of thousands walking through the streets in protest against ‘Covid’ fascism were ignored by the Cult-owned BBC and most of the rest of the mainstream media, but they delighted in reporting how police were injured in ‘clashes with protestors’. The truth was that a group of people gathered in Hyde Park at the end of one march when most had gone home and they were peacefully having a good time with music and chat. Face-Nappies who couldn’t deal with the full-march crowd then waded in with their batons and got more than they bargained for. Instead of just standing for this criminal brutality the crowd used their numerical superiority to push the Face-Nappies out of the

park. Eventually the Nappies turned and ran. Unfortunately two or three idiots in the crowd threw drink cans striking two officers which gave the media and the government the image they wanted to discredit the 99.9999 percent who were peaceful. The idiots walked straight into the trap and we must always be aware of potential agent provocateurs used by the authorities to discredit their targets.

This response from the crowd – the can people apart – must be a turning point when the public no longer stand by while the innocent are arrested and brutally attacked by the Face-Nappies. That doesn't mean to be violent, that's the last thing we need. We'll leave the violence to the Face-Nappies and government. But it does mean that when the Face-Nappies use violence against peaceful people the numerical superiority is employed to stop them and make citizen's arrests or Common Law arrests for a breach of the peace. The time for being passive in the face of fascism is over.

We are the many, they are the few, and we need to make that count before there is no freedom left and our children and grandchildren face an ongoing fascist nightmare.

*COME ON PEOPLE – IT'S TIME.*

### **One final thought ...**

The power of love  
A force from above  
Cleaning my soul  
Flame on burn desire  
Love with tongues of fire  
Purge the soul  
Make love your goal

I'll protect you from the hooded claw  
Keep the vampires from your door  
When the chips are down I'll be around  
With my undying, death-defying  
Love for you

Envy will hurt itself  
Let yourself be beautiful  
Sparkling love, flowers  
And pearls and pretty girls  
Love is like an energy  
Rushin' rushin' inside of me

This time we go sublime  
Lovers entwine, divine, divine,  
Love is danger, love is pleasure  
Love is pure – the only treasure

I'm so in love with you  
Purge the soul  
Make love your goal

The power of love  
A force from above  
Cleaning my soul  
The power of love  
A force from above  
A sky-scraping dove

Flame on burn desire  
Love with tongues of fire  
Purge the soul  
Make love your goal

**Frankie Goes To Hollywood**

## APPENDIX

### Cowan-Kaufman-Morell Statement on Virus Isolation (SOVI)

*Isolation: The action of isolating; the fact or condition of being isolated or standing alone; separation from other things or persons; solitariness*

Oxford English Dictionary

The controversy over whether the SARS-CoV-2 virus has ever been isolated or purified continues. However, using the above definition, common sense, the laws of logic and the dictates of science, any unbiased person must come to the conclusion that the SARS-CoV-2 virus has never been isolated or purified. As a result, no confirmation of the virus' existence can be found. The logical, common sense, and scientific consequences of this fact are:

- the structure and composition of something not shown to exist can't be known, including the presence, structure, and function of any hypothetical spike or other proteins;
- the genetic sequence of something that has never been found can't be known;
- "variants" of something that hasn't been shown to exist can't be known;
- it's impossible to demonstrate that SARS-CoV-2 causes a disease called Covid-19.

In as concise terms as possible, here's the proper way to isolate, characterize and demonstrate a new virus. First, one takes samples (blood, sputum, secretions) from many people (e.g. 500) with symptoms which are unique and specific enough to characterize an illness. Without mixing these samples with ANY tissue or products that also contain genetic material, the virologist macerates, filters and ultracentrifuges i.e. *purifies* the specimen. This common virology technique, done for decades to isolate bacteriophages<sup>1</sup> and so-called giant viruses in every virology lab, then allows the virologist to demonstrate with electron microscopy thousands of identically sized and shaped particles. These particles are the isolated and purified virus.

These identical particles are then checked for uniformity by physical and/or microscopic techniques. Once the purity is determined, the particles may be further characterized. This would include examining the structure, morphology, and chemical composition of the particles. Next, their genetic makeup is characterized by extracting the genetic material directly from the purified particles and using genetic-sequencing techniques, such as Sanger sequencing, that have also been around for decades. Then one does an analysis to confirm that these uniform particles are exogenous (outside) in origin as a virus is conceptualized to be, and not the normal breakdown products of dead and dying tissues.<sup>2</sup> (As of May 2020, we know that virologists have no way to determine whether the particles they're seeing are viruses or just normal breakdown products of dead and dying tissues.)<sup>3</sup>

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1 Isolation, characterization and analysis of bacteriophages from the haloalkaline lake Elmenteita, KenyaJuliah Khayeli Akhwale et al, PLOS One, Published: April 25, 2019.  
<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0215734> – accessed 2/15/21

2 "Extracellular Vesicles Derived From Apoptotic Cells: An Essential Link Between Death and Regeneration," Maojiao Li et al, Frontiers in Cell and Developmental Biology, 2020 October 2.  
<https://www.frontiersin.org/articles/10.3389/fcell.2020.573511/full> – accessed 2/15/21

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3 "The Role of Extracellular Vesicles as Allies of HIV, HCV and SARS Viruses," Flavia Giannessi, et al, *Viruses*, 2020 May

If we have come this far then we have fully isolated, characterized, and genetically sequenced an exogenous virus particle. However, we still have to show it is causally related to a disease. This is carried out by exposing a group of healthy subjects (animals are usually used) to this isolated, purified virus in the manner in which the disease is thought to be transmitted. If the animals get sick with the same disease, as confirmed by clinical and autopsy findings, one has now shown that the virus actually causes a disease. This demonstrates infectivity and transmission of an infectious agent.

None of these steps has even been attempted with the SARS-CoV-2 virus, nor have all these steps been successfully performed for any so-called pathogenic virus. Our research indicates that a single study showing these steps does not exist in the medical literature.

Instead, since 1954, virologists have taken unpurified samples from a relatively few people, often less than ten, with a similar disease. They then minimally process this sample and inoculate this unpurified sample onto tissue culture containing usually four to six other types of material – all of which contain identical genetic material as to what is called a “virus.” The tissue culture is starved and poisoned and naturally disintegrates into many types of particles, some of which contain genetic material. Against all common sense, logic, use of the English language and scientific integrity, this process is called “virus isolation.” This brew containing fragments of genetic material from many sources is then subjected to genetic analysis, which then creates in a computer-simulation process the alleged sequence of the alleged virus, a so-called *in silico* genome. At no time is an actual virus confirmed by electron microscopy. At no time is a genome extracted and sequenced from an actual virus. This is scientific fraud.

The observation that the unpurified specimen — inoculated onto tissue culture along with toxic antibiotics, bovine fetal tissue, amniotic fluid and other tissues — destroys the kidney tissue onto which it is inoculated is given as evidence of the virus' existence and pathogenicity. This is scientific fraud.

From now on, when anyone gives you a paper that suggests the SARS-CoV-2 virus has been isolated, please check the methods sections. If the researchers used Vero cells or any other culture method, you know that their process was not isolation. You will hear the following excuses for why actual isolation isn't done:

1. There were not enough virus particles found in samples from patients to analyze.
2. Viruses are intracellular parasites; they can't be found outside the cell in this manner.

If No. 1 is correct, and we can't find the virus in the sputum of sick people, then on what evidence do we think the virus is dangerous or even lethal? If No. 2 is correct, then how is the virus spread from person to person? We are told it emerges from the cell to infect others. Then why isn't it possible to find it?

Finally, questioning these virology techniques and conclusions is not some distraction or divisive issue. Shining the light on this truth is essential to stop this terrible fraud that humanity is confronting. For, as we now know, if the virus has never been isolated, sequenced or shown to cause illness, if the virus is imaginary, then why are we wearing masks, social distancing and putting the whole world into prison?

Finally, if pathogenic viruses don't exist, then what is going into those injectable devices erroneously called "vaccines," and what is their purpose? This scientific question is the most urgent and relevant one of our time.

We are correct. The SARS-CoV2 virus does not exist.

Sally Fallon Morell, MA

Dr. Thomas Cowan, MD

Dr. Andrew Kaufman, MD

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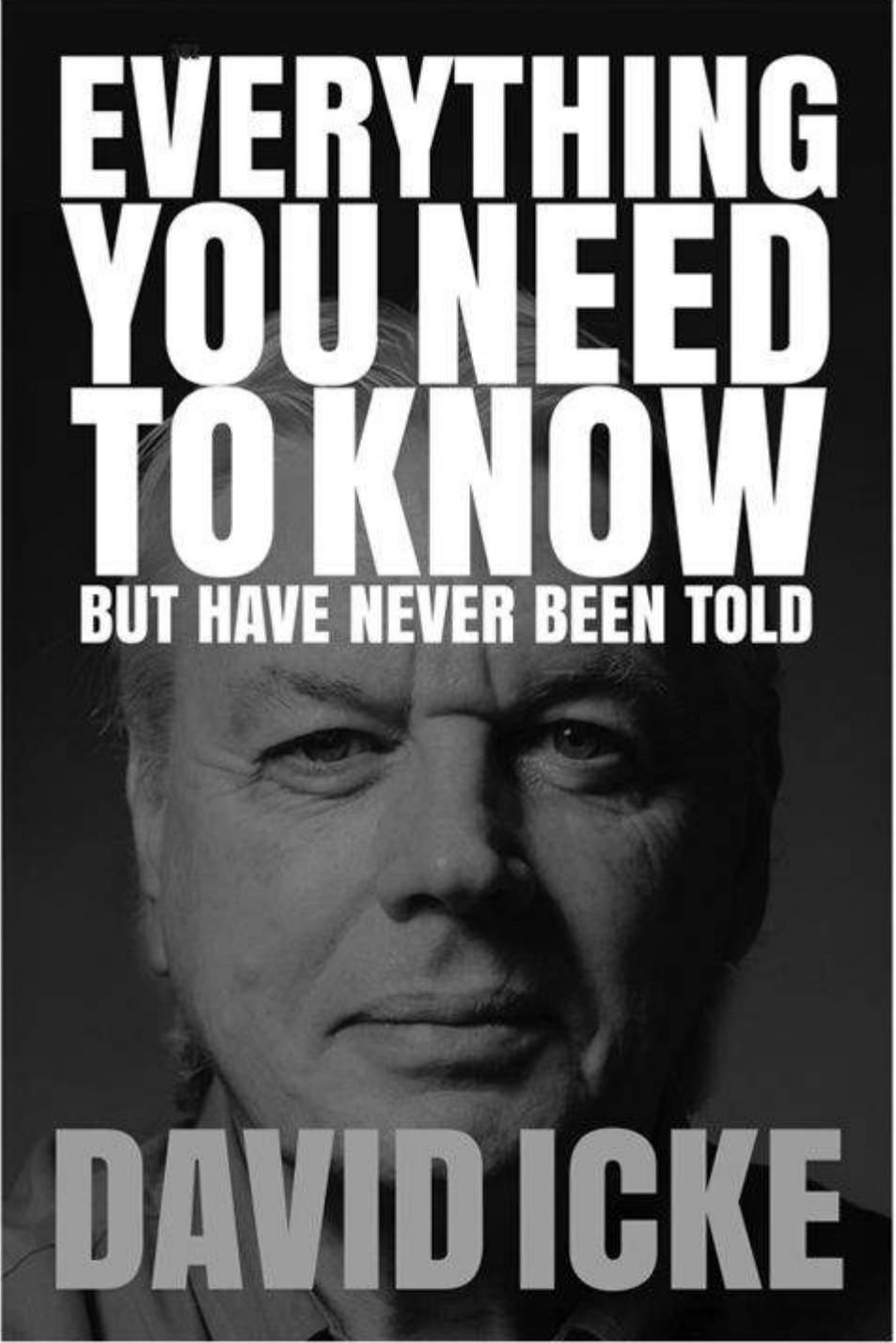
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/'ren-i.gəd/

**noun**

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