



BASIC & CLINICAL PHARMACOLOGY

13th Edition

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BASIC principles

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2- Drug receptors & pharmacodynamics .

3- Pharmacokinetics & Pharmacodynamics : Rational Dosing & the Time Course of Drug Action .

4- Drug Biotransformation .

5- Pharmacogenomics .

Chapter #1: Introduction:

**The Nature of Drugs & Drug Development
& regulation**

Pharmacology

- can be defined as the study of substances that interact with living systems through chemical processes. These substances may be chemicals administered to achieve a beneficial therapeutic effect on some process within the patient.

Toxicology

- is the branch of pharmacology that deals with the undesirable effects of chemicals on living systems, from individual cells to humans to complex ecosystems.

GENERAL PRINCIPLES OF PHARMACOLOGY

THE NATURE OF DRUGS

**A drug
may be
defined as**

any substance that brings about a change in biologic function through its chemical actions.

- The drug molecule interacts as an agonist (activator) or antagonist (inhibitor) with a specific molecule in the biologic system.
- Molecule is called a receptor.
- In a very small number of cases, drugs known as chemical antagonists may interact directly with other drugs, whereas a few drugs (osmotic agents) interact almost exclusively with water molecules.

Drugs

may be synthesized within the body

(eg, hormones)

may be chemicals not synthesized in the body

(ie, xenobiotics, from the Greek *xenos*, meaning “stranger”)

- Poisons are drugs that have almost exclusively harmful effects.
- “The dose makes the poison,” meaning that any substance can be harmful if taken in the wrong dosage.
- Toxins are usually defined as poisons of biologic origin, ie, synthesized by plants or animals, in contrast to inorganic poisons such as lead and arsenic.
- To interact chemically with its receptor, a drug molecule must have the appropriate size, electrical charge, shape, and atomic composition. Furthermore, a drug is often administered at a location distant from its intended site of action.

THE PHYSICAL NATURE OF DRUGS

- Drugs may be solid at room temperature, liquid, or gaseous. These factors often determine the best route of administration.
- A number of useful or dangerous drugs are inorganic elements, eg, lithium, iron, and heavy metals.
- Many organic drugs are weak acids or bases.
- This fact has important implications for the way they are handled by the body, because pH differences in the various compartments of the body may alter the degree of ionization of such drugs.

DRUG SIZE

- The molecular size of drugs varies from very small (MW 7) to very large (MW 59,050).
- most drugs have molecular weights between 100 and 1000.
- The lower limit of this narrow range is probably set by the requirements for specificity of action.
- To have a good “fit” to only one type of receptor, a drug molecule must be sufficiently unique in shape, charge, and other properties, to prevent its binding to other receptors.
- To achieve such selective binding, it appears that a molecule should in most cases be at least 100 MW units in size.
- The upper limit in molecular weight is determined primarily by the requirement that drugs must be able to move within the body (eg, from the site of administration to the site of action).
- very large drugs (usually proteins) must often be administered directly into the compartment where they have their effect.
- In the case of alteplase, a clot-dissolving enzyme, the drug is administered directly into the vascular compartment by intravenous or intra-arterial infusion.

Covalent bonds

- Are very strong and in many cases not reversible under biologic conditions.

Electrostatic bonds

- Much more common than covalent bonding in drug-receptor interactions.

- Vary from relatively strong linkages between permanently charged ionic molecules to weaker hydrogen bonds and very weak induced dipole interactions such as van der Waals forces and similar phenomena.

- Weaker than covalent bonds.

Hydrophobic bonds

- Are usually quite weak and are probably important in the interactions of highly lipid-soluble drugs with the lipids of cell membranes and perhaps in the interaction of drugs with the internal walls of receptor “pockets.”

DRUG REACTIVITY & DRUG-RECEPTOR BONDS

Drugs interact with receptors by means of chemical forces or bonds.

These are of three major types: covalent, electrostatic, and hydrophobic.

The specific nature of a particular drug-receptor bond is of less practical importance than the fact that drugs that bind through weak bonds to their receptors are generally more selective than drugs that bind by means of very strong bonds. This is because weak bonds require a very precise fit of the drug to its receptor if an interaction is to occur. Only a few receptor types are likely to provide such a precise fit for a particular drug structure.

DRUG SHAPE

- The shape of a drug molecule must be such as to permit binding to its receptor site via the bonds just described.
- the phenomenon of chirality (stereoisomerism) is so common in biology that more than half of all useful drugs are chiral molecules; that is, they can exist as enantiomeric pairs.
- Drugs with two asymmetric centers have four diastereomers.
- In most cases, one of these enantiomers is much more potent than its mirror image enantiomer, reflecting a better fit to the receptor molecule.
- If one imagines the receptor site to be like a glove into which the drug molecule must fit to bring about its effect, it is clear why a “left-oriented” drug is more effective in binding to a left-hand receptor than its “right-oriented” enantiomer.

- The more active enantiomer at one type of receptor site may not be more active at another receptor type.
- The (+) enantiomer is a more potent anesthetic and is less toxic than the (-) enantiomer.

Unfortunately, the drug is still used as the racemic mixture.

Finally, because enzymes are usually stereo selective, one drug enantiomer is often more susceptible than the other to drug metabolizing enzymes.

Most studies of clinical efficacy and drug elimination in humans have been carried out with racemic mixtures of drugs rather than with the separate enantiomers. Some drugs are currently available in both the racemic and the pure, active isomer forms.

RATIONAL DRUG DESIGN

Rational design of drugs implies the ability to predict the appropriate molecular structure of a drug on the basis of information about its biologic receptor.

A few drugs now in use were developed through molecular design based on knowledge of the three dimensional structure of the receptor site. Computer programs are now available that can iteratively optimize drug structures to fit known receptors.

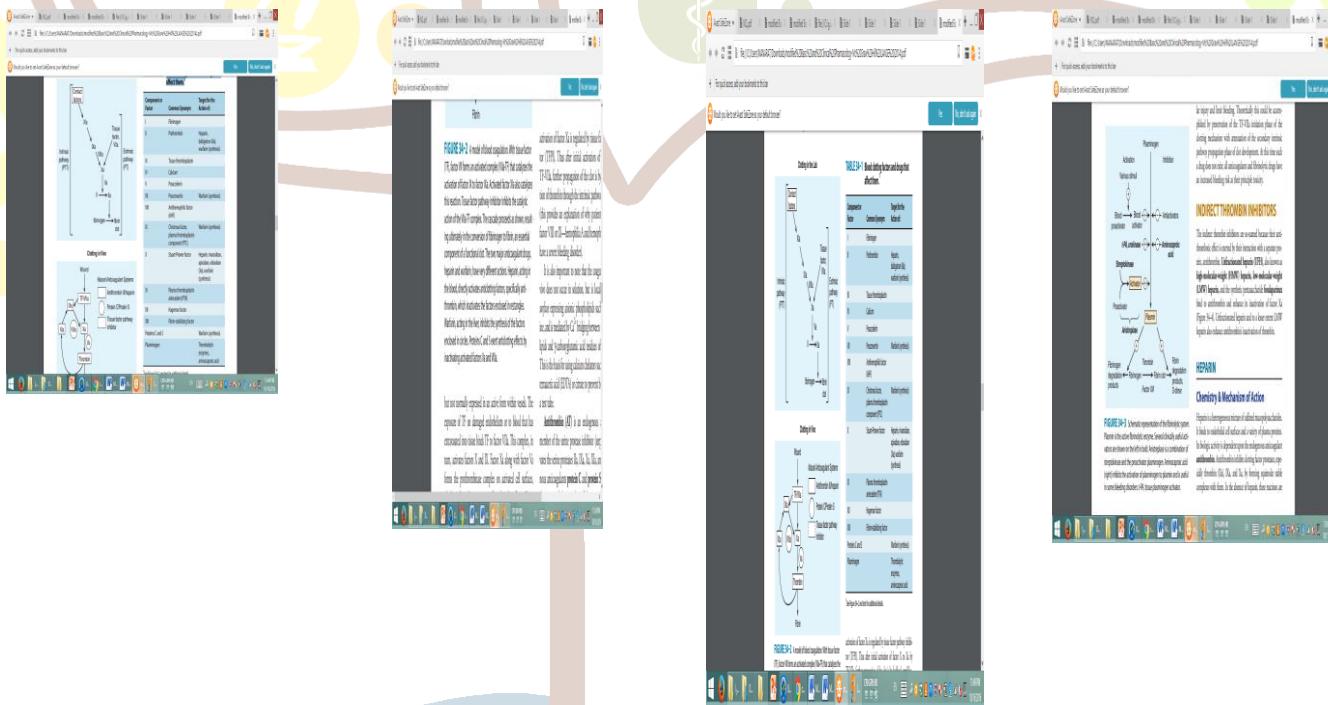
Drug-Body interactions

The actions of the body on the drug are called Pharmacokinetic processes.

Pharmacokinetic processes govern the absorption, distribution, and elimination of drugs and are of great practical importance in the choice and administration of a particular drug for a particular patient.

Pharmacodynamic Principles

Most drugs must bind to a receptor to bring about an effect.
However, at the cellular level, drug binding is only the first in a sequence of steps:



a. Types of Drug-Receptor Interactions

Agonist

Agonist drugs bind to and activate the receptor in some fashion, which directly or indirectly brings about the effect. Some receptors incorporate effector machinery in the same

	<p>molecule, so that drug binding brings about the effect directly, eg, opening of an ion channel or activation of enzyme activity.</p>
Antagonist	<p>Pharmacologic antagonist drugs, by binding to a receptor, compete with and prevent binding by other molecules. Some antagonists bind very tightly to the receptor site in an irreversible or pseudoirreversible fashion and cannot be displaced by increasing the agonist concentration.</p>
Allosteric	<p>Drugs that bind to the same receptor molecule but do not prevent binding of the agonist are said to act allosterically and may enhance or inhibit the action of the agonist molecule. Allosteric inhibition is not overcome by increasing the dose of agonist.</p>

B. Agonists that Inhibit their Binding Molecules

Some drugs mimic agonist drugs by inhibiting the molecules responsible for terminating the action of an endogenous agonist.

For example, acetylcholinesterase inhibitors, by slowing the destruction of endogenous acetylcholine, cause cholinomimetic effects that closely resemble the actions of cholinoreceptor agonist molecules even though cholinesterase inhibitors do not bind or only incidentally bind to cholinoreceptors .

Because they amplify the effects of physiologically released agonist ligands, their effects are sometimes more selective and less toxic than those of exogenous agonists.

C. Agonists, Partial agonists, and Inverse agonists

- ❖ The recognition of constitutive activity may depend on the receptor density, the concentration

of coupling molecules (if a coupled system), and the number of effectors in the system.

- ❖ Many agonist drugs, when administered at concentrations sufficient to saturate the receptor pool, can activate their receptoreffector systems to the maximum extent of which the system is capable; that is, they cause a shift of almost all of the receptor pool to the Ra-D pool. Such drugs are termed **full agonists**.
- ❖ Other drugs, called **partial agonists**, bind to the same receptors and activate them in the same way but do not evoke as great a response, no matter how high the concentration.
- ❖ Partial agonists do not stabilize the Ra configuration as fully as full agonists,

so that a significant fraction of receptors exists in the Ri-D

pool. Such drugs are said to have low intrinsic efficacy.

The presence of the antagonist at the receptor site will block access of agonists to the receptor and prevent the usual agonist effect. Such blocking action can be termed **neutral antagonism**.

d. Duration of drug action

- ❖ Termination of drug action is a result of one of several processes.
- ❖ In some cases, the effect lasts only as long as the drug occupies the receptor, and dissociation of drug automatically terminates the effect.
- ❖ In many cases, the action may persist after the drug has dissociated because some coupling molecule is still present in activated form.
- ❖ In the case of drugs that bind covalently to the receptor site, the effect may persist until the drug-receptor complex is destroyed and new

receptors or enzymes are synthesized.

e. Receptors and Inert Binding sites

To function as a receptor, an endogenous molecule must first be Selective in choosing ligands (drug molecules) to bind; and second, it must change its function upon binding in such a way that the function of the biologic system (cell, tissue, etc) is altered.

Binding of a drug to a nonregulatory molecule such as plasma albumin will result in no detectable change in the function of the biologic system, so this endogenous molecule can be called an inert binding site.

Pharmacokinetic Principles

In practical therapeutics, a drug should be able to reach its intended site of action after administration by some convenient

aprodrug: an inactive precursor chemical that is readily absorbed and distributed must be administered and then converted to the active drug by biologic processes inside the body.

A drug is administered into one body compartment and must move to its site of action in another compartment

This requires that the drug be absorbed into the blood from its site of administration and distributed to its site of action, permeating through the various barriers that separate these compartments, after bringing about its effect, a drug should be eliminated at a reasonable rate by metabolic inactivation, by excretion from the body, or by a combination of these processes

a. Permeation

Drug permeation proceeds by several mechanisms.

- ❖ Passive diffusion.
- ❖ Active processes.
- ❖ In facilitating transport.

1. Aqueous diffusion

- Occurs within the larger aqueous compartments of the

	body (interstitial space, cytosol, etc) and across epithelial membrane tight junctions and the endothelial lining of blood vessels through aqueous pores that—in some tissues—permit the passage of molecules as large as MW 20,000–30,000.
2. Lipid diffusion	<ul style="list-style-type: none"> - Most important limiting factor for drug permeation because of the large number of lipid barriers that separate the compartments of the body. - The lipid: aqueous partition coefficient of a drug determines how readily the molecule moves between aqueous and lipid media. - Ratio of lipid-soluble form to water-soluble form for a weak acid or weak base is expressed by the Henderson-Hasselbalch equation.
3-Special carriers	<ul style="list-style-type: none"> - Exist for many substances that are important for cell function and too large or too insoluble in lipid to diffuse passively through membranes.
4. Endocytosis and exocytosis	<ul style="list-style-type: none"> - A few substances are so large or impairment that they can enter cells only by endocytosis, the process by which the substance is bound at a cell-surface receptor, engulfed by the cell membrane, and carried into the cell by pinching off of the newly formed vesicle inside the membrane.

B. Fick's Law of diffusion

The passive flux of molecules down a concentration gradient is given by Fick's law:

$$\text{Flux (molecules per unit time)} = (C_1 - C_2) \times \frac{\text{Area} \times \text{Permeability coefficient}}{\text{Thickness}}$$

C. Ionization of Weak acids and Weak Bases; the Henderson-Hasselbalch equation

- ❖ The electrostatic charge of an ionized molecule attracts water dipoles and results in a polar, relatively water-soluble and lipid insoluble complex.

- ❖ Because lipid diffusion depends on relatively high lipid solubility, ionization of drugs may markedly reduce their ability to permeate membranes.

A very large percentage
of the drugs in use are

weak acids

a weak acid is best defined as a neutral molecule that can reversibly dissociate into an anion (a negatively charged molecule) and a proton (a hydrogen ion).

The protonated form of a weak acid is the neutral, more lipid-soluble form

weak bases

A weak base can be defined as a neutral molecule that can form a cation (a positively charged molecule) by combining with a proton.

whereas the unprotonated form of a weak base is the neutral form.

- ❖ The law of mass action requires that these reactions move to the left in an acid environment (low pH, excess protons available) and to the right in an alkaline environment.
- ❖ The Henderson-Hasselbalch equation relates the ratio of protonated to unprotonated weak acid or weak base to the molecule's pKa and the pH of the medium as follows:

$$\log \frac{(\text{Protonated})}{(\text{Unprotonated})} = \text{pK}_a - \text{pH}$$

- ❖ Almost all drugs are filtered at the glomerulus. If a drug is in a lipid-soluble form during its passage down the renal tubule, a significant fraction will be reabsorbed by simple passive diffusion.
- ❖ If the goal is to accelerate excretion of the drug (eg, in a case of drug overdose), it is important to prevent its reabsorption from the tubule.
- ❖ This can often be accomplished by adjusting urine pH to make certain that most of the drug is in the ionized state.
- ❖ As a result of this partitioning effect, the drug is “trapped” in the urine. Weak acids are usually excreted faster in alkaline urine; weak bases are usually excreted faster in acidic urine.
- ❖ A large number of drugs are weak bases. Most of these bases are amine-containing molecules.
- ❖ The nitrogen of a neutral amine has three atoms associated with it plus a pair of unshared electrons.

The three atoms may consist of:

- One carbon (designated “R”) and two hydrogens (a primary amine).
- Two carbons and one hydrogen (a secondary amine).
- Three carbon atoms (a tertiary amine).
- Some drugs have a fourth carbon-nitrogen bond; these are quaternary amines.

- ❖ Each of these three forms may reversibly bind a proton with the unshared electrons.
- ❖ Primary, secondary, and tertiary amines may undergo reversible protonation and vary their lipid solubility with pH, but quaternary amines are always in the poorly lipid-soluble charged form.

DRUG DEVELOPMENT & REGULATION

The development of new drugs usually takes place in industrial laboratories because optimization of a class of new drugs requires painstaking and expensive chemical, pharmacologic, and toxicological research.

DRUG DISCOVERY

Most new drugs or drug products are discovered or developed through the following approaches:

1. Identification or elucidation of a new drug target.
2. Rational design of a new molecule based on an understanding of biologic mechanisms and drug receptor structure.
3. Screening for biologic activity of large numbers of natural products, banks of previously discovered chemical entities, or large libraries of peptides, nucleic acids, and other organic molecules.
4. Chemical modification of a known active molecule, resulting in a “me-too” analog.

DRUG SCREENING

- Drug screening involves a variety of assays at the molecular, cellular, organ system, and whole animal levels to define the pharmacologic profile, ie, the activity and selectivity of the drug.
- The type and number of initial screening tests depend on the pharmacologic and therapeutic goal.
- At the molecular level, the compound would be screened for activity on the target, for example, receptor binding affinity to cell membranes containing the homologous animal receptors (or if possible, on the cloned human receptors).
- Early studies would be done to predict effects that might later cause undesired drug metabolism or toxicologic complications.
- Effects on cell function determine whether the drug is an agonist, partial agonist, inverse agonist, or antagonist at relevant receptors.
- Isolated tissues would be used to characterize the pharmacologic activity and selectivity of the new compound in comparison with reference compounds.
- Cardiovascular and renal function studies of new drugs are generally first performed in normal animals.
- For drugs related to or having mechanisms of action similar to those known to cause physical or psychological dependence, abuse potential would also be studied.
- Drug interactions would be examined.

PRECLINICAL SAFETY & TOXICITY TESTING

- All drugs are toxic in some individuals at some dose.
- Candidate drugs that survive the initial screening procedures must be carefully evaluated for potential risks before and during clinical testing.
- Although no chemical can be certified as completely “safe” (free of risk), the objective is to estimate the risk associated with exposure to the drug candidate and to consider this in the context of therapeutic needs and likely duration of drug use.
- The goals of preclinical toxicity studies include identifying potential human toxicities, designing tests to further define the toxic mechanisms,

and predicting the most relevant toxicities to be monitored in clinical trials.

- The maximum dose at which a specified toxic effect is not seen; the minimum lethal dose—the smallest dose that is observed to kill any experimental animal.
- The median lethal dose (LD₅₀)—the dose that kills approximately 50% of the animals. Presently, the LD₅₀ is estimated from the smallest number of animals possible.
- These doses are used to calculate the initial dose to be tried in humans, usually taken as one hundredth to one tenth of the no-effect dose in animals.

TABLE 1-4 Safety tests.

Type of Test	Approach and Goals
Acute toxicity	Usually two species, two routes. Determine the no-effect dose and the maximum tolerated dose. In some cases, determine the acute dose that is lethal in approximately 50% of animals.
Subacute or subchronic toxicity	Three doses, two species. Two weeks to 3 months of testing may be required before clinical trials. The longer the duration of expected clinical use, the longer the subacute test. Determine biochemical, physiologic effects.
Chronic toxicity	Rodent and at least one nonrodent species for ≥ 6 months. Required when drug is intended to be used in humans for prolonged periods. Usually run concurrently with clinical trials. Determine same end points as subacute toxicity tests.
Effect on reproductive performance	Two species, usually one rodent and rabbits. Test effects on animal mating behavior, reproduction, parturition, progeny, birth defects, postnatal development.
Carcinogenic potential	Two years, two species. Required when drug is intended to be used in humans for prolonged periods. Determine gross and histologic pathology.
Mutagenic potential	Test effects on genetic stability and mutations in bacteria (Ames test) or mammalian cells in culture; dominant lethal test and clastogenicity in mice.

Confounding Factors in Clinical trials

a. The Variable Natural History of Most diseases

Many diseases tend to wax and wane in severity; some disappear spontaneously, even, on occasion, cancer.

A good experimental design takes into account the natural history of the disease by evaluating a large enough population of subjects over a sufficient period of time.

B. The Presence of Other diseases and Risk Factors

- ❖ Known and unknown diseases and risk factors (including lifestyles of subjects) may influence the results of a clinical study.
 - ❖ Concentrations of blood or tissue components being monitored as a measure of the effect of the new agent may be influenced by other diseases or other drugs.
- ❖ Attempts to avoid this hazard usually involve the crossover technique (when feasible) and proper selection and assignment of patients to each of the study groups.
 - ❖ This requires obtaining accurate diagnostic tests, medical and pharmacologic histories (including use of recreational drugs), and the use of statistically valid methods of randomization in assigning subjects to particular study groups.
 - ❖ It has been shown that age, gender, and pregnancy influence the pharmacokinetics of some drugs, but these factors have not been adequately studied because of legal restrictions and reluctance to expose these populations to unknown risks.

C. Subject and Observer Bias and Other Factors

- ❖ Most patients tend to respond in a positive way to any therapeutic intervention by interested, caring, and enthusiastic medical personnel.
- ❖ The manifestation of this phenomenon in the subject is the placebo response (Latin, “I shall please”) and may involve objective physiologic and biochemical changes as well as changes in subjective complaints associated with the disease.
- ❖ The placebo response is usually quantitated by administration of an inert material with exactly the same physical appearance, odor, consistency, etc, as the active dosage form.
- ❖ Placebo adverse effects and “toxicity” also occur but usually involve subjective effects: stomach upset, insomnia, sedation, and so on.
- ❖ Subject bias effects can be quantitated and minimized relative to the response measured during active therapy by the single -blind design.
- ❖ Observer bias can be taken into account by disguising the identity of the medication being used placebo or active form from both the subjects and the personnel evaluating the subjects’ responses (double -blind design).
- ❖ In this design, a third party holds the code identifying each medication packet, and the code is not broken until all the clinical data have been collected.
- ❖ Drug effects seen in clinical trials are obviously affected by the patient taking the drugs at the dose and frequency prescribed.
- ❖ In a recent phase 2 study, one third of the patients who said they were taking the drug were found by

blood analysis to have not taken the drug.

- ❖ Confirmation of compliance with protocols (also known as adherence) is a necessary element to consider.

The Food & drug administration

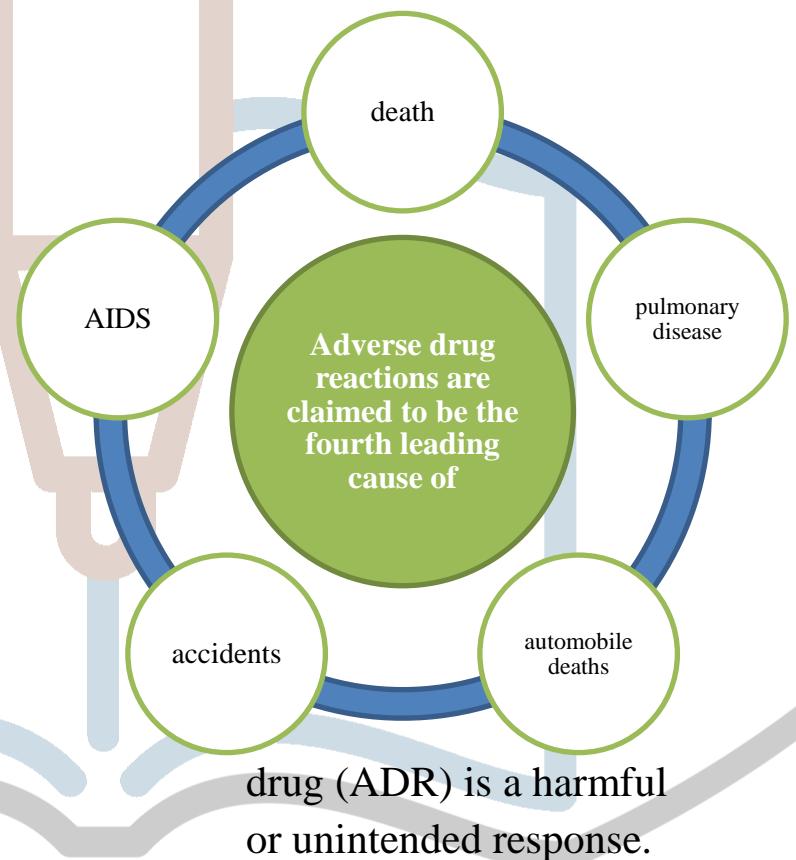
- To receive FDA approval for marketing, the originating institution or company (almost always the latter) must submit evidence of safety and effectiveness.
- The FDA is also responsible for certain aspects of food safety, a role it shares with the US Department of Agriculture (USDA).
- If a drug has not been shown through adequately controlled testing to be “safe and effective” for a specific use, it cannot be marketed in

interstate commerce for this use.

- Complete absence of risk is impossible to demonstrate, but this fact may not be understood by members of the public, who frequently assume that any medication sold with the approval of the FDA should be free of serious “side effects.”

ADVERSE DRUG REACTIONS

- An adverse drug event (ADE) or reaction to a



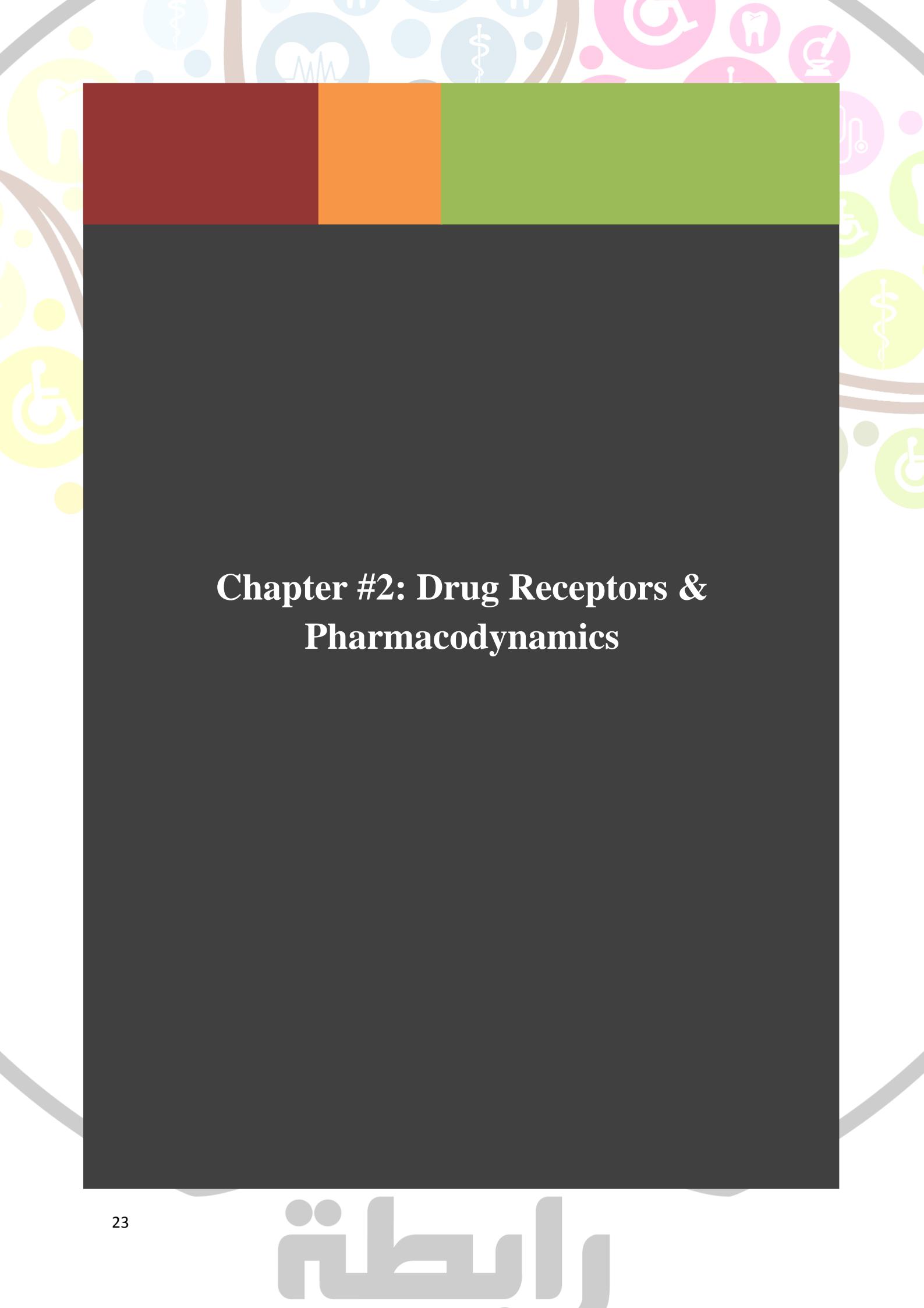
Adverse reactions occurring only in susceptible patients include :

- intolerance
- idiosyncrasy (frequently genetic in origin)
- allergy (usually immunologically mediated)

- During IND studies and clinical trials before FDA approval, all adverse events (serious, life-threatening, disabling, reasonably drug related, or unexpected) must be reported.
- After FDA approval to market a drug, surveillance, evaluation, and reporting must continue for any adverse events that are related to use of the drug, including overdose, accident, failure of expected action, events occurring from drug withdrawal, and unexpected events not listed in labeling.

- Events that are both serious and unexpected must be reported to the FDA within 15 days.
- The ability to predict and avoid adverse drug reactions and optimize a drug's therapeutic index is an increasing focus of pharmacogenetic and personalized medicine.
- Proof of drug safety and efficacy in small populations must be established, but doing so is a complex process.
- The cost of developing a drug can greatly influence priorities when the target population is relatively small.

- Funding for development of drugs for rare diseases or ignored diseases that do not receive priority attention from the traditional industry has received increasing support via philanthropy or similar funding from not-for-profit foundations such as the Cystic Fibrosis Foundation, the Huntington's Disease Society of America, and the Gates Foundation.



Chapter #2: Drug Receptors & Pharmacodynamics

Therapeutic and toxic effects of drugs result from their interactions with molecules in the patient.

Receptor: the component of a cell or organism that interacts with a drug and initiates the chain of events leading to the drug's observed effects. Receptors have become the central focus of investigation of drug effects and their mechanisms of action (pharmacodynamics).

1. Receptors largely determine the quantitative relations between dose or concentration of drug and pharmacologic effects:

- The receptor's affinity for binding a drug determines the concentration of drug required to form a significant number of drug-receptor complexes, and the total number of receptors may limit the maximal effect a drug.

2. Receptors are responsible for selectivity of drug action:

- changes in the chemical structure of a drug can dramatically increase or decrease a new drug's affinities for different classes of receptors, with resulting alterations in therapeutic and toxic effects.

3. Receptors mediate the actions of pharmacologic agonists and antagonists:

- drugs and many natural ligands, regulate the function of receptor macromolecules as agonists; this means that they activate the receptor to signal as a direct result of binding to it. Other drugs act as pharmacologic antagonists; that is, they bind to receptors but do not activate generation of a signal. antagonists, in addition to preventing agonist binding, suppress the "constitutive" activity (basal signaling) of receptors.

MACROMOLECULAR NATURE OF DRUG RECEPTORS

all of the receptors that we discuss in this chapter, are proteins. molecular biology and genome sequencing made it possible to identify receptors by predicted structural homology to other (previously known) receptors.

It also identified a number of “**orphan**” receptors, so-called because their ligands are presently unknown.

The best-characterized drug receptors are **regulatory proteins**, which mediate the actions of endogenous chemical signals such as neurotransmitters, autacoids, and hormones.

Other classes of proteins that have been clearly identified as drug receptors include **enzymes**, transport protein and structural protein .

1. receptors as determinants of the quantitative relation between the concentration of a drug and the pharmacologic response.

This chapter deals with three aspects of drug receptor function, presented in increasing order of complexity:

2. receptors as regulatory proteins and components of chemical signaling mechanisms that provide targets for important drugs.

3. receptors as key determinants of the therapeutic and toxic effects of drugs in patients.

RELATION BETWEEN DRUG CONCENTRATION & RESPONSE

Concentration-Effect Curves & Receptor Binding of Agonists

Responses to low doses of a drug usually increase in direct proportion to dose. As doses increase, however, the response increment diminishes; finally, doses may be reached at which no further increase in response can be achieved.

Receptor-Effector Coupling & Spare Receptors

agonist occupies a receptor, conformational changes occur in the receptor protein that represent receptor activation and pharmacologic response called **coupling**. The efficiency of the coupling is determined at the receptor itself; full agonists tend to shift the conformational equilibrium of receptors more strongly than partial agonists. Coupling is also determined by “downstream”

biochemical events that transduce receptor occupancy into cellular response

Many factors can contribute to nonlinear occupancy-response coupling. A useful concept for thinking about this is that of **receptor reserve or spare receptors**. Receptors are said to be “spare” for a given pharmacologic response if it is possible to elicit a maximal biologic response at a concentration of agonist that does not result in occupancy of the full complement of available receptors.

Experimentally, spare receptors may be demonstrated by using irreversible antagonists to prevent binding of agonist to a proportion of available receptors and showing that high concentrations of agonist can still produce an undiminished maximal response.

Receptors may be simply *spare in number* relative to the total number of downstream signaling mediators present in the cell, so that a maximal response occurs without occupancy of all receptors.

the sensitivity of a cell or tissue to a particular concentration of agonist depends not only on the *affinity* of the receptor for binding the agonist (characterized by the K_d (the equilibrium dissociation constant)) but also on the *degree of spareness*—the total number of receptors present compared with the number actually needed to elicit a maximal biologic response.

Thus, it is possible to change the sensitivity of tissues with spare receptors by changing receptor number.

Competitive & Irreversible Antagonists

Receptor antagonists bind to receptors but do not activate them; the primary action of antagonists is to reduce the effects of agonists that normally

activate receptors. Some antagonists exhibit “inverse agonist” activity. Antagonist drugs are further divided into two classes *competitively* or *noncompetitively* relative to an agonist present at the same time.

In the presence of a fixed concentration of agonist, increasing concentrations of a **competitive antagonist** progressively inhibit the agonist response; high antagonist concentrations prevent response completely. The presence of antagonist increases the agonist concentration required for a given degree of response.

the dissociation constant (K_i) of the antagonist :

$$C'/C = 1 + [I]/K_i$$

Used to determine the K_i of competitive antagonist.

For the clinician, this mathematical relation has two important therapeutic implications:

1. The degree of inhibition produced by a competitive antagonist depends on the concentration of antagonist.

2. Clinical response to a competitive antagonist also depends on the concentration of agonist that is competing for binding to receptors.

noncompetitive antagonist bind to the receptor in an **irreversible** or nearly irreversible fashion. After occupancy the number of remaining unoccupied receptors may be too low for the agonist to elicit a response comparable to the previous maximal response. If spare receptors are present, however, a lower dose of an irreversible antagonist may leave enough receptors unoccupied to allow achievement of maximum response to agonist, although a higher agonist concentration will be required .the duration of action of such an irreversible antagonist is relatively independent of its own rate of

elimination and more dependent on the rate of turnover of receptor molecules.

Antagonists can function noncompetitively in a different way; by binding to a site on the receptor protein separate from the agonist binding site; in this way, the drug can modify receptor activity without blocking agonist binding . Although these drugs act noncompetitively, their actions are often reversible. Such drugs are called *negative allosteric modulators*. Not all allosteric modulators act as antagonists, instead of inhibiting receptor activation, potentiate it.

Partial Agonists

agonists can be divided into two classes: **partial agonists** produce a lower response, at full receptor occupancy, than do **full agonists** . It is important to emphasize that the failure of partial agonists to produce a maximal response is not due to decreased affinity for binding to receptors. the fact that partial agonists competitively inhibit

the responses produced by full agonists . This mixed “agonist-antagonist” property of partial agonists can have both beneficial and deleterious effects in the clinic.

Other Mechanisms of Drug Antagonism

types of antagonism do not involve a receptor at all. one drug acts as a **chemical antagonist** of the other simply by ionic binding that makes the other drug unavailable for interactions with proteins. Another type of antagonism is **physiologic antagonism** between endogenous regulatory pathways mediated by different receptors.

use of a drug as a physiologic antagonist produces effects that are less specific and less easy to control than are the effects of a receptor-specific antagonist. use of this physiologic antagonist would be less rational—and

potentially more dangerous—than use of a receptor-specific antagonist.

SIGNALING MECHANISMS & DRUG ACTION

These protein families include receptors on the cell surface and within the cell, as well as enzymes and other components that generate, amplify, coordinate, and terminate postreceptor signaling by chemical second messengers in the cytoplasm.

Five basic mechanisms of transmembrane signaling are well understood (Figure 2–5). Each represents a different family of receptor protein and uses a different strategy to circumvent the barrier posed by the lipid bilayer of the plasma membrane.

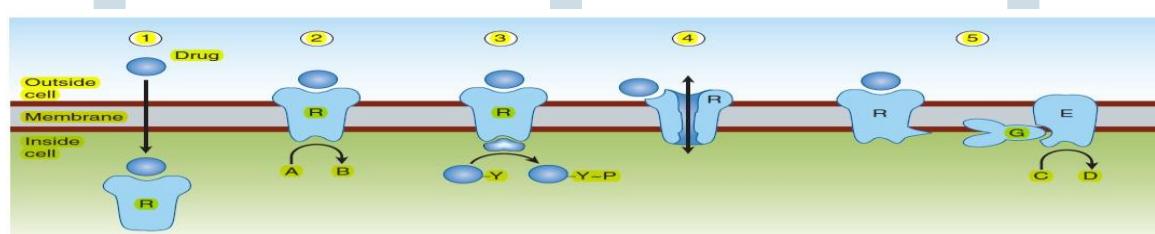


FIGURE 2–5 Known transmembrane signaling mechanisms: 1: A lipid-soluble chemical signal crosses the plasma membrane and acts on an intracellular receptor (which may be an enzyme or a regulator of gene transcription); 2: the signal binds to the extracellular domain of a transmembrane protein, thereby activating an enzymatic activity of its cytoplasmic domain; 3: the signal binds to the extracellular domain of a transmembrane receptor bound to a separate protein tyrosine kinase, which it activates; 4: the signal binds to and directly regulates the opening of an ion channel; 5: the signal binds to a cell-surface receptor linked to an effector enzyme by a G protein. (A, C, substrates; B, D, products; R, receptor; G, G protein; E, effector [enzyme or ion channel]; Y, tyrosine; P, phosphate.)

Intracellular Receptors for Lipid-Soluble Agents

Several biologic ligands are sufficiently lipid-soluble to cross the plasma membrane and act on intracellular receptors such ligands includes steroids and thyroid hormone, whose receptors stimulate the transcription of genes by binding to specific DNA sequences near the gene whose expression is to be regulated.

These “gene-active” receptors belong to a protein family that evolved from a common precursor.

The mechanism used by hormones that act by regulating gene expression has two therapeutically important consequences:

1. All of these hormones produce their effects after a characteristic lag period—the time required for the synthesis of new proteins. This means that the geneactive hormones cannot be expected to alter a pathologic state within minutes.

2. The effects of these agents can persist for hours or days after the agonist concentration has been reduced to zero due to the relatively slow turnover of most enzymes and proteins, which can remain active in cells for hours or days after they have been synthesized. it means that the beneficial (or toxic) effects of a geneactive hormone usually decrease slowly when administration of the hormone is stopped.

Ligand-Regulated Transmembrane Enzymes Including Receptor Tyrosine Kinases

These receptors are polypeptides consisting of an extracellular hormone-binding domain and a cytoplasmic enzyme domain, which may be a protein tyrosine kinase, a serine kinase, or a guanylylcyclase(Figure 2–7). In all these receptors, the two domains are connected by a hydrophobic segment of the polypeptide that crosses the lipid bilayer of the plasma membrane.

The receptor tyrosine kinase signaling pathway begins with binding of ligand, typically a polypeptide hormone or growth factor, to the receptor’s extracellular domain. The resulting change in receptor conformation causes two receptor molecules to bind to one another (*dimerize*), which in turn brings together the tyrosine kinase domains, which become enzymatically active,

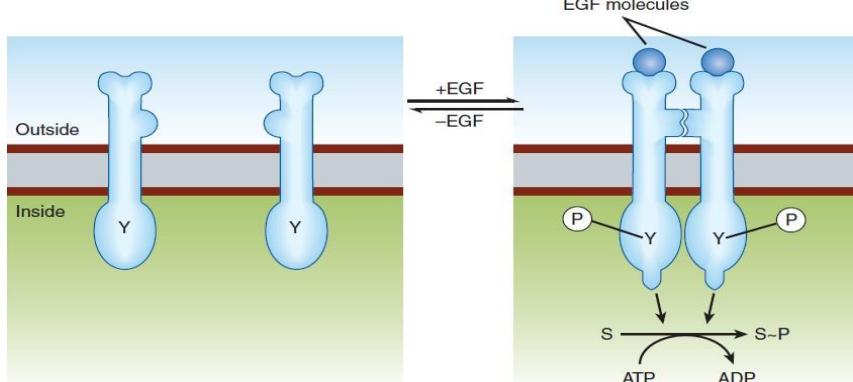


FIGURE 2–7 Mechanism of activation of the epidermal growth factor (EGF) receptor, a representative receptor tyrosine kinase. The receptor polypeptide has extracellular and cytoplasmic domains, depicted above and below the plasma membrane. Upon binding of EGF (circle), the receptor converts from its inactive monomeric state (left) to an active dimeric state (right), in which two receptor polypeptides bind noncovalently. The cytoplasmic domains become phosphorylated (P) on specific tyrosine residues (Y), and their enzymatic activities are activated, catalyzing phosphorylation of substrate proteins (S).

and phosphorylate one another as well as additional downstream signaling proteins. Activated receptors catalyze phosphorylation of tyrosine residues on different target signaling proteins, thereby allowing a single type of activated receptor to modulate a number of biochemical processes.

Inhibitors of particular receptor tyrosine kinases are finding increased use in neoplastic disorders in which excessive growth factor signaling is often involved. Some of these inhibitors are monoclonal antibodies (eg, trastuzumab, cetuximab), which bind to the extracellular domain of a particular receptor and interfere with binding of growth factor.

Other inhibitors are membrane-

permeant small molecule chemicals (eg, gefitinib, erlotinib), which inhibit the receptor's kinase activity in the cytoplasm.

The intensity and duration of action of EGF, PDGF, and other agents that act via receptor tyrosine kinases are often limited by a process called **receptor down-regulation**. Ligand binding often induces accelerated endocytosis of receptors from the cell surface, followed by the degradation of those receptors. When this process occurs at a rate faster than de novo synthesis of receptors, the total number of cell-surface receptors is reduced (down-regulated), and the cell's

responsiveness to ligand is correspondingly diminished.

A number of regulators of growth and differentiation, including TGF- β , act on another class of transmembrane receptor enzymes that phosphorylate serine and threonine residues. Atrial natriuretic peptide (ANP), an important regulator of blood volume and vascular tone, acts on a transmembrane receptor whose intracellular domain, a guanylylcyclase, generates cGMP (see below).

Receptors

in both groups, like the receptor tyrosine kinases, are active in their dimeric forms.

Cytokine Receptors

Cytokine receptors respond to a heterogeneous group of peptide ligands, which include growth hormone, erythropoietin, several kinds of interferon, and other regulators of growth and differentiation. These receptors use a mechanism (Figure 2–8) closely resembling that of receptor tyrosine kinases, except that in this case, the protein tyrosine kinase activity is not intrinsic to the receptor molecule. Instead, a separate protein tyrosine kinase, from the Janus-kinase (JAK) family, binds noncovalently to the receptor.

Ligand- and Voltage-Gated Channels

The natural ligands of such receptors include acetylcholine, serotonin, GABA, and glutamate. All of these agents are synaptic transmitters.

receptors transmits its signal across the plasma membrane by increasing transmembrane conductance of the relevant ion and thereby altering the

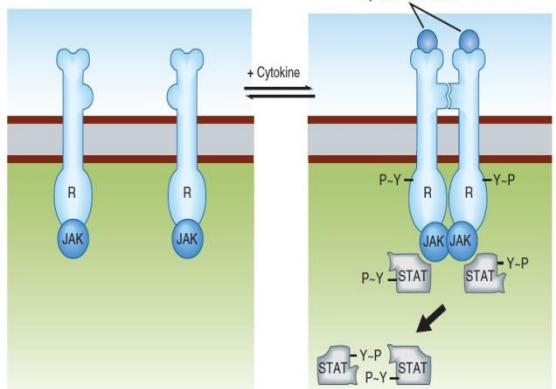


FIGURE 2–8 Cytokine receptors, like receptor tyrosine kinases, have extracellular and intracellular domains and form dimers. However, after activation by an appropriate ligand, separate mobile protein tyrosine kinase molecules (JAK) are activated, resulting in phosphorylation of signal transducers and activation of transcription (STAT) molecules. STAT dimers then travel to the nucleus, where they regulate transcription.

electrical potential across the membrane.

The nAChR is one of the best characterized of all cell-surface receptors for hormones or neurotransmitters (Figure 2–9).

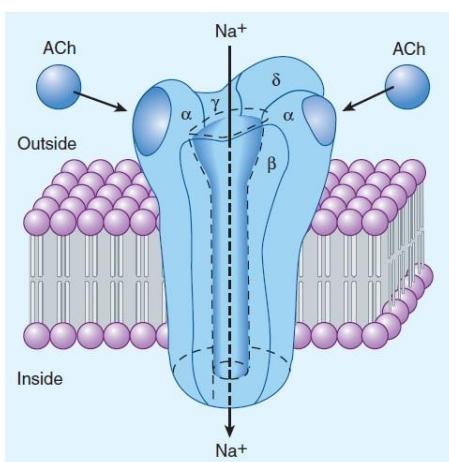


FIGURE 2–9 The nicotinic acetylcholine (ACh) receptor, a ligand-gated ion channel. The receptor molecule is depicted as embedded in a rectangular piece of plasma membrane, with extracellular fluid above and cytoplasm below. Composed of five subunits (two α , one β , one γ , and one δ), the receptor opens a central transmembrane ion channel when ACh binds to sites on the extracellular domain of its α subunits.

The time elapsed between the binding of the agonist to a ligand-gated channel and the cellular response can often be measured in milliseconds..

Ligand-gated ion channels can be regulated by multiple mechanisms, including phosphorylation and endocytosis.

Voltage-gated ion channels do not bind neurotransmitters

directly but are controlled by membrane potential; such channels are also important drug targets. For example, verapamil inhibits voltage-gated calcium channels that are present in the heart and in vascular smooth muscle, producing antiarrhythmic effects and reducing blood pressure without mimicking or antagonizing any known endogenous transmitter.

G Proteins & Second Messengers

Many extracellular ligands act by increasing the intracellular concentrations of second messengers such as **cyclic adenosine-3',5'-monophosphate (cAMP)**, **calcium ion**, or the **phosphoinositides**. First, the extracellular ligand is selectively detected by a cell-surface receptor. The activation of a GTP-binding protein (**G protein**) located on the cytoplasmic face of the plasma membrane, then changes the activity of an effector element,

usually an enzyme or ion channel. This element then changes the concentration of the intracellular second messenger. For cAMP, the effector enzyme is adenylyl cyclase, a membrane protein that converts intracellular adenosine triphosphate (ATP) to cAMP. There are many examples of such receptors, including $\beta\alpha$ adrenoceptors, glucagon receptors, thyrotropin receptors. Gs and other G proteins activate their downstream effectors when bound by GTP and also have the ability to hydrolyze GTP (Figure 2–10); this hydrolysis reaction inactivates the G protein but can occur at a relatively slow rate, effectively amplifying the transduced

signal by allowing the activated (GTP-bound) G protein to have a longer lifetime in the cell than the activated receptor itself. This mechanism also helps explain how signaling by G proteins produces the phenomenon of spare receptors. The family of G proteins contains several functionally diverse subfamilies (table 2–1), each of which mediates effects of a particular set of receptors to a distinctive group of effectors. Note that an endogenous ligand may bind and stimulate receptors that couple to different subsets of G proteins, allows it to elicit different G protein-dependent responses in different cells.

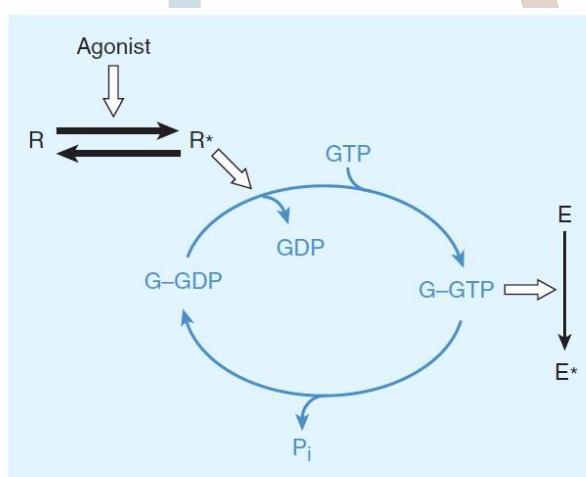


FIGURE 2–10 The guanine nucleotide-dependent activation-inactivation cycle of G proteins. The agonist activates the receptor ($R \rightarrow R^*$), which promotes release of GDP from the G protein (G), allowing entry of GTP into the nucleotide binding site. In its GTP-bound state (G-GTP), the G protein regulates activity of an effector enzyme or ion channel ($E \rightarrow E^*$). The signal is terminated by hydrolysis of GTP, followed by return of the system to the basal unstimulated state. Open arrows denote regulatory effects. (P_i , inorganic phosphate.)

TABLE 2–1 G proteins and their receptors and effectors.

G Protein	Receptors for	Effector/Signaling Pathway
G_s	β -Adrenergic amines, histamine, serotonin, glucagon, and many other hormones	\uparrow Adenylyl cyclase \rightarrow \uparrow cAMP
G_{I1}, G_{I2}, G_{I3}	α_2 -Adrenergic amines, acetylcholine (muscarinic), opioids, serotonin, and many others	Several, including: \downarrow Adenylyl cyclase \rightarrow \downarrow cAMP Open cardiac K ⁺ channels \rightarrow \downarrow heart rate
G_{olf}	Odorants (olfactory epithelium)	\uparrow Adenylyl cyclase \rightarrow \uparrow cAMP
G_o	Neurotransmitters in brain (not yet specifically identified)	Not yet clear
G_q	Acetylcholine (muscarinic), bombesin, serotonin (5-HT ₂), and many others	\uparrow Phospholipase C \rightarrow \uparrow IP ₃ , diacylglycerol, cytoplasmic Ca ²⁺
G_{t1}, G_{t2}	Photons (rhodopsin and color opsins in retinal rod and cone cells)	\uparrow cGMP phosphodiesterase \rightarrow \downarrow cGMP (phototransduction)

cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; IP₃, inositol-1,4,5-trisphosphate.

Receptors that signal via G proteins are often called “G protein-coupled receptors” (GPCRs). GPCRs make up the largest receptor family and are also called “seven-transmembrane” or “serpentine” receptors because the receptor polypeptide chain “snakes” across the plasma membrane seven times.

A few GPCRs require stable assembly into either **homodimers** (complexes of two identical receptor polypeptides) or **heterodimers** (complexes of different isoforms) for functional activity. However, in contrast to tyrosine kinase and cytokine receptors, many GPCRs are thought to be able to function as monomers. GPCRs can bind agonists in a variety of ways, but they all appear to transduce signals across the

plasma membrane in a similar way. (See Figure 2–11).

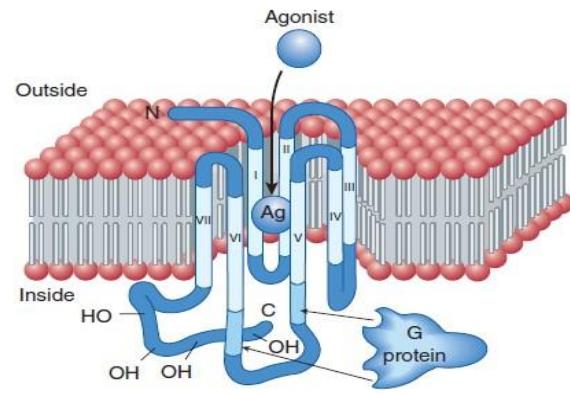


FIGURE 2–11 Transmembrane topology of a typical “serpentine” GPCR. The receptor’s amino (N) terminal is extracellular (above the plane of the membrane), and its carboxyl (C) terminal intracellular, with the polypeptide chain “snaking” across the membrane seven times. The hydrophobic transmembrane segments (light color) are designated by Roman numerals (I–VII). Agonist (Ag) approaches the receptor from the extracellular fluid and binds to a site surrounded by the transmembrane regions of the receptor protein. G protein interacts with cytoplasmic regions of the receptor, especially around the third cytoplasmic loop connecting transmembrane regions V and VI. Lateral movement of these helices during activation exposes an otherwise buried cytoplasmic surface of the receptor that promotes guanine nucleotide exchange on the G protein and thereby activates the G protein, as discussed in the text. The receptor’s cytoplasmic tail contains numerous serine and threonine residues whose hydroxyl (-OH) groups can be phosphorylated. This phosphorylation is associated with diminished receptor-G protein coupling and can promote receptor endocytosis.

Receptor Regulation

G protein-mediated responses to drugs and hormonal agonists often attenuate with time (Figure 2–12A). After reaching an initial high level,

the response diminishes over seconds or minutes, even in the continued presence of the agonist. This

“desensitization” is often rapidly reversible; a second exposure to agonist, if provided a few minutes after termination of the first exposure, results in a response similar to the initial response.

Many GPCRs are regulated by phosphorylation, as illustrated by rapid desensitization of the $\beta\alpha$ adrenoceptor. The agonist-induced change in conformation of the receptor causes it to bind, activate, and serve as a substrate for a family of specific receptor kinases, called G protein-coupled receptor kinases (GRKs). The activated GRK then

phosphorylates serine residues in the receptor’s carboxyl terminal tail (Figure 2–12, panel B).

For $\beta\alpha$ adrenoceptors, and many other GPCRs, β -arrestin binding also accelerates endocytosis of receptors from the plasma membrane.

Endocytosis of receptors promotes their dephosphorylation by a receptor phosphatase that is present at high concentration on endosome membranes, and receptors then return to the plasma membrane. This helps explain the ability of cells to recover receptor-mediated signaling responsiveness very efficiently after agonist-induced desensitization.

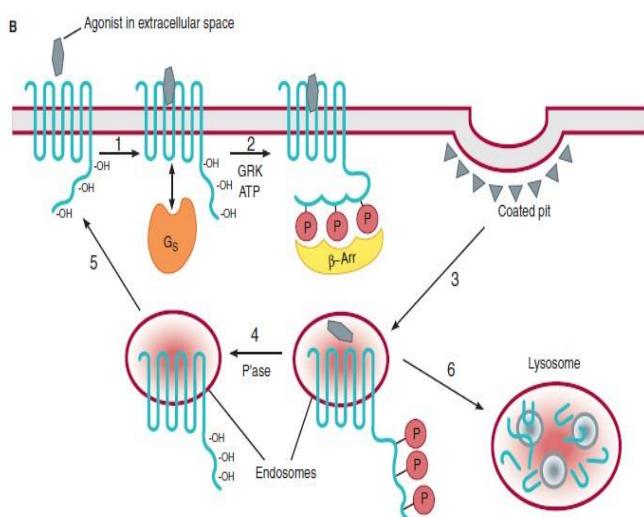
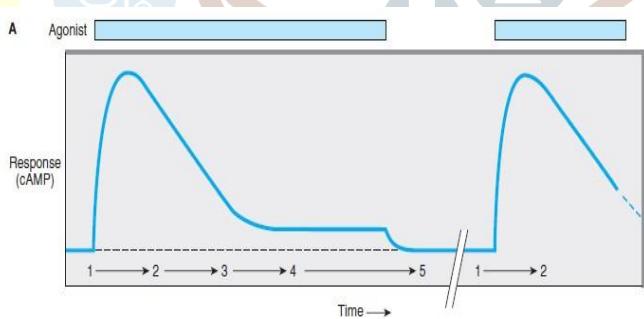


FIGURE 2–12 Rapid desensitization, resensitization, and down-regulation of β adrenoceptors. **A:** Response to a β -adrenoceptor agonist (ordinate) versus time (abscissa). (Numbers refer to the phases of receptor function in **B**.) Exposure of cells to agonist (indicated by the light-colored bar) produces a cyclic AMP response. A reduced cAMP response is observed in the continued presence of agonist; this “desensitization” typically occurs within a few minutes. If agonist is removed after a short time (typically several to tens of minutes, indicated by broken line on abscissa), cells recover full responsiveness to a subsequent addition of agonist (second light-colored bar). This “resensitization” fails to occur, or occurs incompletely, if cells are exposed to agonist repeatedly or over a more prolonged time period. **B:** Agonist binding to receptors initiates signaling by promoting receptor interaction with G proteins (G_s) located in the cytoplasm (step 1 in the diagram). Agonist-activated receptors are phosphorylated by a G protein-coupled receptor kinase (GRK), preventing receptor interaction with G_s and promoting binding of a different protein, β -arrestin (β -Arr), to the receptor (step 2). The receptor-arrestin complex binds to coated pits, promoting receptor internalization (step 3). Dissociation of agonist from internalized receptors reduces β -Arr binding affinity, allowing dephosphorylation of receptors by a phosphatase (Pase, step 4) and return of receptors to the plasma membrane (step 5); together, these events result in the efficient resensitization of cellular responsiveness. Repeated or prolonged exposure of cells to agonist favors the delivery of internalized receptors to lysosomes (step 6), promoting receptor down-regulation rather than resensitization.

Well-Established Second Messengers

A. Cyclic Adenosine Monophosphate (cAMP)

Acting as an intracellular second messenger, cAMP mediates such hormonal responses as the mobilization of stored energy, conservation

of water by the kidney, Ca^{2+} homeostasis and increased rate and contractile force of heart muscle. It also regulates the production of adrenal and sex steroids, relaxation of smooth muscle, and many other endocrine and neural processes.

cAMP exerts most of its effects by stimulating cAMP-dependent protein kinases. These kinases are composed of a cAMP-binding regulatory (R) dimer and two catalytic (C) chains. When cAMP binds to the R dimer, active C chains are released to diffuse through

the cytoplasm and nucleus, where they transfer phosphate from ATP to appropriate substrate proteins, often enzymes.

When the hormonal stimulus stops, the intracellular actions of cAMP are terminated by an elaborate series of enzymes. cAMP-stimulated phosphorylation of enzyme

substrates is rapidly reversed by a diverse group of specific and nonspecific phosphatases. cAMP itself is degraded to 5'-AMP by several cyclic nucleotide phosphodiesterases (PDEs; Figure 2–13)

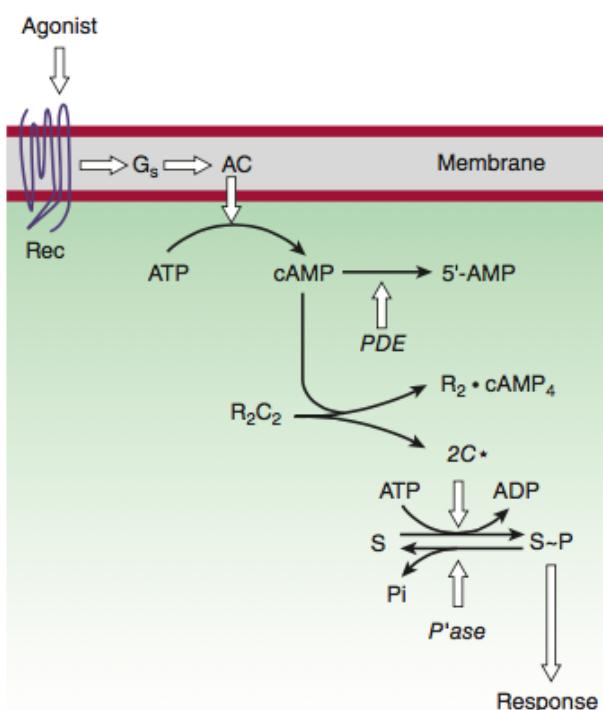


FIGURE 2–13 The cAMP second messenger pathway. Proteins include hormone receptors (Rec), a stimulatory G protein (G_s), catalytic adenylyl cyclase (AC), phosphodiesterases (PDE) that hydrolyze cAMP, cAMP-dependent kinases, with regulatory (R) and catalytic (C) subunits, protein substrates (S) of the kinases, and phosphatases (P'ase), which remove phosphates from substrate proteins. Open arrows denote regulatory effects.

B. Phosphoinositides and Calcium

Another well-studied second messenger system involves hormonal stimulation of

phosphoinositide hydrolysis (Figure 2–14). Some of the hormones, neurotransmitters, and growth factors that trigger this pathway bind to receptors linked to G proteins, whereas others bind to receptor tyrosine kinases. In all cases, the crucial step is stimulation of a membrane enzyme, phospholipase C (PLC), which splits a minor phospholipid component of the plasma membrane, phosphatidylinositol-4,5-bisphosphate (PIP₂), into two second messengers, **diacylglycerol (DAG)** and **inositol- 1,4,5-trisphosphate (IP₃)** or

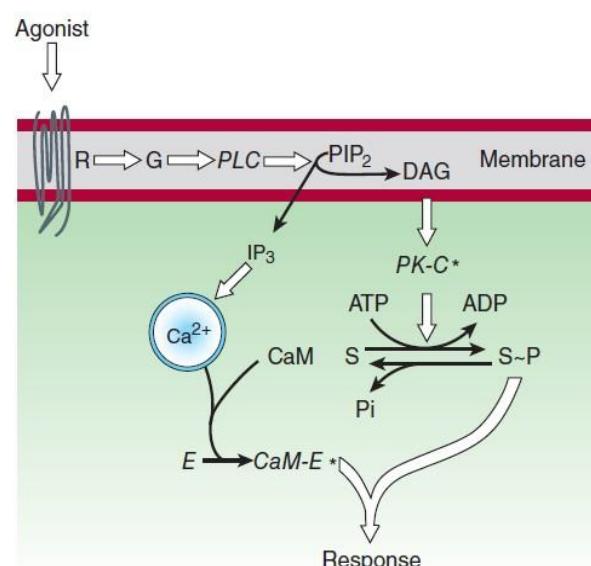


FIGURE 2–14 The Ca^{2+} -phosphoinositide signaling pathway. Key proteins include hormone receptors (R), a G protein (G), a phosphoinositide-specific phospholipase C (PLC), protein kinase C substrates of the kinase (S), calmodulin (CaM), and calmodulin-binding enzymes (E), including kinases, phosphodiesterases, etc. (PIP₂, phosphatidylinositol-4,5-bisphosphate; DAG, diacylglycerol; IP₃, inositol trisphosphate. Asterisk denotes activated state. Open arrows denote regulatory effects.)

InsP3).

The phosphoinositide signaling pathway is much more complex than the cAMP pathway.

Kinases with limited substrate specificity (eg, myosin light-chain kinase) in addition to a general calcium- and calmodulin-dependent kinase that can phosphorylate a wide variety of protein substrates.

Furthermore, at least nine structurally distinct types of protein kinase C have been identified.

C. Cyclic Guanosine Monophosphate (cGMP)

In intestinal mucosa and vascular smooth muscle, the cGMP-based signal transduction mechanism closely parallels the cAMP-mediated signaling mechanism.

Ligands detected by cellsurface receptors stimulate membrane-bound guanylylcyclase to

produce cGMP, and cGMP acts by stimulating a cGMP-dependent protein kinase. The actions of cGMP in these cells are terminated by enzymatic degradation of the cyclic nucleotide and by dephosphorylation of kinase substrates.

Interplay among Signaling Mechanisms

The calcium-phosphoinositide and cAMP signaling pathways oppose one another in some cells and are complementary in others. For example, vasopressor agents that contract smooth muscle act by IP₃-mediated mobilization of Ca²⁺, whereas agents that relax smooth muscle often act by elevation of cAMP. In contrast, cAMP and phosphoinositide second messengers act together to stimulate glucose release from the liver.

Phosphorylation: A Common Theme

Almost all second messenger signaling involves reversible phosphorylation, which performs two principal functions in signaling:

- i. Amplification

ii. Flexible regulation.

Amplification

In amplification, rather like GTP bound to a G protein, the attachment of a phosphoryl group to a serine, threonine, or tyrosine residue powerfully amplifies the initial regulatory signal by recording a molecular memory that the pathway has been activated; dephosphorylation erases the memory, taking a longer time to do so than is required for dissociation of an allosteric ligand.

Flexible regulation

In flexible regulation, differing substrate specificities of the multiple protein kinases regulated by second messengers provide branchpoints in signaling pathways that may be independently regulated. In this way, cAMP, Ca²⁺, or other second messengers can use the presence or absence of particular kinases or kinase substrates to produce quite different effects in different cell types.

RECEPTOR CLASSES & DRUG DEVELOPMENT

Evolution has created many different receptors that function to mediate responses to any individual chemical signal. In some cases, the same chemical acts on completely different structural receptor classes.

The principle of drug selectivity may even apply to structurally identical receptors expressed in different cells. For example, tamoxifen acts as an *antagonist* on estrogen receptors expressed in mammary tissue but as an *agonist* on estrogen receptors in bone.

New drug development is not confined to agents that act on

receptors for extracellular chemical signals. Increasingly, pharmaceutical chemists are determining whether elements of signaling pathways distal to the receptors may also serve as targets of selective and useful drugs.

RELATION BETWEEN DRUG DOSE & CLINICAL RESPONSE

When faced with a patient who needs treatment, the prescriber must make a choice among a

variety of possible drugs and devise a dosage regimen that is likely to produce maximal benefit and minimal toxicity. To make rational therapeutic decisions, the prescriber must

understand how drug-receptor interactions underlie the relations between dose and response in patients.

Dose & Response in Patients

A. Graded Dose-Response Relations

To choose among drugs and to determine appropriate doses of a drug, the prescriber must know the relative **pharmacologic potency** and **maximal efficacy** of the drugs in relation to the desired therapeutic effect.(see Figure 2–15).

Graded Dose-Response Relations

1. Potency

Drugs A and B are said to be more potent than drugs C and D .Potency refers to the concentration (EC50) or dose (ED50) of a drug required to produce 50% of that drug's maximal effect. Thus, the pharmacologic potency of drug A in Figure 2–15 is less than that of drug B, a partial agonist because the EC50 of A is greater than the EC50 of B. Potency of a drug depends in part on the affinity (K_d) of receptors for binding the drug and in part on the efficiency with which drug-receptor interaction is coupled to response.

2. Maximal efficacy

This parameter reflects the limit of the dose-response relation on the **response axis**. Drugs A, C, and D in Figure 2–15 have equal maximal efficacy, and all have greater maximal efficacy than drug B. The maximal efficacy (sometimes referred to simply as efficacy) of a drug is obviously crucial for making clinical decisions when a large response is needed. It may be determined by the drug's mode of interactions with receptors (as with partial agonists) or by characteristics of the receptoreffector system involved.

B. Shape of Dose-Response Curves

Although the responses depicted in curves A, B, and C

of Figure 2–15 approximate the shape of a simple Michaelis-Menten relation (transformed to a logarithmic plot), some

clinical responses do not. Extremely steep dose-response curves (eg, curve D) may have important clinical consequences if the upper portion of the curve represents an undesirable extent of response (eg, coma caused by a sedative-hypnotic). Steep dose-response curves in patients can result from cooperative interactions of several different actions of a drug (eg, effects on brain, heart, and peripheral vessels, all contributing to lowering of blood pressure).

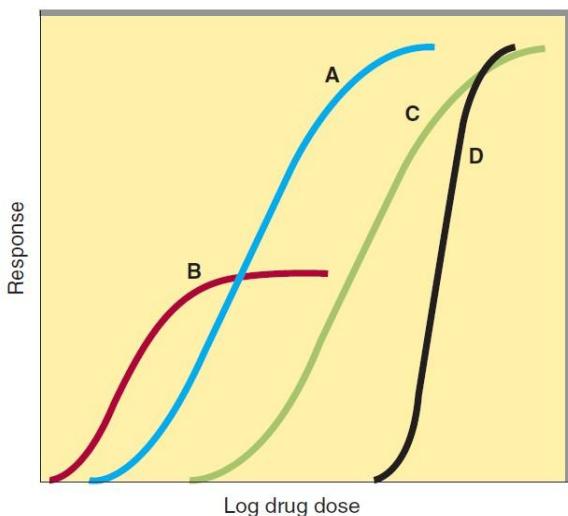


FIGURE 2-15 Graded dose-response curves for four drugs, illustrating different pharmacologic potencies and different maximal efficacies. (See text.)

C. Quantal Dose-Effect Curves

Determining the dose of drug required to produce a specified

magnitude of effect in a large number of individual patients or experimental animals and plotting the cumulative frequency distribution of responders versus the log dose (Figure 2-16). The specified quantal effect may be chosen on the basis of clinical relevance (eg, relief of headache) or for preservation of safety of experimental subjects (eg, using low doses of a cardiac stimulant and specifying an increase in heart rate of 20 bpm as the quantal effect), or it may be an inherently quantal event (eg, death of an experimental animal). For most drugs, the doses required to produce a specified quantal effect in individuals are lognormally distributed; that is, a frequency distribution of such responses plotted against the log of the dose produces a gaussian normal curve of variation (colored areas, Figure 2-16).

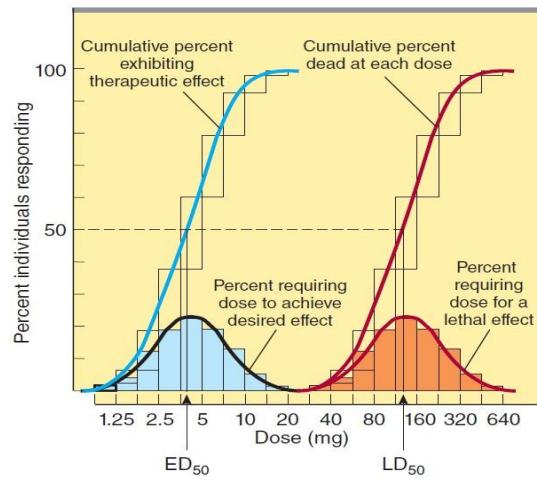
The quantal dose-effect curve is often characterized by stating the **median effective dose (ED₅₀)**, which is the dose at

which 50% of individuals exhibit the specified quantal effect. Similarly, the dose required to produce a particular toxic effect in 50% of animals is called the **median toxic dose**(TD₅₀). If the toxic effect is death of the animal, a **median lethaldose (LD₅₀)** may be experimentally defined.

Quantal dose-effect curves may also be used to generate information regarding the margin of safety to be expected from a particular drug used to produce a specified effect. One measure, which relates the dose of a drug required to produce a desired effect to that which produces an undesired effect, is the **therapeutic index**. The therapeutic index of a drug in humans is almost never known with real precision; instead, drug trials and accumulated clinical experience often reveal a range of usually effective doses and a different (but sometimes overlapping) range of possibly toxic doses. The range between the minimum toxic dose and the

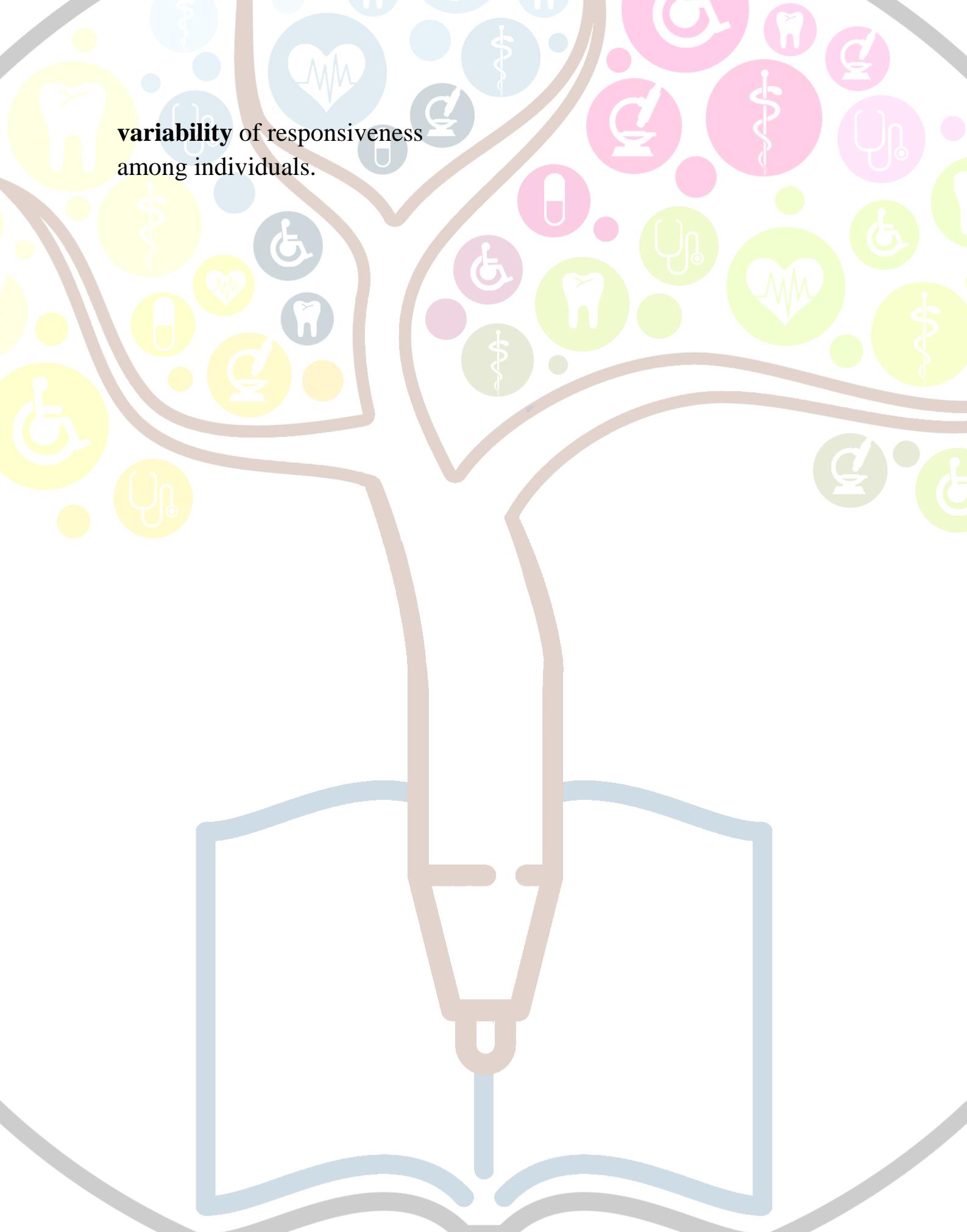
minimum therapeutic dose is called the **therapeutic window**.

Finally, note that the quantal dose-effect curve and the graded dose-response curve summarize somewhat different sets of information, although both appear sigmoid in shape on a semilogarithmic plot (compare Figures 2–15 and 2–16). Critical information required for making rational therapeutic decisions can be obtained from each type of



curve.

Both curves provide information regarding the **potency** and **selectivity** of drugs; the graded dose-response curve indicates the **maximal efficacy** of a drug, and the quantal dose-effect curve indicates the potential



variability of responsiveness
among individuals.

ریکولر

Variation in Drug Responsiveness

Quantitative variations in drug response are in general more common and more clinically important. An individual patient is **hyporeactive** or **hyperreactive** to a drug in that the intensity of effect of a given dose of drug is diminished or increased compared with the effect seen in most individuals. With some drugs, the intensity of response to a given dose may change during the course of therapy; in these cases, responsiveness usually decreases as a consequence of continued drug administration, producing a state of relative **tolerance** to the drug's effects.

When responsiveness diminishes rapidly after administration of a drug, the response is said to be subject to **tachyphylaxis**.

Four general mechanisms may contribute to variation in drug responsiveness among patients or within an individual patient at different times.

A. Alteration in Concentration of Drug That Reaches the Receptor

Patients may differ in the rate of absorption of a drug, in distributing it through body compartments, or in clearing the drug from the blood. Some differences can be predicted on the basis of age, weight, sex, disease state, and liver and kidney function, and by testing specifically for genetic differences that may result from inheritance of a functionally distinctive complement of drug-metabolizing enzymes. Another important mechanism influencing drug availability is active transport of drug from the cytoplasm, mediated by a family of membrane transporters encoded by the so-called multidrug resistance (*MDR*) genes.

B. Variation in Concentration of an Endogenous Receptor Ligand

This mechanism contributes greatly to variability in responses to pharmacologic

antagonists. Thus, propranolol, a B-adrenoceptor antagonist, markedly slows the heart rate of a patient whose endogenous catecholamines are elevated (as in pheochromocytoma) but does not affect the resting heart rate of a well-trained marathon runner.

C. Alterations in Number or Function of Receptors

Experimental studies have documented changes in drug response caused by increases or decreases in the number of receptor sites or by alterations in the efficiency of coupling of receptors to distal effector mechanisms. Genetic factors also can play an important role in altering the number or function of specific receptors.

D. Changes in Components of Response Distal to the Receptor

Although a drug initiates its actions by binding to receptors, the response observed in a patient depends on the functional integrity of biochemical processes in the responding cell and physiologic

regulation by interacting organ systems. Most important class of mechanisms that cause variation in responsiveness. Before initiating therapy with a drug, the prescriber should be aware of patient characteristics that may limit the clinical response. These characteristics include the age and general health of the patient and—most importantly—the severity and pathophysiologic mechanism of the disease. The most important potential cause of failure to achieve a satisfactory response is that the diagnosis diagnosis is wrong or physiologically incomplete.

Clinical Selectivity: Beneficial versus Toxic Effects of Drugs

It is clear that *no drug causes only a single, specific effect.* Even if the chemical structure of a drug allowed it to bind to only one kind of receptor, the biochemical processes controlled by such receptors would take place in many cell types and would be coupled to many other biochemical functions; as a result,

the patient and the prescriber would probably perceive more than one drug effect.

Accordingly, drugs are only *selective*—rather than specific—in their actions, because they bind to one or a few types of receptor more tightly than to others and because these receptors control discrete processes that result in distinct effects.

It is only because of their selectivity that drugs are useful in clinical medicine. Selectivity can be measured by comparing binding affinities of a drug to different receptors or by comparing ED₅₀s for different effects of a drug *in vivo*. In drug development and in clinical medicine, selectivity is usually considered by separating effects into two categories:

- i. **Beneficial or therapeutic effects.**
- ii. **Toxic or adverse effects.**

A. Beneficial and Toxic Effects Mediated by the Same Receptor-Effector Mechanism

Much of the serious drug toxicity in clinical practice represents a direct pharmacologic extension of the therapeutic actions of the drug. In some of these cases, toxicity may be avoided by judicious management of the dose of drug administered, guided by careful monitoring of effect and aided by ancillary measures. In still other cases, the toxicity may be avoided by not administering the drug at all, if the therapeutic indication is weak or if other therapy is available.

In certain situations, a drug is clearly necessary and beneficial but produces unacceptable toxicity when given in doses that produce optimal benefit. In such situations, it may be necessary to add another drug to the treatment regimen.

B. Beneficial and Toxic Effects Mediated by Identical Receptors but in Different Tissues or by Different Effector Pathways

Many drugs produce both their desired effects and adverse effects by acting on a single receptor type in different tissues.

Three therapeutic strategies are used to avoid or mitigate this sort of toxicity:

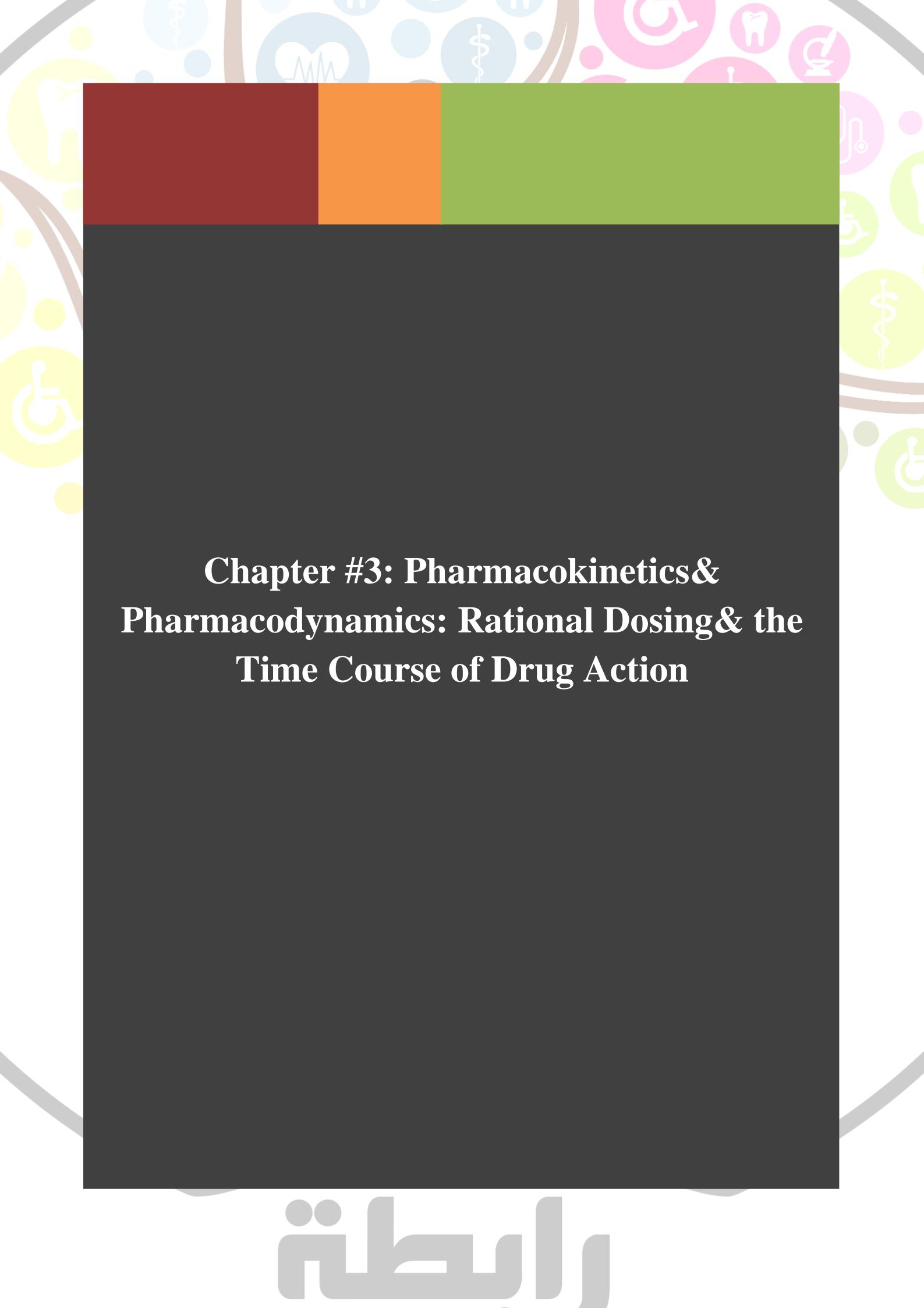
1. the drug should always be administered at the lowest dose that produces acceptable benefit.
2. adjunctive drugs that act through different receptor mechanisms and produce different toxicities may allow lowering the dose of the first drug, thus limiting its toxicity.
3. selectivity of the drug's actions may be increased by manipulating the concentrations of drug available to receptors in different parts of the body.

C. Beneficial and Toxic Effects Mediated by Different Types of Receptors

All receptors are grouped in functional families, each responsive to a small class of endogenous agonists. The receptors and their associated therapeutic uses were discovered by analyzing effects of the physiologic chemical signals—catecholamines, histamine, acetylcholine, and corticosteroids.

Several other drugs were discovered by exploiting therapeutic or toxic effects of chemically similar agents observed in a clinical context.

Often the new agents turn out to interact with receptors for endogenous substances. It is likely that other new drugs will be found to do so in the future, perhaps leading to the discovery of new classes of receptors and endogenous ligands for future drug development. Thus, the propensity of drugs to bind to different classes of receptor sites is not only a potentially vexing problem in treating patients, it also presents a continuing challenge to pharmacology and an opportunity for developing new and more useful drugs.



Chapter #3: Pharmacokinetics& Pharmacodynamics: Rational Dosing& the Time Course of Drug Action

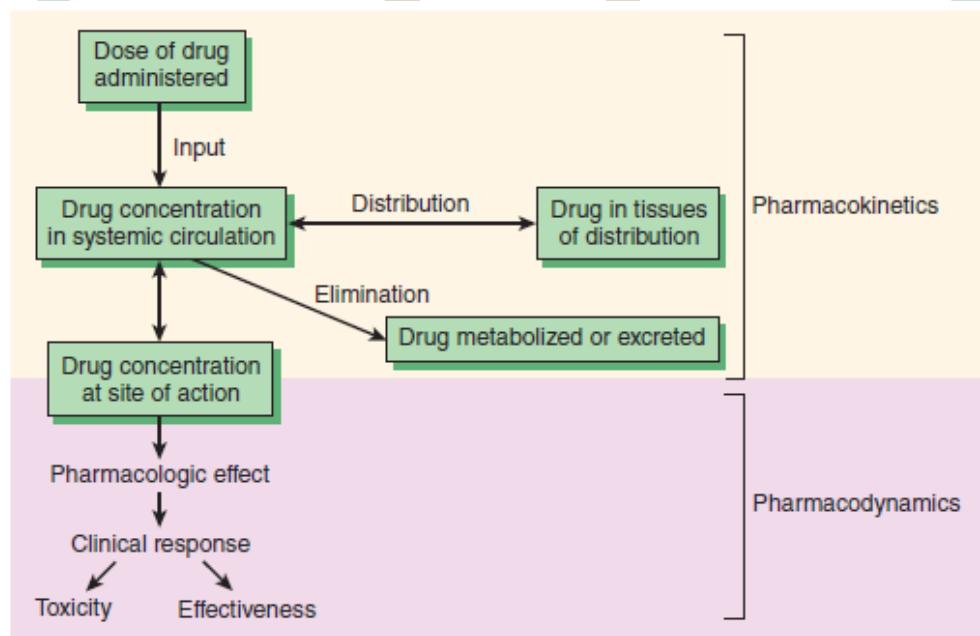


The goal of therapeutics is to achieve a desired beneficial effect with minimal adverse effects. When a medicine has been selected for a patient, the clinician must determine the dose that most closely achieves this goal.

Pharmacodynamics	Pharmacokinetics
<p>Governs the concentration-effect part of the interaction.</p> <p>Concepts of maximum response and sensitivity determine the magnitude of the effect at a particular concentration.</p>	<p>Deals with the dose-concentration part.</p> <p>Processes of absorption, distribution, and elimination determine how rapidly and for how long the drug will appear at the target organ.</p>

The importance of pharmacokinetics and pharmacodynamics in patient care thus rests upon the improvement in therapeutic benefit and reduction in toxicity that can be achieved by application of these principles.

PHARMACOKINETICS



Volume of Distribution

Volume of distribution (V) relates the amount of drug in the body to the concentration of drug (C) in blood or plasma:

$$V = \frac{\text{Amount of drug in body}}{C}$$

The volume of distribution may be defined with respect to blood, plasma, or water (unbound drug), depending on the concentration used in equation (1) (C \square C_b, C_p, or C_u). An apparent volume may be appreciated by comparing the volumes of distribution of drugs.

Clearance

Drug clearance principles are similar to the clearance concepts of renal physiology. Clearance of a drug is the factor that predicts the rate of elimination in relation to the drug concentration (C):

$$CL = \frac{\text{Rate of elimination}}{C}$$

Clearance, like volume of distribution, may be defined with respect to blood (CL_b), plasma (CL_p), or unbound in

water (CL_u), depending on where and how the concentration is measured. total systemic clearance

$$CL_{\text{systemic}} = CL_{\text{kidney}} + CL_{\text{liver}} + CL_{\text{other}}$$

Half-Life

Half-life (t_{1/2}) is the time required to change the amount of drug in the body by one-half during elimination will depend on both the volume of distribution and the clearance:

$$t_{1/2} = \frac{0.7 \times V}{CL}$$

Half-life is useful because it indicates the time required to attain 50% of steady state—or to decay 50% from steady-state conditions—after a change in the rate of drug administration.

Drug Accumulation

Whenever drug doses are repeated, the drug will accumulate in the body until dosing stops. This is because it takes an infinite time (in theory) to eliminate all of a given dose.

In practical terms, this means that if the dosing interval is shorter than four half-lives, accumulation will be detectable.

Bioavailability

Bioavailability is defined as the fraction of unchanged drug reaching the systemic circulation following administration by any route.

For an intravenous dose, bioavailability is assumed to be equal to unity.

For a drug administered orally, bioavailability may be less than

100 % for two main reasons—
incomplete extent of absorption
across the gut wall and first-pass elimination by the liver ;

A. Extent of Absorption

After oral administration, a drug may be incompletely absorbed, eg,
only 70% of a dose of digoxin reaches the systemic circulation.

Intravenous (IV) 100% (by definition)

B. First-Pass Elimination

Following absorption across the gut wall, the portal blood delivers the drug to the liver prior to entry into the systemic circulation.

A drug can be metabolized in the gut wall or even in the portal blood, but most commonly it is the liver that is responsible for metabolism before the drug reaches the systemic circulation.

Rate of Absorption

The rate of absorption is determined by

The site of administration

The drug formulation

Both the rate of absorption and the extent of input can influence the clinical effectiveness of a drug for the three different dosage forms depicted. Differences in the rate of absorption may become important for drugs given as a single dose, such as a hypnotic used to induce sleep. In this case, drug from dosage form A would reach its target concentration.

Extraction Ratio & the First-Pass Effect

Systemic clearance is not affected by bioavailability. However, clearance can markedly affect the extent of availability because it determines the extraction

ratio. Of course, therapeutic blood concentrations may still be reached by the oral route of administration if larger doses are given. However, in this case, the concentrations of the drug metabolites will be increased compared with those that would occur following intravenous administration. Lidocaine and verapamil are both used to treat cardiac arrhythmias and have bioavailability less than 40%, but lidocaine is never given orally because its metabolites are believed to contribute to central nervous system toxicity. Drugs with high extraction ratios will show marked variations in bioavailability

between subjects because of differences in hepatic function and blood flow.

Alternative Routes of Administration & the First-Pass Effect

There are several reasons for different routes of administration used in clinical medicine for convenience

Example:	Reason:
Oral	To maximize concentration at the site of action and minimize it elsewhere.
Topical	To prolong the duration of drug absorption.
Transdermal, sublingual or rectal	To avoid the first-pass effect.

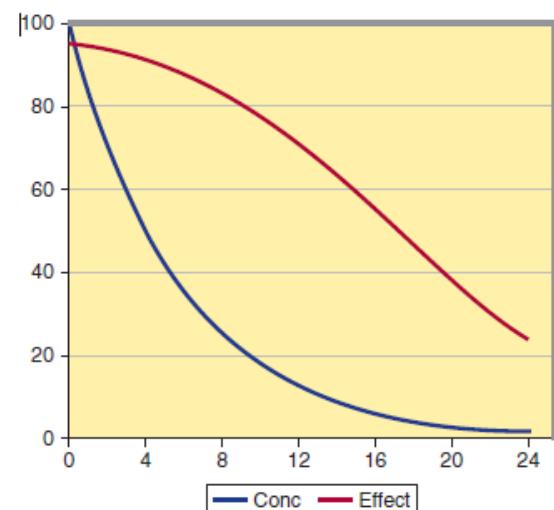
The hepatic first-pass effect can be avoided to a great extent by use of sublingual tablets and transdermal preparations and to a lesser extent by use of rectal suppositories. Sublingual absorption provides direct access to systemic—not portal—veins. The transdermal route offers the same advantage.

Immediate Effects

In the simplest case, drug effects are directly related to plasma concentrations, but this does not necessarily mean that effects simply parallel the time course of concentrations. Because the relationship between drug concentration and effect is not linear, the effect

will not usually be linearly proportional to the concentration.

Consider the effect of an angiotensin-converting enzyme (ACE) inhibitor, such as enalapril, on ACE.



Time course (hours) of angiotensin-converting enzyme (ACE) inhibitor concentrations and effects.

The blue line shows the plasma enalapril concentrations in nanograms per milliliter after a single oral dose. The red line indicates the percentage inhibition of its target, ACE. Note the different shapes of the concentration-time course (exponentially decreasing) and the effect-time course (linearly decreasing in its central portion).

Delayed Effects

Changes in drug effects are often delayed in relation to changes in plasma concentration. This delay may reflect the time required for the drug to distribute from plasma to the site of action. This will be the case for almost all drugs. The delay due to distribution is a pharmacokinetic phenomenon that can account for delays of a few minutes. This distributional process can account for the short delay of effects after rapid intravenous injection of central nervous system (CNS)-active agents such as thiopental. Some drugs bind tightly to receptors, and it is the half-life of dissociation that determines the delay in effect, eg, for digoxin.

Note that it is the dissociation process that controls the time to

receptor equilibrium. This is exactly the same principle as the elimination process controlling the time to accumulate to steady state with a constant rate infusion.

A common reason for more delayed drug effects—especially those that take many hours or even days to occur—is the slow turnover of a physiologic substance that is involved in the expression of the drug effect.

Cumulative Effects

Some drug effects are more obviously related to a cumulative action than to a rapidly reversible one. The renal toxicity of aminoglycoside antibiotics (eg, gentamicin) is greater when administered as a

constant infusion than with intermittent dosing.

It is the accumulation of aminoglycoside in the renal cortex that is thought to cause renal damage.

The effect of many drugs used to treat cancer also reflects accumulative action—eg, the extent of binding of a drug to DNA is proportional to drug concentration and is usually irreversible.

THE TARGET CONCENTRATION APPROACH TO DESIGNING A RATIONAL DOSAGE REGIMEN

A rational dosage regimen is based on the assumption that there is a **target concentration** that will produce the desired therapeutic effect. By considering the pharmacokinetic factors that determine the dose-concentration relationship, it is possible to individualize the

dose regimen to achieve the target concentration.

Maintenance Dose

In most clinical situations, drugs are administered in such a way as to maintain a steady state of drug in the body, ie, just enough drug is given in each dose to replace the drug eliminated since the preceding dose. Thus, calculation of the appropriate maintenance dose is a primary goal. Clearance is the most important pharmacokinetic term to be considered in defining a rational steady-state drug dosage regimen.

The volume of distribution and the half-life need not be known in order to determine the average plasma concentration

$$\text{Maintenance dose} = \text{Dosing rate} \times \text{Dosing interval}$$

expected from a given dosing rate or to predict the dosing rate for a desired target concentration.

Loading Dose

it may be desirable to administer a loading dose that promptly raises the concentration of drug in plasma to the target concentration.

Amount in the body
Loading dose = immediately following the loading dose
 $= V \times TC$

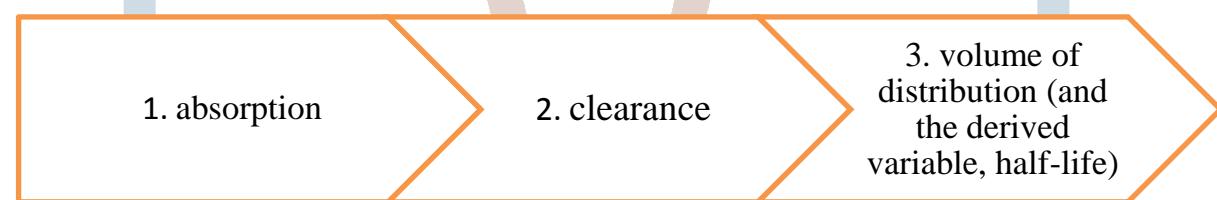
When the time to reach steady state is appreciable, as it is for drugs with long half-lives, reach the average steady-state concentration and will not match the peak steady-state concentration . To match the peak steady-state concentration, the loading dose can be calculated from equation;

Loading dose = Maintenance dose ×
Accumulation factor

TARGET CONCENTRATION INTERVENTION: APPLICATION OF PHARMACOKINETICS & PHARMACODYNAMICS TO DOSE INDIVIDUALIZATION

The basic principles outlined above can be applied to the interpretation of clinical drug concentration measurements on the basis of three major pharmacokinetic variables:

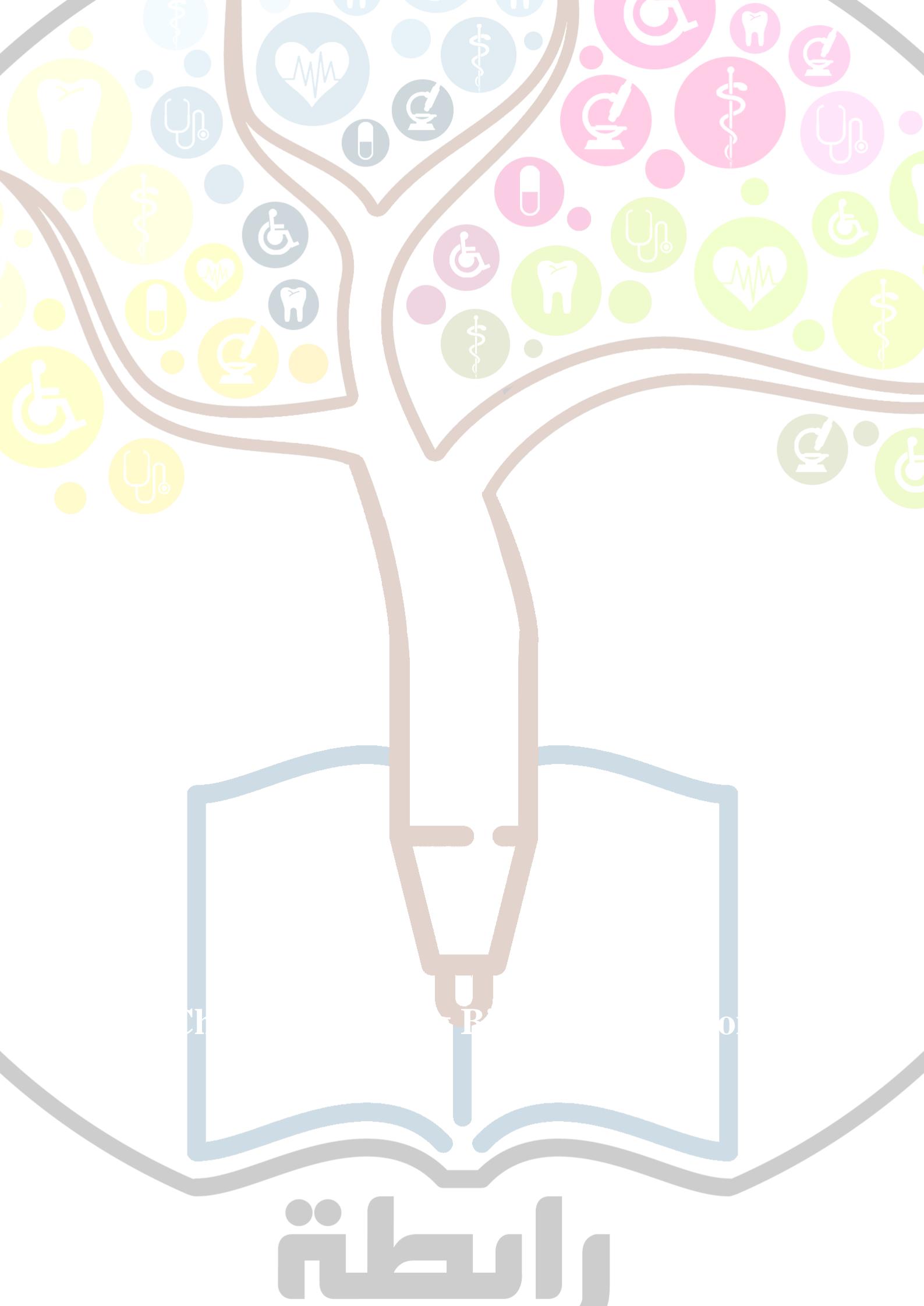
In addition, it may be necessary to consider two pharmacodynamic



variables:

1. maximum effect attainable in the target tissue

2. sensitivity of the tissue to the drug



Pharmacokinetic Variables

A. Input	The amount of drug that enters the body.
B. Clearance	Abnormal clearance may be anticipated when there is major impairment of the function of the kidney, liver, or heart. Creatinine clearance is a useful quantitative indicator of renal function.
C. Volume of Distribution	The apparent volume of distribution reflects a balance between binding to tissues, which decreases plasma concentration and makes the apparent volume larger, and binding to plasma proteins, which increases plasma concentration and makes the apparent volume smaller. Changes in either tissue or plasma binding can change the apparent volume of distribution determined from plasma concentration measurements.
D. Half-Life	The differences between clearance and half-life are important in defining the underlying mechanisms for the effect of a disease state on drug disposition. The metabolic processes responsible for eliminating the drug are fairly constant.

Pharmacodynamic Variables

A. Maximum Effect

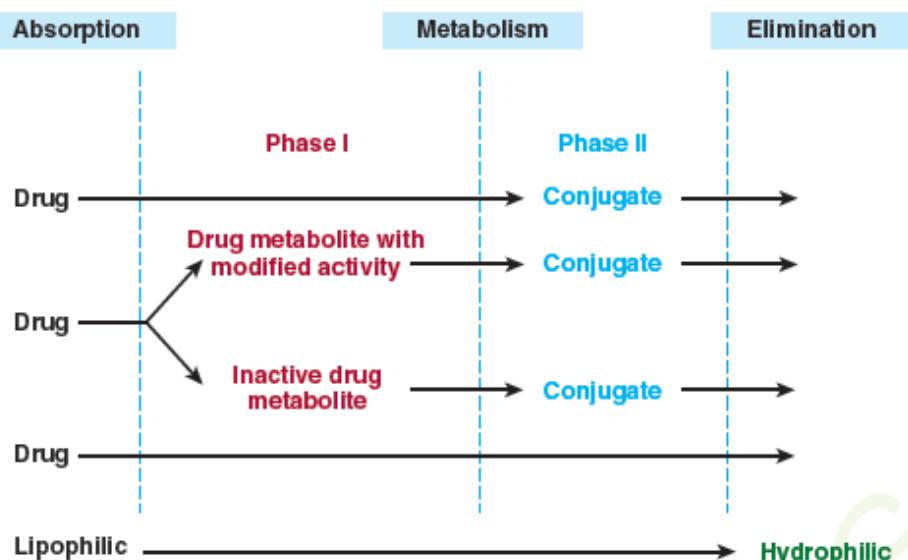
All pharmacologic responses must have a maximum effect (E_{max}).

B. Sensitivity

The sensitivity of the target organ to drug concentration is reflected by the concentration required to produce 50% of maximum effect, the C_{50} .

Biologic responses often depend on conversion of the absorbed substance into an active metabolite.

WHY IS DRUG BIOTRANSFORMATION NECESSARY?



Drug-metabolizing enzymes have been exploited in the design of pharmacologically inactive prodrugs that are converted to active molecules in the body.

THE ROLE OF BIOTRANSFORMATION IN DRUG DISPOSITION

Most metabolic biotransformations occur at some point between absorption of the drug into the circulation and its renal elimination. A few transformations occur in the intestinal lumen or intestinal wall. In general, all of these reactions can be assigned to one of two major categories called **phase I** and **phase II reactions**.

phase I

- Phase I reactions usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group ($-OH$, $-NH_2$, $-SH$). Often these metabolites are inactive, although in some instances activity is only modified or even enhanced. If phase I metabolites are sufficiently polar, they may be readily excreted.

phase II

- However, many phase I products are not eliminated rapidly and undergo a subsequent reaction in which an endogenous substrate such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid combines with the newly incorporated functional group to form a highly polar conjugate. Such conjugation or synthetic reactions are the hallmarks of phase II metabolism. A great variety of drugs undergo these sequential biotransformation reactions, although in some instances the parent drug may already possess a functional group that may form a conjugate directly.

WHERE DO DRUG BIOTRANSFORMATIONS OCCUR?

the liver is the principal organ of drug metabolism.

After oral administration, many drugs (eg, isoproterenol, meperidine, pentazocine, morphine) are absorbed intact from the small intestine and transported first via the portal system to the liver, where they undergo extensive metabolism. This process is called the **first-pass effect**. First-pass effects may limit the bioavailability of orally administered drugs (eg, lidocaine) so greatly that alternative routes of administration must be used to achieve therapeutically effective blood levels. At the subcellular level, these enzymes may be located in the endoplasmic reticulum, mitochondria, cytosol, lysosomes, or even the nuclear envelope or plasma membrane.

MICROSOMAL MIXED FUNCTION OXIDASE SYSTEM & PHASE I REACTIONS

Many drug-metabolizing enzymes are located in the lipophilic endoplasmic reticulum membranes of the liver and other tissues. When these lamellar membranes are isolated by homogenization and fractionation of the cell, they reform into vesicles called **microsomes**.

Microsomal enzymes present in SMR (smooth endoplasmic reticulum) smooth microsomes are relatively rich in enzymes responsible for oxidative drug metabolism. contain the important class of enzymes known as the **mixed function oxidases(MFOs)**, or **monooxygenases**. In this oxidation-reduction process, two microsomal enzymes play a key role:

- The first of these is a flavoprotein, **NADPHcytochrome**

P450

oxidoreductase(POR).

- The second microsomal enzyme is a hemoprotein called **cytochrome P450** .

HUMAN LIVER P450 ENZYMES

selective P450 inhibitors, have identified numerous P450 isoforms (CYP: 1A2, 2A6, 2B6, 2C8, 2C9, 2C18,

2C19, 2D6, 2E1, 3A4, 3A5, 4A11, and 7) in the human liver. Of these, **CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6,CYP2E1, and CYP3A4**. It is noteworthy that CYP3A4 alone is responsible for the metabolism of over 50% of the prescription drugs metabolized by the liver.

Enzyme Induction

- Some of the chemically dissimilar P450 substrate drugs, on repeated administration, *induce* P450 expression by enhancing the rate of its synthesis or reducing its rate of degradation.

Enzyme Inhibition

- Certain drug substrates inhibit cytochrome P450 enzyme activity.

Drug metabolism reactions :

Phase 1 (addition or uncovering of a reactive group)

- * Oxidation
 - * Reduction
 - * Hydrolysis
- Makes the molecule more susceptible to Phase 2 reactions

Phase 2 (conjugation of endogenous molecule with drug)

- * Glucuronide
 - * Sulphate
 - * Amino acids, GSH
 - * Acetylation/methylation
- Makes the molecule more polar, ideal substrates for active transport, and excretion

PHASE II REACTIONS

Parent drugs or their phase I metabolites that contain suitable chemical groups often undergo coupling or conjugation reactions with an endogenous substance to yield **drug conjugates**. Conjugates are polar molecules that are readily excreted and often inactive. Conjugate formation involves high-energy intermediates and specific transfer enzymes. Such enzymes (**transferases**) may be located in microsomes or in the cytosol.

CLINICAL RELEVANCE OF DRUG METABOLISM

The dose and frequency of administration required to achieve effective therapeutic blood and tissue levels vary in different patients because of individual differences in drug distribution and rates of drug metabolism and elimination.

Individual Differences	<ul style="list-style-type: none">Individual differences in metabolic rate depend on the nature of the drug itself.
Genetic Factors	<ul style="list-style-type: none">Genetic factors that influence enzyme levels account for some of these differences.Cigarette smokers metabolize some drugs more rapidly than nonsmokers because of enzyme induction.
Age & Sex	<ul style="list-style-type: none">Young adult male rats metabolize drugs much faster than mature female rats or prepubertal male rats.Differences in drug metabolism also exist in humans for alcohol and estrogen.
Drug-Drug Interactions (DDIs) during Metabolism	<ul style="list-style-type: none">A simultaneously administered drug.Enzyme-inducing drugs include various sedative-hypnotics, antipsychotics, anticonvulsants, the antitubercular drug rifampin, and insecticides.

Chapter #5: Pharmacogenomics

INTRODUCTION

- Pharmacogenomics, the study of genetic factors that underlie variation in drug response, is a modern term for pharmacogenetics.
- more than one genetic variant may contribute to variation in drug response.
- polymorphisms in genes that encode transporters, human leukocyte antigen (HLA) loci, cytokines, and various other proteins are also predictive of variation in therapeutic and adverse drug responses.
- The Clinical Pharmacogenetics Implementation Consortium (CPIC) published a series of guidelines for using genetic information in selecting medications and in dosing.

GENETIC VARIATIONS IN ENZYMES

Phase I enzymes

Biotransformation reactions mediated by P450
phase I enzymes typically modify functional groups (-OH, -SH, -NH₂, -OCH₃) of endogenous and xenobiotic compounds, resulting in an alteration of the biological activity of the compound.

Phase I enzymes are involved in the biotransformation of over 75% of prescription drugs; therefore, polymorphisms in these enzymes may significantly affect blood levels, which in turn may alter response to many drugs.

Phase II enzymes

Phase II enzyme biotransformation reactions typically conjugate endogenous molecules, eg, sulfuric acid, glucuronic acid, and acetic acid, onto a wide variety of substrates in order to enhance their elimination from the body.

Polymorphic phase II enzymes may diminish drug elimination and increase risks for toxicities.

PHASE I ENZYMES

CYP2D6

- cytochrome P450 2D6 is involved in the metabolism of up to one quarter of all drugs used clinically, including predominantly basic compounds such as β blockers, antidepressants, antipsychotics, and opioid analgesics.
- Similar to other polymorphic enzymes, four clinically defined metabolic phenotypes, ie, PMs, IMs, EMs, and UMs, are used to predict therapeutic and adverse responses following the administration of CYP2D6 substrates.

EXAMPLE:

Codeine, like its active metabolite morphine, binds to μ -opioid receptors in the central nervous system (CNS). Morphine is 200 times more potent as an agonist than codeine, and conversion of codeine into morphine is essential for codeine's analgesic activity. The enzyme responsible for the O-demethylation conversion of codeine into morphine is CYP2D6. Patients with normal CYP2D6 activity (ie, EMs) convert sufficient codeine to morphine (~5–10% of an administered dose) to produce the desired analgesic effect. PMs and IMs are more likely to experience insufficient pain relief, while UMs are at an increased risk for side effects, eg, drowsiness and respiratory depression, due to higher systemic concentrations of morphine.

Interestingly, gastrointestinal adverse effects, eg, constipation, are decreased in PMs, whereas the central side effects, eg, sedation and dizziness, do not differ between PMs and EMs. The antitussive properties associated with codeine are not affected by CYP2D6 activity.

CYP2C19

- Cytochrome P450 CYP2C19 is known to preferentially metabolize acidic drugs including proton-pump inhibitors, antidepressants, antiepileptics, and antiplatelet drugs.
- Four clinical phenotypes related to CYP2C19 activity (PM, IM, EM, and UM) are closely associated with genetic biomarkers that may assist in guiding individualized therapeutic dosing strategies.

- The gene that encodes CYP2C19 is highly polymorphic, with over 30 alleles defined, yet just four alleles can account for the majority of phenotypic variability, ie, CYP2C19allele *2and *3are non-functional, CYP2C19allele *1is fully functional, and CYP2C19*17has increased function.

Example:

Clopidogrel is metabolized in the body via one of two main mechanisms; approximately 85% of an administered dose is rapidly hydrolyzed by hepatic esterases to its inactive carboxylic acid derivative, while the remaining ~15% is converted via two sequential CYP mediated oxidation reactions (predominantly CYP2C19) to the active thiol metabolite responsible for antiplatelet activity.

Genetic polymorphisms in the CYP2C19gene that decrease active metabolite formation and consequently reduce the drug's antiplatelet activity are associated with variability in response to clopidogrel. Carriers of the reduced function CYP2C19 *2alleles taking clopidogrel are at increased risk for serious adverse cardiovascular events, particularly in acute coronary syndrome managed with percutaneous coronary intervention (PCI); the hazard ratios (HR) are 1.76 for *2/*2 genotype and 1.55 for *2 heterozygotes compared to noncarriers. The risk associated with stent thrombosis is even greater (HR 3.97 for *2/*2 genotype and 1.55 for *2 heterozygotes compared to noncarriers). However, for other indications, eg, atrial fibrillation and stroke, the effects of the CYP2C19*2allele are less dramatic. Thus, current clinical recommendations from CPIC are specific for acute coronary syndrome with PCI: Standard starting doses are recommended in EMs and UMs, and CPIC recommends use of an alternative antiplatelet agent, eg, prasugrel or ticagrelor, in PMs and IMs.

Dihydropyrimidine Dehydrogenase (DPD)

Example:

Three fluoropyrimidine drugs are used clinically, namely 5-fluorouracil (5-FU), capecitabine, and tegafur (only approved in Europe).

5-FU must be administered intravenously, while both capecitabine and tegafur are oral prodrugs that are rapidly converted to 5-FU in the body.

Only 1–3% of an administered dose of the prodrug is converted to the active cytotoxic metabolites, ie, 5-fluorouridine 5'-monophosphate (5-FUMP) and 5-fluoro-2'-deoxyuridine-5'-monophosphate (5-FdUMP), which effectively target rapidly dividing cancer cells and inhibit DNA synthesis.

The majority of an administered dose (~80%) is subjected to pyrimidine catabolism via DPD and is excreted in the urine.

Complete or partial deficiency of DPD can lead to dramatically reduced clearances of 5-FU, increased half-life of toxic metabolites F-UOMP and F-dUMP, and consequently an increased risk for severe dose-dependent

PHASE II ENZYMES

Uridine 5'-DiphosphoglucuronosylTransferase 1 (UGT1A1)

- The uridine 5'-diphospho-(UDP) glucuronosyltransferase 1A1 (UGT1A1) enzyme, encoded by the UGT1A1 gene, conjugates glucuronic acid onto small lipophilic molecules, eg, bilirubin and a wide variety of therapeutic drug substrates so that they may be more readily excreted into bile.
- The *28 allele is common across three major ethnic groups. Approximately 10% of European populations are homozygous carriers of the *28 allele, ie, UGT1A1 *28/*28 genotype, and are recognized clinically to have Gilbert's syndrome.
- The *28 allele is characterized by an extra TA repeated in the proximal promoter region

and is associated with reduced expression of the UGT1A1 enzyme.

- Clinically, Gilbert's syndrome is generally benign; however, affected individuals may have 60–70% increased levels of circulating unconjugated bilirubin due to a ~30% reduction in UGT1A1 activity.
- Individuals with the UGT1A1*28/*28 genotype are thus at an increased risk for adverse drug reactions with UGT1A1 drug substrates due to reduced biliary elimination.
- The active SN-38 metabolite is responsible for the majority of therapeutic action as well as the dose-limiting bone marrow and gastrointestinal toxicities.

- Inactivation of SN-38 occurs via the polymorphic UGT1A1

enzyme and carriers of the UGT1A1*28 variant are consequently at increased risk for severe life-threatening toxicities due to decreased clearance of SN-38 metabolites.

Thiopurine S-Methyltransferase (TPMT)

- Thiopurine S-methyltransferase (TPMT) covalently attaches a methyl group onto aromatic and heterocyclic sulfhydryl compounds and is responsible for the pharmacologic deactivation of thiopurine drugs.
- Genetic polymorphisms in the gene encoding TPMT may lead to three clinical TPMT activity phenotypes, ie, high, intermediate, and low activity, which are associated with differing rates of inactivation of thiopurine drugs and altered risks for toxicities.

➤ Three thiopurine drugs are used clinically, ie, azathioprine, 6-mercaptopurine (6-MP), and 6-thioguanine (6-TG). All share similar metabolic pathways and pharmacology.

➤ Azathioprine (a prodrug of 6-MP) and 6-MP are used for treating immunologic disorders, while 6-MP and 6-TG are important anti-cancer agents.

➤ 6-MP and 6-TG may be activated by the salvage pathway enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRTase) to form 6-thioguanine nucleotides (TGNs), which are responsible for the majority of therapeutic efficacy as well as bone marrow toxicity.

➤ Alternatively, 6-MP and 6-TG may be inactivated by enzymes such as

polymorphic TPMT and xanthine oxidase, leaving less available substrate to be activated by HGPRTase.

OTHER ENZYMES:

G6PD

- Glucose 6-phosphate dehydrogenase (G6PD) is the first and rate limiting step in the pentose phosphate pathway and supplies a significant amount of reduced NADPH in the body.
- In red blood cells (RBCs), where mitochondria are absent, G6PD is the exclusive source of NADPH and reduced glutathione, which play a critical role in the prevention of oxidative damage.
- Following exposure to exogenous oxidative stressors, G6PD activity in RBCs increases proportionately to meet NADPH demands and ultimately to protect hemoglobin from oxidation.
- Individuals with G6PD deficiency are at increased risk for abnormal RBC destruction, ie, hemolysis, due to reduced antioxidant capacity under oxidative pressures.
- Rasburicase, a recombinant urate-oxidase enzyme, is indicated for the initial management of uric acid levels in cancer patients receiving chemotherapy.
- Rasburicase alleviates the uric acid burden that often accompanies tumor-lysing treatments by converting uric acid into allantoin, a more soluble and easily excreted molecule.
- During the enzymatic conversion of uric acid to allantoin, hydrogen peroxide, a highly reactive oxidant, is formed.
- Hydrogen peroxide must be reduced by glutathione

to prevent free radical formation and oxidative damage.

- Individuals with G6PD deficiency receiving rasburicase therapy are at greatly increased risk for severe hemolytic anemia and methemoglobinemia.

TABLE 5–3 Classification of G6PD deficiency (WHO Working Group, 1989).

World Health Organization Class	Level of Deficiency	Enzyme Activity	Clinical phenotype
I	Severe	<10%	Chronic (non-spherocytic) hemolytic anemia
II	Severe	<10%	Risk of acute hemolytic anemia; intermittent hemolysis
III	Moderate	10–60%	Risk of acute hemolytic anemia; hemolysis with stressors
IV	None	60–150%	Normal
V	None	>150%	Enhanced activity

GENETIC VARIATIONS IN TRANSPORTERS

- Plasma membrane transporters, located on epithelial cells of many tissues mediate selective uptake and efflux of endogenous compounds

and xenobiotics including many drug products.

- Transporters play important roles in determining plasma and tissue concentrations of drugs and their metabolites.
- Genetic differences in transporter genes can dramatically alter drug disposition and response and, thus may increase risk for toxicities.

ORGANIC ANION TRANSPORTER (OATP1B1)

- The OATP1B1 transporter (encoded by the *SLCO1B1* gene) is located on the sinusoidal membrane (facing the blood) of hepatocytes and is responsible for the hepatic uptake of mainly weakly acidic drugs and endogenous compounds, eg, statins, methotrexate, and bilirubin.

- The variant encodes the amino acid change,

Val174Ala, and is associated with reduced membrane expression, likely as a result of impaired trafficking capability.

- HMG-coenzyme A (CoA) reductase inhibitors (statins) Known risk factors include high statin dose, interacting medications, advanced age, and metabolic comorbidities.
- For individuals receiving simvastatin with reduced OATP1B1 function (at least one non-functional allele), CPIC recommends a lower simvastatin dose or an alternative statin.

GENETIC VARIATIONS IN IMMUNE SYSTEM FUNCTION

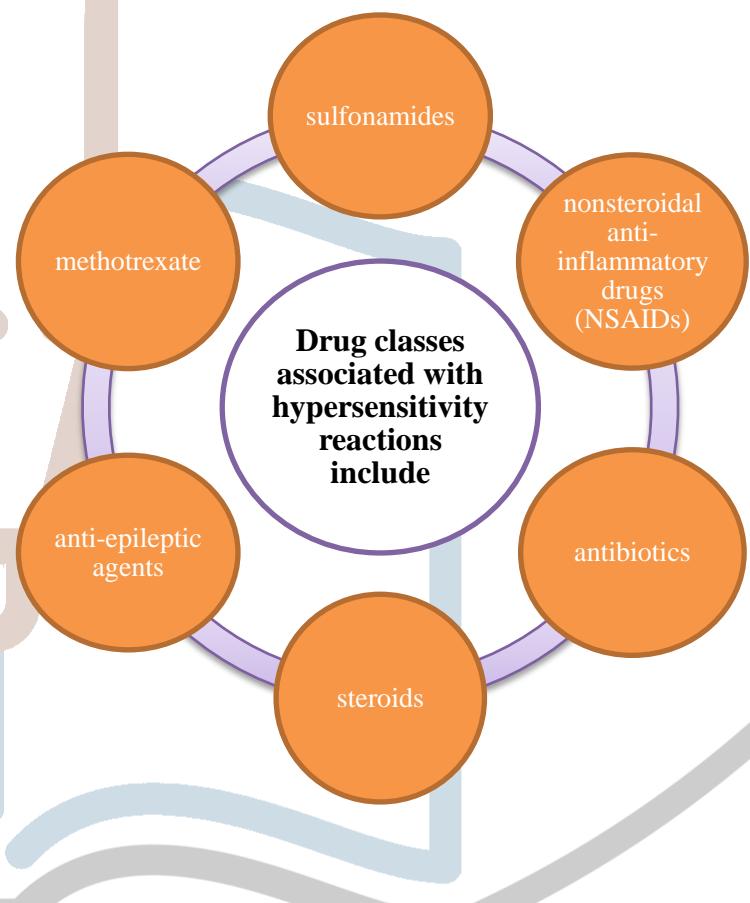
- Genetic predispositions to drug response and toxicities are not limited to genes related to pharmacokinetic

processes, eg, drug metabolizing enzymes and drug transporters.

- Additional genetic sources of variation may include pharmacodynamic genes, such as drug receptors and drug targets.

DRUG-INDUCED HYPERSENSITIVITY REACTIONS

- ❖ Hypersensitivity reactions to various drugs can range from mild rashes to severe skin toxicities.



POLYGENIC EFFECTS

- ❖ Population-based hypersensitivity reactions have been attributed to genetic polymorphisms in the HLA system, the major histocompatibility complex (MHC).
- ❖ Of the several HLA forms, HLA-B, HLA-DQ, and HLA-DR polymorphisms have been associated with many drug-induced hypersensitivity reactions.
- ❖ Many HLA-B polymorphisms have been characterized and have varying allele frequencies depending on the racial and ethnic population result in altered antigen-binding sites in the HLA molecule, which in turn may recognize different peptides.
- ❖ The selective recognition of particular drug-bound peptides by some HLA-B polymorphism products results in population-selective drug hypersensitivity reactions.
- The combinatorial effect of multiple genes on drug response, may more accurately describe individual differences with respect to clinical outcomes.
- This is best exemplified by warfarin, where the effects of two genes, CYP2C9 and VKORC1, on dose requirement have been clearly defined.

CYP2C9 & VKORC1

- CYP2C9 is a phase I drug-metabolizing enzyme that acts primarily on acidic drugs including S-warfarin, phenytoin, and NSAIDs.
- Much of the variability in metabolic clearance of CYP2C9 substrates may be accounted for with just two well studied alleles, CYP2C9*2 and *3.

- Allele CYP2C9*2 encodes an amino acid change (Arg144Cys) located on the outer surface of the CYP2C9 enzyme, which impairs interaction with the microsomal P450 oxidoreductase, and leads to reduced metabolism of CYP2C9 substrates, including a 30–40% reduction in S-warfarin metabolism.
- Allele CYP2C9*3 encodes an amino acid change (Ile359Leu) on the interior of the enzyme, which results in lowered affinity for many CYP2C9 substrates and a more marked (80–90%) reduction in S-warfarin metabolism.
- Additional reduced function alleles, eg, CYP2C9*5, *6, *8, and *11, occur more frequently in African populations.
- Vitamin K epoxide reductase complex subunit 1 (VKORC1), encoded by the VKORC1 gene, is the target of anticoagulant warfarin, and a key enzyme in the vitamin K recycling process.
- Activated vitamin K is an essential cofactor for activation of blood clotting factors II, VII, IX, and X, as well as endogenous anticoagulant proteins C and S.
- A polymorphism common across all major ethnicities is located in a transcription factor-binding site, VKORC1-1639G>A, which results in reduced expression of VKORC1 in the liver.
- The VKORC1-1639G>A polymorphism occurs most frequently in Asian populations (~90%) and least often in Africans (~10%).
- Warfarin, a vitamin K antagonist, is the oldest and most widely prescribed oral anticoagulant worldwide.

- Understanding the factors that contribute to variability in individual warfarin maintenance doses may improve therapeutic outcomes.
- The pharmacologic action of warfarin is mediated through inactivation of VKORC1.
- Individuals with decreased VKORC1 expression, eg, carriers of the -1639G>A polymorphism, are at increased risk for excessive anticoagulation following standard warfarin dosages.
- Warfarin is administered as a racemic mixture of R- and S-warfarin, and patients with reduced-function CYP2C9genotypes are at increased risk for bleeding due to decreased metabolic clearance of the more potent S-warfarin enantiomer.

AUTONOMIC DRUGS



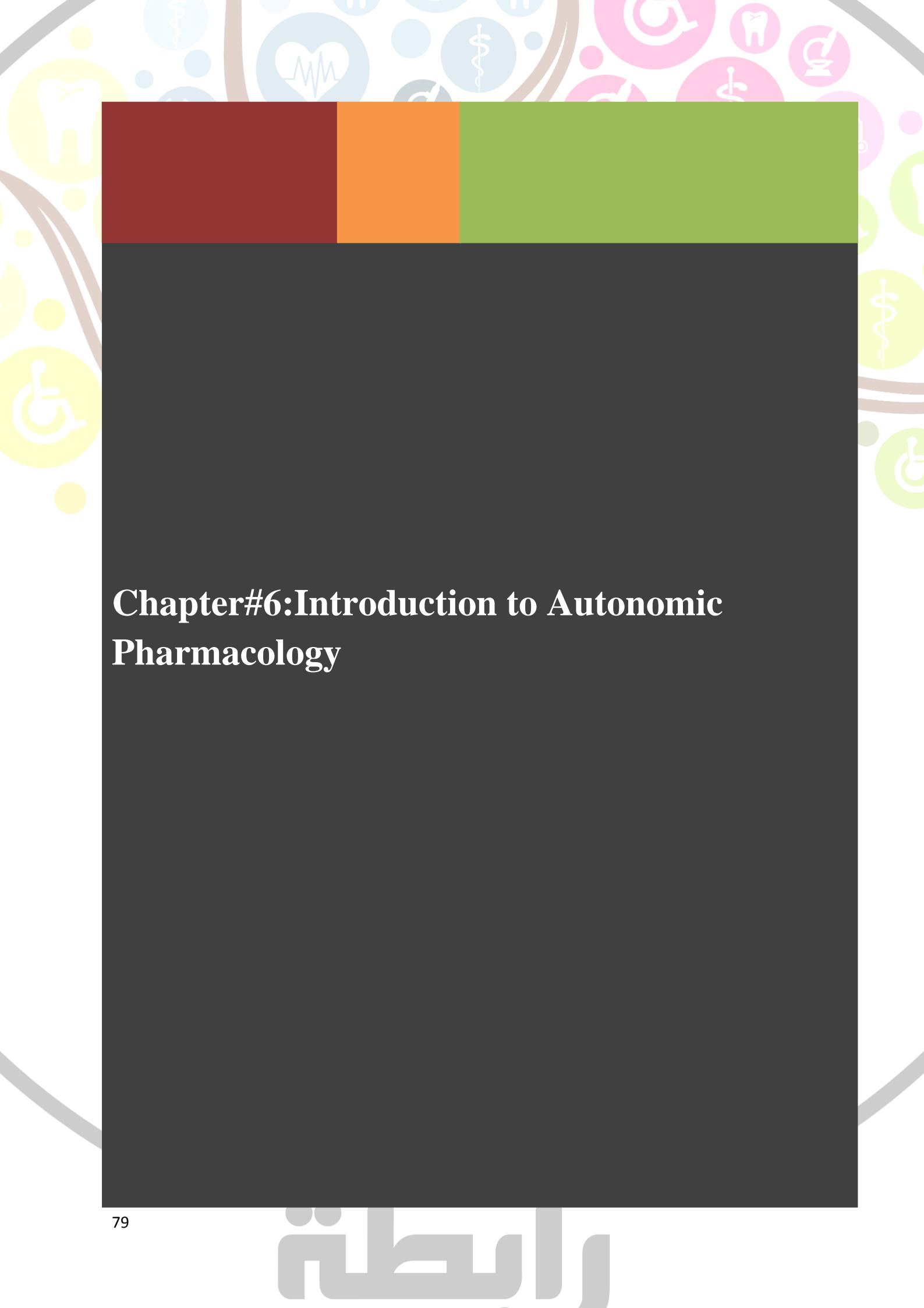
6- Introduction to Autonomic Pharmacology .

**7- Cholinceptor-Activating & Cholinesterase
-Inhibiting Drugs .**

8- Cholinceptor-Blocking Drugs .

9- Adrenoceptor Agonists& Sympathomimetic Drugs .

10- Adrenoceptor Antagonist Drug .



Chapter#6:Introduction to Autonomic Pharmacology

6 Introduction to autonomic pharmacology

The nervous system is conventionally divided into the central nervous system and the peripheral nervous system. The motor (efferent) portion of the nervous system can be divided into two major subdivisions: autonomic and somatic. The autonomic nervous system (ANS) is largely independent (autonomous) in that its activities are not under direct conscious control. It is concerned primarily with visceral functions. Evidence is accumulating that the ANS, especially the vagus nerve, also influences immune function and some CNS functions. recent evidence indicates that autonomic nerves also influence prostate cancer development and progression. The somatic subdivision is largely concerned with consciously controlled functions. Both systems have important afferent (sensory) inputs that provide information regarding the internal and external environments and modify motor output through reflex arcs of varying size and complexity. The nervous system has several properties with the endocrine system. In the nervous system, chemical transmission occurs between nerve cells and

between nerve cells and their effector cells. The transmitter crosses the cleft by diffusion and activates or inhibits the postsynaptic cell by binding to a specialized receptor molecule. By using drugs that mimic or block the actions of chemical transmitters, we can selectively modify many autonomic functions. These functions involve a variety of effector tissues.

Autonomic drugs are useful in many clinical conditions. Unfortunately, a very large number of drugs used for other purposes have unwanted effects on autonomic function.

ANATOMY OF THE AUTONOMIC NERVOUS SYSTEM:

The ANS lends itself to division on anatomic grounds into two major portions: the sympathetic division and the parasympathetic division. Neurons in both divisions originate in nuclei within the CNS and give rise to preganglionic efferent fibers that exit from the brain stem or spinal cord and terminate in motor ganglia. The sympathetic preganglionic fibers leave the CNS through the thoracic and lumbar spinal nerves.

The parasympathetic preganglionic fibers leave the CNS through the cranial nerves , and the third and fourth sacral spinal nerve roots.

Most sympathetic preganglionic fibers are short and terminate in ganglia. The remaining sympathetic preganglionic fibers are somewhat longer and terminate in prevertebral ganglia. From the ganglia, postganglionic sympathetic fibers run to the tissues innervated. Some preganglionic parasympathetic fibers terminate in parasympathetic ganglia located outside the organs .However, the majority of parasympathetic preganglionic fibers terminate on ganglion cells. In addition to these clearly defined peripheral motor portions of the ANS, large numbers of afferent fibers run from the periphery to integrating centers. Many of the sensory pathways that end in the CNS terminate in the hypothalamus and medulla and evoke reflex motor activity that is carried to the effector cells by the efferent fibers. There is increasing evidence that some of sensory fibers also have peripheral motor functions. The enteric nervous system (ENS) is a large and highly organized collection of neurons located in the walls of the (GI) system. It is sometimes considered a third division of the ANS. It is found in the wall of the GI tract from the

esophagus to the distal colon and is involved in both motor and secretory activities of the gut. It is critical in the motor activity of the colon. The ENS includes the myenteric plexus and the submucous plexus. These neuronal networks receive preganglionic fibers from the parasympathetic system and postganglionic sympathetic axons. They also receive sensory input from within the wall of the gut. Fibers from the neuronal cell bodies in these plexuses travel forward, backward, and in a circular direction to the smooth muscle of the gut to control motility and to secretory cells in the mucosa. Sensory fibers transmit chemical and mechanical information from themucosa and from stretch receptors to motor neurons in the plexuses and to postganglionic neurons in the sympathetic ganglia. The parasympathetic and sympathetic fibers that synapse on enteric plexus neurons appear to play a modulatory role, as indicated by the observation that deprivation of input from both ANS divisions does not abolish GI activity. In fact, selective denervation may result in greatly enhanced motor activity.

The ENS functions in a semiautonomous manner, utilizing input from the motor outflow of the ANS for modulation of GI activity and sending sensory information back to the CNS. The ENS also provides the necessary synchronization of impulses. The anatomy of autonomic synapses and junctions determines the localization of transmitter effects around nerve endings. Classic synapses are relatively “tight” in that the nerve terminates in small boutons very close to the tissue innervated, so that the diffusion path from nerve terminal to postsynaptic receptors is very short. The effects are thus relatively rapid and localized. In contrast, junctions between autonomic neuron terminals and effector cells differ from classic synapses in that transmitter is often released from a chain of varicosities in the postganglionic nerve fiber in the region of the smooth muscle cells rather than from boutons, and autonomic junctional clefts are wider than somatic synaptic clefts. Effects are thus slower in onset and discharge of a single motor fiber often activates or inhibits many effector cells.

NEUROTRANSMITTER CHEMISTRY OF THE AUTONOMIC NERVOUS SYSTEM :

An important classification of autonomic nerves is based on the primary transmitter molecules—Ach or norepinephrine. A large number of peripheral ANS fibers synthesize and release acetylcholine. These include all preganglionic efferent autonomic fibers and the somatic, motor fibers to skeletal muscle as well. Thus, almost all efferent fibers leaving the CNS are cholinergic. In addition, most parasympathetic postganglionic and a few sympathetic postganglionic fibers are cholinergic. A significant number of parasympathetic postganglionic neurons utilize nitric oxide or peptides as the primary transmitter. Most postganglionic sympathetic fibers release norepinephrine, they are noradrenergic fibers. Some sympathetic fibers release acetylcholine. Dopamine is a very important transmitter in the CNS. Adrenal medullary cells, which are embryologically analogous to postganglionic sympathetic neurons, release a mixture of epinephrine and norepinephrine. Finally, most autonomic nerves also release several cotransmitter substances.

Five key features of neurotransmitter function provide potential targets for pharmacologic therapy: synthesis, storage, release, termination of action of the transmitter, and receptor effects.

Cholinergic Transmission:

The terminals and varicosities of cholinergic neurons contain large numbers of small membrane-bound vesicles as well as a smaller number of large dense-cored vesicles. The large vesicles contain a high concentration of peptide cotransmitters, whereas the smaller clear vesicles contain most of the acetylcholine. Vesicles are provided with vesicle-associated membrane proteins (VAMPs), which serve to align them with release sites on the inner neuronal cell membrane and participate in triggering the release of transmitter. The release site on the inner surface of the nerve terminal membrane contains synaptosomal nerve-associated proteins (SNAPs), which interact with VAMPs. VAMPs and SNAPs are collectively called fusion proteins. This symporter can be blocked by a group of research drugs called hemicholiniums. Once synthesized, acetylcholine is transported from the cytoplasm into the vesicles by a vesicle-associated transporter (VAT) that is driven by

proton efflux. This antiporter can be blocked by the research drug vesamicol. Most of the vesicular acetylcholine (ACh) is bound to negatively charged vesicular proteoglycan (VPG). Vesicles are concentrated on the inner surface of the nerve terminal facing the synapse through the interaction of so-called SNARE proteins on the vesicle, and on the inside of the terminal cell membrane. Physiologic release of transmitter from the vesicles is dependent on extracellular calcium and occurs when an action potential reaches the terminal and triggers sufficient influx of calcium ions via N-type calcium channels. Calcium interacts with the VAMP synaptotagmin on the vesicle membrane and triggers fusion of the vesicle membrane with the terminal membrane and opening of a pore into the synapse. The opening of the pore results in release of the acetylcholine into the synaptic cleft. One depolarization of a somatic motor nerve may release quanta into the synaptic cleft. One depolarization of an autonomic postganglionic nerve varicosity or terminal probably releases less and releases it over a larger area. After release from the presynaptic terminal, ACh molecules may bind to and activate an ACh receptor (cholinoreceptor).

Eventually, all of the ACh released diffuses within range of an acetylcholinesterase (AChE) molecule.

AChE very efficiently splits acetylcholine into choline and acetate, neither of which has significant transmitter effect, and thereby terminates the action of the transmitter. Most cholinergic synapses are richly supplied with AChE; the half-life of acetylcholine is very short. AChE is also found in other tissues.

Adrenergic Transmission:

Adrenergic neurons transport a precursor amino acid (tyrosine) into the nerve ending, then synthesize the catecholamine transmitter and store it in membrane-bound vesicles. In most sympathetic postganglionic neurons, norepinephrine is the final product. In the adrenal medulla and certain areas of the brain, some norepinephrine is further converted to epinephrine. In dopaminergic neurons, synthesis terminates with dopamine. Nerve terminals are potential sites of drug action. One of these, the conversion of tyrosine to dopa by tyrosine hydroxylase, is the rate-limiting step in catecholamine transmitter synthesis. It can be inhibited by the tyrosine analog metyrosine. A high-affinity

antiporter for catecholamines located in the wall of the storage vesicle, can be inhibited by the reserpine alkaloids. Another transporter carries norepinephrine and similar molecules back into the cell cytoplasm from the synaptic cleft. NET is also commonly called uptake 1 or reuptake 1 and is partially responsible for the termination of synaptic activity. NET can be inhibited by cocaine and certain antidepressant drugs, resulting in an increase of transmitter activity in the synaptic cleft. Release of the vesicular transmitter store from noradrenergic nerve endings is similar to the calcium-dependent process previously described for cholinergic terminals. In addition to the primary transmitter (norepinephrine), (ATP), dopamine- β -hydroxylase,

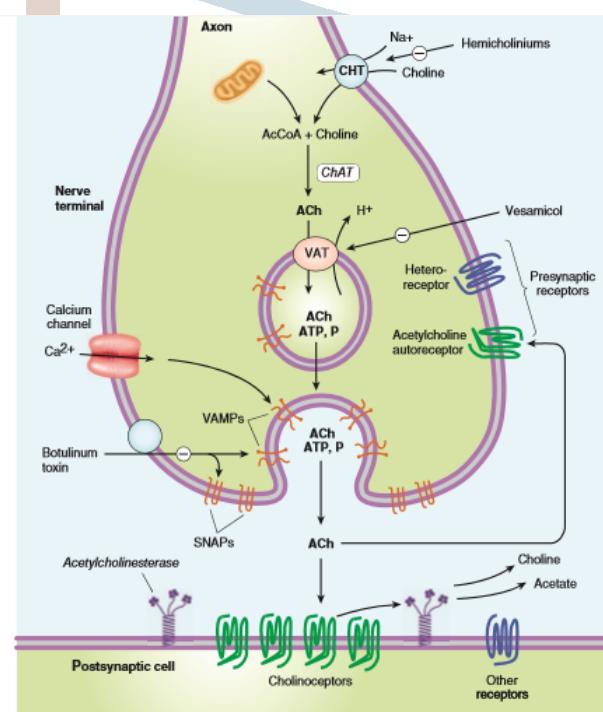


FIGURE 6-3 Schematic illustration of a generalized cholinergic junction (not to scale). Choline is transported into the presynaptic nerve terminal by a sodium-dependent choline transporter (ChT). This transporter can be inhibited by hemicholinium drugs. In the cytoplasm, acetylcholine is synthesized from choline and acetyl-CoA (AcCoA) by the enzyme choline acetyltransferase (ChAT). Acetylcholine (ACh) is then transported into the storage vesicle by a vesicle-associated transporter (VAT), which can be inhibited by vesamicol. Peptides (P), adenosine triphosphate (ATP), and proteoglycan are also stored in the vesicle. Release of transmitters occurs when voltage-sensitive calcium channels in the terminal membrane are opened, allowing an influx of calcium. The resulting increase in intracellular calcium causes fusion of vesicles with the surface membrane and exocytotic expulsion of acetylcholine and cotransmitters into the junctional cleft (see text). This step can be blocked by botulinum toxin. Acetylcholine's action is terminated by metabolism by the enzyme acetylcholinesterase. Receptors on the presynaptic nerve ending modulate transmitter release. SNAPS, synaptosomal nerve-associated proteins; VAMPs, vesicle-associated membrane proteins.

and peptide cotransmitters are also released into the synaptic cleft. Indirectly acting and mixed sympathomimetics, eg, tyramine, amphetamines, and ephedrine, are capable of releasing stored transmitter from noradrenergic nerve endings by a calcium-independent process. Amphetamines also inhibit monoamine oxidase and have other effects that result in increased norepinephrine activity in the synapse. Norepinephrine and epinephrine can be metabolized by several enzymes. Because of the high activity of monoamine oxidase in the mitochondria of the nerve terminal, there is significant turnover of norepinephrine even in the resting terminal. Since the metabolic products are excreted in the urine, an estimate of catecholamine turnover can be obtained from measurement of total metabolites in a 24-hour urine sample. However, metabolism is not the primary mechanism for termination of action of norepinephrine physiologically released from noradrenergic nerves. Termination results from two processes: 1- simple diffusion away from the receptor site. 2- reuptake into the nerve terminal

by NET or into perisynaptic glia or other cells.

Cotransmitters in Cholinergic & Adrenergic Nerves:

The vesicles of both nerves contain other substances in addition to the primary transmitter, sometimes in the same vesicles and sometimes in a separate vesicle population. Some of the substances identified to date are listed in Table 6–1. Many of these substances are also primary transmitters in the nonadrenergic, noncholinergic nerves. They appear to play several roles in the function of nerves that release acetylcholine or norepinephrine. In some cases, they provide a faster or slower action to supplement or modulate the effects of the primary transmitter. They also participate in feedback inhibition of the same and nearby nerve terminals. Growth of neurons and transmitter expression in specific neurons is a dynamic process. In addition, the transmitters released from a specific population of neurons can change in response to environmental factors such as the light-dark cycle.

AUTONOMIC RECEPTORS:

the potency of series of autonomic agonist and antagonist analogs, led to the definition of different autonomic receptor subtypes, including muscarinic and nicotinic cholinoreceptors, and α , β , and dopamine adrenoceptors (Table 6–2). The primary acetylcholine receptor subtypes were named after the alkaloids originally used in their identification: muscarinic and nicotinic receptors. Therefore, the term adrenoceptor is describe receptors that respond to catecholamines. By analogy, the term cholinoreceptor denotes receptors that respond to acetylcholine. The general class of adrenoceptors can be further subdivided into alpha-adrenoceptor, Beta-adrenoceptor, and dopamine-receptor types on the basis of both agonist and antagonist selectivity and on genomic grounds. Development of more selective blocking drugs has led to the naming of subclasses within these major types; α_1 and α_2 receptors differ in both agonist and antagonist selectivity.

TABLE 6–2 Major autonomic receptor types.

Receptor Name	Typical Locations	Result of Ligand Binding
Cholinoreceptors		
Muscarinic M ₁	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites	Formation of IP ₃ and DAG, increased intracellular calcium
Muscarinic M ₂	Myocardium, smooth muscle, some presynaptic sites; CNS neurons	Opening of potassium channels, inhibition of adenylyl cyclase
Muscarinic M ₃	Exocrine glands, vessels (smooth muscle and endothelium); CNS neurons	Like M ₁ receptor-ligand binding
Muscarinic M ₄	CNS neurons; possibly vagal nerve endings	Like M ₂ receptor-ligand binding
Muscarinic M ₅	Vascular endothelium, especially cerebral vessels; CNS neurons	Like M ₁ receptor-ligand binding
Nicotinic N _N	Postganglionic neurons, some presynaptic cholinergic terminals; pentameric receptors typically contain α and β type subunits only (see Chapter 7)	Opening of Na ⁺ , K ⁺ channels, depolarization
Nicotinic N _M	Skeletal muscle neuromuscular end plates; receptors typically contain two $\alpha 1$ and $\beta 1$ type subunits in addition to γ and δ subunits	Opening of Na ⁺ , K ⁺ channels, depolarization
Adrenoceptors		
Alpha ₁	Postsynaptic effector cells, especially smooth muscle	Formation of IP ₃ and DAG, increased intracellular calcium
Alpha ₂	Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle	Inhibition of adenylyl cyclase, decreased cAMP
Beta ₁	Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals, juxtaglomerular apparatus of renal tubules, ciliary body epithelium	Stimulation of adenylyl cyclase, increased cAMP
Beta ₂	Postsynaptic effector cells, especially smooth muscle and cardiac muscle	Stimulation of adenylyl cyclase and increased cAMP Activates cardiac G _i under some conditions.
Beta ₃	Postsynaptic effector cells, especially lipocytes; heart	Stimulation of adenylyl cyclase and increased cAMP ¹
Dopamine receptors		
D ₁ (DA ₁), D ₅	Brain; effector tissues, especially smooth muscle of the renal vascular bed	Stimulation of adenylyl cyclase and increased cAMP
D ₂ (DA ₂)	Brain; effector tissues, especially smooth muscle; presynaptic nerve terminals	Inhibition of adenylyl cyclase; increased potassium conductance
D ₃	Brain	Inhibition of adenylyl cyclase
D ₄	Brain, cardiovascular system	Inhibition of adenylyl cyclase

¹Cardiac β_3 -receptor function is poorly understood, but activation does not appear to result in stimulation of rate or force.

NONADRENERGIC, NONCHOLINERGIC (NANC) NEURONS

It has been known for many years that autonomic effector tissues contain nerve fibers that do not show the histochemical characteristics of either cholinergic or adrenergic fibers. Both motor and sensory NANC fibers are present. Although peptides are the most common transmitter. Capsaicin, a neurotoxin derived from chili peppers, can cause the release of

transmitter from such neurons and, if given in high doses, destruction of the neuron. The enteric system in the gut wall is the most extensively studied system containing NANC neurons in addition to cholinergic and adrenergic fibers. Some neurons contain as many as five different transmitters. The sensory fibers in the nonadrenergic, noncholinergic systems are probably better termed “sensory-efferent” or “sensorylocal effector” fibers. These peptides are potent agonists in many autonomic effector tissues.

FUNCTIONAL ORGANIZATION OF AUTONOMIC ACTIVITY

Autonomic function is integrated and regulated at many levels, from the CNS to the effector cells. Most regulation uses negative feedback, but several other mechanisms have been identified. Negative feedback is important in the responses of the ANS to the administration of autonomic drugs.

Central Integration:

At the highest level—midbrain and medulla—the two divisions of the ANS and the endocrine system are integrated with each other. These interactions are such that early investigators called the parasympathetic system a trophotropic one used to “rest and digest” and the sympathetic system an ergotropic one, which is activated for “fight or flight.” Although such

terms offer little insight into the mechanisms involved, they do provide simple descriptions applicable to many of the actions of the systems (Table 6–3). At a more subtle level of interactions in the brain stem, medulla, and spinal cord, there are important cooperative interactions between the parasympathetic and sympathetic systems.

For some organs, sensory fibers associated with the parasympathetic system exert reflex control over motor outflow in the sympathetic system. Thus, the sensory carotid

sinus baroreceptor fibers in the glossopharyngeal nerve have a major influence on sympathetic outflow from the vasomotor center.

TABLE 6–3 Direct effects of autonomic nerve activity on some organ systems. Autonomic drug effects are similar but not identical (see text).

Organ	Effect of			
	Sympathetic Activity		Parasympathetic Activity	
	Action ¹	Receptor ²	Action	Receptor ²
Eye				
Iris radial muscle	Contracts	α_1	—	—
Iris circular muscle	—	—	Contracts	M_3
Ciliary muscle	[Relaxes]	β	Contracts	M_3
Heart				
Sinoatrial node	Accelerates	β_1, β_2	Decelerates	M_2
Ectopic pacemakers	Accelerates	β_1, β_2	—	—
Contractility	Increases	β_1, β_2	Decreases (atria)	M_2
Blood vessels				
Skin, splanchnic vessels	Contracts	α	—	—
Skeletal muscle vessels	Relaxes	β_2	—	—
	[Contracts]	α	—	—
	Relaxes ³	M_3	—	—
Endothelium of vessels in heart, brain, viscera	—	—	Synthesizes and releases EDRF ⁴	M_3, M_5^5
Bronchiolar smooth muscle	Relaxes	β_2	Contracts	M_3
Gastrointestinal tract				
Smooth muscle				
Walls	Relaxes	$\alpha_{2b},^6 \beta_2$	Contracts	M_3
Sphincters	Contracts	α_1	Relaxes	M_3
Secretion	—	—	Increases	M_3
Genitourinary smooth muscle				
Bladder wall	Relaxes	β_2	Contracts	M_3
Sphincter	Contracts	α_1	Relaxes	M_3
Uterus, pregnant				
	Relaxes	β_2	—	...
	Contracts	α	Contracts	M_3
Penis, seminal vesicles			Ejaculation	α
				Erection
Skin				
Pilomotor smooth muscle	Contracts	α	—	—
Sweat glands				—
Eccrine	Increases	M	—	—
Apocrine (stress)	Increases	α	—	—
Metabolic functions				
Liver	Gluconeogenesis	β_2, α	—	—
Liver	Glycogenolysis	β_2, α	—	—
Fat cells	Lipolysis	β_3	—	—
Kidney	Renin release	β_1	—	—

Integration of

Cardiovascular:

Function Autonomic reflexes are particularly important in understanding cardiovascular responses to autonomic drugs. As indicated in Figure 6–7, the primary controlled variable in cardiovascular function is mean arterial pressure.

Changes in any variable contributing to mean arterial pressure , evoke powerful homeostatic secondary responses that tend to compensate for the directly evoked change. The homeostatic response may be sufficient to reduce the change in mean arterial pressure and to reverse the drug's effects on heart rate. This agent produces direct effects on both vascular and cardiac muscle. In the absence of reflex control in a patient who has had a heart transplant.

Presynaptic Regulation:

The principle of negative feedback control is also found at the presynaptic level of autonomic function. Important presynaptic feedback inhibitory control mechanisms have been shown to exist at most nerve endings. A well-documented mechanism involves the α_2 receptor located on noradrenergic nerve terminals. This receptor is activated by norepinephrine and similar molecules; activation diminishes further release of norepinephrine from these nerve endings (Table 6–4). The mechanism of this G protein mediated effect involves inhibition of the inward calcium current that causes vesicular fusion and transmitter release. Conversely, a presynaptic β receptor appears to facilitate the release of norepinephrine from some adrenergic neurons. Presynaptic receptors that respond to the primary transmitter substance released by the nerve ending are called autoreceptors. Nerve terminals also carry regulatory receptors that respond to many other substances.

Such heteroreceptors may be activated by substances released from other nerve terminals that synapse with the nerve ending. Alternatively, the ligands for these receptors may diffuse to the receptors from the blood or from nearby tissues. Some of the transmitters and receptors identified to date are listed in Table 6–4. Presynaptic regulation by a variety of endogenous chemicals probably occurs in all nerve fibers.

TABLE 6-4 Autoreceptor, heteroreceptor, and modulatory effects on nerve terminals in peripheral synapses.¹

Transmitter/Modulator	Receptor Type	Neuron Terminals Where Found
Inhibitory effects		
Acetylcholine	M ₂ , M ₁	Adrenergic, enteric nervous system
Norepinephrine	Alpha ₂	Adrenergic
Dopamine	D ₂ ; less evidence for D ₁	Adrenergic
Serotonin (5-HT)	5-HT ₁ , 5-HT ₂ , 5-HT ₃	Cholinergic preganglionic
ATP, ADP	P2Y	Adrenergic autonomic and ENS cholinergic neurons
Adenosine	A ₁	Adrenergic autonomic and ENS cholinergic neurons
Histamine	H ₃ , possibly H ₂	H ₃ type identified on CNS adrenergic and serotonergic neurons
Enkephalin	Delta (also mu, kappa)	Adrenergic, ENS cholinergic
Neuropeptide Y	Y ₁ , Y ₂ (NPY)	Adrenergic, some cholinergic
Prostaglandin E ₁ , E ₂	EP ₃	Adrenergic
Excitatory effects		
Epinephrine	Beta ₂	Adrenergic, somatic motor cholinergic
Acetylcholine	N _M	Somatic motor cholinergic
Angiotensin II	AT ₁	Adrenergic

¹A provisional list. The number of transmitters and locations will undoubtedly increase with additional research.

Postsynaptic Regulation:

Postsynaptic regulation can be considered from two perspectives:

1-modulation by previous activity at the primary receptor :

The mechanism: has been well documented in several receptor-effector systems. Up-regulation and down-regulation in response to decreased or increased activation, respectively, of the receptors. An extreme form of up-regulation occurs after denervation of some tissues, resulting in denervation supersensitivity of the tissue to activators of that receptor type. Surgical or traumatic denervation results in marked proliferation of nicotinic cholinoreceptors over all parts of the fiber, including areas not previously associated with any motor nerve junctions. A pharmacologic supersensitivity related to denervation supersensitivity occurs in autonomic effector tissues after administration of drugs that deplete transmitter stores and prevent activation of the postsynaptic receptors for a sufficient period of time.

2- modulation by other simultaneous events.

The mechanism: involves modulation of the primary transmitter-receptor event by events evoked by the same or other transmitters acting on different postsynaptic receptors. The postganglionic cells are activated as a result of binding of an appropriate ligand to a neuronal nicotinic (NN) acetylcholine receptor. The resulting fast excitatory postsynaptic potential (EPSP) evokes a propagated action potential if threshold is reached.

This event is often followed by a small and slowly developing but longer-lasting hyperpolarizing afterpotential—a slow inhibitory postsynaptic potential (IPSP). This hyperpolarization involves opening of potassium channels by M₂ cholinoreceptors. The IPSP is followed by a small, slow excitatory postsynaptic potential caused by closure of potassium channels linked to M₁ cholinoreceptors. Finally, a late, very slow EPSP may be evoked by peptides released from other fibers. These slow potentials serve to modulate the responsiveness of the postsynaptic cell to subsequent primary excitatory presynaptic nerve activity.

PHARMACOLOGIC MODIFICATION OF AUTONOMIC FUNCTION:

Because transmission involves different mechanisms in different segments of the ANS, some drugs produce highly specific effects, whereas others are much less selective in their actions. A summary of the steps in transmission of impulses in Table 6–5). Drugs that block action potential propagation are very nonselective in their action. On the other hand, drugs that act on the biochemical processes involved in transmitter synthesis and storage are more selective. Activation or blockade of effector cell receptors offers maximum flexibility and selectivity of effect attainable with currently available drugs: adrenoceptors are easily distinguished from cholinoreceptors. Furthermore, individual receptor subgroups can often be selectively activated or blocked within each major type. Even greater selectivity may be attainable in the future using drugs that target post-receptor processes.

TABLE 6–5 Steps in autonomic transmission: Effects of drugs.

Process Affected	Drug Example	Site	Action
Action potential propagation	Local anesthetics, tetrodotoxin, ¹ saxitoxin ²	Nerve axons	Block voltage-gated sodium channels; block conduction
Transmitter synthesis	Hemicholiniums	Cholinergic nerve terminals: membrane	Block uptake of choline and slow synthesis
	α -Methyltyrosine (metyrosine)	Adrenergic nerve terminals and adrenal medulla: cytoplasm	Inhibits tyrosine hydroxylase and blocks synthesis of catecholamines
Transmitter storage	Vesamicol	Cholinergic terminals: VAT on vesicles	Prevents storage, depletes
	Reserpine	Adrenergic terminals: VMAT on vesicles	Prevents storage, depletes
Transmitter release	Many ³	Nerve terminal membrane receptors	Modulate release
	ω -Conotoxin GVIA ⁴	Nerve terminal calcium channels	Reduces transmitter release
	Botulinum toxin	Cholinergic vesicles	Prevents release
	α -Latrotoxin ⁵	Cholinergic and adrenergic vesicles	Causes explosive transmitter release
	Tyramine, amphetamine	Adrenergic nerve terminals	Promote transmitter release
Transmitter reuptake after release	Cocaine, tricyclic antidepressants, SNRI antidepressants ⁶	Adrenergic nerve terminals, NET	Inhibit uptake; increase transmitter effect on post-synaptic receptors
Receptor activation or blockade	Norepinephrine	Receptors at adrenergic junctions	Binds α receptors; causes contraction
	Phentolamine	Receptors at adrenergic junctions	Binds α receptors; prevents activation
	Isoproterenol	Receptors at adrenergic junctions	Binds β receptors; activates adenylyl cyclase
	Propranolol	Receptors at adrenergic junctions	Binds β receptors; prevents activation
	Nicotine	Receptors at nicotinic cholinergic junctions (autonomic ganglia, neuromuscular end plates)	Binds nicotinic receptors; opens ion channel in post-synaptic membrane
	Tubocurarine	Neuromuscular end plates	Prevents activation
	Bethanechol	Receptors, parasympathetic effector cells (smooth muscle, glands)	Binds and activates muscarinic receptors
	Atropine	Receptors, parasympathetic effector cells	Binds muscarinic receptors; prevents activation
Enzymatic inactivation of transmitter	Neostigmine	Cholinergic synapses (acetylcholinesterase)	Inhibits enzyme; prolongs and intensifies transmitter action
	Tranylcypromine	Adrenergic nerve terminals (monoamine oxidase)	Inhibits enzyme; increases stored transmitter pool

¹Toxin of puffer fish, California newt.

Chapter #7 : cholinoreceptor-activating & cholinesterase-Inhibiting Drugs

7cholinoreceptor-activating & cholinesterase-Inhibiting Drugs

Acetylcholine-receptor stimulants and cholinesterase inhibitors make up a large group of drugs that mimic acetylcholine (cholinomimetics) (Figure 7-1). Cholinoreceptor stimulants are classified pharmacologically by their spectrum of action, depending on the type of receptor—muscarinic or nicotinic—that is activated. Cholinomimetics are also classified by their mechanism of action because some bind directly to (and activate) cholinoreceptors whereas others act indirectly by inhibiting the hydrolysis of endogenous acetylcholine.

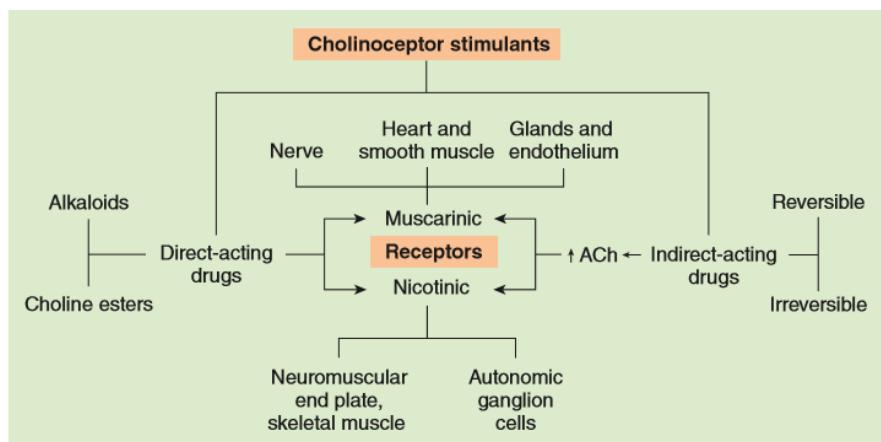


FIGURE 7-1 The major groups of cholinoreceptor-activating drugs, receptors, and target tissues. ACh, acetylcholine.

SPECTRUM OF ACTION OF CHOLINOMIMETIC DRUGS:

Early studies of the parasympathetic nervous system showed that the alkaloid muscarine mimicked the effects of parasympathetic nerve discharge; that is, the effects were parasympathomimetic. Application of muscarine to ganglia and to autonomic effector tissues showed that the parasympathomimetic action of the alkaloid occurred through an action on receptors at effector cells, not those in ganglia.

The effects of Ach itself and of other cholinomimetic drugs at autonomic neuroeffector junctions are called parasympathomimetic effects and are mediated by muscarinic receptors.

In contrast, low concentrations of the alkaloid nicotine stimulated autonomic ganglia and skeletal muscle neuromuscular junctions but not autonomic effector cells. When acetylcholine was later identified as the physiologic transmitter at both muscarinic and nicotinic receptors, both receptors were recognized as cholinoreceptor. Muscarinic receptors contain seven transmembrane domains whose third cytoplasmic loop is coupled to G proteins that function as transducers. These receptors regulate the production of intracellular second messengers and modulate certain ion channels via their G proteins. Agonist selectivity is determined by the subtypes of muscarinic receptors and G proteins. When expressed in cells, muscarinic receptors form dimers or oligomers that are thought to function in receptor movement between the endoplasmic reticulum and plasma membrane and in signaling. Conceivably, agonist or antagonist ligands could signal by changing the ratio of monomeric to oligomeric receptors. Nicotinic receptors are part of a transmembrane polypeptide. Nonselective cholinoreceptor stimulants in sufficient dosage can produce very diffuse and marked alterations in organ system function.

Fortunately, drugs are available that have a degree of selectivity, so that desired effects can often be achieved while avoiding or minimizing adverse effects.

Some drugs stimulate either muscarinic receptors or nicotinic receptors selectively. Some agents stimulate nicotinic receptors at neuromuscular

TABLE 7-1 Subtypes and characteristics of cholinoreceptors.

Receptor Type	Other Names	Location	Structural Features	Postreceptor Mechanism
M ₁		Nerves	Seven transmembrane segments, G _{q/11} protein-linked	IP ₃ , DAG cascade
M ₂	Cardiac M ₂	Heart, nerves, smooth muscle	Seven transmembrane segments, G _{i/o} protein-linked	Inhibition of cAMP production, activation of K ⁺ channels
M ₃		Glands, smooth muscle, endothelium	Seven transmembrane segments, G _{q/11} protein-linked	IP ₃ , DAG cascade
M ₄		CNS	Seven transmembrane segments, G _{i/o} protein-linked	Inhibition of cAMP production
M ₅		CNS	Seven transmembrane segments, G _{q/11} protein-linked	IP ₃ , DAG cascade
N _M	Muscle type, end plate receptor	Skeletal muscle neuromuscular junction	Pentamer ¹ [(α1) ₂ β1δγ] ¹	Na ⁺ , K ⁺ depolarizing ion channel
N _N	Neuronal type, ganglion receptor	CNS, postganglionic cell body, dendrites	Pentamer ¹ with α and β subunits only, eg, (α4) ₂ (β2) ₃ (CNS) or α3α5(β2) ₃ (ganglia)	Na ⁺ , K ⁺ depolarizing ion channel

¹Pentameric structure in *Torpedo* electric organ and fetal mammalian muscle has two α1 subunits and one each of β1, δ, and γ subunits. The stoichiometry is indicated by subscripts, eg, [(α1)₂β1δγ]. In adult muscle, the γ subunit is replaced by an ε subunit. There are twelve neuronal nicotinic receptors with nine α (α2-α10) subunits and three (β2-β4) subunits. The subunit composition varies among different mammalian tissues.

DAG, diacylglycerol; IP₃, inositol triphosphate.

Data from Millar NS: Assembly and subunit diversity of nicotinic acetylcholine receptors. Biochem Soc Trans 2003;31:869.

junctions and have less effect on nicotinic receptors in ganglia. Organ selectivity can also be achieved by using appropriate routes of administration.

MODE OF ACTION OF CHOLINOMIMETIC DRUGS

1- Direct-acting : cholinomimetic agents bind to and activate muscarinic or nicotinic receptors.

2-Indirect-acting : agents produce their primary effects by inhibiting acetylcholinesterase.

the indirect-acting drugs increase the endogenous acetylcholine concentration in synaptic clefts and neuroeffector junctions. These drugs act primarily where acetylcholine is physiologically released and are thus amplifiers of endogenous acetylcholine. Some cholinesterase inhibitors also inhibit butyrylcholinesterase . However, inhibition of butyrylcholinesterase plays little role in the action of indirect-acting cholinomimetic drugs. Some quaternary cholinesterase inhibitors also have a modest direct action as well, which activates neuromuscular nicotinic cholinoreceptors directly in addition to blocking cholinesterase.

BASIC PHARMACOLOGY OF THE DIRECT-ACTING CHOLINOCEPTOR STIMULANT:

The direct-acting cholinomimetic drugs can be divided on the basis of chemical structure into esters of choline and alkaloids. Many of these drugs have effects on both receptors; acetylcholine is typical. A few are highly selective. However, none of the clinically useful drugs is selective for receptor subtypes in either class.

Absorption, Distribution, and Metabolism: Choline esters are poorly absorbed and poorly distributed into the central nervous system because they are hydrophilic. Although all are hydrolyzed in the gastrointestinal tract. Acetylcholine is very rapidly hydrolyzed , large amounts must be infused IV to achieve concentrations sufficient to produce detectable effects. A large IV bolus injection has a brief effect, typically 5–20 seconds, whereas IM and subcutaneous injections produce only local effects. The β -methyl group reduces the potency of these drugs at nicotinic receptors.

The tertiary natural cholinomimetic alkaloids are well absorbed from most sites of administration.

Nicotine, a liquid, is sufficiently lipid-soluble to be absorbed across the skin.

Muscarine, a quaternary amine, is less completely absorbed from the gastrointestinal tract than the tertiary amines but is nevertheless toxic when ingested , and it even enters the brain. These amines are excreted chiefly by the kidneys. Acidification of the urine accelerates clearance of the tertiary amines.

Pharmacodynamics:

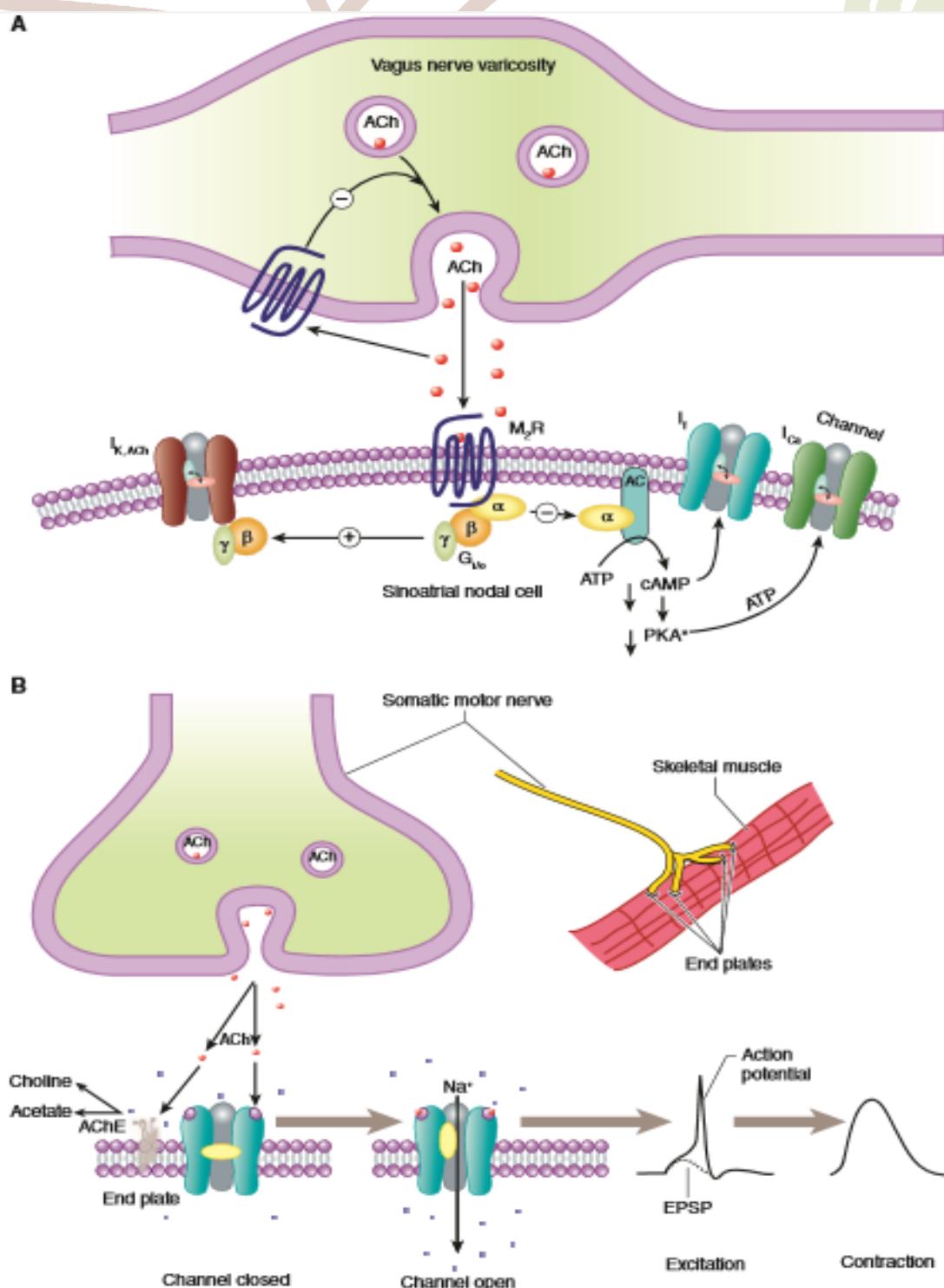
A. Mechanism of Action :

Activation of the parasympathetic nervous system modifies organ function by two major mechanisms. First, acetylcholine released from parasympathetic nerves activates muscarinic receptors on effector cells to alter organ function directly. Second, acetylcholine released from parasympathetic nerves interacts with muscarinic receptors on nerve terminals to inhibit the release of their neurotransmitter. By this mechanism, acetylcholine release and circulating mucarinic agonists indirectly alter organ function by modulating the effects of the parasympathetic and sympathetic nervous systems and perhaps nonadrenergic, noncholinergic (NANC) systems. Several cellular events occur when muscarinic receptors are activated, one or more of which might serve as second messengers frommuscarinic activation. All muscarinic receptors appear to be of the G protein-coupled type table(7-1) . The effect of muscarinic agonists is mediated by the binding of an activated G protein $\beta\gamma$ subunit directly to the channel. These muscarinic effects on cAMP generation reduce the physiologic response of the organ to stimulatory hormones.

The mechanism of nicotinic receptor activation, taking advantage of three factors: (1) the receptor is present in extremely high concentration in the membranes of the electric organs of electric fish; (2) α -bungarotoxin, a component of certain snake venoms, binds to the receptors and is readily labeled as a marker for isolation procedures; and (3) receptor activation results in easily measured electrical and ionic changes in the cells involved. The nicotinic receptor in muscle tissues is a pentamer of four types of

glycoprotein subunits (Figure 7–4B). The neuronal nicotinic receptor consists of α and β subunits only.

Each subunit has four transmembrane segments. The nicotinic receptor has two agonist binding sites at the interfaces formed by the two α subunits and two adjacent subunits (β , γ , ε). Agonist binding to the receptor sites causes a conformational change in the protein that allows sodium and potassium ions to diffuse rapidly down their concentration gradients (calcium ions may also carry charge through the nicotinic receptor ion channel). Binding of an agonist molecule by one of the two receptor sites only modestly increases the probability of channel opening; simultaneous binding of agonist by both of the receptor sites greatly enhances



B. Organ System Effects:

FIGURE 7-4 Muscarinic and nicotinic signaling. **A:** Muscarinic transmission to the sinoatrial node in heart. Acetylcholine (ACh) released from a varicosity of a postganglionic cholinergic axon interacts with a sinoatrial node cell muscarinic receptor (M_2R) linked via $G_{i/o}$ to K^+ channel opening, which causes hyperpolarization, and to inhibition of cAMP synthesis. Reduced cAMP shifts the voltage-dependent opening of pacemaker channels (I_p) to more negative potentials, and reduces the phosphorylation and availability of L-type Ca^{2+} channels (I_{Ca}). Released ACh also acts on an axonal muscarinic receptor (autoreceptor; see Figure 6-3) to cause inhibition of ACh release (autoinhibition). **B:** Nicotinic transmission at the skeletal neuromuscular junction. ACh released from the motor nerve terminal interacts with subunits of the pentameric nicotinic receptor to open it, allowing Na^+ influx to produce an excitatory postsynaptic potential (EPSP). The EPSP depolarizes the muscle membrane, generating an action potential, and triggering contraction. Acetylcholinesterase (AChE) in the extracellular matrix hydrolyzes ACh.

TABLE 7-3 Effects of direct-acting cholinoreceptor stimulants.*

Organ	Response
Eye	
Sphincter muscle of iris	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period
Ventricles	Small decrease in contractile strength
Blood vessels	
Arteries, veins	Dilation (via EDRF). Constriction (high-dose direct effect)
Lung	
Bronchial muscle	Contraction (bronchoconstriction)
Bronchial glands	Stimulation
Gastrointestinal tract	
Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder	
Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands	
Sweat, salivary, lacrimal, nasopharyngeal	Secretion

EDRF, endothelium-derived relaxing factor.



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Chapter #8 : Cholinoreceptor-Blocking Drugs

8 Cholinceptor antagonists:

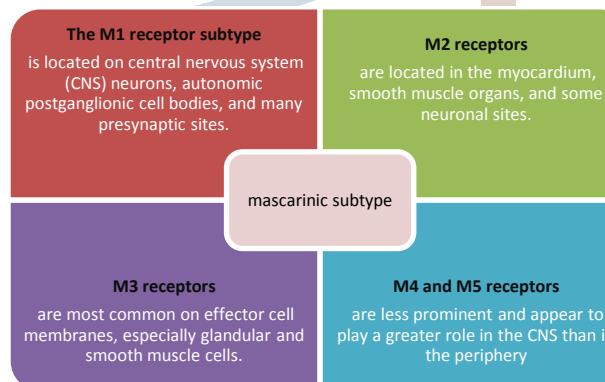
Cholinceptorantagonists, are divided into muscarinic and nicotinic subgroups on the basis of their specific receptor affinities.

Ganglion blockers and neuromuscular junction blockers make up the antinicoticnic drugs. The ganglion-blocking drugs have little clinical use.

This chapter emphasizes drugs that block muscarinic cholinceptors.

Five subtypes of muscarinic receptors have been identified, primarily on the basis of data from ligand-binding and cDNA-cloning experiments.

Table 1: location of muscarinic subtype



BASIC PHARMACOLOGY OF THE MUSCARINIC RECEPTOR BLOCKING DRUGS:

Muscarinic antagonists are sometimes called parasympatholytic because they block the effects of parasympathetic autonomic discharge. However, the term “antimuscarinic” is preferable.

Atropine is the prototype of these drugs. Many similar plant alkaloids are known, and hundreds of synthetic antimuscarinic compounds.

A variety of semisynthetic and fully synthetic molecules have antimuscarinic effects. The tertiary members of these classes are often used for their effects on the eye or the CNS. Many antihistaminic, antipsychotic, and antidepressant drugs have similar structures and, predictably, significant antimuscarinic effects.

a. Absorption

Natural alkaloids and most tertiary antimuscarinic drugs are well absorbed from the gut and conjunctival membranes. Some (eg, scopolamine) are even absorbed across the skin (transdermal route).

In contrast, only 10–30% of a dose of a quaternary antimuscarinic drug is absorbed after oral administration, reflecting the decreased lipid solubility of the charged molecule.

b. Distribution

Atropine and the other tertiary agents are widely distributed in the body. Significant levels are achieved in the CNS within 30 minutes to 1 hour, and this can limit the dose tolerated when the drug is taken for its peripheral effects.

c. Metabolism and Excretion

After administration, the elimination of atropine from the blood occurs in two phases: the $t_{1/2}$ of the rapid phase is 2 hours and that of the slow phase is approximately 13 hours. About 50% of the dose is excreted unchanged in the urine.

Pharmacodynamics:

A. mechanism of action:

Atropine causes reversible blocked of cholinomimetic action at muscarinic receptors; that is, blocked by small dose of atropine can be overcome by a larger concentration of acetylcholine or equivalent muscarinic agonist.

Amino acid (aspartate) is required for binding of antimuscarinic drug. When atropine binds to muscarinic receptor, it prevents actions such as the release of inositol trisphosphate(IP3) and the inhibition of adenylyl cyclase that are caused by muscarinic agonists.

Muscarinic antagonists were traditionally viewed as neutral compounds that occupied the receptor and prevented agonist binding. most drugs that block the actions of acetylcholine are inverse agonists that shift the equilibrium to the inactive state of the receptor. Muscarinic blocking drugs that are inverse agonists include atropine, pirenzepine, trihexyphenidyl, ipratropium, glycopyrrolate, and a methyl derivative of scopolamine. The effectiveness of antimuscarinic drugs varies with the tissue and with the source of agonist. Tissues most sensitive to atropine are the salivary, bronchial, and sweat glands.

Secretion of acid by the gastric parietal cells is the least sensitive. In most tissues, antimuscarinic agents block exogenously administered cholinoreceptor agonists more effectively than endogenously released acetylcholine.

Atropine is highly selective for muscarinic receptors. Most synthetic antimuscarinic drugs are considerably less selective than atropine in interactions with nonmuscarinic receptors.

B. Organ System Effects

1. Central nervous system:

In the doses usually used, atropine has minimal stimulant effects on the CNS, especially the parasympathetic medullary centers, and a slower, longer-lasting sedative effect on the brain. Scopolamine has more marked central effects, producing drowsiness when given in recommended dosages and amnesia in sensitive individuals. In toxic doses can cause excitement, agitation, hallucinations, and coma.

The tremor of Parkinson's disease is reduced by centrally acting antimuscarinic drugs, and atropine first drugs used in the therapy of this disease. parkinsonian tremor and rigidity seem to result from a relative excess of cholinergic activity because of a deficiency of dopaminergic activity in the basal ganglia-striatum system. The combination of an antimuscarinic agent with a dopamine precursor drug (levodopa) can sometimes provide more effective therapy than either drug alone.

2. Eye:

The pupillary constrictor muscle depends on muscarinic cholinoreceptor activation. This activation is blocked by topical atropine and other tertiary antimuscarinic drugs and results in unopposed sympathetic dilator activity and mydriasis. Dilated pupils were considered cosmetically desirable during the Renaissance and account for the name belladonna.

can use of the plant and its extract as eye drops during that time. The important ocular effect of antimuscarinic drugs is to weaken contraction of the ciliary muscle, or cycloplegia. Cycloplegia results in loss of the ability to accommodate; the fully atropinized eye cannot focus for near vision. They are also potentially hazardous, since acute glaucoma may be induced in patients with a narrow anterior chamber angle.

The other ocular effect of antimuscarinic drugs is to reduce lacrimal secretion. Patients occasionally complain of dry or "sandy" eyes when receiving large doses of antimuscarinic drugs.

3. Cardiovascular system:

The sinoatrial node is very sensitive to muscarinic receptor blockade. Moderate to high therapeutic doses of atropine cause tachycardia in the innervated and spontaneously beating heart by blockade of vagal slowing. However, lower doses often result in initial bradycardia before the effects of peripheral vagal block become manifest. This slowing may be due to block of prejunctional M1 receptors on vagal postganglionic fibers that normally limit acetylcholine release in the sinus node and other tissues. The same mechanisms operate in the atrioventricular node; in the presence of high vagal tone, atropine can significantly reduce the PR interval of the electrocardiogram by blocking muscarinic receptors in the atrioventricular node. The ventricles are less affected by antimuscarinic drugs at therapeutic levels because of a lesser degree of vagal control. In toxic concentrations, the drugs can cause intraventricular conduction block that has been attributed to a local anesthetic action.

Most blood vessels, except those in thoracic and abdominal viscera, receive no direct innervation from the parasympathetic system.

However, parasympathetic nerve stimulation dilates coronary arteries, and sympathetic cholinergic nerves cause vasodilation in the skeletal muscle vascular bed. Atropine can block this vasodilation. Furthermore, almost all vessels contain endothelial muscarinic receptors that mediate vasodilation. These receptors are readily blocked by antimuscarinic drugs. At toxic doses, and in some individuals at normal doses, antimuscarinic agents cause cutaneous vasodilation, especially in the upper portion of the body. However, the cardiovascular effects of administered direct-acting muscarinic agonists are easily prevented.

4. Respiratory system:

Both smooth muscle and secretory glands of the airway receive vagal innervation and contain muscarinic receptors. Even in normal individuals, administration of atropine can cause some bronchodilation and reduce secretion. The effectiveness of nonselective antimuscarinic drugs in treating chronic obstructive pulmonary disease (COPD) is limited because block of autoinhibitory M2 receptors on postganglionic parasympathetic nerves

can oppose the bronchodilation caused by block of M₃ receptors on airway smooth muscle.

Nevertheless, antimuscarinic agents selective for M₃ receptors are valuable in some patients with asthma and in many with COPD. Antimuscarinic drugs are frequently used before the administration of inhalant anesthetics to reduce the accumulation of secretions in the trachea and the possibility of laryngospasm.

5. Gastrointestinal tract:

has dramatic effects on motility and some of the secretory functions of the gut. Antimuscarinic drugs have marked effects on salivary secretion; dry mouth occurs frequently in patients taking antimuscarinic drugs for Parkinson's disease or urinary conditions. Gastric secretion is blocked less effectively: the volume and amount of acid, pepsin, and mucin are all reduced, but large doses of atropine may be required.

Basal secretion is blocked more effectively than that stimulated by food, nicotine, or alcohol.

Pirenzepine and a more potent analog, telenzepine, reduce gastric acid secretion with fewer adverse effects than atropine and other less selective agents.

The mechanism of vagal regulation of gastric acid secretion likely involves multiple muscarinic receptor dependent pathways.

Gastrointestinal smooth muscle motility is affected from the stomach to the colon. In general, antimuscarinic drugs diminish the tone and propulsive movements; the walls of the viscera are relaxed.

Therefore, gastric emptying time is prolonged, and intestinal transit time is lengthened. Diarrhea due to overdosage with parasympathomimetic agents is readily stopped, and even diarrhea caused by nonautonomic agents can usually be temporarily controlled.

However, intestinal "paralysis" induced by antimuscarinic drugs is temporary; local mechanisms within the enteric nervous system usually reestablish at least some peristalsis after 1–3 days of antimuscarinic drug therapy.

6. Genitourinary tract:

The antimuscarinic action is relaxes smooth muscle of the ureters and bladder wall and slows voiding.

This action is useful in the treatment of spasm induced by mild inflammation, surgery, and certain neurologic conditions, but it can precipitate urinary retention in men who have prostatic hyperplasia.

The antimuscarinic drugs have no significant effect on the uterus.

7. Sweat glands:

Atropine suppresses thermoregulatory sweating.

Sympathetic cholinergic fibers innervate eccrine sweat glands, and their muscarinic receptors are readily accessible to antimuscarinic drugs. In adults, body temperature is elevated by this effect only if large doses are administered, but in infants and children even ordinary doses may cause "atropine fever."

CLINICAL PHARMACOLOGY OF THE MUSCARINIC RECEPTORBLOCKING DRUGS

Therapeutic Applications

A. Central Nervous System Disorders

1. Parkinson's disease: is often an exercise in polypharmacy, since no single agent is fully effective over the course of the disease. Most antimuscarinic drugs was developed before levodopa became available. Their use is accompanied by all of the adverse effects described below, but the drugs remain useful as adjunctive therapy in some patients.

2. Motion sickness: Certain vestibular disorders respond to antimuscarinic drugs. Scopolamine is one of the oldest remedies for seasickness and is as effective as any more recently introduced agent. The patch formulation produces significant blood levels over 48–72 hours. Useful doses by any route usually cause significant sedation and dry mouth.

B. Ophthalmologic Disorders:

Accurate measurement of refractive error in uncooperative patients.

Also, mydriasis greatly facilitates ophthalmoscopic examination of the retina. Therefore, antimuscarinic agents, administered topically as eye drops or ointment, are very helpful in doing a complete examination.

Formerly, ophthalmic antimuscarinic drugs were selected from the tertiary amine subgroup to ensure good penetration after conjunctival application.

Antimuscarinic drugs should never be used for mydriasis unless cycloplegia or prolonged action is required. Alpha-adrenoceptor stimulant drugs, eg, phenylephrine, produce a short-lasting mydriasis that is usually sufficient for funduscopic examination. A second ophthalmologic use is to prevent synechia (adhesion) formation in uveitis and iritis.

The longer-lasting preparations, especially homatropine, are valuable for this indication.

C. Respiratory Disorders

The use of atropine became part of routine preoperative medication when anesthetics such as ether were used, because these irritant anesthetics markedly increased airway secretions and were associated with frequent episodes of laryngospasm. Preanesthetic injection of atropine or scopolamine could prevent these hazardous effects. Newer inhalational anesthetics are far less irritating to the airways

Ipratropium, tiotropium, and aclidinium are synthetic analogs of atropine, are used as inhalational drugs in COPD. The advantage of aerosol route administration is maximal concentration at the bronchial target tissue with reduced systemic effects. Tiotropium and aclidinium have a longer bronchodilator action than ipratropium and can be given once daily because they dissociate slowly from M3 receptors. Tiotropium reduces the incidence of COPD exacerbations and is a useful adjunct in pulmonary rehabilitation to increase exercise tolerance. The hyperactive neural bronchoconstrictor reflex present in

most individuals with asthma.

Ipratropium and tiotropium are also used as inhalational drugs in asthma.

D. Cardiovascular Disorders

Marked reflex vagal discharge sometimes accompanies the pain of myocardial infarction and may depress sinoatrial or atrioventricular node function sufficiently to impair cardiac output. Parenteral atropine or a similar antimuscarinic drug is appropriate therapy in this situation.

Pathophysiology can influence muscarinic activity in other ways as well. Circulating autoantibodies against the second extracellular loop of cardiac M2 muscarinic receptors have been detected in some patients with idiopathic dilated cardiomyopathy and those afflicted with Chagas' disease caused by the protozoan *Trypanosoma cruzi*.

Patients with Graves' disease (hyperthyroidism) also have such autoantibodies that may facilitate the development of atrial fibrillation.

These antibodies exert parasympathomimetic actions on the heart that are prevented by atropine.

E. Gastrointestinal Disorders

Antimuscarinic agents can provide some relief in the treatment of common traveler's diarrhea and other mild or self-limited conditions of hypermotility.

They are often combined with an opioid antidiarrheal drug. In this combination, however, the very low dosage of the antimuscarinic drug functions primarily to discourage abuse of the opioid agent. The classic combination of atropine with diphenoxylate, a nonanalgesic congener of meperidine, is available under many names in both tablet and liquid form.

F. Urinary Disorders

Atropine and other antimuscarinic drugs have been used to provide symptomatic relief in the treatment of urinary urgency caused by minor inflammatory bladder disorders. In the human urinary bladder, M₂ and M₃ receptors are expressed predominantly with the M₃ subtype mediating direct activation of contraction. Receptors for acetylcholine on the urothelium (the epithelial lining of the urinary tract) and on afferent nerves as well as the detrusor muscle provide a broad basis for the action of antimuscarinic drugs in the treatment of overactive bladder. Oxybutynin, is used to relieve bladder spasm after urologic surgery. Oral oxybutynin or instillation of the drug by catheter into the bladder in such patients appears to improve bladder capacity and continence and to reduce infection and renal damage.

Imipramine, a tricyclic antidepressant drug with strong antimuscarinic actions, has long been used to reduce incontinence in institutionalized elderly patients. It is moderately effective but causes significant CNS toxicity.

Antimuscarinic agents have also been used in urolithiasis to relieve the painful ureteral smooth muscle spasm caused by passage of the stone. However, their usefulness in this condition is debatable.

G. Cholinergic Poisoning

Severe cholinergic excess is a medical emergency, especially in rural communities where cholinesterase inhibitor insecticides are commonly used and in cultures where wild mushrooms are frequently eaten. The potential use of cholinesterase inhibitors as chemical warfare "nerve gases" also requires an awareness of the methods for treating acute poisoning.

1. Antimuscarinic therapy: Both the nicotinic and the muscarinic effects of the cholinesterase inhibitors can be life-threatening. To reverse the muscarinic effects, a tertiary (not quaternary) amine drug must be used (preferably atropine) to treat the CNS effects as well as the peripheral effects of the organophosphate inhibitors.

Large doses of atropine may be needed to oppose the muscarinic effects of extremely potent agents like parathion and chemical warfare nerve gases. The drug may have to be given many times, since the acute effects of the cholinesterase inhibitor may last 24–48 hours or longer.

2. Cholinesterase regenerator compounds: A second class of compounds, composed of substituted oximes capable of regenerating active enzyme from the organophosphorus-cholinesterase complex, is also available to treat organophosphorus poisoning. These oxime agents include pralidoxime (PAM), diacetylmonoxime (DAM), obidoxime, and others.

H. Other Applications:

Hyperhidrosis (excessive sweating) is sometimes reduced by antimuscarinic agents..

Adverse Effects

Treatment with atropine or its congeners directed at one organ system almost always induces undesirable effects in other organ systems. Thus, mydriasis and cycloplegia when used to reduce gastrointestinal secretion or motility, even though they are therapeutic effects when the drug is used in

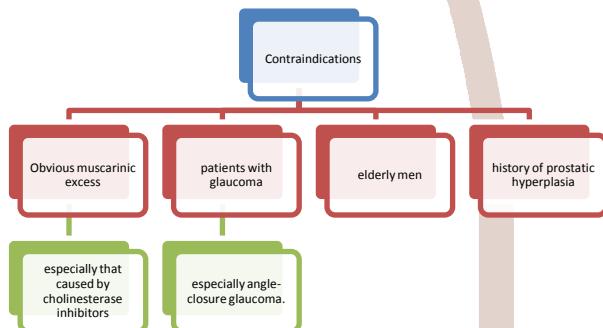
ophthalmology. At higher concentrations, atropine causes block of all parasympathetic functions. However, atropine is a remarkably safe drug in adults. Atropine poisoning has occurred as a result of attempted suicide, but most cases are due to attempts to induce hallucinations. Poisoned individuals manifest dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation, and delirium for as long as 1 week. Body temperature is frequently elevated. Unfortunately, children, especially infants, are very sensitive to the hyperthermic effects of atropine.

Overdoses of atropine or its congeners are generally treated symptomatically. Poison control experts discourage the use of physostigmine or another cholinesterase inhibitor to reverse the effects of atropine overdose because symptomatic management is more effective and less dangerous. Symptomatic treatment may require temperature control with cooling blankets and seizure control with diazepam. Treatment of the antimuscarinic effects, if required, can be carried out with a quaternary cholinesterase inhibitor such as neostigmine. Control of hypotension may require the administration of a sympathomimetic drug such as phenylephrine.

Recent evidence indicates that some centrally acting drugs with antimuscarinic actions impair memory and cognition in older patients like: tricyclic antidepressants, selective serotonin reuptake inhibitors, anti-anxiety agents.

Contraindications

Contraindications to the use of antimuscarinic drugs are relative, not absolute.



- Nonselective antimuscarinic agents should never be used to treat acid-peptic disease.

BASIC & CLINICAL PHARMACOLOGY OF THE GANGLION-BLOCKING DRUGS

Ganglion-blocking agents competitively block the action of acetylcholine and similar agonists at neuronal nicotinic receptors of both parasympathetic and sympathetic

autonomic ganglia. Some members of the group also block the ion channel that is gated by the nicotinic cholinoreceptor. However, their lack of selectivity confers such a broad range of undesirable effects that they have limited clinical use.

Chemistry & Pharmacokinetics

All ganglion-blocking drugs of interest are synthetic amines. Tetraethylammonium (TEA), Hexamethonium ("C6") was developed and was introduced clinically as the first drug effective for management of hypertension. Mecamylamine, a secondary amine, was developed to improve the degree and extent of absorption from the gastrointestinal tract because the quaternary amine ganglion-blocking compounds were poorly and erratically absorbed after oral administration. Trimethaphan, a short-acting, polar, ganglion blocker is no longer available for clinical use.

Pharmacodynamics

A.Organ System Effects

1. Central nervous system:

Mecamylamine, is crosses the blood-brain barrier and readily enters the CNS. Sedation, tremor, choreiform movements, and mental aberrations have been reported as effects of mecamylamine.

2. Eye:

The ganglion-blocking drugs cause a predictable cycloplegia with loss of accommodation because the ciliary muscle receives innervation primarily from the parasympathetic nervous system. Ganglionic blockade often causes moderate dilation of the pupil because parasympathetic tone usually dominates this tissue.

3. Cardiovascular system:

Blood vessels receive chiefly vasoconstrictor fibers from the sympathetic nervous system; therefore, ganglionic blockade causes a marked decrease in arteriolar and venomotor tone. The blood pressure may fall precipitously because both peripheral vascular resistance and venous return are decreased.

Hypotension is especially marked in the upright position (orthostatic or postural hypotension), because

postural reflexes that normally prevent venous pooling are blocked.

Cardiac effects include diminished contractility and, because the sinoatrial node is usually dominated by the parasympathetic nervous system, a moderate tachycardia.

4. Gastrointestinal tract:

Secretion is reduced, although not enough to treat peptic disease effectively. Motility is profoundly inhibited, and constipation can be marked.

5. Other systems:

Genitourinary smooth muscle is partially dependent on autonomic innervation for normal function.

Therefore, ganglionic blockade causes hesitancy in urination and may precipitate urinary retention in men with prostatic hyperplasia.

Thermoregulatory sweating is reduced by the ganglionblocking drugs. However, hyperthermia is not a problem except in very warm environments, because cutaneous vasodilation is usually sufficient to maintain a normal body temperature.

6. Response to autonomic drugs:

Patients receiving ganglion blocking drugs are fully responsive to autonomic drugs acting on muscarinic, α -, and β -adrenergic receptors because these effector cell receptors are not blocked.

Clinical Applications & Toxicity

Ganglion blockers are used rarely because more selective autonomic blocking agents are available. The toxicity of the ganglion-blocking drugs is limited to the autonomic effects already described. For most patients, these effects are intolerable except for acute use.

Chapter #9 : Adrenoceptor Agonists & Sympathomimetic Drugs

9. Adrenoceptor agonists & Sympathomimetic Drugs

The sympathetic nervous system is an important regulator of virtually all organ systems. The ultimate effects of sympathetic stimulation are mediated by release of norepinephrine from nerve terminals, which then activates adrenoceptors on postsynaptic sites. Also, in response to a variety of stimuli such as stress, the adrenal medulla releases epinephrine, which is transported in the blood to target tissues. In other words, epinephrine acts as a hormone, whereas norepinephrine acts as a neurotransmitter. Drugs that mimic the actions of epinephrine or norepinephrine have traditionally been termed sympathomimetic drugs. The sympathomimetics can be grouped by mode of action and by the spectrum of receptors that they activate. Some of these drugs are direct agonists; that is, they directly interact with and activate adrenoceptors. Others are indirect agonists because their actions are dependent on their ability to enhance the actions of endogenous catecholamines.

TABLE 9-1 Adrenoceptor types and subtypes.		
Receptor	Agonist	Antagonist
α_1 type	Phenylephrine	Prazosin
α_{1A}		Tamsulosin
α_{1B}		
α_{1D}		
α_2 type	Clonidine	Yohimbine
α_{2A}	Oxymetazoline	
α_{2B}		Prazosin
α_{2C}		Prazosin
β type	Isoproterenol	Propranolol
β_1	Dobutamine	Betaxolol
β_2	Albuterol	Butoxamine
β_3	Mirabegron	
Dopamine type	Dopamine	
D_1	Fenoldopam	
D_2	Bromocriptine	
D_3		
D_4		Clozapine
D_5		

TABLE 9-2 Relative receptor affinities.

Relative Receptor Affinities	
Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 > \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine ¹	$\beta_1 > \beta_2 >>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

SPECIFIC SYMPATHOMIMETIC

DRUGS

Endogenous Catecholamines

	MOA	Effect
Epinephrine	Agonist at both α and β receptors. It is therefore a very potent vasoconstrictor and cardiac stimulant.	The rise in systolic blood pressure that occurs after epinephrine release or administration is caused by its positive inotropic and chronotropic actions on the heart (predominantly β_1 receptors) and the vasoconstriction induced in many vascular beds (α receptors). Epinephrine also activates β_2 receptors in some vessels (eg, skeletal muscle blood vessels), leading to their dilation.
Norepinephrine (levarterenol, noradrenaline)	It is an agonist at both α_1 and α_2 receptors. Norepinephrine also activates β_1 receptors with similar potency as epinephrine, but has relatively little effect on β_2 receptors.	increases peripheral resistance and both diastolic and systolic blood pressure and positive inotropic effects on the heart.
Dopamine	Is the immediate precursor in the synthesis of norepinephrine	Its promotes vasodilation of renal, splanchnic, coronary, cerebral, and perhaps other resistance vessels, via activation of D1 receptors, it's also activates β_1 receptors in the heart. Endogenous dopamine may have more important effects in regulating sodium excretion and renal function. It is an important neurotransmitter in the CNS.

Direct-Acting Sympathomimetics:

Phenylephrine is pure α_1 agonist. It is an effective mydriatic and decongestant and can be used to raise the blood pressure.

Midodrine is a prodrug that is enzymatically hydrolyzed to desglymidodrine, a selective α_1 -receptor agonist. The primary indication for midodrine is the treatment of orthostatic hypotension.

Alpha2-selective agonists decrease blood pressure through actions in the CNS that reduce sympathetic tone ("sympatholytics") even though direct application to a blood vessel may cause vasoconstriction. Such drugs (eg, clonidine, methyldopa, guanfacine, guanabenz) are useful in the treatment of hypertension.

Oxymetazoline is a direct-acting α agonist used as topical decongestant because of its ability to promote constriction of the nasal mucosa.

Isoproterenol (isoprenaline) is a very potent β -receptor agonist and has little effect on α receptors. The drug has positive chronotropic and inotropic actions, it is a potent vasodilator.

Beta1-selective agents increase cardiac output with less reflex tachycardia than nonselective β agonists such as isoproterenol, because they are less effective in activating vasodilator β_2 receptors.

Dobutamine actions are mediated mostly by activation of α and β receptors, it augments myocardial contractility and promotes coronary and systemic vasodilation.

Beta2-selective agents (albuterol, metaproterenol, terbutaline) are used for pulmonary applications.

Indirect –Acting Sympathomimetics

Indirect-acting sympathomimetics can have one of two different mechanisms. First, they may enter the sympathetic nerve ending and displace stored catecholamine transmitter. Such drugs have been called amphetamine-like or “displacers.” Second, they may inhibit the reuptake of released transmitter by interfering with the action of the norepinephrine transporter, NET.

A. Amphetamine: is a CNS stimulant it has marked stimulant effects on mood and alertness and a depressant effect on appetite. Amphetamine’s actions are mediated through the release of norepinephrine and, to some extent, dopamine.

B. Catecholamine Reuptake Inhibitors: Many inhibitors of the amine transporters for norepinephrine, dopamine, and serotonin are used clinically.

Atomoxetine is a selective inhibitor of the norepinephrine reuptake transporter. It is used in the treatment of attention deficit disorders.

Sibutramine is a serotonin and norepinephrine reuptake inhibitor and was initially approved by the FDA as an appetite suppressant for long-term treatment of obesity.

Duloxetine is a widely used antidepressant with balanced serotonin and norepinephrine reuptake inhibitory effects.

Dopamine Agonists

Levodopa, which is converted to dopamine in the body, and dopamine agonists with central actions are of considerable value in the treatment of Parkinson’s disease and prolactinemia.

Fenoldopam is a D1-receptor agonist that selectively leads to peripheral vasodilation in some vascular beds. The primary indication for fenoldopam is in the intravenous treatment of severe hypertension.

THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS

Cardiovascular Applications:

A. Treatment of Acute Hypotension.

B. Chronic Orthostatic Hypotension: drugs activating α receptors can be used for this purpose.

Midodrine, an orally active α_1 agonist, is frequently used for this indication. Other sympathomimetics, such as oral ephedrine or phenylephrine, can be tried. droxidopa, a synthetic prodrug that is converted to norepinephrine and used to treat neurogenic orthostatic hypotension.

C. Cardiac Applications

Epinephrine is used during resuscitation from cardiac arrest.

Dobutamine is used as a pharmacologic cardiac stress test.

D. Inducing Local Vasoconstriction

Reduction of local or regional blood flow is desirable for achieving hemostasis in surgery, for reducing diffusion of local anesthetics away from the site of administration, and for reducing mucous membrane congestion. In each instance, α -receptor activation is desired, and the choice of agent depends on the maximal efficacy required, the desired duration of action, and the route of administration.

Pulmonary Applications

Anaphylaxis: Anaphylactic shock and related immediate (type I) IgE-mediated reactions affect both the respiratory and the cardiovascular systems. The syndrome of bronchospasm, mucous membrane congestion, angioedema, and severe hypotension usually responds rapidly to the parenteral administration of **epinephrine**.

Ophthalmic Applications:

Phenylephrine is an effective mydriatic agent frequently used to facilitate examination of the retina. It is also a useful decongestant for minor allergic hyperemia and itching of the conjunctival membranes. Sympathomimetics administered as ophthalmic drops are also useful in localizing the lesion in Horner's syndrome. **Apraclonidine** and **brimonidine** are α_2 -selective agonists that also lower intraocular pressure and are approved for use in glaucoma.

Genitourinary Applications:

β_2 -selective agents relax the pregnant uterus. **Ritodrine**, **terbutaline**, and similar drugs have been used to suppress premature labor.

SUMMARY Sympathomimetic Drugs

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
α_1 AGONISTS				
<ul style="list-style-type: none"> • Midodrine • Phenylephrine: Can be used IV for short-term maintenance of BP in acute hypotension and intranasally to produce local vasoconstriction as a decongestant 	Activates phospholipase C, resulting in increased intracellular calcium and vasoconstriction	Vascular smooth muscle contraction increasing blood pressure (BP)	Orthostatic hypotension	Oral • prodrug converted to active drug with a 1-h peak effect • Toxicity: Supine hypertension, piloerection (goose bumps), and urinary retention
α_2 AGONISTS				
<ul style="list-style-type: none"> • Clonidine • α-Methyldopa, guanfacine, and guanabenz: Also used as central sympatholytics • Dexmedetomidine: Prominent sedative effects and used in anesthesia • Tizanidine: Used as a muscle relaxant • Apraclonidine and brimonidine: Used topically in glaucoma to reduce intraocular pressure 	Inhibits adenylyl cyclase and interacts with other intracellular pathways	Vasoconstriction is masked by central sympatholytic effect, which lowers BP	Hypertension	Oral • transdermal • peak effect 1–3 h • $t_{1/2}$ of oral drug ~12 h • produces dry mouth and sedation
β_1 AGONISTS				
<ul style="list-style-type: none"> • Dobutamine¹ 	Activates adenylyl cyclase, increasing myocardial contractility	Positive inotropic effect	Cardiogenic shock, acute heart failure	IV • requires dose titration to desired effect
β_2 AGONISTS				
<ul style="list-style-type: none"> • Albuterol • See other β_2 agonists in Chapter 20 	Activates adenylyl cyclase	Bronchial smooth muscle dilation	Asthma	Inhalation • duration 4–6 h • Toxicity: Tremor, tachycardia
β_3 AGONISTS				
<ul style="list-style-type: none"> • Mirabegron 	Activates adenylyl cyclase	Reduces bladder tone	Urinary urgency	Oral • duration 50 h • Toxicity: Possible hypertension
DOPAMINE AGONISTS				
D₁ Agonists				
<ul style="list-style-type: none"> • Fenoldopam 	Activates adenylyl cyclase	Vascular smooth muscle relaxation	Hypertension	Requires dose titration to desired effect
D₂ Agonists				
<ul style="list-style-type: none"> • Bromocriptine • See other D₂ agonists in Chapters 28 and 37 	Inhibits adenylyl cyclase and interacts with other intracellular pathways	Mimics dopamine actions in the CNS	Parkinson's disease, prolactinemia	Oral • Toxicity: Nausea, headache, orthostatic hypotension

¹Dobutamine has other actions in addition to β_1 -agonist effect. See text for details.

Central Nervous System Applications

Chapter #10 : Adrenoceptor Antagonist Drugs

Catecholamines play a role in many physiologic and pathophysiologic responses. Drugs that block their receptors therefore have important effects. These effects vary dramatically according to the drug's selectivity for α and β receptors.

This chapter deals with pharmacologic antagonist drugs whose major effect is to occupy α_1 , α_2 , or β receptors outside the CNS and prevent their activation by catecholamines and related agonists.

Clinical therapeutics drug	Used
nonselective antagonists	treatment of pheochromocytoma*
α_1 -selective antagonists	in primary hypertension and benign prostatic hyperplasia
Beta-receptor antagonist drugs	treatment of hypertension, ischemic heart disease, arrhythmias, endocrinologic and neurologic disorders, glaucoma, and other conditions.

*(tumors that secrete catecholamines)

BASIC PHARMACOLOGY OF THE ALPHA-RECEPTOR ANTAGONIST DRUGS

mechanism of action of α receptor antagonist

reversible

irreversible

block can be surmounted with sufficiently high concentrations of agonists

do not dissociate and cannot be surmounted.

e.g. Phentolamine & prazosin labetalol drug used for antihypertensive effects

e.g: Phenoxybenzamine

Pharmacologic Effects

Because arteriolar and venous tone are determined to a large extent by α receptors on vascular smooth muscle,

α -receptor antagonist drugs cause

- a lowering of peripheral vascular resistance and blood pressure.

These drugs can prevent

- the pressor effects of usual doses of a agonists

selective α -receptor antagonism

- may convert a pressor to a depressor response .

This change in response is called epinephrine reversal (it illustrates how the activation of both α and β receptors in the vasculature may lead to opposite responses).

Alpha-receptor antagonists cause

reflex tachycardia

orthostatic hypotension

is due to antagonism of sympathetic nervous system stimulation of α receptors in vascular smooth muscle

contraction of veins is an important component of the normal capacity to maintain blood pressure in the upright position since it decreases venous pooling in the periphery. Constriction of arterioles in the legs also contributes to the normal orthostatic response. Tachycardia may be more marked with agents that block α_2 -presynaptic receptors in the heart, since the augmented release of norepinephrine will further stimulate β receptors in the heart.

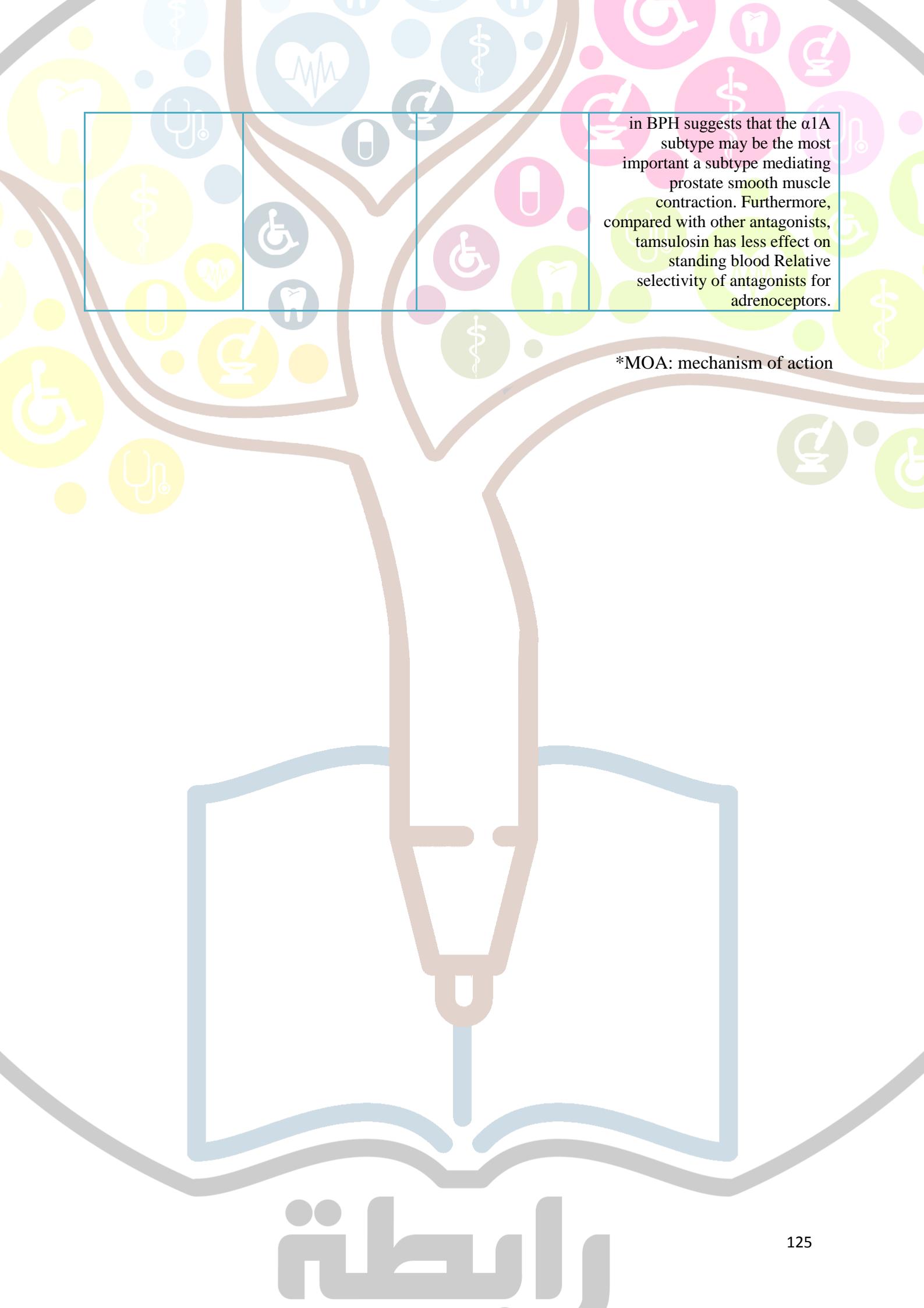
B. Other Effects

Blockade of α receptors in other tissues elicits miosis (small pupils) and nasal stuffiness. They are expressed in the base of the bladder and the prostate, and their blockade decreases resistance to the flow of urine. Alpha blockers are used therapeutically for the treatment of urinary retention due to prostatic hyperplasia.

SPECIFIC AGENT

Name of drug	MOA*	Pharmacologic action	Other information
Phenoxybenzamine	binds covalently to α receptors, causing irreversible blockade of long duration (14–48 hours or longer). The drug also inhibits reuptake of released norepinephrine by presynaptic adrenergic nerve terminals. Also, blocks histamine (H1), acetylcholine, and serotonin receptors as well as α receptors.	are related to antagonism of α -receptor-mediated events.	<p>The most significant effect: is attenuation of catecholamine-induced vasoconstriction, and causes relatively little fall in blood pressure in normal supine individuals, it reduces blood pressure when sympathetic tone is high, Cardiac output may be increased because of reflex effects and because of some blockade of presynaptic α_2 receptors in cardiac sympathetic nerves.</p> <p>Most adverse effects: derive from its α-receptor-blocking action the most important are: orthostatic hypotension, - tachycardia, - Nasal stuffiness - inhibition of ejaculation - also occur.</p> <p>Since phenoxybenzamine enters the CNS, it may cause: fatigue, sedation, and nausea.</p> <p>Because phenoxybenzamine is an alkylating agent.</p> <p>Other:</p> <ul style="list-style-type: none"> - is absorbed after oral administration, although bioavailability is low. - The major use of is in the treatment of pheochromocytoma.
Phentolamine	is a potent competitive antagonist at both α_1 and α_2 receptors . it is reduces peripheral resistance through	Its cardiac stimulation is due to antagonism of presynaptic α_2 receptors (leading to enhanced release of norepinephrine from sympathetic nerves) and sympathetic activation from baroreflex	<p>adverse effects: are related to compensatory cardiac stimulation: which may cause severe tachycardia, arrhythmias, and myocardial ischemia.</p> <p>Other:</p> <ul style="list-style-type: none"> used in the treatment of pheochromocytoma.

	blockade of α_1 receptors and possibly α_2 receptors on vascular smooth muscle.	mechanisms. Phentolamine also has minor inhibitory effects at serotonin receptors and agonist effects at muscarinic and H1 and H2 histamine receptors.	In addition it is sometimes used to reverse local anesthesia in soft tissue sites; local anesthetics are often given with vasoconstrictors that slow their removal. Local phentolamine permits reversal at the end of the procedure.
Prazosin:	is a competitive piperazinylquinazoline effective in the management of hypertension. It is highly selective for α_1 receptors and typically 1000-fold less potent at α_2 receptors.	relaxes both arterial and venous vascular smooth muscle, as well as smooth muscle in the prostate, due to blockade of α_1 receptors.	Other: it is extensively metabolized in humans; because of metabolic degradation by the liver, only about 50% of the drug is available after oral administration. The half-life is normally about 3 hours.
Terazosin:	is reversible α_1 -selective antagonist that is effective in hypertension	it is use in men with urinary retention symptoms due to benign prostatic hyperplasia (BPH).	actionOther: it has high bioavailability but is extensively metabolized in the liver, with only a small fraction of unchanged drug excreted in the urine. The half-life of terazosin is 9–12 hours.
Doxazosin:	-----	is efficacious in the treatment of hypertension and BPH.	Other: It having a longer half-life of about 22 hours. It has moderate bioavailability and is extensively metabolized, with very little parent drug excreted in urine or feces. it has active metabolites, although their contribution to the drug's effects is probably small.
Tamsulosin:	is a competitive α_1 antagonist with a structure quite different from that of most other α_1 -receptor blockers.	-----	Other: It has high bioavailability and a half-life of 9–15 hours. It is metabolized extensively in the liver. it has higher affinity for α_{1A} and α_{1D} receptors than for the α_{1B} subtype. Evidence suggests that tamsulosin has relatively greater potency in inhibiting contraction in prostate smooth muscle versus vascular smooth muscle compared with other α_1 -selective antagonists. The drug's efficacy



in BPH suggests that the α 1A subtype may be the most important a subtype mediating prostate smooth muscle contraction. Furthermore, compared with other antagonists, tamsulosin has less effect on standing blood Relative selectivity of antagonists for adrenoceptors.

*MOA: mechanism of action

OTHER ALPHA-ADRENOCEPTOR ANTAGONISTS

Comment	Drug
is an α_1 -selective quinazoline derivative that is approved for use in BPH. It has a bioavailability of about 60%, is extensively metabolized, and has an elimination half-life of about 5 hours. It may increase risk of QT prolongation in susceptible individuals.	Alfuzosin
Resembles tamsulosin in blocking the α_{1A} receptor, used in the treatment of BPH.	Silodosin
α_1 -selective antagonist that also has efficacy as an antihypertensive.	Indoramin
is an α_1 antagonist (its primary effect) that also has weak α_2 -agonist and 5-HT1A-agonist actions and weak antagonist action	Urapidil

at β_1 receptors. have both α_1 -selective and β -antagonistic effects	Labetalol and carvedilol
Neuroleptic drugs, they are potent dopamine receptor antagonists but are also antagonists at α receptors. Their antagonism of α receptors probably contributes to some of their adverse effects, particularly hypotension. Similarly, the antidepressant trazodone has the capacity to block α_1 receptors. cause reversible α -receptor blockade.	Chlorpromazine and haloperidol
is an α_2 -selective antagonist. It is sometimes used in the treatment of orthostatic hypotension because it promotes norepinephrine release through blockade of α_2 receptors in both the CNS and the periphery.	Yohimbine

CLINICAL PHARMACOLOGY OF THE ALPHA-RECEPTOR-BLOCKING DRUGS

This increases central sympathetic activation and also promotes increased norepinephrine release in the periphery. It was once widely used to treat male erectile dysfunction but has been superseded by phosphodiesterase -5 inhibitors like sildenafil. Also, can greatly elevate blood pressure if administered to patients receiving norepinephrine transport-blocking drugs. it reverses the antihypertensive effects of α_2 -adrenoceptor agonists such as clonidine. It is used in veterinary medicine to reverse anesthesia produced by xylazine.

The major clinical use of phenoxybenzamine is in the management of pheochromocytoma. Patients have many symptoms and signs, including intermittent or sustained hypertension, headaches, palpitations, and increased sweating.

Release of stored catecholamines from pheochromocytomas may occur in:

- response to physical pressure
- chemical stimulation, or spontaneously.

When it occurs during operative manipulation of pheochromocytoma, the resulting hypertension may be controlled with α -receptor blockade or the vasodilator nitroprusside. Nitroprusside is preferred because its effects can be more readily titrated and it has a shorter duration of action. Alpha-receptor antagonists are most useful in the preoperative management of patients with pheochromocytoma.

Administration of phenoxybenzamine in the preoperative period helps to control

hypertension and tends to reverse chronic changes resulting from excessive catecholamine secretion such as plasma volume contraction.

Some physicians give phenoxybenzamine to patients with pheochromocytoma for 1–3 weeks before surgery. Other surgeons prefer to operate on patients in the absence of treatment with phenoxybenzamine, counting on modern anesthetic techniques to control blood pressure and heart rate during surgery. Phenoxybenzamine can be very useful in the chronic treatment of inoperable or metastatic pheochromocytoma. Although there is less experience with alternative drugs, hypertension in patients with pheochromocytoma may also respond to reversible α 1-selective antagonists or to conventional calcium channel antagonists. Beta-receptor antagonists may be required after α -receptor blockade has been instituted to reverse the cardiac effects of excessive catecholamines. Beta antagonists should not be used prior to establishing effective α -receptor blockade,

Pheochromocytoma is sometimes treated with metyrosine (α -methyltyrosine), the α -methyl analog

of tyrosine. This agent is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting step in the synthesis of dopamine, norepinephrine, and epinephrine

Hypertensive Emergencies:

The α -adrenoceptor antagonist drugs have limited application in the management of hypertensive emergencies, but labetalol has been used in this setting. In theory, α -adrenoceptor antagonists are most useful when increased blood pressure reflects excess circulating concentrations of a agonists.

Chronic Hypertension :

Members of the prazosin family of α 1-selective antagonists are efficacious drugs in the treatment of mild to moderate systemic hypertension. They are generally well tolerated, but they are not usually recommended as monotherapy for hypertension because other classes of antihypertensives are more effective in preventing heart failure. Their major adverse effect is orthostatic hypotension, which may be severe after the first few doses but is otherwise uncommon. .

It is interesting that the use of α -adrenoceptor antagonists such as prazosin has been found to be associated with either no changes in plasma lipids or increased concentrations of high-density lipoproteins (HDL)

Peripheral Vascular Disease :

Alpha-receptor-blocking drugs do not seem to be effective in the treatment of peripheral vascular occlusive disease characterized by morphologic changes that limit flow in the vessels.

Urinary Obstruction :

Benign prostatic hyperplasia is common in elderly men. Various surgical treatments are effective in relieving the urinary symptoms of BPH. The mechanism of action in improving urine flow involves partial reversal of smooth muscle contraction in the enlarged prostate and in the bladder base. It has been suggested that some α 1-receptor antagonists may have additional effects on cells in the prostate that help improve symptoms.

Prazosin, doxazosin, and terazosin are all efficacious in patients with BPH. α 1-receptor subtype is most

important for smooth muscle contraction in the prostate: subtype-selective α 1A-receptor antagonists like tamsulosin may have improved efficacy and safety in treating this disease.

Erectile Dysfunction:

Sildenafil and other cGMPphosphodiesterase inhibitors are drugs of choice for erectile dysfunction .

Applications of Alpha2 Antagonists

Alpha2 antagonists have relatively little clinical usefulness. They have definite but limited benefit in male erectile dysfunction. They has a highly selective antagonists for treatment of type 2 diabetes, and for treatment of psychiatricdepression. It is likely that better understanding of the subtypes of α 2 receptors will lead to development of clinically useful subtypeselective α 2 antagonists.

BASIC PHARMACOLOGY OF THE BETA-RECEPTOR ANTAGONIST DRUGS

Betablocking drugs occupy β receptors and competitively reduce receptor occupancy by catecholamines and other β agonists. Most β -blocking drugs in clinical use are pure antagonists; such as albeit less than that caused by the full agonists epinephrine and isoproterenol. Finally, evidence suggests that some β blockers are inverse agonists.

The β -receptor-blocking drugs differ in their relative affinities for β_1 and β_2 receptors.

Some have a higher affinity for β_1 than for β_2 receptors, and this selectivity may have important clinical implications.

Chemically, most β -receptor antagonist drugs resemble isoproterenol to some degree.

Pharmacokinetic Properties of the Beta-Receptor Antagonists

Most of the drugs in this class are well absorbed after oral administration; peak concentrations occur 1–3 hours after ingestion.

Propranolol undergoes

1. Absorption

2. Bioavailability

extensive hepatic (first-pass) metabolism; its bioavailability is relatively low. The proportion of drug reaching the systemic circulation increases as the dose is increased, suggesting that hepatic extraction mechanisms may become saturated.

The β antagonists are rapidly distributed and have large volumes of distribution. Most β antagonists have half-lives in the range of 3–10 hours. Poor metabolizers exhibit threefold to tenfold higher plasma concentrations after administration of metoprolol than extensive metabolizers. The elimination of drugs such as propranolol may be prolonged in the presence of

3. Distribution and Clearance

<p>liver disease, diminished hepatic blood flow, or hepatic enzyme inhibition.</p>		<p>nervous system. chronic drug administration leads to a fall in peripheral resistance in patients with hypertension.</p>	
<h2 style="text-align: center;"><u>Pharmacodynamics of the Beta-Receptor Antagonist Drugs</u></h2> <p>Most of the effects of these drugs are due to occupation and blockade of β receptors.</p>		<p>Blockade of the β_2 receptors in bronchial smooth muscle may lead to an increase in airway resistance, particularly in patients with asthma.</p>	<p>2. Effects on the Respiratory Tract</p>
<p>Comment</p> <p>given chronically lower blood pressure in patients with hypertension. The mechanisms probably include suppression of renin release and effects in the CNS. They very valuable in the treatment of: angina and chronic heart failure and following myocardial infarction. Nonselective and β_1-blocking drugs antagonize the release of renin caused by the sympathetic</p>	<p>Effect</p> <p>1. Effects on the Cardiovascular System</p>	<p>Beta1-receptor antagonists such as metoprolol and atenolol may have some advantage over nonselective β antagonists when blockade of β_1 receptors in the heart is desired and β_2-receptor blockade is undesirable</p>	<p>3. Effects on the Eye</p> <p>Beta-blocking agents reduce intraocular pressure, especially in glaucoma. The mechanism usually reported is decreased aqueous humor production.</p>

<p>The effects on carbohydrate metabolism are less clear, though glycogenolysis in the human liver is at least partially inhibited after β_2-receptor blockade. Beta1-receptor-selective drugs may be less prone to inhibit recovery from hypoglycemia.</p>	<h4>4. Metabolic and Endocrine Effects</h4>	<p>asthma or excessive bradycardia. However, these drugs may not be as effective as the pure antagonists in secondary prevention of myocardial infarction. Local anesthetic action, also known as “membrane-stabilizing” action, is a prominent effect of several β blockers.</p>	
<p>The chronic use of β-adrenoceptor antagonists has been associated with increased plasma concentrations of very-low-density lipoproteins (VLDL) and decreased concentrations of HDL cholesterol.</p>	<h4>5. Effects Not Related to Beta-Blockade</h4>	<p>This action is the result of typical local anesthetic blockade of sodium channels and can be demonstrated experimentally in isolated neurons, heart muscle, and skeletal muscle membrane.</p>	
<p>Partial β-agonist activity may have been considered desirable to prevent untoward effects such as precipitation of</p>		<p>The Treatment of Glaucoma</p> <p>Glaucoma is a major cause of blindness and of great pharmacologic interest because the chronic form often responds to drug therapy. The primary manifestation is increased intraocular pressure not initially</p>	

associated with symptoms. Without treatment, increased intraocular pressure results in damage to the retina and optic nerve, with restriction of visual fields and, eventually, blindness. Two major types of glaucoma are recognized: open angle and closed-angle (also called narrow-angle).

The closed-angle form is associated with a shallow anterior chamber, in which a dilated iris can occlude the outflow drainage pathway at the angle between the cornea and the ciliary body. This form is associated with acute and painful increases of pressure,

which must be controlled on an emergency basis with drugs or prevented by surgical removal of part of the iris (iridectomy). The open-angle form of glaucoma is a chronic condition, and treatment is largely pharmacologic. Because intraocular pressure is a function of the balance between fluid input and drainage out of the globe, the strategies for the treatment of open-angle glaucoma fall into two classes: reduction of aqueous humor secretion and enhancement of aqueous outflow.

Five general groups of drugs (cholinomimetics, a agonists, β blockers, prostaglandin F2a analogs, and diuretics) have been found to be useful in reducing intraocular

pressure and can be related to these strategies. Other drugs that have been reported to reduce intraocular pressure include prostaglandin E2 and marijuana. The use of drugs in acute closed-angle glaucoma is limited to cholinomimetics, acetazolamide, and osmotic agents preceding surgery.

CLINICAL PHARMACOLOGY OF THE BETA-RECEPTOR-BLOCKING DRUGS

Hypertension

The β -adrenoceptor-blocking drugs have proved to be effective and well tolerated in hypertension. There is some evidence that drugs in this class may be less effective in the elderly and in individuals of African ancestry. However, these differences are relatively small and may not apply to an individual patient. Indeed, since effects on blood pressure are easily measured, the therapeutic outcome for this

indication can be readily detected in any patient.

Ischemic Heart Disease :

Beta-adrenoceptor blockers reduce the frequency of anginal episodes and improve exercise tolerance in many patients with angina. These actions are due to blockade of cardiac β receptors, resulting in decreased cardiac work and reduction in oxygen demand. Multiple large-scale prospective studies indicate that the long-term such as timolol, use in patients who have had a myocardial infarction prolongs survival.

It is significant that surveys in many populations have indicated that β -receptor antagonists are underused.

In addition, β -adrenoceptor antagonists are strongly indicated in the acute phase of a myocardial infarction.

Cardiac Arrhythmias

It often effective in the treatment of both supraventricular and ventricular arrhythmias. It has been suggested that the improved survival following myocardial infarction in patients using β antagonists is due to suppression of arrhythmias, but this has not been proved. These drugs can also reduce ventricular ectopic beats, particularly if the ectopic activity has been precipitated by catecholamines.

Esmolol is particularly useful against acute perioperative arrhythmias because it has a short duration of action and can be given parenterally. Heart Failure
Clinical trials have demonstrated that at least three β antagonists—metoprolol, bisoprolol, and carvedilol—are effective in reducing mortality in selected patients with chronic heart failure.

Other Cardiovascular Disorders

Beta-receptor antagonists have been found to increase stroke volume in some patients with obstructive cardiomyopathy. Beta antagonists are useful in dissecting aortic aneurysm to decrease the rate of development of systolic pressure. Beta antagonists have been claimed to prevent adverse cardiovascular outcomes resulting from noncardiac surgery but this is controversial.

Glaucoma (The Treatment of Glaucoma)

Systemic administration of β -blocking drugs for other indications was found serendipitously to reduce intraocular pressure in patients with glaucoma. Subsequently, it was found that topical administration also reduces intraocular pressure. Timolol and related β antagonists are suitable

for local use in the eye because they lack local anesthetic properties. Beta antagonists appear to have an efficacy comparable to that of epinephrine or pilocarpine in open-angle glaucoma and are far better tolerated by most patients.

Hyperthyroidism:

Excessive catecholamine action is an important aspect of the pathophysiology of hyperthyroidism, especially in relation to the heart. The β antagonists are beneficial in this condition.

The effects presumably relate to blockade of adrenoceptors and perhaps in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine.

Propranolol has been used extensively in patients with thyroid storm (severe hyperthyroidism); it is used cautiously in patients with this condition to control supraventricular tachycardias that often precipitate heart failure.

Neurologic Diseases:

Propranolol reduces the frequency and intensity of migraine. The somatic manifestations of anxiety may respond dramatically to low doses of propranolol, particularly when taken prophylactically.

For example, benefit has been found in musicians with performance anxiety ("stage fright").

Miscellaneous:

Beta-receptor antagonists have been found to diminish portal vein pressure in patients with cirrhosis.

CHOICE OF A BETA-ADRENOCEPTOR ANTAGONIST DRUG

Propranolol is the standard against which newer β antagonists for systemic use.

It has been found to be a safe and effective drug for many indications.

CLINICAL TOXICITY OF THE BETARECEPTOR ANTAGONIST DRUGS

Many adverse effects have been reported for propranolol but most are minor. Bradycardia- coolness of hands and feet in winter- CNS effects include mild sedation, vivid dreams, and rarely, depression.

The major adverse effects of β -receptor antagonist drugs relate to the predictable consequences of β blockade. Beta₂-receptor blockade associated with the use of nonselective agents commonly causes worsening of preexisting

asthma and other forms of airway obstruction without having these consequences in normal individuals.

Beta-receptor blockade depresses myocardial contractility and excitability. In patients with abnormal myocardial function,

Beta blockers may interact with the calcium antagonist verapamil; severe hypotension, bradycardia, heart failure, and cardiac conduction abnormalities have all been described.

Patients with ischemic heart disease or renovascular hypertension may be at increased risk if β blockade is suddenly interrupted.

cardiac output may be dependent on sympathetic drive. A very small dose of a β antagonist may provoke severe cardiac failure in a susceptible individual.

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
<ul style="list-style-type: none"> • Carvedilol • Medroxalol[†] • Bucindolol[†] (see labetalol above) 	$\beta > \alpha_1$ block		Heart failure	Oral, long half-life • Toxicity: Fatigue
Esmolol	$\beta_1 > \beta_2$	Very brief cardiac β blockade	Rapid control of BP and arrhythmias, thyrotoxicosis, and myocardial ischemia intraoperatively	Parenteral only • half-life ~10 min • Toxicity: Bradycardia • hypotension
TYROSINE HYDROXYLASE INHIBITOR				
Metyrosine	<ul style="list-style-type: none"> Blocks tyrosine hydroxylase reduces synthesis of dopamine, norepinephrine, and epinephrine 	Lowers BP • may elicit extrapyramidal effects (due to low dopamine in CNS)	Pheochromocytoma	Toxicity: Extrapyramidal symptoms • orthostatic hypotension • crystalluria <small>Not available in the USA</small>

SUMMARY Sympathetic Antagonists

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
ALPHA-ADRENOCEPTOR ANTAGONISTS				
• Phenoxybenzamine	Irreversibly blocks α_1 and α_2 • indirect baroreflex activation	Lowers blood pressure (BP) • heart rate (HR) rises due to baroreflex activation	Pheochromocytoma • high catecholamine states	Irreversible blocker • duration > 1 day • Toxicity: Orthostatic hypotension • tachycardia • myocardial ischemia
• Phentolamine	Reversibly blocks α_1 and α_2	Blocks α -mediated vasoconstriction, lowers BP, increases HR (baroreflex)	Pheochromocytoma	Half-life ~45 min after IV injection
• Prazosin • Doxazosin • Terazosin	Block α_1 , but not α_2	Lower BP	Hypertension • benign prostatic hyperplasia	Larger depressor effect with first dose may cause orthostatic hypotension
• Tamsulosin	Tamsulosin is slightly selective for α_{1A}	α_{1A} blockade may relax prostatic smooth muscle more than vascular smooth muscle	Benign prostatic hyperplasia	Orthostatic hypotension may be less common with this subtype
• Yohimbine	Blocks α_2 • elicits increased central sympathetic activity • increased norepinephrine release	Raises BP and HR	Male erectile dysfunction • hypotension	May cause anxiety • excess pressor effect if norepinephrine transporter is blocked
• Labetalol (see carvedilol section below)	$\beta > \alpha_1$ block	Lowers BP with limited HR increase	Hypertension	Oral, parenteral • Toxicity: Less tachycardia than other α_1 agents
BETA-ADRENOCEPTOR ANTAGONISTS				
• Propranolol • Nadolol • Timolol	Block β_1 and β_2	Lower HR and BP • reduce renin	Hypertension • angina pectoris • arrhythmias • migraine • hyperthyroidism • glaucoma (topical timolol)	Oral, parenteral • Toxicity: Bradycardia • worsened asthma • fatigue • vivid dreams • cold hands
• Metoprolol • Atenolol • Betaxolol • Nebivolol	Block $\beta_1 > \beta_2$	Lower HR and BP • reduce renin • may be safer in asthma	Angina pectoris • hypertension • arrhythmias • glaucoma (topical betaxolol)	Toxicity: Bradycardia • fatigue • vivid dreams • cold hands
• Butoxamine ¹	Blocks $\beta_2 > \beta_1$	Increases peripheral resistance	No clinical indication	Toxicity: Asthma provocation
• Pindolol • Acebutolol • Carteolol • Bopindolol ¹ • Oxprenolol ¹ • Celiprolol ¹ • Penbutolol	β_1, β_2 , with intrinsic sympathomimetic (partial agonist) effect	Lower BP • modestly lower HR	Hypertension • arrhythmias • migraine • may avoid worsening of bradycardia	Oral • Toxicity: Fatigue • vivid dreams • cold hands

section...»

Cardiovascular-Renal Drugs



I 1 - Antihypertensive Agents .

I 2 - Vasodilators & the Treatment of Angina Pectoris .

I 3 - Drugs Used in Heart Failure .

I 4 - Agents Used in Cardiac Arrhythmias .

I 5 - Diuretic Agents .

6 Introduction to autonomic pharmacology

The nervous system is conventionally divided into the central nervous system and the peripheral nervous system. The motor (efferent) portion of the nervous system can be divided into two major subdivisions: autonomic and somatic. The autonomic nervous system (ANS) is largely independent (autonomous) in that its activities are not under direct conscious control. It is concerned primarily with visceral functions. Evidence is accumulating that the ANS, especially the vagus nerve, also influences immune function and some CNS functions. recent evidence indicates that autonomic nerves also influence prostate cancer development and progression. The somatic subdivision is largely concerned with consciously controlled functions. Both systems have important afferent (sensory) inputs that provide information regarding the internal and external environments and modify motor output through reflex arcs of varying size and complexity. The nervous system has several properties with the endocrine system. In the nervous system, chemical transmission occurs between nerve cells and

between nerve cells and their effector cells. The transmitter crosses the cleft by diffusion and activates or inhibits the postsynaptic cell by binding to a specialized receptor molecule. By using drugs that mimic or block the actions of chemical transmitters, we can selectively modify many autonomic functions. These functions involve a variety of effector tissues.

Autonomic drugs are useful in many clinical conditions. Unfortunately, a very large number of drugs used for other purposes have unwanted effects on autonomic function.

ANATOMY OF THE AUTONOMIC NERVOUS SYSTEM:

The ANS lends itself to division on anatomic grounds into two major portions: the sympathetic division and the parasympathetic division. Neurons in both divisions originate in nuclei within the CNS and give rise to preganglionic efferent fibers that exit from the brain stem or spinal cord and terminate in motor ganglia. The sympathetic preganglionic fibers leave the CNS through the thoracic and lumbar spinal nerves.

The parasympathetic preganglionic fibers leave the CNS through the cranial nerves , and the third and fourth sacral spinal nerve roots.

Most sympathetic preganglionic fibers are short and terminate in ganglia. The remaining sympathetic preganglionic fibers are somewhat longer and terminate in prevertebral ganglia. From the ganglia, postganglionic sympathetic fibers run to the tissues innervated. Some preganglionic parasympathetic fibers terminate in parasympathetic ganglia located outside the organs .However, the majority of parasympathetic preganglionic fibers terminate on ganglion cells. In addition to these clearly defined peripheral motor portions of the ANS, large numbers of afferent fibers run from the periphery to integrating centers. Many of the sensory pathways that end in the CNS terminate in the hypothalamus and medulla and evoke reflex motor activity that is carried to the effector cells by the efferent fibers. There is increasing evidence that some of sensory fibers also have peripheral motor functions. The enteric nervous system (ENS) is a large and highly organized collection of neurons located in the walls of the (GI) system. It is sometimes considered a third division of the ANS. It is found in the wall of the GI tract from the

esophagus to the distal colon and is involved in both motor and secretory activities of the gut. It is critical in the motor activity of the colon. The ENS includes the myenteric plexus and the submucous plexus. These neuronal networks receive preganglionic fibers from the parasympathetic system and postganglionic sympathetic axons. They also receive sensory input from within the wall of the gut. Fibers from the neuronal cell bodies in these plexuses travel forward, backward, and in a circular direction to the smooth muscle of the gut to control motility and to secretory cells in the mucosa. Sensory fibers transmit chemical and mechanical information from themucosa and from stretch receptors to motor neurons in the plexuses and to postganglionic neurons in the sympathetic ganglia. The parasympathetic and sympathetic fibers that synapse on enteric plexus neurons appear to play a modulatory role, as indicated by the observation that deprivation of input from both ANS divisions does not abolish GI activity. In fact, selective denervation may result in greatly enhanced motor activity.

The ENS functions in a semiautonomous manner, utilizing input from the motor outflow of the ANS for modulation of GI activity and sending sensory information back to the CNS. The ENS also provides the necessary synchronization of impulses. The anatomy of autonomic synapses and junctions determines the localization of transmitter effects around nerve endings. Classic synapses are relatively “tight” in that the nerve terminates in small boutons very close to the tissue innervated, so that the diffusion path from nerve terminal to postsynaptic receptors is very short. The effects are thus relatively rapid and localized. In contrast, junctions between autonomic neuron terminals and effector cells differ from classic synapses in that transmitter is often released from a chain of varicosities in the postganglionic nerve fiber in the region of the smooth muscle cells rather than from boutons, and autonomic junctional clefts are wider than somatic synaptic clefts. Effects are thus slower in onset and discharge of a single motor fiber often activates or inhibits many effector cells.

NEUROTRANSMITTER CHEMISTRY OF THE AUTONOMIC NERVOUS SYSTEM :

An important classification of autonomic nerves is based on the primary transmitter molecules—Ach or norepinephrine. A large number of peripheral ANS fibers synthesize and release acetylcholine. These include all preganglionic efferent autonomic fibers and the somatic, motor fibers to skeletal muscle as well. Thus, almost all efferent fibers leaving the CNS are cholinergic. In addition, most parasympathetic postganglionic and a few sympathetic postganglionic fibers are cholinergic. A significant number of parasympathetic postganglionic neurons utilize nitric oxide or peptides as the primary transmitter. Most postganglionic sympathetic fibers release norepinephrine, they are noradrenergic fibers. Some sympathetic fibers release acetylcholine. Dopamine is a very important transmitter in the CNS. Adrenal medullary cells, which are embryologically analogous to postganglionic sympathetic neurons, release a mixture of epinephrine and norepinephrine. Finally, most autonomic nerves also release several cotransmitter substances.

Five key features of neurotransmitter function provide potential targets for pharmacologic therapy: synthesis, storage, release, termination of action of the transmitter, and receptor effects.

Cholinergic Transmission:

The terminals and varicosities of cholinergic neurons contain large numbers of small membrane-bound vesicles as well as a smaller number of large dense-cored vesicles. The large vesicles contain a high concentration of peptide cotransmitters, whereas the smaller clear vesicles contain most of the acetylcholine. Vesicles are provided with vesicle-associated membrane proteins (VAMPs), which serve to align them with release sites on the inner neuronal cell membrane and participate in triggering the release of transmitter. The release site on the inner surface of the nerve terminal membrane contains synaptosomal nerve-associated proteins (SNAPs), which interact with VAMPs. VAMPs and SNAPs are collectively called fusion proteins. This symporter can be blocked by a group of research drugs called hemicholiniums. Once synthesized, acetylcholine is transported from the cytoplasm into the vesicles by a vesicle-associated transporter (VAT) that is driven by

proton efflux. This antiporter can be blocked by the research drug vesamicol. Most of the vesicular acetylcholine (ACh) is bound to negatively charged vesicular proteoglycan (VPG). Vesicles are concentrated on the inner surface of the nerve terminal facing the synapse through the interaction of so-called SNARE proteins on the vesicle, and on the inside of the terminal cell membrane. Physiologic release of transmitter from the vesicles is dependent on extracellular calcium and occurs when an action potential reaches the terminal and triggers sufficient influx of calcium ions via N-type calcium channels. Calcium interacts with the VAMP synaptotagmin on the vesicle membrane and triggers fusion of the vesicle membrane with the terminal membrane and opening of a pore into the synapse. The opening of the pore results in release of the acetylcholine into the synaptic cleft. One depolarization of a somatic motor nerve may release quanta into the synaptic cleft. One depolarization of an autonomic postganglionic nerve varicosity or terminal probably releases less and releases it over a larger area. After release from the presynaptic terminal, ACh molecules may bind to and activate an ACh receptor (cholinoreceptor).

Eventually, all of the ACh released diffuses within range of an acetylcholinesterase (AChE) molecule.

AChE very efficiently splits acetylcholine into choline and acetate, neither of which has significant transmitter effect, and thereby terminates the action of the transmitter. Most cholinergic synapses are richly supplied with AChE; the half-life of acetylcholine is very short. AChE is also found in other tissues.

Adrenergic Transmission:

Adrenergic neurons transport a precursor amino acid (tyrosine) into the nerve ending, then synthesize the catecholamine transmitter and store it in membrane-bound vesicles. In most sympathetic postganglionic neurons, norepinephrine is the final product. In the adrenal medulla and certain areas of the brain, some norepinephrine is further converted to epinephrine. In dopaminergic neurons, synthesis terminates with dopamine. Nerve terminals are potential sites of drug action. One of these, the conversion of tyrosine to dopa by tyrosine hydroxylase, is the rate-limiting step in catecholamine transmitter synthesis. It can be inhibited by the tyrosine analog metyrosine. A high-affinity

antiporter for catecholamines located in the wall of the storage vesicle, can be inhibited by the reserpine alkaloids. Another transporter carries norepinephrine and similar molecules back into the cell cytoplasm from the synaptic cleft. NET is also commonly called uptake 1 or reuptake 1 and is partially responsible for the termination of synaptic activity. NET can be inhibited by cocaine and certain antidepressant drugs, resulting in an increase of transmitter activity in the synaptic cleft. Release of the vesicular transmitter store from noradrenergic nerve endings is similar to the calcium-dependent process previously described for cholinergic terminals. In addition to the primary transmitter (norepinephrine), (ATP), dopamine- β -hydroxylase,

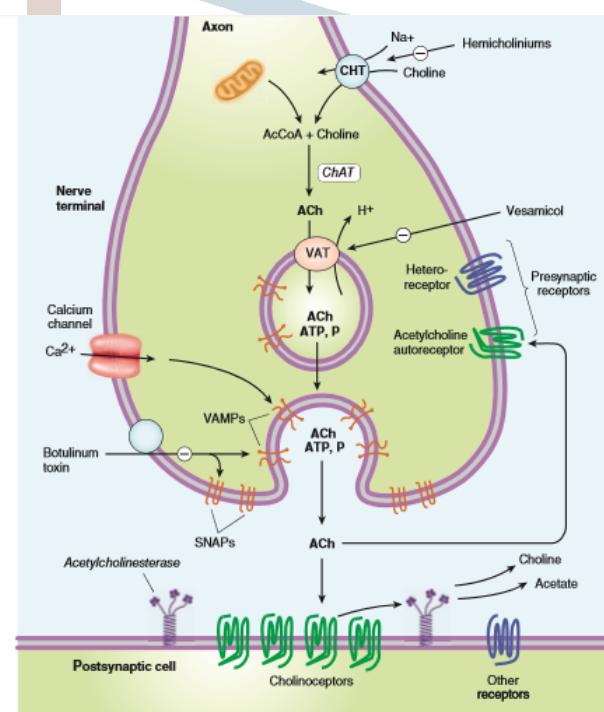


FIGURE 6-3 Schematic illustration of a generalized cholinergic junction (not to scale). Choline is transported into the presynaptic nerve terminal by a sodium-dependent choline transporter (ChT). This transporter can be inhibited by hemicholinium drugs. In the cytoplasm, acetylcholine is synthesized from choline and acetyl-CoA (AcCoA) by the enzyme choline acetyltransferase (ChAT). Acetylcholine (ACh) is then transported into the storage vesicle by a vesicle-associated transporter (VAT), which can be inhibited by vesamicol. Peptides (P), adenosine triphosphate (ATP), and proteoglycan are also stored in the vesicle. Release of transmitters occurs when voltage-sensitive calcium channels in the terminal membrane are opened, allowing an influx of calcium. The resulting increase in intracellular calcium causes fusion of vesicles with the surface membrane and exocytotic expulsion of acetylcholine and cotransmitters into the junctional cleft (see text). This step can be blocked by botulinum toxin. Acetylcholine's action is terminated by metabolism by the enzyme acetylcholinesterase. Receptors on the presynaptic nerve ending modulate transmitter release. SNAPS, synaptosomal nerve-associated proteins; VAMPs, vesicle-associated membrane proteins.

and peptide cotransmitters are also released into the synaptic cleft. Indirectly acting and mixed sympathomimetics, eg, tyramine, amphetamines, and ephedrine, are capable of releasing stored transmitter from noradrenergic nerve endings by a calcium-independent process. Amphetamines also inhibit monoamine oxidase and have other effects that result in increased norepinephrine activity in the synapse. Norepinephrine and epinephrine can be metabolized by several enzymes. Because of the high activity of monoamine oxidase in the mitochondria of the nerve terminal, there is significant turnover of norepinephrine even in the resting terminal. Since the metabolic products are excreted in the urine, an estimate of catecholamine turnover can be obtained from measurement of total metabolites in a 24-hour urine sample. However, metabolism is not the primary mechanism for termination of action of norepinephrine physiologically released from noradrenergic nerves. Termination results from two processes: 1- simple diffusion away from the receptor site. 2- reuptake into the nerve terminal

by NET or into perisynaptic glia or other cells.

Cotransmitters in Cholinergic & Adrenergic Nerves:

The vesicles of both nerves contain other substances in addition to the primary transmitter, sometimes in the same vesicles and sometimes in a separate vesicle population. Some of the substances identified to date are listed in Table 6-1. Many of these substances are also primary transmitters in the nonadrenergic, noncholinergic nerves. They appear to play several roles in the function of nerves that release acetylcholine or norepinephrine. In some cases, they provide a faster or slower action to supplement or modulate the effects of the primary transmitter. They also participate in feedback inhibition of the same and nearby nerve terminals. Growth of neurons and transmitter expression in specific neurons is a dynamic process. In addition, the transmitters released from a specific population of neurons can change in response to environmental factors such as the light-dark cycle.

AUTONOMIC RECEPTORS:

the potency of series of autonomic agonist and antagonist analogs, led to the definition of different autonomic receptor subtypes, including muscarinic and nicotinic cholinoreceptors, and α , β , and dopamine adrenoceptors (Table 6–2). The primary acetylcholine receptor subtypes were named after the alkaloids originally used in their identification: muscarinic and nicotinic receptors. Therefore, the term adrenoceptor is describe receptors that respond to catecholamines. By analogy, the term cholinoreceptor denotes receptors that respond to acetylcholine. The general class of adrenoceptors can be further subdivided into alpha-adrenoceptor, Beta-adrenoceptor, and dopamine-receptor types on the basis of both agonist and antagonist selectivity and on genomic grounds. Development of more selective blocking drugs has led to the naming of subclasses within these major types; α_1 and α_2 receptors differ in both agonist and antagonist selectivity.

TABLE 6–2 Major autonomic receptor types.

Receptor Name	Typical Locations	Result of Ligand Binding
Cholinoreceptors		
Muscarinic M ₁	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites	Formation of IP ₃ and DAG, increased intracellular calcium
Muscarinic M ₂	Myocardium, smooth muscle, some presynaptic sites; CNS neurons	Opening of potassium channels, inhibition of adenylyl cyclase
Muscarinic M ₃	Exocrine glands, vessels (smooth muscle and endothelium); CNS neurons	Like M ₁ receptor-ligand binding
Muscarinic M ₄	CNS neurons; possibly vagal nerve endings	Like M ₂ receptor-ligand binding
Muscarinic M ₅	Vascular endothelium, especially cerebral vessels; CNS neurons	Like M ₁ receptor-ligand binding
Nicotinic N _N	Postganglionic neurons, some presynaptic cholinergic terminals; pentameric receptors typically contain α and β type subunits only (see Chapter 7)	Opening of Na ⁺ , K ⁺ channels, depolarization
Nicotinic N _M	Skeletal muscle neuromuscular end plates; receptors typically contain two $\alpha 1$ and $\beta 1$ type subunits in addition to γ and δ subunits	Opening of Na ⁺ , K ⁺ channels, depolarization
Adrenoceptors		
Alpha ₁	Postsynaptic effector cells, especially smooth muscle	Formation of IP ₃ and DAG, increased intracellular calcium
Alpha ₂	Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle	Inhibition of adenylyl cyclase, decreased cAMP
Beta ₁	Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals, juxtaglomerular apparatus of renal tubules, ciliary body epithelium	Stimulation of adenylyl cyclase, increased cAMP
Beta ₂	Postsynaptic effector cells, especially smooth muscle and cardiac muscle	Stimulation of adenylyl cyclase and increased cAMP. Activates cardiac G _i under some conditions.
Beta ₃	Postsynaptic effector cells, especially lipocytes; heart	Stimulation of adenylyl cyclase and increased cAMP ¹
Dopamine receptors		
D ₁ (DA ₁), D ₅	Brain; effector tissues, especially smooth muscle of the renal vascular bed	Stimulation of adenylyl cyclase and increased cAMP
D ₂ (DA ₂)	Brain; effector tissues, especially smooth muscle; presynaptic nerve terminals	Inhibition of adenylyl cyclase; increased potassium conductance
D ₃	Brain	Inhibition of adenylyl cyclase
D ₄	Brain, cardiovascular system	Inhibition of adenylyl cyclase

¹Cardiac β_3 -receptor function is poorly understood, but activation does not appear to result in stimulation of rate or force.

NONADRENERGIC, NONCHOLINERGIC (NANC) NEURONS

It has been known for many years that autonomic effector tissues contain nerve fibers that do not show the histochemical characteristics of either cholinergic or adrenergic fibers. Both motor and sensory NANC fibers are present. Although peptides are the most common transmitter. Capsaicin, a neurotoxin derived from chili peppers, can cause the release of

transmitter from such neurons and, if given in high doses, destruction of the neuron. The enteric system in the gut wall is the most extensively studied system containing NANC neurons in addition to cholinergic and adrenergic fibers. Some neurons contain as many as five different transmitters. The sensory fibers in the nonadrenergic, noncholinergic systems are probably better termed “sensory-efferent” or “sensorylocal effector” fibers. These peptides are potent agonists in many autonomic effector tissues.

FUNCTIONAL ORGANIZATION OF AUTONOMIC ACTIVITY

Autonomic function is integrated and regulated at many levels, from the CNS to the effector cells. Most regulation uses negative feedback, but several other mechanisms have been identified. Negative feedback is important in the responses of the ANS to the administration of autonomic drugs.

Central Integration:

At the highest level—midbrain and medulla—the two divisions of the ANS and the endocrine system are integrated with each other. These interactions are such that early investigators called the parasympathetic system a trophotropic one used to “rest and digest” and the sympathetic system an ergotropic one, which is activated for “fight or flight.” Although such

terms offer little insight into the mechanisms involved, they do provide simple descriptions applicable to many of the actions of the systems (Table 6–3). At a more subtle level of interactions in the brain stem, medulla, and spinal cord, there are important cooperative interactions between the parasympathetic and sympathetic systems.

For some organs, sensory fibers associated with the parasympathetic system exert reflex control over motor outflow in the sympathetic system. Thus, the sensory carotid

sinus baroreceptor fibers in the glossopharyngeal nerve have a major influence on sympathetic outflow from the vasomotor center.

TABLE 6–3 Direct effects of autonomic nerve activity on some organ systems. Autonomic drug effects are similar but not identical (see text).

Organ	Effect of			
	Sympathetic Activity		Parasympathetic Activity	
	Action ¹	Receptor ²	Action	Receptor ²
Eye				
Iris radial muscle	Contracts	α_1	—	—
Iris circular muscle	—	—	Contracts	M_3
Ciliary muscle	[Relaxes]	β	Contracts	M_3
Heart				
Sinoatrial node	Accelerates	β_1, β_2	Decelerates	M_2
Ectopic pacemakers	Accelerates	β_1, β_2	—	—
Contractility	Increases	β_1, β_2	Decreases (atria)	M_2
Blood vessels				
Skin, splanchnic vessels	Contracts	α	—	—
Skeletal muscle vessels	Relaxes	β_2	—	—
	[Contracts]	α	—	—
	Relaxes ³	M_3	—	—
Endothelium of vessels in heart, brain, viscera	—	—	Synthesizes and releases EDRF ⁴	M_3, M_5^5
Bronchiolar smooth muscle	Relaxes	β_2	Contracts	M_3
Gastrointestinal tract				
Smooth muscle				
Walls	Relaxes	$\alpha_{2s},^6 \beta_2$	Contracts	M_3
Sphincters	Contracts	α_1	Relaxes	M_3
Secretion	—	—	Increases	M_3
Genitourinary smooth muscle				
Bladder wall	Relaxes	β_2	Contracts	M_3
Sphincter	Contracts	α_1	Relaxes	M_3
Uterus, pregnant				
	Relaxes	β_2	—	...
	Contracts	α	Contracts	M_3
Penis, seminal vesicles			Ejaculation	α
				Erection
Skin				
Pilomotor smooth muscle	Contracts	α	—	—
Sweat glands				—
Eccrine	Increases	M	—	—
Apocrine (stress)	Increases	α	—	—
Metabolic functions				
Liver	Gluconeogenesis	β_2, α	—	—
Liver	Glycogenolysis	β_2, α	—	—
Fat cells	Lipolysis	β_3	—	—
Kidney	Renin release	β_1	—	—

Integration of

Cardiovascular:

Function Autonomic reflexes are particularly important in understanding cardiovascular responses to autonomic drugs. As indicated in Figure 6–7, the primary controlled variable in cardiovascular function is mean arterial pressure.

Changes in any variable contributing to mean arterial pressure , evoke powerful homeostatic secondary responses that tend to compensate for the directly evoked change. The homeostatic response may be sufficient to reduce the change in mean arterial pressure and to reverse the drug's effects on heart rate. This agent produces direct effects on both vascular and cardiac muscle. In the absence of reflex control in a patient who has had a heart transplant.

Presynaptic Regulation:

The principle of negative feedback control is also found at the presynaptic level of autonomic function. Important presynaptic feedback inhibitory control mechanisms have been shown to exist at most nerve endings. A well-documented mechanism involves the α_2 receptor located on noradrenergic nerve terminals. This receptor is activated by norepinephrine and similar molecules; activation diminishes further release of norepinephrine from these nerve endings (Table 6–4). The mechanism of this G protein mediated effect involves inhibition of the inward calcium current that causes vesicular fusion and transmitter release. Conversely, a presynaptic β receptor appears to facilitate the release of norepinephrine from some adrenergic neurons. Presynaptic receptors that respond to the primary transmitter substance released by the nerve ending are called autoreceptors. Nerve terminals also carry regulatory receptors that respond to many other substances.

Such heteroreceptors may be activated by substances released from other nerve terminals that synapse with the nerve ending. Alternatively, the ligands for these receptors may diffuse to the receptors from the blood or from nearby tissues. Some of the transmitters and receptors identified to date are listed in Table 6–4. Presynaptic regulation by a variety of endogenous chemicals probably occurs in all nerve fibers.

TABLE 6-4 Autoreceptor, heteroreceptor, and modulatory effects on nerve terminals in peripheral synapses.¹

Transmitter/Modulator	Receptor Type	Neuron Terminals Where Found
Inhibitory effects		
Acetylcholine	M ₂ , M ₁	Adrenergic, enteric nervous system
Norepinephrine	Alpha ₂	Adrenergic
Dopamine	D ₂ ; less evidence for D ₁	Adrenergic
Serotonin (5-HT)	5-HT ₁ , 5-HT ₂ , 5-HT ₃	Cholinergic preganglionic
ATP, ADP	P2Y	Adrenergic autonomic and ENS cholinergic neurons
Adenosine	A ₁	Adrenergic autonomic and ENS cholinergic neurons
Histamine	H ₃ , possibly H ₂	H ₃ type identified on CNS adrenergic and serotonergic neurons
Enkephalin	Delta (also mu, kappa)	Adrenergic, ENS cholinergic
Neuropeptide Y	Y ₁ , Y ₂ (NPY)	Adrenergic, some cholinergic
Prostaglandin E ₁ , E ₂	EP ₃	Adrenergic
Excitatory effects		
Epinephrine	Beta ₂	Adrenergic, somatic motor cholinergic
Acetylcholine	N _M	Somatic motor cholinergic
Angiotensin II	AT ₁	Adrenergic

¹A provisional list. The number of transmitters and locations will undoubtedly increase with additional research.

Postsynaptic Regulation:

Postsynaptic regulation can be considered from two perspectives:

1-modulation by previous activity at the primary receptor :

The mechanism: has been well documented in several receptor-effector systems. Up-regulation and down-regulation in response to decreased or increased activation, respectively, of the receptors. An extreme form of up-regulation occurs after denervation of some tissues, resulting in denervation supersensitivity of the tissue to activators of that receptor type. Surgical or traumatic denervation results in marked proliferation of nicotinic cholinoreceptors over all parts of the fiber, including areas not previously associated with any motor nerve junctions. A pharmacologic supersensitivity related to denervation supersensitivity occurs in autonomic effector tissues after administration of drugs that deplete transmitter stores and prevent activation of the postsynaptic receptors for a sufficient period of time.

2- modulation by other simultaneous events.

The mechanism: involves modulation of the primary transmitter-receptor event by events evoked by the same or other transmitters acting on different postsynaptic receptors. The postganglionic cells are activated as a result of binding of an appropriate ligand to a neuronal nicotinic (NN) acetylcholine receptor. The resulting fast excitatory postsynaptic potential (EPSP) evokes a propagated action potential if threshold is reached.

This event is often followed by a small and slowly developing but longer-lasting hyperpolarizing afterpotential—a slow inhibitory postsynaptic potential (IPSP). This hyperpolarization involves opening of potassium channels by M₂ cholinoreceptors. The IPSP is followed by a small, slow excitatory postsynaptic potential caused by closure of potassium channels linked to M₁ cholinoreceptors. Finally, a late, very slow EPSP may be evoked by peptides released from other fibers. These slow potentials serve to modulate the responsiveness of the postsynaptic cell to subsequent primary excitatory presynaptic nerve activity.

PHARMACOLOGIC MODIFICATION OF AUTONOMIC FUNCTION:

Because transmission involves different mechanisms in different segments of the ANS, some drugs produce highly specific effects, whereas others are much less selective in their actions. A summary of the steps in transmission of impulses in Table 6–5). Drugs that block action potential propagation are very nonselective in their action. On the other hand, drugs that act on the biochemical processes involved in transmitter synthesis and storage are more selective. Activation or blockade of effector cell receptors offers maximum flexibility and selectivity of effect attainable with currently available drugs: adrenoceptors are easily distinguished from cholinoreceptors. Furthermore, individual receptor subgroups can often be selectively activated or blocked within each major type. Even greater selectivity may be attainable in the future using drugs that target post-receptor processes.

TABLE 6–5 Steps in autonomic transmission: Effects of drugs.

Process Affected	Drug Example	Site	Action
Action potential propagation	Local anesthetics, tetrodotoxin, ¹ saxitoxin ²	Nerve axons	Block voltage-gated sodium channels; block conduction
Transmitter synthesis	Hemicholiniums	Cholinergic nerve terminals: membrane	Block uptake of choline and slow synthesis
	α -Methyltyrosine (metyrosine)	Adrenergic nerve terminals and adrenal medulla: cytoplasm	Inhibits tyrosine hydroxylase and blocks synthesis of catecholamines
Transmitter storage	Vesamicol	Cholinergic terminals: VAT on vesicles	Prevents storage, depletes
	Reserpine	Adrenergic terminals: VMAT on vesicles	Prevents storage, depletes
Transmitter release	Many ³	Nerve terminal membrane receptors	Modulate release
	ω -Conotoxin GVIA ⁴	Nerve terminal calcium channels	Reduces transmitter release
	Botulinum toxin	Cholinergic vesicles	Prevents release
	α -Latrotoxin ⁵	Cholinergic and adrenergic vesicles	Causes explosive transmitter release
	Tyramine, amphetamine	Adrenergic nerve terminals	Promote transmitter release
Transmitter reuptake after release	Cocaine, tricyclic antidepressants, SNRI antidepressants ⁶	Adrenergic nerve terminals, NET	Inhibit uptake; increase transmitter effect on post-synaptic receptors
Receptor activation or blockade	Norepinephrine	Receptors at adrenergic junctions	Binds α receptors; causes contraction
	Phentolamine	Receptors at adrenergic junctions	Binds α receptors; prevents activation
	Isoproterenol	Receptors at adrenergic junctions	Binds β receptors; activates adenylyl cyclase
	Propranolol	Receptors at adrenergic junctions	Binds β receptors; prevents activation
	Nicotine	Receptors at nicotinic cholinergic junctions (autonomic ganglia, neuromuscular end plates)	Binds nicotinic receptors; opens ion channel in post-synaptic membrane
	Tubocurarine	Neuromuscular end plates	Prevents activation
	Bethanechol	Receptors, parasympathetic effector cells (smooth muscle, glands)	Binds and activates muscarinic receptors
	Atropine	Receptors, parasympathetic effector cells	Binds muscarinic receptors; prevents activation
Enzymatic inactivation of transmitter	Neostigmine	Cholinergic synapses (acetylcholinesterase)	Inhibits enzyme; prolongs and intensifies transmitter action
	Tranylcypromine	Adrenergic nerve terminals (monoamine oxidase)	Inhibits enzyme; increases stored transmitter pool

¹Toxin of puffer fish, California newt.

Chapter #7 : cholinoreceptor-activating & cholinesterase-Inhibiting Drugs

7cholinoreceptor-activating & cholinesterase-Inhibiting Drugs

Acetylcholine-receptor stimulants and cholinesterase inhibitors make up a large group of drugs that mimic acetylcholine (cholinomimetics) (Figure 7-1). Cholinoreceptor stimulants are classified pharmacologically by their spectrum of action, depending on the type of receptor—muscarinic or nicotinic—that is activated. Cholinomimetics are also classified by their mechanism of action because some bind directly to (and activate) cholinoreceptors whereas others act indirectly by inhibiting the hydrolysis of endogenous acetylcholine.

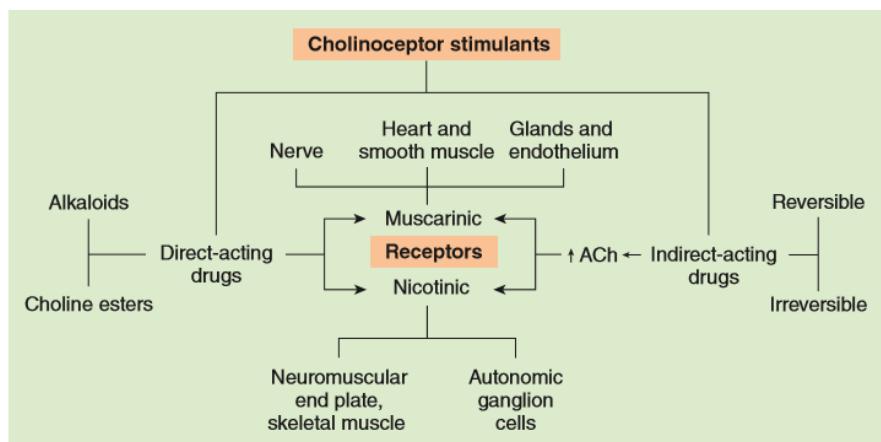


FIGURE 7-1 The major groups of cholinoreceptor-activating drugs, receptors, and target tissues. ACh, acetylcholine.

SPECTRUM OF ACTION OF CHOLINOMIMETIC DRUGS:

Early studies of the parasympathetic nervous system showed that the alkaloid muscarine mimicked the effects of parasympathetic nerve discharge; that is, the effects were parasympathomimetic. Application of muscarine to ganglia and to autonomic effector tissues showed that the parasympathomimetic action of the alkaloid occurred through an action on receptors at effector cells, not those in ganglia.

The effects of Ach itself and of other cholinomimetic drugs at autonomic neuroeffector junctions are called parasympathomimetic effects and are mediated by muscarinic receptors.

In contrast, low concentrations of the alkaloid nicotine stimulated autonomic ganglia and skeletal muscle neuromuscular junctions but not autonomic effector cells. When acetylcholine was later identified as the physiologic transmitter at both muscarinic and nicotinic receptors, both receptors were recognized as cholinoreceptor. Muscarinic receptors contain seven transmembrane domains whose third cytoplasmic loop is coupled to G proteins that function as transducers. These receptors regulate the production of intracellular second messengers and modulate certain ion channels via their G proteins. Agonist selectivity is determined by the subtypes of muscarinic receptors and G proteins. When expressed in cells, muscarinic receptors form dimers or oligomers that are thought to function in receptor movement between the endoplasmic reticulum and plasma membrane and in signaling. Conceivably, agonist or antagonist ligands could signal by changing the ratio of monomeric to oligomeric receptors. Nicotinic receptors are part of a transmembrane polypeptide. Nonselective cholinoreceptor stimulants in sufficient dosage can produce very diffuse and marked alterations in organ system function. Fortunately, drugs are available that have a degree of selectivity, so that desired effects can often be achieved while avoiding or minimizing adverse effects. Some drugs stimulate either muscarinic receptors or nicotinic receptors selectively. Some agents stimulate nicotinic receptors at neuromuscular

TABLE 7-1 Subtypes and characteristics of cholinoreceptors.

Receptor Type	Other Names	Location	Structural Features	Postreceptor Mechanism
M ₁		Nerves	Seven transmembrane segments, G _{q/11} protein-linked	IP ₃ , DAG cascade
M ₂	Cardiac M ₂	Heart, nerves, smooth muscle	Seven transmembrane segments, G _{i/o} protein-linked	Inhibition of cAMP production, activation of K ⁺ channels
M ₃		Glands, smooth muscle, endothelium	Seven transmembrane segments, G _{q/11} protein-linked	IP ₃ , DAG cascade
M ₄		CNS	Seven transmembrane segments, G _{i/o} protein-linked	Inhibition of cAMP production
M ₅		CNS	Seven transmembrane segments, G _{q/11} protein-linked	IP ₃ , DAG cascade
N _M	Muscle type, end plate receptor	Skeletal muscle neuromuscular junction	Pentamer ¹ [(α1) ₂ β1δγ] ¹	Na ⁺ , K ⁺ depolarizing ion channel
N _N	Neuronal type, ganglion receptor	CNS, postganglionic cell body, dendrites	Pentamer ¹ with α and β subunits only, eg, (α4) ₂ (β2) ₃ (CNS) or α3α5(β2) ₃ (ganglia)	Na ⁺ , K ⁺ depolarizing ion channel

¹Pentameric structure in *Torpedo* electric organ and fetal mammalian muscle has two α1 subunits and one each of β1, δ, and γ subunits. The stoichiometry is indicated by subscripts, eg, [(α1)₂β1δγ]. In adult muscle, the γ subunit is replaced by an ε subunit. There are twelve neuronal nicotinic receptors with nine α (α2-α10) subunits and three (β2-β4) subunits. The subunit composition varies among different mammalian tissues.

DAG, diacylglycerol; IP₃, inositol triphosphate.

Data from Millar NS: Assembly and subunit diversity of nicotinic acetylcholine receptors. Biochem Soc Trans 2003;31:869.

junctions and have less effect on nicotinic receptors in ganglia. Organ selectivity can also be achieved by using appropriate routes of administration.

MODE OF ACTION OF CHOLINOMIMETIC DRUGS

1- Direct-acting : cholinomimetic agents bind to and activate muscarinic or nicotinic receptors.

2-Indirect-acting : agents produce their primary effects by inhibiting acetylcholinesterase.

the indirect-acting drugs increase the endogenous acetylcholine concentration in synaptic clefts and neuroeffector junctions. These drugs act primarily where acetylcholine is physiologically released and are thus amplifiers of endogenous acetylcholine. Some cholinesterase inhibitors also inhibit butyrylcholinesterase . However, inhibition of butyrylcholinesterase plays little role in the action of indirect-acting cholinomimetic drugs. Some quaternary cholinesterase inhibitors also have a modest direct action as well, which activates neuromuscular nicotinic cholinoreceptors directly in addition to blocking cholinesterase.

BASIC PHARMACOLOGY OF THE DIRECT-ACTING CHOLINOCEPTOR STIMULANT:

The direct-acting cholinomimetic drugs can be divided on the basis of chemical structure into esters of choline and alkaloids. Many of these drugs have effects on both receptors; acetylcholine is typical. A few are highly selective. However, none of the clinically useful drugs is selective for receptor subtypes in either class.

Absorption, Distribution, and Metabolism: Choline esters are poorly absorbed and poorly distributed into the central nervous system because they are hydrophilic. Although all are hydrolyzed in the gastrointestinal tract. Acetylcholine is very rapidly hydrolyzed , large amounts must be infused IV to achieve concentrations sufficient to produce detectable effects. A large IV bolus injection has a brief effect, typically 5–20 seconds, whereas IM and subcutaneous injections produce only local effects. The β -methyl group reduces the potency of these drugs at nicotinic receptors.

The tertiary natural cholinomimetic alkaloids are well absorbed from most sites of administration.

Nicotine, a liquid, is sufficiently lipid-soluble to be absorbed across the skin.

Muscarine, a quaternary amine, is less completely absorbed from the gastrointestinal tract than the tertiary amines but is nevertheless toxic when ingested , and it even enters the brain. These amines are excreted chiefly by the kidneys. Acidification of the urine accelerates clearance of the tertiary amines.

Pharmacodynamics:

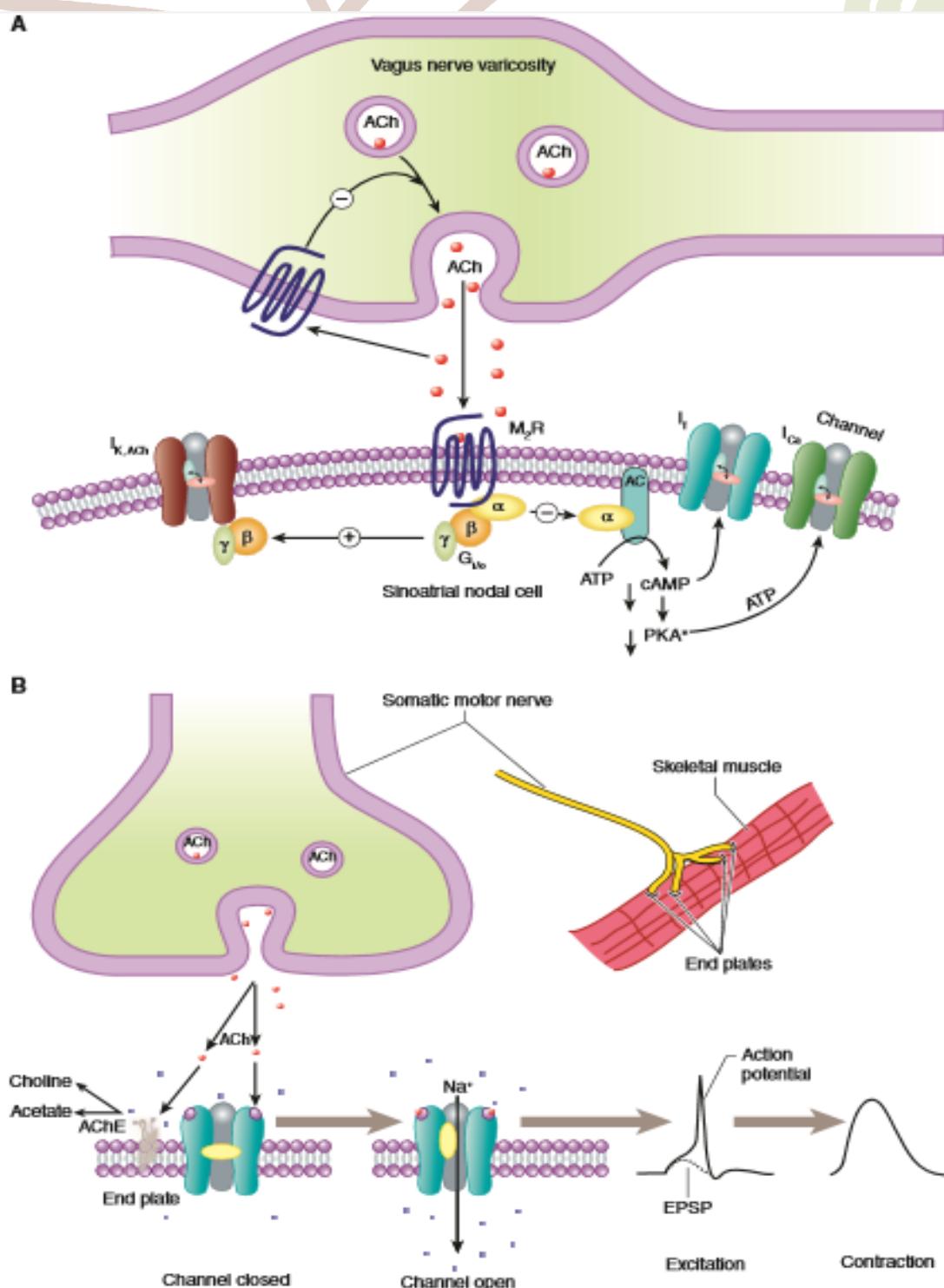
B. Mechanism of Action :

Activation of the parasympathetic nervous system modifies organ function by two major mechanisms. First, acetylcholine released from parasympathetic nerves activates muscarinic receptors on effector cells to alter organ function directly. Second, acetylcholine released from parasympathetic nerves interacts with muscarinic receptors on nerve terminals to inhibit the release of their neurotransmitter. By this mechanism, acetylcholine release and circulating mucarinic agonists indirectly alter organ function by modulating the effects of the parasympathetic and sympathetic nervous systems and perhaps nonadrenergic, noncholinergic (NANC) systems. Several cellular events occur when muscarinic receptors are activated, one or more of which might serve as second messengers frommuscarinic activation. All muscarinic receptors appear to be of the G protein-coupled type table(7-1) . The effect of muscarinic agonists is mediated by the binding of an activated G protein $\beta\gamma$ subunit directly to the channel. These muscarinic effects on cAMP generation reduce the physiologic response of the organ to stimulatory hormones.

The mechanism of nicotinic receptor activation, taking advantage of three factors: (1) the receptor is present in extremely high concentration in the membranes of the electric organs of electric fish; (2) α -bungarotoxin, a component of certain snake venoms, binds to the receptors and is readily labeled as a marker for isolation procedures; and (3) receptor activation results in easily measured electrical and ionic changes in the cells involved. The nicotinic receptor in muscle tissues is a pentamer of four types of

glycoprotein subunits (Figure 7–4B). The neuronal nicotinic receptor consists of α and β subunits only.

Each subunit has four transmembrane segments. The nicotinic receptor has two agonist binding sites at the interfaces formed by the two α subunits and two adjacent subunits (β , γ , ε). Agonist binding to the receptor sites causes a conformational change in the protein that allows sodium and potassium ions to diffuse rapidly down their concentration gradients (calcium ions may also carry charge through the nicotinic receptor ion channel). Binding of an agonist molecule by one of the two receptor sites only modestly increases the probability of channel opening; simultaneous binding of agonist by both of the receptor sites greatly enhances



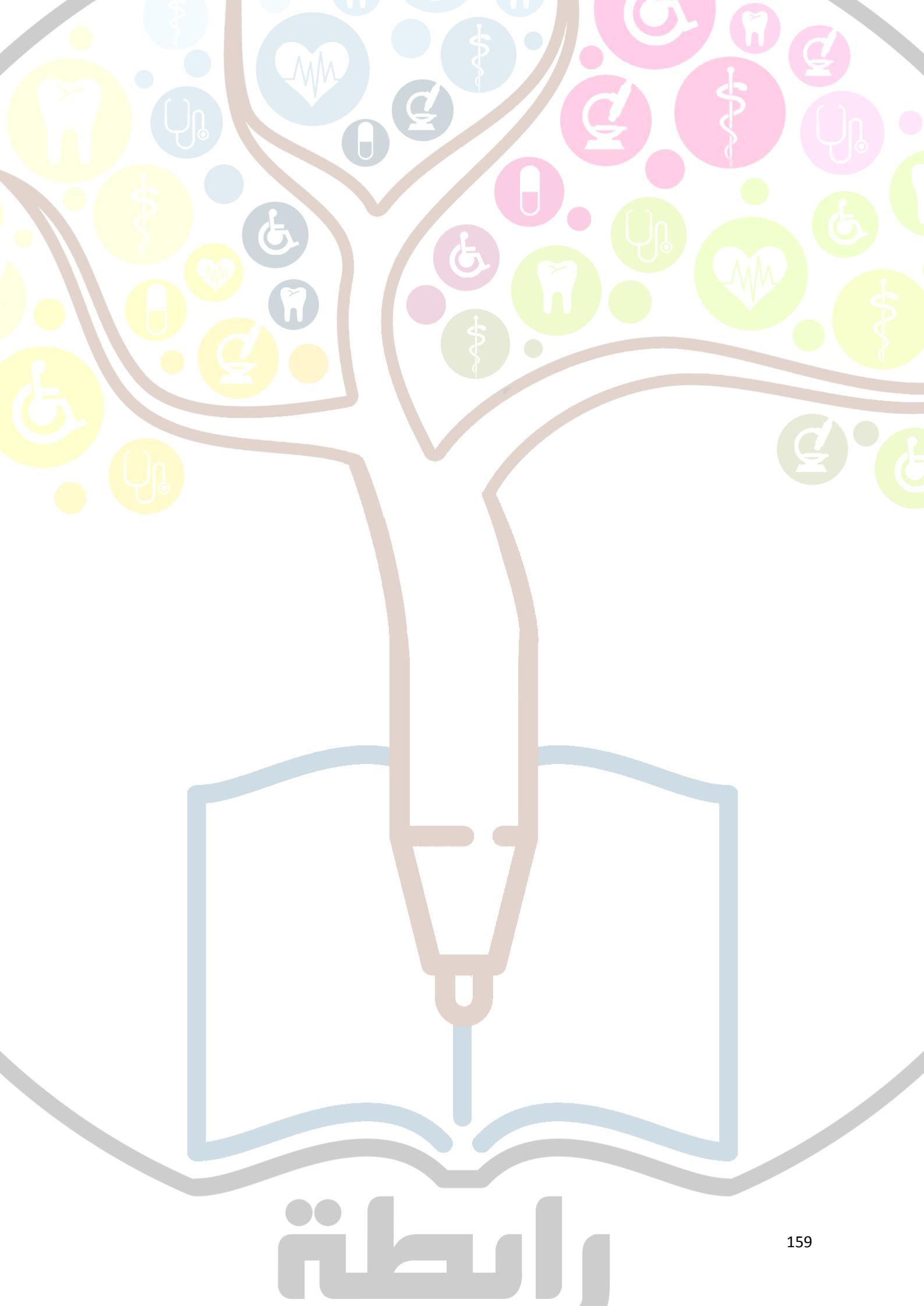
B. Organ System Effects:

FIGURE 7-4 Muscarinic and nicotinic signaling. **A:** Muscarinic transmission to the sinoatrial node in heart. Acetylcholine (ACh) released from a varicosity of a postganglionic cholinergic axon interacts with a sinoatrial node cell muscarinic receptor (M_2R) linked via $G_{i/o}$ to K^+ channel opening, which causes hyperpolarization, and to inhibition of cAMP synthesis. Reduced cAMP shifts the voltage-dependent opening of pacemaker channels (I_p) to more negative potentials, and reduces the phosphorylation and availability of L-type Ca^{2+} channels (I_{Ca}). Released ACh also acts on an axonal muscarinic receptor (autoreceptor; see Figure 6-3) to cause inhibition of ACh release (autoinhibition). **B:** Nicotinic transmission at the skeletal neuromuscular junction. ACh released from the motor nerve terminal interacts with subunits of the pentameric nicotinic receptor to open it, allowing Na^+ influx to produce an excitatory postsynaptic potential (EPSP). The EPSP depolarizes the muscle membrane, generating an action potential, and triggering contraction. Acetylcholinesterase (AChE) in the extracellular matrix hydrolyzes ACh.

TABLE 7-3 Effects of direct-acting cholinoreceptor stimulants.*

Organ	Response
Eye	
Sphincter muscle of iris	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period
Ventricles	Small decrease in contractile strength
Blood vessels	
Arteries, veins	Dilation (via EDRF). Constriction (high-dose direct effect)
Lung	
Bronchial muscle	Contraction (bronchoconstriction)
Bronchial glands	Stimulation
Gastrointestinal tract	
Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder	
Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands	
Sweat, salivary, lacrimal, nasopharyngeal	Secretion

EDRF, endothelium-derived relaxing factor.



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Chapter #8 : Cholinoreceptor-Blocking Drugs

8 Cholinceptor antagonists:

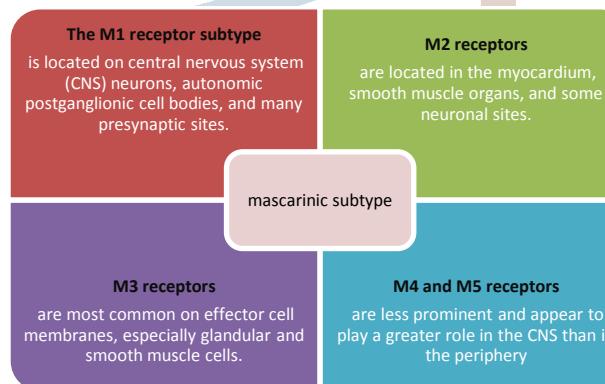
Cholinceptorantagonists, are divided into muscarinic and nicotinic subgroups on the basis of their specific receptor affinities.

Ganglion blockers and neuromuscular junction blockers make up the antinicoticnic drugs. The ganglion-blocking drugs have little clinical use.

This chapter emphasizes drugs that block muscarinic cholinceptors.

Five subtypes of muscarinic receptors have been identified, primarily on the basis of data from ligand-binding and cDNA-cloning experiments.

Table 1: location of muscarinic subtype



BASIC PHARMACOLOGY OF THE MUSCARINIC RECEPTOR BLOCKING DRUGS:

Muscarinic antagonists are sometimes called parasympatholytic because they block the effects of parasympathetic autonomic discharge. However, the term "antimuscarinic" is preferable.

Atropine is the prototype of these drugs. Many similar plant alkaloids are known, and hundreds of synthetic antimuscarinic compounds.

A variety of semisynthetic and fully synthetic molecules have antimuscarinic effects. The tertiary members of these classes are often used for their effects on the eye or the CNS. Many antihistaminic, antipsychotic, and antidepressant drugs have similar structures and, predictably, significant antimuscarinic effects.

a. Absorption

Natural alkaloids and most tertiary antimuscarinic drugs are well absorbed from the gut and conjunctival membranes. Some (eg, scopolamine) are even absorbed across the skin (transdermal route).

In contrast, only 10–30% of a dose of a quaternary antimuscarinic drug is absorbed after oral administration, reflecting the decreased lipid solubility of the charged molecule.

b. Distribution

Atropine and the other tertiary agents are widely distributed in the body. Significant levels are achieved in the CNS within 30 minutes to 1 hour, and this can limit the dose tolerated when the drug is taken for its peripheral effects.

c. Metabolism and Excretion

After administration, the elimination of atropine from the blood occurs in two phases: the $t_{1/2}$ of the rapid phase is 2 hours and that of the slow phase is approximately 13 hours. About 50% of the dose is excreted unchanged in the urine.

Pharmacodynamics:

A. mechanism of action:

Atropine causes reversible blocked of cholinomimetic action at muscarinic receptors; that is, blocked by small dose of atropine can be overcome by a larger concentration of acetylcholine or equivalent muscarinic agonist.

Amino acid (aspartate) is required for binding of antimuscarinic drug. When atropine binds to muscarinic receptor, it prevents actions such as the release of inositol trisphosphate(IP3) and the inhibition of adenylyl cyclase that are caused by muscarinic agonists.

Muscarinic antagonists were traditionally viewed as neutral compounds that occupied the receptor and prevented agonist binding. most drugs that block the actions of acetylcholine are inverse agonists that shift the equilibrium to the inactive state of the receptor. Muscarinic blocking drugs that are inverse agonists include atropine, pirenzepine, trihexyphenidyl, ipratropium, glycopyrrolate, and a methyl derivative of scopolamine. The effectiveness of antimuscarinic drugs varies with the tissue and with the source of agonist. Tissues most sensitive to atropine are the salivary, bronchial, and sweat glands.

Secretion of acid by the gastric parietal cells is the least sensitive. In most tissues, antimuscarinic agents block exogenously administered cholinoreceptor agonists more effectively than endogenously released acetylcholine.

Atropine is highly selective for muscarinic receptors. Most synthetic antimuscarinic drugs are considerably less selective than atropine in interactions with nonmuscarinic receptors.

B. Organ System Effects

1. Central nervous system:

In the doses usually used, atropine has minimal stimulant effects on the CNS, especially the parasympathetic medullary centers, and a slower, longer-lasting sedative effect on the brain. Scopolamine has more marked central effects, producing drowsiness when given in recommended dosages and amnesia in sensitive individuals. In toxic doses can cause excitement, agitation, hallucinations, and coma.

The tremor of Parkinson's disease is reduced by centrally acting antimuscarinic drugs, and atropine first drugs used in the therapy of this disease. parkinsonian tremor and rigidity seem to result from a relative excess of cholinergic activity because of a deficiency of dopaminergic activity in the basal ganglia-striatum system. The combination of an antimuscarinic agent with a dopamine precursor drug (levodopa) can sometimes provide more effective therapy than either drug alone.

2. Eye:

The pupillary constrictor muscle depends on muscarinic cholinoreceptor activation. This activation is blocked by topical atropine and other tertiary antimuscarinic drugs and results in unopposed sympathetic dilator activity and mydriasis. Dilated pupils were considered cosmetically desirable during the Renaissance and account for the name belladonna.

can use of the plant and its extract as eye drops during that time. The important ocular effect of antimuscarinic drugs is to weaken contraction of the ciliary muscle, or cycloplegia. Cycloplegia results in loss of the ability to accommodate; the fully atropinized eye cannot focus for near vision. They are also potentially hazardous, since acute glaucoma may be induced in patients with a narrow anterior chamber angle.

The other ocular effect of antimuscarinic drugs is to reduce lacrimal secretion. Patients occasionally complain of dry or "sandy" eyes when receiving large doses of antimuscarinic drugs.

3. Cardiovascular system:

The sinoatrial node is very sensitive to muscarinic receptor blockade. Moderate to high therapeutic doses of atropine cause tachycardia in the innervated and spontaneously beating heart by blockade of vagal slowing. However, lower doses often result in initial bradycardia before the effects of peripheral vagal block become manifest. This slowing may be due to block of prejunctional M1 receptors on vagal postganglionic fibers that normally limit acetylcholine release in the sinus node and other tissues. The same mechanisms operate in the atrioventricular node; in the presence of high vagal tone, atropine can significantly reduce the PR interval of the electrocardiogram by blocking muscarinic receptors in the atrioventricular node. The ventricles are less affected by antimuscarinic drugs at therapeutic levels because of a lesser degree of vagal control. In toxic concentrations, the drugs can cause intraventricular conduction block that has been attributed to a local anesthetic action.

Most blood vessels, except those in thoracic and abdominal viscera, receive no direct innervation from the parasympathetic system.

However, parasympathetic nerve stimulation dilates coronary arteries, and sympathetic cholinergic nerves cause vasodilation in the skeletal muscle vascular bed. Atropine can block this vasodilation. Furthermore, almost all vessels contain endothelial muscarinic receptors that mediate vasodilation. These receptors are readily blocked by antimuscarinic drugs. At toxic doses, and in some individuals at normal doses, antimuscarinic agents cause cutaneous vasodilation, especially in the upper portion of the body. However, the cardiovascular effects of administered direct-acting muscarinic agonists are easily prevented.

4. Respiratory system:

Both smooth muscle and secretory glands of the airway receive vagal innervation and contain muscarinic receptors. Even in normal individuals, administration of atropine can cause some bronchodilation and reduce secretion. The effectiveness of nonselective antimuscarinic drugs in treating chronic obstructive pulmonary disease (COPD) is limited because block of autoinhibitory M2 receptors on postganglionic parasympathetic nerves

can oppose the bronchodilation caused by block of M₃ receptors on airway smooth muscle.

Nevertheless, antimuscarinic agents selective for M₃ receptors are valuable in some patients with asthma and in many with COPD. Antimuscarinic drugs are frequently used before the administration of inhalant anesthetics to reduce the accumulation of secretions in the trachea and the possibility of laryngospasm.

5. Gastrointestinal tract:

has dramatic effects on motility and some of the secretory functions of the gut. Antimuscarinic drugs have marked effects on salivary secretion; dry mouth occurs frequently in patients taking antimuscarinic drugs for Parkinson's disease or urinary conditions. Gastric secretion is blocked less effectively: the volume and amount of acid, pepsin, and mucin are all reduced, but large doses of atropine may be required.

Basal secretion is blocked more effectively than that stimulated by food, nicotine, or alcohol.

Pirenzepine and a more potent analog, telenzepine, reduce gastric acid secretion with fewer adverse effects than atropine and other less selective agents.

The mechanism of vagal regulation of gastric acid secretion likely involves multiple muscarinic receptor dependent pathways.

Gastrointestinal smooth muscle motility is affected from the stomach to the colon. In general, antimuscarinic drugs diminish the tone and propulsive movements; the walls of the viscera are relaxed.

Therefore, gastric emptying time is prolonged, and intestinal transit time is lengthened. Diarrhea due to overdosage with parasympathomimetic agents is readily stopped, and even diarrhea caused by nonautonomic agents can usually be temporarily controlled.

However, intestinal "paralysis" induced by antimuscarinic drugs is temporary; local mechanisms within the enteric nervous system usually reestablish at least some peristalsis after 1–3 days of antimuscarinic drug therapy.

6. Genitourinary tract:

The antimuscarinic action is relaxes smooth muscle of the ureters and bladder wall and slows voiding.

This action is useful in the treatment of spasm induced by mild inflammation, surgery, and certain neurologic conditions, but it can precipitate urinary retention in men who have prostatic hyperplasia.

The antimuscarinic drugs have no significant effect on the uterus.

7. Sweat glands:

Atropine suppresses thermoregulatory sweating.

Sympathetic cholinergic fibers innervate eccrine sweat glands, and their muscarinic receptors are readily accessible to antimuscarinic drugs. In adults, body temperature is elevated by this effect only if large doses are administered, but in infants and children even ordinary doses may cause "atropine fever."

CLINICAL PHARMACOLOGY OF THE MUSCARINIC RECEPTORBLOCKING DRUGS

Therapeutic Applications

A. Central Nervous System Disorders

1. Parkinson's disease: is often an exercise in polypharmacy, since no single agent is fully effective over the course of the disease. Most antimuscarinic drugs was developed before levodopa became available. Their use is accompanied by all of the adverse effects described below, but the drugs remain useful as adjunctive therapy in some patients.

2. Motion sickness: Certain vestibular disorders respond to antimuscarinic drugs. Scopolamine is one of the oldest remedies for seasickness and is as effective as any more recently introduced agent. The patch formulation produces significant blood levels over 48–72 hours. Useful doses by any route usually cause significant sedation and dry mouth.

B. Ophthalmologic Disorders:

Accurate measurement of refractive error in uncooperative patients.

Also, mydriasis greatly facilitates ophthalmoscopic examination of the retina. Therefore, antimuscarinic agents, administered topically as eye drops or ointment, are very helpful in doing a complete examination.

Formerly, ophthalmic antimuscarinic drugs were selected from the tertiary amine subgroup to ensure good penetration after conjunctival application.

Antimuscarinic drugs should never be used for mydriasis unless cycloplegia or prolonged action is required. Alpha-adrenoceptor stimulant drugs, eg, phenylephrine, produce a short-lasting mydriasis that is usually sufficient for funduscopic examination. A second ophthalmologic use is to prevent synechia (adhesion) formation in uveitis and iritis.

The longer-lasting preparations, especially homatropine, are valuable for this indication.

C. Respiratory Disorders

The use of atropine became part of routine preoperative medication when anesthetics such as ether were used, because these irritant anesthetics markedly increased airway secretions and were associated with frequent episodes of laryngospasm. Preanesthetic injection of atropine or scopolamine could prevent these hazardous effects. Newer inhalational anesthetics are far less irritating to the airways

Ipratropium, tiotropium, and aclidinium are synthetic analogs of atropine, are used as inhalational drugs in COPD. The advantage of aerosol route administration is maximal concentration at the bronchial target tissue with reduced systemic effects. Tiotropium and aclidinium have a longer bronchodilator action than ipratropium and can be given once daily because they dissociate slowly from M3 receptors. Tiotropium reduces the incidence of COPD exacerbations and is a useful adjunct in pulmonary rehabilitation to increase exercise tolerance. The hyperactive neural bronchoconstrictor reflex present in

most individuals with asthma.

Ipratropium and tiotropium are also used as inhalational drugs in asthma.

D. Cardiovascular Disorders

Marked reflex vagal discharge sometimes accompanies the pain of myocardial infarction and may depress sinoatrial or atrioventricular node function sufficiently to impair cardiac output. Parenteral atropine or a similar antimuscarinic drug is appropriate therapy in this situation.

Pathophysiology can influence muscarinic activity in other ways as well. Circulating autoantibodies against the second extracellular loop of cardiac M2 muscarinic receptors have been detected in some patients with idiopathic dilated cardiomyopathy and those afflicted with Chagas' disease caused by the protozoan *Trypanosoma cruzi*.

Patients with Graves' disease (hyperthyroidism) also have such autoantibodies that may facilitate the development of atrial fibrillation.

These antibodies exert parasympathomimetic actions on the heart that are prevented by atropine.

E. Gastrointestinal Disorders

Antimuscarinic agents can provide some relief in the treatment of common traveler's diarrhea and other mild or self-limited conditions of hypermotility.

They are often combined with an opioid antidiarrheal drug. In this combination, however, the very low dosage of the antimuscarinic drug functions primarily to discourage abuse of the opioid agent. The classic combination of atropine with diphenoxylate, a nonanalgesic congener of meperidine, is available under many names in both tablet and liquid form.

F. Urinary Disorders

Atropine and other antimuscarinic drugs have been used to provide symptomatic relief in the treatment of urinary urgency caused by minor inflammatory bladder disorders. In the human urinary bladder, M₂ and M₃ receptors are expressed predominantly with the M₃ subtype mediating direct activation of contraction. Receptors for acetylcholine on the urothelium (the epithelial lining of the urinary tract) and on afferent nerves as well as the detrusor muscle provide a broad basis for the action of antimuscarinic drugs in the treatment of overactive bladder. Oxybutynin, is used to relieve bladder spasm after urologic surgery. Oral oxybutynin or instillation of the drug by catheter into the bladder in such patients appears to improve bladder capacity and continence and to reduce infection and renal damage.

Imipramine, a tricyclic antidepressant drug with strong antimuscarinic actions, has long been used to reduce incontinence in institutionalized elderly patients. It is moderately effective but causes significant CNS toxicity.

Antimuscarinic agents have also been used in urolithiasis to relieve the painful ureteral smooth muscle spasm caused by passage of the stone. However, their usefulness in this condition is debatable.

G. Cholinergic Poisoning

Severe cholinergic excess is a medical emergency, especially in rural communities where cholinesterase inhibitor insecticides are commonly used and in cultures where wild mushrooms are frequently eaten. The potential use of cholinesterase inhibitors as chemical warfare "nerve gases" also requires an awareness of the methods for treating acute poisoning.

1. Antimuscarinic therapy: Both the nicotinic and the muscarinic effects of the cholinesterase inhibitors can be life-threatening. To reverse the muscarinic effects, a tertiary (not quaternary) amine drug must be used (preferably atropine) to treat the CNS effects as well as the peripheral effects of the organophosphate inhibitors.

Large doses of atropine may be needed to oppose the muscarinic effects of extremely potent agents like parathion and chemical warfare nerve gases. The drug may have to be given many times, since the acute effects of the cholinesterase inhibitor may last 24–48 hours or longer.

2. Cholinesterase regenerator compounds: A second class of compounds, composed of substituted oximes capable of regenerating active enzyme from the organophosphorus-cholinesterase complex, is also available to treat organophosphorus poisoning. These oxime agents include pralidoxime (PAM), diacetylmonoxime (DAM), obidoxime, and others.

H. Other Applications:

Hyperhidrosis (excessive sweating) is sometimes reduced by antimuscarinic agents..

Adverse Effects

Treatment with atropine or its congeners directed at one organ system almost always induces undesirable effects in other organ systems. Thus, mydriasis and cycloplegia when used to reduce gastrointestinal secretion or motility, even though they are therapeutic effects when the drug is used in

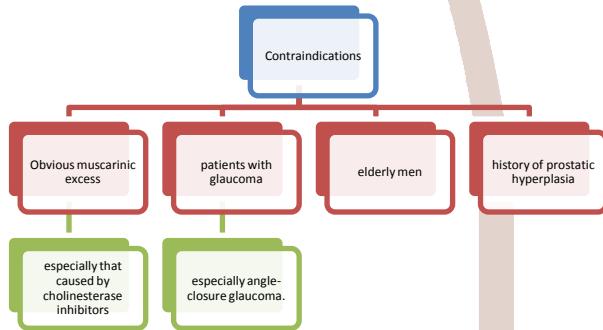
ophthalmology. At higher concentrations, atropine causes block of all parasympathetic functions. However, atropine is a remarkably safe drug in adults. Atropine poisoning has occurred as a result of attempted suicide, but most cases are due to attempts to induce hallucinations. Poisoned individuals manifest dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation, and delirium for as long as 1 week. Body temperature is frequently elevated. Unfortunately, children, especially infants, are very sensitive to the hyperthermic effects of atropine.

Overdoses of atropine or its congeners are generally treated symptomatically. Poison control experts discourage the use of physostigmine or another cholinesterase inhibitor to reverse the effects of atropine overdose because symptomatic management is more effective and less dangerous. Symptomatic treatment may require temperature control with cooling blankets and seizure control with diazepam. Treatment of the antimuscarinic effects, if required, can be carried out with a quaternary cholinesterase inhibitor such as neostigmine. Control of hypotension may require the administration of a sympathomimetic drug such as phenylephrine.

Recent evidence indicates that some centrally acting drugs with antimuscarinic actions impair memory and cognition in older patients like: tricyclic antidepressants, selective serotonin reuptake inhibitors, anti-anxiety agents.

Contraindications

Contraindications to the use of antimuscarinic drugs are relative, not absolute.



- Nonselective antimuscarinic agents should never be used to treat acid-peptic disease.

BASIC & CLINICAL PHARMACOLOGY OF THE GANGLION-BLOCKING DRUGS

Ganglion-blocking agents competitively block the action of acetylcholine and similar agonists at neuronal nicotinic receptors of both parasympathetic and sympathetic

autonomic ganglia. Some members of the group also block the ion channel that is gated by the nicotinic cholinoreceptor. However, their lack of selectivity confers such a broad range of undesirable effects that they have limited clinical use.

Chemistry & Pharmacokinetics

All ganglion-blocking drugs of interest are synthetic amines. Tetraethylammonium (TEA), Hexamethonium ("C6") was developed and was introduced clinically as the first drug effective for management of hypertension. Mecamylamine, a secondary amine, was developed to improve the degree and extent of absorption from the gastrointestinal tract because the quaternary amine ganglion-blocking compounds were poorly and erratically absorbed after oral administration. Trimethaphan, a short-acting, polar, ganglion blocker is no longer available for clinical use.

Pharmacodynamics

A.Organ System Effects

1. Central nervous system:

Mecamylamine, is crosses the blood-brain barrier and readily enters the CNS. Sedation, tremor, choreiform movements, and mental aberrations have been reported as effects of mecamylamine.

2. Eye:

The ganglion-blocking drugs cause a predictable cycloplegia with loss of accommodation because the ciliary muscle receives innervation primarily from the parasympathetic nervous system. Ganglionic blockade often causes moderate dilation of the pupil because parasympathetic tone usually dominates this tissue.

3. Cardiovascular system:

Blood vessels receive chiefly vasoconstrictor fibers from the sympathetic nervous system; therefore, ganglionic blockade causes a marked decrease in arteriolar and venomotor tone. The blood pressure may fall precipitously because both peripheral vascular resistance and venous return are decreased.

Hypotension is especially marked in the upright position (orthostatic or postural hypotension), because

postural reflexes that normally prevent venous pooling are blocked. Cardiac effects include diminished contractility and, because the sinoatrial node is usually dominated by the parasympathetic nervous system, a moderate tachycardia.

4. Gastrointestinal tract:

Secretion is reduced, although not enough to treat peptic disease effectively. Motility is profoundly inhibited, and constipation can be marked.

5. Other systems:

Genitourinary smooth muscle is partially dependent on autonomic innervation for normal function.

Therefore, ganglionic blockade causes hesitancy in urination and may precipitate urinary retention in men with prostatic hyperplasia.

Thermoregulatory sweating is reduced by the ganglionblocking drugs. However, hyperthermia is not a problem except in very warm environments, because cutaneous vasodilation is usually sufficient to maintain a normal body temperature.

6. Response to autonomic drugs:

Patients receiving ganglion blocking drugs are fully responsive to autonomic drugs acting on muscarinic, α -, and β -adrenergic receptors because these effector cell receptors are not blocked.

Clinical Applications & Toxicity

Ganglion blockers are used rarely because more selective autonomic blocking agents are available. The toxicity of the ganglion-blocking drugs is limited to the autonomic effects already described. For most patients, these effects are intolerable except for acute use.

Chapter #9 : Adrenoceptor Agonists & Sympathomimetic Drugs

9. Adrenoceptor agonists & Sympathomimetic Drugs

The sympathetic nervous system is an important regulator of virtually all organ systems. The ultimate effects of sympathetic stimulation are mediated by release of norepinephrine from nerve terminals, which then activates adrenoceptors on postsynaptic sites. Also, in response to a variety of stimuli such as stress, the adrenal medulla releases epinephrine, which is transported in the blood to target tissues. In other words, epinephrine acts as a hormone, whereas norepinephrine acts as a neurotransmitter. Drugs that mimic the actions of epinephrine or norepinephrine have traditionally been termed sympathomimetic drugs. The sympathomimetics can be grouped by mode of action and by the spectrum of receptors that they activate. Some of these drugs are direct agonists; that is, they directly interact with and activate adrenoceptors. Others are indirect agonists because their actions are dependent on their ability to enhance the actions of endogenous catecholamines.

TABLE 9-1 Adrenoceptor types and subtypes.		
Receptor	Agonist	Antagonist
α_1 type	Phenylephrine	Prazosin
α_{1A}		Tamsulosin
α_{1B}		
α_{1D}		
α_2 type	Clonidine	Yohimbine
α_{2A}	Oxymetazoline	
α_{2B}		Prazosin
α_{2C}		Prazosin
β type	Isoproterenol	Propranolol
β_1	Dobutamine	Betaxolol
β_2	Albuterol	Butoxamine
β_3	Mirabegron	
Dopamine type	Dopamine	
D_1	Fenoldopam	
D_2	Bromocriptine	
D_3		
D_4		Clozapine
D_5		

TABLE 9-2 Relative receptor affinities.

Relative Receptor Affinities	
Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 > \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine ¹	$\beta_1 > \beta_2 >>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

SPECIFIC SYMPATHOMIMETIC

DRUGS

Endogenous Catecholamines

	MOA	Effect
Epinephrine	Agonist at both α and β receptors. It is therefore a very potent vasoconstrictor and cardiac stimulant.	The rise in systolic blood pressure that occurs after epinephrine release or administration is caused by its positive inotropic and chronotropic actions on the heart (predominantly β_1 receptors) and the vasoconstriction induced in many vascular beds (α receptors). Epinephrine also activates β_2 receptors in some vessels (eg, skeletal muscle blood vessels), leading to their dilation.
Norepinephrine (levarterenol, noradrenaline)	It is an agonist at both α_1 and α_2 receptors. Norepinephrine also activates β_1 receptors with similar potency as epinephrine, but has relatively little effect on β_2 receptors.	increases peripheral resistance and both diastolic and systolic blood pressure and positive inotropic effects on the heart.
Dopamine	Is the immediate precursor in the synthesis of norepinephrine	Its promotes vasodilation of renal, splanchnic, coronary, cerebral, and perhaps other resistance vessels, via activation of D1 receptors, it also activates β_1 receptors in the heart. Endogenous dopamine may have more important effects in regulating sodium excretion and renal function. It is an important neurotransmitter in the CNS.

Direct-Acting Sympathomimetics:

Phenylephrine is pure α_1 agonist. It is an effective mydriatic and decongestant and can be used to raise the blood pressure.

Midodrine is a prodrug that is enzymatically hydrolyzed to desglymidodrine, a selective α_1 -receptor agonist. The primary indication for midodrine is the treatment of orthostatic hypotension.

Alpha2-selective agonists decrease blood pressure through actions in the CNS that reduce sympathetic tone ("sympatholytics") even though direct application to a blood vessel may cause vasoconstriction. Such drugs (eg, clonidine, methyldopa, guanfacine, guanabenz) are useful in the treatment of hypertension.

Oxymetazoline is a direct-acting α agonist used as topical decongestant because of its ability to promote constriction of the nasal mucosa.

Isoproterenol (isoprenaline) is a very potent β -receptor agonist and has little effect on α receptors. The drug has positive chronotropic and inotropic actions, it is a potent vasodilator.

Beta1-selective agents increase cardiac output with less reflex tachycardia than nonselective β agonists such as isoproterenol, because they are less effective in activating vasodilator β_2 receptors.

Dobutamine actions are mediated mostly by activation of α and β receptors, it augments myocardial contractility and promotes coronary and systemic vasodilation.

Beta2-selective agents (albuterol, metaproterenol, terbutaline) are used for pulmonary applications.

Indirect –Acting Sympathomimetics

Indirect-acting sympathomimetics can have one of two different mechanisms. First, they may enter the sympathetic nerve ending and displace stored catecholamine transmitter. Such drugs have been called amphetamine-like or “displacers.” Second, they may inhibit the reuptake of released transmitter by interfering with the action of the norepinephrine transporter, NET.

A. Amphetamine: is a CNS stimulant it has marked stimulant effects on mood and alertness and a depressant effect on appetite. Amphetamine’s actions are mediated through the release of norepinephrine and, to some extent, dopamine.

B. Catecholamine Reuptake Inhibitors: Many inhibitors of the amine transporters for norepinephrine, dopamine, and serotonin are used clinically.

Atomoxetine is a selective inhibitor of the norepinephrine reuptake transporter. It is used in the treatment of attention deficit disorders.

Sibutramine is a serotonin and norepinephrine reuptake inhibitor and was initially approved by the FDA as an appetite suppressant for long-term treatment of obesity.

Duloxetine is a widely used antidepressant with balanced serotonin and norepinephrine reuptake inhibitory effects.

Dopamine Agonists

Levodopa, which is converted to dopamine in the body, and dopamine agonists with central actions are of considerable value in the treatment of Parkinson’s disease and prolactinemia.

Fenoldopam is a D1-receptor agonist that selectively leads to peripheral vasodilation in some vascular beds. The primary indication for fenoldopam is in the intravenous treatment of severe hypertension.

THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS

Cardiovascular Applications:

A. Treatment of Acute Hypotension.

B. Chronic Orthostatic Hypotension: drugs activating α receptors can be used for this purpose.

Midodrine, an orally active α_1 agonist, is frequently used for this indication. Other sympathomimetics, such as oral ephedrine or phenylephrine, can be tried. droxidopa, a synthetic prodrug that is converted to norepinephrine and used to treat neurogenic orthostatic hypotension.

C. Cardiac Applications

Epinephrine is used during resuscitation from cardiac arrest.

Dobutamine is used as a pharmacologic cardiac stress test.

D. Inducing Local Vasoconstriction

Reduction of local or regional blood flow is desirable for achieving hemostasis in surgery, for reducing diffusion of local anesthetics away from the site of administration, and for reducing mucous membrane congestion. In each instance, α -receptor activation is desired, and the choice of agent depends on the maximal efficacy required, the desired duration of action, and the route of administration.

Pulmonary Applications

Anaphylaxis: Anaphylactic shock and related immediate (type I) IgE-mediated reactions affect both the respiratory and the cardiovascular systems. The syndrome of bronchospasm, mucous membrane congestion, angioedema, and severe hypotension usually responds rapidly to the parenteral administration of **epinephrine**.

Ophthalmic Applications:

Phenylephrine is an effective mydriatic agent frequently used to facilitate examination of the retina. It is also a useful decongestant for minor allergic hyperemia and itching of the conjunctival membranes. Sympathomimetics administered as ophthalmic drops are also useful in localizing the lesion in Horner's syndrome. **Apraclonidine** and **brimonidine** are α_2 -selective agonists that also lower intraocular pressure and are approved for use in glaucoma.

Genitourinary Applications:

β_2 -selective agents relax the pregnant uterus. **Ritodrine**, **terbutaline**, and similar drugs have been used to suppress premature labor.

SUMMARY Sympathomimetic Drugs

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
α_1 AGONISTS				
<ul style="list-style-type: none"> • Midodrine • Phenylephrine: Can be used IV for short-term maintenance of BP in acute hypotension and intranasally to produce local vasoconstriction as a decongestant 	Activates phospholipase C, resulting in increased intracellular calcium and vasoconstriction	Vascular smooth muscle contraction increasing blood pressure (BP)	Orthostatic hypotension	Oral • prodrug converted to active drug with a 1-h peak effect • Toxicity: Supine hypertension, piloerection (goose bumps), and urinary retention
α_2 AGONISTS				
<ul style="list-style-type: none"> • Clonidine • α-Methyldopa, guanfacine, and guanabenz: Also used as central sympatholytics • Dexmedetomidine: Prominent sedative effects and used in anesthesia • Tizanidine: Used as a muscle relaxant • Apraclonidine and brimonidine: Used topically in glaucoma to reduce intraocular pressure 	Inhibits adenylyl cyclase and interacts with other intracellular pathways	Vasoconstriction is masked by central sympatholytic effect, which lowers BP	Hypertension	Oral • transdermal • peak effect 1–3 h • $t_{1/2}$ of oral drug ~12 h • produces dry mouth and sedation
β_1 AGONISTS				
<ul style="list-style-type: none"> • Dobutamine¹ 	Activates adenylyl cyclase, increasing myocardial contractility	Positive inotropic effect	Cardiogenic shock, acute heart failure	IV • requires dose titration to desired effect
β_2 AGONISTS				
<ul style="list-style-type: none"> • Albuterol • See other β_2 agonists in Chapter 20 	Activates adenylyl cyclase	Bronchial smooth muscle dilation	Asthma	Inhalation • duration 4–6 h • Toxicity: Tremor, tachycardia
β_3 AGONISTS				
<ul style="list-style-type: none"> • Mirabegron 	Activates adenylyl cyclase	Reduces bladder tone	Urinary urgency	Oral • duration 50 h • Toxicity: Possible hypertension
DOPAMINE AGONISTS				
D₁ Agonists				
<ul style="list-style-type: none"> • Fenoldopam 	Activates adenylyl cyclase	Vascular smooth muscle relaxation	Hypertension	Requires dose titration to desired effect
D₂ Agonists				
<ul style="list-style-type: none"> • Bromocriptine • See other D₂ agonists in Chapters 28 and 37 	Inhibits adenylyl cyclase and interacts with other intracellular pathways	Mimics dopamine actions in the CNS	Parkinson's disease, prolactinemia	Oral • Toxicity: Nausea, headache, orthostatic hypotension

¹Dobutamine has other actions in addition to β_1 -agonist effect. See text for details.

Central Nervous System Applications

Chapter #10 : Adrenoceptor Antagonist Drugs

Catecholamines play a role in many physiologic and pathophysiologic responses. Drugs that block their receptors therefore have important effects. These effects vary dramatically according to the drug's selectivity for α and β receptors.

This chapter deals with pharmacologic antagonist drugs whose major effect is to occupy α_1 , α_2 , or β receptors outside the CNS and prevent their activation by catecholamines and related agonists.

Clinical therapeutics drug	Used
nonselective antagonists	treatment of pheochromocytoma*
α_1 -selective antagonists	in primary hypertension and benign prostatic hyperplasia
Beta-receptor antagonist drugs	treatment of hypertension, ischemic heart disease, arrhythmias, endocrinologic and neurologic disorders, glaucoma, and other conditions.

*(tumors that secrete catecholamines)

BASIC PHARMACOLOGY OF THE ALPHA-RECEPTOR ANTAGONIST DRUGS

mechanism of action of α receptor antagonist

reversible

irreversible

block can be surmounted with sufficiently high concentrations of agonists

do not dissociate and cannot be surmounted.

e.g. Phentolamine & prazosin labetalol drug used for antihypertensive effects

e.g: Phenoxybenzamine

Pharmacologic Effects

Because arteriolar and venous tone are determined to a large extent by α receptors on vascular smooth muscle,

α -receptor antagonist drugs cause

- a lowering of peripheral vascular resistance and blood pressure.

These drugs can prevent

- the pressor effects of usual doses of a agonists

selective α -receptor antagonism

- may convert a pressor to a depressor response .

This change in response is called epinephrine reversal (it illustrates how the activation of both α and β receptors in the vasculature may lead to opposite responses).

Alpha-receptor antagonists cause

reflex tachycardia

orthostatic hypotension

is due to antagonism of sympathetic nervous system stimulation of α receptors in vascular smooth muscle

contraction of veins is an important component of the normal capacity to maintain blood pressure in the upright position since it decreases venous pooling in the periphery. Constriction of arterioles in the legs also contributes to the normal orthostatic response. Tachycardia may be more marked with agents that block α_2 -presynaptic receptors in the heart, since the augmented release of norepinephrine will further stimulate β receptors in the heart.

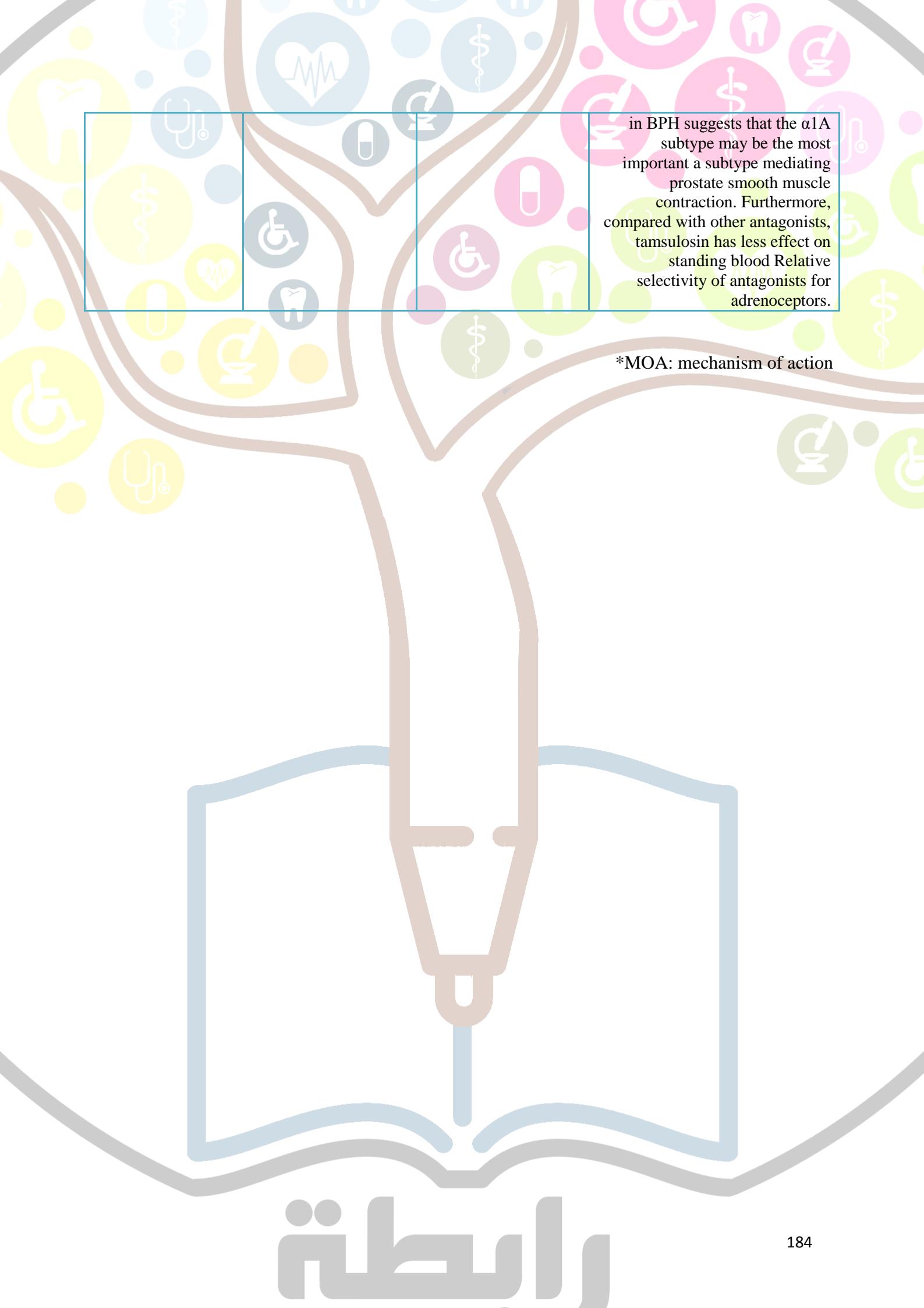
B. Other Effects

Blockade of α receptors in other tissues elicits miosis (small pupils) and nasal stuffiness. They are expressed in the base of the bladder and the prostate, and their blockade decreases resistance to the flow of urine. Alpha blockers are used therapeutically for the treatment of urinary retention due to prostatic hyperplasia.

SPECIFIC AGENT

Name of drug	MOA*	Pharmacologic action	Other information
Phenoxybenzamine	binds covalently to α receptors, causing irreversible blockade of long duration (14–48 hours or longer). The drug also inhibits reuptake of released norepinephrine by presynaptic adrenergic nerve terminals. Also, blocks histamine (H1), acetylcholine, and serotonin receptors as well as α receptors.	are related to antagonism of α -receptor-mediated events.	<p>The most significant effect: is attenuation of catecholamine-induced vasoconstriction, and causes relatively little fall in blood pressure in normal supine individuals, it reduces blood pressure when sympathetic tone is high, Cardiac output may be increased because of reflex effects and because of some blockade of presynaptic α_2 receptors in cardiac sympathetic nerves.</p> <p>Most adverse effects: derive from its α-receptor-blocking action the most important are: orthostatic hypotension, - tachycardia, - Nasal stuffiness - inhibition of ejaculation - also occur.</p> <p>Since phenoxybenzamine enters the CNS, it may cause: fatigue, sedation, and nausea.</p> <p>Because phenoxybenzamine is an alkylating agent.</p> <p>Other:</p> <ul style="list-style-type: none"> - is absorbed after oral administration, although bioavailability is low. - The major use of is in the treatment of pheochromocytoma.
Phentolamine	is a potent competitive antagonist at both α_1 and α_2 receptors . it is reduces peripheral resistance through	Its cardiac stimulation is due to antagonism of presynaptic α_2 receptors (leading to enhanced release of norepinephrine from sympathetic nerves) and sympathetic activation from baroreflex	<p>adverse effects: are related to compensatory cardiac stimulation: which may cause severe tachycardia, arrhythmias, and myocardial ischemia.</p> <p>Other:</p> <ul style="list-style-type: none"> used in the treatment of pheochromocytoma.

	blockade of α_1 receptors and possibly α_2 receptors on vascular smooth muscle.	mechanisms. Phentolamine also has minor inhibitory effects at serotonin receptors and agonist effects at muscarinic and H1 and H2 histamine receptors.	In addition it is sometimes used to reverse local anesthesia in soft tissue sites; local anesthetics are often given with vasoconstrictors that slow their removal. Local phentolamine permits reversal at the end of the procedure.
Prazosin:	is a competitive piperazinylquinazoline effective in the management of hypertension. It is highly selective for α_1 receptors and typically 1000-fold less potent at α_2 receptors.	relaxes both arterial and venous vascular smooth muscle, as well as smooth muscle in the prostate, due to blockade of α_1 receptors.	Other: it is extensively metabolized in humans; because of metabolic degradation by the liver, only about 50% of the drug is available after oral administration. The half-life is normally about 3 hours.
Terazosin:	is reversible α_1 -selective antagonist that is effective in hypertension	it is use in men with urinary retention symptoms due to benign prostatic hyperplasia (BPH).	actionOther: it has high bioavailability but is extensively metabolized in the liver, with only a small fraction of unchanged drug excreted in the urine. The half-life of terazosin is 9–12 hours.
Doxazosin:	-----	is efficacious in the treatment of hypertension and BPH.	Other: It having a longer half-life of about 22 hours. It has moderate bioavailability and is extensively metabolized, with very little parent drug excreted in urine or feces. it has active metabolites, although their contribution to the drug's effects is probably small.
Tamsulosin:	is a competitive α_1 antagonist with a structure quite different from that of most other α_1 -receptor blockers.	-----	Other: It has high bioavailability and a half-life of 9–15 hours. It is metabolized extensively in the liver. it has higher affinity for α_{1A} and α_{1D} receptors than for the α_{1B} subtype. Evidence suggests that tamsulosin has relatively greater potency in inhibiting contraction in prostate smooth muscle versus vascular smooth muscle compared with other α_1 -selective antagonists. The drug's efficacy



in BPH suggests that the α 1A subtype may be the most important a subtype mediating prostate smooth muscle contraction. Furthermore, compared with other antagonists, tamsulosin has less effect on standing blood Relative selectivity of antagonists for adrenoceptors.

*MOA: mechanism of action

OTHER ALPHA-ADRENOCEPTOR ANTAGONISTS

Comment	Drug
is an α_1 -selective quinazoline derivative that is approved for use in BPH. It has a bioavailability of about 60%, is extensively metabolized, and has an elimination half-life of about 5 hours. It may increase risk of QT prolongation in susceptible individuals.	Alfuzosin
Resembles tamsulosin in blocking the α_{1A} receptor, used in the treatment of BPH.	Silodosin
α_1 -selective antagonist that also has efficacy as an antihypertensive.	Indoramin
is an α_1 antagonist (its primary effect) that also has weak α_2 -agonist and 5-HT1A-agonist actions and weak antagonist action	Urapidil

at β_1 receptors. have both α_1 -selective and β -antagonistic effects	Labetalol and carvedilol
Neuroleptic drugs, they are potent dopamine receptor antagonists but are also antagonists at α receptors. Their antagonism of α receptors probably contributes to some of their adverse effects, particularly hypotension. Similarly, the antidepressant trazodone has the capacity to block α_1 receptors. cause reversible α -receptor blockade.	Chlorpromazine and haloperidol
is an α_2 -selective antagonist. It is sometimes used in the treatment of orthostatic hypotension because it promotes norepinephrine release through blockade of α_2 receptors in both the CNS and the periphery.	Yohimbine

CLINICAL PHARMACOLOGY OF THE ALPHA-RECEPTOR-BLOCKING DRUGS

This increases central sympathetic activation and also promotes increased norepinephrine release in the periphery. It was once widely used to treat male erectile dysfunction but has been superseded by phosphodiesterase -5 inhibitors like sildenafil. Also, can greatly elevate blood pressure if administered to patients receiving norepinephrine transport-blocking drugs. it reverses the antihypertensive effects of α_2 -adrenoceptor agonists such as clonidine. It is used in veterinary medicine to reverse anesthesia produced by xylazine.

The major clinical use of phenoxybenzamine is in the management of pheochromocytoma. Patients have many symptoms and signs, including intermittent or sustained hypertension, headaches, palpitations, and increased sweating.

Release of stored catecholamines from pheochromocytomas may occur in:

- response to physical pressure
- chemical stimulation, or spontaneously.

When it occurs during operative manipulation of pheochromocytoma, the resulting hypertension may be controlled with α -receptor blockade or the vasodilator nitroprusside. Nitroprusside is preferred because its effects can be more readily titrated and it has a shorter duration of action. Alpha-receptor antagonists are most useful in the preoperative management of patients with pheochromocytoma.

Administration of phenoxybenzamine in the preoperative period helps to control

hypertension and tends to reverse chronic changes resulting from excessive catecholamine secretion such as plasma volume contraction.

Some physicians give phenoxybenzamine to patients with pheochromocytoma for 1–3 weeks before surgery. Other surgeons prefer to operate on patients in the absence of treatment with phenoxybenzamine, counting on modern anesthetic techniques to control blood pressure and heart rate during surgery. Phenoxybenzamine can be very useful in the chronic treatment of inoperable or metastatic pheochromocytoma. Although there is less experience with alternative drugs, hypertension in patients with pheochromocytoma may also respond to reversible α 1-selective antagonists or to conventional calcium channel antagonists. Beta-receptor antagonists may be required after α -receptor blockade has been instituted to reverse the cardiac effects of excessive catecholamines. Beta antagonists should not be used prior to establishing effective α -receptor blockade,

Pheochromocytoma is sometimes treated with metyrosine (α -methyltyrosine), the α -methyl analog

of tyrosine. This agent is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting step in the synthesis of dopamine, norepinephrine, and epinephrine

Hypertensive Emergencies:

The α -adrenoceptor antagonist drugs have limited application in the management of hypertensive emergencies, but labetalol has been used in this setting. In theory, α -adrenoceptor antagonists are most useful when increased blood pressure reflects excess circulating concentrations of agonists.

Chronic Hypertension :

Members of the prazosin family of α 1-selective antagonists are efficacious drugs in the treatment of mild to moderate systemic hypertension. They are generally well tolerated, but they are not usually recommended as monotherapy for hypertension because other classes of antihypertensives are more effective in preventing heart failure. Their major adverse effect is orthostatic hypotension, which may be severe after the first few doses but is otherwise uncommon. .

It is interesting that the use of α -adrenoceptor antagonists such as prazosin has been found to be associated with either no changes in plasma lipids or increased concentrations of high-density lipoproteins (HDL)

Peripheral Vascular Disease :

Alpha-receptor-blocking drugs do not seem to be effective in the treatment of peripheral vascular occlusive disease characterized by morphologic changes that limit flow in the vessels.

Urinary Obstruction :

Benign prostatic hyperplasia is common in elderly men. Various surgical treatments are effective in relieving the urinary symptoms of BPH. The mechanism of action in improving urine flow involves partial reversal of smooth muscle contraction in the enlarged prostate and in the bladder base. It has been suggested that some α 1-receptor antagonists may have additional effects on cells in the prostate that help improve symptoms.

Prazosin, doxazosin, and terazosin are all efficacious in patients with BPH. α 1-receptor subtype is most

important for smooth muscle contraction in the prostate: subtype-selective α 1A-receptor antagonists like tamsulosin may have improved efficacy and safety in treating this disease.

Erectile Dysfunction:

Sildenafil and other cGMPphosphodiesterase inhibitors are drugs of choice for erectile dysfunction .

Applications of Alpha2 Antagonists

Alpha2 antagonists have relatively little clinical usefulness. They have definite but limited benefit in male erectile dysfunction. They has a highly selective antagonists for treatment of type 2 diabetes, and for treatment of psychiatricdepression. It is likely that better understanding of the subtypes of α 2 receptors will lead to development of clinically useful subtypeselective α 2 antagonists.

BASIC PHARMACOLOGY OF THE BETA-RECEPTOR ANTAGONIST DRUGS

Betablocking drugs occupy β receptors and competitively reduce receptor occupancy by catecholamines and other β agonists. Most β -blocking drugs in clinical use are pure antagonists; such as albeit less than that caused by the full agonists epinephrine and isoproterenol. Finally, evidence suggests that some β blockers are inverse agonists.

The β -receptor-blocking drugs differ in their relative affinities for β_1 and β_2 receptors.

Some have a higher affinity for β_1 than for β_2 receptors, and this selectivity may have important clinical implications.

Chemically, most β -receptor antagonist drugs resemble isoproterenol to some degree.

Pharmacokinetic Properties of the Beta-Receptor Antagonists

Most of the drugs in this class are well absorbed after oral administration; peak concentrations occur 1–3 hours after ingestion.

Propranolol undergoes

1. Absorption

2. Bioavailability

extensive hepatic (first-pass) metabolism; its bioavailability is relatively low. The proportion of drug reaching the systemic circulation increases as the dose is increased, suggesting that hepatic extraction mechanisms may become saturated.

The β antagonists are rapidly distributed and have large volumes of distribution. Most β antagonists have half-lives in the range of 3–10 hours. Poor metabolizers exhibit threefold to tenfold higher plasma concentrations after administration of metoprolol than extensive metabolizers. The elimination of drugs such as propranolol may be prolonged in the presence of

3. Distribution and Clearance

<p>liver disease, diminished hepatic blood flow, or hepatic enzyme inhibition.</p>		<p>nervous system. chronic drug administration leads to a fall in peripheral resistance in patients with hypertension.</p>	
<h2 style="text-align: center;"><u>Pharmacodynamics of the Beta-Receptor Antagonist Drugs</u></h2> <p>Most of the effects of these drugs are due to occupation and blockade of β receptors.</p>		<p>Blockade of the β_2 receptors in bronchial smooth muscle may lead to an increase in airway resistance, particularly in patients with asthma.</p>	<p>2. Effects on the Respiratory Tract</p>
<p>Comment</p> <p>given chronically lower blood pressure in patients with hypertension. The mechanisms probably include suppression of renin release and effects in the CNS. They very valuable in the treatment of: angina and chronic heart failure and following myocardial infarction. Nonselective and β_1-blocking drugs antagonize the release of renin caused by the sympathetic</p>	<p>Effect</p> <p>1. Effects on the Cardiovascular System</p>	<p>Beta1-receptor antagonists such as metoprolol and atenolol may have some advantage over nonselective β antagonists when blockade of β_1 receptors in the heart is desired and β_2-receptor blockade is undesirable</p> <p>3. Effects on the Eye</p> <p>Beta-blocking agents reduce intraocular pressure, especially in glaucoma. The mechanism usually reported is decreased aqueous humor production.</p>	

<p>The effects on carbohydrate metabolism are less clear, though glycogenolysis in the human liver is at least partially inhibited after β_2-receptor blockade. Beta1-receptor-selective drugs may be less prone to inhibit recovery from hypoglycemia.</p>	<h4>4. Metabolic and Endocrine Effects</h4>	<p>asthma or excessive bradycardia. However, these drugs may not be as effective as the pure antagonists in secondary prevention of myocardial infarction. Local anesthetic action, also known as “membrane-stabilizing” action, is a prominent effect of several β blockers.</p>
<p>The chronic use of β-adrenoceptor antagonists has been associated with increased plasma concentrations of very-low-density lipoproteins (VLDL) and decreased concentrations of HDL cholesterol.</p>	<h4>5. Effects Not Related to Beta-Blockade</h4>	<p>This action is the result of typical local anesthetic blockade of sodium channels and can be demonstrated experimentally in isolated neurons, heart muscle, and skeletal muscle membrane.</p>
<p>Partial β-agonist activity may have been considered desirable to prevent untoward effects such as precipitation of</p>		<p>The Treatment of Glaucoma</p> <p>Glaucoma is a major cause of blindness and of great pharmacologic interest because the chronic form often responds to drug therapy. The primary manifestation is increased intraocular pressure not initially</p>

associated with symptoms. Without treatment, increased intraocular pressure results in damage to the retina and optic nerve, with restriction of visual fields and, eventually, blindness. Two major types of glaucoma are recognized: open angle and closed-angle (also called narrow-angle).

The closed-angle form is associated with a shallow anterior chamber, in which a dilated iris can occlude the outflow drainage pathway at the angle between the cornea and the ciliary body. This form is associated with acute and painful increases of pressure,

which must be controlled on an emergency basis with drugs or prevented by surgical removal of part of the iris (iridectomy). The open-angle form of glaucoma is a chronic condition, and treatment is largely pharmacologic. Because intraocular pressure is a function of the balance between fluid input and drainage out of the globe, the strategies for the treatment of open-angle glaucoma fall into two classes: reduction of aqueous humor secretion and enhancement of aqueous outflow.

Five general groups of drugs (cholinomimetics, a agonists, β blockers, prostaglandin F2a analogs, and diuretics) have been found to be useful in reducing intraocular

pressure and can be related to these strategies. Other drugs that have been reported to reduce intraocular pressure include prostaglandin E2 and marijuana. The use of drugs in acute closed-angle glaucoma is limited to cholinomimetics, acetazolamide, and osmotic agents preceding surgery.

CLINICAL PHARMACOLOGY OF THE BETA-RECEPTOR-BLOCKING DRUGS

Hypertension

The β -adrenoceptor-blocking drugs have proved to be effective and well tolerated in hypertension. There is some evidence that drugs in this class may be less effective in the elderly and in individuals of African ancestry. However, these differences are relatively small and may not apply to an individual patient. Indeed, since effects on blood pressure are easily measured, the therapeutic outcome for this

indication can be readily detected in any patient.

Ischemic Heart Disease :

Beta-adrenoceptor blockers reduce the frequency of anginal episodes and improve exercise tolerance in many patients with angina. These actions are due to blockade of cardiac β receptors, resulting in decreased cardiac work and reduction in oxygen demand. Multiple large-scale prospective studies indicate that the long-term such as timolol, use in patients who have had a myocardial infarction prolongs survival.

It is significant that surveys in many populations have indicated that β -receptor antagonists are underused.

In addition, β -adrenoceptor antagonists are strongly indicated in the acute phase of a myocardial infarction.

Cardiac Arrhythmias

It often effective in the treatment of both supraventricular and ventricular arrhythmias. It has been suggested that the improved survival following myocardial infarction in patients using β antagonists is due to suppression of arrhythmias, but this has not been proved. These drugs can also reduce ventricular ectopic beats, particularly if the ectopic activity has been precipitated by catecholamines.

Esmolol is particularly useful against acute perioperative arrhythmias because it has a short duration of action and can be given parenterally. Heart Failure
Clinical trials have demonstrated that at least three β antagonists—metoprolol, bisoprolol, and carvedilol—are effective in reducing mortality in selected patients with chronic heart failure.

Other Cardiovascular Disorders

Beta-receptor antagonists have been found to increase stroke volume in some patients with obstructive cardiomyopathy. Beta antagonists are useful in dissecting aortic aneurysm to decrease the rate of development of systolic pressure. Beta antagonists have been claimed to prevent adverse cardiovascular outcomes resulting from noncardiac surgery but this is controversial.

Glaucoma (The Treatment of Glaucoma)

Systemic administration of β -blocking drugs for other indications was found serendipitously to reduce intraocular pressure in patients with glaucoma. Subsequently, it was found that topical administration also reduces intraocular pressure. Timolol and related β antagonists are suitable

for local use in the eye because they lack local anesthetic properties. Beta antagonists appear to have an efficacy comparable to that of epinephrine or pilocarpine in open-angle glaucoma and are far better tolerated by most patients.

Hyperthyroidism:

Excessive catecholamine action is an important aspect of the pathophysiology of hyperthyroidism, especially in relation to the heart. The β antagonists are beneficial in this condition.

The effects presumably relate to blockade of adrenoceptors and perhaps in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine.

Propranolol has been used extensively in patients with thyroid storm (severe hyperthyroidism); it is used cautiously in patients with this condition to control supraventricular tachycardias that often precipitate heart failure.

Neurologic Diseases:

Propranolol reduces the frequency and intensity of migraine. The somatic manifestations of anxiety may respond dramatically to low doses of propranolol, particularly when taken prophylactically.

For example, benefit has been found in musicians with performance anxiety ("stage fright").

Miscellaneous:

Beta-receptor antagonists have been found to diminish portal vein pressure in patients with cirrhosis.

CHOICE OF A BETA-ADRENOCEPTOR ANTAGONIST DRUG

Propranolol is the standard against which newer β antagonists for systemic use.

It has been found to be a safe and effective drug for many indications.

CLINICAL TOXICITY OF THE BETARECEPTOR ANTAGONIST DRUGS

Many adverse effects have been reported for propranolol but most are minor. Bradycardia- coolness of hands and feet in winter- CNS effects include mild sedation, vivid dreams, and rarely, depression.

The major adverse effects of β -receptor antagonist drugs relate to the predictable consequences of β blockade. Beta₂-receptor blockade associated with the use of nonselective agents commonly causes worsening of preexisting

asthma and other forms of airway obstruction without having these consequences in normal individuals.

Beta-receptor blockade depresses myocardial contractility and excitability. In patients with abnormal myocardial function,

Beta blockers may interact with the calcium antagonist verapamil; severe hypotension, bradycardia, heart failure, and cardiac conduction abnormalities have all been described.

Patients with ischemic heart disease or renovascular hypertension may be at increased risk if β blockade is suddenly interrupted.

cardiac output may be dependent on sympathetic drive. A very small dose of a β antagonist may provoke severe cardiac failure in a susceptible individual.

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
<ul style="list-style-type: none"> • Carvedilol • Medroxalol[†] • Bucindolol[†] (see labetalol above) 	$\beta > \alpha_1$ block		Heart failure	Oral, long half-life • Toxicity: Fatigue
Esmolol	$\beta_1 > \beta_2$	Very brief cardiac β blockade	Rapid control of BP and arrhythmias, thyrotoxicosis, and myocardial ischemia intraoperatively	Parenteral only • half-life ~10 min • Toxicity: Bradycardia • hypotension
TYROSINE HYDROXYLASE INHIBITOR				
Metyrosine	<ul style="list-style-type: none"> Blocks tyrosine hydroxylase reduces synthesis of dopamine, norepinephrine, and epinephrine 	Lowers BP • may elicit extrapyramidal effects (due to low dopamine in CNS)	Pheochromocytoma	Toxicity: Extrapyramidal symptoms • orthostatic hypotension • crystalluria <small>Not available in the USA</small>



section 3



Cardiovascular-Renal Drugs

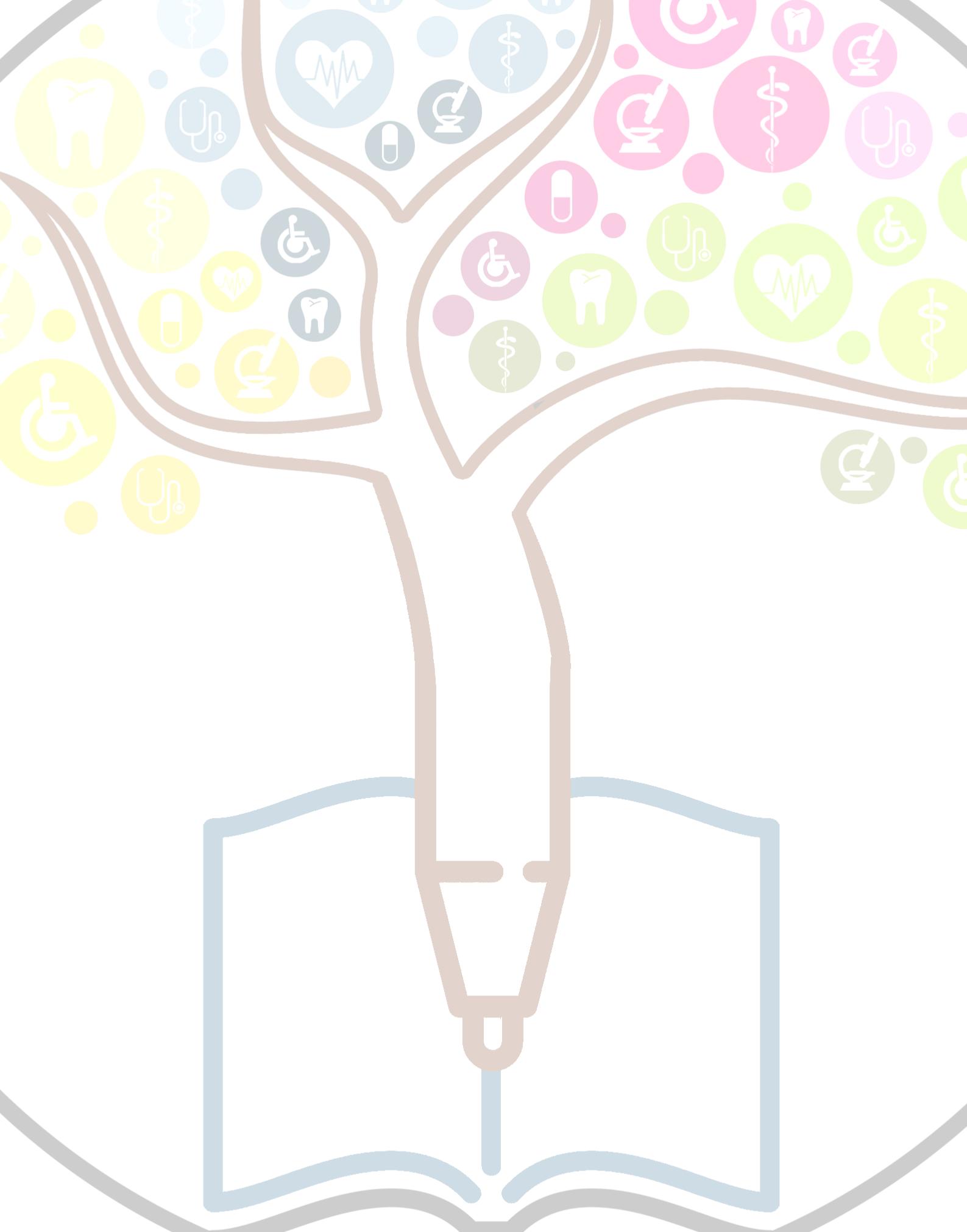
I 1 - Antihypertensive Agents .

I 2 - Vasodilators & the Treatment of Angina Pectoris .

I 3 - Drugs Used in Heart Failure .

I 4 - Agents Used in Cardiac Arrhythmias .

I 5 - Diuretic Agents .



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Chapter #11 : Antihypertensive Agents

HYPERTENSION is the most common cardiovascular disease. The prevalence varies with age, race, education, and many other variables.

According to some studies, 60–80% of both men and women will develop hypertension by age 80. Sustained arterial hypertension damages blood vessels in kidney, heart, and brain and leads to an increased incidence of renal failure, coronary disease, heart failure, stroke, and dementia. Effective pharmacologic lowering of blood pressure has been shown to prevent damage to blood vessels and to substantially reduce morbidity and mortality rates.

Diagnosis

The diagnosis of hypertension is based on repeated, reproducible measurements of elevated blood pressure (Table 11–1).

Systolic/Diastolic Pressure (mm Hg)	Category
< 120/80	Normal
120–135/80–89	Prehypertension
≥ 140/90	Hypertension
140–159/90–99	Stage 1
≥ 160/100	Stage 2

Even mild hypertension (blood pressure 140/90 mm Hg) increases the risk of eventual end-organ damage.

Starting at 115/75 mm Hg, cardiovascular disease risk doubles with each increment of 20/10 mm Hg throughout the blood pressure range.

Etiology of Hypertension

In most cases, elevated blood pressure is associated with an overall increase in resistance to flow of blood through arterioles, whereas cardiac output is usually normal. Evidence points to genetic factors, psychological stress, and environmental and dietary factors.

(increased salt and decreased potassium or calcium intake) as contributing to the development of hypertension.

Functional variations of the genes for angiotensinogen, angiotensin-converting enzyme (ACE), the β_2 adrenoceptor, and a adducin (a cytoskeletal protein) appear to contribute to some cases of essential hypertension

Normal Regulation of Blood Pressure

According to the hydraulic equation

$$BP = CO \times PVR$$

Physiologically, arterioles, postcapillary venules

) capacitance vessels), and heart. A fourth anatomic control site, the kidney, contributes to maintenance of blood pressure by regulating the volume of intravascular fluid. Baroreflexes, mediated by autonomic nerves, act in combination with humoral mechanisms, including the renin-angiotensin-aldosterone system, to coordinate function at these four control sites and to maintain normal blood pressure

BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

Drug	mechanisms
Diuretics	which lower blood pressure by depleting the body of sodium and reducing blood volume and perhaps by other mechanisms
Sympatholytic agents	which lower blood pressure by reducing peripheral vascular resistance, inhibiting cardiac function, and increasing venous pooling in

Direct vasodilators Agents that block production or action of angiotensin	<i>capacitance vessels . which reduce pressure by relaxing vascular smooth muscle, thus dilating resistance vessels and varying degrees reduce peripheral vascular resistance and (potentially (blood volume</i>
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Mechanisms of Action & Hemodynamic

Effects of Diuretics

Diuretics lower blood pressure primarily by depleting body sodium stores. Initially, diuretics reduce blood pressure by reducing bloodvolume and cardiac output.Sodium is believed to contribute to vascular resistance by increasing vessel stiffness andneural reactivity, possibly related to altered sodium-calcium exchange with a resultant increase in intracellular calcium. These effects are reversed by diuretics or dietary sodium restriction. Diuretics often provide adequate treatment for mild or moderate essential hypertension. In more severe hypertension, diuretics are used in combination with sympathoplegic and vasodilator drugs to control the tendency toward sodium retention caused by these agents

Use of Diuretics

Toxicity of Diuretics

*Thiazide diuretics are appropriate for most patients with mild or moderate hypertension and normal renal and cardiac function. thiazide diuretics are more natriuretic at higher doses (up to 100–200 mg of hydrochlorothiazide), when used as a single agent ,lower doses (25–50 mg)

* Chlorthalidone may be more effective than hydrochlorothiazide because it has a longer half-life

*furosemide are necessary in severe

* In the treatment of hypertension, the most common adverse effect of diuretics (except for potassium-sparing diuretics) is potassium depletion., hypokalemia may be hazardous in persons taking digitalis, those who have chronic arrhythmias, or those with acute myocardial infarction or left ventricular dysfunction.

*may also cause magnesium depletion, impair glucose tolerance, and increase serum lipid concentrations

* Diuretics increase uric acid concentrations

hypertension, when multiple drugs with sodium-retaining properties are used; in renal insufficiency, when glomerular filtration rate is less than 30–40 mL/min; and in cardiac failure or cirrhosis, in which sodium retention is marked

**Potassium-sparing diuretics are useful both to avoid excessive potassium depletion and to enhance the natriuretic effects of other diuretics*

**Aldosterone receptor antagonists in particular also have a favorable effect on cardiac function in people with heart failure*

and may precipitate gout. The use of low doses minimizes these adverse metabolic effects without impairing the antihypertensive action

**Potassium-sparing diuretics may produce hyperkalemia, particularly in patients with renal insufficiency and those taking ACE inhibitors or angiotensin receptor blockers; spironolactone (a steroid) is associated with gynecomastia*

DRUGS THAT ALTER SYMPATHETIC NERVOUS SYSTEM FUNCTION

Drugs that lower blood pressure by actions on the central nervous system tend to cause sedation and mental depression and may produce disturbances of sleep, including nightmares. Drugs that act chiefly by reducing release of norepinephrine from sympathetic nerve endings cause effects that are similar to those of surgical sympathectomy, including inhibition of ejaculation, and hypotension that is increased by upright posture and after exercise.

CENTRALLY ACTING SYMPATHOLEGIC DRUGS

Mechanisms & Sites of Action

Methyldopa

Clonidine

*Methyldopa (*l*- α -methyl-3, 4-dihydroxyphenylalanine) is an analog of *l*-dopa and is converted to α -methyldopamine and α -methylnorepinephrine; this pathway directly parallels the synthesis of norepinephrine from dopa. Alpha methylnorepinephrine is stored in adrenergic nerve vesicles, where it stoichiometrically replaces norepinephrine, and is released by nerve stimulation to interact with postsynaptic adrenoceptors. This replacement of norepinephrine by a false transmitter in peripheral neurons is not responsible for methyldopa's antihypertensive effect, because the α -methylnorepinephrine released is an effective agonist at the α adrenoceptors that mediate peripheral sympathetic constriction of arterioles and venules. In fact, methyldopa's antihypertensive action appears to be due to stimulation of central α adrenoceptors by α -methylnorepinephrine or α -methyldopamine.*

The antihypertensive action of clonidine, a 2-imidazoline derivative. After intravenous injection, clonidine produces a brief rise in blood pressure followed by more prolonged hypotension. The pressor response is due to direct stimulation of α adrenoceptors in arterioles. The drug is classified as a partial agonist at α receptors because it also inhibits pressor effects of other α agonists. Clonidine reduces sympathetic and increases parasympathetic tone, resulting in blood pressure lowering and bradycardia. The reduction in pressure is accompanied by a decrease in circulating catecholamine levels. These observations suggest that clonidine sensitizes brainstem vasomotor centers to inhibition by baroreflexes.

CENTRALLY ACTING SYMPATHOLEGIC DRUGS

Drug

Pharmacokinetics & Dosage

Toxicity

METHYLDOPA

Methyldopa used primarily for hypertension during pregnancy. It lowers blood pressure chiefly by reducing peripheral vascular resistance, with a variable reduction in heart rate and cardiac output.

Postural (orthostatic) hypotension sometimes occurs, particularly in volume-depleted patients. One potential advantage of methyldopa is that it causes reduction in renal vascular resistance

Methyldopa enters the brain via an aromatic amino acid transporter. The usual oral dose of methyldopa produces its maximal antihypertensive effect in 4–6 hours, and the effect can persist for up to 24 hours. Because the effect depends on accumulation and storage of a metabolite (α -methylnorepinephrine) in the vesicles of nerve endings, the action persists after the parent drug has disappeared from the circulation.

The most common undesirable

effect of methyldopa is sedation, particularly at the onset of treatment. With long-term therapy, patients may complain of persistent mental lassitude and impaired mental concentration. Nightmares, mental depression, vertigo, and extrapyramidal, positive Coombs test

CLONIDINE

Blood pressure lowering by clonidine results from reduction of cardiac output due to decreased heart rate and relaxation of capacitance vessels, as well as a reduction in peripheral vascular resistance. Reduction in arterial blood pressure by clonidine is accompanied by decreased renal vascular resistance and maintenance of renal blood flow

Clonidine is lipid-soluble and rapidly enters the brain from the circulation. Because of its relatively short half-life and the fact that its antihypertensive effect is directly related to blood concentration, oral clonidine must be given twice a day to maintain smooth blood pressure control. A transdermal preparation of clonidine that reduces blood pressure for 7 days after a single application is also available. This preparation appears to produce less sedation than clonidine tablets but

Dry mouth and sedation are common.

Clonidine should not be given to patients who are at risk for mental depression and should be withdrawn if depression occurs during therapy. Concomitant treatment with tricyclic antidepressants may block the antihypertensive effect of

is often associated with local skin reactions

*clonidine. The interaction
is believed to be due to α-*

*adrenoceptor-blocking actions of
the tricyclics*

Patients exhibit nervousness,

tachycardia, headache, and

sweating after omitting one or

two doses of the drug. Because of

the risk of severe hypertensive

crisis when clonidine is suddenly

withdrawn, all patients who take

clonidine should be warned of

the possibility. If the drug must

be stopped, it should be done

gradually

while other antihypertensive

agents are being substituted.

CENTRALLY ACTING SYMPATHOLEGIC DRUGS

Ganglion blockers competitively block nicotinic cholinoreceptors on postganglionic neurons in both sympathetic and parasympathetic ganglia. In addition, these drugs may directly block the nicotinic acetylcholine channel, in the same fashion as neuromuscular nicotinic blockers.

The adverse effects of ganglion blockers are direct extensions of their pharmacologic effects. These effects include both sympathoplegia (excessive orthostatic hypotension and sexual

dysfunction (and parasympathoplegia (constipation, urinary retention, precipitation of glaucoma, blurred vision, dry mouth, etc). These severe toxicities are the major reason for the abandonment of ganglion blockers for the therapy of hypertension .

ADRENERGIC NEURON-BLOCKING AGENTS

Drug	Pharmacokinetics & Dosage	Toxicity
<p><i>Reserpine blocks the ability of aminergic transmitter vesicles to take up and store biogenic amines, probably by interfering with the vesicular membrane-associated transporter . This effect occurs throughout the body, resulting in depletion of norepinephrine, dopamine, and serotonin in both central and peripheral neurons. Chromaffin granules of the adrenal medulla are also depleted of catecholamines, although to a lesser extent than are the</i></p>	<p>See Table 11-2.</p>	<p>*At the low doses usually administered, reserpine produces little postural hypotension. Most of the unwanted effects of reserpine result from actions on the brain or gastrointestinal tract.</p> <p>*low doses of reserpine produce extrapyramidal effects resembling Parkinson's disease, probably as a result of dopamine depletion in the corpus striatum</p> <p>*High doses of reserpine characteristically produce sedation, lassitude, nightmares, and severe mental depression these occur even in</p>

vesicles of neurons. Reserpine's effects on adrenergic vesicles appear irreversible; trace amounts of the drug remain bound to vesicular membranes for many days

patients receiving low doses

BETA-ADRENOCEPTOR-BLOCKINGAGENTS

All β -adrenoceptor-blocking agents are useful for lowering blood pressure in mild to moderate hypertension. In severe hypertension, β blockers are especially useful in preventing the reflex tachycardia that often results from treatment with direct vasodilators

Drug	Pharmacokinetics & Dosage	Toxicity
Propranolol nonselective β blockade effective in hypertension and ischemic heart disease. Propranolol inhibits the stimulation of renin production by catecholamines (mediated by β_1 receptors). It is likely that propranolol's effect is due in part to depression of the renin- angiotensin- aldosterone system. Beta blockers might also act on peripheral presynaptic β adrenoceptors to reduce sympathetic vasoconstrictor nerve activity. In mild to moderate hypertension, propranolol produces a significant reduction in blood pressure without prominent postural hypotension	Propranolol can be administered twice daily, and slow release once-daily preparations are available	The most important of these predictable extensions of the β_1 -blocking action occur in patients with bradycardia or cardiac conduction disease, and those of the β_2 -blocking action occur in patients with asthma, peripheral vascular insufficiency, and diabetes. When β blockers are discontinued after prolonged regular use, some patients experience a withdrawal syndrome, manifested by nervousness, tachycardia, increased intensity of angina, and increase of blood pressure. Myocardial infarction has been reported in a few patients. Although the incidence of these complications is probably low, β blockers should not be discontinued abruptly. The withdrawal syndrome may involve upregulation or supersensitivity of β adrenoceptors

Metoprolol inhibiting stimulation of β 1 adrenoceptors . Relative cardioselectivity is advantageous in treating hypertensive patients who also suffer from asthma, diabetes, or peripheral vascular disease. Although cardioselectivity is not complete, metoprolol causes less bronchial constriction than propranolol at doses that produce equal inhibition of β 1-adrenoceptor responses.

Metoprolol is extensively metabolized by CYP2D6 with high firstpass metabolism. The drug has a relatively short half-life of 4–6 hours, but the extended-release preparation can be dosed once daily (Table 11–2).

Atenolol is not extensively metabolized and is excreted primarily in the urine with a half-life of 6 hours; it is usually dosed once daily. Atenolol is reported to be less effective than metoprolol in preventing the complications of hypertension. A possible reason for this difference is that once-daily dosing does not maintain adequate blood levels of atenolol. The usual dosage is 50–100 mg/d. Patients with reduced renal function should receive lower doses

Nadolol and **carteolol**, nonselective β -receptor antagonists, are not appreciably metabolized and are excreted to a considerable extent in the urine .Nadolol is usually begun at a dosage of 40 mg/d, carteolol at 2.5 mg/d . Patients with reduced renal function should receive correspondingly reduced doses of nadolol and carteolol.

Betaxolol and bisoprolol are β 1-selective blockers that are primarily metabolized in the liver but have long half-lives. Because of these relatively long half-lives, these drugs can be administered once daily betaxolol at 10 mg/d, and bisoprolol at 5 mg/d

Pindolol, acebutolol, and penbutolol are partial agonists, ie, β blockers with some intrinsic sympathomimetic activity. They lower blood pressure by decreasing vascular resistance and appear to depress cardiac output or heart rate less than other β blockers, perhaps because of significantly greater agonist than antagonist effects at β 2 receptors. This may be particularly beneficial for patients with bradyarrhythmias or peripheral vascular disease . Daily doses of pindolol start at 10 mg; of acebutolol, at 400 mg; and of penbutolol, at 20 mg

Esmolol is a β 1-selective blocker that is rapidly metabolized via hydrolysis by red blood cell esterases. It has a short half-life (9–10 minutes) and is administered by intravenous infusion. Esmolol is generally administered as a loading dose (0.5–1 mg/kg), followed by a constant infusion. The infusion is typically started at 50–150 mcg/kg/min, and the dose increased every 5 minutes, up to 300 mcg/kg/min, as needed to achieve the desired therapeutic effect. Esmolol is used for management of intraoperative and postoperative hypertension, and sometimes for hypertensive emergencies, particularly when hypertension is associated with tachycardia or when there is concern about toxicity such as

aggravation of severe heart failure, in which case a drug with a short duration of action that can be discontinued quickly is advantageous

Labetalol, These drugs have both β -blocking and vasodilating effects. Blood pressure is lowered by reduction of systemic vascular resistance (via α blockade) without significant alteration in heart rate or cardiac output. Because of its combined α - and β -blocking activity, labetalol is useful in treating the hypertension of pheochromocytoma and hypertensive emergencies.

Oral daily doses of labetalol range from 200 to 2400 mg/d. Labetalol is given as repeated intravenous bolus injections of 20–80 mg to treat hypertensive emergencies

Carvedilol, The isomers are stereoselectively metabolized in the liver, which means that their elimination half-lives may differ. The average half-life is 7–10 hours. The usual starting dosage of carvedilol for ordinary hypertension is 6.25 mg twice daily.

Carvedilol reduces mortality in patients with heart failure and is therefore particularly useful in patients with both heart failure and hypertension

Nebivolol is a β_1 -selective blocker with vasodilating properties that are not mediated by a blockade. Nebivolol has highly selective β_1 blocking effects. The vasodilating effect may be due to an increase in endothelial release of nitric oxide via induction of endothelial nitric oxide synthase.

The hemodynamic effects of nebivolol therefore differ from those of pure β blockers in that peripheral vascular resistance is acutely lowered (by nebivolol) as opposed to increased acutely (by the older agents). Nebivolol is extensively metabolized and has active metabolites. The half-life is 10–12 hours, but the drug can be given once daily. Dosing is generally started at 5 mg/d, with dose escalation as high as 40 mg/d, if necessary. The efficacy of nebivolol is similar to that of other antihypertensive agents, but several studies report fewer adverse effects

PRAZOSIN & OTHER ALPHA1 BLOCKERS

Drug	Pharmacokinetics & Dosage	Toxicity
<p>Prazosin, terazosin, and doxazosin</p> <p>Alpha blockers reduce arterial pressure by dilating both resistance and capacitance vessels. As expected, blood pressure is reduced more in the upright than in the supine position. Retention of salt and water occurs when these drugs are administered without a diuretic. The drugs are more effective when used in combination with other agents, such as a β blocker and a diuretic, than when used alone. Owing to their beneficial effects in men with prostatic hyperplasia and bladder obstruction symptoms, these drugs are used primarily in men with concurrent hypertension and benign prostatic hyperplasia</p>	<p>Terazosin is also extensively metabolized but undergoes very little first-pass metabolism and has a half-life of 12 hours. Doxazosin has an intermediate bioavailability and a half-life of 22 hours. Terazosin can often be given once daily, with doses of 5–20 mg/d. Doxazosin is usually given once daily starting at 1 mg/d and progressing to 4 mg/d or more as needed. Doses should be small and should be administered at bedtime</p>	<p>The α_1 blockers are relatively infrequent and mild. These include dizziness, palpitations, headache, and lassitude. Some patients develop a positive test for antinuclear factor in serum while on prazosin therapy, but this has not been associated with rheumatic symptoms</p>

Drug	Pharmacokinetics & Dosage	Toxicity
<p>HYDRALAZINE, dilates arterioles but not veins. The benefits of combination therapy are now recognized, and</p>	<p>Hydralazine is well absorbed and rapidly metabolized by the liver during the first pass.</p>	<p>The most common adverse effects of hydralazine are headache, nausea, anorexia, palpitations, sweating, and flushing. In</p>

hydralazine may be used more effectively, particularly in severe hypertension. The combination of hydralazine with nitrates is effective in heart failure and should be considered in patients with both hypertension and heart failure, especially in African-American patients

The half-life of hydralazine ranges from 1.5 to 3 hours, but vascular effects persist longer than do blood concentrations, possibly due to avid binding to vascular tissue. Usual dosage ranges from 40 mg/d to 200 mg/d.

patients with ischemic heart disease, reflex tachycardia and sympathetic stimulation may provoke angina or ischemic arrhythmias. With dosages of 400 mg/d or more, there is a 10–20% incidence—chiefly in persons who slowly acetylate the drug—of a syndrome characterized by arthralgia, myalgia, skin rashes, and fever that resembles lupus erythematosus. The syndrome is not associated with renal damage and is reversed by discontinuance of hydralazine. Peripheral neuropathy and drug fever are other serious but uncommon adverse effects

Minoxidil is a very efficacious orally active vasodilator. The effect results from the opening of potassium channels in smooth muscle membranes by minoxidil sulfate, the active metabolite.

Increased potassium

permeability stabilizes the membrane at its resting potential and makes contraction less likely. Like hydralazine, minoxidil dilates arterioles but not veins. Because of its greater potential antihypertensive effect,

minoxidil should replace hydralazine when maximal doses of the latter are not effective or in patients with renal failure and severe

Tachycardia, palpitations, angina, and edema are observed when doses of co-administered β blockers and diuretics are inadequate. Headache, sweating, and hypertrichosis

<p><i>hypertension, who do not respond well to hydralazine</i></p>		
<p>Sodium nitroprusside is a powerful parenterally administered vasodilator that is used in treating hypertensive emergencies as well as severe heart failure. Nitroprusside dilates both arterial and venous vessels, resulting in reduced peripheral vascular resistance and venous return. The action occurs as a result of activation of guanylyl cyclase, either via release of nitric oxide or by direct stimulation of the enzyme. The result is increased intracellular cGMP, which relaxes vascular smooth muscle (see Figure 12–2). In the absence of heart failure, blood pressure decreases, owing to decreased vascular resistance, whereas cardiac output does not change or decreases slightly. In patients with heart failure and low cardiac output, output often increases owing to afterload reduction</p>	<p><i>Nitroprusside is a complex of iron, cyanide groups, and a nitroso moiety. It is rapidly metabolized by uptake into red blood cells with release of nitric oxide and cyanide. Cyanide in turn is metabolized by the mitochondrial enzyme rhodanese, in the presence of a sulfur donor, to the less toxic thiocyanate. Dosage typically begins at 0.5 mcg/kg/min and may be increased up to 10 mcg/kg/min as necessary to control blood pressure</i></p>	<p>toxicity is related to accumulation of cyanide; metabolic acidosis, arrhythmias, excessive hypotension, and death have resulted. Both have been advocated for prophylaxis or treatment of cyanide poisoning during nitroprusside infusion. Thiocyanate toxicity is manifested as weakness, disorientation, psychosis, muscle spasms, and convulsions, and the diagnosis is confirmed by finding serum concentrations greater than 10 mg/dL. Rarely, delayed hypothyroidism occurs, owing to thiocyanate inhibition of iodide uptake by the thyroid</p>
<p>Diazoxide is an effective and relatively long-acting parenterally administered arteriolar dilator that is occasionally used to treat hypertensive emergencies. Injection of diazoxide results in a rapid fall in systemic vascular resistance and mean arterial blood pressure. Studies of its mechanism suggest that it prevents vascular smooth muscle contraction by opening potassium channels and stabilizing the membrane potential at the resting level</p>	<p><i>Its half-life is approximately 24 hours, but the relationship between blood concentration and hypotensive action is not well established. The blood pressure-lowering effect after a rapid injection is established within 5 minutes and lasts for 4–12 hours. Beginning with smaller</i></p>	<p>The most significant toxicity from diazoxide has been excessive hypotension, resulting use a fixed dose of 300 mg in all patients. Such hypotension has resulted in stroke and myocardial infarction. The reflex sympathetic response can provoke angina, electrocardiographic evidence of ischemia, and cardiac failure in patients with ischemic heart</p>

Coads (50–150 mg). If necessary, doses of 150 mg may be repeated every 5–15 minutes until blood pressure is lowered satisfactorily. Nearly all patients respond to a maximum of three or four doses. Alternatively, diazoxide may be administered by intravenous infusion at rates of 15–30 mg/min. Because of reduced protein binding, hypotension occurs after smaller doses in persons with chronic renal failure, and smaller doses should be administered to these patients.

disease, also causes renal salt and water retention

FENOLDOPAM

Fenoldopam is a peripheral arteriolar dilator used for hypertensive emergencies and postoperative hypertension. It acts primarily as an agonist of dopamine D1 receptors, resulting in dilation of peripheral arteries and natriuresis. Fenoldopam is rapidly metabolized, primarily by conjugation. Its half-life is 10 minutes. The drug is administered by continuous intravenous infusion. Fenoldopam is initiated at a low dosage (0.1 mcg/kg/min), and the dose is then titrated upward every 15 or 20 minutes to a maximum

dose of 1.6 mcg/kg/min or until the desired blood pressure reduction is achieved. As with other direct vasodilators, the major toxicities are reflex tachycardia, headache, and flushing. Fenoldopam also increases intraocular pressure and should be avoided in patients with glaucoma

CALCIUM CHANNEL BLOCKERS

The mechanism of action in hypertension (and, in part, in angina) is inhibition of calcium influx into arterial smooth muscle cells Verapamil, diltiazem, and the dihydropyridine family (amlodipine, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine) are all equally effective in lowering blood pressure,

other dihydropyridine agents are more selective as vasodilators and have less cardiac depressant effect than verapamil and diltiazem. Reflex sympathetic activation with slight tachycardia maintains or increases cardiac output in most patients given dihydropyridines. Verapamil has the greatest depressant effect on the heart and may decrease heart rate and cardiac output .otherdihydropyridine agents are more selective as vasodilators and have less cardiac depressant effect than verapamil and diltiazem. Reflex sympathetic activation with slight tachycardia maintains or increases cardiac output in most patients given dihydropyridines. Verapamil has the greatest depressant effect on the heart and may decrease heart rate and cardiac output . Some epidemiologic studies reported an increased risk of myocardial infarction or mortality in patients receiving short-acting nifedipine for hypertension. It is therefore recommended that short-acting oral dihydropyridines not be used for hypertension

INHIBITORS OF ANGIOTENSIN

Renin acts upon angiotensinogen to yield the inactive precursor decapeptide angiotensin I. Angiotensin I is then converted, primarily by endothelial ACE, to the arterial vasoconstrictor octapeptide angiotensin II , which is in turn converted in the adrenal gland to angiotensin III. Angiotensin II has vasoconstrictor and sodium-retaining activity. Angiotensin II and III both stimulate aldosterone release

ANGIOTENSIN-CONVERTING ENZYME

(ACE) INHIBITORS

this class inhibit the converting enzyme peptidyldipeptidase that hydrolyzes angiotensin I to angiotensin II and (under the name plasma kininase) inactivates bradykinin. Enalapril is an oral prodrug that is converted by hydrolysis to a converting enzyme inhibitor, enalaprilat, with effects similar to those of captopril.

Enalaprilat itself is available only for intravenous use, primarily for hypertensive emergencies. Lisinopril is a lysine derivative of enalaprilat. Benazepril, fosinopril, moexipril perindopril, quinapril, ramipril, and trandolapril are other long-acting members of the class.

All are prodrugs, like enalapril, and are converted to the active agents by hydrolysis, primarily in the liver. ACE inhibitors have a particularly useful role in treating patients with chronic kidney disease because they diminish proteinuria and stabilize renal function (even in the absence of lowering of blood pressure). This effect is particularly valuable in diabetes, and these drugs are now recommended in diabetes even in the absence of hypertension

Toxicity

adverse effects common to all ACE inhibitors include acute renal failure (particularly in patients with bilateral renal artery stenosis or stenosis of the renal artery of a solitary kidney), hyperkalemia, dry cough sometimes accompanied by wheezing, and angioedema. Hyperkalemia is more likely to occur in patients with renal insufficiency or diabetes. ACE inhibitors are contraindicated during the second and third trimesters of pregnancy because of the risk of fetal hypotension, anuria, and renal failure, sometimes associated with fetal malformations or death. Recent evidence also implicates first-trimester exposure to ACE inhibitors in increased teratogenic risk. Captopril, particularly when given in high doses to patients with renal insufficiency,

may cause neutropenia or proteinuria. Minor toxic effects seen more typically include altered sense of taste, allergic skin rashes, and drug fever, which may occur in up to 10% of patients. Important drug interactions include those with potassium supplements or potassium-sparing diuretics, which can result in hyperkalemia.

ANGIOTENSIN RECEPTOR-BLOCKING AGENTS

Losartan and **valsartan** were the first marketed blockers of the angiotensin II type 1 (AT1) receptor. **Candesartan**, **eprosartan**, **irbesartan**, **telmisartan**, and **olmesartan** are also available. The adverse effects are similar to those described for ACE inhibitors, including the hazard of use during pregnancy. Cough and angioedema can occur but are uncommon. Angiotensin receptor blocking drugs are most commonly used in patients who have had adverse reactions to ACE inhibitors

CLINICAL PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

the physician must establish with certainty that hypertension is persistent and requires treatment and must exclude secondary causes of hypertension that might be treated by definitive surgical procedures. Ambulatory blood pressure monitoring may be the best predictor of risk and therefore of need for therapy in mild hypertension, and is recommended for initial evaluation of all patients in the guidelines of some countries. The patient must be educated about the nature of hypertension and the importance of treatment so that he or she can make an informed decision regarding therapy.

OUTPATIENT THERAPY OF HYPERTENSION

treating hypertension may be nonpharmacologic.

As discussed previously, sodium restriction may be effective treatment for many patients with mild hypertension. Eating a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat, and

moderation of alcohol intake (no more than two drinks per day) also lower blood pressure. Weight reduction, Regular exercise . For pharmacologic management of mild hypertension, blood pressure can be normalized in many patients with a single drug. Most patients moderate to severe hypertension require two or more antihypertensive medications . The presence of concomitant disease should influence selection of antihypertensive drugs because two diseases may benefit from a single drug. For example, drugs that inhibit the renin-angiotensin system are particularly useful in patients with diabetes or evidence of chronic kidney disease with proteinuria . Race may also affect drug selection: African Americans respond better on average to diuretics and calcium channel blockers than to β blockers and ACE inhibitors . noncompliance with medication, causes of failure to respond to drug therapy include excessive sodium intake and inadequate diuretic therapy with excessive blood volume, and drugs such as tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, over-the-counter sympathomimetics, abuse of stimulants (amphetamine or cocaine), or excessive doses of caffeine and oral contraceptives that can interfere with actions of some antihypertensive drugs or directly raise blood pressure .

Clinical Presentation & Pathophysiology

Hypertensive emergencies include hypertension associated with vascular damage (termed malignant hypertension) and hypertension associated with hemodynamic complications such as heart failure, stroke, or dissecting aortic aneurysm. The underlying pathologic process in malignant hypertension is a progressive arteriopathy with inflammation and necrosis of arterioles. Vascular lesions occur in the kidney, which releases renin, which in turn stimulates production of angiotensin and aldosterone, which further increase blood pressure.

Hypertensive encephalopathy is a classic feature of malignant

hypertension. Its clinical presentation consists of severe headache, mental confusion, and apprehension. Blurred vision, nausea and vomiting, and focal neurologic deficits are common. If untreated, the syndrome may progress over a period of 12–48 hours to convulsions, stupor, coma, and even death.

Treatment of Hypertensive Emergencies

The general management of hypertensive emergencies requires monitoring the patient in an intensive care unit with continuous recording of arterial blood pressure. Fluid intake and output must

be monitored carefully and body weight measured daily as an indicator of total body fluid volume during the course of therapy.

Parenteral antihypertensive medications are used to lower blood pressure rapidly

blood pressure can be reduced

to normal levels using oral medications over several weeks. The parenteral drugs used to treat hypertensive emergencies include sodium nitroprusside, nitroglycerin, labetalol, calcium channel blockers, fenoldopam, and hydralazine. Esmolol is often used to manage intraoperative and postoperative hypertension. Diuretics such as furosemide are administered to prevent the volume expansion that typically occurs during administration of powerful vasodilators

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DIURETICS				
- Thiazides: Hydrochlorothiazide, chlorothalidone - Loop diuretics: Furosemide - Spironolactone, eplerenone	Block Na/Cl transporter in renal distal convoluted tubule Block Na/K/2Cl transporter in renal loop of Henle Block aldosterone receptor in renal collecting tubule	Reduce blood volume and poorly understood vascular effects Like thiazides • greater efficacy Increase Na and decrease K excretion • poorly understood reduction in heart failure mortality	Hypertension, mild heart failure Severe hypertension, heart failure Aldosteronism, heart failure, hypertension	See Chapter 15
SYMPATHOLEGICS, CENTRALLY ACTING				
- Clonidine, methyldopa	Activate α_2 adrenoceptors	Reduce central sympathetic outflow • reduce norepinephrine release from noradrenergic nerve endings	Hypertension • clonidine also used in withdrawal from abused drugs	Oral • clonidine also as patch • Toxicity: sedation • methyldopa hemolytic anemia
SYMPATHETIC NERVE TERMINAL BLOCKERS				
- Reserpine - Guanethidine	Blocks vesicular amine transporter in noradrenergic nerves and depletes transmitter stores Interferes with amine release and replaces norepinephrine in vesicles	Reduces all sympathetic effects, especially cardiovascular, and reduce blood pressure Same as reserpine	Hypertension but rarely used Same as reserpine	Oral • long duration (days) • Toxicity: psychiatric depression, gastrointestinal disturbances Severe orthostatic hypotension • sexual dysfunction

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
α BLOCKERS				
- Prazosin - Terazosin - Doxazosin	Selectively block α_1 adrenoceptors	Prevent sympathetic vasoconstriction • reduce prostatic smooth muscle tone	Hypertension • benign prostatic hyperplasia	Oral • Toxicity: Orthostatic hypotension
β BLOCKERS				
- Metoprolol, others - Carvedilol - Nebivolol - Propranolol: Nonselective prototype β blocker - Metoprolol and atenolol: Very widely used β_1 -selective blockers	Block β_1 receptors; carvedilol also blocks α receptors; nebivolol also releases nitric oxide	Prevent sympathetic cardiac stimulation • reduce renin secretion	Hypertension • heart failure • coronary disease	See Chapter 10
VASODILATORS				
- Verapamil - Diltiazem - Nifedipine, amlodipine, other dihydropyridines - Hydralazine - Minoxidil	Nonselective block of L-type calcium channels Block vascular calcium channels > cardiac calcium channels Causes nitric oxide release Metabolite opens K channels in vascular smooth muscle	Reduce cardiac rate and output • reduce vascular resistance Reduce vascular resistance Vasodilation • reduces vascular resistance • arterioles more sensitive than veins • reflex tachycardia	Hypertension, angina, arrhythmias Hypertension, angina	See Chapter 12 See Chapter 12 Oral • Toxicity: Angina, tachycardia • Hydralazine: Lupus-like syndrome Minoxidil: Hypertrichosis
PARENTERAL AGENTS				
- Nitroprusside - Fenoldopam - Diazoxide - Labetalol	Releases nitric oxide Activates D ₁ receptors Opens K channels α , β blocker	Powerful vasodilation	Hypertensive emergencies	Parenteral • short duration • Toxicity: Excessive hypotension, shock
ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS				
- Captopril, many others	Inhibit angiotensin-converting enzyme	Reduce angiotensin II levels • reduce vasoconstriction and aldosterone secretion • increase bradykinin	Hypertension • heart failure, diabetes	Oral • Toxicity: Cough, angioedema • hyperkalemia • renal impairment • teratogenic
ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)				
- Losartan, many others	Block AT ₁ angiotensin receptors	Same as ACE inhibitors but no increase in bradykinin	Hypertension • heart failure	Oral • Toxicity: Same as ACE inhibitors but less cough
RENIN INHIBITOR				
- Aliskiren	Inhibits enzyme activity of renin	Reduces angiotensin I and II and aldosterone	Hypertension	Oral • Toxicity: Hyperkalemia, renal impairment • potential teratogen

Chapter #12 : Vasodilators & the Treatment of Angina Pectoris

Chapter 12

Vasodilators & the Treatment of Angina Pectoris

Introduction:

Ischemic heart disease is one of the most common cardiovascular diseases in developed countries, and angina pectoris is the most common condition involving tissue ischemia in which vasodilator drugs are used. The primary cause of angina pectoris is an imbalance between the oxygen requirement of the heart and the oxygen supplied to it via the coronary vessels. The imbalance occurs when the myocardial oxygen requirement increases, especially during exercise, and coronary blood flow does not increase proportionately. The resulting ischemia usually leads to pain. However, in some individuals, the ischemia is not always accompanied by pain, resulting in "silent" or "ambulatory" ischemia. The imbalance between oxygen delivery and myocardial oxygen demand can be corrected by decreasing oxygen demand or by increasing delivery (by increasing coronary flow). In effort angina, oxygen demand can be reduced by decreasing cardiac work or, according to some studies, by shifting myocardial metabolism to substrates that require less oxygen per unit of adenosine triphosphate (ATP) produced.

BASIC PHARMACOLOGY OF DRUGS USED TO

TREAT ANGINA

The three drug groups traditionally used in angina (organic nitrates, calcium channel blockers, and β blockers)

decrease myocardial oxygen requirement by decreasing the determinants of oxygen demand (heart rate, blood pressure, and contractility).

NITRATES & NITRITES

Subclass, Drug	<i>Nitroglycerin</i>
Mechanism of Action	Releases nitric oxide in smooth muscle, which activates guanylylcyclase and increases cGMP
Effects	Smooth muscle relaxation, especially in vessels • other smooth muscle is relaxed but not as markedly • vasodilation decreases venous return and heart size • may increase coronary flow in some areas and in variant angina
Clinical Application	Angina: Sublingual form for acute episodes • oral and transdermal forms for prophylaxis • IV form for acute coronary syndrome
Pharmacokinetics, Toxicities, Interactions	High first-pass effect, so sublingual dose is much smaller than oral • high lipid solubility ensures rapid absorption • Toxicity: Orthostatic hypotension, tachycardia, head-ache • Interactions: Synergistic hypotension with phosphodiesterase type 5 inhibitors (sildenafil, etc)

*Isosorbidedinitrate: Very similar to nitroglycerin, slightly longer duration of action

*Isosorbidemononitrate: Active metabolite of the dinitrate; used orally for prophylaxis

BETA BLOCKERS

Subclass, Drug	<i>Propranolol</i>
Mechanism of Action	Nonselective competitive antagonist at $\alpha_1, \alpha_2, \beta_1, \beta_2$ adrenoceptors
Effects	Decreased heart rate, cardiac output, and blood cardiac oxygen demand
Clinical Application	Prophylaxis of angina

Pharmacokinetics, Toxicities, Interactions	Oral and parenteral, 4–6 h duration Toxicity: Asthma, atrio- ventricular block, acute heart fail- Interactions: Additive with all cardiac depressants
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*Atenolol, metoprolol, others: β_1 -selective blockers, less risk of bronchospasm, but still significant

CALCIUM CHANNEL BLOCKERS

Subclass, Drug	<i>Verapamil, Diltiazem</i>
Mechanism of Action	Nonselective block of L-type calcium channels in vessels and heart
Effects	Reduced vascular resistance, cardiac rate, and cardiac force results in decreased oxygen demand
Clinical Application	Prophylaxis of angina, hypertension, others
Pharmacokinetics, Toxicities, Interactions	Toxicity: Atrioventricular block, acute heart Interactions: Additive with other cardiac depressants and hypotensive drugs

CALCIUM CHANNEL BLOCKERS

Subclass, Drug	<i>Nifedipine(a dihydropyridine)</i>
Mechanism of Action	Block of vascular L-type calcium channels > cardiac channels
Effects	Like verapamil and diltiazem; less cardiac effect
Clinical Application	Prophylaxis of angina and treatment of hypertension but prompt release nifedipine is contraindicated
Pharmacokinetics, Toxicities, Interactions	Toxicity: Excessive hypotension, barorecep- Interactions: Additive with other vasodilators

*Other dihydropyridines: Like nifedipine but slower onset and longer duration (up to 12 h or more)

MISCELLANEOUS

Subclass, Drug	<i>Ranolazine</i>
Mechanism of Action	Inhibits late sodium current in heart Also modify fatty acid oxidation
Effects	Reduces cardiac oxygen demand. Fatty acid oxidation modification may improve efficiency of cardiac oxygen utilization.
Clinical Application	Prophylaxis of angina
Pharmacokinetics, Toxicities, Interactions	<i>Oral, duration 6-8 hours</i> <i>Toxicity:</i> QT interval prolongation (but no increase of torsades de pointes), <i>Interactions:</i> Inhibitors of CYP3A increase ranolazine concentration and duration of action

*Ivabradine: Investigational inhibitor of sinoatrial pacemaker; reduction of heart rate reduces oxygen demand

Chapter #13 : Drugs Used in Heart Failure

Drugs Used in Heart Failure

Introduction:

Heart failure occurs when cardiac output is inadequate to provide the oxygen needed by the body. It is a progressive disease that is characterized by a gradual reduction in cardiac performance, punctuated in many cases by episodes of acute decompensation, often requiring hospitalization. Treatment is therefore directed at two somewhat different goals:(1) reducing symptoms and slowing progression as much as possible during relatively stable periods.(2) managing acute episodes of decompensated failure. Although it is believed that the primary defect in early systolic heart failure resides in the excitation-contraction coupling machinery of the myocardium, the clinical condition also involves many other processes and organs, including the baroreceptor reflex, the sympathetic nervous system, the kidneys, angiotensin II and other peptides, aldosterone, and apoptosis of cardiac cells. Recognition of these factors has resulted in evolution of a variety of drug treatmentstrategies.

(Table 13-1).TABLE 13-1 Therapies used in heart failure.

Chronic Systolic Heart Failure	Acute Heart Failure
Diuretics	Diuretics
Aldosterone receptor antagonists	Vasodilators
Angiotensin-converting enzyme inhibitors	Beta agonists
Angiotensin receptor blockers	Bipyridines
Beta blockers	Natriuretic peptide
Cardiac glycosides	Left ventricular assist device
Vasodilators	
Resynchronization therapy	

Drugs Used in Heart Failure

Cardiac Glycoside

Subclass, Drug	Digoxin
Mechanism of Action	Na ⁺ /K ⁺ -ATPase inhibition results in reduced Ca ²⁺ expulsion and increased Ca ²⁺ stored in sarcoplasmic reticulum
Effects	Increases cardiac contractility. Cardiac para-sympathomimetic effect (slowed sinus heart rate, slowed atrioventricular conduction)
Pharmacokinetics,	<i>Oral, parenteral.</i> <i>Toxicity: Nausea, vomiting, diarrhea, cardiac arrhythmia.</i>

DIURETICS

Subclass, Drug	Furosemide and Hydrochlorothiazide
Mechanism of Action	Furosemide: Loop diuretic: Decreases NaCl and KCl reabsorption in thick ascending limb of the loop of Henle in the nephron. Hydrochlorothiazide : Decreases NaCl reabsorption in the distal convoluted tubule
Effects	Furosemide: Increased excretion of salt and water, reduce preload and afterload peripheral edema Hydrochlorothiazide : Same as furosemide, but much less efficacious
Clinical Application	Furosemide: Acute and chronic heart failure, severe hypertension and edematous condition. Hydrochlorothiazide: Mild chronic failure, mild moderate hypertension and hypercalciuria.
Pharmacokinetics, Toxicities, Interactions	Furosemide : Oral and IV. <i>Toxicity:</i> Hypovolemia, hypokalemia, orthostatic hypotension, ototoxicity, sulfonamide allergy Hydrochlorothiazide : Oral only. <i>Toxicity:</i> Hyponatremia, hypokalemia, hyperglycemia, hyperuricemia, hyperlipidemia, sulfonamide allergy

* Three other loop diuretics: Bumetanide and torsemide similar to furosemide; ethacrynic acid not a sulfonamide

* Many other thiazides: All basically similar to hydrochlorothiazide, differing only in pharmacokinetics

ALDOSTERONE ANTAGONISTS

Mechanism of Action	Blocks cytoplasmic aldosterone receptors in collecting tubules of nephron possible membrane effect
Effects	Increased salt and water excretion. Reduces remodeling
Clinical Application	Chronic heart failure, aldosteronism(cirrhosis, adrenal tumor). Hypertension
Pharmacokinetics, Toxicities, Interactions	Oral (slow onset and offset) Toxicity: hyperkalemia, antiandrogene action.

Angiotensin Antagonists

Mechanism of Action	Captopril: Inhibits ACE. Reduces AII formation by inhibiting conversion of AI and AII Losartan: Antagonize AII effects at AT receptors
Effects	Captopril: Arteriolar and venous dilation. Aldosterone secretion. Reduces cardiac remodeling. Losartan: Like ACE inhibitors
Clinical Application	Captopril: Chronic heart failure, hypertension, diabetic renal disease. Losartan: Like ACE inhibitors. Used in patient intolerant to ACE inhibitors. Has shown to reduce mortal
Pharmacokinetics, Toxicities, Interactions	Captopril: Oral. Half life 2-4 h. toxicity: cough, hyperkalemia, angioneurotic edema. Losartan: Oral. Toxicity: hyperkalemia, antiandrogene action. Angioneurotic edema

*Enalapril, many other ACE inhibitors: Like captopril

*Candesartan, many other ARBs: Like losartan

Beta Blockers

Subclass, Drug	<i>Carvedilol</i>
Mechanism of Action	Competitively blocks beta 1 receptors
Effects	Slows heart rate. Reduces blood pressure. Poorly understood effects.
Clinical Application	Chronic heart failure: to slow progression. Reduce mortality in moderate and severe heart failure.
Pharmacokinetics, Toxicities	Oral. Toxicity: Bronchospasm, bradycardia, atrioventricular block, acute cardiac decompensation.

Na^+/K^+ -ATPase inhibition results in reduced Ca^{2+} expulsion and increased Ca^{2+} stored in sarcoplasmic reticulum

BIPYRIDINES

Subclass, Drug	<i>Milrinone</i>
Mechanism of Action	Phosphodiesterase type 3 inhibitor. Decrease cAMP breakdown
Effects	Vasodilator; lower peripheral vascular resistance also increase cardiac contractility
Clinical Application	Acute decompensated heart failure. <i>increases</i> mortality in chronic failure
Pharmacokinetics, Toxicities	IV only. <i>Toxicity: Interactions:</i> Additive with other arrhythmogenic. Interaction: additive with other arrhythmogenic agents.

NATRIURETIC PEPTIDE

Subclass, Drug	Nesiritide
Mechanism of Action	Activates BNP receptors, increases Cgmp
Effects	Vasodilation, diuresis
Clinical Application	Acute decompensated failure. Has not shown to reduce mortality
Pharmacokinetics, Toxicities	<i>IV only.</i> Toxicity: Renal damage, hypotension, may <i>increase</i> mortality

1-Vasodilators

Subclass, Drug	Venodilators: Isosobidedintirate		
Mechanism of Action	Releases nitric oxide (NO) and activates guanylyl cyclase		
Effects	Venodilation. Reduces preload and ventricular stretch		
Clinical Application	Acute and chronic heart failure and angina.		
Pharmacokinetics, Toxicities	<i>Oral</i>	<i>Toxicity:</i> Postural hypotension. Tachycardia, headache. <i>Interactions:</i> Additive with other vasodilators and synergistic with phosphodiesterase type 5 inhibitors	

2-Vasodilators

Subclass, Drug	Arteriolar dilators: Hydralazine		
Mechanism of Action	Probably increases NO synthesis in endothelium		
Effects	Reduces blood pressure and afterload. Results in increased cardiac output		
Clinical Application	Hydralazine plus nitrates have reduced mortality		
Pharmacokinetics, Toxicities	<i>Oral</i>	<i>Toxicity:</i> Tachycardia, fluid retention, lupus-like syndrome	

3-Vasodilators

Subclass, Drug	Combined arteriolar and venodilator: Nitroprusside
Mechanism of Action	Releases NO spontaneously and activates guanylylcyclase
Effects	Marked vasodilation and reduces preload and after-load
Clinical Application	Acute cardiac decompensation and hypertensive emergencies (malignant hypertension)
Pharmacokinetics, Toxicities	<i>IV only</i> Toxicity: Excessive hypotension, thiocyanate and cyanide toxicity. Interactions: Additive with other vasodilators

BETA-ADRENOCEPTOR AGONISTS

Subclass, Drug	Dobutamine and Dopamine
Mechanism of Action	Dobutamine: Beta1-selective agonist and increases cAMP synthesis Dopamine: Dopamine receptor agonist. Higher doses activate beta and alpha adrenoceptors.
Effects	Dobutamine: Increases cardiac contractility, output. Dopamine: increases renal blood flow and in higher doses increase cardiac force and blood pressure
Clinical Application	Dobutamine: Acute decompensated heart failure. intermittent therapy in chronic failure reduces symptoms Dopamine : Acute decompensated heart failure and shock
	Dobutamine: IV only. <i>Toxicity: arrhythmias. Interactions:</i> Additive with other sympathomimetic



Chapter #14 : Agents Used in Cardiac Arrhythmias

Chapter 14

agents Used in cardiac arrhythmias

Heart condition where disturbances in

- 1) Pacemaker impulse formation
- 2) Contraction impulse conduction
- 3) Combination of the two

Results in rate and/or timing of contraction of heart muscle that is insufficient to maintain normal cardiac output (CO).

Causes of arrhythmias:

- 1) Cardiac ischemia.
- 2) □Excessive discharge or sensitivity to autonomic.
- 3) □transmitters Exposure to toxic substances.
- 4) Unknown etiology.

Electrophysiology - resting potential

Normal cardiac beats (60-100) bpm.

A transmembrane electrical gradient (potential) is maintained, with the interior of the cell negative with respect to outside the cell Caused by unequal distribution of ions inside vs. outside cell :

- Na⁺ higher outside than inside cell.
- Ca⁺ much higher outside than inside cell.
- K⁺ higher inside cell than outside.

Cardiac Action Potential

Divided into five phases (0,1,2,3,4)

■ BASIC PHARMACOLOGY OF THE ANTIARRHYTHMIC AGENTS

Mechanisms of Action

The aim of therapy of the arrhythmias is to reduce ectopic pacemaker activity and modify conduction or refractoriness in reentry circuits to disable circus movement.

Major pharmacologic mechanisms currently available for accomplishing these goals are:

- (1) sodium channel blockade.
- (2) blockade of sympathetic autonomic effects in the heart.
- (3) prolongation of the effective refractory period.
- (4) calcium channel blockade.

■ SPECIFIC ANTIARRHYTHMIC AGENTS

Class 1 :

sodium channel blockade.

class 1A action prolong the APD and dissociate from the channel with intermediate kinetics;

class 1B action shorten the APD in some tissues of the heart and dissociate from the channel with rapid kinetics;

class 1C action have minimal effects on the APD and dissociate from the channel with slow kinetics.

Class 2 :

the action is sympatholytic. Drugs with this action reduce β -adrenergic activity in the heart.

Class3 :

the action manifests as prolongation of the APD. Most drugs with this action block the rapid component of the delayed rectifierpotassium current, IKr.

Class4 :

the action is blockade of the cardiac calcium current. This action slows conduction in regions where the action potential upstroke is calcium dependent, eg, the SA and AV nodes.

SODIUM CHANNEL-BLOCKING DRUGS (CLASS 1)

local anesthetic action block sodium channels and reduce the sodium current, INa. They are the oldest group of antiarrhythmic drugs and are still widely used.

Class a1 drug	PROCAINAMIDE
Cardiac effect	blocking sodium channels, slows the upstroke of the action potential, slows conduction, and prolongs the QRS duration of the ECG.more effective in blocking sodium channels in depolarized cells.
Extracardiac effects	Ganglion-blocking properties and can cause hypotension, with IV use. Hypotension is usually associated with rapid procainamide infusion or the presence of severe underlying left ventricular dysfunction.
Toxicity	Action potential and QT-interval prolongation, and induction of TdP(<i>torsades de pointes – abnormal heart rhythm</i>) arrhythmia and syncope.Long term use can cause syndrome resembling lupus erythematosus, arthralgia and arthritis. Others (rash, fever, nausea, diarrhea, and hepatitis).
Pharmacokinetic & dosage	IV and IM routes and is well absorbed orally. Accumulation of NAPA(<i>the metabolite -N-Acetylprocainamide</i>), in renal failure patient. Eliminated by hepatic to NAPA and by renal. Half life (3-4 hours). Reduce Dose in RF, HF patient. IV loading dose (12 mg/kg) maintenance dosage (2-5 mg/kg) with monitoring of plasma levels. GI or cardiac toxicity rises at plasma conc. more than

	8mcg/mL or NAPA more than 20 mcg/mL.
Therapeutic use	Atrial and ventricular arrhythmias. Avoid long-term therapy. Procainamide is the drug of second or third choice (after lidocaine or amiodarone). Using it in arrhythmias associated with acute myocardial infarction.

Class 1A		QUINIDINE
Cardiac effect	It slows the upstroke of the action potential and conduction. Prolongs the QRS duration of the ECG, by blockade of Na channels, also prolongs the action potential duration by blockade of several K channels.	
Extracardiac effects	Diarrhea, nausea, and vomiting. A syndrome of headache, dizziness, and tinnitus (<i>hearing sounds -cinchonism</i>) is observed at toxic drug concentrations. Idiosyncratic or immunologic reactions, including thrombocytopenia, hepatitis, angioneurotic edema, and fever, are observed rarely.	
Toxicity	Excessive QT-interval prolongation and induction of TdP arrhythmia, also produce excessive Na channel blockade with slowed conduction throughout the heart. It also has modest antimuscarinic actions in the heart.	
Pharmacokinetic & dosage	Readily absorbed from the GI tract and eliminated by hepatic metabolism.	
Therapeutic use	It is rarely used because of cardiac and extracardiac adverse effects and the availability of better-tolerated antiarrhythmic drugs.	

Class 1A		DISOPYRAMIDE
Cardiac effect	Similar to procainamide and quinidine. Its cardiac antimuscarinic effects are even more marked than those of quinidine. A drug that slows AV conduction <u>should be</u> administered with disopyramide when treating atrial flutter or fibrillation.	
Toxicity	HF de novo or in patients with preexisting depression of left ventricular function. It should not be used in patients with HF. Disopyramide's atropine-like activity accounts for most of its symptomatic adverse effects: urinary retention (in male patients with prostatic hyperplasia), dry mouth, blurred vision, constipation, and worsening of preexisting glaucoma. These effects may require discontinuation of the drug.	
Pharmacokinetic & dosage	Only for oral use. The typical oral dosage is 150 mg 3 times/day, but up to 1 g/d has been used. In patients with renal impairment, dosage must be reduced. Because of the danger of precipitating HF, loading doses are not recommended.	

Therapeutic use	in the USA it is approved only for the treatment of ventricular arrhythmias
Class 1B	LIDOCAINE
Cardiac effect	It blocks activated and inactivated Na channels with rapid kinetics. In depolarized cells, the increased inactivation and slower unbinding kinetics result in the selective depression of conduction. Little effect is seen on the ECG(<i>electrocardiography</i>) in normal sinus rhythm.
Toxicity	large doses in patients with preexisting HF, lidocaine may cause hypotension. Adverse effect are neurologic: paresthesias, tremor, nausea of central origin, lightheadedness, hearing disturbances, slurred speech, and convulsions. These occur most commonly in elderly. The effects are dose-related and usually short-lived; seizures respond to IV diazepam. If plasma levels above 9 mcg/mL are avoided, lidocaine is well tolerated.
Pharmacokinetic & dosage	Extensive first-pass hepatic metabolism. Lidocaine must be given parenterally. Half life (1-2 hours). Loading dose of 150–200 mg administered over about 15 minutes, should be followed by a maintenance infusion of 2–4 mg/min to achieve a therapeutic plasma level of 2–6 mcg/mL. Patients with myocardial infarction or other acute illness require (and tolerate) higher concentrations. Drugs that decrease liver blood flow (eg, propranolol, cimetidine) reduce lidocaine clearance and so increase the risk of toxicity unless infusion rates are decreased.
Therapeutic use	Agent of choice for termination of ventricular tachycardia and prevention of ventricular fibrillation after cardioversion in the setting of acute ischemia. Administer IV lidocaine only to patients with arrhythmias.

Class 1B	Mexiletine
Cardiac effect	It is an orally active congener of lidocaine. Its action are Similar to those of lidocaine.
Pharmacokinetic & dosage	Elimination half-life is 8–20 hours and permits administration 2or3 times\ day. The daily dosage of is 600–1200 mg/d. Dose-related adverse effects are neurologic, including tremor, blurred vision, and lethargy. Nausea is also a common effect. Relieving chronic pain, especially pain due to diabetic neuropathy and nerve injury. The usual dosage is 450–750 mg/d orally.
Therapeutic use	Used in the treatment of ventricular arrhythmias.

Class 1C**Moricizine**

Class 1C		Flecainide
Cardiac effect	Potent blocker of Na and K channels with slow unblocking kinetics. It is currently used for patients with otherwise normal hearts who have supraventricular arrhythmias. It has no antimuscarinic effects. very effective in suppressing premature ventricular contractions.	
Toxicity	Severe exacerbation of arrhythmia even when normal doses are administered to patients with preexisting ventricular tachyarrhythmias and those with a previous myocardial infarction and ventricular ectopy (<i>an irregular heart rhythm due to a premature heartbeat</i>).	
Pharmacokinetic & dosage	well absorbed and has a half-life of approximately 20 hours. Elimination is both by hepatic metabolism and by the kidney. The usual dosage of flecainide is 100–200 mg twice a day.	
Overview	It was used for treatment of ventricular arrhythmias. It is a relatively potent Na channel blocker that does not prolong action potential duration. Moricizine has been withdrawn from the US market.	

Class 1C**Propafenone**

Cardiac effect	Has similarities to propranolol and possesses weak β-blocking activity. It does not prolong the action potential. Its Na channel-blocking kinetics are similar to those of flecainide.
Toxicity and adverse effects	The most common adverse effects are a metallic taste and constipation; arrhythmia exacerbation can also occur.
Pharmacokinetic & dosage	metabolized in the liver, with an average half-life of 5–7 hours. The usual daily dosage of propafenone is 450–900 mg/d in three divided doses.

Therapeutic use

The drug is used primarily for supraventricular arrhythmias.

BETA-ADRENOCEPTOR-BLOCKING DRUGS(CLASS 2)

Propranolol have antiarrhythmic properties by virtue of their β -receptor-blocking action and direct membrane effects. Although β blockers have efficacy for suppression of ventricular ectopic depolarizations is lower than that of sodium channel blockers. Can prevent recurrent infarction and sudden death in patients recovering from acute myocardial infarction. Esmolol is a short-acting β blocker used primarily as an antiarrhythmic drug for intraoperative and other acute arrhythmias. Sotalol is a nonselective β -blocking drug that prolongs the action potential (class 3 action).

Drugs That Prolong Effective Refractory Period By Prolonging the Action Potential (Class 3)

These drugs prolong action potentials, usually by blocking K channels in cardiac muscle or by enhancing inward current, eg, through Na channels. Although most drugs in the class evoke QT prolongation, there is considerable variability among drugs in their proarrhythmic tendency to cause torsades de pointes despite significant QT-interval prolongation.

Class 3	AMIODARONE
Cardiac effect	Prolongs the action potential duration (and the QT interval on the ECG) by blockade of IKr. It blocks inactivated Na channels. It is also has weak adrenergic and Ca channel-blocking actions. The broad spectrum of actions may account for its relatively high efficacy and its low incidence of TdP despite significant QT-interval prolongation.
Extracardiac effects	Causes peripheral vasodilation. This action is prominent after IV administration and may be related to the action of the vehicle.

Toxicity	Symptomatic bradycardia and heart block in patients with preexisting sinus or AV node disease. The drug accumulates in many tissues, including the heart (10–50 times more so than in plasma), lung, liver, and skin, and is concentrated in tears. Dose-related pulmonary toxicity is the most important adverse effect. Even on a low dose of 200 mg/d or less, fatal pulmonary fibrosis.
Pharmacokinetic & dosage	Bioavailability (35–65%). Hepatic metabolism, and the major metabolite, desethylamiodarone, is bioactive. The half-life with a <u>rapid</u> component of 3–10 days and a <u>slower</u> component of several weeks. After discontinuation of the drug, effects are maintained for 1–3 months. Measurable tissue levels may be observed up to 1 year after discontinuation. A loading dose of 10 g is usually achieved with 0.8–1.2 g/day. The maintenance dose is 200–400 mg/day. Pharmacologic effects achieved rapidly by IV loading. Its levels are increased by drugs that inhibit this enzyme, (cimetidine, rifampin) warfarin should be reduced by one third to one half following initiation of amiodarone, and prothrombin times should be closely monitored.
Therapeutic use	Low doses (100–200 mg/d) of amiodarone maintaining normal sinus rhythm in patients with atrial fibrillation. may be used for ventricular tachycardia as adjuvant therapy to decrease the frequency of uncomfortable cardioverter-defibrillator discharges.

Class 3		DRONEDARONE
Cardiac effect		Like amiodarone, dronedarone has multichannel actions, including blocking IKr, IKs, ICa, and INa. It also has β -adrenergic-blocking action.
Toxicity		liver toxicity, including two severe cases requiring liver transplantation, has been reported.
Pharmacokinetic & dosage		Half-life of 24 hours and can be administered twice daily at a fixed dose of 400 mg. Absorption increases when taken with food. Elimination is primarily nonrenal. It inhibits tubular secretion of creatinine, resulting in a 10–20% increase in serum creatinine. It is both a substrate and an inhibitor of CY3A4 and should not be co-administered with potent inhibitors of this enzyme, such as the (azole and similar antifungal agents, and protease inhibitors).
Therapeutic use		Restores sinus rhythm of patients with an atrial fibrillation. The drug carries a “ black box ” warning against its use in acute decompensated or advanced (class IV) heart failure.

Class 3		SOTALOL
Cardiac effect		Has both β -adrenergic receptor-blocking (class 2) and action potential-prolonging (class 3) actions.
		A dose-related incidence of TdP that approaches 6% at the highest

Toxicity	recommended daily dose. Patients with overt HF may experience further depression of left ventricular function during treatment with sotalol.
Pharmacokinetic & dosage	Well absorbed orally with bioavailability of nearly 100%. It is not metabolized in the liver and is not bound to plasma proteins. Excretion is predominantly by the kidneys in the unchanged form with a half-life of approximately 12 hours.
Therapeutic use	Treatment of life-threatening ventricular arrhythmias and the maintenance of sinus rhythm in patients with atrial fibrillation. Also treatment of supraventricular and ventricular arrhythmias in the pediatric age group. Sotalol decreases the threshold for cardiac defibrillation.

Class 3		DOFETILIDE
Cardiac effect	Its action is a dose-dependent blockade of the rapid component of the delayed rectifier K current (IKr) and the blockade of IKr increases in hypokalemia.	
Pharmacokinetic & dosage	100% bioavailable. Verapamil increases peak plasma dofetilide concentration by increasing intestinal blood flow. Oral dose eliminated unchanged by the kidneys. Inhibitors of the renal cation secretion mechanism, eg, cimetidine, prolong the half-life of dofetilide. Dofetilide dosage must be based on the estimated creatinine clearance.	
Therapeutic use	approved for the maintenance of normal sinus rhythm in patients with atrial fibrillation. It is also effective in restoring normal sinus rhythm in patients with atrial fibrillation.	

Class 3		IBUTILIDE
Cardiac effect	Slows cardiac repolarization by blockade of the rapid component (IKr) of the delayed rectifier K current.	
Toxicity	The most important adverse effect is excessive QT-interval prolongation and TdP.	
Pharmacokinetic & dosage	It is rapidly cleared by hepatic metabolism and the elimination half-life averages 6 hours after an IV . The metabolites are excreted by the kidney. The IV is used for the acute conversion of atrial flutter and atrial fibrillation to normal sinus rhythm. Patients require continuous ECG monitoring for 4 hours after ibutilide infusion or until QTc returns to baseline.	

CALCIUM CHANNEL-BLOCKING DRUGS (CLASS 4)

Verapamil and diltiazem have antiarrhythmic effects. The dihydropyridines (eg, nifedipine) do not share antiarrhythmic efficacy and may precipitate arrhythmias.

Class 4	VERAPAMIL
Cardiac effect	blocks both activated and inactivated L-type Ca channels. usually slows the SA node by its direct action, but its hypotensive action may occasionally result in a small reflex increase of SA rate.
Extracardiac effects	causes peripheral vasodilation, which may be beneficial in hypertension and peripheral vasospastic disorders. Its effects on smooth muscle produce a number of extracardiac effects.
Toxicity	cardiotoxic effects are dose-related and usually avoidable. Hypotension and ventricular fibrillation can occur. Negative inotropic effects. Induce AV block when used in large doses or in patients with AV nodal disease. Adverse extracardiac effects include constipation, lassitude(<i>fatigue</i>), nervousness, and peripheral edema.
Pharmacokinetic & dosage	The half-life is 4–7 hours. It is metabolized by the liver after oral administration, bioavailability (20%). Must be administered with caution in patients with hepatic dysfunction or impaired hepatic perfusion. In adult patients without HF or SA or AV nodal disease. Dosage is an initial bolus of 5 mg administered over 2–5 minutes, followed a few minutes later by a second 5mg bolus if needed. Doses of 5–10 mg can be administered every 4–6 hours, or a constant infusion of 0.4 mcg/kg/min may be used. Effective oral dosages are higher than IV dosage because of first-pass metabolism and range from 120 mg to 640 mg daily, divided into 3 or 4 doses.
Therapeutic use	Supraventricular tachycardia. Can also reduce the ventricular rate in atrial fibrillation and flutter. Useful in ventricular arrhythmias.

DILTIAZEM

Similar in efficacy to verapamil in the management of supraventricular arrhythmias, including rate control in atrial fibrillation. An intravenous form of diltiazem is available for the latter indication and causes hypotension or bradyarrhythmias relatively infrequently.

MISCELLANEOUS ANTIARRHYTHMIC AGENTS & OTHER DRUGS THAT ACT ON CHANNELS

These include digitalis, adenosine, magnesium, and potassium. It is also becoming clear that certain nonantiarrhythmic drugs, such as drugs acting on the renin-angiotensin-aldosterone system, fish oil, and statins, can reduce recurrence of tachycardias and fibrillation in patients with coronary heart disease or congestive heart failure.

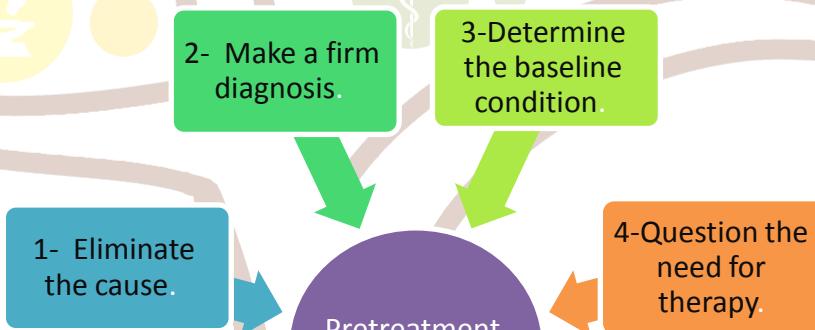
ADENOSINE	Its half-life in the blood is less than 10 seconds. MOA involves activation of an inward rectifier K ⁺ current and inhibition of Ca current. It is the drug of choice for prompt conversion of paroxysmal supraventricular tachycardia to sinus rhythm because of its high efficacy (90–95%) and very short duration of action. It is given in a bolus dose of 6 mg. The drug is <u>less effective</u> in the presence of adenosine receptor blockers such as (theophylline or caffeine), and its effects are <u>potentiated</u> by adenosine uptake inhibitors such as dipyridamole. Toxicity Flushing and shortness of breath or chest burning, Atrial fibrillation may occur. Less common toxicities include headache, hypotension, nausea, and paresthesias.
IVABRADINE	An attractive therapeutic target for heart rate control. It is a selective blocker of If, reduces heart rate without affecting myocardial contractility, ventricular repolarization, or intracardiac conduction. Antianginal and anti-ischemic effects of ivabradine have been demonstrated in patients with CAD and chronic stable angina. Effective alternative to slow the heart rate in patients with inappropriate sinus tachycardia. The drug is administered in doses of 5–10 mg as needed.
RANOLAZINE	An antianginal agent and blocks of multiple ion channels. The block of both components of the Na current is frequency- and voltage-dependent. It prevents the induction of and may terminate atrial fibrillation.
MAGNESIUM	used for patients with digitalis-induced arrhythmias who were hypomagnesemic, Mag recognized to influence Na ⁺ /K ⁺ -ATPase, Na channels, certain K channels, and Ca channels. It is also indicated in some patients with TdP even if serum magnesium is normal. 1 g given IV over 20 minutes.
POTASSIUM	increasing serum K ⁺ can be summarized as (1) a resting potential depolarizing action and (2) a membrane potential stabilizing action, the latter caused by increased potassium permeability.

The Nonpharmacologic Therapy of Cardiac Arrhythmias :

Radiofrequency catheter ablation or extreme cold, Cryoablation .

implantable cardioverter-defibrillator (ICD).

■ PRINCIPLES IN THE CLINICAL USE OF ANTIARRHYTHMIC AGENTS



actual observed effects of **hyperkalemia** include reduced action potential duration, slowed conduction,
↓ pacemaker rate,
and ↓ pacemaker arrhythmogenesis.

changes in serum potassium on cardiac action potential duration, pacemaker rate, and arrhythmias can appear

Effects of potassium

actual observed effects of **hypokalemia** include prolonged action potential duration,
↑ pacemaker rate, and
↑ pacemaker arrhythmogenesis.

In the heart, changes in serum potassium concentration have the additional effect of altering potassium conductance (increased extracellular potassium increases potassium conductance)



Chapter #15 : Diuretic Agents

CHAPTER 15

Diuretic

Introduction:

"diuretic" is an agent that increases urine volume, whereas a "natriuretic" causes an increase in renal sodium excretion and an "aquaretic" increases excretion of solute-free water. and it is Drugs that block specific transport functions of the renal tubules are valuable clinical tools in the treatment of these disorders.

Effects of Diuretic may be:

- 1-effects on specific membrane transport proteins in renal tubular epithelial cells.
- 2- osmotic effects that prevent water reabsorption
- 3- inhibit enzymes
- 4- interfere with hormone receptors in renal epithelial cells.

RENAL TUBULE TRANSPORT MECHANISMS:

Segment	Functions	Water Permeability	Primary Transporters and Drug Targets at Apical Membrane	Diuretic with Major Action
Glomerulus	Formation of glomerular filtrate	Extremely high	None	None
Proximal convoluted tubule (PCT)	Reabsorption of 65% of filtered Na^+/K^+ / Ca^{2+} , and Mg^{2+} ; 85% of NaHCO_3 , and nearly 100% of glucose and amino acids. Isosmotic reabsorption of water.	Very high	Na/H^1 (NHE3), carbonic anhydrase; $\text{Na}/\text{glucose cotransporter 2 (SGLT2)}$	Carbonic anhydrase inhibitors, Adenosine antagonists (under investigation)
Proximal tubule, straight segments	Secretion and reabsorption of organic acids and bases, including uric acid and most diuretics	Very high	Acid (eg, uric acid) and base transporters	None
Thin descending limb of Henle's loop	Passive reabsorption of water	High	Aquaporins	None
Thick ascending limb of Henle's loop (TAL)	Active reabsorption of 15–25% of filtered $\text{Na}^+/\text{K}^+/\text{Cl}^-$; secondary reabsorption of Ca^{2+} and Mg^{2+}	Very low	$\text{Na}/\text{K}/2\text{Cl}$ (NKCC2)	Loop diuretics
Distal convoluted tubule (DCT)	Active reabsorption of 4–8% of filtered Na^+ and Cl^- ; Ca^{2+} reabsorption under parathyroid hormone control	Very low	Na/Cl (NCC)	Thiazides
Cortical collecting tubule (CCT)	Na^+ reabsorption (2–5%) coupled to K^+ and H^+ secretion	Variable ²	Na channels (ENaC), K channels, ¹ H^+ transporter, ¹ aquaporins	K^+ -sparing diuretics Adenosine antagonists (under investigation)
Medullary collecting duct	Water reabsorption under vasopressin control	Variable ²	Aquaporins	Vasopressin antagonists

¹ Not a target of currently available drugs

² Controlled by vasopressin activity.

BASIC PHARMACOLOGY OF DIURETIC AGENTS:

1-CARBONIC ANHYDRASE INHIBITORS:

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
CARBONIC ANHYDRASE INHIBITORS				
<ul style="list-style-type: none"> Acetazolamide, others Brinzolamide, dorzolamide: Topical for glaucoma 	Inhibition of the enzyme prevents dehydration of H_2CO_3 and hydration of CO_2 in the proximal convoluted tubule	<ul style="list-style-type: none"> Reduce reabsorption of HCO_3^-, causing self-limited diuresis hyperchloremic metabolic acidosis reduce body pH, reduce intraocular pressure 	Glaucoma, mountain sickness, edema with alkalosis	<ul style="list-style-type: none"> Oral and topical preparations available duration of action ~8–12 h Toxicity: Metabolic acidosis, renal stones, hyperammonemia in cirrhosis

Other uses:

(قلوية البول) 1- Urinary Alkalization

2- Carbonic anhydrase inhibitors have been used as adjuvants in the treatment of epilepsy and in some forms of hypokalemic periodic paralysis.

3- useful in treating patients with CSF leakage (usually caused by tumor or head trauma, but often idiopathic (مجھول السبب)).

Toxicity:

1- Renal Potassium Wasting

2- Drowsiness and paresthesias(تمل)

Contraindications:

(فرط أمونيا الدم) contribute to the development of hyperammonemia (الاعلال الدماغي الكبدي)

In patients with cirrhosis (الاعلال الدماغي الكبدي) and hepatic encephalopathy (الاعلال الدماغي الكبدي)

2-SODIUM GLUCOSE COTRANSPORTER 2 (SGLT2)

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
SGLT2 INHIBITORS				
<ul style="list-style-type: none"> Canagliflozin Dapagliflozin: similar to canagliflozin 	Inhibition of sodium/glucose cotransporter (SGLT2) results in decreased Na ⁺ and glucose reabsorption	Inhibition of glucose reabsorption lowers serum glucose concentration, and reduced Na ⁺ reabsorption causes mild diuresis	Diabetes mellitus; approved for the treatment of hyperglycemia, not as a diuretic	Available orally. Half-life 10–12 h • not recommended in severe renal or liver disease

INHIBITORS:

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
LOOP DIURETICS				
<ul style="list-style-type: none"> Furosemide 	Inhibition of the Na/K/2Cl transporter in the ascending limb of Henle's loop	Marked increase in NaCl excretion, some K wasting, hypokalemic metabolic alkalosis, increased urine Ca and Mg	Pulmonary edema, peripheral edema, heart failure, hypertension, acute hypercalcemia, anion overdose	Oral and parenteral preparations • duration of action 2–4 h • Toxicity: Ototoxicity, hypovolemia, K wasting, hyperuricemia, hypomagnesemia
<ul style="list-style-type: none"> Bumetanide, torsemide: Sulfonamide loop agents like furosemide Ethacrynic acid: Not a sulfonamide but has typical loop activity and some uricosuric action 				

3-LOOP DIURETICS:

Other uses:

1- (زيادة البوتاسيوم في الدم) Hyperkalemia(

2- (الفشل الكلوي الحاد) Acute Renal Failure (

Loop agents can increase the rate of urine flow and enhance K⁺ excretion in acute renal failure. However, they cannot prevent or shorten the duration of renal failure. Loop agents can actually worsen cast formation in myeloma and light-chain nephropathy because increased distal Cl⁻ concentration enhances secretion of Tamm-Horsfall protein, which then aggregates with myeloma Bence Jones proteins.

Contraindications:

Furosemide, bumetanide, and torsemide may exhibit allergic cross-reactivity in patients who are sensitive to other sulfonamides, but this appears to be very rare.

4-THIAZIDES:

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
THIAZIDES <ul style="list-style-type: none"> Hydrochlorothiazide Metolazone: Popular for use with loop agents for synergistic effects Chlorothiazide: Only parenteral thiazide available (IV) Chlorthalidone: Long half-life (50–60 h) due to binding to red blood cells 	Inhibition of the Na/Cl transporter in the distal convoluted tubule	Modest increase in NaCl excretion • some K wasting • hypokalemic metabolic alkalosis • decreased urine Ca	Hypertension, mild heart failure, nephrolithiasis, nephrogenic diabetes insipidus	Oral • duration 8–12 h • Toxicity: Hypokalemic metabolic alkalosis, hyperuricemia, hyperglycemia, hyponatremia

Thiazides and related diuretics

Drug	Total Daily Oral Dose	Frequency of Daily Administration
Bendroflumethiazide	2.5–10 mg	Single dose
Chlorothiazide	0.5–2 g	Two divided doses
Chlorthalidone ¹	25–50 mg	Single dose
Hydrochlorothiazide	25–100 mg	Single dose
Hydroflumethiazide	12.5–50 mg	Two divided doses
Indapamide ¹	2.5–10 mg	Single dose
Methyclothiazide	2.5–10 mg	Single dose
Metolazone ¹	2.5–10 mg	Single dose
Polythiazide	1–4 mg	Single dose
Quinethazone ¹	25–100 mg	Single dose
Trichlormethiazide	1–4 mg	Single dose

¹Not a thiazide but a sulfonamide qualitatively similar to the thiazides.

Other Toxicity:

1- Impaired Carbohydrate Tolerance

(ارتفاع الدهون في الدم) 2- Hyperlipidemia (

Contraindications:

Excessive use of any diuretic is dangerous in patients with hepatic cirrhosis, borderline renal failure, or heart failure(قصور القلب).

5- POTASSIUM-SPARING DIURETICS:

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
POTASSIUM-SPARING DIURETICS				
• Spironolactone	Pharmacologic antagonist of aldosterone in collecting tubules • weak antagonism of androgen receptors	Reduces Na retention and K wasting in kidney • poorly understood antagonism of aldosterone in heart and vessels	Aldosteronism from any cause • hypokalemia due to other diuretics • post-myocardial infarction	Slow onset and offset of effect • duration 24–48 h • Toxicity: Hyperkalemia, gynecomastia (spironolactone, not eplerenone) • additive interaction with other K-retaining drugs
• Amiloride	Blocks epithelial sodium channels in collecting tubules	Reduces Na retention and K wasting • increases lithium clearance	Hypokalemia from other diuretics • reduces lithium-induced polyuria Liddle's syndrome	Orally active • duration 24 h • Toxicity: Hyperkalemic metabolic acidosis

*• Eplerenone: Like spironolactone, more selective for aldosterone receptor
• Triamterene: Mechanism like amiloride, much less potent, more toxic*

6-OSMOTIC DIURETICS

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
OSMOTIC DIURETICS				
• Mannitol	Physical osmotic effect on tissue water distribution because it is retained in the vascular compartment	Marked increase in urine flow, reduced brain volume, decreased intraocular pressure, initial hyponatremia, then hypernatremia	Renal failure due to increased solute load (rhabdomyolysis, chemotherapy), increased intracranial pressure, glaucoma	IV administration • Toxicity: Nausea, vomiting, headache

7-ANTIDIURETIC HORMONE ANTAGONISTS

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
VASOPRESSIN (ADH) ANTAGONISTS				
• Conivaptan	Antagonist at V _{1a} and V ₂ ADH receptors	Reduces water reabsorption, increases plasma Na concentration, vasodilation	Hyponatremia, congestive heart failure	IV only, usually continuous • Toxicity: Infusion site reactions, thirst, polyuria, hypernatremia
• Tolvaptan	Selective antagonist at V ₂ ADH receptors	Reduces water reabsorption, increases plasma Na concentration	Hyponatremia, SIADH	Oral • duration 12–24 h • Toxicity: Polyuria (frequency), thirst, hypernatremia

■ CLINICAL PHARMACOLOGY OF DIURETIC AGENTS:

1-EDEMATOUS STATES:

A common reason for diuretic use is for reduction of peripheral or pulmonary edema that has accumulated as a result of cardiac, renal, or vascular diseases that reduce blood flow to the kidney.

1-HEART FAILURE

2-KIDNEY DISEASE AND RENAL FAILURE

3- HEPATIC CIRRHOSIS (تليف الكبد)

4- IDIOPATHIC EDEMA (syndrome found most often in 20- to 30-year-old women)

2-NONEDEMATOUS STATES:

1-HYPERTENSION

2- NEPHROLITHIASIS

3-HYPERCALCEMIA (زيادة كالسيوم الدم)

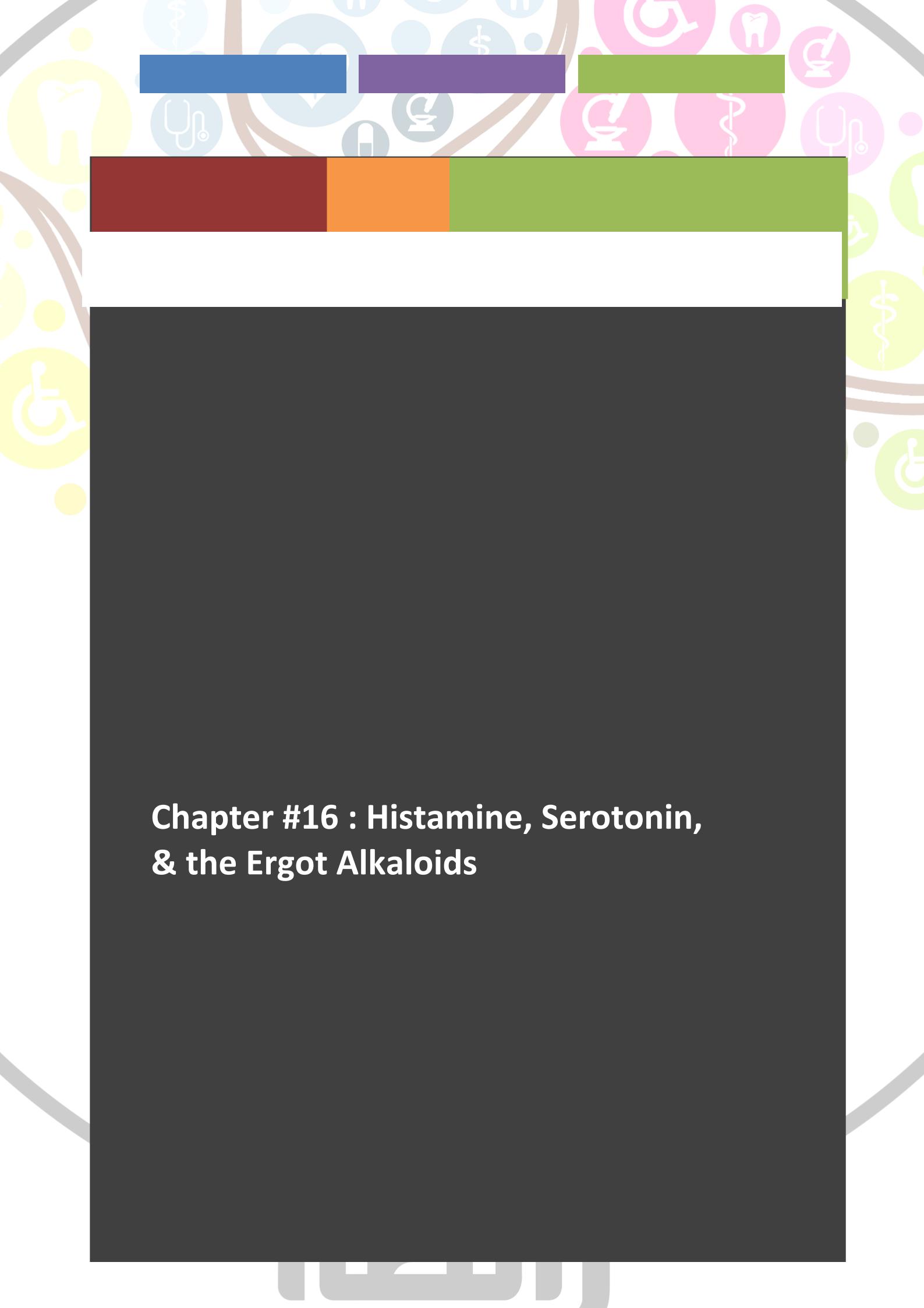
4- DIABETES INSIPIDUS (مرض السكري الكاذب)





DRUGS WITH IMPORTANT ACTIONS ON SMOOTH MUSCLE

- Histamine, Serotonin, & the Ergot Alkaloids .
- Vasoactive Peptides .
- The Eicosanoids: Prostaglandins, Thromboxanes, Leukotrienes, & Related Compounds .
- Nitric Oxide .
- Drugs Used in Asthma .



Chapter #16 : Histamine, Serotonin, & the Ergot Alkaloids

16 Histamine, Serotonin, & the ergot alkaloids

INTRODUCTION:

It has long been known that many tissues contain substances that, when released by various stimuli, cause physiologic effects such as reddening of the skin, pain or itching, and bronchospasm. Later, it was discovered that many of these substances are also present in nervous tissue and have multiple functions.

Histamine and serotonin (5-hydroxytryptamine, 5-HT) are biologically active amines that function as neurotransmitters and are found in non-neuraltissues, have complex physiologic and pathologic effects throughmultiple receptor subtypes, and are often released locally.

HISTAMINE

Pharmacodynamics

A. Mechanism of Action:

Histamine exerts its biologic actions by combining with specific receptors located on the cell membrane. Four different histamine receptors have been characterized and are designated H₁-H₄; they are described in Table 16-1.

TABLE 16–1 Histamine receptor subtypes.

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists or Inverse Agonists
H ₁	Smooth muscle, endothelium, brain	G _q , ↑ IP ₃ , DAG	Histaprodifen	Mepyramine, ¹ triprolidine, cetirizine
H ₂	Gastric mucosa, cardiac muscle, mast cells, brain	G _s , ↑ cAMP	Amthamine	Cimetidine, ¹ ranitidine, ¹ tiotidine
H ₃	Presynaptic autoreceptors and heteroreceptors: brain, myenteric plexus, other neurons	G _i , ↓ cAMP	R-α-Methylhistamine, imetit, immepip	Thioperamide, ¹ iodophenpropit, clobenpropit, ¹ tiprolisant ¹
H ₄	Eosinophils, neutrophils, CD4 T cells	G _i , ↓ cAMP	Clobenpropit, imetit, clozapine	Thioperamide ¹

¹Inverse agonist.

cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP₃, inositol trisphosphate.

B. Tissue and Organ System Effects of Histamine:

1. **Nervous system** — Histamine is a powerful stimulant of sensory nerve endings, especially those mediating pain and itching.
2. **Cardiovascular system** — In humans, injection or infusion of histamine causes a decrease in systolic and diastolic blood pressure and an increase in heart rate. The blood pressure changes are caused by the direct vasodilator action of histamine on arterioles.
3. **Bronchiolar smooth muscle** — Histamine causes bronchoconstriction mediated by H₁ receptors.
4. **Gastrointestinal tract smooth muscle** — Histamine causes contraction of intestinal smooth muscle. Large doses of histamine may cause diarrhea, partly as a result of this effect.
5. **Other smooth muscle organs** — In humans, histamine generally has insignificant effects on the smooth muscle of the eye and genitourinary tract. However, pregnant women suffering anaphylactic reactions may abort as a result of histamine-induced contractions.

6. Secretory tissue—Histamine has long been recognized as a powerful stimulant of gastric acid secretion and, to a lesser extent, of gastric pepsin and intrinsic factor production.

7. Metabolic effects—Recent studies of H₃-receptor knockout mice demonstrate that absence of this receptor results in animals with increased food intake, decreased energy expenditure, and obesity.

8. The “triple response”—Intradermal injection of histamine causes a characteristic red spot, edema, and flare response.

9. Other effects possibly mediated by histamine receptors—In addition to the local stimulation of peripheral pain nerve endings via H₃ and H₁ receptors, histamine may play a role in nociception in the central nervous system.

CLINICAL PHARMACOLOGY OF HISTAMINE

Clinical Uses

- In pulmonary function laboratories, histamine aerosol has been used as a **provocative test** of bronchial hyperreactivity.
Histamine has no other current clinical applications.

Toxicity & Contraindications

TOXICITY

Flushing, hypotension, tachycardia, headache, wheals, bronchoconstriction, and gastrointestinal upset are noted.

CONTRAINDICATIONS

Histamine should not be given to patients with asthma or to patients with active ulcer disease or gastrointestinal bleeding.

HISTAMINE ANTAGONISTS:

The effects of histamine released in the body can be reduced in several ways.

Physiologic antagonists, especially epinephrine, have smooth muscle actions opposite to those of histamine, but they act at different receptors.

Release inhibitors reduce the degranulation of mast cells that results from immunologic triggering by antigen-IgE interaction.

Histamine receptor antagonists represent a third approach to the reduction of histamine-mediated responses.

HISTAMINE RECEPTOR ANTAGONISTS

H₁-RECEPTOR ANTAGONISTS

BASIC PHARMACOLOGY OF H₁-RECEPTOR ANTAGONIST

Chemistry & Pharmacokinetics:

The H₁ antagonists are conveniently divided into first-generation and second-generation agents. These groups are distinguished by



the relatively strong sedative effects of most of the first-generation drugs. The first-generation agents are also more likely to block autonomic receptors.

-These agents are rapidly absorbed after oral administration, with peak blood concentrations occurring in 1–2 hours, the first-generation drugs enter the central nervous system readily.

-Most of the drugs have an effective duration of action of 4–6 hours following a single dose, but meclizine and several second-generation agents are longer-acting.

Clinical use of antihistaminic drugs are shown in (table 16-2)

TABLE 16-2 Some H₁ antihistaminic drugs in clinical use.

Drugs	Usual Adult Dose	Anticholinergic Activity	Comments
FIRST-GENERATION ANTIHISTAMINES			
Ethanolamines			
Carbinoxamine (Clistin)	4–8 mg	+++	Slight to moderate sedation
Dimenhydrinate (salt of diphenhydramine) (Dramamine)	50 mg	+++	Marked sedation; anti-motion sickness activity
Diphenhydramine (Benadryl, etc)	25–50 mg	+++	Marked sedation; anti-motion sickness activity
Piperazine derivatives			
Hydroxyzine (Atarax, etc)	15–100 mg	nd	Marked sedation
Cyclizine (Marezine)	25–50 mg	-	Slight sedation; anti-motion sickness activity
Meclizine (Bonine, etc)	25–50 mg	-	Slight sedation; anti-motion sickness activity
Alkylamines			
Brompheniramine (Dimetane, etc)	4–8 mg	+	Slight sedation
Chlorpheniramine (Chlor-Trimeton, etc)	4–8 mg	+	Slight sedation; common component of OTC "cold" medication
Phenothiazine derivative			
Promethazine (Phenergan, etc)	10–25 mg	+++	Marked sedation; antiemetic; α block
Miscellaneous			
Cyproheptadine (Periactin, etc)	4 mg	+	Moderate sedation; significant antiserotonin activity

SECOND-GENERATION ANTIHISTAMINES			
Piperidine			
Fexofenadine (Allegra)	60 mg	-	
Miscellaneous			
Loratadine (Claritin), desloratadine (Claritin)	10 mg (desloratadine, 5 mg)	-	Longer action; used at 5 mg dosage
Cetirizine (Zyrtec)	5–10 mg	-	

nd, no data found.

CLINICAL PHARMACOLOGY OF H1-RECEPTOR ANTAGONISTS

Clinical Uses

- First-generation H1-receptor blockers are still commonly used over-the-counter drugs.
- The prevalence of allergic conditions and the relative safety of the drugs contribute to this heavy use.

A. Allergic Reactions

The H1 antihistaminic agents are often the first drugs used to prevent or treat the symptoms of allergic reactions.

In allergic rhinitis (hay fever), the H1 antagonists are second-line drugs after glucocorticoids administered by nasal spray.

Angioedema may be precipitated by histamine release but appears to be maintained by peptide kinins that are not affected by antihistaminic agents.

The second-generation H1 antagonists are used mainly for the treatment of allergic rhinitis and chronic urticaria.

B. Motion Sickness and Vestibular Disturbances

The antihistaminic drugs with the greatest effectiveness in this application are **diphenhydramine** and **promethazine**.

Scopolamine and certain first-generation H1 antagonists are the most effective agents available for the prevention of motion sickness.

C. Nausea and Vomiting of Pregnancy

-Several H1-antagonist drugs have been studied for possible use in treating “morning sickness.”

Toxicity:

Common toxic effects: sedation and antimuscarinic action.

Less common toxic effects: excitation and convulsions in children, postural hypotension, and allergic responses.

Drug Interactions:

-Terfenadine and astemizole should be considered to be contraindicated in patients taking ketoconazole, itraconazole, or macrolides (enzyme inhibitor) and in patients with liver disease.

-Grapefruit juice also inhibits CYP3A4 and has been shown to increase blood levels of terfenadine significantly.

H2-RECEPTOR ANTAGONISTS

-The development of H2-receptor antagonists was based on the observation that H1 antagonists had no effect on histamine induced acid secretion in the stomach.

-These medications blocked acid secretion and had no H1 agonist or antagonist effects.

H3- & H4-RECEPTOR ANTAGONISTS

Tiprolisant:

-It is an inverse H3-receptor agonist, has been shown to reduce sleep cycles in mutant mice and in humans with narcolepsy.

-Increased obesity has been demonstrated in both H1- and H3-receptor.

-H4 blockers have potential in chronic inflammatory conditions such as asthma.

-No selective H4 ligand is available for use in humans.

SEROTONIN (5-HYDROXYTRYPTAMINE)

Pharmacodynamics

A. Mechanisms of Action

The actions of serotonin are mediated through a remarkably large number of cell membrane receptors. The serotonin receptors that have been characterized thus far are listed in Table 16-3 .

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
5-HT _{1A}	Raphe nuclei, hippocampus	G _i , ↓ cAMP	8-OH-DPAT, ¹ repinotan	WAY100635 ¹
5-HT _{1B}	Substantia nigra, globus pallidus, basal ganglia	G _i , ↓ cAMP	Sumatriptan, L69424 ¹	
5-HT _{1D}	Brain	G _i , ↓ cAMP	Sumatriptan, eletriptan	
5-HT _{1E}	Cortex, putamen	G _i , ↓ cAMP		
5-HT _{1F}	Cortex, hippocampus	G _i , ↓ cAMP	LY3344864 ¹	
5-HT _{1P}	Enteric nervous system	G _o , slow EPSP	5-Hydroxyindalpine	Renzapride
5-HT _{2A}	Platelets, smooth muscle, cerebral cortex	G _q , ↑ IP ₃	α-Methyl-5-HT, DOI ¹	Ketanserin
5-HT _{2B}	Stomach fundus	G _q , ↑ IP ₃	α-Methyl-5-HT, DOI ¹	RS127445 ¹
5-HT _{2C}	Choroid, hippocampus, substantia nigra	G _q , ↑ IP ₃	α-Methyl-5-HT, DOI ¹ , Iorcaserin	Mesulergine
5-HT ₃	Area postrema, sensory and enteric nerves	Receptor is a Na ⁺ /K ⁺ ion channel	2-Methyl-5-HT, m-chlorophenylbiguanide	Granisetron, ondansetron, others
5-HT ₄	CNS and myenteric neurons, smooth muscle	G _s , ↑ cAMP	BIMU8, ¹ renzapride, metoclopramide	GR113808 ¹
5-HT _{5A,B}	Brain	↓ cAMP		
5-HT _{6,7}	Brain	G _s , ↑ cAMP		Clozapine (5-HT ₇)

¹Research agents; for chemical names see Alexander SPH, Mathie A, Peters JA: Guide to receptors and channels (GRAC). Br J Pharmacol 2009;158 (Suppl 1):S12.

B. Tissue and Organ System Effects

1. **Nervous system**—Serotonin is present in a variety of sites in the brain.
2. **Respiratory system**—Serotonin has a small direct stimulant effect on bronchiolar smooth muscle in normal humans.
3. **Cardiovascular system**—Serotonin directly causes the contraction of vascular smooth muscle, mainly through 5-HT₂ receptors.
4. **Gastrointestinal tract**—Serotonin is a powerful stimulant of gastrointestinal smooth muscle, increasing tone and facilitating peristalsis.
5. **Skeletal muscle and the eye**—5-HT₂ receptors are present on skeletal muscle membranes, **serotonin syndrome** is associated with skeletal muscle contractions.

CLINICAL PHARMACOLOGY OF SEROTONIN

Serotonin Agonists

- Serotonin has no clinical applications as a drug
- agonists (**triptans**, e.g. **sumatriptan**) are used almost exclusively for migraine headache.

SEROTONIN-RECEPTOR ANTAGONISTS

-**Phenoxybenzamine** has a long-lasting blocking action at 5-HT2 receptors.

-Ketanserin is available in Europe for the treatment of hypertension and vasospastic conditions but has not been approved in the USA.

-**Cyproheptadine** has potent H 1 -receptor-blocking as well as 5-HT 2 –blocking actions.

The major clinical applications of cyproheptadine are in the treatment of the smooth muscle manifestations of carcinoid tumor and in cold-induced urticaria.

-**Ondansetron** This drug and its analogs are very important in the prevention of nausea and vomiting associated with surgery and cancer chemotherapy.

THE ERGOT ALKALOIDS

Pharmacodynamics

A. Mechanism of Action

Their effects include agonist, partial agonist, and antagonist actions at α adrenoceptors and serotonin receptors.

B. Organ System Effects on

1. Central nervous system

In spite of extensive research, no clinical value has been discovered for central nervous system effects.

2. Vascular smooth muscle

Vasospasm (This response is partially blocked by conventional α -blocking agents).

3. Uterine smooth muscle

-Combine α agonist and serotonin agonist.

-In very small doses, ergot preparations can evoke rhythmic contraction and relaxation of the uterus. At higher concentrations, these drugs induce powerful and prolonged contracture.

CLINICAL PHARMACOLOGY

OF ERGOT ALKALOIDS

Clinical Uses

A-Migraine (الصداع النصفي)

- Ergot derivatives are highly specific for migraine pain; they are not analgesic for any other condition.
- Ergotamine tartrate is available for oral, sublingual, rectal suppository, and inhaler use. It is often combined with caffeine (100 mg caffeine for each 1 mg ergotamine tartrate) to facilitate absorption of the ergot alkaloid.

C. Hyperprolactinemia (elevated serum prolactin)

(فطير برولاكتين الدم)

- Increased serum levels of the anterior pituitary hormone prolactin are associated with secreting tumors of the gland.
- Bromocriptine** is extremely effective in reducing the high levels of prolactin that result from pituitary tumors.
-Cabergoline is similar but more potent.

C. Postpartum Hemorrhage (نزيف ما بعد الولادة)

-Therefore, ergot derivatives should be used only for control of postpartum uterine bleeding and should never be given before delivery.

D. Diagnosis of Variant Angina

-Ergonovine given intravenously produces prompt vasoconstriction during coronary angiography.

E. Senile Cerebral Insufficiency (قصور دماغي)

-Dihydroergotoxine are more recently for the treatment of Alzheimer's dementia.

Toxicity :

-The most common toxic effects of the ergot derivatives are gastrointestinal disturbances, including diarrhea, nausea, and vomiting.

-There is no evidence that ordinary use of ergotamine for migraine is hazardous in pregnancy.

SUMMARY Drugs with Actions on Histamine and Serotonin Receptors; Ergot Alkaloids

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
H₁ ANTIHISTAMINES				
First generation:				
• Diphenhydramine	Competitive antagonism/inverse agonism at H ₁ receptors	Reduces or prevents histamine effects on smooth muscle, immune cells • also blocks muscarinic and α adrenoceptors • highly sedative	IgE immediate allergies, especially hay fever, urticaria • often used as a sedative, antiemetic, and anti-motion sickness drug	Oral and parenteral • duration 4–6 h • Toxicity: Sedation when used in hay fever, muscarinic blockade symptoms, orthostatic hypotension • Interactions: Additive sedation with other sedatives, including alcohol • some inhibition of CYP2D6, may prolong action of some β blockers
Second generation:				
• Cetirizine	Competitive antagonism/inverse agonism at H ₁ receptors	Reduces or prevents histamine effects on smooth muscle, immune cells	IgE immediate allergies, especially hay fever, urticaria	Oral • duration 12–24 h • Toxicity: Sedation and arrhythmias in overdose • Interactions: Minimal
• Other first-generation H ₁ blockers: Chlorpheniramine is a less sedating H ₁ blocker with fewer autonomic effects • Other second-generation H ₁ blockers: Loratadine, desloratadine, and fexofenadine are very similar to cetirizine				
H₂ ANTIHISTAMINES				
• Cimetidine (see Chapter 62)				
SEROTONIN AGONISTS				
5-HT_{1B/1D}:				
• Sumatriptan	Partial agonist at 5-HT _{1B/1D} receptors	Effects not fully understood • may reduce release of calcitonin gene-related peptide and perivascular edema in cerebral circulation	Migraine and cluster headache	Oral, nasal, parenteral • duration 2 h • Toxicity: Paresthesias, dizziness, coronary vasoconstriction • Interactions: Additive with other vasoconstrictors
• Other triptans: Similar to sumatriptan except for pharmacokinetics (2–6 h duration of action); much more expensive than generic sumatriptan				
5-HT₄:				
• Tegaserod (see Chapter 62)				
ERGOT ALKALOIDS				
Vasoselective:				
• Ergotamine	Mixed partial agonist effects at 5-HT ₂ and α adrenoceptors	Causes marked smooth muscle contraction but blocks α-agonist vasoconstriction	Migraine and cluster headache	Oral, parenteral • duration 12–24 h • Toxicity: Prolonged vasospasm causing angina, gangrene; uterine spasm
Uteroselective:				
• Ergonovine	Mixed partial agonist effects at 5-HT ₂ and α adrenoceptors	Same as ergotamine • some selectivity for uterine smooth muscle	Postpartum bleeding • migraine headache	Oral, parenteral (methylergonovine) • duration 2–4 h • Toxicity: Same as ergotamine
CNS selective:				
• Lysergic acid diethylamide	Central nervous system (CNS) 5-HT ₂ and dopamine agonist • 5-HT ₂ antagonist in periphery	Hallucinations • psychotomimetic	None • widely abused	Oral • duration several hours • Toxicity: Prolonged psychotic state, flashbacks
• Bromocriptine, pergolide: Ergot derivatives used in Parkinson's disease (see Chapter 28) and prolactinoma (see Chapter 37)				

Chapter #17 : Vasoactive Peptides

17 .Vasoactive Peptides

Introduction

Peptides are used by most tissues for cell-to-cell communication. They play important roles as transmitters in the autonomic and central nervous systems. Several peptides exert important direct effects on vascular and other smooth muscles.

This chapter focuses on the smooth muscle actions of the peptides and on drugs that alter their biosynthesis or actions.

Renin

- Renin is an aspartyl protease enzyme that specifically catalyzes the hydrolytic release angiotensin 1- from angiotensinogen.
- Renin in the circulation originates in the kidneys. Within the kidney, renin is synthesized and stored in the juxtaglomerular apparatus of the nephron.

Angiotensinogen

- Angiotensinogen is the circulating protein substrate from which renin cleaves ANG I.
- The production of angiotensinogen is increased by corticosteroids, estrogens, thyroid hormones, and ANG II.

Angiotensin I

- Although ANG I contains the peptide sequences necessary for all of the actions of the renin-angiotensin system, it has little or no biologic activity.
- Instead, it must be converted to ANG II by Angiotensin converting enzyme (Figure 17–1).

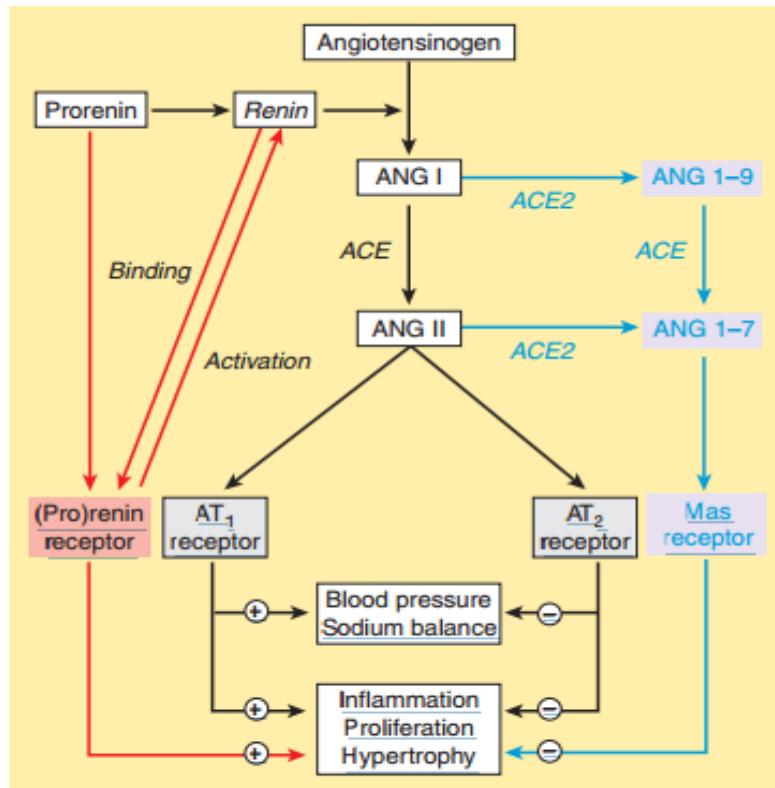


FIGURE 17-3 The renin-angiotensin system showing the established system (black) and recently discovered pathways involving the (pro)renin receptor (red) and ANG 1-7 (blue). (Redrawn, with permission.)

ANGIOTENSIN RECEPTORS & MECHANISM OF ACTION:

- There are two types of angiotensin II receptors AT1 and AT2 and all are G-protein coupled receptors. They are widely distributed in the body and responsible for angiotensin II biological effects.
- Most of the known actions of ANG II are mediated by the AT 1 receptor.
- Binding of ANG II to AT 1 receptors in vascular smooth muscle result in smooth muscle contraction.

INHIBITION OF THE RENIN-ANGIOTENSIN SYSTEM

Drugs block renin release.

- Drugs inhibit the conversion of ANG I to ANG II either by block angiotensin AT 1 receptors, or inhibit the enzymatic action of renin.

Drugs that Block Renin Release:

Drugs that interfere with the sympathetic nervous system inhibit the release of renin. Like β -adrenoceptor-blocking drugs which block the renal control of renin release.

Angiotensin-Converting Enzyme Inhibitors:

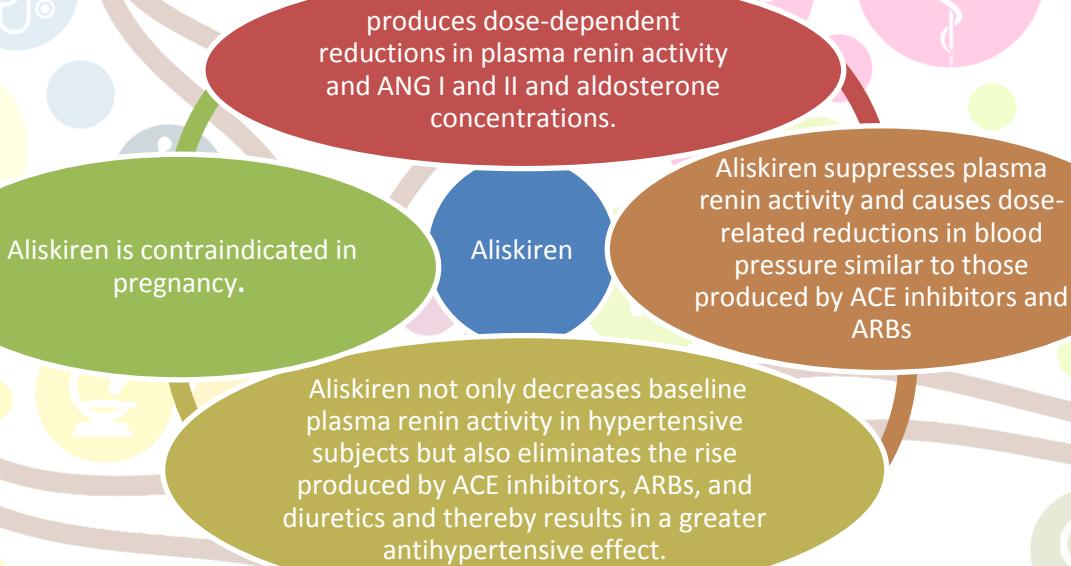
action	<ul style="list-style-type: none">•inhibit ANG II synthesis by inhibiting ACE
side effect	<ul style="list-style-type: none">•cough•angioedema (تورم تحت سطح الجلد مع أو بدون احمرار. يمكن أن يحدث في الجفون والشفاه ، اليد ، الساقين ،)
examples	<ul style="list-style-type: none">•captopril•enalopril
pregnancy	<ul style="list-style-type: none">•contraindicated in pregnancy .

Angiotensin Receptor Blockers:

action	<ul style="list-style-type: none">•block the action of ANG II•by antagonizing AT1 receptors
other actions	<ul style="list-style-type: none">•lower incidence of cough•slow the progression of diabetic nephropathy
examples	<ul style="list-style-type: none">•Losartan•Valsartan
pregnancy	<ul style="list-style-type: none">•contraindicated in pregnancy .

INHIBITION OF THE RENIN-ANGIOTENSIN SYSTEM

Renin Inhibitors:



KININS

PHYSIOLOGIC & PATHOLOGIC EFFECTS OF

Effects on the Cardiovascular System

Kinins produce marked arteriolar dilation in several vascular beds, including the heart, skeletal muscle, kidney, liver, and intestine.

Role in Inflammation & Pain

Bradykinin has long been known to produce the four classic symptoms of inflammation (redness, local heat, swelling, and pain).

Kinins are rapidly generated after tissue injury and play role in the development of these inflammatory processes.

Effects on Endocrine & Exocrine Glands

Since kinins have such marked effects on smooth muscle, they may modulate the tone of salivary and pancreatic ducts, help regulate gastrointestinal motility, and act as local modulators of blood flow.

Other effect :

it has been implicated in cancer and some central nervous system diseases.

KININ RECEPTORS & MECHANISMS OF ACTION:

- The biologic actions of kinins are mediated by specific receptors located on the membranes of the target tissues.

- Two types of kinin receptors, termed B1 and B2, have been defined both are G protein-coupled receptors.

DRUGS AFFECTING THE KALLIKREIN-KININ SYSTEM:

Competitive antagonists of both B 1 and B 2 receptors are available for research use.

Icatibant

- It is a second-generation B 2 receptor antagonist.
- Uses: Icatibant has been shown to be effective in the treatment of hereditary angioedema, an autosomal dominant disorder characterized by recurrent episodes of bradykinin-mediated angioedema of the airways, gastrointestinal tract, extremities, and genitalia.

VASOPRESSIN

- Vasopressin (arginine vasopressin, AVP; antidiuretic hormone, ADH) plays an important role in the long-term control of blood pressure through its action on the kidney to increase water reabsorption.

VASOPRESSIN RECEPTORS & ANTAGONISTS:

- Three subtypes of AVP receptors have been identified; all are G protein-coupled.
- V1a receptors mediate the vasoconstrictor action of AVP.
- V1b receptors mediate release of ACTH by pituitary corticotropes.
- V2 receptors mediate the antidiuretic action.
- AVP has proved beneficial in the treatment of vasodilatory shock states.

NATRIURETIC PEPTIDES:

- Include atrial natriuretic peptide (ANP) brain natriuretic peptide, (BNP) and C-type natriuretic peptide (CNP).
- ANP is synthesized primarily in cardiac atrial cells, but it is also synthesized in ventricular myocardium, by neurons in the central and peripheral nervous systems, and in the lungs.
- The most important stimulus to the release of ANP from the heart is atrial stretch via mechanosensitive ion channels.
- ANP release is also increased by volume expansion, changing from the standing to the supine position, and exercise. ANP release can also be increased by sympathetic stimulation via $\alpha_1 A$ adrenoceptors.
- BNP is synthesized primarily in the heart, CNP has less natriuretic and diuretic activity than ANP and BNP but is a potent vasodilator and may play a role in the regulation of peripheral resistance.

VASOPEPTIDASE INHIBITORS:

- Vasopeptidase inhibitors constitute a new class of cardiovascular drugs that inhibit two metalloprotease enzymes, and ACE. They thus simultaneously increase the levels of natriuretic peptides and decrease the formation of ANG II. As a result, they enhance vasodilation.
- Recently developed vasopeptidase inhibitors include **omapatrilat, sampatrilat, and fasidotrilat.**

ENDOTHELINS:

- they cause potent dose-dependent vasoconstriction in most vascular beds.

- Endothelins also exert direct positive inotropic and chronotropic actions on the heart and are potent coronary vasoconstrictors.
- They act on the kidneys to cause vasoconstriction and decrease glomerular filtration rate and sodium and water excretion.
 - In the respiratory system, they cause potent contraction of tracheal and bronchial smooth muscles.
 - Endothelins interact with several endocrine systems, increasing the secretion of renin, aldosterone, AVP, and ANP.

INHIBITORS OF ENDOTHELIN SYNTHESIS & ACTION:

Bosentan is a nonselective receptor blocker.

Ambrisentan, has been approved by the FDA to treat pulmonary artery hypertension.

Sitaxsentan a new dual endothelin receptor antagonist.

Macitentan, has recently been approved by the Food FDA. It appears to have increased efficacy in pulmonary hypertension compared with the other antagonists and is well tolerated with fewer side effects.

VASOACTIVE INTESTINAL PEPTIDE (VIP):

- VIP is widely distributed in the central and peripheral nervous systems, where it functions as one of the major peptide neurotransmitters.

- It is present in cholinergic presynaptic neurons in the central nervous system, and in peripheral peptidergic neurons innervating diverse tissues including the heart, lungs, gastrointestinal and urogenital tracts, skin, eyes, ovaries, and thyroid gland.
- VIP exerts significant effects on the cardiovascular system. It produces marked vasodilation in most vascular beds.
- In the heart, VIP causes coronary vasodilation and exerts positive inotropic and chronotropic effects. It may thus participate in the regulation of coronary blood flow, cardiac contraction, and heart rate.

Supstance p:

-Substance P belongs to the tachykinin family of peptides.

- Substance P is present in the central nervous system, where it is a neurotransmitter and in the gastrointestinal tract, where it may play a role as a transmitter in the enteric nervous system and as a local hormone.

-It is a potent arteriolar vasodilator, producing marked hypotension in humans and several animal species..

- The vasodilation is mediated by release of nitric oxide from the endothelium. Conversely, substance P causes contraction of venous, intestinal, and bronchial smooth muscle.

NEUROTENSIN:

- Neurotensin (NT) is a tridecapeptide that was first isolated from the central nervous system but subsequently was found to be present in the gastrointestinal tract. It is also present in the circulation and in several organs including the heart, lungs, liver, pancreas, and spleen.

- When administered centrally, NT exerts potent effects including hypothermia (انخفاض حرارة الجسم), antinociception (reducing sensitivity to painful stimuli), and modulation of dopamine and glutamate neurotransmission.
- When administered into the peripheral circulation, it causes vasodilation, hypotension, increased vascular permeability, increased secretion of several anterior pituitary hormones, hyperglycemia, inhibition of gastric acid and pepsin secretion, and inhibition of gastric motility. It also exerts effects on the immune system.

CALCITONIN GENE-RELATED PEPTIDE:

- When CGRP is injected into the central nervous system, it produces a variety of effects, including hypertension and suppression of feeding.

- When injected into the systemic circulation, the peptide causes hypotension and tachycardia.

ADRENOMEDULLIN:

- Adrenomedullin (AM) was first discovered in human adrenal medullary pheochromocytoma tissue.
- In animals, AM dilates resistance vessels in the kidney, brain, lung, hind limbs, and mesentery, resulting in a marked, long-lasting hypotension.
- The hypotension in turn causes reflex increases in heart rate and cardiac output.
- AM also acts on the kidneys to increase sodium excretion and renin release, and it exerts other endocrine effects including inhibition of aldosterone and insulin secretion. It

acts on the central nervous system to increase sympathetic outflow.

NEUROPEPTIDE Y

- NPY is one of the most abundant neuropeptides in both the central and peripheral nervous systems.
- In the sympathetic nervous system, NPY is frequently localized in noradrenergic neurons and apparently functions both as a vasoconstrictor and as a cotransmitter with norepinephrine.
- NPY produces a variety of central nervous system effects, including increased feeding, hypotension, hypothermia, respiratory depression, and activation of the hypothalamic-pituitary-adrenal axis.

UROTENSIN

- Urotensin II (UII) was originally identified in fish, but isoforms are now known to be present in the human and other mammalian species.
- Major sites of UII expression in humans include the brain, spinal cord, and kidneys.
- UII is a potent constrictor of vascular smooth muscle; its activity depends on the type of blood vessel and the species from which it was obtained. However, under

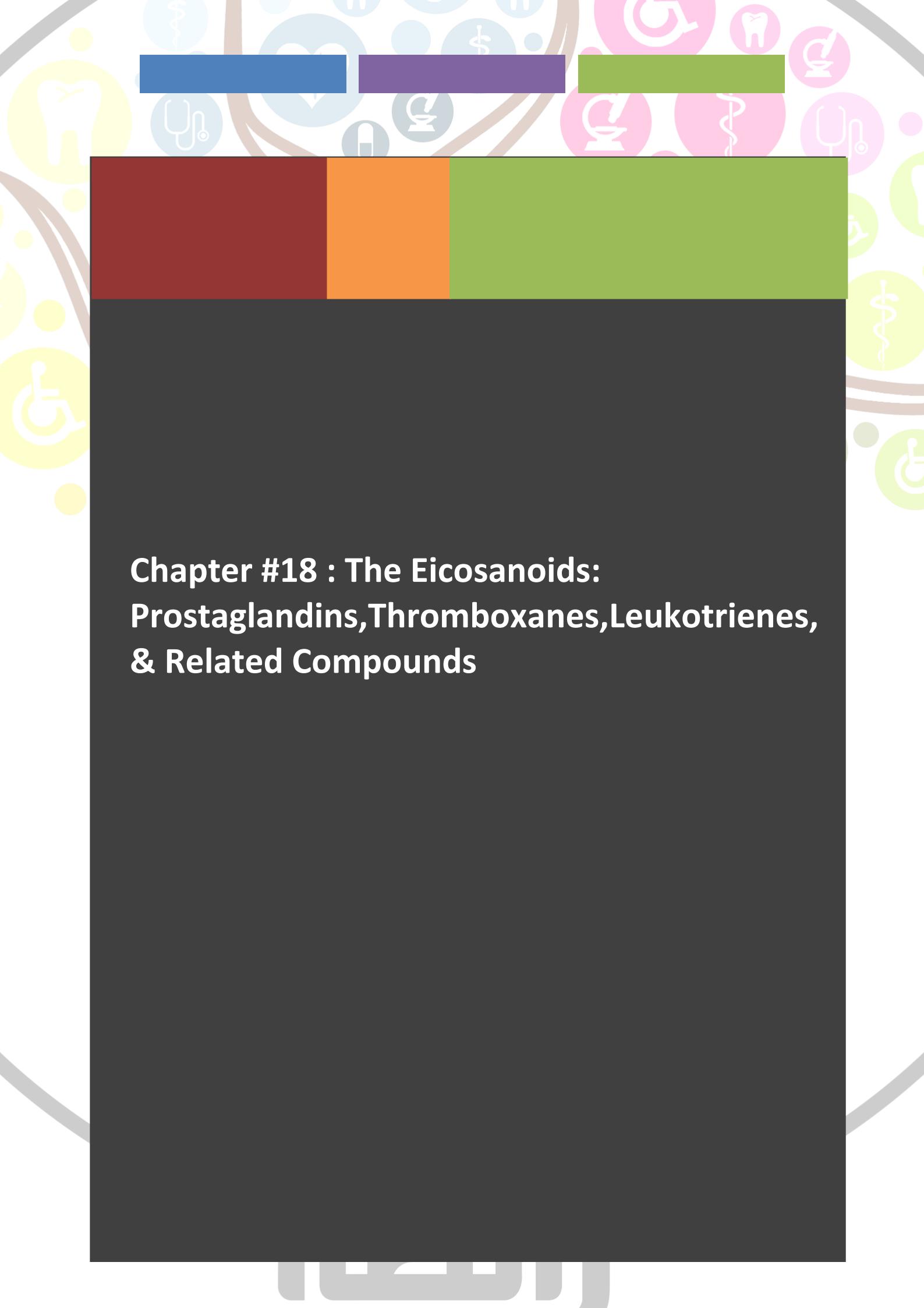
ABBREVIATIONS :

ANG I : Angiotensin 1

ANG II : Angiotensin 2

AT 1 Receptor :

eptor



Chapter #18 : The Eicosanoids: Prostaglandins,Thromboxanes,Leukotrienes, & Related Compounds

18 The Eicosanoids: Prostaglandins, Thromboxanes, Leukotrienes, & Related Compounds

Introduction :

The eicosanoids are oxygenation products of polyunsaturated long chain fatty acids. They are ubiquitous in the animal kingdom and are also found—together with their precursors—in a variety of plants. They constitute a very large family of compounds that are highly potent and display an extraordinarily wide spectrum of biologic activity. Because of their biologic activity, the eicosanoids, their specific receptor antagonists and enzyme inhibitors, and their plant and fish oil precursors have great therapeutic potential.

ARACHIDONIC ACID& OTHER POLYUNSATURATED PRECURSORS:

Arachidonic acid (AA), or 5,8,11,14-eicosatetraenoic acid, the most abundant of the eicosanoid precursors, is a 20-carbon (C20) fatty acid. Figure 18-1. Page 314.

BASIC PHARMACOLOGY OF EICOSANOIDS

MECHANISMS & EFFECTS OF EICOSANOIDS

Receptor Mechanisms

As a result of their short half-lives, the eicosanoids act mainly in an autocrine and a paracrine fashion, ie, close to the site of their synthesis, and not as circulating hormones.

TABLE 18-1 Eicosanoid receptors.¹

Receptor (human)	Endogenous Ligand	Secondary Ligands	G Protein; Second Messenger	Major Phenotype(s) in Knockout Mice
DP ₁	PGD ₂		G _q ; ↑cAMP	↓Allergic asthma
DP ₂ , CRTH2	PGD ₂	15d-PGJ ₂	G _q ; ↑Ca ²⁺ _i , ↓cAMP	↑Allergic airway inflammation ↓Cutaneous inflammation
EP ₁	PGE ₂	PGI ₂	G _q ; ↑Ca ²⁺ _i	↓Colon carcinogenesis
EP ₂	PGE ₂		G _q ; ↑cAMP	Impaired ovulation and fertilization Salt-sensitive hypertension
EP ₃ I, II, III, IV, V, VI, e, f	PGE ₂		G _q ; ↓cAMP, ↑Ca ²⁺ _i	Resistance to pyrogens
			G _q ; ↑cAMP	↓Acute cutaneous inflammation
			G _q ; ↑PLC, ↑Ca ²⁺ _i	
EP ₄	PGE ₂		G _q ; ↑cAMP	↓Bone mass/density in aged mice ↑Bowel inflammatory/immune response ↓Colon carcinogenesis Patent ductus arteriosus
FP _{A,B}	PGF _{2α}	isoPs	G _q ; ↑PLC, ↑Ca ²⁺ _i	Parturition failure
IP	PGI ₂		G _q ; ↑cAMP	↑Thrombotic response ↑Response to vascular injury ↑Atherosclerosis ↑Cardiac fibrosis
				Salt-sensitive hypertension
				↓Joint inflammation
TP _{α,β}	TXA ₂	isoPs	G _q , G _{12/13} , G ₁₆ ; ↑PLC, ↑Ca ²⁺ _i , Rho activation	↑Bleeding time
				↓Response to vascular injury
				↓Atherosclerosis
				↑Survival after cardiac allograft
BLT ₁	LTB ₄		G ₁₆ , G _q ; ↑Ca ²⁺ _i , ↓cAMP	Some suppression of inflammatory response
BLT ₂	LTB ₄	12(S)-HETE	G _q -like, G _i -like, G ₁₂ -like, ↑Ca ²⁺ _i	Not known
		12(R)-HETE		
CysLT ₁	LTD ₄	LTC ₄ /LTE ₄	G _q ; ↑PLC, ↑Ca ²⁺ _i	↓Innate and adaptive immune vascular permeability response ↑Pulmonary inflammatory and fibrotic response
CysLT ₂	LTC ₄ /LTD ₄	LTE ₄	G _q ; ↑PLC, ↑Ca ²⁺ _i	↓Pulmonary inflammatory and fibrotic response

¹Splice variants for the eicosanoid receptors are indicated where appropriate.

Ca²⁺_i, intracellular calcium; cAMP, cyclic adenosine 3'5'-monophosphate; PLC, phospholipase C; isoPs, isoprostanes; 15d-PGJ₂, 15-deoxy-Δ^{12,14}-PGJ₂.

Effects of Prostaglandins & Thromboxanes

The prostaglandins and thromboxanes have major effects on smooth muscle in the vasculature, airways, and gastrointestinal and reproductive tracts.

Other important targets include platelets and monocytes, kidneys, the central nervous system, autonomic presynaptic nerve terminals, sensory nerve endings, endocrine organs, adipose tissue, and the eye (the effects on the eye may involve smooth muscle).

A Smooth Muscle

1. Vascular

TXA₂ is a potent vasoconstrictor. It is also a smooth muscle cell mitogen and is the only eicosanoid that has convincingly been shown to have this effect.

PGF_{2α} is also a vasoconstrictor but is not a smooth muscle mitogen.

Vasodilator prostaglandins, especially PGI₂ and PGE₂, promote vasodilation by increasing cAMP and decreasing smooth muscle intracellular calcium.

PGD₂ may also function as a vasodilator, in particular as a dominant mediator of flushing induced by the lipid-lowering drug niacin.

2. Gastrointestinal tract

Longitudinal muscle is contracted by PGE₂ (via EP₃) and PGF_{2α} (via FP), whereas circular muscle is contracted strongly by PGF_{2α} and weakly by PGI₂, and is relaxed by PGE₂ (via EP₄).

3. Airways

- Respiratory smooth muscle is relaxed by PGE2 and PGI2 and contracted by PGD2, TXA2, and PGF2 α .
- Bronchospasm occurs in about 10% of people taking NSAIDs, possibly because of a shift in arachidonate metabolism from COX metabolism to leukotriene formation.

B. Platelets

Platelet aggregation is markedly affected by eicosanoids. Low concentrations of PGE2 enhance (via EP3 receptors), whereas higher concentrations inhibit (via IP receptors), platelet aggregation. Both PGD2 and PGI2 also inhibit aggregation .

A. Kidney

The major renal eicosanoid products are PGE2 and PGI2, followed by PGF2 α and TXA2.

Prostaglandins play important roles in maintaining blood pressure and regulating renal function, particularly in marginally functioning kidneys and volume-contracted states.

D. Reproductive Organs

1. Female reproductive organs

Uterine muscle is contracted by PGF_{2α}, TXA₂, and low concentrations of PGE₂.

PGI₂ and high concentrations of PGE₂ cause relaxation. PGF_{2α}, together with oxytocin, is essential for the onset of parturition

2. male reproductive organs

- Men with a low seminal fluid concentration of prostaglandins are relatively infertile.
- Smooth muscle-relaxing prostaglandins such as PGE₁ enhance penile erection by relaxing the smooth muscle of the corpora cavernosa.

E. Central and Peripheral Nervous Systems

1. Fever

PGE₂ increases body temperature, predominantly via EP₃, although EP₁ also plays a role. Endogenous pyrogens release interleukin-1, which in turn promotes the synthesis and release of PGE₂. This synthesis is blocked by aspirin, other antipyretic NSAIDs, and acetaminophen.

2. Sleep

- PGD₂ induces natural sleep (as determined by electroencephalographic analysis) via activation of DP₁ receptors and secondary release of adenosine.
- PGE₂ infusion into the posterior hypothalamus causes wakefulness.

3. Neurotransmission

PGE compounds inhibit the release of norepinephrine from postganglionic sympathetic nerve endings.

F. Inflammation and Immunity

PGE₂ and PGI₂ are the predominant prostanoids associated with inflammation. Both markedly enhance edema formation and leukocyte infiltration

PGE₂ and TXA₂ may play a role in T-lymphocyte development by regulating apoptosis of immature thymocytes.

PGI₂ contributes to immune suppression by interfering with dendritic cell maturation and antigen uptake for presentation to immune cells.

PGD₂, a major product of mast cells, is a potent chemoattractant for eosinophils in which it also induces degranulation and leukotriene biosynthesis.

PGD₂ also induces chemotaxis and migration of Th2 lymphocytes, mainly via activation of DP₂.

G. Bone Metabolism

The major effect of prostaglandins (especially PGE₂, acting on EP₄) in vivo is to increase bone turnover, ie, stimulation of bone resorption and formation.

H. Cancer

PGE₂, which is considered the principal oncogenic prostanoid, facilitates tumor initiation, progression, and metastasis through multiple biologic effects, increasing proliferation and

angiogenesis, inhibiting apoptosis, augmenting cellular invasiveness, and modulating immunosuppression.

Effects of Lipoxygenase & Cytochrome P450-Derived Metabolites: Blood Cells and Inflammation

- LTB₄, acting at the BLT1 receptor, is a potent chemoattractant for T lymphocytes, neutrophils, eosinophils, monocytes, and possibly mast cells.
- LTB₄ also contributes to activation of neutrophils and eosinophils, and to monocyte-endothelial adhesion.

Gastrointestinal tract

Human colonic epithelial cells synthesize LTB₄, a chemoattractant for neutrophils.
The colonic mucosa of patients with inflammatory bowel disease contains substantially increased amounts of LTB₄.

It appears that activation of the BLT2 receptor, possibly by agonists other than LTB₄, is protective in colonic epithelium and contributes to maintenance of barrier function.

Airways

- The leukotrienes, particularly LTC4 and LTD4, are potent bronchoconstrictors and cause increased microvascular permeability, plasma exudation, and mucus secretion in the airways.

INHIBITION OF EICOSANOID SYNTHESIS:

Corticosteroids

- Block all the known pathways of eicosanoid synthesis, perhaps in part by stimulating the synthesis of several inhibitory proteins collectively called annexins or lipocortins.
- They inhibit phospholipase A2 activity, probably by interfering with phospholipid binding, thus preventing the release of arachidonic acid.

NSAIDs (eg, indomethacin, ibuprofen)

- Block both prostaglandin and thromboxane formation by reversibly inhibiting COX activity
- Aspirin is an irreversible COX inhibitor
- NSAIDs usually do not inhibit lipoxygenase activity at concentrations attained clinically that inhibit COX activity.

CLINICAL PHARMACOLOGY OF EICOSANOIDS:

- Numerous studies have shown that PGE₂, PGF_{2α}, and their analogs effectively initiate and stimulate labor.
- There appears to be no difference in the efficacy of PGE₂ and PGF_{2α} when they are administered intravenously; however, the most common usage is local application of PGE₂ analogs (dinoprostone) to promote labor through ripening of the cervix.
- These agents and oxytocin have similar success rates and comparable induction-to-delivery intervals.
- PGE₂ must be infused at a rate about 20 times faster than that used for induction of labor to decrease blood pressure and increase heart rate.

Female Reproductive System:

A. Abortion

PGE₂ and PGF_{2α} have potent oxytocic actions. The ability of the E and F prostaglandins and their analogs to terminate pregnancy at any stage by promoting uterine contractions has been adapted to common clinical use.

Dinoprostone, a synthetic preparation of PGE₂, is administered vaginally for oxytocic use.

Antiprogestins (eg, mifepristone) have been combined with an oral oxytocic synthetic analog of PGE₁ (misoprostol) to produce early abortion.

b. Facilitation of Labor

The most common usage is local application of PGE₂ analogs (dinoprostone) to promote labor through ripening of the cervix.

The adverse effects of the prostaglandins are moderate, with a slightly higher incidence of nausea, vomiting, and diarrhea than that produced by oxytocin.

B. Dysmenorrhea

Primary dysmenorrhea is attributable to increased endometrial synthesis of PGE₂ and PGF_{2α} during menstruation, with contractions of the uterus that lead to ischemic pain.

-NSAIDs successfully inhibit the formation of these prostaglandins and so relieve dysmenorrhea in 75–85% of

cases. Some of these drugs are available over the counter. Aspirin is also effective in dysmenorrheal.

Male Reproductive System:

- Intracavernosal injection or transurethral suppository therapy with alprostadil (PGE1) is a second-line treatment for erectile dysfunction.
- Penile pain is a frequent side effect, which may be related to the analgesic effects of PGE derivatives; however, only a few patients discontinue the use because of pain.
- When given by injection, alprostadil may be used as monotherapy or in combination with either papaverine or phentolamine.

Renal System

- Increased biosynthesis of prostaglandins has been associated with one form of Bartter's syndrome. This is a rare disease characterized by low-to-normal blood pressure, decreased sensitivity to angiotensin, hyperreninemia, hyperaldosteronism, and excessive loss of K+.
- There also is an increased excretion of prostaglandins, especially PGE metabolites, in the urine.
- After long-term administration of COX inhibitors, sensitivity to angiotensin, plasma renin values, and the concentration of aldosterone in plasma return to normal.

Cardiovascular System:

A. Pulmonary Hypertension

- PGI₂ lowers peripheral, pulmonary, and coronary vascular resistance. It has been used to treat primary pulmonary hypertension as well as secondary pulmonary hypertension, which sometimes occurs after mitral valve surgery.

(epoprostenol)
approved for treatment of primary pulmonary hypertension.

Iloprost is usually inhaled six to nine times per day

Treprostinil may be delivered by subcutaneous or intravenous infusion or by inhalation.

Patent Ductus Arteriosus

Patency of the fetal ductus arteriosus depends on COX-2-derived PGE2 acting on the EP4 receptor. At birth, reduced PGE2 levels, a consequence of increased PGE2 metabolism, allow ductus arteriosus closure. In certain types of congenital heart disease (eg, transposition of the great arteries, pulmonary atresia, pulmonary artery stenosis), it is important to maintain the patency of the neonate's ductus arteriosus until corrective surgery can be carried out. This can be achieved with alprostadil (PGE1). Like PGE2, PGE1 is a vasodilator and an inhibitor of platelet aggregation, and it contracts uterine and intestinal smooth muscle.

Blood

- Chronic administration of low-dose aspirin (81 mg/d) selectively and irreversibly inhibits platelet COX-1, and its dominant product TXA2.
- nonselective NSAIDs (eg, ibuprofen) do not reproduce this effect, although naproxen, because of its variably prolonged half life, may provide antiplatelet benefit in some individuals.
- selective COX-2 inhibitors do not alter platelet TXA2 biosynthesis and are not platelet inhibitors.

Respiratory System:

- PGE2 is a powerful bronchodilator when given in aerosol form.
- PGF2 α and TXA2 are both strong bronchoconstrictors and were once thought to be primary mediators in asthma.
- cysteinyl leukotrienes—LTC4, LTD4, and LTE4—probably dominate during asthmatic constriction of the airways.
- leukotriene-receptor inhibitors (**eg, zafirlukast, montelukast**) are effective in asthma. A lipoxygenase inhibitor (**zileuton**) has also been used in asthma but is not as popular as the receptor inhibitors.

Gastrointestinal system:

- **Misoprostol** is an orally active synthetic analog of PGE1. The FDA-approved indication is for prevention of NSAID-induced peptic ulcers.
 - **Misoprostol** use is low, probably because of its adverse effects including abdominal discomfort and occasional diarrhea.

Glaucoma: Latanoprost, bimatoprost, travoprost, and unoprostone. These drugs act at the FP receptor and are administered as drops into the conjunctival sac once or twice

daily. Adverse effects include irreversible brown

pigmentation of the iris and eyelashes, drying of the eyes

DIETARY MANIPULATION OF ARACHIDONIC ACID METABOLISM:

Dietary intake of linoleic and α -linolenic acids, which are, respectively, omega-6 and omega-3 essential fatty acids, can

Chapter 19

Nitric Oxide

Nitric Oxide (NO) is a gaseous and highly reactive signaling molecule. NO should not be confused with nitrous oxide (N₂O), an anesthetic gas; nor with nitrogen dioxide (NO₂), a toxic pulmonary irritant gas.

Signaling Mechanisms.

NO mediates its effects by covalent modification of proteins.

There are three major targets of NO :

1. Metalloproteins—NO interacts with metals, especially iron in heme. Interaction of NO with other metalloproteins mediates some of the cytotoxic effects, For example, NO inhibits metalloproteins involved in cellular respiration.
2. Thiols—NO reacts with thiols (compounds containing the –SH group) to form nitrosothiols. is highly specific and can alter the function, stability, or localization of target proteins.
3. Tyrosinenitration

NO reacts very efficiently with superoxide (which is synthesized by Several cellular enzymes)to form peroxynitrite (ONOO⁻), a highly reactive oxidant that leads to DNA damage, nitration of tyrosine, and oxidation of cysteine.

Nitric Oxide Donors.

1. Organic nitrates—Nitroglycerin, which dilates veins and coronary arteries, is metabolized to NO.
2. Organic nitrites—such as the antianginal inhalant amyl nitrite.

NITRIC OXIDE IN DISEASE VASCULAR EFFECTS.

act by increasing intracellular calcium levels in endothelial cells, leading to the synthesis of NO.

NO diffuses to vascular smooth muscle leading to vasorelaxation.

NO also has antithrombotic effects.

NO may have an additional inhibitory effect on blood coagulation by enhancing fibrinolysis via an effect on plasminogen.

SEPTIC SHOCK.

NO plays a protective role in the body via immune cell function.

When challenged with foreign antigens.

NO stimulates synthesis of inflammatory prostaglandins by activating cyclooxygenase isoenzyme 2 (COX-2). Prolonged or excessive NO production may exacerbate tissue injury. Thus, inhibition of the NO pathway may have a beneficial effect on a variety of inflammatory diseases.

THE CENTRAL NERVOUS SYSTEM.

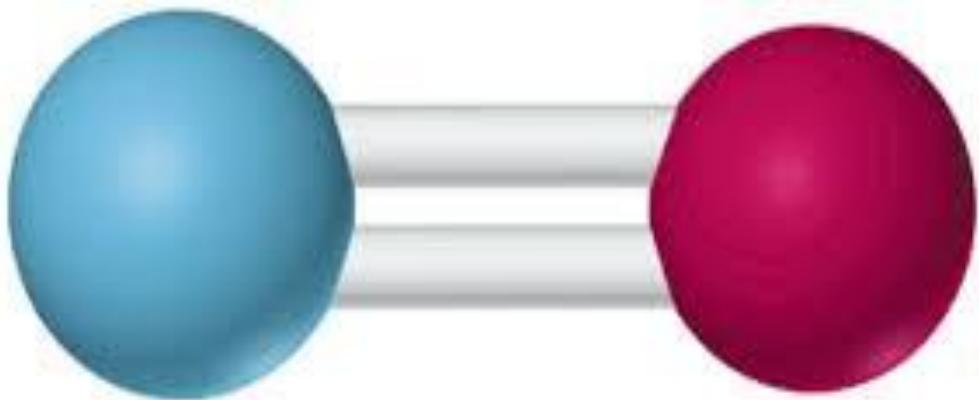
NO has an important role in the central nervous system as a neurotransmitter. Unlike classic transmitters which are stored in synaptic vesicles, NO is not stored, but rather is synthesized on demand and immediately diffuses to neighboring cells. Excessive NO synthesis is linked to excitotoxic neuronal death in several neurologic diseases.

THE PERIPHERAL NERVOUS SYSTEM.

NO promotes relaxation of the smooth muscle in the corpora cavernosa—the initiating factor in penile erection—and inhibitors of NOS have been shown to prevent erection.

RESPIRATORY DISORDERS.

NO is administered by inhalation to newborns with hypoxic respiratory failure associated with pulmonary hypertension. Inhaled NO has also been shown to improve cardiopulmonary function in adult patients with pulmonary artery hypertension. NO inhalation does not typically exert pronounced effects on the systemic circulation.



Nitric oxide

Chapter #20 : Drugs Used in Asthma

20. Drugs Used in Asthma

Clinical Features of Asthma

- shortness of breath •
- chest tightness •
- wheezing •
- coughing •

Physiologic Features of Asthma

- Reversible narrowing of the bronchial airways. •
- Increase in bronchial responsiveness to •
- inhaled stimuli

Pathologic Features of Asthma

- lymphocytic and eosinophilic inflammation of the bronchial mucosa. .

The spectrum of asthma's severity is wide, and patients are classified as having "mild intermittent," "mild persistent," "moderate persistent," and "severe persistent," either based on the frequency and severity of symptoms.

PATHOGENESIS OF ASTHMA

Classic allergic asthma is regarded as mediated by immune globulin (IgE), produced in response to exposure to foreign proteins like those from house dust mite and pollens. These qualify as allergens on the basis of their induction of IgE antibody production in people exposed to them.

Once produced, IgE binds to high-affinity receptors (Fc ϵ R-1) on mast cells in the airway mucosa so that

re-exposure to the allergen triggers the release of mediators stored in the mast cells' granules. Most asthma attacks are not triggered by inhalation of allergens, but instead by viral respiratory infections. Some adults with asthma can provoke bronchospasm by nonallergenic stimuli such as exercise, cold air, And cigarette smoke. This tendency to develop bronchospasm on encountering nonallergenic stimuli is described as "bronchial hyper-reactivity."

BASIC PHARMACOLOGY OF AGENTS USED IN THE TREATMENT OF ASTHMA :

SYMPATHOMIMETIC AGENTS

used as "relievers" or bronchodilators. Adrenoceptor agonists are mainstays in the treatment of asthma. Their binding to β receptors—on airway smooth muscle

cells—stimulates adenylyl cyclase and increases the formation

of intracellular cAMP, thereby relaxing airway smooth muscle and inhibiting release of bronchoconstricting mediators from mast cells.

Adverse effects, especially of adrenoceptor agonists that activate β_1 as well as β_2 receptors, include tachycardia, skeletal muscle tremor, and decreases in serum potassium levels. Because epinephrine and isoproterenol increase the rate and force

of cardiac contraction (mediated mainly by β_1 receptors), they are reserved for special situations. In general, adrenoceptor agonists are best delivered by inhalation. This results in the greatest local effect on airway smooth muscle

with the least systemic toxicity.

Epinephrine

rapidly acting bronchodilator when injected subcutaneously or inhaled. Maximal bronchodilation is achieved 15 minutes after inhalation and lasts 60–90 minutes. Because epinephrine stimulates α_1 and β_1 as well as β_2 receptors, tachycardia, arrhythmias, and worsening of angina pectoris, because of this troublesome adverse effects its use reserved for special situations.

Ephedrine

ephedrine is now used infrequently in treating asthma. Compared with epinephrine, ephedrine has a longer duration, oral activity, more pronounced central effects, and much lower potency. Because of the development of more efficacious and β_2 -selective agonists.

Isoproterenol

is a potent nonselective β_1 and β_2 bronchodilator. cause maximal bronchodilation within 5 minutes and has a 60– to 90-minutes duration of action.

Beta₂-Selective Drugs

Are now the most widely used sympathomimetics for the treatment of the bronchoconstriction of asthma. They have a longer duration of action than epinephrine or isoproterenol. These agents cause bronchodilation equivalent to that produced by

isoproterenol. Bronchodilation is maximal within 15 minutes and persists for 3–4 hours.

Albuterol and **terbutaline** are available in oral form. Their principal adverse effects are skeletal muscle tremor, nervousness, and occasional weakness. This route of administration presents no advantage over inhaled treatment and is rarely prescribed.

A newer generation of long-acting β_2 -selective agonists includes **salmeterol** (a partial agonist) and **formoterol** (a full agonist). These long-acting β agonists (LABA) are potent selective β_2 agonists that achieve their long duration of action (12 hours or more) as a result of high lipid solubility. Because they have no anti-inflammatory action, they should not be used as monotherapy for asthma.

Ultralong-acting β agonists, **indacaterol**, **olodaterol**, and **vilanterol**, need to be taken only once a day but are currently FDA-approved only for the treatment of chronic obstructive pulmonary disease (COPD).

METHYLXANTHINE DRUGS:

The three important methylxanthines are theophylline, theobromine, and caffeine. The use of theophylline has waned with demonstration of other drugs with greater efficacy, also because of theophylline's toxicities.

Mechanism of Action:

Several mechanisms have been proposed for the actions of methylxanthines.

At high concentrations, they can be shown *in vitro* to inhibit several members of the phosphodiesterase (PDE) enzyme family thereby increasing concentrations of intracellular cAMP. Of the various isoforms of PDE identified, inhibition of PDE3 involved in relaxing airway smooth muscle and inhibition of PDE4 in inhibiting release of cytokines and chemokines, which results in a decrease in immune cell migration and activation. This anti-inflammatory effect is achieved at doses lower than those necessary for bronchodilation.

*Cyclic AMP regulates many cellular functions including, but not limited to, stimulation of cardiac function, relaxation of smooth muscle, and reduction in the immune and inflammatory activity of specific cells.

Another proposed mechanism is inhibition of cell surface receptors for adenosine. Because adenosine has been shown to provoke contraction of isolated airway smooth muscle and histamine release from airway mast cells.

A third mechanism of action may underlie theophylline's efficacy: enhancement of histone deacetylation. Acetylation of core histones is necessary for activation of inflammatory gene transcription. Corticosteroids act, at least in part, by recruiting histone deacetylases to the site of inflammatory gene transcription, this action enhanced by low-dose theophylline.

Pharmacodynamics

Theophylline is most selective in its smooth muscle effects, whereas caffeine has the most marked central nervous system effects.

A. Central Nervous System Effects	All methylxanthines—but especially caffeine—cause mild cortical arousal with increased alertness and deferral of fatigue. The large dose necessary for effective bronchodilation cause nervousness and tremor.
B. Cardiovascular Effects	Methylxanthines have positive chronotropic and inotropic effects on the heart.
C. Effects on Gastrointestinal Tract	Methylxanthines stimulate secretion of both gastric acid and digestive enzymes.
D. Effects on Kidney	The methylxanthines—especially theophylline—are weak diuretics. The diuresis is not of sufficient magnitude to be therapeutically useful.
E. Effects on Smooth Muscle	The bronchodilation is the major therapeutic action in asthma. In addition these agents—in sufficient concentration— inhibit antigen induced release of histamine from lung tissue.
F. Effects on Skeletal Muscle	They improve contractility of skeletal muscle and reverse fatigue of the diaphragm in patients with COPD.

Clinical uses :

theophylline is the most effective bronchodilator. Theophylline improves long-term control of asthma when taken as the sole maintenance treatment or

when added to inhaled corticosteroids. It is inexpensive, and it can be taken orally as sustained-release preparations are available and can produce therapeutic blood levels for 12 hours or more. It is metabolized by the liver, so usual doses may lead to toxic concentrations in patients with liver disease. Its use, requires occasional measurement of plasma levels; it often causes unpleasant minor side effects (especially insomnia); and accidental or intentional overdose can result in severe toxicity or death. Typically, theophylline is rarely used as monotherapy and, when prescribed, is most commonly used as add-on therapy when treatment with other agents.

ANTIMUSCARINIC AGENTS

Observation of the use of leaves from *Datura stramonium* for asthma treatment in India led to the discovery of atropine, a potent competitive inhibitor of acetylcholine at postganglionic muscarinic receptors.

Mechanism of Action

Muscarinic antagonists competitively inhibit the action of acetylcholine at muscarinic receptors. In the airways, acetylcholine is released and muscarinic antagonists (ANTIMUSCARINIC AGENTS) block the contraction of airway smooth muscle and the increase in secretion of mucus.

Clinical Uses

Antimuscarinic agents are effective bronchodilators. They especially useful for patients intolerant of inhaled β -agonist agents.

<i>Atropine</i>	<i>Ipratropium bromide</i>	<i>Tiotropium and Aclidinium</i>
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The bronchodilation achievable with *Atropine*, is limited by absorption into the circulation and across the blood-brain barrier

- Greater bronchodilation, with less toxicity from systemic absorption, is achieved by treatment with a selective quaternary ammonium derivative of *atropine*
- Poorly absorbed into the circulation and does not readily enter the central nervous system.
- Ipratropium appears to be as effective as albuterol in patients with COPD who have at least partially reversible obstruction.

- Are approved for maintenance therapy of COPD.
- These drugs bind to M₁, M₂, and M₃ receptors with equal affinity, but dissociate most rapidly from M₂ receptors. This means that they do not inhibit the M₂-receptor-mediated inhibition of acetylcholine release and thus benefit from a degree of receptor selectivity.
- They are taken by inhalation. A single dose of 18 mcg of *tiotropium* has a 24-hour duration of action, whereas inhalation of 400 mcg of *aclidinium* has a 12-hour duration of action and is thus taken twice daily.
- Daily inhalation of tiotropium has been shown to improve functional capacity of patients with COPD,

and reduce the frequency of exacerbations of their condition.

CORTICOSTEROIDS:

Mechanism of Action:

Corticosteroids (specifically, glucocorticoids) have long been used in the treatment of asthma and are presumed to act by their broad anti-inflammatory efficacy, mediated in part by inhibition of production of inflammatory cytokines. They do not

relax airway smooth muscle directly but reduce bronchial hyperreactivity and reduce the frequency of asthma exacerbations. Their effect on airway obstruction is due in part to their contraction of engorged vessels in the bronchial mucosa and their potentiation of the effects of β -receptor agonists, but their most important action is inhibition of the infiltration of asthmatic airways by lymphocytes, eosinophils, and mast cells.

Clinical Uses

Inhaled corticosteroids are not curative. Because of severe adverse effects when given chronically, oral and parenteral corticosteroids are reserved for patients who require urgent treatment. Inhalational treatment is the most effective way to avoid the systemic adverse effects. A special problem

caused by inhaled topical corticosteroids is the occurrence of oropharyngeal candidiasis. Ciclesonide, the most recently approved it is a prodrug activated by bronchial esterases, and though no more effective in the treatment of asthma, has been associated with less frequent candidiasis. Although a majority of the inhaled dose is deposited in the oropharynx and swallowed, they are subject to first-pass metabolism in the liver. Chronic use may increase the risks of osteoporosis and cataracts.

CROMOLYN & NEDOCROMIL

Cromolyn sodium and nedocromil Sodium were once widely used for asthma management, especially in children, but have now been supplanted so completely by other therapies. Both are poorly absorbed from the gastrointestinal tract, and must be inhaled.

Mechanism of Action

They are thought to alter the function of delayed chloride channels in cell membranes, inhibiting cell activation. This action on airway nerves is thought to mediate inhibition of cough; on mast cells and eosinophils, the drugs inhibit the early and the late response to antigen challenge.

Clinical Uses

These drugs have no effect on airway smooth muscle tone and are ineffective in reversing asthmatic bronchospasm but effectively blocks the bronchoconstriction caused by allergen inhalation, exercise. This acute protective effect makes cromolyn useful for administration shortly before exercise or before unavoidable exposure to an

allergen. When taken regularly both agents significantly reduce symptomatic severity and the need for bronchodilator medications particularly in young patients with allergic asthma. Also useful in reducing symptoms of allergic rhinoconjunctivitis. Because the drugs are so poorly absorbed, adverse effects of cromolyn and nedocromil are minor and are localized to the sites of deposition.

LEUKOTRIENE PATHWAY INHIBITORS

Leukotriene involve in many inflammatory diseases. Leukotrienes result from the action of 5-lipoxygenase on arachidonic acid and are synthesized by a variety of inflammatory cells in the airways. LTC4 and LTD4 exert many effects known to occur in asthma, including bronchoconstriction, increased bronchial reactivity, mucosal edema, and mucus hypersecretion. Two approaches to interrupting the leukotriene pathway:

- 1- inhibition of 5-lipoxygenase, thereby preventing leukotriene synthesis such as **zileuton**
- 2- inhibition of the binding of LTD4 to its receptor on target tissues, thereby preventing its action such as **zafirlukast** and **montelukast**.

Their principal advantage is that they are taken orally; some patients—especially children—comply poorly with inhaled therapies. Of these agents, montelukast is by far the most prescribed, probably because it can be taken without regard to meals, because of the convenience of once-daily treatment. Zileuton is

the least prescribed because of reports of liver toxicity.

OTHER DRUGS IN THE TREATMENT OF ASTHMA

Anti-IgE Monoclonal Antibodies

The monoclonal antibody-developed **omalizumab**

Mechanism of action	Its specific target is the portion of IgE that binds to its receptors on mast cells and other inflammatory cells. It inhibits the binding of IgE but does not activate IgE already bound to mast cells and thus does not provoke mast cell degranulation. It lowers free plasma IgE to undetectable levels and significantly reduces the magnitude of both early and late bronchospastic responses to antigen challenge.
Clinical use	Its use is restricted to patients with evidence of allergic

	sensitization. Most important clinical effect is reduction in the frequency and severity of asthma exacerbations.
Dose	the dose Administered is adjusted for total IgE level and body weight. Given by subcutaneous injection every 2–4 weeks

CLINICAL PHARMACOLOGY OF DRUGS USED IN THE TREATMENT OF ASTHMA

BRONCHODILATORS	Patients with only occasional symptoms of asthma require no more than an inhaled bronchodilator taken on an as-needed basis.
MUSCARINIC ANTAGONISTS	*They are used largely as alternative therapies for patients intolerant of β_2 -adrenoceptor agonists.*As a treatment for COPD, these agents improve functional capacity

CORTICOSTEROIDS	Used for patients with severe asthmatic symptoms or severe airflow obstruction. "initial treatment with a combination of inhaled and oral corticosteroid is appropriate. Once clinical improvement is noted, usually after 7–10 days, the inhaled corticosteroid should be continued, but the oral dose should be tapered to the minimum necessary to control symptoms."
LEUKOTRIENE ANTAGONISTS; CROMOLYN & NEDOCROMIL	*A leukotriene antagonist taken as an oral tablet is an alternative to inhaled corticosteroid treatment in patients with symptoms occurring more than twice a week or those who are awakened from sleep by asthma more than twice a month. *Are commonly used in the treatment of children.
ANTI-IGE MONOCLONAL ANTIBODY	*It reserved for patients with chronic severe asthma inadequately controlled by high-dose inhaled corticosteroid plus long acting β -agonist combination treatment.

*Reserved also for patients with demonstrated IgE-mediated sensitivity. an IgE level within a range that can be reduced sufficiently by twice-weekly subcutaneous injection.

PROSPECTS FOR PREVENTION

The high prevalence of asthma calls for a strategy for primary prevention. Strict antigen avoidance during infancy has now been shown to be ineffective. In fact, growing up from birth on a farm with domestic animals appears to protect against developing asthma. The best hope seems to lie in understanding the mechanisms by which microbial exposures during infancy foster development of a balanced immune response and then mimicking the effects.

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD is characterized by airflow limitation that is not fully reversible with bronchodilator treatment. Although asthma and COPD are both characterized by airway inflammation, reduction in maximum expiratory flow, and episodic exacerbations of airflow obstruction. They differ in many important respects, the most important among them are:

- *differences in the populations affected
- *characteristics of airway inflammation
- *reversibility of airflow obstruction
- *responsiveness to corticosteroid treatment

*COPD occurs in older patients, is associated with neutrophilic rather than eosinophilic inflammation, is poorly responsive even to high-dose inhaled corticosteroid therapy, and is associated with progressive, inexorable loss of pulmonary function over time.

Despite these differences, the approaches to treatment are similar, although the benefits expected (and achieved) are less for COPD than for asthma.

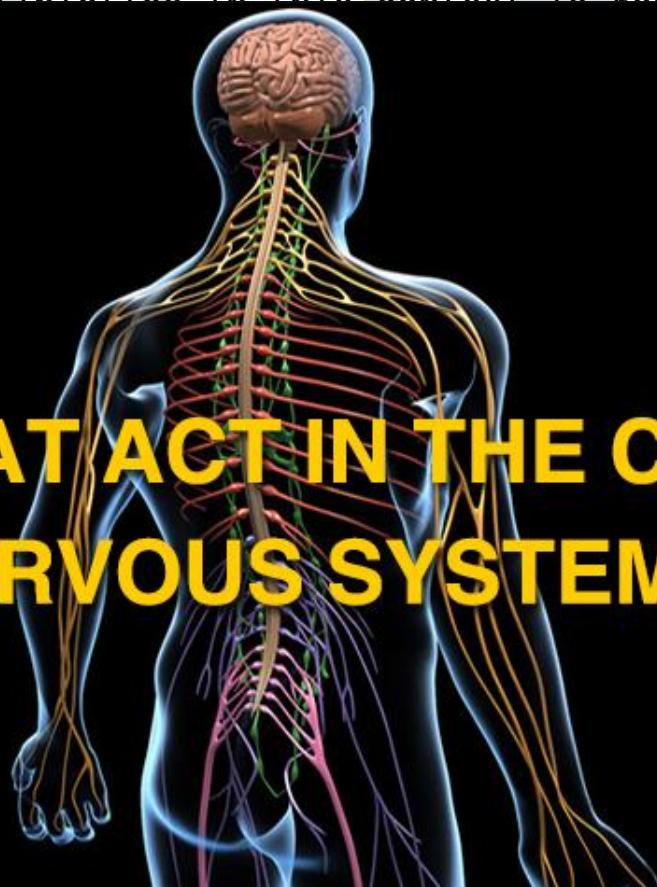
For relief of acute symptoms, inhalation of a short-acting β agonist (eg, albuterol), or of an anticholinergic drug (eg, ipratropium bromide), or of the two in combination is usually effective.

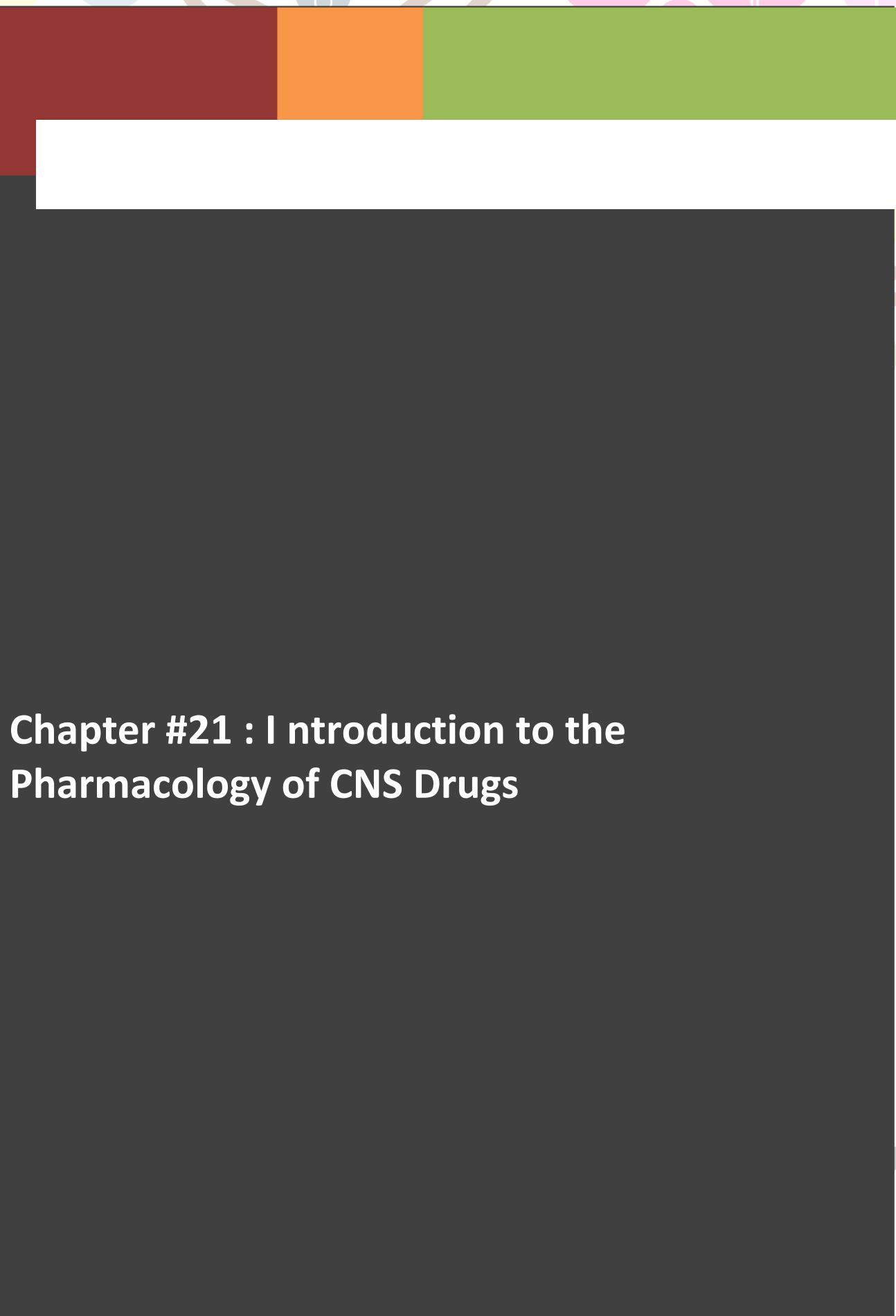
Theophylline may have a particular place in the treatment of COPD, as it may improve contractile function of the diaphragm, thus improving ventilatory capacity.

The use of antibiotics in this context is routine.

section 5

DRUGS THAT ACT IN THE CENTRAL NERVOUS SYSTEM





Chapter #21 : I ntroduction to the Pharmacology of CNS Drugs

21. Introduction to the pharmacology of CNS D



Drugs acting in the CNS were among the first to be discovered by primitive humans and are still the most widely used group of pharmacologic agents. These include medications used to:

- 1-Treat a wide range of neurologic and psychiatric conditions.
- 2-Drugs that relieve pain, suppress nausea, and reduce fever.
- 3-Many CNS-acting drugs are used without prescription to increase the sense of well-being.

A full appreciation of the effects of a drug on the CNS requires an understanding of the multiple levels of brain organization, from genes → Circuits → Behavior.

Organization of the CNS:

The CNS comprises the **brain and spinal cord** and is responsible for:

- 1-Integrating sensory information.
- 2-Generating motor output.
- 3-Other behaviors needed to successfully interact with the environment and enhance species survival.

Neurons:

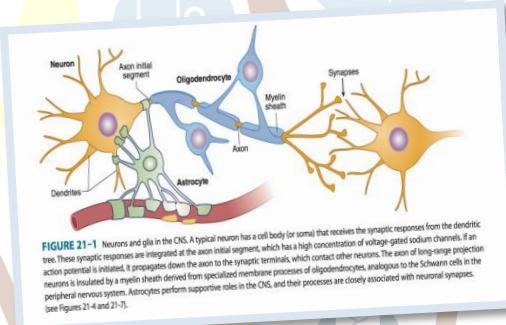
Neurons are electrically excitable cells that process and transmit information via an electrochemical process.

Classified of neurons in the following ways:

by function

by location

by the neurotransmitter they release



Note: Neurons may have hundreds of dendrites

Neuroglia or glia:

There are a large number of non-neuronal support cells.

- ✚ Astrocytes are the most abundant glial cells in the brain, They have two characteristics:
 - A- play homeostatic support roles, including providing metabolic nutrients to neurons and maintaining extracellular ion concentrations.

B-astrocyte processes are closely associated with neuronal synapses where they are involved in the removal and recycling of neurotransmitters after release and play increasingly appreciated roles in regulating neurotransmission.

- ✚ Oligodendrocytes are cells that wrap around the axons of projection neurons in the CNS forming the myelin sheath , Similar to the Schwann cells in peripheral neurons, the myelin sheath created by the oligodendrocytes insulates the axons and increases the speed of signal propagation

Not: Damage to oligodendrocytes occurs in multiple sclerosis and

thus is a target of drug discovery efforts.

- ✚ Microglia are specialized macrophages derived from the bone marrow that are found in the CNS.

It's considered as a major immune defense system in the brain and involved in neuroinflammatory processes in many pathological states including neurodegenerative diseases.

Blood-Brain Barrier:

Is a protective functional separation of the circulating blood from the extracellular fluid of the CNS that limits the penetration of substances, including drugs.

Therefore, to enter the CNS, drugs must either be highly hydrophobic or engage specific transport mechanisms.

Some parts of the brain (circumventricular organs) lack a normal BBB. These include:

A-Regions that sample the blood such as area postrema vomiting center.

B-Regions that secrete neurohormones into the circulation.

Ion channels and neurotransmitter receptors:

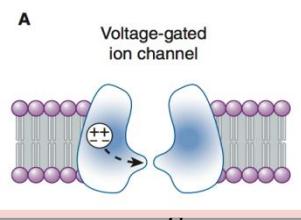
The membranes of neurons contain two types of channels

Voltage-gated
Ex: Ca & K channels

ligand-gated

- Respond to changes in the membrane

- In nerve cells, these channels are highly concentrated



of the axon , which initiates the all-or-nothing fast action potential and along

the length of the axon where they propagate the action potential to the nerve

terminal.

B-ligand-gated channels:

Neurotransmitters exert their effects on neurons by binding to two distinct classes of receptor. The first class is referred to as ligand-gated channels, or ionotropic receptors. These receptors consist of multiple subunits, and binding of the neurotransmitter

TABLE 21–1 Some toxins used to characterize ion channels.

Channel Types	Mode of Toxin Action	Source
Voltage-gated		
Sodium channels		
Tetrodotoxin (TTX)	Blocks channel from outside	Puffer fish
Batrachotoxin (BTX)	Slows inactivation, shifts activation	Colombian frog
Potassium channels		
Apamin	Blocks "small Ca-activated" K channel	Honeybee
Charybdotoxin	Blocks "big Ca-activated" K channel	Scorpion
Calcium channels		
Omega conotoxin (ω -CTX-GVIA)	Blocks N-type channel	Pacific cone snail
Agatoxin (ω -AGAIVA)	Blocks P-type channel	Funnel web spider
Ligand-gated		
Nicotinic ACh receptor		
α -Bungarotoxin	Irreversible antagonist	Marine snake
GABA _A receptor		
Picrotoxin	Blocks channel	South Pacific plant
Glycine receptor		
Strychnine	Competitive antagonist	Indian plant
AMPA receptor		
Philanthotoxin	Blocks channel	Wasp

The communication between neurons in the CNS occurs through chemical synapses in the majority of cases.

Steps in synaptic transmission:

1-An action potential propagating down the axon of the presynaptic neuron enters the synaptic terminal.

2-Activates voltage-sensitive calcium channels.(The calcium channels responsible for the release of neurotransmitter)

3-As calcium flows into the terminal, the increase in intraterminal calcium concentration promotes the fusion of synaptic vesicles with the presynaptic membrane.

4,5,6-The neurotransmitter contained in the vesicles is released into the synaptic cleft and diffuses to the receptors on the postsynaptic membrane.

7-The neurotransmitter binds to its receptor and opens channels (either directly or indirectly as described above) causing a brief change in membrane conductance (permeability to ions) of the postsynaptic cell.

Pathway of Postsynaptic Potentials:

excitatory postsynaptic potential (EPSP)

a depolarizing potential change (increase the size)

opening of sodium or calcium channels

inhibitory postsynaptic potential (IPSP)

a hyperpolarizing potential change

opening of potassium or chloride channels.

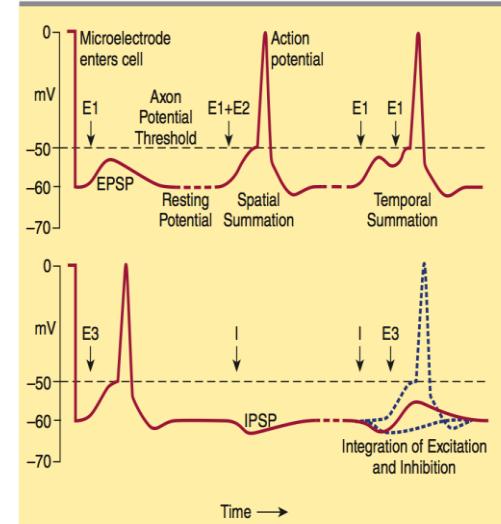
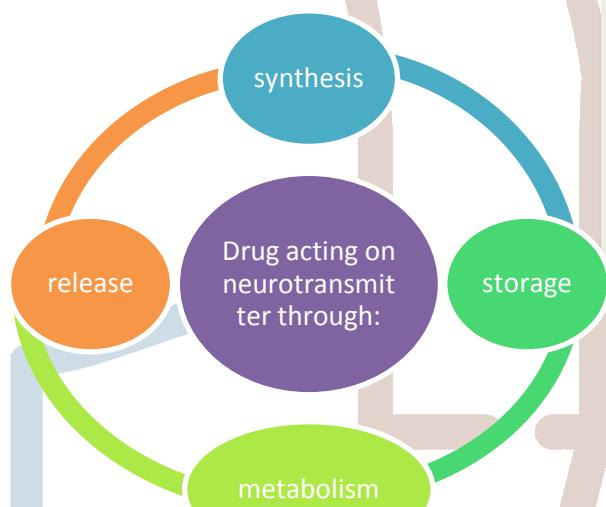


FIGURE 21-3 Postsynaptic potentials and action potential generation. **A** (top) shows the voltage recorded upon entry of a microelectrode into a postsynaptic cell and subsequent recording of a resting membrane potential of -60 mV. Stimulation of an excitatory pathway (E1, left) generates transient depolarization called an excitatory postsynaptic potential (EPSP). Simultaneous activation of multiple excitatory pathways (E1 + E2, right) can summate spatially to reach the threshold for action potential generation.

Site of drug action:

The transmitter-dependent actions can be divided into: **B** (bottom) demonstrates the interaction of excitatory and inhibitory synapses. On the left, a suprathreshold excitatory stimulus (E3) evokes an action potential. In the center, an inhibitory pathway (I) generates a small hyperpolarizing current called an inhibitory postsynaptic potential (IPSP). On the right, if the previously suprathreshold excitatory input (E3) is given shortly after the inhibitory input (I), the IPSP prevents the excitatory potential from reaching threshold.

A-Presynaptic categories:



- ✚ Synaptic transmission can be depressed by blockade of transmitter synthesis or storage.
- ✚ Blockade of transmitter catabolism inside the nerve terminal → transmitter concentrations → the amount of transmitter released per impulse.

action is terminated either by

uptake mechanisms

degradation

For most neurotransmitter

into the:
-synaptic terminal
-surrounding neuroglia.

B-Postsynaptic categories:

- ❖ In the postsynaptic region, the transmitter receptor provides the primary site of drug action.
- ❖ Drugs can act either as neurotransmitter agonists, or they can block receptor function.
- ❖ Receptor antagonism is a common mechanism of action for CNS drugs.
- ❖ Drugs can also act directly on:

1-The ion channel of ionotropic receptors: (are transmembrane molecules that can “open” or “close” a channel that would allow different kinds of ions to travel in and out of the cell).

2-Metabotropic receptors: (do not have a “channel” that opens or closes. Instead, they are linked to another small chemical called a “G-protein.”), drugs can act at any of the steps downstream of the receptor.

The selectivity of CNS drug action is based on two primary factors.

First, with a few exceptions, different neurotransmitters are released by different groups of neurons.

Second, there is a multiplicity of receptors for each neurotransmitter.

Cellular organization of the brain:

Most of the neuronal systems in the CNS can be divided into two broad categories:

hierarchical systems

nonspecific or diffuse neuronal systems

A-Hierarchical systems:

- ❖ Include all the pathways directly involved in sensory perception and motor control.
- ❖ Being composed of large myelinated fibers that can often conduct action potentials at a rate of more than 50 m/s.

Within each nucleus and in the cortex, there are two types of cel

relay or projection neurons	Local circuit neurons
Form the interconnecting pathways that transmit signals over long distances.	A special class of local circuit neurons in the spinal cord forms axon collaterals that synapse on the terminals of other neurons. They also form synapses on the terminals of their own axons.
Their cell bodies are relatively large	They are typically smaller than those of projection neurons.
Their axons can project long distances but also emit small collaterals that synapse onto local interneurons.	Their axons arborize "فرع" in a treelike branching pattern throughout the immediate vicinity of the cell body. In these systems a limited number of transmitters are used by these neurons indicates that any major change in transmitter levels will alter the overall excitability of the system.
Excitatory neurons	Inhibitory neurons
Release excitatory transmitter (glutamate)	B-Non-Specific or Diffuse Neuronal Systems: Release inhibitory transmitter (GABA or glycine)
Their involvement in the nervous system is very limited.	They synapse primarily on the cell body of the projection neurons. They also synapse on the dendrites and axons of projection neurons as well as on the cell bodies of other projection neurons.
These neurotransmitters are produced by only a limited number of neurons whose cell bodies are located in small discrete nuclei, often in the brainstem.	Common types of pathways formed by these neurons include: Current feed-back pathway : From these limited nuclei, these neurons project widely and diffusely throughout the brain and spinal cord. Because the axons from these diffusely projecting neurons are fine and unmyelinated, they conduct very slowly, at about 0.5 m/s.

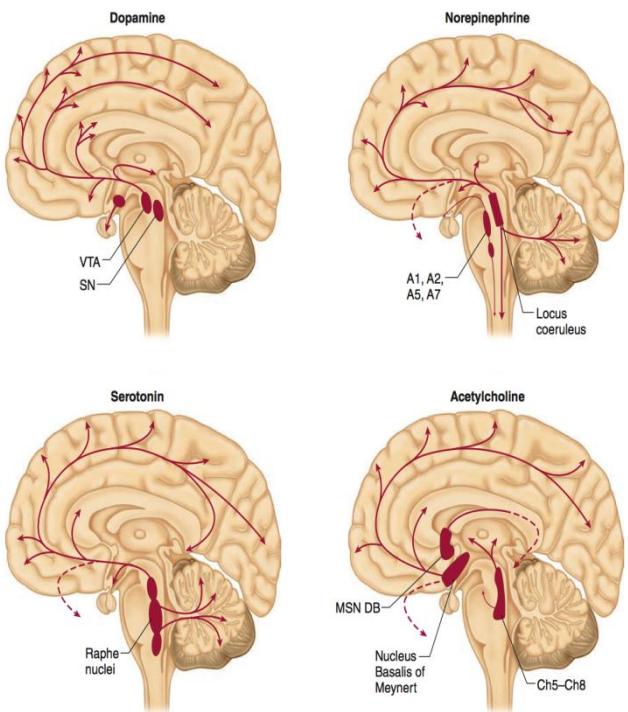


FIGURE 21-6 Diffuse neurotransmitter pathways in the CNS. For each of the neurotransmitter pathways shown, the cell bodies are located in discrete brainstem or basal forebrain nuclei and project widely throughout the CNS. These diffuse systems largely modulate the function of the hierarchical pathways. Serotonin neurons, for example, are found in the midline raphe nuclei in the forebrain and send extraordinarily divergent projections to nearly all regions of the CNS. Other diffusely projecting neurotransmitter pathways include the histamine and orexin systems (not shown). VTA, ventral tegmental area; SN, substantia nigra; A1-A7, adrenergic brainstem nuclei; MSN, medial septal nucleus; DB, diagonal band of Broca; C5-C8, cholinergic brainstem nuclei.

- Most neurotransmitters utilized by this system, including norepinephrine, act predominantly on metabotropic receptors and therefore initiate long-lasting synaptic effects.
- that these systems have been implicated in such global functions as sleeping and waking, attention, appetite, and emotional states.

Central neurotransmitters:

- Drug selectivity is based on the fact {that different pathways use different transmitters}

A primary goal of neuroscientists has been to identify the neurotransmitters in CNS pathways.

- Establishing that a chemical substance is a transmitter has been far more difficult for central synapses than for peripheral synapses.
-

The criteria have been established for transmitter identification:

1. **Localization:** A suspected transmitter must reside in the presynaptic terminal of the pathway of interest.
2. **Release:** A suspected transmitter must be released from a neuron in response to neuronal activity and in a calcium-dependent manner.
3. **Synaptic mimicry:** Application of the candidate substance should produce a response that mimics the action of the transmitter released by nerve stimulation, and application of a selective antagonist should block the response.

>>Using the criteria above, a vast number of small molecules have been isolated from the brain, and studies using a variety of approaches suggest that the agents listed in Table 21-2 are neurotransmitters.

Neurotransmitter in the central nervous system.

Amino Acid

Acetylcholine

Monoamine

Neuropeptides

Orexin

Other Signaling Substances

- A. Glutamate
- B. GABA and Glycine

- A. Dopamine
- B. Norepinephrine
- C. 5-Hydroxytryptamine
- D. Histamine

opioid peptides

- A. Endocannabinoids
- B. Nitric Oxide
- C. Purines

TABLE 21–2 Summary of neurotransmitter pharmacology in the central nervous system. (Continued)

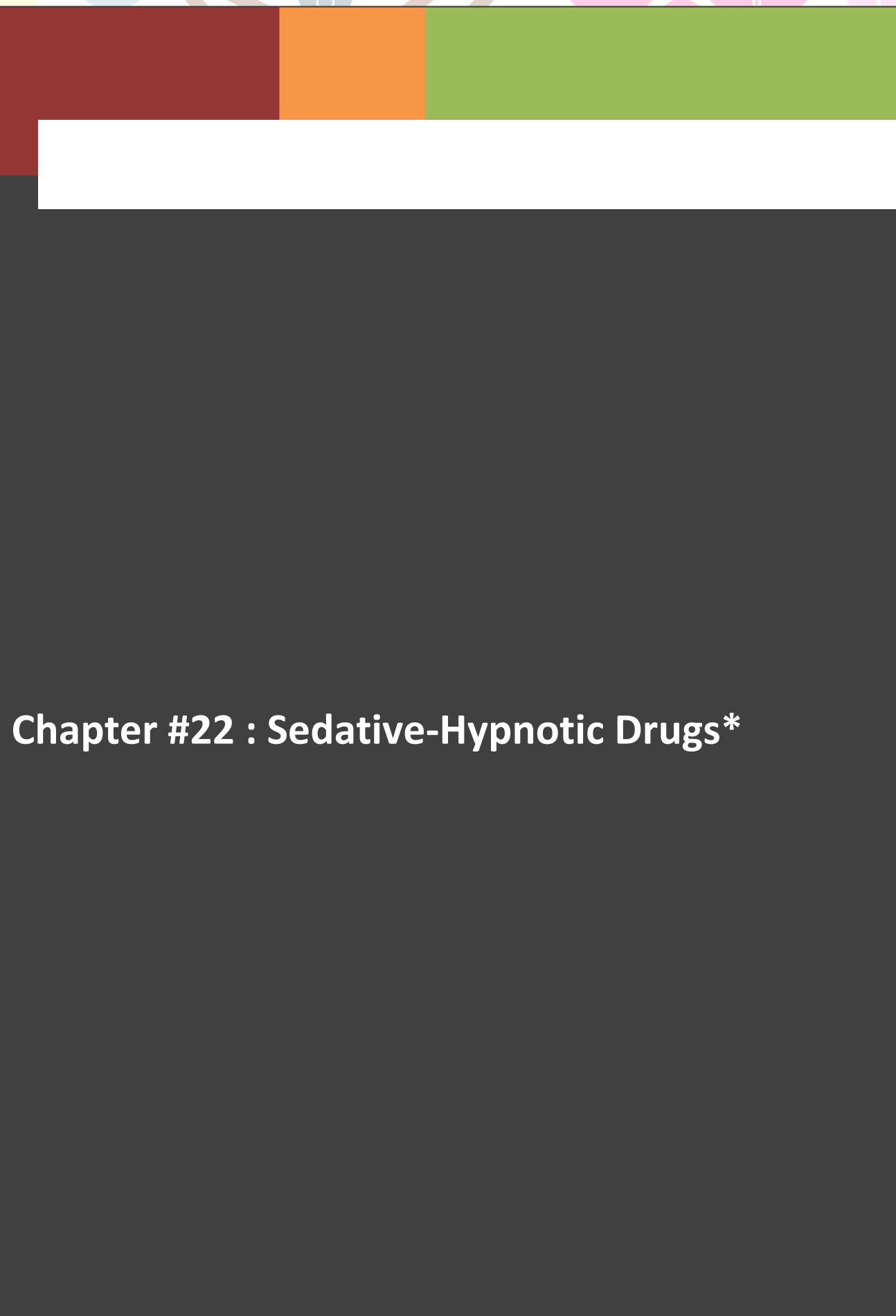
Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Opioid peptides	Cell bodies at all levels; long and short connections	Mu: bendorphin	Naloxone	Inhibitory (presynaptic): $\downarrow \text{Ca}^{2+}$ conductance, $\downarrow \text{cAMP}$
		Delta: enkephalin	Naloxone	Inhibitory (postsynaptic): $\uparrow \text{K}^+$ conductance, $\downarrow \text{cAMP}$
		Kappa: dynorphin, salvanorin A	Naloxone	Inhibitory (postsynaptic): $\uparrow \text{K}^+$ conductance, $\downarrow \text{cAMP}$
Orexins	Cell bodies in hypothalamus; project widely	OX ₁ : orexin A	Suvorexant	Excitatory, Glutamate co-release
		OX ₂ : orexins A and B	Suvorexant	
Tachykinins	Primary sensory neurons, cell bodies at all levels; long and short connections	NK1: substance P methylester, aprepitant	Aprepitant	Excitatory: $\downarrow \text{K}^+$ conductance, $\uparrow \text{IP}_3, \text{DAG}$
		NK2: neurokinin A	Saredutant	
		NK3: neurokinin B	Osanetant	
Endocannabinoids	Widely distributed	CB1: anandamide, 2-arachidonoylglycerol	Rimonabant	Inhibitory (presynaptic): $\downarrow \text{Ca}^{2+}$ conductance, $\downarrow \text{cAMP}$

Note: Many other central transmitters have been identified (see text).

ACET, (S)-1-(2-amino-2-carboxyethyl)-3-(2-carboxy-5-phenylthiophene-3-yl-methyl)-5-methylpyrimidine-2,4-dione; ACPD, *trans*-1-amino-cyclopentyl-1,3-dicarboxylate; AMPA, DL- α -amino-3-hydroxy-5-methylisoxazole-4-propionate; cAMP, cyclic adenosine monophosphate; CQNX, 6-cyano-7-nitroquinoxaline-2,3-dione; DAG, diacylglycerol; IP₃, inositol trisphosphate; LSD, lysergic acid diethylamide; MCPG, α -methyl-4-carboxyphenylglycine; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(β)quinoxaline.

TABLE 21–2 Summary of neurotransmitter pharmacology in the central nervous system.

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Acetylcholine	Cell bodies at all levels; long and short connections	Muscarinic (M_1): muscarine	Pirenzepine, atropine	Excitatory: \downarrow in K^+ conductance; \uparrow IP_{3} , DAG
		Muscarinic (M_2): muscarine, bethanechol	Atropine, methocarbamol	Inhibitory: \uparrow K^+ conductance; \downarrow cAMP
	Motoneuron-Renshaw cell synapse	Nicotinic: nicotine	Dihydro- β -erythroidine, α -bungarotoxin	Excitatory: \uparrow cation conductance
Dopamine	Cell bodies at all levels; short, medium, and long connections	D_1 : dihydrexidine	Phenothiazines	Inhibitory (?): \uparrow cAMP
		D_2 : bromocriptine	Phenothiazines, butyrophenones	Inhibitory (presynaptic): \downarrow Ca^{2+} ; Inhibitory (postsynaptic): \uparrow in K^+ conductance, \downarrow cAMP
GABA	Supraspinal and spinal interneurons involved in pre- and postsynaptic inhibition	$GABA_A$: muscimol	Bicuculline, picrotoxin	Inhibitory: \uparrow Cl^- conductance
		$GABA_B$: baclofen	2-OH saclofen	Inhibitory (presynaptic): \downarrow Ca^{2+} conductance; Inhibitory (postsynaptic): \uparrow K^+ conductance
Glutamate	Relay neurons at all levels and some interneurons	<i>N</i> -Methyl-D-aspartate (NMDA): NMDA	2-Amino-5-phosphonovalerate, dizocilpine	Excitatory: \uparrow cation conductance, particularly Ca^{2+}
		AMPA: AMPA	NBQX	Excitatory: \uparrow cation conductance
		Kainate: kainic acid, domoic acid	ACET	Excitatory: \uparrow cation conductance
		Metabotropic: ACPD, quisqualate	MCPG	Inhibitory (presynaptic): \downarrow Ca^{2+} conductance, \downarrow cAMP; Excitatory: \downarrow K^+ conductance, \uparrow IP_3 , DAG
Glycine	Spinal interneurons and some brainstem interneurons	Taurine, β -alanine	Strychnine	Inhibitory: \uparrow Cl^- conductance
5-Hydroxytryptamine (serotonin)	Cell bodies in mid-brain and pons project to all levels	5-HT _{1A} : eptaziprole	Metergoline, spiperone	Inhibitory: \uparrow K^+ conductance, \downarrow cAMP
		5-HT _{2A} : LSD	Ketanserin	Excitatory: \downarrow K^+ conductance, \uparrow IP_3 , DAG
		5-HT ₃ : 2-methyl-5-HT	Ondansetron	Excitatory: \uparrow cation conductance
Norepinephrine	Cell bodies in pons and brainstem project to all levels	5-HT ₄ : cisapride	Piboserod	Excitatory: \downarrow K^+ conductance
		α_1 : phenylephrine	Prazosin	Excitatory: \downarrow K^+ conductance, \uparrow IP_3 , DAG
		α_2 : clonidine	Yohimbine	Inhibitory (presynaptic): \downarrow Ca^{2+} conductance; Inhibitory: \uparrow K^+ conductance, \downarrow cAMP
		β_1 : isoproterenol, dobutamine	Atenolol, propranolol	Excitatory: \downarrow K^+ conductance, \uparrow cAMP
		β_2 : albuterol	Butoxamine	Inhibitory: may involve \uparrow in electrogenic sodium pump; \uparrow cAMP
Histamine	Cells in ventral posterior hypothalamus	H ₁ : 2-(<i>m</i> -fluorophenyl)-histamine	Mepyramine	Excitatory: \downarrow K^+ conductance, \uparrow IP_3 , DAG
		H ₂ : dimaprit	Ranitidine	Excitatory: \downarrow K^+ conductance, \uparrow cAMP
		H ₃ : R- α -methyl-histamine	Thioperamide	Inhibitory autoreceptors



Chapter #22 : Sedative-Hypnotic Drugs*

22. Sedative-Hypnotic Drugs

Sedative-hypnotic drugs in this class can cause sedation (with anti-anxiety effect) or help to sleep (hypnosis). Because there is significant chemical variation within the group, this drug classification based on clinical uses rather than on similarities in chemical structure.

BASIC PHARMACOLOGY OF SEDATIVE-HYPNOTICS

A sedative (anxiolytic) agent should reduce anxiety and exert a calming effect. A hypnotic drug should produce drowsiness and maintenance of sleep. The hypnotic effect has more noticeable depression of the CNS than sedation, and this can be achieved with many drugs in this class, simply by increasing the dose. Graded dose-dependent depression of CNS function is a characteristic of most sedative-hypnotics. An increase in the dose higher than that needed for hypnosis may lead to a state of general anesthesia, and higher doses may depress respiratory and vasomotor centers in the medulla, leading to coma and death.

TABLE 22-1 Pharmacokinetic properties of some benzodiazepines and newer hypnotics in humans.

Drug	T _{max} ^a (hours)	t _{1/2} (hours)	Comments
Alprazolam	1-2	12-15	Rapid oral absorption
Chlordiazepoxide	2-4	15-40	Active metabolites; erratic bioavailability from IM injection
Clorazepate	1-2 (nordiazepam)	50-100	Prodrug; hydrolyzed to active form in stomach
Diazepam	1-2	20-80	Active metabolites; erratic bioavailability from IM injection
Eszopiclone	1	6	Minor active metabolite
Flurazepam	1-2	40-100	Active metabolites with long half-lives
Lorazepam	1-6	10-20	No active metabolites
Oxazepam	2-4	10-20	No active metabolites
Temazepam	2-3	10-40	Slow oral absorption
Triazolam	1	2-3	Rapid onset; short duration of action
Zaleplon	<1	1-2	Metabolized via aldehyde dehydrogenase
Zolpidem	1-3	15-35	No active metabolites

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inetics Pharmacodynamics of Benzodiazepines, Barbiturates, & Newer Hypnotics

A. Molecular Pharmacology of the GABA_A Receptor

benzodiazepines, zolpidem, zaleplon, and eszopiclone bind selectively because these drugs interact only with GABA_A-receptor isoforms that contain α1 subunits. The heterogeneity of GABA_A receptors may constitute the molecular basis for the varied pharmacologic actions of benzodiazepines and related drugs.

B. Neuropharmacology

Barbiturates are less selective in their actions than benzodiazepines, this multiplicity of sites of action of barbiturates may be the basis for their ability to induce full surgical anesthesia and for their more pronounced central depressant effects compared with benzodiazepines and the newer hypnotics.

C. Benzodiazepine Binding Site Ligands

The components of the GABA_A receptor-chloride ion channel macromolecule that function as benzodiazepine binding sites exhibit heterogeneity.

progress to convulsions.

Most sedative-hypnotics—including benzodiazepines—are capable of causing physiologic dependence when used on a long-term basis.

However, the severity of withdrawal symptoms differs among individual drugs and depends also on the magnitude of the dose used immediately before cessation of use. When higher doses of sedativehypnotics are used, abrupt withdrawal leads to more serious withdrawal signs. Differences in the severity of withdrawal symptoms

resulting from individual sedative-hypnotics relate in part to half-life,

since drugs with long half-lives are eliminated slowly enough to

accomplish gradual withdrawal with few physical symptoms. The

use of drugs with very short half-lives for hypnotic effects may lead

to signs of withdrawal even between doses. For example, triazolam, a

benzodiazepine with a half-life of about 4 hours, has been reported

to cause daytime anxiety when used to treat sleep disorders. The

abrupt cessation of zolpidem, zaleplon, or

eszopiclone may also result in withdrawal symptoms, though usually of less intensity than those seen with benzodiazepines.

BENZODIAZEPINE ANTAGONIST:

FLUMAZEMIL Flumazenil is one of several 1,4-benzodiazepine derivatives with a high affinity for the benzodiazepine binding site

on the GABA_A receptor that act as competitive antagonists. It blocks many of the actions of benzodiazepines, zolpidem, zaleplon, and eszopiclone. Flumazenil is approved for use in reversing the CNS depressant effects of benzodiazepine overdose. When given

intravenously,

flumazenil acts rapidly but has a short half-life (0.7–1.3 hours) due

to rapid hepatic clearance. Because all

benzodiazepines have a longer duration of action than flumazenil, sedation commonly recurs,

requiring repeated administration of the

tolerance: Psychologic & Physiologic Dependence

Tolerance—decreased responsiveness to a drug following repeated exposure—is a common feature of sedative-hypnotic use. It may result in the need for an increase in the dose required to maintain symptomatic improvement or to promote sleep.

Physiologic dependence can be described as an altered physiologic state that requires continuous drug administration to prevent an abstinence or withdrawal syndrome. In the case of sedativehypnotics, this syndrome is characterized by states of increased anxiety, insomnia, and CNS excitability that may



antagonist. In patients who have ingested benzodiazepines with tricyclic antidepressants, seizures and cardiac arrhythmias may follow flumazenil administration.

CLINICAL PHARMACOLOGY OF SEDATIVE-HYPNOTICS

TREATMENT OF ANXIETY STATES

Psychic awareness of Anxiety is accompanied characterized by enhanced vigilance, motor tension, and autonomic hyperactivity. Anxiety is often secondary to organic disease states—acute myocardial infarction, angina pectoris, gastrointestinal ulcers, etc.—which themselves require specific therapy. Other class of secondary anxiety states (situational anxiety) results from events that may have to be dealt with only once or a few times, including anticipation of frightening medical or dental procedures and family illness or other stressful event. Situational anxiety tends to be self-limiting, in some cases, the short-term use of sedative-hypnotics may be appropriate.

GAD (generalized anxiety disorder), panic disorders, and agoraphobia are also manageable with drug therapy, sometimes in combination with psychotherapy. The benzodiazepines still widely used for the management of acute anxiety states, rapid control of panic attacks, the long-term management of GAD and panic disorders.

The choice of benzodiazepines for anxiety is based on several sound pharmacologic principles:

(1) A rapid onset of action.

(2) A relatively high therapeutic index, plus availability of flumazenil for the treatment of overdose;

(3) A low risk of drug interactions based on liver enzyme induction;

(4) Minimal effects on cardiovascular or autonomic functions.

Disadvantages of the benzodiazepines include the risk of dependence, depression of CNS functions, and amnestic effects. Benzodiazepines exert additive CNS depression when administered with other drugs, including ethanol. In the treatment of generalized anxiety disorders and certain

phobias, newer antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are now considered by many authorities to be drugs of first choice, these slow onset of action and thus minimal effectiveness in acute anxiety states. Sedative-hypnotics should be used with caution to minimize adverse effects. A dose should be prescribed that does not impair mentation or motor functions during waking hours. (given at bedtime) Prescriptions should be written for short periods since there is little justification for long-term therapy (therapeutic doses for 2 months or longer). Avoid the combination of antianxiety agents and people taking sedatives should be warned about the consumption of alcohol and the use of over-the-counter medications containing antihistaminic or anticholinergic drugs.

TABLE 22–2 Clinical uses of sedative-hypnotics.

For relief of anxiety
For insomnia
For sedation and amnesia before and during medical and surgical procedures
For treatment of epilepsy and seizure states
As a component of balanced anesthesia (intravenous administration)
For control of ethanol or other sedative-hypnotic withdrawal states
For muscle relaxation in specific neuromuscular disorders
As diagnostic aids or for treatment in psychiatry

TREATMENT OF SLEEP PROBLEMS

Sleep disorders are common and often result from inadequate treatment of underlying medical conditions or psychiatric illness.

Nonpharmacologic therapies that are useful for sleep problems include proper diet and exercise, avoiding stimulants before retiring, ensuring a comfortable sleeping environment, and retiring at a regular time each night.

A sedative-hypnotic prescribed for a limited period. It should be noted that the sudden discontinuance of many drugs in this class can lead to rebound insomnia.

The newer hypnotics, zolpidem, zaleplon, and eszopiclone, are less likely than the benzodiazepines to change sleep patterns.

The drug selected should be one that provides sleep of relatively rapid onset and sufficient duration, with minimal “hangover” effects such as drowsiness, dysphoria, and mental or motor depression the following day.

Daytime sedation is more common with benzodiazepines that have slow elimination rates (e.g., lorazepam) and those that are biotransformed to active metabolites (e.g., flurazepam, quazepam). If benzodiazepines used nightly, tolerance can occur, which may lead to dose increases by the patient to produce the desired effect. Anterograde amnesia occurs to some degree with all

benzodiazepines used for hypnosis.

Favorable clinical features of Zolpidem and the other newer hypnotics include rapid onset of action and modest day-after psychomotor depression with few amnestic effects. Zaleplon acts rapidly, and because of its short half-life, the drug appears to have value in the management of patients who awaken early in the sleep cycle. At recommended doses, zaleplon and eszopiclone (despite its relatively long half-life) appear to cause less amnesia or day-after somnolence than zolpidem or benzodiazepines.

+++Note: The failure of insomnia to remit after 7–10 days of treatment may indicate the presence of a primary psychiatric or medical illness that should be evaluated. Long-term use of hypnotics is an irrational and dangerous medical practice.

OTHER THERAPEUTIC USES

- For sedative effects during medical or surgical procedures such as endoscopy and bronchoscopy.
- Premedication before anesthesia (oral, short-acting drugs are preferred.)
- Long-acting drugs such as chlordiazepoxide, diazepam, and phenobarbital administered in progressively decreasing doses to patients during withdrawal from physiologic dependence on ethanol or other sedative-hypnotics.
- Parenteral lorazepam is used to suppress the symptoms of delirium tremens.
- Meprobamate and the benzodiazepines have frequently been used as central muscle relaxants, though evidence for general efficacy without accompanying sedation is lacking.
- Psychiatric uses of benzodiazepines also in the initial management of mania and the

control of drug-induced hyperexcitability states (eg, phencyclidine intoxication).

Sedative-hypnotics are also used occasionally as diagnostic aids in neurology and psychiatry.

CLINICAL TOXICOLOGY OF SEDATIVE-HYPNOTICS

Direct Toxic Actions

Many of the common adverse effects of sedative-hypnotics result from dose-related depression of the CNS. Relatively low doses may lead to drowsiness, impaired judgment, and reduced motor skills, sometimes with a significant impact on driving ability, job performance, and personal relationships. Sleep-driving and other somnambulistic behavior with no memory of the event have occurred with the sedative-hypnotic drugs used in sleep disorders.

Benzodiazepines may cause a significant dose-related anterograde amnesia; they can significantly impair the ability to learn new information, while leaving the retrieval of previously learned information intact.

At higher doses, toxicity may present as lethargy or a state of exhaustion or, alternatively as gross symptoms equivalent to those of ethanol intoxication. Increased sensitivity to sedative-hypnotics is

more common in patients with cardiovascular disease, respiratory disease, or hepatic impairment and in older patients.

Alprazolam is purportedly more toxic in overdose than other benzodiazepines. Cardiovascular depression further complicates successful resuscitation. In such patients, treatment consists of ensuring a patent airway, with mechanical ventilation if needed, and maintenance of plasma volume, renal output, and cardiac function. Use of a positive inotropic drug such as dopamine, which preserves renal blood flow, is sometimes indicated. Hemodialysis or hemoperfusion may be used to hasten

elimination of some of these drugs. Flumazenil reverses the sedative actions of benzodiazepines, and those of eszopiclone, zaleplon, and zolpidem, although experience with its use in overdose of the newer hypnotics is limited.

However, its duration of action is short, its antagonism of respiratory depression is unpredictable, and there is a risk of precipitation of withdrawal symptoms in long-term users of benzodiazepines.

Consequently, the use of flumazenil in benzodiazepine overdose remains controversial and *must* be accompanied by adequate monitoring and support of respiratory function.

Adverse effects of the sedative-hypnotics that are not referable to their CNS actions infrequently occur e.g., Hypersensitivity reactions, skin rashes.

Reports of teratogenicity leading to fetal deformation following use of certain benzodiazepines have resulted in FDA assignment of individual benzodiazepines to either category D or X in terms of pregnancy risk. Most barbiturates are FDA pregnancy category D. Eszopiclone, ramelteon, zaleplon, and zolpidem are category C, while buspirone is a category B drug in

terms of use in pregnancy.	According to the FDA	
	Name of drug	pregnancy risk
	benzodiazepines	category D or X
	barbiturates	category D
	Eszopiclone, ramelteon, zaleplon, and zolpidem	category C
	buspirone	category B

ALTERATIONS IN DRUG RESPONSE

Depending on the dosage and the duration of use, tolerance occurs in varying degrees to many of the pharmacologic effects of sedativehypnotics. However, it should not be assumed that the degree of

tolerance achieved is identical for all pharmacologic effects. Cross-tolerance between the different sedative-hypnotics, including ethanol, can lead to an unsatisfactory therapeutic response when standard doses of a drug are used in a patient with a recent history of excessive use of these agents. However, there have been very few reports of tolerance development when eszopiclone, zolpidem, or zaleplon was used for less than 4 weeks.

With the long-term use of sedative-hypnotics, especially if doses are increased, a state of physiologic dependence can occur. This may develop to a degree unparalleled by any other drug group, including the opioids.

Withdrawal from a sedative-hypnotic can have severe and life-threatening manifestations. Withdrawal symptoms range from restlessness, anxiety, weakness, and orthostatic hypotension to hyperactive reflexes and generalized seizures. Symptoms of withdrawal are usually more severe followed discontinuance of sedative-hypnotics with shorter half-lives. However, eszopiclone, zolpidem, and zaleplon appear to be exceptions to this, because withdrawal symptoms are minimal following sudden discontinuance of these newer short-acting agents. Symptoms are less with longer-acting drugs, which may partly accomplish their own “tapered” withdrawal by virtue of their slow elimination.

Cross-dependence is the ability of one drug to suppress abstinence symptoms from discontinuance of another drug, is quite marked among sedative-hypnotics. This provides the justification for therapeutic regimens in the management of withdrawal states: Longer-acting drugs such as chlordiazepoxide, diazepam, and phenobarbital can be used to alleviate withdrawal symptoms of shorter-acting drugs, including ethanol.

Drug Interactions

The most common drug interactions involving sedative-hypnotics

are interactions with other CNS depressant drugs, leading to additive effects. These interactions have some therapeutic usefulness

SUMMARY Sedative-Hypnotics

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
BENZODIAZEPINES				
• Alprazolam • Chlordiazepoxide • Clonazepam • Clorazepate • Diazepam • Estazolam • Flurazepam • Lorazepam • Midazolam • Oxazepam • Quazepam • Temazepam • Triazolam	Bind to specific GABA _A receptor subunits at central nervous system (CNS) neuronal synapses facilitating GABA-mediated chloride ion channel opening frequency • enhance membrane hyperpolarization	Dose-dependent depressant effects on the CNS including sedation and relief of anxiety • amnesia • hypnosis • anesthesia • coma • and respiratory depression	Acute anxiety states • panic attacks • generalized anxiety disorder • insomnia and other sleep disorders • relaxation of skeletal muscle • anesthesia (adjunctive) • seizure disorders	Half-lives from 2-40 h (clorazepate longer) • oral activity • hepatic metabolism—some active metabolites • Toxicity: Extensions of CNS depressant effects • dependence liability • Interactions: Additive CNS depression with ethanol and many other drugs
BENZODIAZEPINE ANTAGONIST				
• Flumazenil	Antagonist at benzodiazepine-binding sites on the GABA _A receptor	Blocks actions of benzodiazepines and zolpidem but not other sedative-hypnotic drugs	Management of benzodiazepine overdose	IV, short half-life • Toxicity: Agitation, confusion • possible withdrawal symptoms in benzodiazepine dependence
BARBITURATES				
• Amobarbital • Butabarbital • Mephobarbital • Pentobarbital • Phenobarbital • Secobarbital	Bind to specific GABA _A receptor subunits at CNS neuronal synapses facilitating GABA-mediated chloride ion channel opening duration • enhance membrane hyperpolarization	Dose-dependent depressant effects on the CNS including sedation and relief of anxiety • amnesia • hypnosis • anesthesia • coma and respiratory depression • steeper dose-response relationship than benzodiazepines	Anesthesia (thiopental) • insomnia (secobarbital) • seizure disorders (phenobarbital)	Half-lives from 4-60 h (phenobarbital longer) • oral activity • hepatic metabolism—phenobarbital 20% renal elimination • Toxicity: Extensions of CNS depressant effects • dependence liability > benzodiazepines • Interactions: Additive CNS depression with ethanol and many other drugs • induction of hepatic drug-metabolizing enzymes
NEWER HYPNOTICS				
• Eszopiclone • Zaleplon • Zolpidem	Bind selectively to a subgroup of GABA _A receptors, acting like benzodiazepines to enhance membrane hyperpolarization	Rapid onset of hypnosis with few amnestic effects or day-after psychomotor depression or somnolence	Sleep disorders, especially those characterized by difficulty in falling asleep	Oral activity • short half-lives • CYP substrates • Toxicity: Extensions of CNS depressant effects • dependence liability • Interactions: Additive CNS depression with ethanol and many other drugs
MELATONIN RECEPTOR AGONISTS				
• Ramelteon • Tasimelteon: Orally active MT ₁ and MT ₂ agonist, recently approved for non-24 hour sleep disorder	Activates MT ₁ and MT ₂ receptors in suprachiasmatic nuclei in the CNS	Rapid onset of sleep with minimal rebound insomnia or withdrawal symptoms	Sleep disorders, especially those characterized by difficulty in falling asleep • not a controlled substance	Oral activity • forms active metabolite via CYP1A2 • Toxicity: Dizziness • fatigue • endocrine changes • Interactions: Fluvoxamine inhibits metabolism
5-HT-RECEPTOR AGONIST				
• Buspirone	Mechanism uncertain: Partial agonist at 5-HT receptors but affinity for D ₂ receptors also possible	Slow onset (1-2 weeks) of anxiolytic effects • minimal psychomotor impairment—no additive CNS depression with sedative-hypnotic drugs	Generalized anxiety states	Oral activity • forms active metabolite • short half-life • Toxicity: Tachycardia • pares-thesias • gastrointestinal distress • Interactions: CYP3A4 inducers and inhibitors

when these drugs are used as adjuvants in anesthesia practice. Additive effects can be predicted with

concomitant use of alcoholic beverages, opioid analgesics, anticonvulsants, and phenothiazines.

Less obvious but just as important is enhanced CNS depression with a variety of antihistamines, antihypertensive agents, and antidepressant drugs of the tricyclic class.

Chapter #23 : The Alcohols

23. The Alcohols

- Alcohol, primarily in the form of ethyl alcohol (ethanol), has occupied an important place in the history of humankind for at least 8000 years.
- Like other sedative-hypnotic drugs, alcohol in low to moderate amounts relieves anxiety and fosters a feeling of well-being or even euphoria.
- It is the most commonly abused drug in the world

Table 1: Terminology definitions

Alcohol-use disorder	Using alcohol in dangerous situations
Alcohol abuse	Continuing to drink alcohol in spite of adverse consequences
Alcohol dependence	Characteristics of alcohol abuse in addition to physical dependence. (tolerance to alcohol and signs and symptoms upon withdrawal))

BASIC PHARMACOLOGY OF ETHANOL

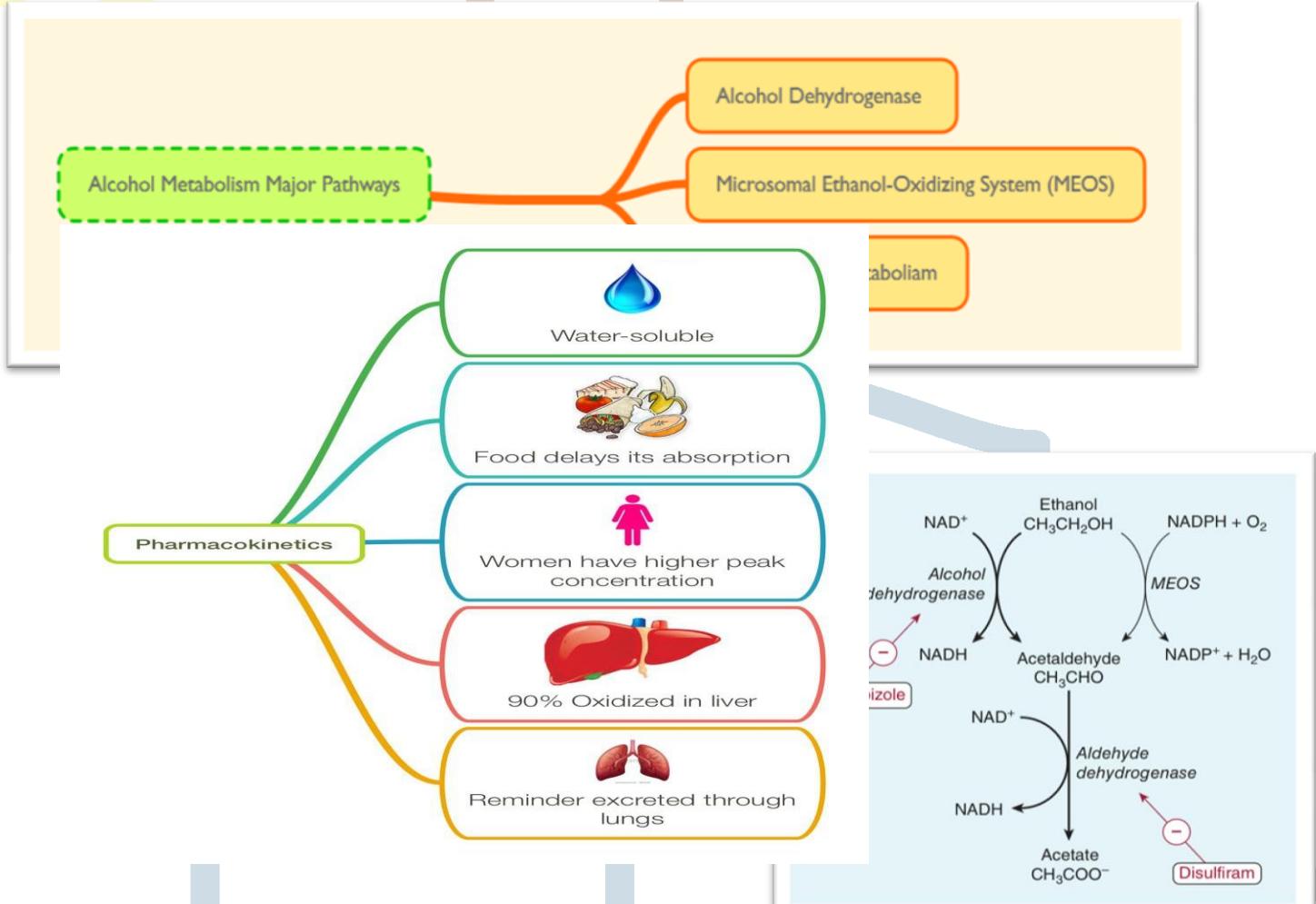


Figure 1: Alcohol metabolism pathways

Table 2: Alcohol Metabolism Major Pathways

Alcohol Dehydrogenase (ADH)	Microsomal Ethanol-Oxidizing System (MEOS)	Acetaldehyde Metabolism
<ul style="list-style-type: none"> - Is a family of cytosolic enzymes than catalyze the conversion of alcohol to acetaldehyde. - These enzymes are mainly found in liver, but small amounts found in other organs such as the brain and stomach. - Some metabolism of ethanol by ADH occurs in the stomach in men, but smaller amounts in women due to the lower levels of gastric enzyme. - During conversion of ethanol by ADH to acetaldehyde, hydrogen ion is transferred from ethanol to the cofactor nicotinamide adenine dinucleotide (NAD+) to form NADH. -As a net result, alcohol oxidation generates an excess of reducing equivalents in the liver, chiefly as NADH. The excess NADH production appears to contribute to the metabolic disorders that accompany chronic alcoholism and to both the lactic acidosis and hypoglycemia that frequently accompany acute alcohol poisoning. 	<ul style="list-style-type: none"> - Also known as the mixed function oxidase system , uses NADPH as a cofactor in the metabolism of ethanol and consists primarily of cytochrome P450 2E1, 1A2, and 3A4 . -During chronic alcohol consumption, MEOS activity is induced. As a result, chronic alcohol consumption results in significant increases not only in ethanol metabolism but also in the clearance of other drugs eliminated by the cytochrome P450s that constitute the MEOS system, and in the generation of the toxic byproducts of cytochrome P450 reactions (toxins, free radicals, H₂O₂). 	<ul style="list-style-type: none"> - Much of the acetaldehyde formed from alcohol is oxidized in the liver in a reaction catalyzed by mitochondrial NAD-dependent aldehyde dehydrogenase (ALDH). - The product is acetate, which can be further metabolized to CO₂ and water, or used to form acetyl-CoA. -When ethanol is consumed in the presence of disulfiram, acetaldehyde accumulates and causes an unpleasant reaction of facial flushing, nausea, vomiting, dizziness, and headache. Several other drugs (eg, metronidazole, cefotetan, trimethoprim) inhibit ALDH and can cause a disulfiram-like reaction if combined with ethanol. - Oxidation of acetaldehyde is

inhibited by **disulfiram**.

Table 3: Consequences of Alcohol Consumption

Acute Ethanol Consumption		Chronic Alcohol Consumption	
A. Central Nervous System	<p>The CNS is markedly affected by acute alcohol consumption.</p> <p>Alcohol causes sedation, relief of anxiety and , at higher concentrations, slurred speech, ataxia, impaired judgment, and disinhibited behavior, a condition usually called intoxication or drunkenness. These CNS effects are most marked as the blood level is rising, because acute tolerance to the effects of alcohol occurs after a few hours of drinking. For chronic drinkers who are tolerant to the effects of alcohol, higher concentrations are needed to elicit these CNS effects.</p>	A. Liver and Gastrointestinal Tract	<p>Chronic heavy drinkers eventually develop severe liver disease. Alcoholic fatty liver, a liver disease, alcoholic fatty liver which may progress to hepatitis and finally to cirrhosis and liver failure. Chronic pancreatitis, gastritis and liver failure. Women appear to be more susceptible to alcohol hepatotoxicity than men. Concurrent infection with hepatitis B or C virus increases the risk of severe liver disease.</p> <p>The pathogenesis of alcoholic liver disease is a multifactorial process involving metabolic repercussions of ethanol oxidation in the liver, dysregulation of fatty acid oxidation and synthesis, and activation of the innate immune system by a combination of direct effects of ethanol and its metabolites and by bacterial endotoxins that access the liver as a result of ethanol-induced changes in the intestinal tract.</p> <p>In addition to its direct toxic effect on pancreatic acinar cells, alcohol alters pancreatic epithelial permeability and promotes the formation of protein plugs and calcium carbonate-containing stones.</p> <p>Individuals with chronic alcoholism are prone to gastritis and have increased susceptibility to blood and plasma protein loss during drinking, which may contribute to anemia and protein malnutrition.</p> <p>Alcohol also injures the small intestine, leading to diarrhea, weight loss, and multiple vitamin deficiencies.</p> <p>Malnutrition from dietary deficiency and vitamin deficiencies due to malabsorption are common in alcoholism. Malabsorption of water-soluble vitamins is especially severe.</p>
B. Heart	<p>Significant depression of myocardial contractility has been observed in individuals who acutely consume moderate amounts of alcohol, ie, at a blood concentration above</p>	B. Nervous System	<p>1) Tolerance and dependence: Tolerance to the intoxicating effects of alcohol is a complex process involving changes in the nervous system as well as the metabolic changes described earlier. As with other sedative-hypnotic drugs, there is a limit to tolerance, so that only a relatively small increase in the <i>lethal dose</i> occurs with increasing alcohol use.</p> <p>-Psychological dependence on alcohol is characterized by a compulsive</p>

C. Smooth Muscle	100 mg/dL.	<p>desire to experience the rewarding effects of alcohol, for current drinkers, a desire to avoid the negative consequences of withdrawal. People who have recovered from alcoholism and become abstinent still experience periods of intense craving for alcohol that can be triggered by environmental cues associated in the past with drinking, such as familiar places, groups of people, or events.</p> <p>-Alcohol withdrawal symptoms usually consist of hyperexcitability in mild cases and seizures, toxic psychosis, and delirium tremens in severe ones.</p> <p>2) Neurotoxicity: Generalized symmetric peripheral nerve injury is the most common abnormality. Wernick-Korsakoff syndrome is uncommon but important entity characterized by paralysis of the external eye muscles, ataxia, and a confused state that can progress to coma and death. It is associated with thiamine deficiency but is rarely seen in the absence of alcoholism. Because of the importance of thiamine in this pathologic condition and the absence of toxicity associated with thiamine administration, all patients suspected of having Wernicke-Korsakoff syndrome (including virtually all patients who present to the emergency department with altered consciousness, seizures, or both) should receive thiamine therapy. Often, the ocular signs, ataxia, and confusion improve promptly upon administration of thiamine.</p> <p>-most patients are left with a chronic disabling memory disorder known as Korsakoff's psychosis.</p> <p>Alcohol may also impair visual acuity, with painless blurring that occurs over several weeks of heavy alcohol consumption. Changes are usually bilateral and symmetric and may be followed by optic nerve degeneration.</p>
C. Smooth Muscle	<p>Vasodilator, and muscle relaxant caused by its metabolite, acetaldehyde. In severe overdose hypothermia—caused by vasodilation—may be marked in cold environments.</p> <p>C. Cardiovascular System</p>	<p>1) Cardiomyopathy and heart failure: Heavy alcohol consumption of long duration is associated with a dilated cardiomyopathy with ventricular hypertrophy and fibrosis. They include membrane disruption, depressed function of mitochondria and sarcoplasmic reticulum, intracellular accumulation of phospholipids and fatty acids, and up-regulation of voltage-gated calcium channels.</p> <p>2) Arrhythmias: Heavy drinking are associated with both atrial and ventricular arrhythmias. Patients undergoing alcohol withdrawal syndrome can develop severe arrhythmias that may reflect abnormalities of potassium or magnesium metabolism as well as enhanced release of catecholamines. Seizures, syncope, and sudden death during alcohol withdrawal may be due to these arrhythmias.</p> <p>3) Hypertension: Alcohol is estimated to be responsible for approximately 5% of cases of hypertension, making it one of the most common causes of reversible hypertension. This association is independent of obesity, salt intake, coffee drinking, and cigarette smoking. A reduction in alcohol intake appears to be effective in lowering blood pressure in hypertensive individuals who are also heavy drinkers; the hypertension seen in this population is also responsive to standard blood pressure medications.</p> <p>4) Coronary heart disease: Although the deleterious effects of excessive alcohol use on the cardiovascular system are well established, there is strong epidemiologic evidence that moderate alcohol consumption actually prevents coronary heart disease (CHD), ischemic stroke, and peripheral arterial disease. This type of relationship between mortality and the dose of a drug is called a "J-shaped" relationship.</p> <p>-Results of these clinical studies are supported by ethanol's ability to raise serum levels of high-density lipoprotein (HDL) cholesterol (the form of cholesterol that appears to protect against atherosclerosis), by its ability to inhibit some of the inflammatory processes that underlie atherosclerosis while also increasing production of the endogenous anticoagulant tissue plasminogen activator atherosclerosis.</p>
		<p>D. Blood</p> <p>Alcohol indirectly affects hematopoiesis through metabolic and nutritional effects and may also directly inhibit the proliferation of all cellular elements in bone marrow. The most common hematologic disorder seen in chronic drinkers is mild anemia resulting from alcohol-related folic acid deficiency. Iron deficiency anemia may result from gastrointestinal bleeding.</p>

		E. Endocrine System and Electrolyte Balance Chronic alcohol use has important effects on the endocrine system and on fluid and electrolyte balance. Clinical reports of gynecomastia and testicular atrophy in alcoholics with or without cirrhosis suggest a derangement in steroid hormone balance. Individuals with chronic liver disease may have disorders of fluid and electrolyte balance, including ascites, edema, and effusions. Alterations of whole body potassium induced by vomiting and diarrhea, as well as severe secondary aldosteronism, may contribute to muscle weakness and can be worsened by diuretic therapy. The metabolic derangements caused by metabolism of large amounts of ethanol can result in hypoglycemia, as a result of impaired hepatic gluconeogenesis, and in ketosis, caused by excessive lipolytic factors, especially increased cortisol and growth hormone.
	F. Fetal Alcohol Syndrome	Chronic maternal alcohol abuse during pregnancy is associated with teratogenic effects, and cause of mental retardation and congenital malformation. The abnormalities that have been characterized as fetal alcohol syndrome include (1) intrauterine growth retardation, (2) microcephaly, (3) poor coordination, (4) underdevelopment of midfacial region (appearing as a flattened face), and (5) minor joint anomalies. -Ethanol rapidly crosses the placenta and reaches concentrations in the fetus that are similar to those in maternal blood. -The fetal liver has little or no alcohol dehydrogenase activity, so the fetus must rely on maternal and placental enzymes for elimination of alcohol. -The neuropathologic abnormalities seen in humans and in animal models of fetal alcohol syndrome indicate that ethanol triggers apoptotic neurodegeneration and also causes aberrant neuronal and glial migration in the developing nervous system.
	G. Immune System	Inhibited in some tissues (eg lungs), whereas pathologic, hyperactive immune function in other tissues (eg liver).
H. Increased Risk of Cancer		Mouth, pharynx, larynx, esophagus and liver cancer.

Alcohol-Drug interaction

- The most common alcohol-drug interactions stem from alcohol-induced increases of drug metabolizing enzymes.
- Prolonged intake of alcohol without liver damage can enhance the metabolic biotransformation of other drugs. Ethanol-mediated induction of hepatic cytochrome P450 is important with regard to acetaminophen.
- Chronic consumption (3 drinks or more per day) increase the risk of hepatotoxicity with

high or even therapeutic acetaminophen levels.

- Acute consumption inhibit the metabolism of other drugs because of decreased enzyme activity or liver blood flow.
- Alcohol has an additive CNS depression when combined with other CNS depressants.
- Potentiates pharmacological effect of nonsedative drugs, including vasodilators and oral hypoglycemic agents.

SUMMARY The Alcohols and Associated Drugs

Subclass, Drug	Mechanism of Action, Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
ALCOHOLS			
• Ethanol	Multiple effects on neurotransmitter receptors, ion channels, and signaling pathways	Antidote in methanol and ethylene glycol poisoning	Zero-order metabolism • duration depends on dose • Toxicity: Acutely, central nervous system depression and respiratory failure • chronically, damage to many systems, including liver, pancreas, gastrointestinal tract, and central and peripheral nervous systems • Interactions: Induces CYP2E1 • increased conversion of acetaminophen to toxic metabolite
<ul style="list-style-type: none"> • Methanol: Poisonings result in toxic levels of formate, which causes characteristic visual disturbance plus coma, seizures, acidosis, and death due to respiratory failure • Ethylene glycol: Poisoning creates toxic aldehydes and oxalate, which causes kidney damage and severe acidosis 			
DRUGS USED IN ACUTE ETHANOL WITHDRAWAL			
• Benzodiazepines (eg, chlordiazepoxide, diazepam, lorazepam)	BDZ receptor agonists that facilitate GABA-mediated activation of GABA _A receptors	Prevention and treatment of acute ethanol withdrawal syndrome	See Chapter 22
• Thiamine (vitamin B ₁)	Essential vitamin required for synthesis of the coenzyme thiamine pyrophosphate	Administered to patients suspected of having alcoholism (those exhibiting acute alcohol intoxication or alcohol withdrawal syndrome) to prevent Wernicke-Korsakoff syndrome	Administered parenterally • Toxicity: None • Interactions: None
DRUGS USED IN CHRONIC ALCOHOLISM			
• Naltrexone	Nonselective competitive antagonist of opioid receptors	Reduced risk of relapse in individuals with alcoholism	Available as an oral or long-acting parenteral formulation • Toxicity: GI effects and liver toxicity; will precipitate a withdrawal reaction in individuals physically dependent on opioids and will prevent the analgesic effect of opioids
• Acamprosate	Poorly understood NMDA receptor antagonist and GABA _A agonist effects	Reduced risk of relapse in individuals with alcoholism	Toxicity: GI effects and rash
• Disulfiram	Inhibits aldehyde dehydrogenase, resulting in aldehyde accumulation during ethanol ingestion	Deterrent to drinking in individuals with alcohol dependence	Toxicity: Little effect alone but severe and potentially dangerous flushing, headache, nausea, vomiting, and hypotension when combined with ethanol
DRUGS USED IN ACUTE METHANOL OR ETHYLENE GLYCOL TOXICITY			
• Fomepizole	Inhibits alcohol dehydrogenase, prevents conversion of methanol and ethylene glycol to toxic metabolites	Methanol and ethylene glycol poisoning	Orphan drug • Toxicity: Headache, nausea, dizziness, rare allergic reactions
<ul style="list-style-type: none"> • Ethanol: Higher affinity than methanol or ethylene glycol for alcohol dehydrogenase; used to reduce metabolism of methanol and ethylene glycol to toxic products 			

Chapter #24 : Antiseizure Drugs

24 ANTISEIZURE DRUGS

The epilepsy, the third most common neurologic disorder after dementia and stroke. Although standard therapy permits control of seizures in 80% of these patients. Epilepsy is a heterogeneous symptomcomplex—a chronic disorder characterized by recurrent seizures.

-Seizures are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons. The causes of seizures are many and include the full range of neurologic diseases—from infection to neoplasm and head injury. The term “epilepsy” is not usually applied to such patients unless chronic seizures develop later.

-Seizures are occasionally caused by an acute underlying toxic or metabolic disorder.

DRUG DEVELOPMENT FOR EPILEPSY:

For a long time it was assumed that a single antiepileptic drug (AED) could be developed for the treatment of all forms of epilepsy. therapy to date shows little evidence of etiologic some specificity. according to seizure type (Table 24–1), which

is most clearly seen with generalized seizures of the absence type. which respond to ethosuximideand valproate but can be exacerbated by phenytoin and carbamazepine .Drugs acting selectively on absence seizures.

-In contrast,The maximal electroshock test as the major initial screen for new drugs.Existingantiseizure drugs provide adequate seizure control inabout two thirds of patients. So-called “drug resistance”. Some of the drug-resistant population may respond to vagus nerve stimulation (VNS), a nonpharmacologic treatment for epilepsy .for the treatment of medically refractory partial epilepsy is the responsive neurostimulator (RNS) system. New antiseizure drugs are being sought not only by the screening tests sought that act by one of three mechanisms:

1. enhancement of GABAergic (inhibitory) transmission,
2. diminution of excitatory (usually glutamatergic) transmission, or
3. modification of ionic conductances.

Neuronal targets for current and potential antiseizure drugs include both glutamatergic (excitatory) and gabaergic (inhibitory) synapses.

TABLE 24-1 Classification of seizure types.

Partial (focal) seizures
Simple partial seizures
Complex partial seizures
Partial seizures secondarily generalized
Generalized seizures
Generalized tonic-clonic (grand mal) seizures
Absence (petit mal) seizures
Tonic seizures
Atonic seizures
Clonic and myoclonic seizures
Infantile spasms ¹

¹An epileptic syndrome rather than a specific seizure type; drugs useful in infantile spasms will be reviewed separately.

BASIC PHARMACOLOGY OF ANTISEIZURE DRUGS: PHARMACOKINETICS

1. These are selected for oral activity and all must enter the central nervous system.
2. Absorption is usually good, with 80–100% of the dose reaching the circulation.
3. Most antiseizure drugs (other than phenytoin, tiagabine, and valproic acid) are not highly bound to plasma proteins.
4. Many antiseizure drugs are converted to active metabolites that are also cleared by the liver.
5. These drugs are predominantly distributed into total body water.
6. Plasma clearance is relatively slow; many antiseizure drugs are therefore considered to be medium to long acting.
7. Some have half-lives longer than 12 hours.
8. Many of the older antiseizure drugs are potent inducers of hepatic microsomal enzyme activity.

DRUGS USED IN PARTIAL SEIZURES & GENERALIZED TONIC-CLONIC SEIZURES

The classic major drugs for partial and generalized tonic-clonic seizures are phenytoin (and congeners), carbamazepine, valproate, and the barbiturates. And the newer drugs eslicarbazepine, lamotrigine, levetiracetam, gabapentin, oxcarbazepine, pregabalin, retigabine, topiramate, vigabatrin, lacosamide, and zonisamide.

1)PHENYTOIN

Phenytoin is the oldest nonsedativeantiseizure drug. It was known for decades as diphenylhydantoin

Mechanism of Action:	Clinical Uses	Pharmacokinetics	Therapeutic Levels & Dosage	Drug Interactions & Interference with Laboratory Tests	Toxicity	MEPHENYTOIN , ETHOTOIN , &PHENACEMIDE:
*It alters Na+, K+, and Ca2+ conductance, membrane potentials, and the concentrations of amino acids and the neurotransmitters norepinephrine, acetylcholine, and aminobutyric acid (GABA). * phenytoin blocks sustainedhigh-frequency repetitive firing of action potentials that is a use-dependent effect on Na+ conductance, arising from preferential binding to—and prolongation of—the inactivated state of the Na+ channel. * the major action of phenytoin is to block Na+ channels and inhibit the generation of rapidly repetitiveaction potentials. Presynaptic actions on glutamate and GABA release probably arise from actions other than those on voltagegated Na+ channels. Fig 24-4	Phenytoin is effective against partial seizures and generalized tonic clonic seizures, it appears to be effective against attacks that are either primary or secondary to another seizure type.	Absorption : 1)Absorption of phenytoin sodium from the GIT is nearly complete in most patients. 2)In contrast, fosphenytoin, a more soluble phosphate prodrug of phenytoin, is well absorbed for parenteral use. Distribution: 1)Phenytoin is highly bound to plasma proteins. The total plasma level . Drug concentration in cerebrospinal 2)fluid is proportionate to the free plasma level. 3) Phenytoin accumulates in brain, liver, muscle, and fat. Metabolism&elimination : 1)Phenytoin is metabolized to inactive metabolites that areexcreted in the urine. Only a very small proportion of the dose isexcreted unchanged. 2) phenytoin metabolism follows first-order kinetics. 3)The elimination of phenytoin is dose-dependent. At very low blood levels. 4) The half-life of phenytoin varies from 12 to 36 hours, with anaverage of 24 hours for most patients in the low to mid therapeutic range.	* The therapeutic plasma level of phenytoin for most patients is between 10 and 20 mcg/mL *using fosphenytoin, is the method of choice for convulsive status epilepticus . * oral therapy is common to begin adults at a dosage of 300 mg/d, . it frequently yields steady-state blood levels below 10mcg/mL, which is the minimum therapeutic level for most patients. *The phenytoin dosage should be increased each time byonly 25–30 mg in adults, and ample time should be allowed forthe new steady state to be achieved before further increasing thedosage. *In children, a dosage of 5 mg/kg/dshould be followed.	Drug interactions involving : 1)phenytoin is 90% bound toplasma proteins, other highly bound drugs, such as phenylbutazone and sulfonamides, can displace phenytoin from its binding site. that may cause a transient increase in free drug. 2)A decrease in protein binding— eg, from hypoalbuminemia —results in a decrease in the total plasma concentration of drug but not the free concentration. 3) Intoxication may occur 4)The protein binding of phenytoin is decreased in the presenceof renal disease. 5)The drug has an affinity for thyroid-binding globulin,which confuses some tests of thyroid function. 6)Phenytoin has been shown to induce microsomal enzymes.	-Dose-related adverse effects are often *Nystagmus occurs early. Diplopia and ataxia that is requiring dosage adjustment; *sedation usually occurs only at considerablyhigher levels. *Gingival hyperplasia and hirsutism *Long-term use is associated in some patients with coarseningof facial features and with mild peripheral neuropathy. also result in abnormalities of vitamin D metabolism, leading to osteomalacia. * Low folate levels and megaloblastic anemia. -Idiosyncratic reactions to phenytoin are relatively rare: * A skin rash may indicate hypersensitivity to the drug. Fever,And in rare cases the skin lesions may be severe and exfoliative. *Lymphadenopathy may be difficult to distinguish from malignant lymphoma. *agranulocytosis has been reported in combination with fever and rash.	1) Mephenytoin and ethotoin are most effective against generalized tonic-clonic seizures and partial seizures. 2) The incidence of severe reactions such as dermatitis, agranulocytosis,or hepatitis is higher for mephenytoin than for phenytoin. 3)Ethotoin may be recommended for patients who are hypersensitive to phenytoin. The adverse effects and toxicity are generally less severe than those associated with phenytoin. 5)Careful monitoring of the patient during dosage alterations with either drug is essential. Therapeutic levels for mephenytoin range from 5 to 16 mcg/mL, and therapeutic range for ethotoin has not been established.

2)CARBAMAZEPINE:

Closely related to imipramine and other antidepressants, carbamazepine, is a tricyclic compound effective in treatment of bipolar depression and trigeminal neuralgia but has proved useful for epilepsy as well.

Mechanism of Action:	Clinical Uses:	Pharmacokinetics:	Therapeutic Levels & Dosage	Drug Interactions:
<ul style="list-style-type: none"> It is similar to that phenytoin, carbamazepine shows activity against maximal electroshock seizures. blocks Na⁺ channels at therapeutic concentrations and inhibits high-frequency repetitive firing in neurons in culture It also acts presynaptically to decrease synaptic transmission. Potentiation of a voltage-gated K⁺ current has also been described. These effects probably account for the anticonvulsant action of carbamazepine. 	<ul style="list-style-type: none"> It is the drug of choice for both partial seizures and generalized tonic-clonic seizures. Carbamazepine is not sedative in its usual therapeutic range. The drug is also very effective in some patients with trigeminal neuralgia. Carbamazepine is also useful for controlling mania in some patients with bipolar disorder. 	<p>Absorption</p> <p>1) Although almost complete absorption apparently occurs in all. Peak levels are usually achieved 6–8 hours after administration.</p> <p>2) Slowing absorption by giving the drug after meals helps the patient tolerate larger total daily doses.</p> <p>Distribution</p> <p>1) is slow, and the volume of distribution is roughly.</p> <p>2) The drug is approximately 70% bound to plasma proteins, no displacement of other drugs from protein binding sites.</p> <p>- The drug has a notable ability to induce microsomal enzymes.</p> <p>- The half-life of 36 hours observed in subjects after an initial single dose decreases to as little as 8–12 hours at continuous therapy.</p> <p>Metabolism:</p> <p>Carbamazepine is completely metabolized in humans to several derivatives.</p>	<p>-The therapeutic level is usually 4–8 mcg/mL.</p> <p>-Although many patients complain of diplopia at drug levels above 7 mcg/mL, others can tolerate levels above 10 mcg/mL, especially with monotherapy.</p>	<p>1) The increased metabolic capacity of the hepatic enzymes may cause a reduction in steady-state carbamazepine concentrations and an increased rate of metabolism of other drugs, eg, primidone, phenytoin, ethosuximide, valproic acid, and clonazepam.</p> <p>2) Other drugs such as valproic acid may inhibit carbamazepine clearance and increase steady-state carbamazepine blood levels.</p> <p>3) Other anticonvulsants such as phenytoin and phenobarbital, may decrease steady-state concentrations of carbamazepine through enzyme induction.</p>

OXCARBAZEPINE

- Oxcarbazepine is closely related to carbamazepine and is useful in the same seizure types, but it may have an improved toxicity profile.
- Oxcarbazepine has a half-life of only 1–2 hours.
- Oxcarbazepine is less potent than carbamazepine. Clinical doses of oxcarbazepine may need to be 50% higher than those of carbamazepine to seizure control.
- The drug appears to induce hepatic enzymes to a lesser extent than carbamazepine
- Hyponatremia occur more commonly with oxcarbazepine than with carbamazepine.

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ESLICARBAZINE

Esllicarbazine acetate (ESL) is a prodrug that has been approved as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization.

- ESL is more rapidly converted to licarbazine (eslicarbazine) than is oxcarbazepine; clearly both prodrugs have the same metabolite as active product.
- The mechanism of action is similar to that in carbamazepine, oxcarbazepine, Clinically, the drug is similar to carbamazepine and Oxcarbazepine
- Oral contraceptives may be less effective with concomitant ESL administration.

PHENOBARBITAL

phenobarbital is the oldest of available antiseizure drugs. Although it has long been considered one of the safest of the antiseizure agents, the use of other medications with lesser sedative effects has been urged. Many consider the barbiturates the drugs of choice for seizures only in infants.

Mechanism of Action:	Clinical Uses:	Pharmacokinetics, Therapeutic Levels, & Dosage:
<ul style="list-style-type: none"> • The exact mechanism of action of phenobarbital is unknown but enhancement of inhibitory processes and diminution of excitatory transmission probably contribute significantly . • phenobarbital suppresses high-frequency repetitive firingin neurons in culture through an action on Na⁺ conductance, but only at high concentrations. Also at high concentrations. • Barbiturates block some Ca²⁺ currents (L-type and N-type). • Phenobarbital binds to an allosteric regulatory site on the GABA_A receptor, and it enhances the GABA receptor-mediated current by prolonging the openings of the Cl⁻ channels *Phenobarbital can also decrease excitatory responses. An effect on glutamate release is probably more significant than blockade of AMPA responses • Both the enhancement of GABA-mediated inhibitionand the reduction of glutamate-mediated excitation are seen with therapeutically relevant concentrations of phenobarbital. 	<p>Phenobarbital is useful in the treatment of partial seizures and generalized tonic-clonic seizures, and for virtually every seizure type. There is little evidence for its effectiveness in generalized seizures such as absence, atonic attacks, and infantile spasms;it may worsen certain patients with these seizure types. Some physicians prefer either metharbital or mephobarbital to phenobarbital because of supposed decreased adverse effects.</p>	<p>For pharmacokinetics, drug interactions, and toxicity of phenobarbital(see Chapter 22). The therapeutic levels of phenobarbital in most patients rangefrom 10 mcg/mL to 40 mcg/mL.</p>

PRIMIDONE

Primidone, or 2-desoxyphenobarbital , It was later reported that primidone metabolized to phenobarbital and phenylethylmalonamide(PEMA). All three compounds are active anticonvulsants.

Mechanism of Action:	Clinical Uses:	Pharmacokinetics:	Therapeutic Levels & Dosage:	Toxicity:
Although primidone is converted to phenobarbital, the mechanism of action of primidone itself may be more like that of phenytoin.	<p>It is effective against partial seizures and generalized tonic-clonic seizures. It was previously considered to be the drug of choice for complex partial seizures.</p> <p>Primidone has been shown to be effective in controlling seizures in older patients beginning treatment with primidone.</p> <p>primidone has anticonvulsant action independent of its conversion to phenobarbital and PEMA .</p>	<p>Absorption: Primidone is completely absorbed, usually reaching peak concentrations about 3 hours after oral administration.</p> <p>Distributions: Primidone is generally distributed in total body water . It is not highly bound to plasma proteins; approximately 70% circulates as unbound drug.</p> <p>Metabolism : Primidone is metabolized by oxidation to phenobarbital, which accumulates very slowly. -Both primidone and phenobarbital also undergo subsequent conjugation and excretion.</p> <p>Primidone has a larger clearance than most other antiseizure drugs (2 L/kg/d), corresponding to a half-life of 6–8 hours .</p>	<ul style="list-style-type: none"> • Primidone is most efficacious when plasma levels are in the range of 8–12 mcg/mL. • Concomitant levels of its metabolite, phenobarbital, at steady state usually vary from 15 to 30 mcg/mL. • Increase over days to a few weeks to avoid prominent sedation and gastrointestinal complaints. 	The dose-related adverse effects of primidone are similar to those of its metabolite, phenobarbital, except that drowsiness occurs early in treatment and may be prominent if the initial dose is too large.

FELBAMATE

- Although it is effective in some patients with partial seizures, the drug causes aplastic anemia and severe hepatitis at unexpectedly high rates .
- It has multiple mechanisms of action, It produces a use-dependent block of the NMDA receptor, with selectivity for the NR1-2B subtype, It also produces a barbiturate like potentiation of GABA A receptor responses.
- It has a half-life of 20 hours .
- It is metabolized by hydroxylation and conjugation; and the drug is excreted unchanged in the urine.
- When added to treatment with other antiseizure drugs, felbamate increases plasma phenytoin and valproic acid levels but decreases level of carbamazepine.
- It is usefulness in partial seizures, aslo it is effective against the seizures that occur in Lennox-Gastaut syndrome.

GABAPENTIN & PREGABALIN

Gabapentin is an analog of GABA, Originally planned as a spasmolytic. Pregabalin is another GABA analog, closely related to gabapentin, for both antiseizure activity and for its analgesic properties.

Mechanism of Action:	Clinical Uses:	Pharmacokinetics:
<ul style="list-style-type: none"> Gabapentin and pregabalin do not act directly on GABA receptors. They may, modify the synaptic or nonsynaptic release of GABA. Increase in brain GABA concentration , Gabapentin is transported into the brain by the l-amino acid transporter. Gabapentin and pregabalin bind avidly to the $\alpha 2\delta$ subunit of voltage-gated N-type Ca²⁺ channels, which isdecreasing Ca²⁺ entry. A decrease in the synaptic release of glutamate provides the antiepileptic effect. 	<ul style="list-style-type: none"> Gabapentin is effective as an adjunct against partial seizures and generalized tonic-clonic seizures. Gabapentin is now indicated for postherpetic neuralgia in adults. The most common adverse effects are somnolence, dizziness, ataxia, headache, and tremor. Pregabalin is approved for the adjunctive treatment of partial seizures, with or without secondary generalization. and for use in neuropathic pain, including painful diabetic peripheral neuropathy and post herpetic neuralgia. 	<ul style="list-style-type: none"> Gabapentin is not metabolized and does not induce hepaticenzymes. Absorption is nonlinear and dose-dependent at very highDoses. The drug is not bound to plasma proteins. Elimination is via renal mechanisms; the drug is excretedunchanged. The half-life is relatively short, ranging from 5 to 8Hours. Pregabalin, like gabapentin, is not metabolized and is almostentirely excreted unchanged in the urine. It is not bound to plasma. The half-life of pregabalin ranges from about 4.5 hours to 7.0 hours.

LACOSAMIDE

Lacosamide has been studied in both pain syndromes and partial seizures.

Mechanism of Action:	Clinical Uses:	Pharmacokinetics:
<ul style="list-style-type: none"> It does not act directly on GABA or glutamate receptors. Lacosamide enhances slow inactivation of voltage-gated Na⁺ channels (in contrast to the prolongationof fast inactivation shown by other AEDs). Slow inactivation does not result in complete blockade of Na⁺ channels. blocking the effect of neurotrophic factor. 	<ul style="list-style-type: none"> Lacosamide is adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy who are age 16–17 years and older. Treatment was effective at both 200 and 400 mg/d.. Adverse effects were dizziness, headache, nausea, and diplopia. 	<p>Absorption :</p> <ul style="list-style-type: none"> Oral lacosamide is rapidly and completely absorbed in adults, with no food effect. Bioavailability is nearly 100%. An elimination half-life of 13 hours. There are no active metabolitesand protein binding is minimal. Lacosamide does not induce or inhibit cytochrome P450 isoenzymes.

LAMOTRIGINE

Mechanism of Action:	Clinical Uses:	Pharmacokinetics:
<ul style="list-style-type: none">Lamotrigine, like phenytoin, suppresses sustained rapid firing of neurons and produces a voltage- and use-dependent blockade of Na⁺ channels.This action probably explains lamotrigine's efficacy in focal epilepsy.It also inhibits voltage-gated Ca²⁺ channels .Lamotrigine also decreases the synaptic release of glutamate	<ul style="list-style-type: none">The drug is effective as monotherapy for partial seizures.*The drug is also active against absence and myoclonic seizures in children and for seizure control in the Lennox-Gastaut syndrome.Lamotrigine is also effective for bipolar disorder.Adverse effects include dizziness, headache, diplopia, nausea, somnolence, and skin rash.life-threatening dermatitis will develop in 1–2% of pediatric patients.	<ul style="list-style-type: none">Lamotrigine is almost completely absorbed .Protein binding is only about 55%, and is metabolized by glucuronidation which is excreted in the urine.Lamotrigine has a half-life of approximately 24 hours.Lamotrigine is effective against partial seizures in adults .Twofold increase in the drug's half-life; in patients receiving valproate,

LEVETIRACETAM

Levetiracetam is a piracetam analog that is ineffective against seizures induced by maximum electroshock . This is the first major drug is effective against partial seizures.

Mechanism of Action:	Clinical Uses:	Pharmacokinetics:
<ul style="list-style-type: none">Levetiracetam binds selectively to the synaptic vesicular protein SV2A.levetiracetam inhibits N-type calcium channels and inhibits calcium release from intracellular stores.	<ul style="list-style-type: none">Levetiracetam is the adjunctive treatment of partial seizures in adults and children for primary generalized tonic-clonic seizures and for the myoclonic seizures of juvenile myoclonic epilepsy.Adverse effects include somnolence, asthenia, ataxia, and dizziness. Less common but more serious are mood and behavioral changes; psychotic reactions are rare.	<ul style="list-style-type: none">Oral absorption of levetiracetam is nearly complete; it is rapid and unaffected by food.Protein binding is less than 10%. The plasma.half-life is 6–8 hours, but may be longer in the elderly.The drug is excreted unchanged in the urine.

PERAMPANEL

Perampanel is an orally active AMPA antagonist for the treatment of partial seizures.

Mechanism of Action:	Clinical Uses:	Pharmacokinetics	Drug Interactions:
<ul style="list-style-type: none"> It acts selectively at postsynaptic AMPA receptors. It binds to an allosteric site on the glutamate-gated Na^+/K^+ AMPA channel and is noncompetitive in its action. blockade of the NMDA receptor shortens the duration of repetitive discharge in model neuronal systems. 	<ul style="list-style-type: none"> Perampanel is the adjunctive treatment of partial seizures with or without secondary generalization in patients 12 years of age or older. Serious or life-threatening behavioral adverse reactions including aggression, hostility, irritability, and anger, with or without a previous history of psychiatric disorders. More common adverse effects were dizziness, somnolence, and headache. Although a rash occurred in 1–2% of patients. 	<ul style="list-style-type: none"> Perampanel has a long half-life, typically ranging from 70 to 110 hours. The half-life is prolonged in moderate hepatic failure. Absorption is rapid and the drug is fully bioavailable. Perampanel is 95% bound to plasma proteins. The drug is metabolized via initial oxidation and subsequent glucuronidation. 	<ul style="list-style-type: none"> The drug interactions with perampanel are with potent CYP3A inducer antiseizure drugs such as carbamazepine, oxcarbazepine, and phenytoin. Interactions are also with alcohol and with oral contraceptives containing levonorgestrel. Potent CYP3A inducers may increase the clearance of perampanel when using these drugs concomitantly. When perampanel was administered with carbamazepine, the half-life decreased from 105 hours to 25 hours.

RETIG ABINE (EZOGABINE)

- Retigabine for the adjunctive treatment of partial-onset seizures in adults.
- It is a potassium channel facilitator in its mechanism of action.
- Absorption is not affected by food.
- Most adverse effects are dose related and include dizziness, somnolence, blurred vision, confusion, and dysarthria.
- Bladder dysfunction, mostly mild.
- blue pigmentation on the skin and lips on long-term therapy, And retinal pigment abnormalities are less common Decreased visual acuity.
- the discontinuation of retigabine.

RUFIN AMIDE

Rufinamide is a triazole derivative with little similarity to other antiseizure drugs.

Mechanism of Action	Clinical Uses	Pharmacokinetics
<ul style="list-style-type: none"> It decreases sustained high-frequency firing of neurons is thought to prolong the inactive state of the Na⁺ channel. 	<ul style="list-style-type: none"> It is an adjunctive treatment of seizures associated with the Lennox-Gastaut syndrome in patients age 4 years and older. The drug is effective against all seizure types in this syndrome, especially against tonic-clonic seizures. The drug should be given with food. The most common adverse events are somnolence, vomiting, pyrexia, and diarrhea. 	<ul style="list-style-type: none"> Rufinamide is well absorbed. but plasma concentrations peak between 4 and 6 hours. The half-life is 6–10 hours. The drug is extensively metabolized to inactive products. Most of the drug is excreted in the urine.

STIRIPENTOL

- The drug is used with clobazam and valproate in the adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy of infancy (SMEI, Dravet's syndrome)
- It has been shown to enhance GABAergic transmission in the brain, partly through a barbiturate-like effect, ie, prolonged opening of the Cl⁻ channels in GABAA receptors.
- It also increases GABA levels in the brain.
- Adverse effects of stiripentol may increase the levels of valproate, clobazam, and the active metabolite (norclobazam.).

TIAGABINE

Mechanism of Action	Clinical Uses	Pharmacokinetics
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<ul style="list-style-type: none"> Tiagabine is an inhibitor of GABA uptake in both neurons and glia. It preferentially inhibits the transporter isoform 1 (GAT-1) and increases extracellular GABA levels in the forebrain and hippocampus. It prolongs the inhibitory action of synaptically released GABA, but its most significant effect may be potentiation of tonic inhibition. 	<ul style="list-style-type: none"> Tiagabine is indicated for the adjunctive treatment of partial seizures. Minor adverse events are dose related and include nervousness, dizziness, tremor, difficulty in concentrating, and depression. Excessive confusion, somnolence, or ataxia may require discontinuation. Psychosis occurs rarely. The drug can cause seizures in some patients. Rash is an uncommon idiosyncratic adverse effect. 	<ul style="list-style-type: none"> Tiagabine is 90–100% bioavailable and is highly protein bound. The half-life is 5–8 hours and decreases in the presence of enzyme-inducing drugs. Hepatic impairment causes a slight decrease in clearance. The drug is oxidized in the liver by CYP3A. Elimination is primarily in the feces (60–65%) and urine (25%).
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TOPIRAMATE

Mechanism of Action:	Clinical Uses:	Pharmacokinetics:
<ul style="list-style-type: none"> Topiramate blocks repetitive firing of cultured spinal cord neurons. Its mechanism of action, is likely to involve blocking of voltage-gated Na⁺ channels. It also acts on high-voltage activated (L-type) Ca²⁺ channels. Topiramate potentiates the inhibitory effect of GABA, acting at a site different from the benzodiazepine or barbiturate sites. Topiramate also depresses the excitatory action of kainate on glutamate receptors. 	<ul style="list-style-type: none"> It is as monotherapy demonstrated efficacy against partial and generalized tonic-clonic seizures. The drug is also used for the Lennox-Gastaut syndrome, and effective in infantile spasms and even absence seizures. Topiramate is also used for the treatment of migraine headaches. The dose-related adverse effects occur most frequently in the first 4 weeks and include: somnolence, fatigue, dizziness, cognitive slowing, paresthesias, nervousness, confusion, Acute myopia, glaucoma, And Urolithiasis . The drug is teratogenic and hypospadias in male infants exposed in utero to topiramate. 	<p>Absorption:</p> <ul style="list-style-type: none"> Topiramate is rapidly absorbed (about 2 hours) and is 80% bioavailable. There is no food effect on absorption Only moderate (20–50%) metabolism; no active metabolites are formed. The drug is primarily excreted unchanged in the urine. The half-life is 20–30 hours. Although increased levels are seen with renal failure and hepatic impairment Drug. The major effect is on topiramate levels rather than on the levels of other antiseizure drugs.

VIGABATRIN

GABA transaminase inhibitors, and GABA uptake inhibitors. Vigabatrin is one such drug.

Mechanism of Action	Clinical Uses
<ul style="list-style-type: none"> Vigabatrin is an irreversible inhibitor of GABA aminotransferase (GABA-T), the enzyme responsible for the degradation of GABA. It may also inhibit the vesicular GABA transporter. 	<ul style="list-style-type: none"> Vigabatrin is useful in the treatment of partial seizures and infantile spasms. The half-life is approximately 6–8 hours Typical toxicities include drowsiness, dizziness, and weight gain. Less common but more troublesome adverse reactions are agitation, confusion, and psychosis; preexisting mental illness is a relative contraindication. This phenomenon has now been detected in infants taking the drug. long-term therapy with vigabatrin has been associated with development of peripheral visual field defects in 30–50% of patients. The lesions are located in the retina, increase with drug exposure.

ZONISAMIDE

- Zonisamide is a sulfonamide derivative.
- Its primary site of action appears to be the Na⁺ channel; it also acts on T-type voltage-gated Ca²⁺ channels.
- The drug is effective against partial and generalized tonic-clonic seizures and may also be useful against infantile spasms and certain myoclonias.
- It has good bioavailability, low protein-binding, renal excretion, and a half-life of 1–3 days.
- Adverse effects include drowsiness, cognitive impairment, and potentially serious skin rashes.
- Zonisamide does not interact with other antiseizure drugs

DRUGS USED IN GENERALIZED SEIZURES

ETHOSUXIMIDE

It was introduced as a “pure petit mal” drug.

Mechanism of Action	Clinical Uses	Pharmacokinetics	Therapeutic Levels & Dosage	Drug Interactions & Toxicity
<ul style="list-style-type: none"> Ethosuximide has an important effect on Ca²⁺ currents, reducing the low-threshold (T-type) current. This effect is seen at therapeutically relevant concentrations in thalamic neurons. The T-type Ca²⁺ currents are thought to provide a pacemaker current in thalamic neurons responsible for generating the rhythmic cortical discharge of an absence attack. 	<ul style="list-style-type: none"> Ethosuximide is particularly effective against absence seizures, but has a very narrow spectrum of clinical activity. Ethosuximide and valproate are the drugs of choice for absence seizures and are more effective than lamotrigine. 	<ul style="list-style-type: none"> Absorption is complete of the oral dosage forms. Ethosuximide is not protein-bound. The drug is completely metabolized, principally by hydroxylation, to inactive metabolites. Ethosuximide has a very low total body clearance. This corresponds to a half-life of approximately 40 hours. 	<ul style="list-style-type: none"> Therapeutic levels of 60–100 mcg/mL can be achieved in adults with dosages of 750–1500 mg/d. Ethosuximide has a linear relationship between dose and steady-state plasma levels. 	<ul style="list-style-type: none"> Administration of ethosuximide with valproic acid results in a decrease in ethosuximide clearance and higher steady-state concentrations owing to inhibition of metabolism. The most common dose-related adverse effect of ethosuximide is gastric distress, including pain, nausea, and vomiting. Other dose-related adverse effects are transient lethargy or fatigue and, much less commonly, headache, dizziness, hiccup, and euphoria. Behavioral changes are usually in the direction of improvement.

PHENSUXIMIDE & METHSUXIMIDE

- They are used primarily as anti-absence drugs.
- Methsuximide is generally considered more toxic, and phensuximide less effective, than ethosuximide.
- Unlike ethosuximide, these two compounds have some activity against maximal electroshock seizures, and methsuximide has been used for partial seizures.

VALPROIC ACID & SODIUM VALPROATE

- Sodium valproate, also used as the free acid, valproic acid, was found to have antiseizure properties.
- Valproic acid is fully ionized at body pH.
- valproic acid or a salt of the acid is administered.

Mechanism of Action	Clinical Uses	Pharmacokinetics	Therapeutic Levels & Dosage	Drug Interactions	Toxicity
<ul style="list-style-type: none"> The mechanism of action of valproic acid .Like phenytoin and carbamazepine, valproate blocks sustained high-frequency repetitive firing of neurons in culture at therapeutically relevant concentrations. Its action against partial seizures effect on Na⁺ currents. At very high concentrations, valproate inhibits GABA transaminase in the brain, thus blocking degradation of GABA 	<ul style="list-style-type: none"> Valproate is very effective against absence seizures and is often when the patient has concomitant generalized tonic-clonic attacks. Valproate is unique in its ability to control certain types of myoclonic seizures. The drug is effective in tonic-clonic seizures, especially those that are primarily generalized. Its use in epilepsy is at least as broad as that of any other drug. Other uses of valproate include management of bipolar disorder and migraine prophylaxis. 	<ul style="list-style-type: none"> Valproate is well absorbed after oral administration, with bioavailability greater than 80%. Food may delay absorption, and decreased toxicity may result if the drug is given after meals. Valproic acid is 90% bound to plasma proteins. Its distribution is essentially confined to extracellular water. At higher doses, clearance for valproate is low and dose dependent; its half-life varies from 9 to 18 hours. Approximately 20% of the drug is excreted as a direct conjugate of valproate. 	<ul style="list-style-type: none"> Dosages of 25–30 mg/kg/d others may require 60 mg/kg/d or even more. Therapeutic levels of valproate range from 50 to 100 mcg/mL. 	<ul style="list-style-type: none"> Valproate displaces phenytoin from plasma proteins. Binding interactions, valproate inhibits the metabolism of several drugs, including phenobarbital, phenytoin, and carbamazepine, leading to higher steady-state concentrations of these agents. The inhibition of phenobarbital metabolism, for example, may cause levels of the barbiturate to rise steeply, causing stupor or coma. Valproate can decrease the clearance of lamotrigine. Valproate can decrease the clearance of lamotrigine. 	<ul style="list-style-type: none"> The most common dose-related adverse effects of valproate are nausea, vomiting, and other gastrointestinal complaints such as abdominal pain and heartburn. A fine tremor is frequently seen at higher levels. Other reversible adverse effects, seen in a small number of patients, include weight gain, increased appetite, and hair loss. The idiosyncratic toxicity of valproate is largely limited to hepatotoxicity. The risk is greatest for patients under 2 years of age and for those taking multiple medications. Careful monitoring of liver function is recommended. The other observed idiosyncratic response with valproate is thrombocytopenia. Increase in the incidence of spina bifida in the offspring of women who took valproate during pregnancy. Increased incidence of cardiovascular, orofacial, and digital abnormalities.

OXAZOLIDINEDIONES

- Trimethadione, the first oxazolidinedione is remained the drug of choice for absence seizures .

Use of the oxazolidinediones—trimethadione, paramethadione, and dimethadione.

- These compounds are active against pentylenetetrazole-induced seizures.
- Trimethadione raises the threshold for seizure discharges after repetitive thalamic stimulation.
- Its active metabolite dimethadione—has the same effect on thalamic Ca²⁺ currents as ethosuximide (reducing the T-type Ca²⁺ current).
- Trimethadione is rapidly absorbed, within 1 hour after drug administration.
- It is not bound to plasma proteins.
- Trimethadione is completely metabolized in the liver by demethylation to dimethadione, .
- Dimethadione has an extremely long half-life(240 hours).
- The most common and bothersome dose-related adverse effect of the oxazolidinediones is sedation.
- Trimethadione has been associated with many other toxic and severe adverse effects.
- These drugs should not be used during pregnancy.

OTHER DRUGS USED IN MANAGEMENT OF EPILEPSY

Some drugs not classifiable by application to seizure type are discussed in this section.

BENZODIAZEPINES

- Six benzodiazepines used in the therapy of epilepsy [Chapter 22](#).
- They have two mechanisms of antiseizure action Potentiates GABA responses (the latter effect correlating with an action at the GABA-benzodiazepine allosteric receptor sites). [Chapter 22](#).
- diazepam is effective for generalized tonicclonic, And status epilepticus .
- Lorazepam appears to be more effective and longer acting than diazepam in the treatment of status epilepticus .
- Clonazepam is a long-acting drug is efficacy against absence seizures, It is also effective in some cases of myoclonic seizures and in infantile spasms.
- Sedation is prominent, especially on initiation of therapy; starting doses should be small. Maximal tolerated doses are usually in the range of 0.1–0.2 mg/kg .
- Nitrazepam
1) is used in especially for infantile spasms and myoclonicseizures.
2)It is less potent than clonazepam
- Clorazepate dipotassium is as an adjunct to treatment of complex partial seizures in adults.
- Drowsiness and lethargy are common adverse effects, but as long as the drug is increased gradually.
- Clobazam
1) is widely used in a variety of seizure types, And has less sedative potential.
2) It has a halflife of 18 hours
3) It has an active metabolite, norclobazam. The drug is used for treatment Lennox-Gastaut syndrome.

Pharmacokinetics

[Chapter 22](#).

Limitations

Two prominent aspects of benzodiazepines limit their usefulness.

- 1) is their pronounced sedative effect, which is unfortunate both in the treatment of status epilepticus and in chronic therapy.

*Children may manifest a paradoxical hyperactivity, as with barbiturates.

- 2) is tolerance, in which seizures may respond initially but recur within a few months.

ACETAZOLAMIDE

- Acetazolamide is a diuretic whose main action is the inhibition of carbonic anhydrase [Chapter 15](#).
- Mild acidosis in the brain may be the mechanism by which the drug exerts its antiseizure activity; alternatively, the depolarizing action of bicarbonate ions moving out of neurons via GABA receptor ion channels .
- Acetazolamideis used for all types of seizures but is severely limited by the rapid development of tolerance, with return of seizures usually within a few weeks.
- The drug may have a special role in epileptic women who experience seizure exacerbations at the time of menses.

■ CLINICAL PHARMACOLOGYOF ANTISEIZURE DRUGS

SEIZURE CLASSIFICATION

- In general, the type of medication used for epilepsy depends on the empiric nature of the seizure.
- Errors in seizure diagnosis cause use of the wrong drugs.
- Seizuresare divided into two groups: **partial** and **generalized**.
- classification of epileptic seizures is presented in [Table 24-1](#).

1)Partial (Focal) Seizures	2)the complex partial seizure	3)Generalized Seizures
<ul style="list-style-type: none">• Partial seizures are those in which a localized onset of the attack.• can be ascertained, either by clinical observation or by electroencephalographic recording; the attack begins in a specific locus in the brain.• There are three types of partial seizures.• The least complicated partial seizure is the – simple partial seizurecharacterizedby minimal spread of the abnormal discharge such that normal consciousness and awareness .	<ul style="list-style-type: none">• 1.2the complex partial seizure also has a localized onset, but the discharge becomes more widespread (usually bilateral) and almost always involves the limbic system.• Most complex partial seizures arise from one of the temporal lobes.• The patient may have a brief warning followed by analteration of consciousness during which some patients stare andothers stagger or even fall.	<p>Generalized seizures are those in which there is no evidence of localized onset.</p>

<ul style="list-style-type: none"> For example, the patient may have a sudden onset of clonic jerking of an extremity lasting 60–90 seconds. residual weakness may last for 15–30 minutes after the attack. The patient is completely aware of the attack and can describe it in detail. The electroencephalogram may show an abnormal discharge highly localized to the involved portion of the brain. 	<ul style="list-style-type: none"> motor behavior called automatisms for which the patient has no memory. And typical automatisms are : lip smacking, swallowing, fumbling, scratching, walking about. After 30–120 seconds, the patient makes a gradual recovery to normal consciousness but may feel tired or ill for several hours after the attack. -The secondarily generalized attack. which a partial seizure immediately precedes a generalized tonic-clonic (grand mal) seizure. This seizure type is described in the text that follows. 	
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Generalized tonic-clonic (grand mal):	Theary generalized tonic-clonic seizures	The absence (petit mal)	Myoclonic seizures	Atonic seizures	Infantile spasms
<ul style="list-style-type: none"> seizures are the most dramatic of all epileptic seizures . are characterized by : <ol style="list-style-type: none"> tonic rigidity of all extremities, followed in 15–30 seconds by a tremor. The attack enters the clonic phase, with massive jerking of the body. The clonic jerking slows over 60–120 seconds, and the patient is usually left in a stuporous state. The tongue or cheek may be bitten, and urinary incontinence is common. 	<ul style="list-style-type: none"> Begin without evidence of localized onset, whereas secondary generalized tonic-clonic seizures are preceded by another seizure type, usually a partial seizure. The medical treatment of both primary and secondary generalized tonic-clonic seizures is the same and uses drugs appropriate for <i>partial</i> seizures. 	<ol style="list-style-type: none"> Is characterized by both sudden onset and abrupt cessation. Its duration is usually less than 10 seconds and rarely more than 45 seconds. Consciousness is altered; the attack may also be associated with mild clonic jerking of the eyelids or extremities, with postural tone changes, autonomic phenomena, and automatisms. Absence attacks begin in childhood or adolescence and may occur up to hundreds of times a day. Atypical absence patients have seizures with postural changes that are more abrupt. 	<ul style="list-style-type: none"> is including generalized tonic-clonic seizures, partial seizures, absence seizures, and infantile spasms. Treatment of seizures that include myoclonic jerking should be directed at the primary seizure type rather than at the myoclonus. Some patients, have myoclonic jerking as the major seizure type. 	<ol style="list-style-type: none"> which the patient has sudden loss of postural tone. If standing, the patient falls suddenly to the floor and may be injured. If seated, the head and torso may suddenly drop forward. Although most often seen in children, this seizure type is not unusual in adults. 	<ul style="list-style-type: none"> are an epileptic syndrome and not a seizure type. These attacks are most characterized by: recurrent myoclonic jerks of the body with sudden flexion or extension of the body and limbs. Most patients are intellectually delayed, presumably from the same cause as the spasms.

MANAGEMENT OF EPILEPSY

PARTIAL SEIZURES & GENERALIZED TONIC-CLONIC SEIZURES

GENERALIZED SEIZURES

- | | |
|---|--|
| <ul style="list-style-type: none"> • The choice of drugs for partial and tonic-clonic seizures was usually limited to phenytoin, carbamazepine, or barbiturates. • Most newer drugs have a broader spectrum of activity, and many are well tolerated and are preferred in the older ones. • Most of these newer drugs confer an increased risk of non traumatic fractures, choosing a drug on this basis is not yet practical. | <ul style="list-style-type: none"> • The drugs used for generalized tonic-clonic seizures are the same as for partial seizures; in addition, valproate is clearly useful. • Three drugs are effective against absence seizures. • Two are nonsedating and are preferred: E ethosuximide and valproate. • Clonazepam Lamotrigine and topiramate are also highly effective. • Specific myoclonic syndromes are usually treated with valproate (IV). • Zonisamide and levetiracetam are useful. Another specific myoclonic syndrome, juvenile myoclonic epilepsy, can be aggravated by phenytoin or carbamazepine; valproate is the drug of choice followed by lamotrigine and topiramate. <p>Atonic seizures that is valproate may be beneficial. Benzodiazepines improve seizure control in some of these patients but may worsen the attacks in others.</p> |
|---|--|

DRUGS USED IN INFANTILE SPASMS:

- The treatment is limited to improvement of control of the seizures rather than other features of the disorder, such as retardation.
- Most patients receive a course of intramuscular corticotropin.
- Therapy must often be discontinued because of adverse effects.
- Other drugs widely used are the benzodiazepines such as clonazepam or nitrazepam.
- Vigabatrin is effective and is considered the drug of choice by many pediatric neurologists.

STATUS EPILEPTICUS

- The most common status epilepticus is **generalized tonic-clonic status epilepticus**
- It is a life-threatening emergency, requiring immediate cardiovascular, respiratory, and metabolic management as well as pharmacologic therapy.
- Diazepam(IV) is the most effective drug in most patients for stopping the attacks .
- Diazepam(IV) may depress respiration (less frequently, cardiovascular function) during its administration.
- The effect of diazepam is not lasting, but the 30- to 40-minute seizure-free interval.
- Some psychics prefer lorazepam, which is equivalent to diazepam in effect and has longer acting.
- Treatment for status epilepticus was phenytoin(IV) which is effective and nonsedating.
- Careful monitoring of cardiac rhythm and blood pressure is necessary, especially in elderly people.
- Fosphenytoin, which is freely soluble in IV solutions.
- phenytoin dose-related toxicity such as ataxia.
- can be given in large doses IV, Respiratory depression is a common complication.
- other drugs such as lidocaine have been recommended for the treatment of generalized tonic-clonic status epilepticus.
- general anesthesia is usually necessary in highly resistant cases.
- patients in absence status, benzodiazepines are still drugs of first choice.

SPECIAL ASPECTS OF THE TOXICOLOGY OF ANTISEIZUREDRUGS:

TERATOGENICITY	WITHDRAWAL	OVER DOSE	SUICIDALITY
<ul style="list-style-type: none"> -resulting from long term and high doses of drug in treatment many patients. -In children born to mothers taking antiseizure drugs have an increased risk of congenital malformations. -Phenytoin has has specific syndrome called fetal hydantoin syndrome. -Valproate, has also a specific malformation, spina bifida. in pregnant woman . 	<ul style="list-style-type: none"> -Withdrawal of antiseizuredrugs, cause increased seizure frequency and severity. -The two factors to consider are the effects of the withdrawal itself in the individual: <ol style="list-style-type: none"> 1) that the abrupt discontinuance of antiseizure drugs ordinarily does not cause seizures in nonepileptic Patients. 2) provided that the drug levels are not above the usual therapeutic range when the drug is stopped. -Barbiturates and benzodiazepines are the most difficult to discontinue; weeks or months may be required, with very gradual dosage. 	<ul style="list-style-type: none"> -Antiseizure drugs are central nervous system depressants but are rarely lethal. -Very high blood levels are usually necessary before overdoses can be considered life-threatening. -The most dangerous effect of antiseizure drugs after large overdoses is respiratory depression, which may be potentiated by other agents, such as alcohol. -Treatment of antiseizure drug overdose Efforts to hasten removal of antiseizure drugs, such as alkalization of the urine (phenytoin is a weak acid), are usually ineffective. 	<ul style="list-style-type: none"> The presence of either suicidal behavior or suicidal ideation was 0.37% in patients taking active drugs and 0.24% in patients taking placebo.

ANTISEIZURE DRUGSIN DEVELOPMENT

Three potential new antiseizure drugs are in phase 2 or phase 3 development; these are brivaracetam,

Chapter #25 : General Anesthetics



25. General Anesthetics

Humankind has relied on natural medicines and physical methods to control surgical pain. The neurophysiologic state produced by general anesthetics characterized by five primary effects:**unconsciousness, amnesia, analgesia, inhibition of autonomic reflexes, and skeletal muscle relaxation.**

None of the currently available anesthetic agents, when used alone, can produce all five of these desired effects well. An ideal

anesthetic drug should induce fast, smooth loss of consciousness, quickly reversible upon discontinuation, and safe.

The modern practice of anesthesiology relies on the use of combinations of intravenous and inhaled drugs to take advantage of the favorable properties of each agent while minimizing their adverse effects. The choice of the anesthetic method determined by the type of diagnostic, therapeutic, or surgical intervention performed

MECHANISM OF GENERAL ANESTHETIC ACTION

Anesthetic action superseded by a more complex picture of molecular targets located at multiple levels of the central nervous system (CNS). Anesthetics affect neurons at various cellular locations, but the primary focus has been on the synapse. A presynaptic action may alter the release of neurotransmitters, whereas a postsynaptic effect may change the frequency or amplitude of impulses exiting the synapse.

Chloride channels (γ -aminobutyric acid-A [GABA_A] and glycine receptors) and potassium channels (K₂P, possibly K_V, and K_{ATP} channels) remain the primary inhibitory ion channels considered legitimate candidates of anesthetic action. Excitatory ion channel targets include those activated by acetylcholine (nicotinic and muscarinic receptors), by glutamate (amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid [AMPA], kainate, and N-methyl-d-aspartate [NMDA] receptors), or by serotonin (5-HT₂ and 5-HT₃ receptors). Figure 25-1 depicts the relation of these inhibitory and excitatory targets of anesthetics within the context of the nerve terminal.

■ INHALED ANESTHETICS

A clear difference between volatile and gaseous anesthetics, both of which are administered by inhalation. Volatile anesthetics (**halothane, enflurane, isoflurane, desflurane, sevoflurane**) have low vapor pressures and thus high boiling points (they are liquids at room temperature), whereas gaseous anesthetics (**nitrous oxide, xenon**) have high vapor pressures and low boiling points such that they are in gas form at room temperature.

PHARMACOKINETICS

Inhaled anesthetics, volatile as well as gaseous, are taken up through gas exchange in the alveoli of the lung. Uptake from the alveoli into the blood and distribution and partitioning into the effect compartments are important determinants of the kinetics of these agents

Uptake & Distribution

A. Factors Controlling Uptake

1. Inspired concentration and ventilation

Two parameters that can be controlled by the anesthesiologist determine how quickly the alveolar concentration changes: (1) inspired concentration (2) alveolar ventilation. The partial pressure of an inhaled anesthetic in the inspired gas mixture directly affects the maximum partial pressure that can be achieved in the alveoli as well as the rate of increase of the partial pressure in the alveoli. Increases in the inspired partial pressure increase the gradient between inspired and alveolar partial pressure to accelerate induction. The increase of partial pressure in the alveoli is usually expressed as a ratio of alveolar concentration (F_A) over inspired

concentration (F_A); the faster F_A/F_I approaches 1 (representing inspired-to-alveolar equilibrium), the faster anesthesia will occur during an inhaled induction.

2. Solubility

The rate of rise of F_A/F_I is an important determinant of the speed of induction, but is opposed by the uptake of anesthetic into the blood. Uptake is determined by pharmacokinetic characteristics of each anesthetic agent as well as patient factors.

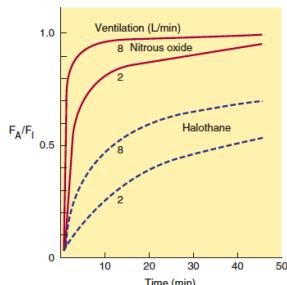


FIGURE 25–3 Effect of ventilation on F_A/F_I and induction of anesthesia. Increased ventilation (8 L/min versus 2 L/min) accelerates the rate of rise toward equilibration of both halothane and nitrous oxide but results in a larger percentage increase for halothane in the first few minutes of induction.

One of the most important factors influencing the transfer of an anesthetic from the lungs to the arterial blood is its solubility characteristics. When an anesthetic with low blood solubility diffuses from the lung into the arterial blood, relatively few molecules are required to raise its partial pressure; therefore, the arterial tension rises rapidly.

3. Cardiac output

Changes in pulmonary blood flow have

obvious effects on the uptake of anesthetic gases from the alveolar space. An increase in pulmonary blood flow (ie, increased cardiac output) will increase the uptake of anesthetic, thereby decreasing the rate by which F_A/F_I rises, which will decrease the rate of induction of anesthesia.

To better understand this mechanism, one should think about the effect of cardiac output in combination with the tissue distribution and uptake of anesthetic into other tissue compartments.

TABLE 25–1 Pharmacologic properties of inhaled anesthetics.

Anesthetic	Blood:Gas Partition Coefficient ¹	Brain:Blood Partition Coefficient ¹	Minimal Alveolar Concentration (MAC) (%) ²	Metabolism	Comments
Nitrous oxide	0.47	1.1	>100	None	Incomplete anesthetic; rapid onset and recovery
Desflurane	0.42	1.3	6–7	<0.05%	Low volatility; poor induction agent (pungent); rapid recovery
Sevoflurane	0.69	1.7	2.0	2–5% (fluoride)	Rapid onset and recovery; unstable in soda-lime
Isoflurane	1.40	2.6	1.40	<2%	Medium rate of onset and recovery
Enflurane	1.80	1.4	1.7	8%	Medium rate of onset and recovery
Halothane	2.30	2.9	0.75	>40%	Medium rate of onset and recovery

4. Alveolar-venous partial pressure difference

Depending on the rate and extent of tissue uptake, venous blood returning to the lungs may contain significantly less anesthetic than arterial blood. The greater this difference in anesthetic gas tensions, the more time it will take to achieve equilibrium with brain tissue.

Anesthetic uptake into tissues is influenced by factors similar to those that determine transfer of the anesthetic from the lung to the intravascular space, including tissue: blood partition coefficients, rates of blood flow to the tissues, and concentration gradients.

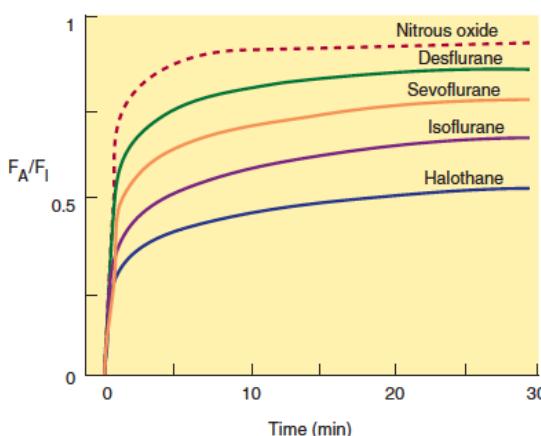


FIGURE 25-4 The alveolar anesthetic concentration (F_A) approaches the inspired anesthetic concentration (F_I) fastest for the least soluble agents.

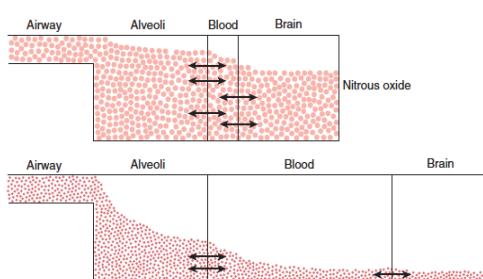


FIGURE 25-5 Why induction of anesthesia is slower with more soluble anesthetic gases. In this schematic diagram represented by the relative size of the blood compartment (the more soluble, the larger the compartment). Relatively agents in the compartments are indicated by the degree of filling of each compartment. For a given concentration of anesthetic gases in the inspired air, it will take much longer for the blood partial pressure of the more soluble gas to reach the same partial pressure as in the alveoli. Since the concentration of the anesthetic agent in the brain can rise no faster than in the blood, the onset of anesthesia will be slower with halothane than with nitrous oxide.

B. Elimination

The time to recovery from inhalation anesthesia depends on the rate of elimination of the anesthetic from the brain. One of the most important factors of the anesthetic agent rate of recovery is the blood:gas barrier coefficient. Other factors controlling the rate of recovery include pulmonary blood flow, the degree of ventilation, and tissue solubility of the anesthetic.

Two points differentiate the recovery phase from the induction phase. First, transfer of an anesthetic from the lungs to blood can be enhanced by increasing its concentration in inspired air, but the reverse transfer process cannot be enhanced because the concentration in the lungs cannot be reduced below zero. Second, at the beginning of the recovery phase, the anesthetic gas tension in different tissues may be quite variable,

depending on the particular agent and the duration of anesthesia. In contrast, at the start of induction of anesthesia, the initial anesthetic tension is zero in all tissues.

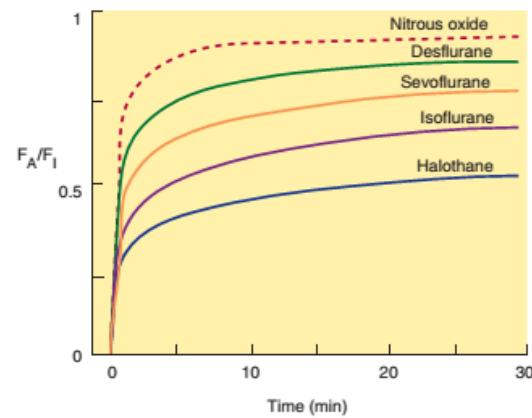


FIGURE 25-4 The alveolar anesthetic concentration (F_A) approaches the inspired anesthetic concentration (F_I) fastest for the least soluble agents.

1. Ventilation

Two parameters that can be manipulated by the anesthesiologist are useful in controlling the speed of induction of and recovery from inhaled anesthesia: (1) concentration of anesthetic in the inspired gas and (2) alveolar ventilation.

Because the concentration of anesthetic in the inspired gas cannot be reduced below zero, **hyperventilation is the only way to speed recovery.**

2. Metabolism

Modern inhaled anesthetics are eliminated mainly by ventilation and are only metabolized to a very small extent.

Hepatic metabolism may also contribute to the elimination of and recovery from some older volatile anesthetics. For example, halothane is eliminated more rapidly during recovery than enflurane,

which would not be predicted from their respective tissue solubility. This increased elimination occurs because over 40% of inspired halothane is metabolized during an average anesthetic procedure,

whereas less than 10% of enflurane is metabolized over the same period.

In terms of the extent of hepatic metabolism, the rank order for **halothane** >**enflurane**>**sevoflurane**>**isoflurane**>**desflurane**> **nitrous oxide**.

Human tissues do not metabolize nitrous oxide, bacteria in the gastrointestinal tract may be able to break down the nitrous oxide molecule.

PHARMACODYNAMICS

Organ System Effects of Inhaled Anesthetics

A. Cerebral Effects

Anesthetic potency is currently described by the minimal alveolar concentration (MAC) required to prevent a response to a surgical incision. Inhaled anesthetics decrease the metabolic activity of the brain. Decreased cerebral metabolic rate (CMR) generally reduces blood flow within the brain.

Nitrous oxide can increase cerebral blood flow and cause increased intracranial pressure. Therefore, nitrous oxide may be combined with other agents(intravenous anesthetics) or techniques (hyperventilation) that reduce cerebral blood flow in patients with increased intracranial pressure. Traditionally, anesthetic effects on the brain produce four stages of increasing depth of CNS depression :

Stage I—analgesia: The patient initially experiences analgesia without amnesia. Later in stage I, both analgesia and amnesia are produced.

Stage II—excitement: During this stage, the patient appears delirious, may vocalize but is completely amnesic. Respiration is rapid, and heart rate and blood pressure increase. Duration and severity of this stage is shortened by rapidly increasing the concentration of the agent.

Stage III—surgical anesthesia: This stage begins with slowing of respiration and heart rate and apnea . stage III are described based on changes in ocular

movements, eye reflexes, and pupil size, indicating increasing depth of anesthesia.

Stage IV—medullary depression: This deep stage of anesthesia represents severe depression of the CNS, including the vasomotor center in the medulla and respiratory center in the brain stem. Without circulatory and respiratory support, death would rapidly ensue.

B. Cardiovascular Effects

All volatile agents tend to decrease mean arterial pressure in direct proportion to their alveolar concentration. With halothane and enflurane, the reduced arterial pressure is caused primarily by myocardial depression (reduced cardiac output) and there is little change in systemic vascular resistance. In contrast, isoflurane, desflurane, and sevoflurane produce greater vasodilatation with minimal effect on cardiac output. These differences may have important implications for patients with heart failure.

Inhaled anesthetics tend to reduce myocardial oxygen consumption, which reflects depression of normal cardiac contractility and decreased arterial blood pressure. In addition, inhaled anesthetics produce coronary vasodilation. The net effect of decreased oxygen demand and increased coronary flow (oxygen supply) is improved myocardial oxygenation.

C. Respiratory Effects:

All volatile anesthetics possess varying degrees of bronchodilating properties, an effect of value in patients with active wheezing and *in status asthmaticus*.

The bronchodilating action of halothane and sevoflurane makes them the agents of choice in patients with underlying airway problems. Nitrous oxide is nonpungent and can facilitate inhalational induction of anesthesia in a patient with bronchospasm. The control of breathing is significantly affected by inhaled anesthetics. With the exception of nitrous oxide, all

inhaled anesthetics in current use cause a dose-dependent decrease in tidal volume and an increase in respiratory rate, resulting in a rapid, shallow breathing pattern. During prolonged exposure to inhaled anesthetics, mucus pooling and plugging may result in atelectasis and the development of postoperative respiratory complications, including hypoxemia and respiratory infections.

D. Renal Effects

Inhaled anesthetics tend to decrease glomerular filtration rate (GFR) and urine flow.

E. Hepatic Effects

Volatile anesthetics cause a concentration-dependent decrease in portal vein blood flow that parallels the decline in cardiac output produced by these agents.

F. Effects on Uterine Smooth Muscle

Nitrous oxide appears to have little effect on uterine musculature. However, the halogenated anesthetics are potent uterine muscle relaxants and produce this effect in a concentration-dependent fashion.

Toxicity of Anesthetic Agents

A. Acute Toxicity

1. Nephrotoxicity—Metabolism of enflurane and sevoflurane may generate compounds that are potentially nephrotoxic.

2. Hematotoxicity—Prolonged exposure to nitrous oxide decreases methionine synthase activity, which theoretically could cause megaloblastic anemia.

3. Malignant hyperthermia—Malignant hyperthermia is a heritable genetic disorder of skeletal muscle that occurs in susceptible individuals exposed to volatile anesthetics while undergoing general anesthesia.

4. Hepatotoxicity (halothane hepatitis)—Hepatic dysfunction following surgery and general anesthesia is most likely caused by hypovolemic shock, infection conferred by blood transfusion, or other surgical stresses

rather than by volatile anesthetic toxicity.

B. Chronic Toxicity

1. Mutagenicity, teratogenicity, and reproductive effects—

Under normal conditions, inhaled anesthetics including nitrous oxide are neither mutagens nor carcinogens in patients. Nitrous oxide can be directly teratogenic in animals under conditions of extremely high exposure.

Halothane, enflurane, isoflurane, desflurane, and sevoflurane may be teratogenic in rodents as a result of physiologic changes associated with the anesthesia rather than through a direct teratogenic effect.

2. Carcinogenicity—Most operating rooms now use scavenging systems to remove trace concentrations of anesthetics released from anesthetic machines.

■ INTRAVENOUS ANESTHETICS

Intravenous nonopioid anesthetics play an essential role in the practice of modern anesthesia. They are used to facilitate rapid induction of anesthesia and have replaced inhalation as the preferred method of anesthesia induction in most settings except for pediatric anesthesia.

PROPOFOL

Pharmacokinetics

Propofol is rapidly metabolized in the liver; the resulting water soluble compounds are presumed to be inactive and are excreted through the kidneys. Plasma clearance is high and exceeds hepatic blood flow, which presumably occurs in the lungs, elimination of up to 30% of a bolus dose of the drug.

The recovery from propofol is more complete, with less “hangover” than that observed with thiopental. As with other intravenous agents, awakening after an induction dose of propofol usually occurs within 8–10 minutes.

Organ System Effects

A. CNS Effects

Propofol acts as hypnotic but does not have analgesic properties. Although the drug leads to a general suppression of CNS activity, excitatory effects such as twitching or spontaneous movement are occasionally observed during induction of anesthesia.

B. Cardiovascular Effects

Compared with other induction drugs, propofol produces the most pronounced decrease in systemic blood pressure; this is a result of profound vasodilation in both arterial and venous circulations leading to reductions in preload and after load. This effect on systemic blood pressure is more pronounced with increased age, in patients with reduced intravascular fluid volume, and with rapid injection.

C. Respiratory Effects

Propofol is a potent respiratory depressant and generally produces apnea after an induction dose.

D. Other Effects

Unexpected tachycardia occurring during propofol anesthesia should prompt laboratory evaluation for possible metabolic acidosis. An interesting and desirable side effect of propofol is its antiemetic activity. Pain on injection is a common complaint and can be reduced by premedication with an opioid or co-administration with lidocaine.

Clinical Uses & Dosage

The most common use of propofol is to facilitate induction of general anesthesia by bolus injection of 1–2.5 mg/kg IV.

Increasing age, reduced cardiovascular reserve, or premedication with benzodiazepines or opioids reduces the required induction dose; children require higher doses (2.5–3.5 mg/kg IV). Propofol is often used for maintenance of anesthesia either as part of a balanced anesthesia regimen in combination with volatile anesthetics, nitrous oxide, sedative-hypnotics, and opioids or as part of a total intravenous anesthetic technique.

FOSPROPOFOL

Fospropofol is a water-soluble prodrug of propofol, rapidly metabolized by alkaline phosphatase, and producing propofol, phosphate, and formaldehyde. The available fospropofol formulation is a sterile, aqueous, colorless, and clear solution that is supplied in a single-dose.

Pharmacokinetics & Organ System Effects

Because the active compound is propofol and fospropofol is a prodrug that requires metabolism to form propofol, the pharmacokinetics are more complex than for propofol itself. Multi-compartment models with two compartments for fospropofol and three for propofol have been used to describe the kinetics. The effect profile

is similar to that of propofol, but onset and recovery are prolonged compared with propofol because the prodrug must first be converted into an active form.

Clinical Uses & Dosage

Fospropofol is approved for sedation during monitored anesthesia care. Supplemental oxygen must be administered to all patients receiving the drug.

The recommended standard dosage is an initial bolus dose of 6.5 mg/kg IV followed by supplemental doses of 1.6 mg/kg IV as needed. For patients weighing more than 90 kg or less than 60 kg, 90 or 60 kg should be used to calculate the dose, respectively. The dose should be reduced by 25% in patients older than 65 years and in those with an American Society of Anesthesiologists status of 3 or 4.

BARBITURATES

This section focuses on the use of thiopental and methohexitol for induction of general anesthesia; however, these barbiturate hypnotics have been largely replaced as induction agents by propofol.

Pharmacokinetics

Thiopental and methohexitol undergo hepatic metabolism, mostly by oxidation but also by N-dealkylation, desulfuration, and destruction of the barbituric acid ring structure. Barbiturates should not be administered to patients with acute intermittent porphyria. Methohexitol has a shorter elimination half-time than thiopental due to its larger plasma clearance, leading to a faster and more complete recovery after bolus injection.

Organ System Effects

A. CNS Effects

Barbiturates produce dose-dependent CNS depression ranging from sedation to general anesthesia when administered as bolus injections. The ability of barbiturates to decrease ICP and CMRO₂ makes these drugs useful in the management of patients with space-occupying intracranial lesions. They may provide neuroprotection from focal cerebral ischemia.

B. Cardiovascular Effects

The decrease in systemic blood pressure associated with administration of barbiturates for induction of anesthesia is primarily due to peripheral vasodilation and is usually smaller than the blood pressure decrease associated with propofol. There are also direct negative inotropic effects on the heart.

C. Respiratory Effects

Barbiturates are respiratory depressants, and a usual induction dose of thiopental or methohexitol typically produces transient apnea, which will be more pronounced if other respiratory depressants are also administered.

Barbiturates lead to decreased minute ventilation through reduced tidal volumes and respiratory rate and also decrease the ventilatory responses to hypercapnia and hypoxia.

D. Other Effects

Accidental intra-arterial injection of barbiturates results in excruciating pain and intense vasoconstriction, often leading to severe tissue injury involving gangrene. Approaches to treatment include blockade of the sympathetic nervous system (eg, stellate ganglion block) in the involved extremity.

Clinical Uses & Dosage

Benzodiazepines are most commonly used for preoperative medication, intravenous sedation, and suppression of seizure activity. Less frequently, midazolam and diazepam may also be used to induce general anesthesia. The slow onset and prolonged duration of action of lorazepam limit its usefulness for preoperative medication or induction of anesthesia, especially when rapid and sustained awakening at the end of surgery is desirable. General anesthesia can be induced by the administration of midazolam (0.1–0.3 mg/kg IV), but the onset of unconsciousness is slower than after the administration of thiopental, propofol, or etomidate. Delayed awakening is a potential disadvantage, limiting the usefulness of benzodiazepines for induction of general anesthesia despite their advantage of less pronounced circulatory effects.

ETOMIDATE

Etomidate is an intravenous anesthetic with hypnotic but not analgesic effects and is often chosen for its minimal hemodynamic effects. Although its pharmacokinetics are favorable, endocrine side effects limit its use for continuous infusions.

Pharmacokinetics

An induction dose of etomidate produces rapid onset of anesthesia, and recovery depends on redistribution to inactive tissue sites, comparable to thiopental and propofol. Metabolism is primarily by ester hydrolysis to inactive metabolites, which are then excreted in urine and bile. Clearance of etomidate is about five times that of thiopental, as reflected by a shorter elimination half-time

Organ System Effects

A. CNS Effects

Etomidate is a potent cerebral vasoconstrictor, as reflected by decreases in cerebral blood flow and ICP.

These effects are similar to those produced by comparable doses of thiopental.

B. Cardiovascular Effects

A characteristic and desired feature of induction of anesthesia with etomidate is cardiovascular stability after bolus injection. In this regard, decrease in systemic blood pressure is modest or absent and principally reflects a decrease in systemic vascular resistance.

C. Respiratory Effects

The depressant effects of etomidate on ventilation are less pronounced than those of barbiturates, although apnea may occasionally follow rapid intravenous injection of the drug.

D. Endocrine Effects

Etomidate causes adrenocortical suppression by producing a dose dependent inhibition of 11 β -hydroxylase, an enzyme necessary for the conversion of cholesterol to cortisol.

Clinical Uses & Dosage

Etomidate is an alternative to propofol and barbiturates for the rapid intravenous induction of anesthesia, especially in patients with compromised myocardial contractility. After a standard induction dose (0.2–0.3 mg/kg IV), the onset of unconsciousness is comparable to that achieved by thiopental and propofol. There is a high incidence of pain, which may be followed by venous irritation. Involuntary myoclonic movements are also common but may be masked by the concomitant administration of neuromuscular blocking drugs.

KETAMINE

Ketamine is a partially water-soluble and highly lipid soluble phencyclidine derivative differing from most other intravenous anesthetics in that it produces significant analgesia.

Pharmacokinetics

The high lipid solubility of ketamine ensures a rapid onset of its effect. As with other intravenous induction drugs, the effect of a single bolus injection is terminated by redistribution to inactive tissue sites. Metabolism occurs primarily in the liver and involves N-

demethylation by the cytochrome P450 system.

A. CNS Effects

In contrast to other intravenous anesthetics, ketamine is considered to be a cerebral vasodilator that increases cerebral blood flow, as well as CMRO₂. For these reasons, ketamine has traditionally not been recommended for use in patients with intracranial pathology, especially increased ICP.

B. Cardiovascular Effects

Ketamine can produce transient but significant increases in systemic blood pressure, heart rate, and cardiac output, presumably by centrally mediated sympathetic stimulation.

These effects, which are associated with increased cardiac workload and myocardial oxygen consumption, are not always desirable and can be blunted by co-administration of benzodiazepines, opioids, or inhaled anesthetics.

C. Respiratory Effects

Ketamine is not thought to produce significant respiratory depression.

When it is used as a single drug, the respiratory response to hypercapnia is preserved and blood gases remain stable.

Clinical Uses & Dosage

Its unique properties, including profound analgesia, stimulation of the sympathetic nervous system, bronchodilation, and minimal respiratory depression, make ketamine an important alternative to the other intravenous anesthetics and a desirable adjunct in many cases despite the unpleasant psychotomimetic effects. Induction of anesthesia can be achieved with ketamine, 1–2 mg/kg intravenously or 4–6 mg/kg intramuscularly. Small bolus doses of ketamine (0.2–0.8 mg/kg IV) may be useful during regional anesthesia

DEXMEDETOMIDINE

Dexmedetomidine is a highly selective α₂-adrenergic agonist.

Recognition of the usefulness of α₂ agonists is based on observations of decreased anesthetic requirements in patients receiving chronic clonidine therapy.

Pharmacokinetics

Dexmedetomidine undergoes rapid hepatic metabolism involving N-methylation and hydroxylation, followed by conjugation. Metabolites are excreted in the urine and bile. Clearance is high, and the elimination half-time is short.

Organ System Effects

Dexmedetomidine produces its selective α₂-agonist effects through activation of CNS α₂ receptors. Hypnosis presumably results from stimulation of α₂ receptors in the locus caeruleus, and the analgesic effect originates at the level of the spinal cord.

B. Cardiovascular Effects

Dexmedetomidine infusion results in moderate decreases in heart rate and systemic vascular resistance and, consequently, a decrease in systemic blood pressure. A bolus injection may produce a transient increase in systemic blood pressure and pronounced decrease in heart rate, an effect that is probably mediated through activation of peripheral α₂ adrenoceptors.

C. Respiratory Effects

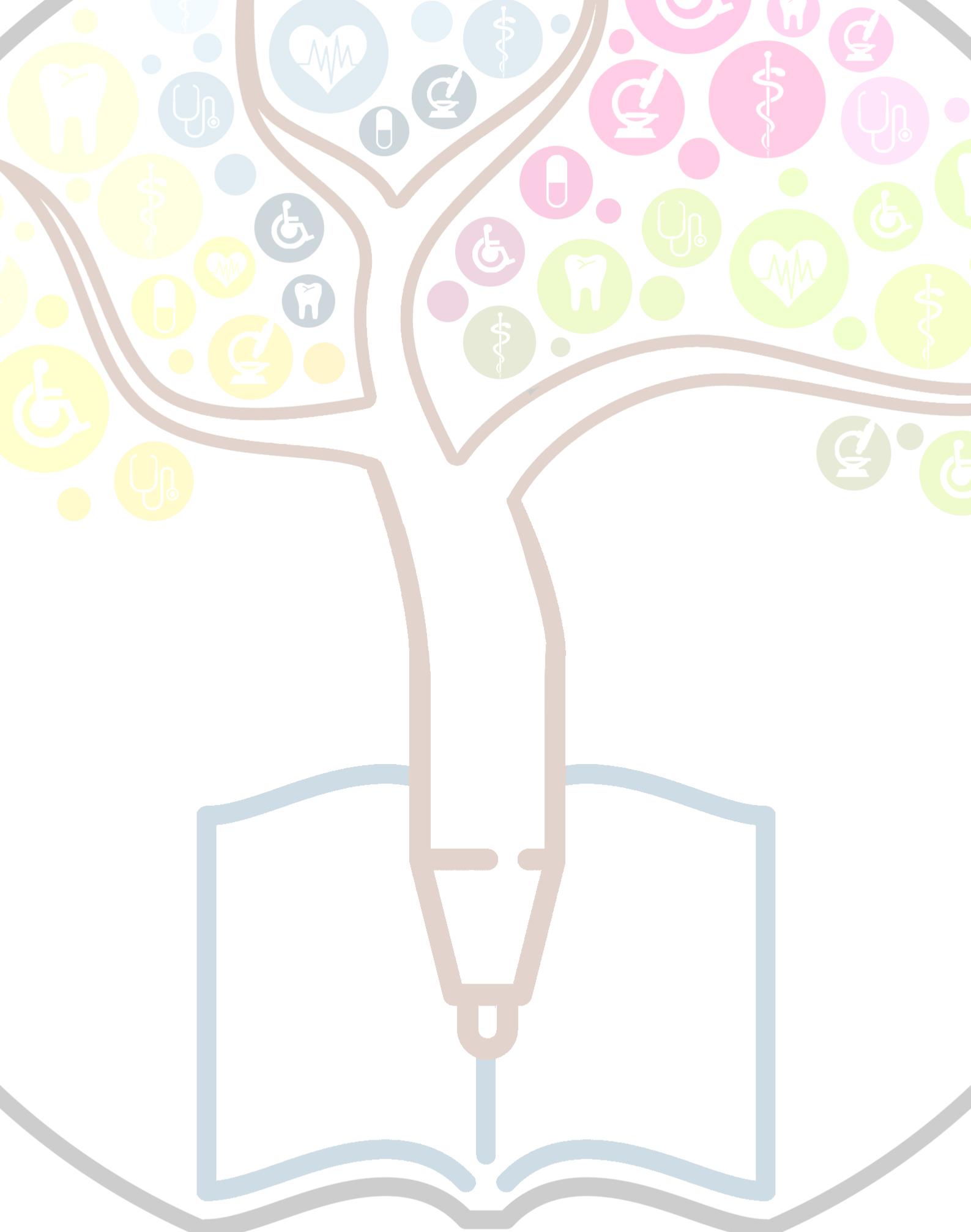
The effects of dexmedetomidine on the respiratory system are a small to moderate decrease in tidal volume and very little change in the respiratory rate.

Clinical Uses & Dosage

Dexmedetomidine is principally used for the short-term sedation of intubated and ventilated patients in an ICU setting. In the operating room, dexmedetomidine may be used as an adjunct to general anesthesia or to provide sedation. The dose of dexmedetomidine is (0.5–1 mcg/kg loading dose over 15 minutes, followed by an infusion of 0.2–0.7 mcg/kg/h) decreases the dose requirements for inhaled and injected anesthetics.

OPIOID ANALGESICS

Opioids are analgesic agents and are distinct from general anesthetics and hypnotics. Even when high doses of opioid analgesics are administered, recall cannot be prevented reliably unless hypnotic agents such as benzodiazepines are also used. Opioid analgesics are routinely used to achieve postoperative analgesia and intraoperatively as part of a bal-



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Chapter #26 : Local Anesthetics

26. Local Anesthetics:

Simply stated, local anesthesia refers to loss of sensation in a limited region of the body. Although local anesthetics are often used as analgesics, it is their ability to provide complete loss of all sensory modalities that is their distinguishing characteristic.

■ BASIC PHARMACOLOGY OF LOCAL ANESTHETICS:

Pharmacokinetics:

When local anesthetics are used for local, peripheral, and central neuraxial anesthesia -their most common clinical applications-systemic absorption, distribution, and elimination serve only to diminish or terminate their effect. Thus, classic pharmacokinetics plays a lesser role than with systemic therapeutics, yet remains important to the anesthetic's duration and critical to the potential development of adverse reactions, specifically cardiac and central nervous system (CNS) toxicity.

A. Absorption:

Systemic absorption of injected local anesthetic from the site of administration is determined by several factors, including dosage, site of injection, drug-tissue binding, local tissue blood flow, use of a vasoconstrictor (eg, epinephrine), and the physicochemical properties of the drug itself. Anesthetics that are more lipid soluble are generally more potent, have a longer duration of action, and take longer to achieve their clinical effect. Extensive protein binding also serves to increase the duration of action. When vasoconstrictors are used with local anesthetics, the resultant reduction in blood flow serves to reduce the rate of systemic absorption and thus diminishes peak serum levels. This effect is generally most evident with the shorter-acting, less potent, and less lipid-soluble anesthetics.

B. Distribution:

1. Localized—As local anesthetic is usually injected directly at the site of the target organ, distribution within this compartment plays an essential role with respect to achievement of clinical effect.

2. Systemic—The peak blood levels achieved during major conduction anesthesia will be minimally affected by the concentration of anesthetic or the speed of injection. The disposition of these agents can be well approximated by a two-compartment model. The initial alpha phase reflects rapid distribution in blood and highly perfused organs (eg, brain, liver, heart, kidney), characterized by a steep exponential decline in concentration. This is followed by a slower declining beta phase reflecting distribution into less well perfused tissue (eg, muscle, gut), and may assume a nearly linear rate of decline.

C. Metabolism and Excretion:

The local anesthetics are converted to more water-soluble metabolites in the liver (amide type) or in plasma (ester type), which are excreted in the urine. Since local anesthetics in the uncharged form diffuse readily through lipid membranes, little or no urinary excretion of the neutral form occurs. Acidification of urine promotes ionization of the tertiary amine base to the more water-soluble charged form, leading to more rapid elimination. Ester-type local anesthetics are hydrolyzed very rapidly in the blood by circulating butyrylcholinesterase to inactive metabolites. The amide local anesthetics undergo complex biotransformation in the liver, which includes hydroxylation and N-dealkylation by liver microsomal cytochrome P450 isozymes.

Pharmacodynamics:

The primary mechanism of action of local anesthetics is blockade of voltage-gated sodium channels. The blockade of sodium channels by most local anesthetics is both voltage and time dependent. Therefore, the effect of a given drug concentration is more marked in rapidly firing axons than in resting fibers

■ COMMONLY USED LOCAL ANESTHETICS & THEIR APPLICATIONS: ARTICAIN

Approved for use in the USA as a dental anesthetic in April 2000, it is widespread popularity in dental anesthesia, where it is generally considered to be more effective, and possibly safer, than lidocaine.

BENZOCAIN

Benzocaine's pronounced lipophilicity has relegated its application to topical anesthesia. However, despite over a century of use for this purpose, its popularity has recently diminished owing to increasing concerns regarding its potential to induce methemoglobinemia.

BUPIVACAIN

Based on concerns for cardiotoxicity, bupivacaine is often avoided for techniques that demand high volumes of concentrated anesthetic, such as epidural or peripheral nerve blocks performed for surgical anesthesia. In contrast, relatively low concentrations ($\leq 0.25\%$) are frequently used to achieve prolonged peripheral anesthesia and analgesia for postoperative pain control, and the drug enjoys similar popularity where anesthetic infiltration is used to control pain from a surgical incision. It is often the agent of choice for epidural infusions used for postoperative pain control and for labor analgesia. Finally, it has a comparatively unblemished record as a spinal anesthetic.

COCAINE

Current clinical use of cocaine is largely restricted to topical anesthesia for ear, nose, and throat procedures, where its intense vasoconstriction can serve to reduce bleeding. Even here, use has diminished in favor of other anesthetics combined with vasoconstrictors because of concerns about systemic toxicity, as well as the inconvenience of dispensing and handling this controlled substance.

ETIDOCAIN

Introduced along with bupivacaine, etidocaine has had limited application due to its poor block characteristics.

LEVOBUPIVACAIN

As previously discussed, this *S*(-) enantiomer of bupivacaine is somewhat less cardiotoxic than the racemic mixture. It is also less potent, and tends to have a longer duration of action, though the magnitude of these effects is too small to have any substantial clinical significance.

LIDOCAINE:

Aside from the issue of a high incidence of TNS with spinal administration, lidocaine has had an excellent record as an intermediate duration anesthetic, and remains the reference standard against which most anesthetics are compared.

MEPIVACAIN

mepivacaine displays clinical properties that are comparable to lidocaine. However, it differs from lidocaine with respect to vasoactivity, as it has a tendency toward vasoconstriction rather than vasodilation. This characteristic

likely accounts for its slightly longer duration of action, which has made it a popular choice for major peripheral blocks. Lidocaine has retained its dominance over mepivacaine for epidural anesthesia. Mepivacaine is slowly metabolized by the fetus, making it a poor choice for epidural anesthesia in the parturient. When used for spinal anesthesia, mepivacaine has a slightly lower incidence of TNS than lidocaine.

PRILOCAINE

Prilocaine has the highest clearance of the amino-amide anesthetics, imparting reduced risk of systemic toxicity. Unfortunately, this is somewhat offset by its propensity to induce methemoglobinemia. Prilocaine's duration of action is slightly longer than that of lidocaine, and the limited data suggest it carries a low risk of TNS.

ROPIVACAINE

Its perceived reduced cardiotoxicity has led to widespread use for high volume peripheral blocks. It is also a popular choice for epidural infusions for control of labor and postoperative pain.

EMLA

Lidocaine and prilocaine can combine to form such a mixture, which is marketed as EMLA (Eutectic Mixture of Local Anesthetics). This formulation, containing 2.5% of lidocaine and 2.5% prilocaine, is commonly used in pediatrics to anesthetize the skin prior to venipuncture for intravenous catheter placement.

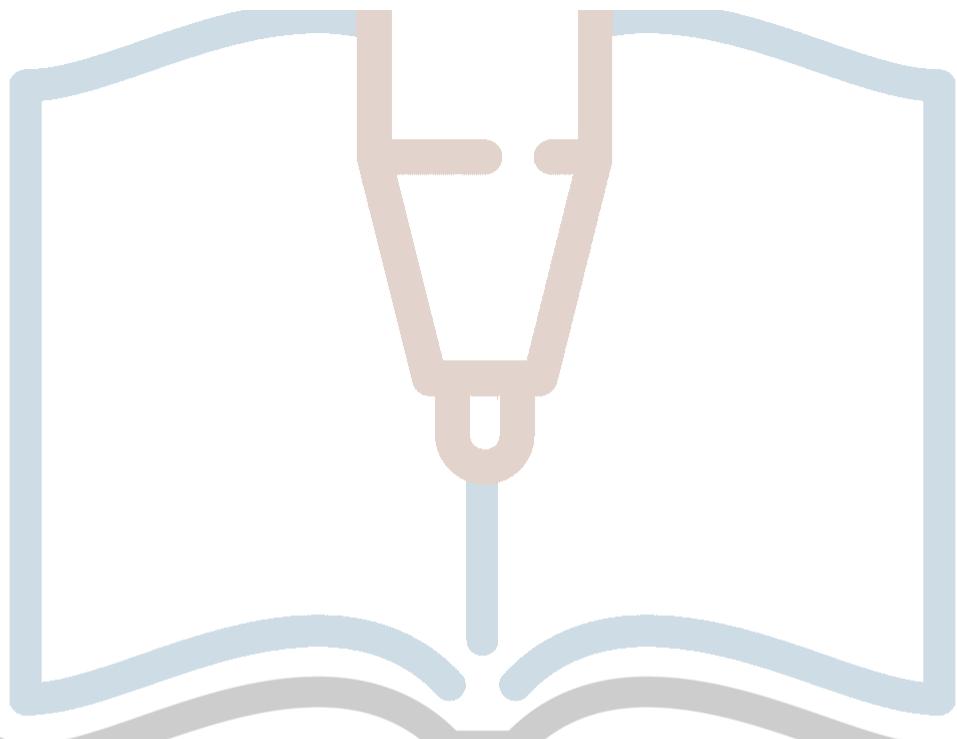
FUTURE DEVELOPMENTS

Sustained-Release Formulations: Sustained-release delivery has the potential added advantage of reducing risk of systemic toxicity.

Less Toxic Agents; More Selective Agents: It has been clearly demonstrated that anesthetic neurotoxicity does not result from blockade of the voltage-gated sodium channel.

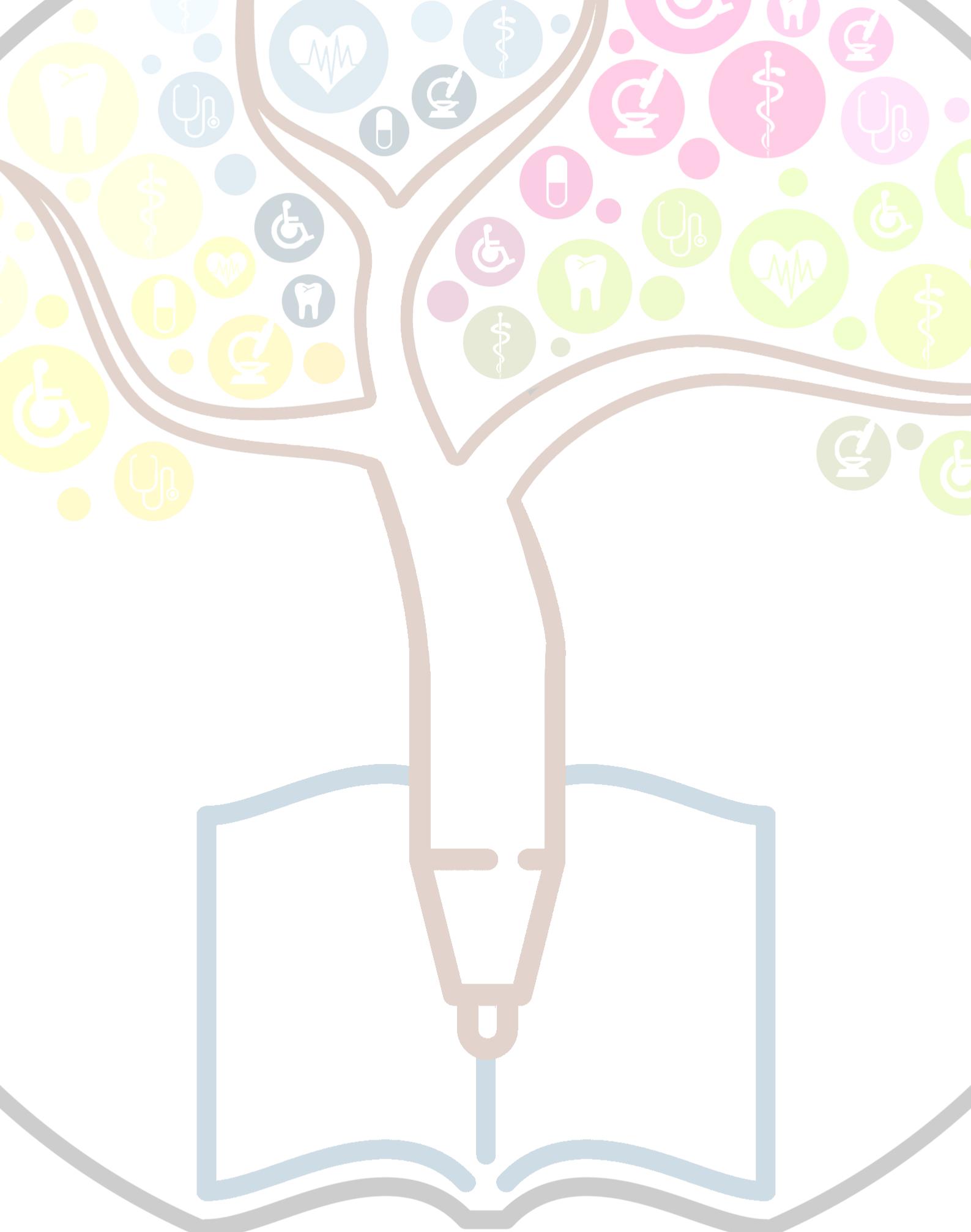
SUMMARY Drugs Used for Local Anesthesia

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities
AMIDES				
• Lidocaine	Blockade of sodium channels	Slows, then blocks, action potential propagation	Short-duration procedures • topical (mucosal), intravenous, infiltration, spinal, epidural, minor and major peripheral blocks	Parenteral (eg, peripheral block, but varies significantly based on specific site) • duration 1–2 h • 2–4 h with epinephrine • Toxicity: Central nervous system (CNS) excitation (high-volume blocks) and local neurotoxicity
• Bupivacaine	Same as lidocaine	Same as lidocaine	Longer-duration procedures (but not used topically or intravenously)	Parenteral • duration 3–6 h • Toxicity: CNS excitation • cardiovascular collapse (high-volume blocks)
<ul style="list-style-type: none"> • <i>Prilocaine, mepivacaine:</i> Like lidocaine (but also risk of methemoglobinemia with prilocaine) • <i>Articaine:</i> popular dental anesthetic • <i>Ropivacaine, levobupivacaine:</i> Like bupivacaine 				
ESTERS				
• Chlorprocaine	Like lidocaine	Like lidocaine	Very short procedures (not generally used topically or intravenously)	Parenteral • duration 30–60 min • 60–90 min with epinephrine • Toxicity: Like lidocaine
• Cocaine	Same as above • also has sympathomimetic effects	Same as above	Procedures requiring high surface activity and vasoconstriction	Topical or parenteral • duration 1–2 h • Toxicity: CNS excitation, convulsions, cardiac arrhythmias, hypertension, stroke
<ul style="list-style-type: none"> • <i>Procaine:</i> Like chlorprocaine (but not used epidurally) • <i>Tetracaine:</i> Used primarily for spinal anesthesia; duration 2–3 h • <i>Benzocaine:</i> used exclusively for topical anesthesia 				



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Chapter #27: Skeletal Muscle Relaxants



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Skeletal muscle relaxants 27

Drugs that affect skeletal muscle function include two different therapeutic groups:

1. neuromuscular blockers

- they are used during surgical procedures and in the intensive care unit (ICU)
- ❖ they interfere with transmission at the neuromuscular end plate and lack central nervous system (CNS) activity

2. spasmolytics

- they are used to reduce spasticity in a variety of painful conditions
- ❖ they have traditionally been called “centrally acting” muscle relaxants and are used primarily to treat chronic back pain and painful fibromyalgic conditions.

Normal Neuromuscular Function :

1-The arrival of an action potential at the motor nerve terminal causes an influx of calcium and release of the neurotransmitter acetylcholine.

2- Acetylcholine then diffuses across the synaptic cleft to activate nicotinic receptors located on the motor end plate .

3-The binding of two acetylcholine molecules to receptors on the α - β and δ - α subunits causes opening of the channel.

4-The subsequent movement of sodium and potassium through the channel is associated with a graded depolarization of the end plate membrane. The magnitude of the end plate potential is directly related to the amount of acetylcholine released .

- If the potential is small, the permeability and the end plate potential return to normal without an impulse being propagated from the end plate region to the rest of the muscle membrane.
- if the end plate potential is large, the adjacent muscle membrane is depolarized, and an action potential will be propagated along the entire muscle fiber. Muscle contraction is then initiated by excitation-contraction coupling.

5- The released acetylcholine is quickly removed by both diffusion and the local acetylcholinesterase enzyme.

6- Skeletal muscle relaxation and paralysis can occur from interruption of function at several sites along the pathway from the CNS to myelinated somatic nerves, unmyelinated motor nerve terminals, nicotinic acetylcholine receptors, the motor end plate, the muscle membrane, and the intracellular muscular contractile apparatus itself.

7- Blockade of end plate function can be accomplished by two basic mechanisms.
a- pharmacologic blockade of the physiologic agonist acetylcholine is characteristic of the antagonist neuromuscular blocking drugs.

b-produced by an excess of a depolarizing agonist, such as acetylcholine.

8-The prototypical depolarizing blocking drug is succinylcholine.

9-A similar depolarizing block can be produced by acetylcholine itself when high local concentrations are achieved in the synaptic cleft.

BASIC PHARMACOLOGY OF NEUROMUSCULAR BLOCKING DRUGS

a- Pharmacokinetics of Neuromuscular Blocking Drugs

All of the neuromuscular blocking drugs are highly polar compounds and inactive orally; they must be administered parenterally.

1-Nondepolarizing Relaxant Drugs (e.g. steroid muscle relaxants)

Neuromuscular blocking drugs are highly ionized, do not readily cross cell membranes, and are not strongly bound in peripheral tissues. Therefore, their volume of distribution (80–140 mL/kg) is only slightly larger than the blood volume.

- Drugs that are excreted by the kidney typically have longer half-lives, leading to longer durations of action
- Drugs eliminated by the liver tend to have shorter half-lives and durations of action
 - All steroidal muscle relaxants are metabolized to their 3-hydroxy, 17-hydroxy, or 3,17-dihydroxy products in the liver
 - The intermediate-acting steroid muscle relaxants (eg, vecuronium and rocuronium) tend to be more dependent on biliary excretion or hepatic metabolism for their elimination. These muscle relaxants are more commonly used clinically than the long-acting steroid-based drugs (eg, pancuronium). The duration of action of these relaxants may be prolonged significantly in patients with impaired liver function.
 - **Atracurium:** is no longer in clinical use
 - The main breakdown products are laudanosine and a related quaternary acid
 - **Cisatracurium:** has less dependence on hepatic inactivation, produces less laudanosine, and is much less likely to release histamine. , cisatracurium has all the advantages of atracurium with fewer adverse effects

2-Depolarizing Relaxant Drugs (e.g. succinylcholine)

-the circulating levels of plasma cholinesterase influence the duration of action by determining the amount of the drug that reaches the motor end plate.

-The extremely short duration of action of succinylcholine (5–10 minutes) is due to its rapid hydrolysis by butyrylcholinesterase and pseudocholinesterase in the liver and plasma, respectively.

- Neuromuscular blockade produced by succinylcholine can be prolonged in patients with an abnormal genetic variant of plasma cholinesterase . The dibucaine number is a measure of the ability of a patient to metabolize succinylcholine and can be used to identify at-risk patients .

-avoid the use of succinylcholine in patients with a possible family history of plasma cholinesterase deficiency.

Table Pharmacokinetic and dynamic properties of neuromuscular blocking drugs

Drug	Elimination	Clearance (mL/kg/min)	Approximate Duration of Action (minutes)	Approximate Potency Relative to Tubocurarine
Isoquinoline derivatives				
Atracurium	Spontaneous	6.6	20-35	1.5
Cisatracurium	Mostly spontaneous	5-6	25-44	1.5
Tubocurarine	Kidney (40%)	2.3-2.4	>50	1
Steroid derivatives				
Pancuronium	Kidney (80%)	1.7-1.8	>35	6
Rocuronium	Liver (75–90%) and kidney	2.9	20-35	0.8
Vecuronium	Liver (75–90%) and kidney	3-5.3	20-35	6
Depolarizing agent				
Succinylcholine	Plasma ChE2* (100%)	>100	<8	0.4

*²Butyrylcholinesterase (pseudocholinesterase).

b- Mechanism of action.

1- Nondepolarizing Relaxant Drugs.

- When small doses of nondepolarizing muscle relaxants are administered, they act predominantly at the nicotinic receptor site by competing with acetylcholine.
- The least potent nondepolarizing relaxants have the fastest onset and the shortest duration of action. (eg, rocuronium).
- In larger doses, nondepolarizing drugs can enter the pore of the ion channel to produce a more intense motor blockade. This action further weakens neuromuscular transmission and diminishes the ability of the acetylcholinesterase inhibitors to antagonize the effect of nondepolarizing muscle relaxants.
- Nondepolarizing relaxants can also block prejunctional sodium channels.

2- Depolarizing Relaxant Drugs. (succinylcholine)

1- Phase I block (depolarizing) :

- succinylcholine produces a longer effect at the myoneural junction.
- Succinylcholine reacts with the nicotinic receptor to open the channel and cause depolarization of the motor end plate causing contractions of muscle motor units.

-depolarizing blockers can enter the channel to produce a prolonged “flickering” of the ion conductance Because succinylcholine is not metabolized effectively at the synapse.

-In contrast to the nondepolarizing drugs, this so-called phase I (depolarizing) block is augmented, not reversed, by cholinesterase inhibitors.

2- Phase II block (desensitizing) :

-With prolonged exposure to succinylcholine, the initial end plate depolarization decreases and the membrane becomes repolarized.

-Later in phase II, the characteristics of the blockade are nearly identical to those of a nondepolarizing block with possible reversal by acetylcholinesterase inhibitors.

Comparison of a typical nondepolarizing muscle relaxant (rocuronium) and a depolarizing muscle relaxant (succinylcholine)..

		Succinylcholine	
		Phase I	Phase II
Administration of tubocurarine	Additive	Antagonistic	Augmented1
Administration of succinylcholine	Antagonistic	Additive	Augmented1
Effect of neostigmine	Antagonistic	Augmented1	Antagonistic
Initial excitatory effect on skeletal muscle	None	Fasciculations	None
Response to a tetanic stimulus	Unsustained (fade)	Sustained2 (no fade)	Unsustained (fade)
Posttetanic facilitation	Yes	no	Yes
Rate of recovery	30–60 min3	4–8 min	> 20 min3

CLINICAL PHARMACOLOGY OF NEUROMUSCULAR BLOCKING DRUGS

Skeletal Muscle Paralysis

neuromuscular blocking drugs makes it possible to achieve adequate muscle relaxation for all types of surgical procedures without the cardiorespiratory depressant effects produced by deep anesthesia.

Assessment of Neuromuscular Transmission.

Monitoring the effect of muscle relaxants involves the use of a device that produces transdermal

electrical stimulation of one of the peripheral nerves to the hand or facial muscles and recording of the evoked contractions (ie, twitch responses) . The standard approach for monitoring

the clinical effects of muscle relaxants are visually observed by the anesthesiologist.

-The three most commonly used patterns include:

1- single-twitch stimulation

(a single supramaximal electrical stimulus is applied to a peripheral nerve at frequencies from 0.1 Hz to 1.0 Hz.)

2- train-of-four (TOF) stimulation

(involves four successive supramaximal stimuli given at intervals of 0.5 second (2 Hz)).

3- tetanic stimulation

(consists of a very rapid (30–100 Hz) delivery of electrical stimuli for several seconds)

-Two other modalities are also available to monitor neuromuscular transmission :

-(double-burst stimulation and posttetanic count).

The double-burst stimulation pattern is another mode of electrical nerve stimulation developed with the goal of allowing for manual detection of residual neuromuscular blockade when it is not possible to record the responses to single-twitch, TOF, or tetanic stimulation.

-A more quantitative approach to neuromuscular monitoring involves monitoring using a force transducer for measuring the evoked response (ie, movement) of the thumb to TOF stimulation over the ulnar nerve at the wrist. This device has the advantage of being integrated in the anesthesia machine and also provides a more accurate graphic display of the percentage of fade to TOF stimulation.

A. Nondepolarizing Relaxant Drugs

During anesthesia, administration of tubocurarine, 0.1–0.4 mg/kg IV, initially causes motor weakness, followed by the skeletal muscles becoming flaccid and inexcitable to electrical stimulation.

- In general, larger muscles are more resistant to neuromuscular blockade and recover more rapidly than smaller muscles

-The diaphragm is usually the last muscle to be paralyzed.

-When administration of muscle relaxants is discontinued, recovery of muscles usually occurs in reverse order, with the diaphragm regaining function first.

-The pharmacologic effect of tubocurarine, 0.3 mg/ kg IV, usually lasts 45–60 minutes. However, subtle evidence of residual muscle paralysis may last for another hour.

-The most important property distinguishing the nondepolarizing relaxants is the time to onset of the blocking effect.

-rocuronium has the most rapid onset time (60–120 seconds).

B. Depolarizing Relaxant Drugs

-administration of succinylcholine, 0.75–1.5 mg/kg IV, transient muscle fasciculations occur over the chest and abdomen within 30 seconds.

-general anesthesia and the prior administration of a small dose of a nondepolarizing muscle relaxant tends to attenuate them.

-paralysis develops rapidly (< 90 seconds), the arm, neck, and leg muscles are initially relaxed

followed by the respiratory muscles.

-succinylcholine rapidly hydrolysis by cholinesterase in the plasma (and liver), the duration of neuromuscular block typically lasts less than 10 minutes.

Cardiovascular Effects Vecuronium, cisatracurium, and rocuronium have minimal, if any, cardiovascular effects. The other nondepolarizing muscle relaxants (ie, pancuronium and atracurium) produce cardiovascular effects that are mediated by autonomic or histamine receptors

Effects of neuromuscular blocking drugs on other tissues

Drug	Effect on Autonomic Ganglia	Effect on Cardiac Muscarinic Receptors	Tendency to Cause Histamine Release
Isoquinoline derivatives			
Atracurium	None	None	Slight
Cisatracurium	None	None	None
Tubocurarine	Weak block	None	Moderate
Steroid derivatives			
Pancuronium	None	Moderate block	None
Rocuronium	None	Slight	None
Vecuronium	None	None	None
Other agents			
Gallamine	None	Strong block	None
Succinylcholine	Stimulation	Stimulation	Slight

Other Adverse Effects of Depolarizing Blockade

- 1- Hyperkalemia
- 2- Increased Intraocular Pressure
- 3-Increased Intragastric Pressure
- 4- Muscle Pain

Interactions with Other Drugs

A. Anesthetics

(inhaled anesthetics augment the effects of muscle relaxants in the following order: isoflurane (most); sevoflurane, desflurane, halothane; and nitrous oxide (least))

B. Antibiotics

(enhancement of neuromuscular blockade by antibiotics (eg, aminoglycosides)).

C. Local Anesthetics and Antiarrhythmic Drugs

(In small doses, local anesthetics can depress posttetanic potentiation via a prejunctional neural effect. In large doses, local anesthetics can block neuromuscular transmission).

D. Other Neuromuscular Blocking Drugs

(The end plate-depolarizing effect of succinylcholine can be antagonized by administering a small dose of a nondepolarizing blocker. To prevent the fasciculations associated with succinylcholine administration, a small nonparalyzing dose of a nondepolarizing drug can be given before succinylcholine (eg, d-tubocurarine, 2 mg IV, or pancuronium, 0.5 mg IV)).

Effects of Diseases & Aging on the Neuromuscular Response

- Myasthenia gravis enhances the neuromuscular blockade produced by these drugs
- Advanced age is associated with a prolonged duration of action from nondepolarizing relaxants as a result of decreased clearance of the drugs by the liver and kidneys.
- patients with severe burns and those with upper motor neuron disease are resistant to nondepolarizing muscle relaxants.

Reversal of Nondepolarizing Neuromuscular Blockade

- The cholinesterase inhibitors effectively antagonize the neuromuscular blockade caused by nondepolarizing drugs.
- Neostigmine and pyridostigmine antagonize nondepolarizing neuromuscular blockade by increasing the availability of acetylcholine at the motor end plate, mainly by inhibition of acetylcholinesterase.
- edrophonium antagonizes neuromuscular blockade purely by inhibiting acetylcholinesterase activity.
- These differences are important in determining recovery from residual block
- Unsuspected residual block may result in hypoventilation, leading to hypoxia and even apnea, especially if patients have received central depressant medications in the early recovery period.
- Sugammadex is a novel reversal agent approved in Europe (Its approval has been delayed over concerns that it may induce coagulopathy and hypersensitivity reactions.)
 - sugammadex decreases the free plasma concentration and establishes a concentration gradient for rocuronium to diffuse away from the neuromuscular junction back into the circulation.
 - Sugammadex will bind to and can reverse effects of other steroidal neuromuscular blockers such as vecuronium and pancuronium,

Uses of Neuromuscular Blocking Drugs

A. Surgical Relaxation

SPASMOlytic DRUGS SUMMARY Skeletal Muscle Relaxants

(in facilitating intracavitary surgery, especially in intraabdominal and intrathoracic procedures.)

B. Endotracheal Intubation

(By relaxing the pharyngeal and laryngeal muscles, neuromuscular blocking drugs facilitate laryngoscopy and placement of an endotracheal tube).

C. Control of Ventilation

(In critically ill patients who have ventilatory failure from various causes).

D. Treatment of Convulsions

(Neuromuscular blocking drugs (ie, succinylcholine) are occasionally used to attenuate the peripheral (motor) manifestations of convulsions associated with status epilepticus, local anesthetic toxicity, or electroconvulsive therapy).

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DEPOLARIZING NEUROMUSCULAR BLOCKING AGENT				
• Succinylcholine	Agonist at nicotinic acetylcholine (ACh) receptors, especially at neuromuscular junctions • depolarizes • may stimulate ganglionic nicotinic ACh and cardiac muscarinic ACh receptors	Initial depolarization causes transient contractions, followed by prolonged flaccid paralysis • depolarization is then followed by repolarization that is also accompanied by paralysis	Placement of endotracheal tube at start of anesthetic procedure • rarely, control of muscle contractions in status epilepticus	Rapid metabolism by plasma cholinesterase • normal duration, ~5 min • Toxicities: Arrhythmias • hyperkalemia • transient increased intraabdominal, Intraocular pressure • postoperative muscle pain
NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS				
• d-Tubocurarine	Competitive antagonist at nACh receptors, especially at neuromuscular junctions	Prevents depolarization by ACh, causes flaccid paralysis • can cause histamine release with hypotension • weak block of cardiac muscarinic ACh receptors	Prolonged relaxation for surgical procedures • superseded by newer nondepolarizing agents	Renal excretion • duration, ~40–60 min • Toxicities: Histamine release • hypotension • prolonged apnea
• Cisatracurium	Similar to tubocurarine	but lacks histamine release and antimuscarinic effects	Prolonged relaxation for surgical procedures • relaxation of respiratory muscles to facilitate mechanical ventilation in intensive care unit	Like tubocurarine Not dependent on renal or hepatic function • duration, ~25–45 min • Toxicities: Prolonged apnea but less toxic than atracurium
• Rocuronium	Similar to cisatracurium	Like cisatracurium but slight antimuscarinic effect	Like cisatracurium • useful in patients with renal impairment	Hepatic metabolism • duration, ~20–35 min • Toxicities: Like cisatracurium
• Vecuronium: Intermediate duration; metabolized in liver				
CENTRALLY ACTING SPASMOlytic DRUGS				
• Baclofen	GABAB agonist, facilitates spinal inhibition of motor neurons	Pre- and postsynaptic inhibition of motor output	Severe spasticity due to cerebral palsy, multiple sclerosis, stroke	Oral, intrathecal • Toxicities: Sedation, weakness
• Cyclobenzaprine	Poorly understood inhibition of muscle stretch reflex in spinal cord	Reduction in hyperactive muscle reflexes • antimuscarinic effects	Acute spasm due to muscle injury • inflammation	Hepatic metabolism • duration, ~4–6 h • Toxicities: Strong antimuscarinic effects
Chlorphenesin, methocarbamol, orphenadrine, others: Like cyclobenzaprine with varying degrees of antimuscarinic effect				
• Diazepam	Facilitates GABAergic transmission in central nervous system	Increases interneuron inhibition of primary motor afferents in spinal cord • central sedation	Chronic spasm due to cerebral palsy, stroke, spinal cord injury • acute spasm due to muscle injury	Hepatic metabolism • duration, ~12–24 h
• Tizanidine	α2-Adrenoceptor agonist in the spinal cord	Presynaptic and postsynaptic inhibition of reflex motor output	Spasm due to multiple sclerosis, stroke, amyotrophic lateral sclerosis	Renal and hepatic elimination • duration, 3–6 h • Toxicities: Weakness, sedation • hypotension
DIRECT-ACTING MUSCLE RELAXANT				
•Dantrolene	Blocks RyR1 Ca2+-release channels in the sarcoplasmic reticulum of skeletal muscle	Reduces actin-myosin interaction • weakens skeletal muscle contraction	IV: Malignant hyperthermia • Oral: Spasm due to cerebral palsy, spinal cord injury, multiple sclerosis	IV, oral • duration, 4–6 h • Toxicities: Muscle weakness

• Botulinum toxin	Cleaves fusion proteins in nerve endings	Flaccid paralysis	Spasm due to cerebral palsy, multiple sclerosis, overactive bladder, migraine	Direct injection into muscle • duration 2-3 months • Toxicities: muscle weakness, Falls
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Chapter #28: Pharmacologic Management of Parkinsonism & Other Movement Disorders

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28. Pharmacologic Management of Parkinsonism & Other Movement Disorders:

■ PARKINSONISM:

Parkinsonism is characterized by a combination of rigidity, bradykinesia, tremor, and postural instability that can occur for a variety of reasons but is usually idiopathic.

Pathogenesis:

The pathogenesis of parkinsonism seems to relate to a combination of impaired degradation of proteins and mutations of several genes. Environmental or endogenous toxins may also be important in the etiology of the disease. The normally high concentration of dopamine in the basal ganglia of the brain is reduced in parkinsonism, and pharmacologic attempts to restore dopaminergic activity with levodopa and dopamine agonists alleviate many of the motor features of the disorder.

LEVODOPA

Dopamine does not cross the blood-brain barrier and if given into the peripheral circulation has no therapeutic effect in parkinsonism. However, levodopa, the immediate metabolic precursor of dopamine, does enter the brain (via an L-amino acid transporter, LAT), where it is decarboxylated to dopamine.

Pharmacokinetics

Levodopa is rapidly absorbed from the small intestine, but its absorption depends on the rate of gastric emptying and the pH of the gastric contents. Unfortunately, only about 1–3% of administered levodopa actually enters the brain unaltered; the remainder is metabolized extracerebrally, predominantly by decarboxylation to dopamine, which does not penetrate the blood-brain barrier. Accordingly, levodopa must be given in large amounts when used alone. However, when given in combination with a dopa decarboxylase inhibitor (**carbidopa**) that does not penetrate the blood-brain barrier, the peripheral metabolism of levodopa is reduced, plasma levels of levodopa are higher, plasma half-life is longer, and more dopa is available for entry into the brain.

Adverse Effects

Gastrointestinal upset, arrhythmias, dyskinésias, on-off and wearing-off phenomena, behavioral disturbances.

Drug Interactions

Pharmacologic doses of pyridoxine (vitamin B6) enhance the extracerebral metabolism of levodopa and may therefore prevent its therapeutic effect unless a peripheral decarboxylase inhibitor is also taken. Levodopa should not be given to patients taking monoamine oxidase A inhibitors or within 2 weeks of their discontinuance because such a combination can lead to hypertensive crises.

Contraindications

Levodopa should not be given to psychotic patients because it may exacerbate the mental disturbance. It is also contraindicated in patients with angle-closure glaucoma. Patients with active peptic ulcer must also be managed carefully, gastrointestinal bleeding has occasionally occurred with levodopa.

DOPAMINE RECEPTOR AGONISTS:

Drugs acting directly on postsynaptic dopamine receptors may have a beneficial effect in addition to that of levodopa. Unlike levodopa, they do not require enzymatic conversion to an active metabolite, and do not compete with other substances for active transport into the blood and across the blood-brain barrier. The older dopamine agonists (bromocriptine and pergolide) are ergot (ergoline) derivatives and are rarely—if ever—used to treat parkinsonism. Their side effects are of more concern than those of the newer agents (pramipexole and ropinirole). Apomorphine is a potent dopamine agonist. Dopamine agonists have an important role as first-line therapy for Parkinson's disease and their use is associated with a lower incidence of the response fluctuations and dyskinesias that occur with long-term levodopa therapy. Dopamine agonists may also be given to patients with parkinsonism who are taking levodopa and who have end-of-dose akinesia or on-off phenomenon or are becoming resistant to treatment with levodopa.

Bromocriptine

Bromocriptine is a D₂ agonist. This drug has been widely used to treat Parkinson's disease in the past but is now rarely used for this purpose. The usual daily dose is varies between 7.5 -30mg.

Pergolide

Pergolide, another ergot derivative, directly stimulates both D₁ and D₂ receptors.

Pramipexole

Pramipexole is not an ergot derivative, but it has preferential affinity for the D₃ family of receptors. It is effective as monotherapy for mild parkinsonism and is also helpful in patients with advanced disease. Further increments in the daily dose are by 0.75 mg at weekly intervals, depending on response and tolerance. Most patients require between 0.5 and 1.5 mg three times daily. Renal insufficiency may necessitate dosage adjustment.

Rotigotine

The dopamine agonist rotigotine, delivered daily through a skinpatch, is approved for treatment of early Parkinson's disease.

Adverse Effects of Dopamine Agonists

Nausea and vomiting, postural hypotension, dyskinesias, confusion, impulse control disorders, sleepiness.

Contraindications

Dopamine agonists are contraindicated in patients with a history of psychotic illness or recent myocardial infarction, or with active peptic ulceration. The ergot-derived agonists are best avoided in patients with peripheral vascular disease.

MONOAMINE OXIDASE INHIBITORS:

Two types of monoamine oxidase have been distinguished in the nervous system. Monoamine oxidase A metabolizes norepinephrine, serotonin, and dopamine; monoamine oxidase B metabolizes dopamine selectively. **Selegiline** (deprenyl) a selective irreversible inhibitor of monoamine oxidase B at normal doses (at higher doses it inhibits monoamine oxidase A as well), retards the breakdown of dopamine. In consequence, it enhances and prolongs the antiparkinsonism effect. The standard dose of selegiline is 5 mg with breakfast and 5 mg with lunch. Selegiline may cause insomnia when taken later during the day. Selegiline has only a minor therapeutic effect on parkinsonism when given alone. **Rasagiline**, another monoamine oxidase B inhibitor, is more potent than selegiline in preventing MPTP-induced parkinsonism. The standard dosage is 1 mg/d, and also used as adjunctive therapy at a dosage of 0.5 or 1 mg/d to prolong the effects of levodopa/carbidopa in patients with advanced disease. Neither selegiline nor rasagiline should be taken by patients receiving meperidine, tramadol, methadone, propoxyphene, cyclobenzaprine, or St. John's wort. And the antitussive dextromethorphan should also be avoided by patients taking one of the monoamine oxidase B inhibitors. Rasagiline or selegiline should be used with care in patients receiving tricyclic antidepressants or serotonin reuptake inhibitors, and the combined administration of levodopa and an inhibitor of both forms of monoamine oxidase (ie, a nonselective inhibitor) must be avoided, because it may lead to hypertensive crises.

CATECHOL-O-METHYLTRANSFERASE INHIBITORS:

Selective COMT inhibitors such as **tolcapone** and **entacapone** also prolong the action of levodopa by diminishing its peripheral metabolism. Tolcapone and entacapone are both widely available, but entacapone is generally preferred because it has not been associated with hepatotoxicity. The pharmacologic effects of tolcapone and entacapone are similar, and both are rapidly absorbed, bound to plasma proteins, and metabolized before excretion. However, tolcapone has both central and peripheral effects, whereas the effect of entacapone is peripheral. Tolcapone is taken in a standard dosage of 100 mg three times daily, some patients require a daily dose of twice that amount. By contrast, entacapone (200 mg) needs to be taken with each dose of levodopa, up to six times daily. Adverse effects of the COMT inhibitors relate in part to increased levodopa exposure and include dyskinesias, nausea, and confusion. It is often necessary to lower the daily dose of levodopa by about 30% in the first 48 hours to avoid or reverse such complications. Tolcapone may cause an increase in liver enzyme levels and has been associated rarely with death from acute hepatic failure. The commercial preparation named **Stalevo** consists of a combination of levodopa with both carbidopa and entacapone. It is available in three strengths: Stalevo 50, Stalevo 100, Stalevo 150. The combination agent may provide greater symptomatic benefit than levodopa-carbidopa alone.

APOMORPHINE:

Subcutaneous injection of apomorphine hydrochloride (Apokyn). The optimal dose is identified by administering increasing test doses until adequate benefit is achieved or a maximum of 0.6 mL (6 mg) is reached. Apomorphine treatment; accordingly, pretreatment with the antiemetic trimethobenzamide (300 mg three times daily) for 3 days is recommended before apomorphine is introduced and is then continued for at

least 1 month. Apomorphine should be prescribed only by physicians, It should not be used in patients taking serotonin 5-HT3 antagonists because severe hypotension may result.

AMANTADINE:

Amantadine, an antiviral agent, was by chance found to have relatively weak antiparkinsonism properties. It has been reported to antagonize the effects of adenosine at adenosine A2A receptors, which may inhibit D2 receptor function, and it is an antagonist of the NMDA type glutamate receptor, suggesting an antidyskinetic effect

Pharmacokinetics:

Peak plasma concentrations of amantadine are reached 1–4 hours after an oral dose. The plasma half-life is between 2 and 4 hours, most of the drug being excreted unchanged in the urine

Clinical Use

Amantadine is less efficacious than levodopa, and its benefits may be short-lived, often disappearing after only a few weeks of treatment. The standard dosage is 100 mg orally two or three times daily

Adverse Effects

Amantadine has a number of undesirable central nervous system effects, including restlessness, depression, irritability, insomnia, agitation, excitement, hallucinations, and confusion. Overdosage may produce an acute toxic psychosis. Other adverse reactions to amantadine include headache, heart failure, postural hypotension, urinary retention, and gastrointestinal disturbance. Amantadine should be used with caution in patients with a history of seizures or heart failure.

ACETYLCHOLINE-BLOCKING DRUGS:

A number of centrally acting antimuscarinic preparations are available that differ in their potency and in their efficacy in different patients. These agents may improve the tremor and rigidity of parkinsonism but have little effect on bradykinesia.

Clinical Use

Treatment is started with a low dose of one of the drugs in this category, the Adverse Effects:

Antimuscarinic drugs are poorly tolerated by the elderly or cognitively impaired. Dyskinesias occur in rare cases. Acute suppurative parotitis sometimes occurs as a complication of dryness of the mouth.

SURGICAL PROCEDURES

In patients with advanced disease that is poorly responsive to pharmacotherapy, worthwhile benefit may follow thalamotomy (for conspicuous tremor).

NEUROPROTECTIVE THERAPY

Among the compounds under investigation as potential neuroprotective agents that may slow disease progression are antioxidants, antiapoptotic agents, glutamate antagonists, intraparenchymally administered glial-derived neurotrophic factor, and anti-inflammatory drugs.

GENE THERAPY

Several phase 1 (safety) or phase 2 trials of gene therapy for Parkinson's disease. All trials involved infusion into the striatum of adeno-associated virus type 2 as the vector for the gene to increase metabolism of levodopa to dopamine; and for neurturin (a growth factor that may enhance the survival of dopaminergic neurons).

DRUG-INDUCED PARKINSONISM

Reserpine and the related drug tetrabenazine deplete biogenic monoamines from their storage sites, whereas haloperidol, metoclopramide, and the phenothiazines block dopamine receptors. These drugs may therefore produce a parkinsonian syndrome, usually within 3 months after introduction. In 1983, a drug-induced form of parkinsonism was discovered in individuals who attempted to synthesize and use a narcotic drug.

OTHER MOVEMENT DISORDERS:

Tremor:

Tremor consists of rhythmic oscillatory movements. Physiologic postural tremor, which is a normal phenomenon, is enhanced in amplitude by anxiety, fatigue, thyrotoxicosis, and intravenous epinephrine or isoproterenol. **Essential tremor** is a postural tremor. **Intention tremor** is present during movement but not at rest and **Rest tremor** is usually due to parkinsonism. **Propranolol** reduces its amplitude. Certain drugs—especially the bronchodilators, valproate, tricyclic antidepressants, and lithium—may produce a dose-dependent exaggeration of the normal physiologic tremor that is reversed by discontinuing the drug. Total daily doses of propranolol on the order of 120 mg or more (range, 60–320 mg) are usually required, divided into two doses. Propranolol should be used with caution in patients with heart failure, heart block, asthma, depression, or hypoglycemia. Adverse effects include fatigue, malaise, lightheadedness, and impotence. Some patients prefer to take a single dose of propranolol when they anticipate their tremor is likely to be exacerbated, like **Primidone** (an antiepileptic drug) in gradually increasing doses up to 250 mg three times daily. **Topiramate**, another antiepileptic drug, may also be helpful in a dose of 400 mg daily, built up gradually. And **Alprazolam** (in doses up to 3 mg daily) or **gabapentin** (100–2400 mg/d; typically 1200 mg/d)

Huntington's Disease:

Huntington's disease is an autosomal dominant inherited disorder caused by an abnormality (expansion of a CAG trinucleotide repeat that codes for a polyglutamine tract) of the *huntingtin* gene on chromosome 4. Huntington's disease is characterized by progressive chorea and dementia that usually begin in adulthood. The development of chorea seems to be related to an imbalance of dopamine, acetylcholine, GABA, and perhaps other

neurotransmitters in the basal ganglia. Drugs that impair dopaminergic neurotransmission, either by depleting central monoamines (eg, reserpine, tetrabenazine) or by blocking dopamine receptors (eg, phenothiazines, butyrophenones), often alleviate chorea, whereas dopamine-like drugs such as levodopa tend to exacerbate it. **Tetrabenazine** (12.5–50 mg orally three times daily), Tetrabenazine is metabolized by cytochrome P450(CYP2D6), **Haloperidol** is started in a small dose, eg, 1 mg twice daily, and increased every 4 days depending on the response. If haloperidol is not helpful, treatment with increasing doses of **fluphenazine** in a similar dose, eg, 1 mg twice daily, sometimes helps. Several recent reports suggest that **olanzapine** may also be useful; the dose varies with the patient, but 10 mg daily is often sufficient, although doses as high as 30 mg daily are sometimes required.

Other Forms of Chorea

Benign hereditary chorea is inherited (usually autosomal dominant; possibly also autosomal recessive) or arises spontaneously. Chorea develops in early childhood and does not progress during adult life. Treatment of these hereditary disorders is symptomatic. Tetrabenazine (0.5 mg/kg/d for children and 37.5 mg/d for adults) may improve chorea in some instances AND Treatment is directed at the underlying cause when chorea occurs as a complication of general medical disorders.

Ballismus

The biochemical basis of ballismus is unknown, but the pharmacologic approach to management is the same as for chorea

Athetosis & Dystonia

The pharmacologic basis of these disorders is unknown, and there is no satisfactory medical treatment for them

Tics

The pathophysiologic basis of tics is unknown. Chronic multiplets (**Gilles de la Tourette's syndrome**) may require symptomatic treatment if the disorder is severe or is having a significant impact on the patient's life. Treatment is with drugs that block dopamine receptors or deplete dopamine stores, such as fluphenazine, pimozide, and tetrabenazine. **pimozide** may be helpful in patients as a first-line treatment, Treatment is started at 1 mg/d, and the dosage is increased by 1 mg every 5 days; most patients require 7–16 mg/d.. **Haloperidol** has been used for many years to treat tic disorders , treatment is started with a small dosage (eg, 0.25 or 0.5 mg daily) and then increased gradually (eg, by 0.25 mg every 4 or 5 days).and also treatment by a2-adrenergic agonists because they are less likely to cause extrapyramidal side effects than neuroleptic agents, like **Clonidine** reduces motor or vocal tics in about 50% of children, It is introduced at a dose of 2–3 mcg/kg/d, increasing after 2 weeks to 4 mcg/kg/d and then, if required, to 5 mcg/kg/d. The most common adverse effect is sedation, **Guanfacine**, has also been used .Both of these drugs may be particularly helpful for behavioral symptoms. Injection of botulinum toxin A at the site of problematic tics is sometimes helpful when these are focal simple, and Atypical antipsychotics, such as risperidone and aripiprazole, may be especially worthwhile in patients with significant behavioral problems.

Drug-Induced Dyskinesias

Levodopa or dopamine agonists produce diverse dyskinesias as a dose-related phenomenon in patients with Parkinson's disease; dose reduction reverses them. Chorea may also develop in patients receiving phenytoin, carbamazepine, amphetamines, lithium, and oral contraceptives, Dystonia has resulted from administration of dopaminergic agents, lithium, serotonin reuptake inhibitors, carbamazepine, and metoclopramide; and postural tremor from theophylline, caffeine, lithium, valproic acid, thyroid hormone, tricyclic antidepressants, and isoproterenol, **Tardive dyskinesia**, a disorder characterized by a variety of abnormal movements, is a common complication of long-term neuroleptic or metoclopramide drug treatment. The drugs most likely to provide immediate symptomatic benefit are those interfering with dopaminergic function, either by depletion (eg, reserpine, tetrabenazine) or receptor blockade (eg, phenothiazines, butyrophenones). Paradoxically, the

receptorblockingdrugs are the very ones that also cause the dyskinesia, **Tardive dystonia** is usually segmental or focal; generalizeddystonia is less common and occurs in younger patients, focal dystonias may also respond to local injection of botulinum A toxin. **Tardive akathisia** is treated similarly to drug-induced parkinsonism. antimuscarinic drugs should not be prescribed routinely in patients receiving neuroleptics, because the combination may increase the likelihood of dyskinesia.

Restless Legs Syndrome:

Restless legs syndrome is characterized by an unpleasant creepingdiscomfort that seems to arise deep within the legs and occasionallythe arms. Symptoms occur particularly when patients are relaxed, symptoms may delay the onset of sleep. Dopaminergic therapyis the preferred treatment for restless legs syndrome and shouldbe initiated with long-acting dopamine agonists (eg, **pramipexole**0.125–0.75 mg or **ropinirole**0.25–4.0 mg once daily) AND Gabapentin is effective and is taken once or twice daily (inthe evening and before sleep, **Clonazepam**, 1 mg daily, is also sometimeshelpful, Oxycodone is often effective; the dose isindividualized.

Wilson's Disease:

Wilson's disease is characterized biochemically by reduced serum copper and ceruloplasmin concentrations, Treatment involves the removal of excess copper, followed by maintenance of copper balance. Dietary copper should also be kept below 2 mg daily. **Penicillamine**(dimethylcysteine) is used to remove copper, A common starting dose in adults is 500 mg three or four times daily. Adverse effects include nausea and vomiting, nephrotic syndrome, a lupus-like syndrome, pemphigus, myasthenia, arthropathy, optic neuropathy, and various blood dyscrasias.**Trientine hydrochloride**, another chelating agent It may be used in a daily dose of 1–1.5 g. Trientine appears to have few adverse effects other than mild anemia.**Tetrathiomolybdate**may be better than trientine for preserving neurologic function in patients with neurologic andis taken both with and between meals. Zinc acetate administered orally, The dose is 50 mg three times a day. Zinc sulfate (200 mg/d orally) Its main advantage is its low toxicity compared with that of other anticopper agents

Chapter #29: Antipsychotic Agents & Lithium

29. Antipsychotic Agents & Lithium

ANTIPSYCHOTIC AGENTS

Antipsychotic drugs are able to reduce psychotic symptoms in a wide variety of conditions, including schizophrenia, bipolar disorder, psychotic depression, senile psychoses, various organic psychoses, and drug-induced psychoses. They are also able to improve mood and reduce anxiety and sleep disturbances, but they are not the treatment of choice when these symptoms are the primary disturbance in nonpsychotic patients. A **neuroleptic** is a subtype of antipsychotic drug that produces a high incidence of extrapyramidal side effects (EPS) at clinically effective doses, or catalepsy in laboratory animals. The “**atypical**” **antipsychotic drugs** are now the most widely used type of antipsychotic drug.

Table 1: Nature of Psychosis & Schizophrenia

(ذهان) <i>Psychosis</i>	(فصام) <i>Schizophrenia</i>
<ul style="list-style-type: none">- A variety of mental disorders: the presence of delusions (false beliefs), hallucinations, usually auditory or visual but sometimes tactile or olfactory, and grossly disorganized thinking in a clear sensorium.	<ul style="list-style-type: none">- A neurodevelopmental disorder (structural and functional changes in brain).- A particular kind of psychosis characterized mainly by a clear sensorium but a marked thinking disturbance.- Psychosis is not unique to schizophrenia and is not present in all patients with schizophrenia at all times.

Schizophrenia Hypothesis

The serotonin hypothesis

The dopamine hypothesis

The glutamate hypothesis

Table 2: Schizophrenia Hypothesis

The serotonin hypothesis	The dopamine hypothesis	The glutamate hypothesis
<ul style="list-style-type: none">- The discovery that indole hallucinogens such as LSD (lysergic acid diethylamide) and mescaline are serotonin (5-HT) agonists led to the search for endogenous hallucinogens in the urine, blood, and brains of patients with schizophrenia.	<p>It is highly relevant to understanding the major dimensions of schizophrenia, such as positive and negative symptoms (emotional blunting, social withdrawal, lack of motivation), cognitive impairment, and possibly depression.</p>	<p>Glutamate is the major excitatory neurotransmitter in the brain. Phencyclidine (PCP) and ketamine are noncompetitive inhibitors of the NMDA receptor that exacerbate both cognitive impairment and psychosis in patients with</p>



This proved fruitless, but the identification of many 5-HT-receptor subtypes led to the pivotal discovery that 5-HT_{2A}-receptor and possibly 5-HT_{2C} stimulation was the basis for the hallucinatory effects of these agents.

It has been found that 5-HT_{2A}-receptor blockade is a key factor in the mechanism of action of the main class of atypical antipsychotic drugs, of which clozapine is the prototype, and includes, in order of their introduction around the world, melperone, risperidone, zotepine, blonanserin, olanzapine, quetiapine, ziprasidone, aripiprazole, sertindole, paliperidone, iloperidone, asenapine, and lurasidone. These drugs are *inverse agonists* of the 5-HT_{2A} receptor; that is, they block the constitutive activity of these receptors. These receptors modulate the release of dopamine, norepinephrine, glutamate, GABA, and acetylcholine, among other neurotransmitters in the cortex, limbic region, and striatum. Stimulation of 5-HT_{2A} receptors leads to depolarization of glutamate neurons, but also stabilization of N-methyl-d-aspartate (NMDA) receptors on postsynaptic neurons. Recently, it has been found that hallucinogens can modulate the stability of a complex consisting of 5-HT_{2A} and NMDA receptors.

It is also essential to understanding the mechanisms of action of most and probably all antipsychotic drugs. **Several lines of evidence suggest that excessive limbic dopaminergic activity plays a role in psychosis**

- 1) Many antipsychotic drugs strongly block postsynaptic D₂ receptors in the central nervous system, especially in the mesolimbic and striatal-frontal system; this includes partial dopamine agonists, such as aripiprazole and bifeprunox.
- (2) Drugs that increase dopaminergic activity, such as levodopa, amphetamines, and bromocriptine and apomorphine, either aggravate schizophrenia psychosis or produce psychosis de novo in some patients.
- (3) Dopamine-receptor density has been found postmortem to be increased in the brains of schizophrenics who have not been treated with antipsychotic drugs.
- (4) Some but not all postmortem studies of schizophrenic subjects have reported increased dopamine levels and D₂-receptor density in the nucleus accumbens, caudate, and putamen.
- (5) Imaging studies have shown increased amphetamine-induced striatal dopamine release, increased baseline occupancy of striatal D₂ receptors by extracellular dopamine, and other measures consistent with increased striatal dopamine synthesis and release.

schizophrenia. PCP and a related drug, MK-801, increase locomotor activity and, acutely or chronically, a variety of cognitive impairments in rodents and primates. These effects are widely employed as a means to develop novel antipsychotic and cognitive-enhancing drugs.

Selective 5-HT_{2A} antagonists, as well as atypical antipsychotic drugs, are much more potent than D₂ antagonists in blocking these effects of PCP and MK-801. This was the starting point for the hypothesis that hypofunction of NMDA receptors, located on GABAergic interneurons, leading to diminished inhibitory influences on neuronal function, contributed to schizophrenia.

The diminished GABAergic activity can induce disinhibition of downstream glutamatergic activity, which can lead to hyperstimulation of cortical neurons through non-NMDA receptors. Preliminary evidence suggests that LY2140023, a drug that acts as an agonist of the metabotropic 2/3 glutamate receptor (mGluR2/3), may be effective in schizophrenia.

BASIC PHARMACOLOGY oF ANTISSCHIZOPHRENIC AGENTS

Chemical Types

A number of chemical structures have been associated with antipsychotic properties. The drugs can be classified into several groups:



A. Phenothiazine Derivatives

Three subfamilies of phenothiazines, based primarily on the side chain of the molecule, were once the most widely used of the antipsychotic agents. Aliphatic derivatives (eg, **chlorpromazine**) and piperidine derivatives (eg, **thioridazine**) are the least potent.

B. Thioxanthene Derivatives

This group of drugs is exemplified primarily by **thiothixene**.

C. Butyrophenone Derivatives

Haloperidol, a butyrophenone, is the most widely used typical antipsychotic drug, despite its high level of EPS relative to typical antipsychotic drugs. Diphenylbutylpiperidines are closely related compounds.

D. Miscellaneous Structures

Pimozide and **molindone** are typical antipsychotic drugs. There is no significant difference in efficacy between these newer typical and the older typical antipsychotic drugs.

E. Atypical Antipsychotic Drugs

Clozapine, **asenapine**, **olanzapine**, **quetiapine**, **paliperidone**, **risperidone**, **sertindole**, **ziprasidone**, **zotepine**, and **aripiprazole** are atypical antipsychotic drugs. These drugs have complex pharmacology but they share a greater ability to alter 5-HT_{2A}-receptor activity than to interfere with D

2-receptor action. In most cases, they act as partial agonists at the 5-HT_{1A} receptor, which produces synergistic effects with 5-HT_{2A} receptor antagonism. Most are either 5-HT₆ or 5-HT₇ receptor antagonists.

Sulpiride and sulpiride constitute another class of atypical agents. They have equivalent potency for D₂ and D₃ receptors, but they are also 5-HT₇ antagonists. They dissociate EPS and antipsychotic efficacy. However, they also produce marked increases in serum prolactin levels and are not as free of the risk of tardive dyskinesia as are drugs such as clozapine and quetiapine.

Cariprazine represents another class of atypical agents. In addition to D₂/5-HT₂ antagonism, cariprazine is also a D₃ partial agonist with selectivity for the D₃ receptor. Cariprazine's selectivity for the D₃ receptor may be associated with greater effects on the negative symptoms of schizophrenia.

F. Glutamatergic Antipsychotics

No glutamate-specific agents are currently approved for the treatment of schizophrenia. However, several agents are in late clinical testing. Among these is **bitopertin**, a glycine transporter 1 receptor inhibitor (GlyT1). Glycine is a required co-agonist with glutamate at NMDA receptors. Phase 2 studies indicated that bitopertin used adjunctively

with standard antipsychotics significantly improved negative symptoms of schizophrenia. **Sarcosine** (*N*-methylglycine), another

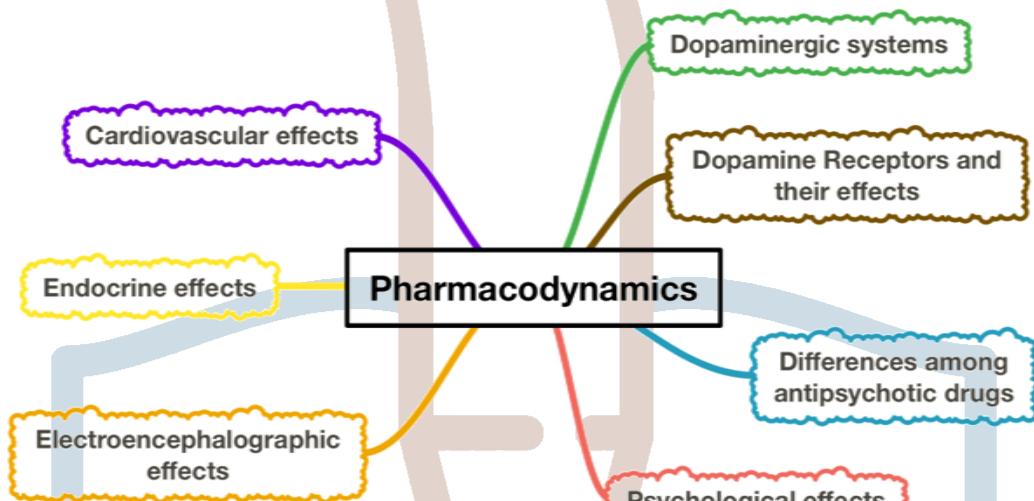
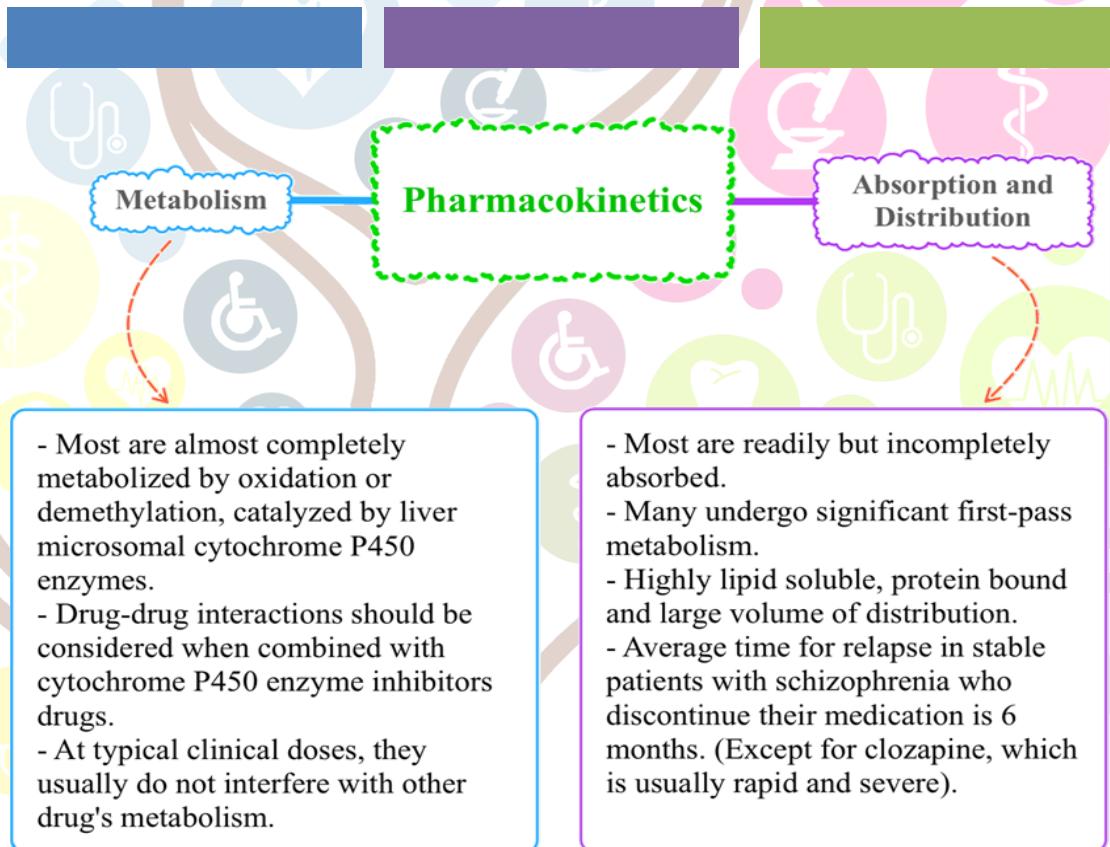
GlyT1 inhibitor, in combination with a standard antipsychotic has also shown benefit in improving both negative and positive symptoms of schizophrenia in acutely ill as well as in more chronic patients with schizophrenia.

TABLE 29-1 Antipsychotic drugs: Relation of chemical structure to potency and toxicities.

Chemical Class	Drug	D ₂ /5-HT _{2A} Ratio ¹	Clinical Potency	Extrapyramidal Toxicity	Sedative Action	Hypotensive Actions
Phenothiazines						
Aliphatic	Chlorpromazine	High	Low	Medium	High	High
Piperazine	Fluphenazine	High	High	High	Low	Very low
Thioxanthene	Thiothixene	Very high	High	Medium	Medium	Medium
Butyrophenone	Haloperidol	Medium	High	Very high	Low	Very low
Dibenzodiazepine	Clozapine	Very low	Medium	Very low	Low	Medium
Benzisoxazole	Risperidone	Very low	High	Low ²	Low	Low
Thienobenzodiazepine	Olanzapine	Low	High	Very low	Medium	Low
Dibenzothiazepine	Quetiapine	Low	Low	Very low	Medium	Low to medium
Dihydroindolone	Ziprasidone	Low	Medium	Very low	Low	Very low
Dihydrocarbostyryl	Aripiprazole	Medium	High	Very low	Very low	Low

¹Ratio of affinity for D₂ receptors to affinity for 5-HT_{2A} receptors.

²At dosages below 8 mg/d.



1) Dopaminergic Systems:

Five dopaminergic systems or pathways are important for understanding the antipsychotic drugs' mechanism of action. They are the **mesolimbic-mesocortical** pathway, the **nigrostriatal** pathway (blockade of D₂ receptors in this pathway is responsible for EPS), the **tuberoinfundibular** system, the **medullary-periventricular** pathway and the **incertohypothalamic** pathway. The antipsychotic action is now thought to be produced (at least in part) by their ability to block the effect of dopamine to inhibit the activity of adenylyl cyclase in the mesolimbic system.

2) Dopamine Receptors and Their Effects:

At present, five dopamine receptors have been described, consisting of two separate families, the D₁-like receptor and D₂-like receptor groups.

a) **D₁-like receptor family:** D₁ and D₅ increases cAMP.

b) **D₂-like receptor family:** D₂ decreases cAMP, inhibits calcium channels but opens potassium channels. D₅ and D₄ also decreases cAMP.

The typical antipsychotic agents block D₂ receptors with strong affinity and must be given in sufficient doses to achieve at least 60% occupancy, while atypical antipsychotic are effective at lower occupancy levels 30-50%, most likely because of their concurrent high occupancy of 5-HT_{2A} receptors.

It has not been convincingly demonstrated that antagonism of any dopamine receptor other than D₂ plays a role in the action of antipsychotic drugs.

3) Differences among Antipsychotic Drugs:

Although all effective antipsychotic drugs block D₂ receptors, the degree of this blockade in relation to other actions on receptors varies considerably among drugs. The differences in receptor effects of various antipsychotics explain many of their toxicities. In particular, extrapyramidal toxicity appears to be associated with high D₂ potency.

Table 3: Adverse pharmacological effects of antipsychotic drugs.

Type	Manifestations	Mechanism
Autonomic nervous system	Loss of accommodation, dry mouth, difficulty urinating, constipation Orthostatic hypotension, impotence, failure to ejaculate	Muscarinic cholinoreceptor blockade α-Adrenoceptor blockade
Central nervous system	Parkinson's syndrome, akathisia, dystonias Tardive dyskinesia Toxic-confusional state	Dopamine-receptor blockade Supersensitivity of dopamine receptors Muscarinic blockade
Endocrine system	Amenorrhea-galactorrhea, infertility, impotence	Dopamine-receptor blockade resulting in hyperprolactinemia
Other	Weight gain	Possibly combined H ₁ and 5-HT ₂ blockade

4) Psychological Effects:

Most antipsychotic drugs cause unpleasant subjective effects in nonpsychotic individuals. Psychotic individuals show improvement in their performance the psychosis is alleviated.

5) Electroencephalographic Effects:

Antipsychotic drugs produce shifts in the pattern of (EEG) frequencies, usually showing them and increasing their synchronization.

6) Endocrine Effects:

Older typical antipsychotic drugs produce elevations of prolactin, Newer antipsychotics cause no or minimal increase of prolactin and reduced EPS.

7) Cardiovascular Effects:

The atypical antipsychotics are associated with a metabolic syndrome that may increase the risk of coronary artery disease, stroke, and hypertension.

Clinical Pharmacology of Antipsychotic Agents

Indications

Psychiatric Indications

Schizophrenia

Schizoaffective disorders

Bipolar affective disorder

Acute bipolar depression

Unipolar depression

Agitation control

Tourette's syndrome

Disturbed behavior in Alzheimer's disease

Nonpsychiatric indications

Antiemetic

H1-receptor-blocking (pruritus & preoperative sedative)

Neuroleptanesthesia

Drug choice

Choice among antipsychotic drugs is

based mainly on differences in adverse effects and possible differences in efficacy. In addition, cost and the availability of a given agent on drug formularies also influence the choice of a specific antipsychotic. The best guide for selecting a drug for an individual patient is the patient's past response to drugs

Adverse Reactions

Behavioral Effects

Neurologic Effects

Autonomic Nervous System Effects

Metabolic and Endocrine Effects

Toxic or Allergic Reactions

Ocular Complications

Cardiac Toxicity

Use in Pregnancy; Dysmorphogenesis

Neuroleptic Malignant Syndrome

Table 4: Some representative antipsychotic drug.

Drug Class	Drug	Advantages	Disadvantages
Phenothiazines			
Aliphatic	Chlorpromazine ¹	Generic, inexpensive	Many adverse effects, especially autonomic
Piperidine	Thioridazine ²	Slight extrapyramidal syndrome; generic	800 mg/d limit; no parenteral form; cardiotoxicity
Piperazine	Fluphenazine ³	Depot form also available (enanthate, decanoate)	Possible increased tardive dyskinesia
Thioxanthene	Thiothixene	Parenteral form also available; possible decreased tardive dyskinesia	Uncertain
Butyrophenone	Haloperidol	Parenteral form also available; generic	Severe extrapyramidal syndrome
Dibenzoxazepine	Loxapine	Possible no weight gain	Uncertain
Dibenzodiazepine	Clozapine	May benefit treatment-resistant patients; little extrapyramidal toxicity	May cause agranulocytosis in up to 2% of patients; dose-related lowering of seizure threshold
Benzisoxazole	Risperidone	Broad efficacy; little or no extrapyramidal system dysfunction at low doses	Extrapyramidal system dysfunction and hypotension with higher doses
Thienobenzodiazepine	Olanzapine	Effective against negative as well as positive symptoms; little or no extrapyramidal system dysfunction	Weight gain; dose-related lowering of seizure threshold
Dibenzothiazepine	Quetiapine	Similar to olanzapine; perhaps less weight gain	May require high doses if there is associated hypotension; short $t_{1/2}$ and twice-daily dosing
Dihydroindolone	Ziprasidone	Perhaps less weight gain than clozapine, parenteral form available	QT _c prolongation
Dihydrocarbostyril	Aripiprazole	Lower weight gain liability, long half-life, novel mechanism potential	Uncertain, novel toxicities possible

Dosage

Table 5: Adverse Reactions of Antipsychotic Agents

Behavioral effects		Pseudodepression
Neurologic effects		Parkinson's syndrome, akathisia, acute dystonic reactions, tardive dyskinesia and seizures.
Autonomic nervous system effects		Antimuscarinic, orthostatic hypotension and impaired ejaculation.
Metabolic and endocrine effects		Weight gain, hyperglycemia, hyperlipidemia and hyperprolactinemia.
Toxic or allergic reactions		Agranulocytosis, cholestatic jaundice and skin eruptions.
Ocular complications		Deposits in the anterior portions of the eye associated with browng of vision.
Cardiac toxicity		Minor abnormalities of T waves, ventricular arrhythmias, QT prolongation, myocarditis and sudden death due to arrhythmias is common in schizophrenia.
Pregnancy		Although relatively safe, a small increase in teratogenic risk could be missed.
Neuroleptic malignant syndrome		Life-threatening disorder occurs in extremely sensitive patients to the extrapyramidal effects.

Dosage

The range of effective dosages among various antipsychotic agents is broad. Therapeutic margins are substantial. At appropriate dosages, antipsychotics—with the exception of clozapine and perhaps olanzapine—are of equal efficacy in broadly selected groups of patients. However, some patients who fail to respond to one drug may respond to another; for this reason, several drugs may have to be tried to find the one most effective for an individual patient.

Table 6: Dose relationships of antipsychotics.

Parenteral Preparations

Well-tolerated parenteral forms of the high potency older drugs haloperidol and fluphenazine are available for rapid initiation of treatment as well as for maintenance treatment in noncompliant patients. Fluphenazine decanoate and haloperidol decanoate are suitable for long-term parenteral maintenance therapy in patients who cannot or will not take oral medication. Newer long-acting injectable (LAI) second generation antipsychotics are now available.

	Minimum Effective Therapeutic Dose (mg)	Usual Range of Daily Doses (mg)
Chlorpromazine	100	100–1000
Thioridazine	100	100–800
Trifluoperazine	5	5–60
Perphenazine	10	8–64
Fluphenazine	2	2–60
Thiothixene	2	2–120
Haloperidol	2	2–60
Loxapine	10	20–160
Molindone	10	20–200
Clozapine	50	300–600
Olanzapine	5	10–30
Quetiapine	150	150–800
Risperidone	4	4–16
Ziprasidone	40	80–160
Aripiprazole	10	10–30

Maintenance Treatment

A very small minority of schizophrenic patients may recover from an acute episode and require no further drug therapy for prolonged periods.

The choice depends on social factors such as the availability of family or friends familiar with the early symptoms of relapse and ready access to care.

Drug Combination

Antipsychotic agents may be combined with:

- Tricyclic antidepressant and serotonin reuptake inhibitors for depression symptoms.

- Electroconvulsive therapy for positive symptom control.

- Benzodiazepines for anxiety symptoms and insomnia.

Drug interactions

Antipsychotics produce more important pharmacodynamic than pharmacokinetic interactions because of their multiple effects. Additive effects may occur when these drugs are combined with others that have sedative effects, α-adrenoceptor blocking action, anticholinergic effects, and—for thioridazine and ziprasidone quinidine-like action. A variety of pharmacokinetic interactions have been reported, but none are of major clinical significance.

Overdoses

Poisonings with antipsychotic agents (unlike tricyclic antidepressants) are rarely fatal, with the exception of those due to mesoridazine and thioridazine (due to their induction of ventricular tachyarrhythmias). In general, drowsiness proceeds to coma,

with an intervening period of agitation. Patients should be given the usual “ABCD” treatment for poisonings.

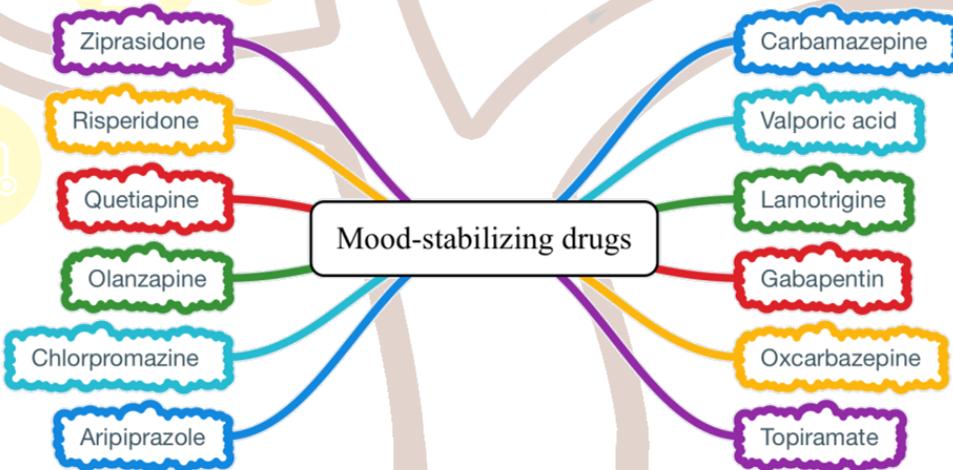
Psychosocial Treatment & Cognitive Remediation

Patients with schizophrenia need psychosocial support based around activities of daily living. First-episode patients are particularly needful of this support because they often deny their illness and are noncompliant with medication.

Benefits & Limitations of Drug Treatment

Antipsychotic drugs have had a major impact on psychiatric treatment. First, they have shifted the vast majority of patients from long term hospitalization to the community. Second, these antipsychotic drugs have markedly shifted psychiatric thinking to a more biologic orientation. Although most schizophrenic patients obtain some degree of benefit from these drugs—in some cases substantial benefit—none are made well by them.

LITHIUM, MOOD-STABILIZING DRUGS, & OTHER TREATMENT FOR BIPOLAR DISORDER



Nature of Bipolar Affective Disorder

- The key symptoms of bipolar disorder in the manic phase are expansive or irritable mood, hyperactivity, impulsivity, disinhibition, diminished need for sleep, racing thoughts, psychotic symptoms in some (but not all) patients, and cognitive impairment.
- Depression in bipolar patients is phenomenologically similar to that of major depression, with the key features being depressed mood, diurnal variation, sleep disturbance, anxiety, and sometimes, psychotic symptoms.
- Mixed manic and depressive symptoms are also seen.
- Patients with bipolar disorder are at high risk for suicide.

Basic Pharmacology of Lithium

Pharmacokinetics

Table 7: Pharmacokinetics of lithium.

Absorption	Virtually complete within 6–8 hours; peak plasma levels in 30 minutes to 2 hours
Distribution	In total body water; slow entry into intracellular compartment. Initial volume of distribution is 0.5 L/kg, rising to 0.7–0.9 L/kg; some sequestration in bone. No protein binding.
Metabolism	None
Excretion	Virtually entirely in urine. Lithium clearance about 20% of creatinine. Plasma half-life about 20 hours.

Pharmacodynamics

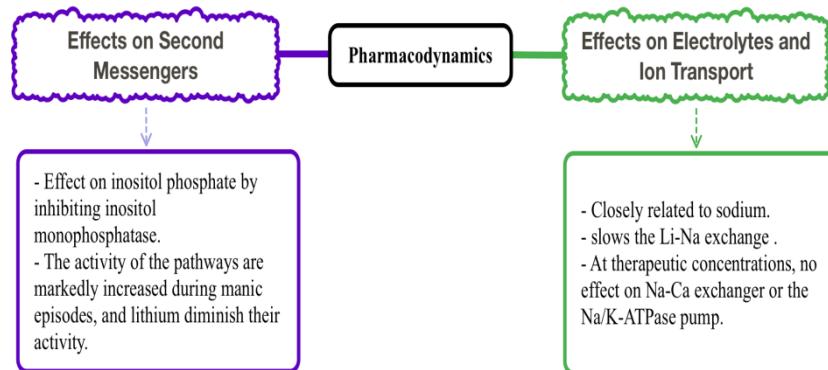


Table 8: Enzymes affected by lithium at therapeutic concentrations.

Enzyme	Enzyme Function; Action of Lithium
Inositol monophosphatase	The rate-limiting enzyme in inositol recycling; inhibited by lithium, resulting in depletion of substrate for IP ₃ production (Figure 29–4)
Inositol polyphosphate 1-phosphatase	Another enzyme in inositol recycling; inhibited by lithium, resulting in depletion of substrate for IP ₃ production (Figure 29–4)
Bisphosphate nucleotidase	Involved in AMP production; inhibited by lithium; may be target that results in lithium-induced nephrogenic diabetes insipidus
Fructose 1,6-biphosphatase	Involved in gluconeogenesis; inhibition by lithium of unknown relevance
Phosphoglucomutase	Involved in glycogenolysis; inhibition by lithium of unknown relevance
Glycogen synthase kinase-3	Constitutively active enzyme that appears to limit neurotrophic and neuroprotective processes; lithium inhibits

AMP, adenosine monophosphate; IP₃, inositol 1,4,5-trisphosphate.

Clinical Pharmacology of Lithium

Bipolar Affective Disorder

- Lithium was universally preferred treatment for bipolar disorder, but with the new drugs; smaller percentage of bipolar patients receive it now.

- The depressive phase of manic-depressive disorder requires concurrent use of other agents including antidepressants which may be destabilizing and precipitate to mania.

Other Applications

Recurrent depression, acute major depression, schizoaffective disorder and schizophrenia (rarely successful alone).

Monitoring Treatment

Clinicians rely on measurements of serum lithium concentrations for assessing both the dosage required for treatment of acute mania and for prophylactic maintenance. These measurements are customarily taken 10–12 hours after the last dose, so all data in the literature pertaining to these concentrations reflect this interval. Once the desired concentration has been achieved, levels can be measured at increasing intervals unless the schedule is influenced by intercurrent illness or the introduction of a new drug into the treatment program.

Maintenance Treatment

The decision to use lithium as prophylactic treatment depends on many factors: the frequency and severity of previous episodes, a crescendo pattern of appearance, and the degree to which the patient is willing to follow a program of indefinite maintenance therapy. Patients with a history of two or more mood cycles or any clearly defined bipolar I diagnosis are probable candidates for maintenance treatment.

Drug Interactions

- Renal clearance of lithium is reduced about 25% by diuretics and newer nonsteroidal anti-inflammatory drugs.

- All neuroleptics with possible exception of clozapine and the newer atypical antipsychotics may produce severe extrapyramidal syndromes when combined with lithium.

Adverse Effects & Complications

Miscellaneous adverse effects

Use during pregnancy

Cardiac adverse effects

Adverse effects & complications

Neurologic & psychiatric adverse effects

Decreased thyroid function

Nephrogenic diabetes insipidus & other renal adverse effects

Edema

SUMMARY Antipsychotic Drugs & Lithium

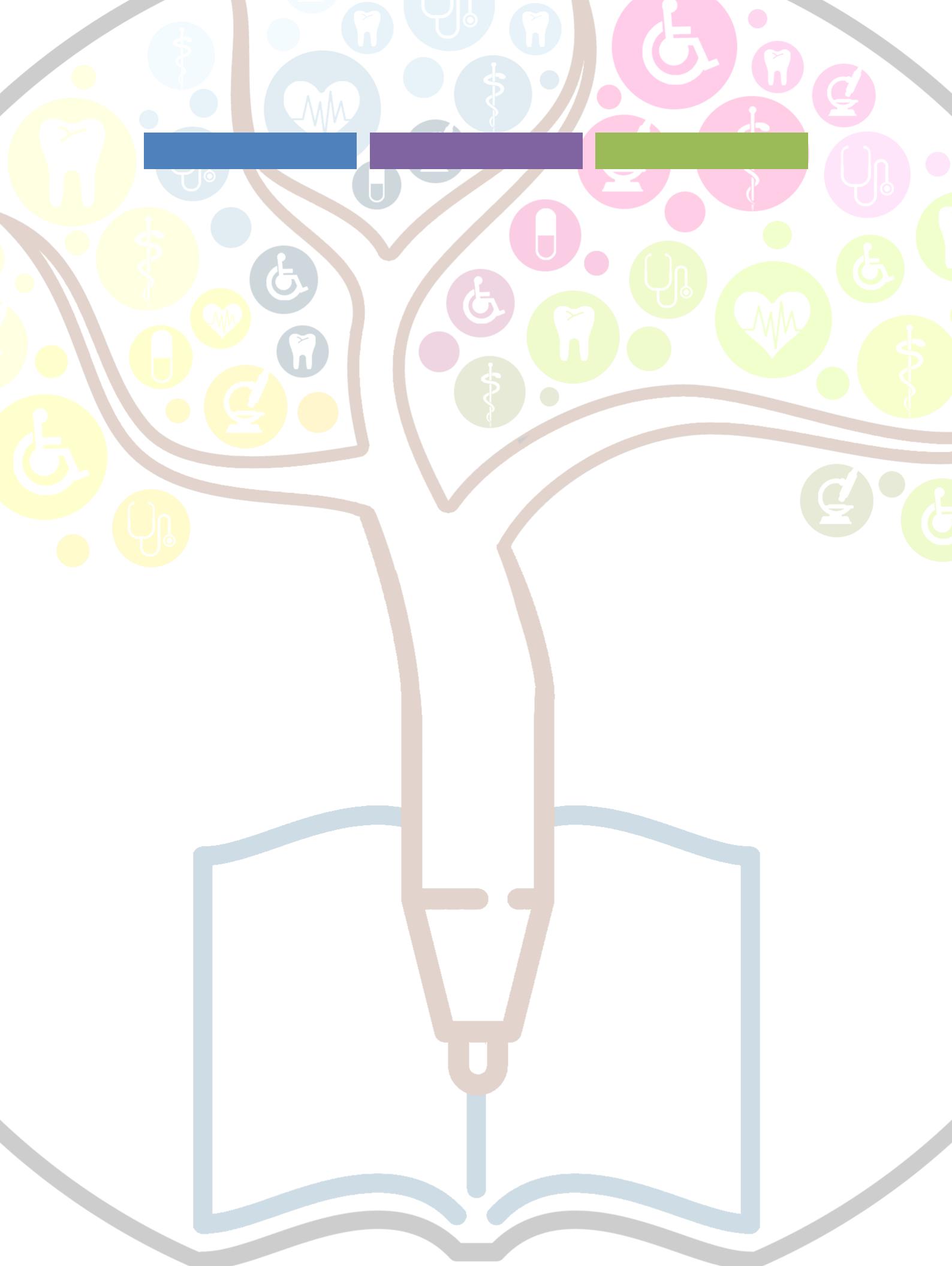
Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
PHENOTHIAZINES				
<ul style="list-style-type: none"> Chlorpromazine Fluphenazine Thioridazine 	Blockade of D ₂ receptors >> 5-HT _{2A} receptors	α-Receptor blockade (fluphenazine least) • muscarinic (M)-receptor blockade (especially chlorpromazine and thioridazine) • H ₁ -receptor blockade (chlorpromazine, thiothixene) • central nervous system (CNS) depression (sedation) • decreased seizure threshold • QT prolongation (thioridazine)	Psychiatric: schizophrenia (alleviate positive symptoms), bipolar disorder (manic phase) • nonpsychiatric: antiemesis, preoperative sedation (promethazine) • pruritus	Oral and parenteral forms, long half-lives with metabolism-dependent elimination • Toxicity: Extrusions effects on α- and M-receptors • blockade of dopamine receptors may result in akathisia, dystonia, parkinsonian symptoms, tardive dyskinesia, and hyperprolactinemia
THIOXANTHENE				
<ul style="list-style-type: none"> Thiothixene 				
BUTYROPHENONE				
<ul style="list-style-type: none"> Haloperidol 	Blockade of D ₂ receptors >> 5-HT _{2A} receptors	Some α blockade, but minimal M-receptor blockade and much less sedation than the phenothiazines	Schizophrenia (alleviates positive symptoms), bipolar disorder (manic phase), Huntington's chorea, Tourette's syndrome	Oral and parenteral forms with metabolism-dependent elimination • Toxicity: Extrapyramidal dysfunction is major adverse effect
ATYPICAL ANTIPSYCHOTICS				
<ul style="list-style-type: none"> Aripiprazole Clozapine Olanzapine Quetiapine Risperidone Ziprasidone 	Blockade of 5-HT _{2A} receptors > blockade of D ₂ receptors	Some α blockade (clozapine, risperidone, ziprasidone) and M-receptor blockade (clozapine, olanzapine) • variable H ₁ -receptor blockade (all)	Schizophrenia—improve both positive and negative symptoms • bipolar disorder (olanzapine or risperidone adjunctive with lithium) • agitation in Alzheimer's and Parkinson's patients (low doses) • major depression (aripiprazole)	Toxicity: Agranulocytosis (clozapine), diabetes (clozapine, olanzapine), hypercholesterolemia (clozapine, olanzapine), hyperprolactinemia (risperidone), QT prolongation (ziprasidone), weight gain (clozapine, olanzapine)

Overdoses

Therapeutic overdoses of lithium are more common than those due to deliberate or accidental ingestion of the drug. Therapeutic overdoses are usually due to accumulation of lithium resulting from some change in the patient's status. Because lithium is a small ion, it is dialyzed readily. Both peritoneal dialysis and hemodialysis are effective, although the latter is preferable.

LITHIUM	Mechanism of action uncertain • suppresses inositol signaling and inhibits glycogen synthase kinase-3 (GSK-3), a multifunctional protein kinase	No significant antagonistic actions on autonomic nervous system receptors or specific CNS receptors • no sedative effects	Bipolar affective disorder—prophylactic use can prevent mood swings between mania and depression	Oral absorption, renal elimination • half-life 20 h • narrow therapeutic window (monitor blood levels) • Toxicity: Tremor, edema, hypothyroidism, renal dysfunction, dysrhythmias • pregnancy category D • Interactions: Clearance decreased by thiazides and some NSAIDs
NEWER AGENTS FOR BIPOLAR DISORDER				
<ul style="list-style-type: none"> Carbamazepine Lamotrigine Valproic acid 	Mechanism of action in bipolar disorder unclear (see Chapter 24 for putative actions in seizure disorders)	See Chapter 24	Valproic acid is increasingly used as first choice in acute mania • carbamazepine and lamotrigine are also used both in acute mania and for prophylaxis in depressive phase	Oral absorption • once-daily dosing • carbamazepine forms active metabolite • lamotrigine and valproic acid form conjugates • Toxicity: Hematotoxicity and induction of P450 drug metabolism (carbamazepine), rash (lamotrigine), tremor, liver dysfunction, weight gain, inhibition of drug metabolism (valproic acid)

Chapter #30: Antidepressant Agents



30. Antidepressant Agents

- ❖ The diagnosis of depression still rests primarily on the clinical interview.
- ❖ Major depressive disorder (MDD) is characterized by:
 - 1- Depressed mood most of the time for at least 2 weeks
 - 2- Loss of interest or pleasure in most activities, or both.
 - 3- Disturbances in sleep and appetite as well as deficits in cognition and energy.
 - 4- Thoughts of guilt, worthlessness, and suicide.
- ❖ MDD represents one of the most common causes of disability in the developed world.
- ❖ According to the Centers for Disease Control, antidepressants are consistently among the three most commonly prescribed classes of medications in the USA "United States of America".
- ❖ When depression coexists with other medical conditions, the patient's disease burden increases, and the quality of life and often the prognosis for effective treatment decreases significantly.
- ❖ Antidepressants have a broad spectrum of use in medical practice for conditions other than major depression. However, their primary use remains the treatment for MDD.

Neurotrophic Hypothesis:

Evidence to support the monoamine hypothesis comes from several sources.

It has been known for many years that reserpine treatment, which is known to deplete monoamines, is associated with depression in a subset of patients.	Depressed patients who respond to serotonergic antidepressants such as fluoxetine often rapidly suffer relapse when given diets free of tryptophan, a precursor of serotonin synthesis.	Patients who respond to noradrenergic antidepressants such as desipramine are less likely to relapse on a tryptophan-free diet.	Depleting catecholamines in depressed patients who have previously responded to noradrenergic agents likewise tends to be associated with relapse.	Another line comes from genetic studies. A functional polymorphism exists for the promoter region of the serotonin transporter gene, which regulates how much of the transporter protein is available.
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- ❖ There is substantial evidence that nerve growth factors such as brain-derived neurotrophic factor (BDNF) are critical in the regulation of neural plasticity, resilience, and neurogenesis.
- ❖ The evidence suggests that depression is associated with the loss of neurotrophic support and that effective antidepressant therapies increase neurogenesis and synaptic connectivity in cortical areas such as the hippocampus.
- ❖ BDNF is thought to exert its influence on neuronal survival and growth effects by activating the tyrosine kinase receptor B in both neurons and glia.

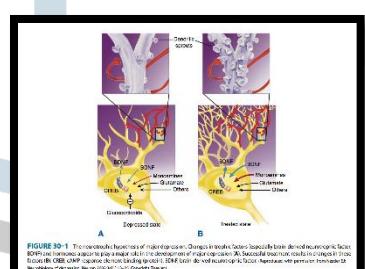
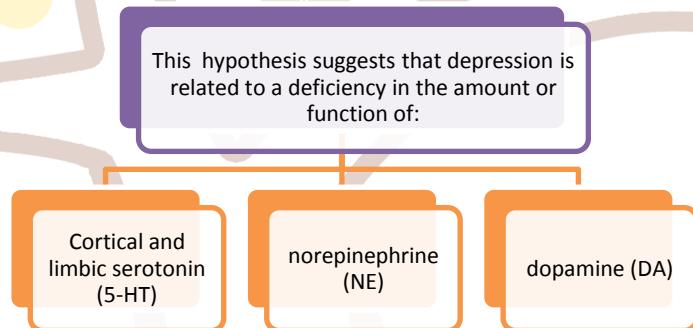


FIGURE 30-1 The hippocampus undergoes changes in health and disease. **A:** Normal hippocampus. **B:** Hippocampus in depression. Note the shrinkage of the hippocampus and the decrease in BDNF levels. (Courtesy of Dr. Michael S. Meaney, Department of Psychology, McGill University.)

- ❖ A proposed explanation for the discrepant findings on the role of neurotrophic factors in depression is that there are polymorphisms for BDNF that may yield very different effects.
- ❖ Loss of volume in structures such as the hippocampus also appears to increase as a function of the duration of illness and the amount of time that the depression remains untreated.
- ❖ Another source of evidence supporting the neurotrophic hypothesis of depression comes from studies of the direct effects of BDNF on emotional regulation like effect in animal models.
- ❖ All known classes of antidepressants are associated with an increase in BDNF levels in animal models with chronic (but not acute) administration and increased neurogenesis in the hippocampus.
- ❖ Other interventions thought to be effective in the treatment of major depression, including [Electroconvulsive therapy](#).
- ❖ Much evidence supports the neurotrophic hypothesis of depression, but not all evidence is consistent with this concept.

Monoamines & Other Neurotransmitters:



- ❖ **Perhaps the most convincing line of evidence supporting the monoamine hypothesis is the fact that (at the time of this writing) all available antidepressants appear to have significant effects on the monoamine system.**
- Finally, The monoamine hypothesis, like the neurotrophic hypothesis, is at best incomplete.
- ❖ Antidepressants are known to impact glutamate neurotransmission in a variety of ways, there has been a growing interest in the development of pharmaceutical agents that might modulate the glutamate system.

Neuroendocrine Factors in the Pathophysiology of Depression:

- ❖ Depression is known to be associated with a number of hormonal abnormalities, It's associated with elevated:
 - cortisol levels.
 - nonsuppression of adrenocorticotropic hormone (ACTH)
 - corticotropin-releasing hormone(chronic).
- ❖ Thyroid dysregulation ([Clinical hypothyroidism](#)) has also been reported in depressed patients.These abnormalities include:
 - A blunting of response of thyrotropin tothyrotropin-releasing hormone.
 - Elevations in circulating thyroxine during depressed states.
- ❖ Sex steroids are also implicated in the pathophysiology of depression.
 - A-Estrogen deficiency states**, which occur in the postpartum and postmenopausal periods, are thought to play a role in the etiology of depression in some women.
 - B- severe testosterone deficiency in men** is sometimes associated with depressive symptoms.
- **Hormone replacement therapy** in hypogonadal men and women may be associated with an improvement in mood and depressive symptoms.

Integration of Hypotheses Regarding the Pathophysiology of Depression:

- ❖ The several pathophysiologic hypotheses just described are not mutually exclusive.
- ❖ It is evident that the [monoamine](#), [neuroendocrine](#), and [neurotrophic systems](#) are interrelated in important ways.
- ❖ The chronic activation of monoamine receptors by antidepressants appears to have:

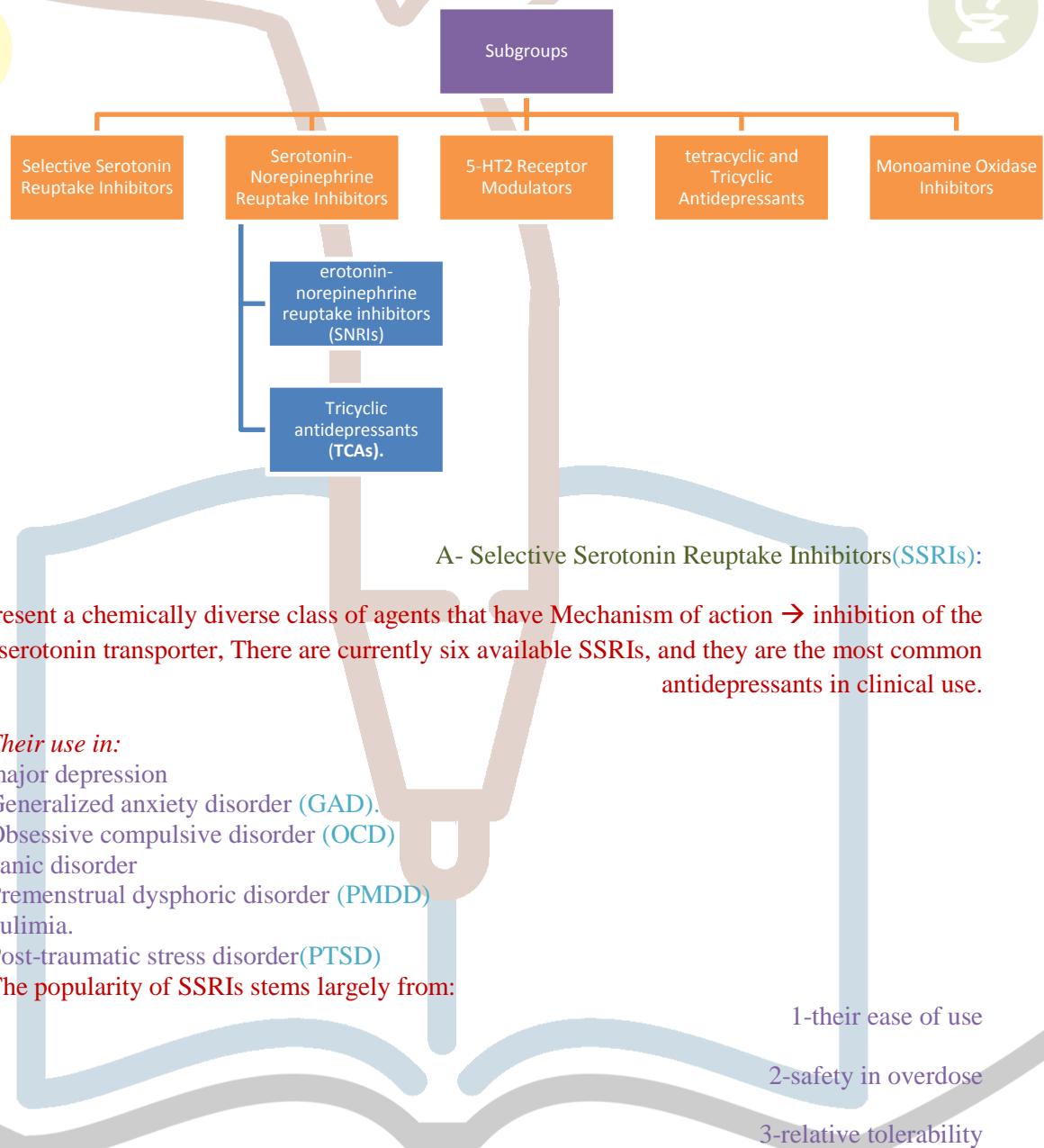
A-the opposite effect of stress results in an increase in BDNF (Brain derived neurotrophic factor) transcription.

B- down-regulate the HPA axis and may normalize The HPA (hypothalamic pituitary adrenal axis) function.

- ❖ One of the weaknesses of the monoamine hypothesis is the fact that amine levels increase immediately with antidepressant use, but maximum beneficial effects of most antidepressants are not seen for many weeks.
 - The time required to synthesize neurotrophic factors has been proposed as an explanation for this delay of antidepressant effects.

Basic pharmacology of antidepressants:

These differences and the differences in their molecular targets provide the basis for distinguishing several subgroups.



4-cost(all are available as generic products)

5-broad spectrum of uses.

- ❖ Fluoxetine was introduced in the United States in 1988 and quickly became one of the most commonly prescribed medications in medical practice.



1-Increased serotonergic activity in the gut is commonly associated with nausea, gastrointestinal upset, diarrhea, increase in headaches and insomnia or hypersomnia and other gastrointestinal symptoms.

2-Increasing serotonergic tone at the level of the spinal cord and above is associated with diminished sexual function and interest.

3-loss of libido, delayed orgasm, or diminished arousal.

4-Some patients gain weight while taking SSRIs, particularly paroxetine.

5-Sudden discontinuation of short half-life SSRIs such as paroxetine and sertraline is associated with a discontinuation syndrome in some patients characterized by dizziness, paresthesias, and other symptoms beginning 1 or 2 days after stopping the drug and persisting for 1 week or longer.

6-There is an association of paroxetine with cardiac septal defects in first trimester exposures.

7-post-birth complications, including pulmonary hypertension, have not been clearly established.

B- Serotonin-Norepinephrine Reuptake Inhibitors:

Two classes of antidepressants act as combined serotonin and norepinephrine reuptake inhibitors:

1- Selective serotonin-norepinephrine reuptake inhibitors(SNRIs):

The SNRIs include venlafaxine, its metabolite desvenlafaxine, duloxetine, and levomilnacipran.

- ❖ SNRIs are also used in the treatment of:
 - pain disorders including neuropathies and fibromyalgia.
 - generalized anxiety
 - stress urinary incontinence
 - vasomotor symptoms of menopause.
- ❖ SNRIs are chemically unrelated to each other.
- ❖ All SNRIs bind the serotonin (SERT) and norepinephrine (NET) transporters, as do the Tricyclic antidepressants(TCAs) , However, unlike the TCAs, the SNRIs do not have much affinity for other receptors.

2. Tricyclic antidepressants (TCAs)

- ❖ The TCAs were the dominant class of antidepressants until the introduction of SSRIs in the 1980s and 1990s, Nine TCAs are available in the USA, and they all have an iminodibenzyl (tricyclic) core.
- ❖ The chemical differences between the TCAs are relatively subtle. However, this minor difference results in a substantial change in their pharmacologic profiles.
- ❖ Imipramine is highly anticholinergic and is a relatively strong serotonin as well as norepinephrine reuptake inhibitor. In contrast, desipramine is much less anticholinergic and is a more potent and somewhat more selective than is imipramine.

- ❖ Uses for TCAs include the treatment of:
 - primarily in depression that is unresponsive to more commonly used antidepressants such as the SSRIs or SNRIs.
 - pain conditions
 - enuresis
 - insomnia.

- ❖ Their loss of popularity stems in large part from:
 - 1-relatively poorer tolerability compared with newer agents
 - 2-difficulty of use
 - 3-lethality in overdose.

Adverse Effects:

- 1-noradrenergic effects, including increased blood pressure and heart rate, and CNS activation, such as insomnia, anxiety, and agitation.
- 2-A dose-related increase in blood pressure has been seen more commonly with the immediate-release form of venlafaxine than with other SNRIs.
- 3-cardiac toxicity with venlafaxine overdose
- 4-Duloxetine is rarely associated with hepatic toxicity in patients with a history of liver damage.
- 5-All the SNRIs have been associated with a discontinuation syndrome resembling that seen with SSRI discontinuation.
- 6- Anticholinergic effects are dry mouth, constipation, urinary retention, blurred vision, and confusion.
- 7-The potent α -blocking property of TCAs often results in orthostatic hypotension.
- 8-H1 antagonism by the TCAs is associated with weight gain and sedation.
- 9-The TCAs are class 1A antiarrhythmic agents and are arrhythmogenic at higher doses.
- 10-Sexual effects are common, particularly with highly serotonergic TCAs such as clomipramine.
- 11-The TCAs have a prominent discontinuation syndrome characterized by cholinergic rebound and flulike symptoms.

C- 5-HT2 Receptor Modulators:

- ❖ Two antidepressants: **trazodone and nefazodone**.
- ❖ Mechanism of action →act as antagonists (inhibitors) at the 5-HT2 receptor.
- **Trazodone:** was among the most commonly prescribed antidepressants until it was supplanted by the SSRIs in the late 1980s.
The most common use of trazodone in current practice is as an unlabeled hypnotic, since it is highly sedating and not associated with tolerance or dependence.

- **Nefazodone:** received an FDA black box warning in 2001 implicating it in hepatotoxicity, including lethal cases of hepatic failure. Though still available generically, no longer commonly prescribed.
- ❖ Both have also been used in the treatment of:
 - major depression
 - anxiety disorders.
- **Vortioxetine:** is a newer agent but its actions are not primarily related to Serotonin 5-HT Transporters (SERT) inhibition and it is therefore not classified as an SSRI.

Adverse Effects:

- 1-The most common adverse effects are:
A-sedation(particularly with trazodone)
- B-gastrointestinal disturbances(appear to be dose-related and are less pronounced than those seen with SNRIs or SSRIs).
- 2-Sexual effects are uncommon with nefazodone or trazodone treatment as a result of the relatively selective serotonergic effects of these drugs.
- 3-trazodone has rarely been associated with inducing priapism.

4-Nefazodone has been associated with hepatotoxicity, including rare fatalities and cases of fulminant hepatic failure requiring transplantation.

5-Both nefazodone and trazodone are α -blocking agents and may result in a dose-related orthostatic hypotension in some patients.

6-As with the SSRIs, the most common adverse effects of vortioxetine are serotonergic and include dose-dependent gastrointestinal effects, particularly nausea, as well as sexual dysfunction.

7-Higher doses of vortioxetine tend to increase the rate of GI and sexual side effects.

D- Tetracyclic and Unicyclic Antidepressants:

- ❖ A number of antidepressants do not fit neatly into the other classes.
- ❖ Among these are **bupropion, mirtazapine, amoxapine, vilazodone, and maprotiline.**
- **Bupropion:**has unique structure results in a different side effect profile than most antidepressants. somewhat resembles amphetamine in chemical structure and, like the stimulant, has central nervous system (CNS) activating properties.
- **Mirtazapine:** was introduced in 1994 and, like bupropion, is one of the few antidepressants not commonly associated with sexual effects.
- **Amoxapine:** is the N-methylated metabolite of loxapine, an older antipsychotic drug. Amoxapine and maprotiline share structural similarities and side effects comparable to the TCAs.
- ❖ thesetetracyclics are not commonly prescribed in current practice. Their primary use is in MDD that is unresponsive to other agents.
- **Vilazodone:** has a multiring structure that allows it to bind potently to the serotonin transporter but minimally to the dopamine and norepinephrine transporter.

Adverse effects:

1-Amoxapine is sometimes associated with a parkinsonian syndrome due to its D2-blocking action.

2-Mirtazapine has significant sedative effect.

3-Maprotiline has a moderately high affinity for norepinephrine transporter (NET) and may cause Tricyclic Antidepressants(

TCA)-like adverse effects and, rarely, seizures.

4-Bupropion is occasionally associated with agitation, insomnia, and anorexia. Vilazodone may have somewhat higher rates of gastrointestinal upset, including diarrhea and nausea, than the SSRIs.

E- Monoamine Oxidase Inhibitors(MAOIs):

- ❖ Arguably the first modern class of antidepressants, were introduced in the 1950s but are now rarely used in clinical practice because of toxicity and potentially lethal food and drug interactions.
- ❖ Their primary use now is in the treatment of:
 - depression unresponsive to other antidepressants.
 - used historically to treat anxiety states, including social anxiety and panic disorder.
 - selegiline is used in the treatment of Parkinson's disease
- ❖ Current MAOIs include the hydrazine derivatives phenelzine and isocarboxazid and the non hydrazines tranylcypromine, selegiline, and moclobemide (the latter is not available in the USA).
 - The hydrazines and tranylcypromine: bind irreversibly and nonselectively with MAO-A and -B, whereas other MAOIs may have more selective or reversible properties.
 - Tranylcypromine: resemble amphetamine in chemical structures
 - selegiline: have amphetamine-like metabolites.
- ❖ As a result, these MAOIs tend to have substantial CNS-stimulating effects.

Adverse effects:

1-The most common adverse effects are orthostatic hypotension and weight gain.

2-the irreversible nonselective MAOIs are associated with the highest rates of sexual effects of all the antidepressants.

3-Anorgasmia(persistent inability to achieve orgasm despite responding to sexual stimulation)is fairly common with therapeutic doses of some MAOIs.

4-The amphetamine-like properties of some MAOIs contributes to activation, insomnia, and restlessness in some patients.

5-Phenelzine tends to be more sedating than either selegiline or tranylcypromine.

6-Confusion is also sometimes associated with higher doses of MAOIs.

7-MAOIs have been associated with a sudden discontinuation syndrome manifested in delirium-like presentation with psychosis, excitement, and confusion.

Pharmacokinetics:

The antidepressants share several pharmacokinetic features. Most have fairly rapid oral absorption, achieve peak plasma levels within 2–3 hours, are tightly bound to plasma proteins, undergo hepatic metabolism, and are renally cleared. However, even within classes, the pharmacokinetics of individual antidepressants varies considerably.

TABLE 30-1 Pharmacokinetic profiles of selected antidepressants.

Class, Drug	Bioavailability (%)	Plasma t _{1/2} (hours)	Azto Metabolism (%)	Vcmax (L/h)	t _{1/2} (hours)	Distribution (L/kg)	Protein Binding (%)
SSRIs							
Citalopram	80	33–38	ND	15	80		
Escitalopram	80	27–32	ND	12–15	80		
Fluoxetine	70	48–72	180	12–97	95		
Fluvoxamine	90	14–18	14–16	25	80		
Paroxetine	50	20–23	ND	28–31	94		
Sertraline	45	22–27	62–104	20	98		
SNRIs							
Duloxetine	50	12–15	ND	10–14	97		
Milnacipran	85–90	6–8	ND	5–6	13		
Venlafaxine ¹	45	8–11	9–13	4–10	27		
Tryptics							
Amitriptyline	45	31–46	20–92	5–10	90		
Clomipramine	50	19–37	54–77	7–20	97		
Imipramine	40	9–24	14–62	15–30	84		
5-HT modulators							
Nefazodone	20	2–4	ND	0.5–1	99		
Trazadone	95	3–6	ND	1–3	96		
Vortioxetine	75	66	ND	ND	98		
Tetracyclics and unicyclic							
Amoxapine	ND	7–12	5–30	0.9–1.2	85		
Buproprion	70	11–14	15–25	20–30	85		
Maprotiline	70	43–45	ND	23–27	88		
Mirtazapine	50	20–40	20–40	3–7	85		
Vilazodone	72	25	ND	ND	ND		
MAOIs							
Phenelzine	ND	11	ND	ND	ND		
Selegiline	4	8–10	9–11	8–10	99		

¹Desvenlafaxine has similar properties but is less completely metabolized.

MAOIs, monoamine oxidase inhibitors; ND, no data found; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

TABLE 30-2 Antidepressant effects on several receptors and transporters.

Antidepressant	ACh M	α ₁	H ₁	5-HT ₂	NET	SERT
Amitriptyline	+++	+++	++	0/+	+	++
Amoxapine	+	++	+	+++	++	+
Bupropion	0	0	0	0	0/+	0
Citalopram, escitalopram	0	0	0		0	+++
Clomipramine	+	++	+	+	+	+++
Desipramine	+	+	+	0/+	+++	+
Doxepin	++	+++	+++	0/+	+	+
Fluoxetine	0	0	0	0/+	0	+++
Fluvoxamine	0	0	0	0	0	+++
Imipramine	++	+	+	0/+	+	++
Maprotiline	+	+	++	0/+	++	0
Mirtazapine	0	0	+++	+	+	0
Nefazodone	0	+	0	++	0/+	+
Nortriptyline	+	+	+	+	++	+
Paroxetine	+	0	0	0	+	+++
Protriptyline	+++	+	+	+	+++	+
Sertaline	0	0	0	0	0	+++
Trazadone	0	++	0/+	++	0	+
Trimipramine	++	++	+++	0/+	0	0
Venlafaxine	0	0	0	0	+	++
Vortioxetine ¹	ND	ND	ND	ND	+	+++

¹Vortioxetine is an agonist or partial agonist at 5-HT_{1A} and 5-HT_{1B} receptors, an antagonist at 5-HT₃ and 5-HT₇ receptors, and an inhibitor of SERT.

ACh M, acetylcholine muscarinic receptor; α₁, alpha₁-adrenoreceptor; H₁, histamine₁ receptor; 5-HT₂, serotonin 5-HT₂ receptor; NET, norepinephrine transporter; SERT, serotonin transporter.

0+, minimal affinity; +, mild affinity; ++, moderate affinity; +++, high affinity.

Clinical pharmacology of antidepressants:

Clinical Indications

A. Depression:

- ❖ The FDA indication for the use of the antidepressants in the treatment of major depression is fairly broad.
- ❖ Most antidepressants are approved for both acute and long-term treatment of major depression.
- ❖ The goal of acute treatment of MDD is remission of all symptoms.
- ❖ The antidepressants are successful in achieving remission in about 30–40% of patients within a single trial of 8–12 weeks.
- ❖ If an inadequate response is obtained, therapy is often switched to another agent or augmented by addition of another drug.
- ❖ Once an adequate response is achieved, continuation therapy is recommended for a minimum of 6–12 months to reduce the substantial risk of relapse. Approximately 85% of patients who have a single episode of MDD will have at least one recurrence in a lifetime.
- ❖ Many patients have multiple recurrences may progress to more serious, chronic, and treatment-resistant episodes.
- ❖ long-term studies with TCAs, SNRIs, and SSRIs suggest a significant protective benefit when given chronically if they have had two or more serious MDD episodes in the previous 5 years or three or more serious episodes in a lifetime.
- ❖ It is not clear whether antidepressants are useful for all subtypes of depression.
- ❖ Psychotherapeutic interventions such as cognitive behavioral therapy appear to be as effective as antidepressant treatment for mild to moderate forms of depression. However, cognitive behavioral therapy tends to take longer to be effective and is generally more expensive than antidepressant treatment. Psychotherapy is often combined with antidepressant treatment, and the combination appears more effective than either strategy alone.

B. Anxiety Disorders:

- ❖ After major depression, anxiety disorders represent the most common application of antidepressants.
- ❖ older antidepressants and drugs of the sedative-hypnotic class are still occasionally used for the treatment of anxiety disorders, SSRIs and SNRIs have largely replaced them.
- **The benzodiazepines:** provide much more rapid relief of both generalized anxiety and panic than do any of the antidepressants.
- However, the antidepressants appear to be at least as effective as, and perhaps more effective than, benzodiazepines in the long-term treatment of these anxiety disorders.
- Furthermore, antidepressants do not carry the risks of dependence and tolerance that may occur with the benzodiazepines.
- ❖ A number of SSRIs and SNRIs have been approved for all the major anxiety disorders, including **Post-traumatic stress disorder(PTSD)**, **Obsessive compulsive disorder(OCD)**, **social anxiety disorder**, **Generalized anxiety disorder(GAD)**, and **panic disorder**.
- **Panic disorder:** is characterized by recurrent episodes of brief overwhelming anxiety, which often occur without precipitant.
- **GAD:** is characterized by a chronic, free-floating anxiety and undue worry that tends to be chronic in nature.
- **OCD:** is known to respond to serotonergic antidepressants. It is characterized by repetitive anxiety-provoking thoughts (obsessions) or repetitive behaviors aimed at reducing anxiety (compulsions). **Clomipramine and several of the SSRIs** are approved for the treatment of OCD, and they are moderately effective.
- **Social anxiety disorder:** is an uncommonly diagnosed but a fairly common condition in which patients experience severe anxiety in social interactions. This anxiety may limit their ability to function adequately in their jobs or interpersonal relationships. **Several SSRIs and venlafaxine** are approved for the treatment of social anxiety.
- **PTSD:** is manifested when a traumatic or life-threatening event results in intrusive anxiety-provoking thoughts or imagery, hypervigilance, nightmares, and avoidance of situations that

remind the patient of the trauma. **SSRIs** are considered first-line treatment for PTSD and can benefit a number of symptoms including anxious thoughts and hypervigilance.

- ❖ Behavior therapy is usually combined with the antidepressant for additional benefits.

C. Pain Disorders:

TCA s have been used in the treatment of neuropathic and other pain conditions and SNRIs are increasingly used

Medications that possess both norepinephrine and 5-HT reuptake blocking properties are often useful in treating pain disorders.

- **Iduloxetine:** was approved for the treatment of chronic joint and muscle pain.
- **milnacipran:** is approved for the treatment of fibromyalgia in the USA
- **Other SNRIs, eg, desvenlafaxine:** are being investigated for a variety of pain conditions from postherpetic neuralgia to chronic back pain.

D. Premenstrual Dysphoric Disorder(PMDD):

Approximately 5% of women in the child-bearing years will have prominent mood and physical symptoms include anxiety, depressed mood, irritability, insomnia, fatigue during the late luteal phase of almost every cycle

These symptoms are more severe than those typically seen in premenstrual syndrome (PMS) and can be quite disruptive to vocational and interpersonal activities.

- The **SSRIs** are known to be beneficial may be associated with rapid increases in pregnenolone levels., and **fluoxetine** and **sertraline** are approved for this indication.

Treating for **2 weeks** out of the month in the luteal phase may be as effective as continuous treatment.

E. Smoking Cessation:

- **Bupropion:** was approved in 1997 as a treatment for smoking cessation.

- ❖ Characteristics of Bupropion:

1-effective as nicotine patches in smoking cessation.

2-experience fewer mood symptoms and possibly less weight gain while withdrawing from nicotine dependence.

3-reduced urge to smoke.

- ❖ Mechanism of action: may mimic nicotine's effects on dopamine and norepinephrine and may antagonize nicotinic receptors.
- **Nortriptyline:** has been shown to be helpful in smoking cessation, but the effects have not been as consistent as those seen with bupropion.

F. Eating Disorders:

Bulimia nervosa and anorexia nervosa are potentially devastating disorders.

- ❖ Bulimia is characterized by:

1- episodic intake of large amounts of food (binges) followed by ritualistic purging through emesis

2- the use of laxatives, or other methods.

3-Medical complications of the purging, such as hypokalemia, are common and dangerous.

Anorexia: is a disorder in which reduced food intake results in a loss of weight of 15% or more of ideal body weight, and the person has a morbid fear of gaining weight and a highly distorted body image. is often chronic and may be fatal in 10% or more of cases.

❖ The primary treatment for anorexia at this time is:

1-refeeding

2-family therapy

3-cognitive behavioral therapy.

❖ Antidepressants appear to be helpful in the treatment of bulimia but not anorexia.

❖ Nondepressed, obese patients treated with bupropion were able to lose somewhat more weight but the ability to weight loss was not robust, and there appear to be more effective options for weight loss.

G. Other Uses for Antidepressants:

Antidepressants are used for many other on- and off-label applications.

Enuresis in children is an older labeled use for some TCAs, but they are less commonly used now because of their side effects.

- The SNRI duloxetine: is approved in Europe for the treatment of urinary stress incontinence.
- ❖ Many of the serotonergic antidepressants, venlafaxine, and nefazodone appear to be helpful for treating vasomotor symptoms in perimenopause.
- Although serotonergic antidepressants are commonly associated with inducing sexual adverse effects, bupropion has been used to treat sexual adverse effects but the efficacy for this use has not been consistently demonstrated in controlled trials.

Choosing an Antidepressant:

The choice depends first on the indication. Not all conditions are equally responsive to all antidepressants.

However, in the treatment of MDD, it is difficult to demonstrate that one antidepressant is consistently more effective than another. Thus, the choice of treatment rests primarily on practical considerations such as:

1-cost

2-availability

3-adverse effects

4-potential drug interactions

5-the patient's history of response or lack thereof

6-patient preference.

7-Other factors such as the patient's age, gender, and medical status

- At present, **SSRIs** are the most commonly prescribed first-line agents in the treatment of both MDD and anxiety disorders. The starting dose is usually the same as the therapeutic dose for most patients.

In addition, most SSRIs are now generically available and inexpensive. Other agents, including the **SNRIs**, bupropion (*seasonal "winter" depression*), and mirtazapine, are also reasonable first-line agents for the treatment of MDD.

- The **TCAs and MAOIs** are now relegated to second- or third-line treatments for MDD.

Both are:

- 1-potentially lethal in overdose
- 2-require titration to achieve a therapeutic dose
- 3-have serious drug interactions
- 4-have many trouble- some adverse effects.

As a consequence, their use in the patients have been unresponsive to other agents, there are patients whose depression responds only to MAOIs or TCAs (*treatment-resistant depressed patients*).

- **SSRIs and the highly serotonergic TCA, clomipramine**, are effective in the treatment of OCD, but noradrenergic antidepressants have not proved to be as helpful for this condition.
- **Bupropion and nortriptyline** have usefulness in the treatment of smoking cessation, but SSRIs have not been proven useful.

The use of antidepressants outside the treatment tends to require known benefit of a particular antidepressant or class for a particular indication.

Dosing

TABLE 30-3 Antidepressant dose ranges.

Drug	Usual Therapeutic Dosage (mg/d)
SSRIs	
Citalopram	20–60
Escitalopram	10–30
Fluoxetine	20–60
Fluvoxamine	100–300
Paroxetine	20–60
Sertraline	50–200
SNRIs	
Venlafaxine	75–375
Desvenlafaxine	50–200
Duloxetine	40–120
Milnacipran	100–200
Tricyclics	
Amitriptyline	150–300
Clomipramine	100–250
Desipramine	150–300
Doxepin	150–300
Imipramine	150–300
Nortriptyline	50–150
Protriptyline	15–60
Trimipramine maleate	150–300
5-HT₂ antagonists	
Nefazodone	300–500
Trazodone	150–300
Tetracyclics and unicyclics	
Amoxapine	150–400
Bupropion	200–450
Maprotiline	150–225
Mirtazapine	15–45
MAOIs	
Isocarboxazid	30–60
Phenelzine	45–90
Selegiline	20–50
Tranylcypromine	30–60

MAOIs, monoamine oxidase inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

Overdose:

Treatment typically involves:

1-cardiac monitoring

2-airway support

3-gastric lavage.

Overdose is the most common method used in suicide attempts, and antidepressants, especially the TCAs, are frequently involved.

Overdose can induce:

1-lethal arrhythmias, including ventricular tachycardia and fibrillation.

2-blood pressure changes

3-anticholinergic effects including altered mental status and seizures are sometimes seen in TCA overdoses.

- Sodium bicarbonate is often administered to displace the TCA from cardiac sodium channels.
- ❖ A 1500 mg dose of **imipramine or amitriptyline** (less than 7 days' supply at antidepressant doses) is enough to be lethal in many patients.
- ❖ Toddlers taking 100 mg will likely show evidence of toxicity.
- ❖ An overdose with an **MAOI** can produce a variety of effects including autonomic instability, hyperadrenergic symptoms, psychotic symptoms, confusion, delirium, fever, and seizures.
- Management of MAOI overdoses usually involves cardiac monitoring, vital signs support, and lavage.

- ❖ venlafaxine has been associated with some cardiac toxicity in overdose and appears to be less safe than SSRIs.
- ❖ Bupropion is associated with seizures in overdose
- ❖ mirtazapine may be associated with sedation, disorientation, and tachycardia.
- ❖ With the newer agents, fatal overdoses often involve the combination of the antidepressant with other drugs, including alcohol.
- Management of overdose with the newer antidepressants usually involves emptying of gastric contents and vital sign support as the initial intervention.

Drug Interactions:

TABLE 30-4 Some antidepressant–CYP450 drug interactions.

Enzyme	Substrates	Inhibitors	Inducers
1A2	Tertiary amine tricyclic antidepressants (TCAs), duloxetine, theophylline, phenacetin, TCAs (demethylation), clozapine, diazepam, caffeine	Fluvoxamine, fluoxetine, moclobemide, ramelteon	Tobacco, omeprazole
2C19	TCAs, citalopram (partly), warfarin, tolbutamide, phenytoin, diazepam	Fluoxetine, fluvoxamine, sertraline, imipramine, ketoconazole, omeprazole	Rifampin
2D6	TCAs, benztropine, prophenazine, clozapine, haloperidol, codeine/oxycodone, risperidone, class IC antiarrhythmics, β blockers, trazodone, paroxetine, maprotiline, amoxapine, duloxetine, mirtazapine (partly), venlafaxine, bupropion	Fluoxetine, paroxetine, duloxetine, hydroxybupropion, methadone, cimetidine, haloperidol, quinidine, ritonavir	Phenobarbital, rifampin
3A4	Citalopram, escitalopram, TCAs, glucocorticoids, androgens/estrogens, carbamazepine, erythromycin, Ca^{2+} channel blockers, levomilnacipran, protease inhibitors, sildenafil, alprazolam, triazolam, vincristine/vinblastine, tamoxifen, zolpidem	Fluvoxamine, nefazodone, sertraline, fluoxetine, cimetidine, fluconazole, erythromycin, protease inhibitors, ketoconazole, verapamil	Barbiturates, glucocorticoids, rifampin, modafinil, carbamazepine

Summary

SUMMARY Antidepressants

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)				
<ul style="list-style-type: none"> Fluoxetine Citalopram Escitalopram Paroxetine Sertraline 	Highly selective blockade of serotonin transporter (SERT) • little effect on norepinephrine transporter (NET)	Acute increase of serotonergic synaptic activity • slower changes in several signaling pathways and neurotrophic activity	<ul style="list-style-type: none"> Major depression, anxiety disorders • panic disorder obsessive-compulsive disorder • post-traumatic stress disorder • perimenopausal vasomotor symptoms • eating disorder (bulimia) 	Half-lives from 15–75 h • oral activity • Toxicity: Well tolerated but cause sexual dysfunction • risk of serotonin syndrome with MAOIs • Interactions: Some CYP inhibition (fluoxetine 2D6, 3A4; fluvoxamine 1A2; paroxetine 2D6)
<ul style="list-style-type: none"> Fluvoxamine: Similar to above but approved only for obsessive-compulsive behavior 				
SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)				
<ul style="list-style-type: none"> Duloxetine Venlafaxine Levomilnacipran 	Moderately selective blockade of NET and SERT	Acute increase in serotonergic and adrenergic synaptic activity • otherwise like SSRIs	<ul style="list-style-type: none"> Major depression, chronic pain disorders • fibromyalgia, perimenopausal symptoms 	Toxicity: Anticholinergic, sedation, hypertension (venlafaxine) • Interactions: Some CYP2D6 inhibition (duloxetine, desvenlafaxine) • CYP3A4 interactions with levomilnacipran
<ul style="list-style-type: none"> Desvenlafaxine: Desmethyl metabolite of venlafaxine, metabolism is by phase II rather than CYP phase I Milnacipran: Approved only for fibromyalgia in the USA; significantly more selective for NET than SERT; little effect on DAT 				
TRICYCLIC ANTIDEPRESSANTS (TCAs)				
<ul style="list-style-type: none"> Imipramine Many others 	Mixed and variable blockade of NET and SERT	Like SNRIs plus significant blockade of autonomic nervous system and histamine receptors	<ul style="list-style-type: none"> Major depression not responsive to other drugs chronic pain disorders • incontinence • obsessive-compulsive disorder (clomipramine) 	Long half-lives • CYP substrates • active metabolites • Toxicity: Anticholinergic, α-blocking effects, sedation, weight gain, arrhythmias, and seizures in overdose • Interactions: CYP inducers and inhibitors
5-HT RECEPTOR MODULATORS				
<ul style="list-style-type: none"> Nefazodone Trazodone Vortioxetine 	Inhibition of 5-HT _{2A} receptor • nefazodone also blocks SERT weakly Antagonist at 5-HT ₃ , 5-HT ₅ , 5-HT _{1D} receptors; partial agonist at 5-HT _{1B} receptor, agonist at 5-HT _{1A} receptor; inhibits SERT	Trazodone forms a metabolite (m-cpp) that blocks 5-HT _{2A/2C} receptors Complex modulation of serotonergic systems	<ul style="list-style-type: none"> Major depression • sedation and hypnosis (trazodone) Major depression 	Relatively short half-lives • active metabolites • Toxicity: Modest α- and H ₁ -receptor blockade (trazodone) • Interactions: Nefazodone inhibits CYP3A4 Extensively metabolized via CYP2D6 and glucuronic acid conjugation • Toxicity: GI disturbances, sexual dysfunction • Interactions: Additive with serotonergic agents
TETRACYCLICS, UNICYCLIC				
<ul style="list-style-type: none"> Bupropion Amoxapine Maprotiline Mirtazapine 	Increased norepinephrine and dopamine activity (bupropion) • NET > SERT inhibition (amoxapine, maprotiline) • increased release of norepinephrine, 5-HT (mirtazapine)	Presynaptic release of catecholamines but no effect on 5-HT (bupropion) • amoxapine and maprotiline resemble TCAs	<ul style="list-style-type: none"> Major depression • smoking cessation (bupropion) • sedation (mirtazapine) • amoxapine and maprotiline rarely used 	Extensive metabolism in liver • Toxicity: Lowers seizure threshold (amoxapine, bupropion); sedation and weight gain (mirtazapine) • Interactions: CYP2D6 inhibitor (bupropion)
MONOAMINE OXIDASE INHIBITORS (MAOIs)				
<ul style="list-style-type: none"> Phenelzine Tranylcypromine Selegiline 	Blockade of MAO-A and MAO-B (phenelzine, nonselective) • MAO-B irreversible selective MAO-B inhibition (low-dose selegiline)	Transdermal formulation of selegiline achieves levels that inhibit MAO-A	<ul style="list-style-type: none"> Major depression unresponsive to other drugs • Parkinson's disease (selegiline) 	Very slow elimination • Toxicity: Hypotension, insomnia • Interactions: Hypertensive crisis with tyramine, other indirect sympathomimetics • serotonin syndrome with serotonergic agents, meperidine

31-Opioid Agonists & Antagonists

Morphine, the prototypic opioid agonist, has long been known to relieve severe pain with remarkable efficacy. It remains the standard against which all drugs that have strong analgesic action are compared.

■ BASIC PHARMACOLOGY OF THE OPIOIDS

Classification & Chemistry:	Endogenous Opioid Peptides:
<p>The term opioid describes all compounds that work at opioid receptor. The term opiate specifically describes the naturally occurring alkaloids: morphine, codeine, thebaine, and papaverine. In contrast, narcotic was originally used to describe sleep-inducing. Morphine is a full agonist at the μ(mu)-opioid receptor, the major analgesic opioid receptor. Opioids may also differ in receptor binding affinity. Other opioid receptor subtypes include δ (delta) and κ (kapra) receptors plus addition of a single hydroxyl group results in naloxone, a strong μ-receptor antagonist. The structures of some of these compounds Some opioids, eg, nalbuphine, a mixed agonist-antagonist, are capable of producing an agonist (or partial agonist) effect at one opioid receptor subtype and an antagonist effect at another.</p>	<p>Three families of endogenous opioid peptides have been described: the endorphins, the pentapeptide enkephalins (methionine enkephalin [met-enkephalin] and leucine-enkephalin [leu-enkephalin]), and the dynorphins.</p>

Chapter #31: Opioid Agonists & Antagonists

Pharmacokinetics

A. Absorption:

Most opioid analgesics are well absorbed when given by subcutaneous, intramuscular, and oral routes. However, because of the first-pass effect, the oral dose of the opioid (eg, morphine) to elicit a therapeutic effect may need to be much higher than the parenteral dose due to considerable interpatient variability in first-pass opioid metabolism. Analgesics such as codeine and oxycodone are effective orally because they have reduced metabolism. Na of certain opioid result in therapeutic levels.

TABLE 31-1

B-Distribution:

The uptake of opioids by various organs and tissues is a function of both physiologic and chemical factors. All opioids bind to plasma proteins. The drugs rapidly leave the blood compartment and localize in highest concentrations in highly perfused tissues such as the brain, lungs, liver, kidneys. Drug concentrations in skeletal muscle may be much lower.

Opioid receptor subtypes, their functions, and their endogenous peptide affinities.

Receptor Subtype	Functions	Endogenous Opioid Peptide Affinity
μ (mu)	Supraspinal and spinal analgesia; sedation; inhibition of respiration; slowed gastrointestinal transit; modulation of hormone and neurotransmitter release	Endorphins > enkephalins > dynorphins
δ (delta)	Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release	Enkephalins > endorphins and dynorphins
κ (kappa)	Supraspinal and spinal analgesia; psychotomimetic effects; slowed gastrointestinal transit	Dynorphins > > endorphins and enkephalins

C-Metabolism:

The opioids are converted in large part to polar metabolites (mostly glucuronides), which are then readily excreted by the kidneys approximately 10% of morphine is metabolized to morphine-6-glucuronide (M6G), an active metabolite. However, these relatively polar metabolites have limited ability to cross the blood-brain barrier and probably do not contribute significantly to the usual CNS effects.

D. Excretion:

Polar metabolites, including glucuronide conjugates of opioid analgesics, are excreted mainly in the urine. Small amounts of unchanged drug may also be found in the urine. In addition, glucuronide conjugates are found in the bile.

Pharmacodynamics

A. Mechanism of Action : Opioid agonists produce analgesia by binding to

specific G protein coupled receptors that are located in brain and spinal cord



regions involved in the transmission and modulation of pain. Some effects may be mediated by opioid receptors on peripheral sensory nerve endings.

1. Receptor types three major classes of opioid receptors (μ , δ , κ) have been identified in various Multiple receptor subtypes have been proposed based on pharmacologic criteria, including μ_1 , μ_2 ; δ_1 , δ_2 ; and κ_1 , κ_2 , and κ_3 . Since an opioid may function with different potencies as an agonist, partial agonist, or antagonist at more than one receptor.

2. Cellular actions opioid receptors

form a family of proteins that physically couple to G proteins and through this interaction affect ion channel gating. protein-coupled actions on neurons: (1) they close voltage-gated Ca^{2+} channels on presynaptic nerve terminals and thereby reduce transmitter release, and (2) they open K^+ channels and hyperpolarize and thus inhibit postsynaptic neurons. The presynaptic action—depressed transmitter release—has been demonstrated for a large number of neurotransmitters, including glutamate, acetylcholine, norepinephrine, serotonin, and substance P.

3. Relation of physiologic effects to receptor type—The majority of currently available opioid analgesics act primarily at the μ -opioid receptor. Analgesia and the euphoriant, respiratory depressant, and physical dependence properties of morphine result principally from actions at μ receptors. Opioid analgesic effects are complex and include interaction with δ and κ receptors.

4. Receptor distribution and neural mechanisms of analgesia—Opioid receptor binding sites have been localized with antibodies to unique peptide sequences in each receptor subtype. All three major receptors are present in high concentrations in the dorsal horn of the spinal cord.

5. Tolerance and dependence With frequently repeated therapeutic doses of morphine or its surrogates, there is a gradual loss in effectiveness; this loss of effectiveness is termed tolerance. Larger dose must be administered. develops. Physical dependence is defined as a characteristic withdrawal or abstinence syndrome when a drug is stopped or an antagonist is administered. Methadone, a μ receptor agonist used for the treatment of opioid tolerance and dependence,

6. Opioid-induced hyperalgesia opioid analgesics can increase the sensation of pain, resulting in a state of hyperalgesia. This phenomenon can be produced with several opioid analgesics, including morphine, fentanyl, and remifentanil.

TABLE 31-3 Degrees of tolerance that may develop to some of the effects of the opioids.

High	Moderate	Minimal or None
Analgesia	Bradycardia	Miosis
Euphoria, dysphoria		Constipation
Mental clouding		Convulsions
Sedation		
Respiratory depression		
Antidiuresis		
Nausea and vomiting		
Cough suppression		

Pharmacodynamics cont.

B. Organ System Effects of Morphine and Its Surrogates

1. Central nervous system effects The principal effects of opioid analgesics with affinity μ receptors are on the CNS. The principal effects of opioid analgesics

a. Analgesia Pain consists of both sensory and affective (emotional) components.	b. Euphoria pleasant floating sensation with lessened anxiety and distress. However, dysphoria, an unpleasant state characterized by restlessness and malaise	c. Sedation —Drowsiness and clouding of mentation are common effects of opioids. Sleep is induced by opioids more frequently in the elderly than in young	d. Respiratory depression —All of the opioid analgesics can produce significant respiratory depression by inhibiting indicator of this depression is a depressed response to carbon dioxide challenge.	e. Cough suppression —Suppression of the cough reflex is a well-recognized action of opioids. Codeine in particular has been used to advantage in persons suffering from pathologic cough
f. Miosis —Constriction of the pupils is seen with virtually all opioid agonists. Miosis is a pharmacologic action to which little or no tolerance develops and can be blocked by atropine.	g. Truncal rigidity Several opioids can intensify tone in the large trunk muscles	h. Nausea and vomiting —The opioid analgesics can activate the brainstem chemoreceptor trigger zone to produce nausea and vomiting	i. Temperature —Homeostatic regulation of body temperature is mediated in part by the action of endogenous opioid peptides in the brain.	j. Sleep architecture they can decrease percentage of stages 3 and 4 sleep which may result in fatigue and other sleep disorders including sleep disordered breathing

Pharmacodynamics cont.

B. Organ System Effects of Morphine and Its Surrogates

2. Peripheral effects

Clinical Use of Opioid Analgesics	Gastrointestinal tract —Constipation has long been recognized as an effect of opioids.	Biliary tract The opioids contract biliary smooth muscle. The sphincter of Oddi may constrict, resulting in reflux of biliary fluid and pancreatic secretions.	Renal —Renal function is depressed by opioids.
A. Analgesia Severe, constant pain is usually relieved with opioid analgesics having high intrinsic activity, fixed-interval administration of opioid medication	B. Acute Pulmonary Edema The relief provided by morphine in patients with dyspnea from pulmonary edema	C. Cough Suppression Suppression of cough can be obtained at doses lower than those	D. Diarrhea from almost any cause can be controlled with opioid Analgesics. Crude opium preparations (eg, paregoric) were u
e. Uterus: The opioid analgesics may prolong labor both μ - and κ opioid receptors are expressed in human uterine muscle. Fentanyl and meperidine (pethidine) inhibit uterine contractility	f. Endocrinology: Opioids stimulate the release of ADH, but inhibit the release of luteinizing hormone. Patients receiving chronic opioid therapy can have low testosterone	g. Pruritus such as morphine and codeine, produce flushing and warming of the skin accompanied sometimes by sweating, urticaria, and itching. Peripheral histamine release is an important contributor,	h. Immune —The opioids modulate the immune system by effects on lymphocyte proliferation, natural killer cell cytolytic activity and lymphocyte proliferative responses to mitogens are usually inhibited by opioids.

■ CLINICAL PHARMACOLOGY OF THE OPIOID ANALGESICS

is more effective in achieving pain relief. However, there is little evidence to support long-term (greater than 6 months) use of sustained release opioids to manage chronic pain in the non-cancer. If it occurs, immediate injection of the antagonist naloxone will reverse the depression. The drugs meperidine appear to produce less depression.

associated with left ventricular heart failure is remarkable. Mechanisms include reduced anxiety (shortness of breath) and reduced cardiac preload and afterload. If respiratory depression is a problem, furosemide may be preferred for the treatment of pulmonary edema.

needed for analgesia

in the past to combat diarrhea, but now synthetic surrogates with more selective gastrointestinal effects eg, diphenoxylate or loperamide.

E. Shivering Although all opioid agonists have some propensity to reduce shivering, meperidine is reported to have the most pronounced antishivering properties. Meperidine apparently blocks shivering mainly α_2 adrenoceptor.

F. Applications in Anesthesia The opioids are frequently used as premedicant drugs before anesthesia and surgery because of their sedative, anxiolytic, and analgesic properties. Opioids are most commonly used in cardiovascular surgery. Opioids can also be used as regional analgesics.

G. Alternative Routes of Administration Rectal suppositories of morphine have been used when oral and parenteral routes are undesirable. The **transdermal fentanyl patch** provides stable blood levels of drug and better pain control while avoiding the need for repeated parenteral injections. The **intranasal route** avoids repeated parenteral injections and the first-pass metabolism of orally administered drugs. Butorphanol is the only opioid currently available in the USA in nasal formulation **buccal transmucosal route**.

Toxicity & Undesired Effects

A. Tolerance and Dependence Drug dependence of the opioid type is marked by a relatively specific withdrawal or abstinence syndrome

B. Diagnosis and Treatment of Opioid Overdosage: Intravenous injection of naloxone dramatically reverses coma due to opioid overdose

C. Contraindications and Cautions in Therapy

1. Opioid tolerance—is the phenomenon whereby repeated doses of opioids have a diminishing analgesic effect. Clinically, it has been described as an increasing opioid dose requirement to achieve the analgesia observed at the initiation of opioid administration. Tolerance begins with the first dose of an opioid, high degree of tolerance may develop to the analgesic, sedating, and respiratory depressant effects.

Adverse effects such as hallucinations, sedation, hypothermia

2. Dependence The development of physical dependence is an invariable accompaniment of tolerance to repeated administration of an opioid of the μ type. The signs and symptoms of withdrawal include rhinorrhea, lacrimation, yawning, chills, gooseflesh (piloerection), hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhea, anxiety, withdrawal signs usually start within 6–10 hours after the last dose

3. Addiction is a primary, chronic disease of brain reward motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biologic, psychological, and social manifestations.

1. Use of pure agonists with weak partial agonists thus combining a full agonist with partial agonist opioids should be avoided

4. Use in patients with impaired pulmonary function the depressant properties of the opioid analgesics may lead to acute respiratory failure

2. Use in patients with head injuries Carbon dioxide retention caused by respiratory depression results in cerebral vasodilation

5. Use in patients with impaired hepatic or renal function morphine metabolized primarily Half-life is prolonged in patients with impaired renal function, and morphine and its active glucuronide metabolite may accumulate; dosage can often be reduced in such patients

3. Use during pregnancy In pregnant women who are chronically using opioids, the fetus may become physically dependent signs and symptoms including irritability shrill crying When withdrawal symptoms are judged to be relatively mild treatment is aimed at control of these symptoms using such drugs as diazepam

6. Use in patients with endocrine disease—Patients with adrenal insufficiency (Addison's disease) and those with hypothyroidism (myxedema) may have prolonged and exaggerated responses to opioids.

Drug Interactions

TABLE 31–5 Opioid drug interactions.

Drug Group	Interaction with Opioids
Sedative-hypnotics	Increased central nervous system depression, particularly respiratory depression.
Antipsychotic agents	Increased sedation. Variable effects on respiratory depression. Accentuation of cardiovascular effects (antimuscarinic and α -blocking actions).
Monoamine oxidase inhibitors	Relative contraindication to all opioid analgesics because of the high incidence of hyperpyrexic coma; hypertension has also been reported.

■ SPECIFIC AGENTS

STRONG AGONISTS :

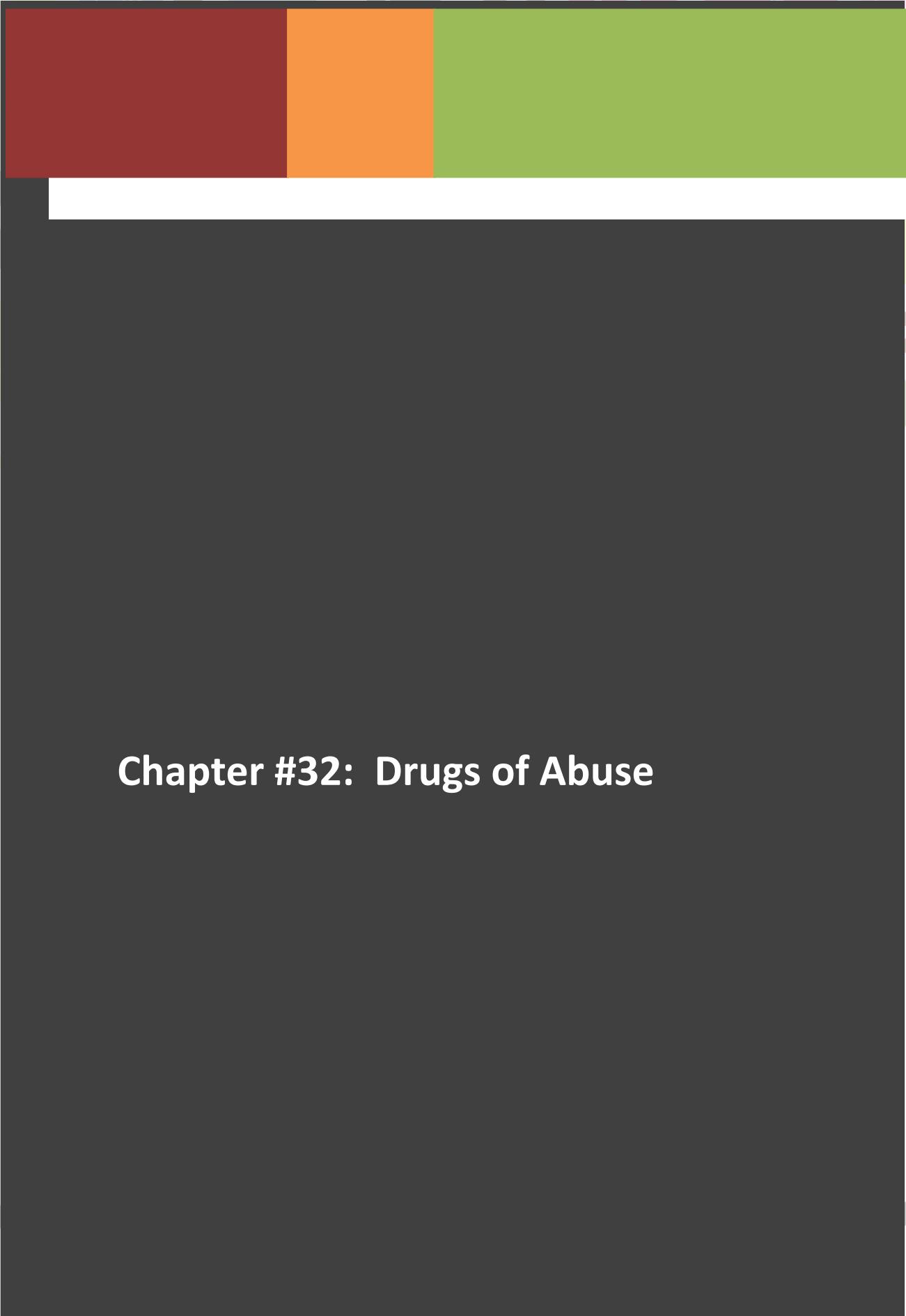
Phenanthrenes	Phenylheptylamine s:	Phenylpiperidines:	Morphinans:
Morphine, hydromorphone, and oxymorphone are strong agonists useful in treating severe pain. These prototypic agents Heroin (diamorphine, heroin is more effective than morphine in relieving severe chronic pain, at least when given by the intramuscular route	Methadone as a potent and clinically useful analgesic. It can be administered by the oral, intravenous, subcutaneous, spinal, and rectal. can also block both NMDA receptors and monoaminergic reuptake transporters. Methadone is widely used in the treatment of opioid abuse	Fentanyl is one of the most widely used agents in the family of synthetic opioids. subgroup now includes sufentanil, alfentanil, remifentanil and Sufentanil is five to seven times more potent than fentanyl. Alfentanil is considerably less potent than fentanyl, but acts more rapidly and has a markedly shorter duration of action. fentanyl is now the predominant analgesic in this class	Levorphanol is a synthetic opioid analgesic

MILD TO MODERATE AGONISTS

Phenanthrenes:	Phenylheptylamines:	Phenylpiperidines:
<p>Codeine, dihydrocodeine, and hydrocodone have lower binding affinity to μ-opioid receptors than morphine</p> <p>Oxycodone is more potent and is prescribed alone in higher. Combinations of hydrocodone or oxycodone with acetaminophen are the predominant formulations of orally administered analgesics for the treatment of mild to moderate pain.</p>	<p>Propoxyphene is chemically related to methadone but has extremely low analgesic activity. Its low efficacy makes it unsuitable even in combination with aspirin</p>	<p>Diphenoxylate and its metabolite, difenoxin, are not used for analgesia but for the treatment of diarrhea.</p> <p>Loperamide is a phenylpiperidine derivative used to control diarrhea. Due to action on peripheral μ-opioid receptors and lack of effect on CNS receptors</p>

OPIOIDS WITH MIXED RECEPTOR ACTIONS

Phenanthrenes:	Morphinans:	Benzomorphans
<p>buprenorphine is a potent and long-acting phenanthrene derivative that is a partial μ-receptor agonist (low intrinsic activity) buprenorphine is used as an analgesic, it can antagonize the action of more potent μ agonists such as morphine</p> <p>Administration by the sublingual route is preferred. Buprenorphine's long duration of action is due to its slow dissociation from μ receptors. buprenorphine is also available combined with naloxone.</p> <p>Pentazocine (a benzomorphan) and nalbuphine are other examples of opioid analgesics with mixed agonist-antagonist properties. Nalbuphine is a strong κ-receptor <i>agonist</i> and a partial μ-receptor <i>antagonist</i>; it is given parenterally</p>	<p>Butorphanol produces analgesia equivalent to nalbuphine</p> <p>Butorphanol is considered to be predominantly a κ agonist. However, it may also act as a partial agonist or antagonist at the μ receptor</p>	<p>Pentazocine is a agonist with weak μ-antagonist or partial agonist properties available. It may be used orally or parenterally</p>



Chapter #32: Drugs of Abuse

32 Drug abuse

BASIC NEUROBIOLOGY OF DRUG ABUSE

-DEPENDENCE VERSUS ADDICTION

Dependence means physical dependence whereas addiction means “psychological dependence. Every addictive drug causes its own characteristic spectrum of acute effects, but all have in common that they induce strong feelings of euphoria and reward. With repetitive exposure, addictive drugs induce adaptive changes such as tolerance (ie, escalation of dose to maintain effect)

-Once the abused drug is no longer available, signs of withdrawal become apparent.
-withdrawal syndrome : defines dependence. (it can also occur with many classes of nonpsychoactive drugs)

-Addiction: consists of compulsive, relapsing drug use despite negative consequences. Although dependence invariably occurs with chronic exposure, only a small percentage of subjects develop a habit, lose control, and become addicted.

-ADDICTIVE DRUGS INCREASE THE LEVEL OF DOPAMINE: REINFORCEMENT.

-combination of approaches in animals and humans, including functional imaging, has revealed the mesolimbic dopamine system as the prime target of addictive drugs. This system originates in the ventral tegmental area (VTA), a tiny structure at the tip of the brainstem, which projects to the nucleus accumbens, the amygdala.

-Most projection neurons of the VTA are dopamine-producing neurons. When the dopamine neurons of the VTA begin to fire in bursts, large quantities of dopamine are released in the nucleus accumbens and the prefrontal cortex.

-Direct application of drugs into the VTA also acts as a strong reinforcer, and systemic administration of drugs of abuse causes release of dopamine.

-As a general rule, all addictive drugs activate the mesolimbic dopamine system.

-An appealing hypothesis is that mesolimbic dopamine codes for the difference between expected and actual reward and thus constitutes a strong learning signal.

-Since each addictive drug has a specific molecular target that engages distinct cellular mechanisms to activate the mesolimbic system, three classes can be distinguished :

a- G protein-coupled receptors

In the VTA, the action of these drugs is preferentially on the γ -aminobutyric acid (GABA) neurons that act as local inhibitory interneurons.

b-ionotropic receptors or ion channels.

Addictive drugs that bind to ionotropic receptors and ion channels can have combined effects on dopamine neurons and GABA neurons, eventually leading to enhanced release of dopamine.

c-dopamine transporter

addictive drugs that interfere with monoamine transporters block reuptake or stimulate nonvesicular release of dopamine, causing an accumulation of extracellular dopamine in target structures. Since neurons of the VTA also express somatodendritic transporters, which normally clear dopamine released by the dendrites. Also increase dopamine level in the VTA.

This is consistent with the observations that antidepressants that block serotonin and norepinephrine uptake, but not dopamine uptake, do not cause addiction even after prolonged use.

DEPENDENCE: TOLERANCE & WITHDRAWAL

-With chronic exposure to addictive drugs, the brain shows signs of adaptation.(For example, if morphine is used at short intervals, the dose has to be progressively increased over the course of several days to maintain rewarding or analgesic effects) This phenomenon is called tolerance.

-It may become a serious problem because of increasing side effects

-Tolerance to opioids may be due to a reduction of the concentration of a drug or a shorter duration of action in a target system (pharmacokinetic tolerance). Alternatively, it may involve changes

of μ -opioid receptor function (pharmacodynamic tolerance).

-many μ -opioid receptor agonists promote strong receptor phosphorylation that triggers the recruitment of the adaptor protein b-arrestin, causing G proteins to uncouple from the receptor and to internalize within minutes.

-However, morphine, which strongly induces tolerance, does not recruit b-arrestins and fails to promote receptor internalization.

-morphine, by failing to trigger receptor endocytosis, disproportionately stimulates adaptive processes, which eventually cause tolerance.

-Adaptive changes become fully apparent once drug exposure is terminated. This state is called withdrawal and is observed to varying degrees after chronic exposure to most drugs of abuse.

-Withdrawal from opioids in humans is particularly strong.

ADDICTION: A DISEASE OF MALADAPTIVE LEARNING

-Addiction is characterized by a high motivation to obtain and use a drug despite negative consequences.

-With time, drug use becomes compulsive ("wanting without liking").

-The central problem is that even after successful withdrawal and prolonged drug-free periods, addicted individuals have a high risk of relapsing. Relapse is typically triggered by one of the following three conditions:

1- It appears that when paired with drug use, a neutral stimulus may undergo a switch and motivate ("trigger") addiction-related behavior. This phenomenon may involve synaptic plasticity in the target nuclei of the mesolimbic projection. Pharmacologic stimulation of the mesolimbic dopamine systems will generate an unusually strong learning signal. Unlike natural rewards, addictive drugs continue to increase dopamine even when reward is expected.

2-The involvement of learning and memory systems in addiction. The role of context in relapse is supported by the report that soldiers who became addicted to heroin during the Vietnam War had significantly better outcomes when treated after their return home, compared with addicts who remained in the environment where they had taken the drug.

3-Non-substance-dependent disorders, such as pathologic gambling and compulsive shopping, share many clinical features of addiction. Several lines of arguments suggest that they also share the underlying neurobiologic mechanisms. Patients may develop a habit for recreational activities, such as shopping, eating compulsively, or hypersexuality.

-Large individual differences exist also in vulnerability to substance-related addiction. Whereas one person may become "hooked" after a few doses, others may be able to use a drug occasionally during their entire lives without ever having difficulty in stopping. Even when dependence is induced with chronic exposure, only a small percentage of dependent users progress to addiction

-The transition to addiction is determined by a combination of environmental and genetic factor.

NONADDICTIVE DRUGS OF ABUSE

-Some drugs of abuse do not lead to addiction. This is the case for substances that alter perception without causing sensations of reward and euphoria, such as the hallucinogens and the dissociative anesthetics.

-these agents primarily target cortical and thalamic circuits. Lysergic acid diethylamide (LSD), for example, activates the serotonin 5-HT_{2A} receptor in the prefrontal cortex, enhancing glutamatergic transmission onto pyramidal neurons.

-The principal mechanism of action is a use-dependent inhibition of glutamate receptors of the NMDA type.

-The classification of NMDA antagonists as nonaddictive drugs was based on early assessments, which, in the case of PCP, have recently been questioned.

-Psychosis-like symptoms can be observed with cannabinoids, amphetamines, and cocaine, which may reflect their effects on thalamocortical structures.

-Hallucinogens and NMDA antagonists, even if they do not produce dependence or addiction, can still have long-term effects.

-Chronic use of PCP may lead to an irreversible schizophrenia-like psychosis.



BASIC PHARMACOLOGY OF DRUGS OF ABUSE

Since all addictive drugs increase dopamine concentrations in target structures of the mesolimbic projections, we classify them on the basis of their molecular targets and the underlying mechanisms

a-the opioids,cannabinoids, γ -hydroxybutyric acid (GHB), and the hallucinogens.
Which all exert their action through G protein-coupled receptors.

b-nicotine, alcohol, the benzodiazepines, dissociative anesthetics, and some inhalants.
which interact with ionotropic receptors or ion channels.

c-cocaine, amphetamines, and ecstasy
which all bind to monoamine transporters

-The nonaddictive drugs are classified using the same criteria.

DRUGS THAT ACTIVATE G PROTEIN-COUPLED RECEPTORS

OPPIOIDS

Opioids may have been the first drugs to be abused and are still among the most commonly used for nonmedical purposes.

Pharmacology & Clinical Aspects

-opioids comprise a large family of endogenous and exogenous agonists at: the μ -, κ -, and δ -opioid receptors.

- μ -opioid receptors are selectively expressed on GABA neurons which they inhibit (responsible for euphoria)

- κ -opioid receptors are expressed on and inhibit dopamine neurons (responsible for dysphoria).

-The most commonly abused μ opioids include morphine, heroin (diacetylmorphine).codeine, and oxycodone. Meperidine abuse is common among health professionals.

-All of these drugs induce strong tolerance and dependence. The withdrawal syndrome may be very severe (except for codeine) includes intense dysphoria, nausea or vomiting, muscle aches, lacrimation, rhinorrhea, mydriasis, piloerection, sweating, diarrhea, yawning, and fever.

-individuals who have received opioids as analgesics only rarely develop addiction. In contrast, when taken for recreational purposes, opioids are highly addictive.

CANNABINOID

-Endogenous cannabinoids binds to CB1 receptors, where they inhibit the release of either glutamate or GABA.

- may contribute to the induction of synaptic plasticity during learning and memory formation.

-Exogenous cannabinoids, (eg in marijuana), include several pharmacologically active substances including : Δ9-tetra-hydrocannabinol(THC)

- THC :

- a powerful psychoactive substance.
- THC causes disinhibition of dopamine neurons, mainly by presynaptic inhibition of GABA neurons in the VTA.
- The half-life of THC is about 4 hours.
- The most prominent effects are euphoria, relaxation and altered perception of passage of time.
- Cannabinoids can also create a dysphoric state and, in rare cases following the use of very high doses.
- Chronic exposure to marijuana leads to dependence, which is revealed by a distinctive, but mild and short-lived, withdrawal syndrome that includes restlessness, irritability, mild agitation, insomnia, nausea, and cramping.
- The synthetic Δ9-THC analog dronabinol is an FDA-approved cannabinoid agonist currently marketed.

GAMMA-HYDROXYBUTYRIC ACID

-(GHB, or sodium oxybate for its salt form) is produced during the metabolism of GABA.

-GHB is complex because there are two distinct binding sites.

- The protein that contains a high-affinity binding site (1 μM)
- The low-affinity binding site (1 mM) has been identified as the GABAB receptor.

-In mice that lack GABAB receptors, even very high doses of GHB have no effect; this suggests that GABAB receptors are the sole mediators of GHB's pharmacologic action.

-GHB was first introduced as a general anesthetic.

-Because of its narrow safety margin and its addictive potential, it is not available in the USA for this purpose.

-Sodium oxybate can, however, be prescribed to treat narcolepsy.

-Before causing sedation and coma, GHB causes euphoria, enhanced sensory perceptions, a feeling of social closeness, and amnesia.

-street names such as “liquid ecstasy,” “grievous bodily harm,” or “date rape drug.”

-It is rapidly absorbed after ingestion and reaches a maximal plasma concentration 20–30 minutes after ingestion.

-GABA neurons are much more sensitive to GHB than are dopamine neurons.

-Because GHB is a weak agonist, only GABA neurons are inhibited at the concentrations typically obtained with recreational use.

-At higher doses, however, GHB also hyperpolarizes dopamine neurons.

LSD, MESCALINE, & PSILOCYBIN

-They are commonly called hallucinogens because of their ability to alter consciousness.

-They also produce somatic symptoms.(dizziness, nausea, paresthesias, and blurred vision).

-they induce neither dependence nor addiction. However, repetitive exposure still leads to rapid tolerance.

-hallucinogens increase glutamate release in the cortex.

-LSD

- an ergot alkaloid
- When LSD is swallowed, psychoactive effects typically appear after 30 minutes and last 6–12 hours.
- During this time, subjects have impaired ability to make rational judgments and understand common dangers, which puts them at risk for accidents and personal injury.
- In an adult, a typical dose is 20–30 mcg.
- LSD is not considered neurotoxic, but may lead to strong contractions of the uterus that can induce abortion.
- The main molecular target of LSD and other hallucinogens is the 5-HT2A receptor.

DRUGS THAT MEDIATE THEIR EFFECTS VIA IONOTROPIC RECEPTORS

NICOTINE

-addiction to nicotine exceeds all other forms of addiction, affecting more than 50% of all adults in some countries.

-Nicotine is a selective agonist of the nicotinic acetylcholine receptor (nAChR) that is normally activated by acetylcholine.

-The rewarding effect of nicotine requires involvement of the VTA, in which nAChRs are expressed on dopamine neurons.

-When nicotine excites projection neurons, dopamine is released in the nucleus accumbens and the prefrontal cortex.

-thus fulfilling the dopamine requirement of addictive drugs.

-Nicotine withdrawal is mild compared with opioid withdrawal and involves irritability and sleep problems.

BENZODIAZEPINES

-they are commonly prescribed as anxiolytics and sleep medications.

-they are abused by some persons for their euphoriant effects.

-**Barbiturates**, which preceded benzodiazepines as the most commonly abused sedative-hypnotics.

- are now rarely prescribed to outpatients and therefore constitute a less common prescription drug problem than they did in the past.
- Management of barbiturate withdrawal and addiction is similar to that of benzodiazepines

-Benzodiazepine dependence is very common.

-Withdrawal from benzodiazepines occurs within days of stopping the medication.



- Symptoms include irritability, insomnia, phonophobia and photophobia, depression, muscle cramps, and even seizures.
- these symptoms taper off within 1–2 weeks.

-Benzodiazepines are positive modulators of the GABA_A receptor.
-The rewarding effects of benzodiazepines are, mediated by α1-containing GABA_A receptors expressed on VTA neurons.

ALCOHOL

- is regularly used by a majority of the population in many Western countries.
- abuse is a very serious public health problem because of the social costs and many diseases associated with alcoholism.

- The pharmacology of alcohol is complex, and no single receptor mediates all of its effects.
- alcohol alters the function of several receptors and cellular functions, including GABA_A receptors.
- It is not clear which of these targets is responsible for the increase of dopamine release from the mesolimbic reward system.
- (ENT1) seems to be involved in alcohol dependence through an accumulation of adenosine.

-Dependence becomes apparent 6–12 hours after cessation of heavy drinking as a withdrawal syndrome that may include tremor (mainly of the hands), nausea and vomiting, excessive sweating, agitation, and anxiety.

- Generalized seizures may manifest after 24–48 hours.
- 48–72 hours after cessation, an alcohol withdrawal delirium (delirium tremens) may become apparent in which the person hallucinates, is disoriented, and shows evidence of autonomic instability.

KETAMINE & PHENCYCLIDINE (PCP)

-Ketamine and PCP were developed as general anesthetics.

-Both drugs, along with others, are now classified as “club drugs”.

-They owe their effects to their use-dependent, noncompetitive antagonism of the NMDA receptor.

-they are sold as liquids, capsules, or pills, which can be snorted, ingested, injected, or smoked.

-Psychedelic effects last for about 1 hour and also include

- increased blood pressure, impaired memory function, and visual alterations.
- At high doses, unpleasant out-of-body and near-death experiences have been reported.

-chronic exposure, particularly to PCP, may lead to long-lasting psychosis closely resembling schizophrenia.

- intravenous administration of ketamine can eliminate episodes of depression within hours.

The antidepressive mechanism is believed to involve the antagonism of NMDA receptors.

INHALANTS

- Inhalant abuse is defined as recreational exposure to chemical vapors, such as nitrates, ketones, and aliphatic and aromatic hydrocarbons.
- develops. Inhalant abuse is particularly prevalent in children and young adults.
- Most inhalants produce euphoria.
- Other substances, such as amyl nitrite ("poppers"), primarily produce smooth muscle relaxation and enhance erection, but are not addictive.

DRUGS THAT BIND TO TRANSPORTERS OF BIOGENICAMINES

Cocaine

- Cocaine is highly addictive, and its use is associated with a number of complications.
 - it is used in clinical medicine, mainly as a local anesthetic and to dilate pupils in ophthalmology.
- Cocaine hydrochloride is a water-soluble salt that can be injected or absorbed by any mucosal membrane.
- When heated in an alkaline solution, it is transformed into the free base, "crack cocaine," which can then be smoked.
 - In the peripheral nervous system, cocaine inhibits voltage-gated sodium channels.
- In the central nervous system, cocaine blocks the uptake of **dopamine**, **noradrenaline**, and **serotonin**.
 - The block of the dopamine transporter (DAT), by increasing dopamine concentrations in the nucleus accumbens, has been implicated in the rewarding effects of cocaine.
 - Users typically lose their appetite, are hyperactive, and sleep little.
- Cocaine exposure .
 - the risk for intracranial hemorrhage, ischemic stroke, myocardial infarction, and seizures.
 - Cocaine overdose may lead to hyperthermia, coma, and death.
 - it was suggested that the drug is particularly harmful to the fetus in addicted pregnant women.
- Susceptible individuals may become dependent and addicted after only a few exposures to cocaine.

AMPHETAMINES

- Amphetamines are a group of synthetic, indirect-acting sympathomimetic drugs that cause the release of endogenous biogenic amines, such as dopamine and noradrenaline
- Together with GHB and ecstasy, amphetamines are often referred to as "club drugs" because they are increasingly popular in the club scene.
- more common with amphetamines, especially methamphetamine. In general, amphetamines lead to elevated catecholamine levels that increase arousal and reduce sleep.



- the effects on the dopamine system mediate euphoria but may also cause abnormal movements and precipitate psychotic episodes.
- Effects on serotonin transmission may play a role in the hallucinogenic and anorexigenic.
- Amphetamines are typically taken initially in pill form by abusers, but can also be smoked or injected.
- Within hours after oral ingestion, amphetamines increase alertness and cause euphoria, agitation, and confusion.
- with increasing dosage these agents often lead to tachycardia and dysrhythmias. Hypertensive crisis and vasoconstriction may lead to stroke.
- With chronic use, amphetamine tolerance may develop, leading to dose escalation.
- escalation. Withdrawal consists of dysphoria, drowsiness (in some cases, insomnia), and general irritability.

ECSTASY (MDMA)

- MDMA was originally used in some forms of psychotherapy, but no medically useful effects were Documented.
- Similar to the amphetamines, MDMA causes release of biogenic amines.
- With repetitive administration, serotonin depletion may become permanent, which has triggered a debate on its neurotoxicity.
- MDMA has several acute toxic effects, in particular hyperthermia, which along with dehydration.

-Withdrawal is marked by a mood "offset" characterized by depression lasting up to several weeks.

SUMMARY Drugs Used to Treat Dependence and Addiction

Subclass, Drug	Mechanism of Action	Effects	Clinical Application	Pharmacokinetics, Toxicities, Interactions
OPIOID RECEPTOR ANTAGONIST				
- Naloxone	Nonselective antagonist of opioid receptors	Reverses the acute effects of opioids; can precipitate severe abstinence syndrome	Opioid overdose	Effect much shorter than morphine (1-2 h); therefore several injections required
- Naltrexone	Antagonist of opioid receptors	Blocks effects of illicit opioids	Treatment of alcoholism, opioid addiction	Half-life 10 h (oral); 5-10 days (depot injection)
SYNTHETIC OPIOID				
- Methadone	Slow-acting agonist of μ -opioid receptor	Acute effects similar to morphine (see text)	Substitution therapy for opioid addicts	High oral bioavailability - half-life highly variable among individuals (range 4-130 h) - Toxicity: Respiratory depression, constipation, miosis, tolerance, dependence, and withdrawal symptoms
PARTIAL μ-OPIOID RECEPTOR AGONIST				
- Buprenorphine	Partial agonist at μ -opioid receptors	Attenuates acute effects of morphine	Oral substitution therapy for opioid addicts	Long half-life (40 h) - formulated together with naloxone to avoid illicit IV injections
NICOTINIC RECEPTOR PARTIAL AGONIST				
- Varenicline	Partial agonist of nicotinic acetylcholine receptor of the $\alpha 4\beta 2$ -type	Occludes "rewarding" effects of smoking - heightened awareness of colors	Smoking cessation	Toxicity: Nausea and vomiting, convulsions, psychiatric changes
- Cytisine: Natural analog (extracted from laburnum flowers) of varenicline				
BENZODIAZEPINES				
- Oxazepam, others	Positive modulators of the $GABA_A$ receptors, increase frequency of channel opening	Enhances GABAergic synaptic transmission; attenuates withdrawal symptoms (tremor, hallucinations, anxiety) In alcoholics - prevents withdrawal seizures	Delirium tremens	Half-life 4-15 h - pharmacokinetics not affected by decreased liver function
- Lorazepam: Alternate to oxazepam with similar properties				
N-METHYL-D-ASPARTATE (NMDA) ANTAGONIST				
- Acamprosate	Antagonist of NMDA glutamate receptors	May interfere with forms of synaptic plasticity that depend on NMDA receptors	Treatment of alcoholism - effective only in combination with counseling	Allergic reactions, arrhythmia, and low or high blood pressure, headaches, insomnia, and impotence - hallucinations, particularly in elderly patients
CANNABINOID RECEPTOR INVERSE AGONIST				
- Rimonabant	CB ₁ receptor inverse agonist	Decreases neurotransmitter release at GABAergic and glutamatergic synapses	Approved in Europe from 2004 to 2008 to treat obesity, then withdrawn because of major side effects - Smoking cessation has never been approved, but remains an off-label indication	Major depression, including increased risk of suicide

weeks.

section 6

DRUGS USED TO TREAT DISEASES OF



رالطب

33. Agents used in Cytopenias; Hematopoietic Growth Factors

The hematopoietic requires three essential nutrients: iron, vitamin B12, and folic acid.

Anemia: a deficiency in oxygen-carrying erythrocytes.

AGENTS USED IN ANEMIAS

IRON :

1. Iron deficiency is the most common cause of chronic anemia.
2. Leads to: pallor, fatigue, dizziness, exertional dyspnea, and other generalized symptoms of tissue hypoxia.
3. A normal individual absorbs 5–10% of iron, or about 0.5–1 mg daily.
4. The average American diet contains 10–15 mg.
5. Total iron absorption increases to 1–2 mg/d in menstruating women and may be as high as 3–4 mg/d in pregnant women.
6. Iron is available abundant in meat.
7. Absorption decreases by the presence of dilators or complex agent in intestine lumen.
8. Absorption increases in the presence of hydrochloric acid and vitamin C.
9. Iron is transported in the plasma bound to **transferrin**.

Pharmacokinetic

1. **Absorption :**
2. Absorbed in duodenum and proximal jejunum in small intestine.
3. A normal individual absorbs 5–10% of iron, or about 0.5–1 mg daily.
4. The average American diet contains 10–15 mg.
5. Total iron absorption increases to 1–2 mg/d in menstruating women and may be as high as 3–4 mg/d in pregnant women.
6. Iron is available abundant in meat.
7. Absorption decreases by the presence of dilators or complex agent in intestine lumen.
8. Absorption increases in the presence of hydrochloric acid and vitamin C.
9. Iron is transported in the plasma bound to **transferrin**.

- Increased erythropoiesis is associated with an increase in the number of **transferrin**.

C. Storage

- Iron is stored in intestinal mucosal cells, primarily as ferritin, in macrophages in the liver, spleen, and bone, and in parenchymal liver cells.

TABLE 33-1

	Iron Content (mg)	
	Men	Women
Hemoglobin	3050	1700
Myoglobin	430	300
Enzymes	10	8
Transport (transferrin)	8	6
Storage (ferritin and other forms)	750	300
Total	4248	2314

¹Values are based on data from various sources and assume that normal men weigh 80 kg and have a hemoglobin level of 16 g/dL and that normal women weigh 55 kg and have a hemoglobin level of 14 g/dL.

- D. Elimination**
- No mechanism for excretion of iron.
 - Small amounts are lost in the feces by exfoliation of intestinal mucosal cell.
 - Trace amounts are excreted in bile, urine, and sweat.

- No more than 1 mg of iron per day.

Clinical Pharmacology

Indications for the Use of Iron:

-The only clinical indication for the use of iron preparations is the treatment or prevention of iron deficiency anemia.

-Iron deficiency is commonly seen in populations with increased iron requirements. These include infants, especially premature infants; children during rapid growth periods; pregnant and lactating women; and patients with chronic kidney disease.

Treatment

1. Oral iron therapy

2. Parenteral iron therapy consist:

Iron dextran (complex of ferric hydroxide)

sodiumferric gluconate complex and Iron sucrose complex are alternative parenteral iron preparations. (IM,IV, infusion).

Clinical Toxicity

A. Acute Iron Toxicity

- 10 tablets of any of the commonly available oral iron 2. preparations can be lethal in young children.
- Children who are poisoned with oral iron experience necrotizing gastroenteritis with vomiting, abdominal pain, and bloody diarrhea followed by shock, lethargy, and dyspnea, followed by severe metabolic acidosis, coma, and death.

1. Treatment:

- **Whole bowel irrigation** should be performed to flush out unabsorbed pills.
- **Deferoxamine** (a potent iron-chelating compound) can be given intravenously.

B. Chronic Iron Toxicity

- Called iron overload or **hemochromatosis**. (results when excess iron is deposited in the heart, liver, pancreas, and other organs).

- Lead to the organ failure and death.

Treatment:

- 3. **intermittent phlebotomy** (One unit of blood can be removed every week or so until all of the excess iron is removed).

- 4. Or **deferoxamine IV**.

VITAMIN B12

Vitamin B12 (cobalamin) serves as a cofactor

Deficiency of vitamin B12 leads to: megaloblastic anemia, gastrointestinal symptoms, and neurologic abnormalities.

Pharmacokinetics

-Once absorbed, vitamin B12 is bound to transcobalamin I, II, and III and transported to the various cells of the body.

-The average American diet contains 5–30 mcg of vitamin B12 daily, 1–5 mcg of which is usually absorbed.

Pharmacodynamics

- Cofactor for several reaction in the body conversion of the major dietary and storage folate to tetrahydrofolate.
- DNA synthesis
- Isomerization of methylmalonyl-CoA to succinyl-CoA by the enzyme methylmalonyl-CoA to avoid neurologic disorder.

Clinical use

For pernicious anemia and anemia caused by gastric reaction.

Section 1 shows the vitamin B₁₂-dependent reaction that allows most dietary folates to enter the tetrahydrofolate cofactor pool and becomes the “folate trap” in vitamin B₁₂ deficiency.

Section 2 shows the deoxythymidine mono-phosphate (dTMP) cycle.

Section 3 shows the pathway by which folic acid enters the tetrahydrofolate cofactor pool. Double arrows indicate pathways with more than one intermediate step. dUMP, deoxyuridine monophosphate.

FOLIC ACID

5. Cofactor for transfer reaction of one carbon.
6. Play role in normal DNA synthesis.
7. Converted to tetrahydrofolate by dehydrofolate reductase.
8. Deficiency megaloblastic anemia often caused by inadequate dietary intake
9. Dose of 1 mg is sufficient
10. Folic acid deficiency associated with cancer and leukemia.

Clinical pharmacology:

Pharmacodynamics:

Hematopoietic Growth Factors

Hematopoiesis regulates the proliferation and differentiation of hematopoietic progenitor cells in the bone marrow.

The factors are:

1. Erythropoietin (Epoetin alfa and beta).
2. Granulocyte colony-stimulating factor(G-CSF).
3. Granulocyte-macrophage colony-stimulating factor (G-CSF).
4. Interleukin-11 (IL-11).
5. Thrombopoietin.

Erythropoietin

Chemistry and pharmacokinetics:

6. 34-39 kDa glycoprotein.
7. The first isolated growth factor.
8. Originally purified from urine of patients with severe anemia.
9. Half-life after IV administration is 4-13 hours.
10. It is not cleared by dialysis.
11. Darbepoetin alfa has longer half-life.
12. Stimulates erythroid proliferation and differentiation by interacting with specific receptors (JAK/STAT cytokine receptor) on red cell progenitor.
13. Also induces release of reticulocytes from the bone marrow.
14. Produced in the kidney in response to hypoxia through increased rate of transcription of the gene.

-
15. Needs active bone marrow (no deficiency, no primary bone marrow disease and no suppression by drugs or chronic diseases).
 16. Normal serum level 20 IU/L.
 17. Elevated in most of anemias (up to thousands) but lowered in anaemia of chronic renal failure.
 18. Erythropoiesis stimulating agents (ESAs), an agent that stimulates red blood cell production.
 19. Improve the hematocrit and hemoglobin level in 2-6 weeks.
 20. Patients with chronic renal failure.
 21. Patients with aplastic anaemia.
 22. Anaemias associated with chronic inflammation, AIDS, and cancer

Clinical uses:

Clinical pharmacology:

23. Due to rapid increases in

Hematopoietic Growth Factor	Clinical Condition Being Treated or Prevented	Recipients
Erythropoietin, darbepoetin alfa	Anemia	Patients with chronic renal failure HIV-infected patients treated with zidovudine Cancer patients treated with myelosuppressive cancer chemotherapy Patients scheduled to undergo elective, noncardiac, nonvascular surgery
Granulocyte colony-stimulating factor (G-CSF; filgrastim) and granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim)	Neutropenia Stem cell or bone marrow transplantation Mobilization of peripheral blood progenitor cells (PBPCs)	Cancer patients treated with myelosuppressive cancer chemotherapy Patients with severe chronic neutropenia Patients recovering from bone marrow transplantation Patients with nonmyeloid malignancies or other conditions being treated with stem cell or bone marrow transplantation Donors of stem cells for allogeneic or autologous transplantation
Interleukin-11 (IL-11, oprelvekin)	Thrombocytopenia	Patients with nonmyeloid malignancies who receive myelosuppressive cancer chemotherapy
Romiplostim, eltrombopag	Thrombocytopenia	Patients with idiopathic thrombocytopenic purpura

Table 33-4 Clinical uses of hematopoietic growth factors and agents that mimic their actions.

hematocrit and hemoglobin: hypertension and thrombotic complications.

24. Allergic reactions are infrequent and mild.

Myeloid Growth Factors

Toxicity:

Chemistry and pharmacokinetics:

Pharmacodynamics

- Has a half-life of 2-7 hours.
- G-CSF:
 - 25. Works on (JAK/STAT) receptors.
 - 26. Stimulates proliferation and differentiation of progenitors committed to the neutrophil lineage.
 - 27. Activates the phagocytic activity of mature neutrophils and prolongs their survival in the circulation.
 - 28. Mobilizes hemopoietic stem cells into the peripheral circulation.
 - GM-CSF:
 - 29. Has broader actions. Also works on JAK/STAT receptors.
- 30. Stimulates proliferation and differentiation of early and late granulocytic progenitor cells as well as erythroid and megakaryocyte progenitors.
- 31. With interleukin-2, also stimulates T-cell proliferation.
- 32. Locally, it is an active factor of inflammation.
- 33. Mobilizes peripheral blood stem cells, but less than G-CSF.

Clinical pharmacology:

A. Cancer Chemotherapy-Induced Neutropenia:

Granulocyte transfusion is not practical.

G-CSF accelerates neutrophil recovery, leading to reduced episodes of febrile neutropenia, need for antibiotics and days of hospitalization, but do not improve survival.

G-CSF is reserved for risky patients.

GM-CSF can produce fever on its own.

They are safe even in the postchemotherapy supportive care of patients with AML.

B.other application:

Congenital neutropenia.

Cyclic neutropenia.

Myelodysplasia.

Aplastic anemia.

Autologous Stem Cell Transplantation:

High dose chemotherapy regimens produce extreme

myelosuppression, which is counteracted by reinfusion of the patient's own hematopoietic stem cells which are collected before the chemotherapy.

Allogenic Bone Marrow Transplantation.

Mobilization of peripheral blood stem cells (PBSCs).

Patients or donors are given GM-CSF (5-10 mcg/kg/day) for 4 days, then leukapheresis, CD34 is used

as a marker for the stem cells. At least 5×10^6 CD34 cells/kg should be reinfused to ensure effective engraftment.

Toxicity:

Bone pain.

Fever, malaise, arthralgia, myalgia.

Capillary Leak Syndrome: peripheral edema, pleural or pericardial effusions.

Allergic reactions.

Splenic rupture.

Megakaryocyte Growth Factors

Chemistry and pharmacokinetics:

Interleukin-11 (IL-11):

65-85 kDa protein.

Produced by fibroblasts and stromal cells in the bone marrow.

Half life is 7-8 hours after sc

Oprelvekin:

Is the recombinant form.

Produced by expression in E.coli

Pharmacodynamics:

Interleukin-11 (IL-11):

Acts through a specific receptor.

Stimulates the growth of multiple lymphoid and myeloid cells.

Stimulates the growth of primitive megakaryocytic progenitors.

Increases the number of peripheral platelets and neutrophils.

Clinical pharmacology:

Clinical Applications of IL-11:

Thrombocytopenia

Platelets transfusion is an alternative.

IL-11 Approved for the secondary injection. prevention of thrombocytopenia in patients receiving cytotoxic chemotherapy for treatment of nonmyeloid cancers.

Does not appear to have an effect on leukopenia caused by myelosuppressive chemotherapy.

Given by SC injection, 50mcg/kg/day for 2-3 weeks after chemotherapy. Or, until platelet count rises to <50,000 cells/ μ l.

Toxicity:

Fatigue, headache, dizziness, anemia, dyspnea, transient atrial arrhythmias and hypokalemia.

Chapter 34

Drugs Used in Disorders of Coagulation

Homeostasis refers to the finely regulated dynamic process of maintaining fluidity of the blood, repairing vascular injury, and limiting blood loss while avoiding vessel occlusion (thrombosis) and inadequate perfusion of vital organs.

With Injuries → endothelial cells undergo to rapid changes (procoagulant properties)

thrombogenesis

- Reactivation of subendothelial proteins such as (collagen & van Willebrand factors)

- Synthesis and secretion of vasoconstrictors such as (Thromboxane A2 (TXA2), Adenosine diphosphate (ADP) & Serotonin (5-HT)) *

- Change in (IIb/IIIa) receptor → bind fibrinogen to receptor

- Thrombin generation
- Fibrin clot

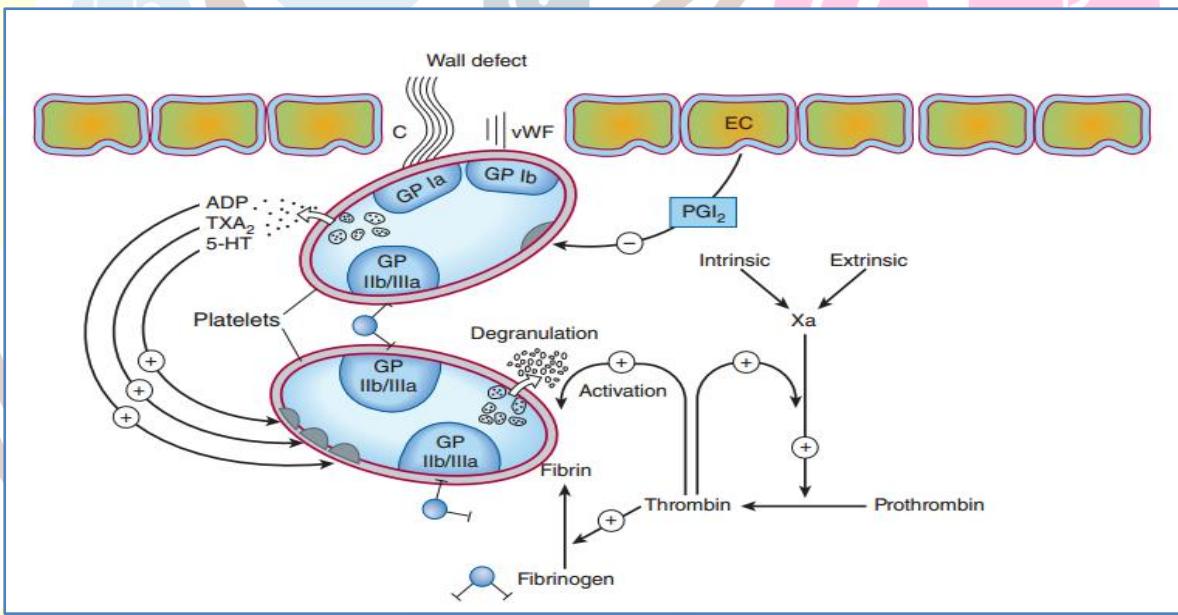
MECHANISMS OF BLOOD COAGULATION:

In Normal → endothelial cells have (anti-coagulant properties).

No thrombogenesis (platelet/clotting factors do not adhere)

* - Thromboxane A2 (TXA2): platelet activator and potent vasoconstrictor.

- Adenosine diphosphate (ADP) & Serotonin (5-HT): stimulates platelet aggregation and vasoconstrictors.



Why it's important to know the haemostatic mechanism?

Because it's important for diagnosis of bleeding disorders where:

- Patient with defect in the formation of primary platelet plug → bleed from surface sites (Gingival, skin, heavy menses)
- Patient with defect in the clotting mechanism) → bleed into deep tissues (joint, muscle, retroperitoneum).

FIGURE 34–1 Thrombus formation at the site of the damaged vascular wall (EC, endothelial cell) and the role of platelets and clotting factors. Platelet membrane receptors include the glycoprotein (GP) Ia receptor, binding to collagen (C); GP Ib receptor, binding von Willebrand factor (vWF); and GP IIb/IIIa, which binds fibrinogen and other macromolecules. Antiplatelet prostacyclin (PGI₂) is released from the endothelium. Aggregating substances released from the degranulating platelet include adenosine diphosphate (ADP), thromboxane A₂ (TXA₂), and serotonin (5-HT). Production of factor Xa by intrinsic and extrinsic pathways is detailed in

Initiation of clotting: the tissue factor-VIIa complex:

Blood coagulation cascade:

Blood Coagulates due to transformation of soluble fibrinogen into insoluble fibrin by the enzyme thrombin.

Cascade process:

Clotting factors zymogen →
limited proteolysis → active
protease → activates next clotting
factor → solid fibrin clot

Sequence:

Fibrinogen (factor I; soluble fiber precursor) substrate for thrombin (enzyme, factor IIa) → fibrin clot

Thrombin is a potential platelets activator and mitogen.

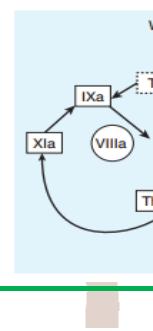
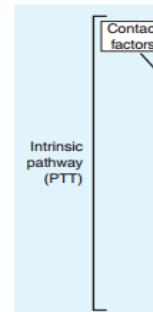


FIGURE 34-2 A model of the action of factor VIIa-TF complex. Factor VIIa converts factor IXa to IXa*, which activates factor Xa. Factor Xa converts prothrombin to thrombin. Thrombin converts fibrinogen to fibrin. Heparin and warfarin inhibit the action of factor VIIa-TF complex. Warfarin acts on the liver. Proteins involved in the reaction are enclosed in circles.

Component or Factor	Common Synonym	Target for the Action of:
I	Fibrinogen	
II	Prothrombin	Heparin, dabigatran (IIa); warfarin (synthesis)
III	Tissue thromboplastin	
IV	Calcium	
V	Proaccelerin	
VII	Proconvertin	Warfarin (synthesis)
VIII	Antihemophilic factor (AHF)	
IX	Christmas factor, plasma thromboplastin component (PTC)	Warfarin (synthesis)
X	Stuart-Prower factor	Heparin, rivaroxaban, apixaban, edoxaban (Xa); warfarin (synthesis)
XI	Plasma thromboplastin antecedent (PTA)	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
Proteins C and S		Warfarin (synthesis)
Plasminogen		Thrombolytic enzymes, aminocaproic acid

Thrombin formed from activation
of its zymogen, prothrombin
(factor II)

Prothrombin (factor II): bound by a calcium to platelet phospholipid

(PL); activated factor X (Xa) + activated factor Va converts prothrombin (factor II) → circulating thrombin.

Possible initiation step:

Tissue factor (TF) + factor VII

Regulation factors:

Tissue factor pathway inhibitor (TFPI)

Antithrombin (AT) is an endogenous anticoagulants: protein C, protein S: down-regulation of blood clotting amplification by proteolysis factors Va, VIIIa and IXa.

Fibrinolysis:

Major process: conversion plasminogen (inactive) to plasmin (proteolytic enzyme, active)

Plasminogen activators: released from damaged cells

Plasmin:

Limits thrombosis extension (by proteolytic fibrin digestion)

Inactivation of coagulation proteins (away from injury site)

Plasma Protease Inhibitors:

$\alpha 1$ -antiprotease

$\alpha 2$ -macroglobulin

$\alpha 2$ -antiplasmin

Antithrombin III

Failure of plasma protease inhibitor system:

Disseminated Intravascular Coagulation (DIC) may occur following:

Massive tissue injury

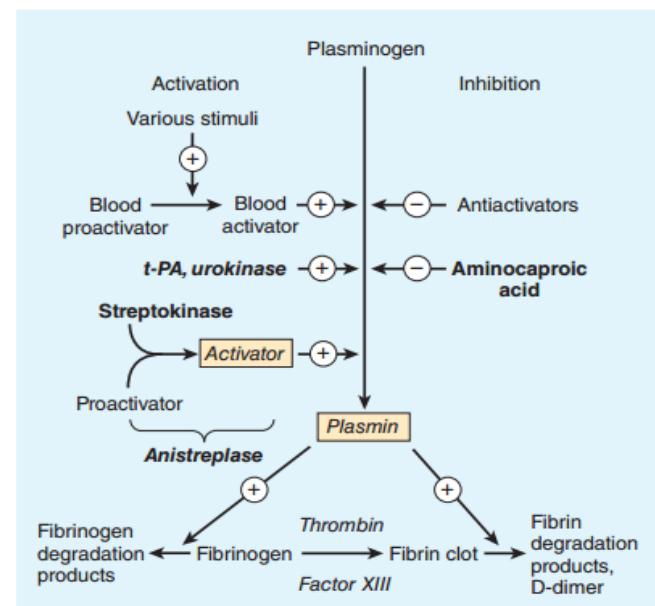


FIGURE 34-3 Schematic representation of the fibrinolytic system. Plasmin is the active fibrinolytic enzyme. Several clinically useful activators are shown on the left in bold. Anistreplase is a combination of streptokinase and the proactivator plasminogen. Aminocaproic acid (right) inhibits the activation of plasminogen to plasmin and is useful in some bleeding disorders. t-PA, tissue plasminogen activator.

TABLE 34-1 Blood clotting factors and drugs that affect them.¹

Advance cancer
Obstetrical emergencies (abruptio placenta; bacterial sepsis)

Activators of fibrinolysis:

Tissue plasminogen activator (t-PA)

Urokinase

Streptokinase

Inhibitors of fibrinolysis:

Aminocaproic acid.

Basic pharmacology of the anticoagulant drugs:

**Indirect thrombin inhibitors*

Heparin

Mechanisms of action:

Heparin is a heterogeneous mixture of sulfated mucopolysaccharides. It binds to endothelial cell surface membrane.

Heparin activity dependent on: the endogenous anticoagulant **antithrombin**. Antithrombin inhibits **clotting factor proteases**, especially thrombin (IIa), IXa, and Xa, by forming equimolar stable complexes with them.

The presence of Heparin activates the reaction by 1000 fold without Heparin → reaction is slow.

Acceleration mechanism: heparin binding induces a change in antithrombin III inhibitor form resulting in increased complex formation activity.

Following antithrombin-protease complex formation, heparin is released; available for binding to other antithrombin molecules:

-A heparin high-molecular-weight (HMW) fraction has higher affinity for antithrombin compared to other fractions.

-A heparin lower affinity for antithrombin but inhibits factor Xa (activated)

-A low-molecular-weight fraction (LMW), enoxaparin is FDA approved for primary prevention of deep venous thrombosis

following hip replacement surgery.

-Dalteparin and danaparoid have been also approved for prevention of the venous thrombosis following hip replacement surgery

Contraindicated in:

Hypersensitive

Actively bleeding

Hemophilia

Thrombocytopenia

Sever Hypertension

Intracranial hemorrhage

Advanced renal or hepatic disease

Toxicity

A. bleeding and miscellaneous effect:

Major adverse effect of heparin is bleeding.

Risk managed by attention to:

- Patient selection
- Dosage control
- Monitoring of partial thromboplastin time (PTT)

Factors predisposing to hemorrhage: Elderly and Renal failure patients.

Long-term heparin use increased incidence of: Osteoporosis and Spontaneous fractures

Administration and dosage:

Not effective orally

SC/ IV administration

Onset immediate, peak in 5-10mins

Metabolized in liver

Excretion through kidney.

Therapeutic use:

Acute deep vein thrombosis

Pulmonary embolism

Prophylactically to prevent postoperative venous thrombosis

B. Heparin-induced Thrombocytopenia(HIT):

Caution in patient with allergy

in patients undergoing elective surgery.

Low-dose prophylaxis is 5000 unit every 8-12 hours.

Prophylactic Enoxaparin is given subcutaneously in a dosage of 30mg twice daily or 40 mg once daily.

Acute phase of myocardial infarction

Anticoagulant of choice for treating pregnant women with prosthetic heart valves or venous thromboembolism, because these agents do not cross the placenta

Fondaparinux is given via injection once daily

It is licensed for initial treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for venous thromboembolism prevention in patients undergoing surgery for hip fracture or hip/knee replacement

Reversal of Heparin Effects:

Drug discontinuation.

Use specific antagonist, e.g. protamine sulfate (note: excess protamine also has an anticoagulant effect)

Warfarin and the Coumarin anticoagulants

Pharmacokinetics:

Coumarin: produces plasma prothrombin deficiency

Active agent:-

bishydroxycoumarin (synthesis - dicumarol)

Uses:

Rodenticide

Humans: antithrombotic agent

Oral anticoagulants:

Warfarin agent in use

High bioavailability; most bound to plasma albumin (99%)

Mechanism of Action:

Block the γ -carboxylation of several glutamate residue in

prothrombine and factors VII, IX, and X

As well as the endogenous anticoagulant proteins C and S

Absorption rapid –high plasma protein binding binds to albumin, there is 8- to 12-hour delay in the action of warfarin

Clearance is slow - 36 hrs

Overdose - reversed by vitamin K infusion

Can cross placenta -do not use during late pregnancies.

Toxicity:

Warfarin: crosses the placenta → hemorrhagic fetal disorder

Fetal abnormal bone formation
(Warfarin effects on fetal proteins with g-carboxylglutamate residues).

Never administer Warfarin during pregnancy

Other Adverse Effects:

Cutaneous necrosis related to reduced protein C activity

Rare: reduced protein C activity → breast, fatty tissues, intestine, extremity infarction

Drug Interactions:

The interaction can be broadly divided into pharmacokinetics and pharmacodynamics effect.

Enzyme inducer : barbiturates

Competitive antagonist: Vit K

Increased Prothrombin Time	Decreased Prothrombin Time
Pharmacokinetic	Pharmacokinetic
Amiodarone	Barbiturates
Cimetidine	Cholestyramine
Disulfiram	Rifampin
Fluconazole ¹	
Metronidazole ¹	
Phenylbutazone ¹	
Sulfinpyrazone ¹	
Trimethoprim-sulfamethoxazole	
Pharmacodynamic	Pharmacodynamic
Drugs	Drugs
Aspirin (high doses)	Diuretics
Cephalosporins, third-generation	Vitamin K
Heparin, argatroban, dabigatran, rivaroxaban, apixaban	
Body factors	Body factors
Hepatic disease	Hereditary resistance
Hyperthyroidism	Hypothyroidism

¹Stereoselectively inhibits the oxidative metabolism of the S-warfarin enantiomorph of racemic warfarin.

High PPBR: aspirin, quinidine, sulfonamide, phenylbutazone

Enzyme inhibitor: cimetidine, isoniazid

PLT inhibitors: aspirin.

Reversal of Warfarin anticoagulant effects:

Discontinue drug administration

Administer vitamin K1 (phytonadione) & fresh-frozen plasma or factor IX concentrates

Pharmacology:

Rivaroxaban, apixaban, and edoxaban inhibit factor Xa,

in the final common pathway of clotting (see Figure 34–2). These drugs are given as fixed doses and do not require monitoring. They have a rapid onset of action and shorter half-lives than warfarin.

Rivaroxaban:

High oral bioavailability when taken with food.

The peak plasma level is achieved within 2–4 hours.

Extensively protein-bound.

It is a substrate for the cytochrome P450 system and the P-glycoprotein transporter.

Inhibiting both CYP3A4 and P-glycoprotein (eg, ketoconazole) result in increased rivaroxaban effect. One third of the drug is excreted unchanged in the urine and the remainder is metabolized and excreted in the urine and feces.

The drug half-life is 5–9 hours in patients aged 20–45 years and is

TABLE 34–2 Pharmacokinetic and pharmacodynamic drug and body interactions with oral anticoagulants.

Oral direct factorXa inhibitors:

Oral Xa inhibitors, including rivaroxaban, apixaban, and edoxaban represent a new class of oral anticoagulant drugs that require no monitoring.

increased in the elderly and in those with impaired renal or hepatic function.

Administration & Dosage

Apixaban:
Has an oral bioavailability of 50% and prolonged absorption. a half-life of 12 hours with repeat dosing.

The drug is a substrate of the cytochrome P450 system and P-glycoprotein and is excreted in the urine and feces.

Similar to rivaroxaban, drugs inhibiting both CYP3A4 and P-glycoprotein, and impairment of renal or hepatic function result in increased drug effect.

Edoxaban:

is an oral anti-Xa drug in clinical development. Randomized controlled trials versus warfarin for treatment of DVT/PE and for prophylaxis of atrial fibrillation were published in 2013 and showed non-inferiority to warfarin for thrombotic events and decreased bleeding events.

Rivaroxaban:
Is approved for prevention of embolic stroke in patients with atrial fibrillation without valvular heart disease, prevention of venous thromboembolism following hip or knee surgery, and treatment of venous thromboembolic disease (VTE). The prophylactic dosage is 10 mg orally per day for 35 days for hip replacement or 12 days for knee replacement. For treatment of DVT/PE the dosage is 15 mg twice daily for 3 weeks followed by 20 mg/d. Depending on clinical presentation and risk factors, patients with VTE are treated for 3–6 months; rivaroxaban is also approved for prolonged therapy in selected patients to reduce recurrence risk.

Apixaban:

Is approved for prevention of stroke in nonvalvular atrial fibrillation. The dosage for atrial fibrillation is 5 mg twice daily. All of these drugs are excreted in part

by the kidneys and liver. Therefore use of these agents is not recommended for patients with significant renal or hepatic impairment. In contrast with warfarin, whose effect can be reversed with vitamin K or plasma concentrates, no antidotes exist for direct Xa inhibitors.

Direct thrombin inhibitors:

The direct thrombin inhibitors (DTIs) exert their anticoagulant effect by directly binding to the active site of thrombin, thereby inhibiting thrombin's downstream effects. Hirudin and bivalirudin are large, bivalent DTIs that bind at the catalytic or active site of thrombin as well as at a substrate recognition site. Argatroban and melagatran are small molecules that bind only at the thrombin active site.

PARENTERAL DIRECT THROMBIN INHIBITORS:

Direct thrombin inhibitors (DTIs)

Hirudin: bind at both the catalytic or active site of thrombin as well as at a substrate recognition site

Lepirudin: derived from medicinal leech saliva and produced in yeast cells by recombinant DNA technology

Bivalirudin: Synthetic polypeptide, used parenterally, Short half life

Argatroban: small synthetic molecule parenteral anticoagulant directly inhibits thrombin.

ORAL DIRECT THROMBIN INHIBITORS

Advantages of oral direct thrombin inhibitors include predictable pharmacokinetics and bioavailability, which allow for fixed dosing and predictable anticoagulant response, and make routine coagulation monitoring unnecessary. In addition, these

agents do not interact with P450-interacting drugs, and their rapid onset and offset of action allow for immediate anticoagulation, thus avoiding the need for overlap with additional anticoagulant drugs.

Dabigatran etexilate mesylate is the first oral direct thrombin inhibitor approved by the FDA to reduce risk of stroke and systemic embolism with nonvalvular atrial fibrillation.

Administration & Dosage

For prevention of stroke and systemic embolism in nonvalvular atrial fibrillation, 150 mg should be given twice daily to patients with CrCl >30 mL / min and 75 mg for CrCl 15-30 mL / min twice daily.

Toxicity

Pharmacology

Specific, competitive, reversible univalent thrombin inhibitor

Pro-drug converted to active form

Rapid onset within 2 hours

Bioavailability, 3-7% in Normal volunteer.

Low protein binding

Half-life 12-17 hours

Renal clearance as glucuronic acid conjugate: 85%

Should be avoided in patients with severe renal impairment

The primary toxicity of dabigatran is bleeding. In one study, there was an increase in gastrointestinal adverse reactions and gastrointestinal bleeding compared with warfarin. There was also a trend toward increased bleeding with dabigatran in patients older than 75 years. There is no antidote for dabigatran. In a drug overdose situation, it is important to maintain renal function or dialyze if necessary. Use of recombinant factor VIIa or prothrombin complex concentrates may be considered as an unproven, off-label use in cases of life-

threatening bleeding associated with dabigatran use.

BASIC PHARMACOLOGY OF THE FIBRINOLYTIC DRUGS:

Lyse thrombi by catalyzing plasmin (serine protease) formation from plasminogen (the zymogen precursor).

Pharmacology, indication and dosage:

All act either direct or indirect to convert plasminogen to plasmin, which in turn cleaves fibrin, thus lysing thrombi.

Clot dissolution occurs with a higher frequency when therapy is initiated early after clot formation.

CLINICAL USES:

Used for the treatment of deep-vein thrombosis, serious pulmonary embolism, acute myocardial infarction, peripheral arterial thrombosis, etc.

Streptokinase (SK):

Is a protein (but not an enzyme in itself) synthesized by streptococci that combines with the pro-activator plasminogen.

This enzymatic complex catalyses the conversion of inactive plasminogen to active plasmin

Mechanism: acts indirectly

SK-plasminogen complex → activate plasminogen

Clinical uses:

Thrombolytic therapy: early,< 6h

Intravenous route: DVT, multiple pulmonary emboli

Intra-arterial route: myocardial infarction

Streptokinase is administered by intravenous infusion of a loading dose of 250,000 units, followed by 100,000 units/h for 24–72 hours.

Patients with antistreptococcal antibodies can develop fever, allergic reactions, and therapeutic resistance.

Adverse reactions:

bleeding, hypotension Plasminogen can also be activated endogenously by tissue plasminogen activators (t-PAs).

Urokinase(UK):

Is a human enzyme synthesized by the kidney that directly converts plasminogen to active plasmin.

Plasmin formed inside a thrombus by these activators is protected from plasma antiplasmins, which allows it to lyse the thrombus from within.

Mechanism of action: activating plasminogen directly

Clinical uses: Same use as SK, especially cerebral embolism

Urokinase requires a loading dose of 300,000 units given over 10 minutes

and a maintenance dose of 300,000 units/h for 12 hours

Adverse reactions: bleeding, but no antigenicity.

Tissue plasminogen activator (t-PA):

Human t-PA is manufactured as ALTEPLASE by means of recombinant DNA technology

Alteplase (t-PA) is given as a 15 mg bolus followed by 0.75 mg/kg (up to 50 mg) over 30 minutes and then 0.5 mg/kg (up to 35 mg) over 60 minutes. Reteplase is given as two 10-unit bolus injections, the second administered 30 minutes after the first injection

BASIC PHARMACOLOGY OF ANTI PLATELET AGENTS:

Drug that inhibits platelets from aggregating to form a plug. They are used to prevent clotting and alter the natural course of atherosclerosis. Platelet function is regulated by three categories of substances:

1-Agents generated outside the platelet interact with platelet membrane receptors, eg,

catecholamines, collagen, thrombin, and prostacyclin.

2-Agents generated within the platelet interact with membrane receptors, eg, ADP, prostaglandin D2, prostaglandin E2, and serotonin.

3-Agents generated within the platelet that act within the platelet, eg,

Prostaglandin endoperoxides and thromboxane A2, the cyclic nucleotides cAMP and cGMP, and calcium ion.

From this list of agents, several targets for platelet inhibitory drugs have been identified:

Inhibition of prostaglandin synthesis (aspirin), inhibition of ADP-induced platelet aggregation (clopidogrel, ticlopidine), and blockade of glycoprotein IIb/IIIa receptor on platelets (abciximab, tirofiban, and eptifibatide).

Dipyridamole and cilostazol are additional antiplatelet drugs.

ASPIRIN

Aspirin inhibits the synthesis of thromboxane A2 by irreversible acetylation of the enzyme cyclooxygenase 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. The recommended dose of aspirin ranges from 50 to 325 mg.

Formerly known as “baby aspirin,” 81-mg aspirin is most commonly used in the United States.

Ticlopidine, clopidogrel, and prasugrel

These drugs irreversibly inhibit the binding of ADP to its receptors on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other. The duration of the antiplatelet effect is 7–10 days. These drugs have no effect on

prostaglandin metabolism.

Commonly used in patients undergoing placement of a coronary stent for prevention of atherosclerotic events following recent myocardial infarction.

Adverse effects of ticlopidine include nausea, dyspepsia, and diarrhea in up to 20% of patients, hemorrhage in 5%, and, most seriously, leukopenia in 1%.

Clopidogrel has fewer adverse effects than ticlopidine and is rarely associated with neutropenia.

BLOCKADE OF PLATELET GLYCOPROTEIN IIb/IIIa RECEPTORS:

There are 3 drugs that target the platelet GP IIb/IIIa receptor complex which are abciximab, Eptifibatide and tirofiban.

Abciximab

Platelet GP IIb/IIIa receptor monoclonal antibody. By binding to GP IIb/IIIa, the antibody blocks the binding of fibrinogen and von

Willebrand factor, and,

consequently, aggregation does not occur. Abciximab is given iv in percutaneous coronary intervention for the prevention of cardiac ischemic complications.

Used for unresponsive unstable angina and for prophylactic use in myocardial infarction. After cessation of infusion, platelet function gradually returns to normal, with the antiplatelet effect persisting for 24 to 48 hours.

Major adverse effect is the potential for bleeding. Abciximab is expensive, limiting its use in some settings.

Eptifibatide and tirofiban

These two antiplatelet drugs act similarly to abciximab, namely, by blocking the GP IIb/IIIa receptor. When intravenous (IV) infusion is stopped, these agents are rapidly cleared from the plasma, but their effect can persist for as long as 4 hours. The major adverse effect of both drugs is bleeding.

ADDITIONAL ANTIPLATELET-DIRECTED DRUGS:

Dipyridamole:

A coronary vasodilator, is used prophylactically to treat angina pectoris. It is usually given in combination with aspirin or warfarin.

It increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase, resulting in decreased thromboxane A₂ synthesis.

It may potentiate the effect of prostacyclin to antagonize platelet stickiness and, therefore, decrease platelet adhesion to thrombogenic surfaces.

In combination with warfarin, however, dipyridamole is effective for inhibiting embolization from prosthetic heart valves.

Cilostazol:

A newer phosphodiesterase inhibitor that promotes

vasodilation and inhibition of platelet aggregation.

Used to treat intermittent claudication, vascular sclerosis complicating diabetes mellitus, and the improvement of symptoms in patients with chronic cerebral ischemia.

Causing a decrease in plasma triglycerides and an increase in HDL.

Headache and GI side effects are the most common adverse effects.

CLINICAL PHARMACOLOGY OF DRUGS USED TO PREVENT CLOTTING

VENOUS THROMBOSIS

Risk Factors

A. Inherited Disorders

The inherited disorders characterized by a tendency to form thrombi (thrombophilia) derive from either quantitative or

qualitative abnormalities of the natural anticoagulant system.

B. Acquired Disease

The increased risk of thromboembolism associated with atrial fibrillation, with the placement of mechanical heart valves, prolonged bed rest, high-risk surgical procedures, and the presence of cancer are clearly associated with an increased incidence of deep venous thrombosis and embolism. Antiphospholipid antibody syndrome is another important acquired risk factor.

Antithrombotic Management

A. Prevention

Heparin and warfarin may be used to prevent venous thrombosis. Subcutaneous administration of low-dose unfractionated heparin, LMW heparin, or fondaparinux provides effective prophylaxis.

B. Treatment of Established Disease

Treatment for established venous thrombosis may be initiated with rivaroxaban alone. Alternatively, patients may be treated with unfractionated or LMW heparin for the first 5–7 days, with an overlap with warfarin. Superficial thrombi confined to the calf veins respond well to short courses of LMW heparin. Warfarin readily crosses the placenta. It can cause hemorrhage at any time during pregnancy as well as developmental defects in the fetus when administered during the first trimester. Therefore, venous thromboembolic disease in pregnant women is generally treated with heparin, best administered by subcutaneous injection.

ARTERIAL THROMBOSIS

Activation of platelets is considered an essential process for arterial thrombosis. Thus, treatment with platelet-inhibiting

drugs such as aspirin and clopidogrel or ticlopidine is indicated in patients with TIAs and strokes or unstable angina and acute myocardial infarction. As discussed above, prasugrel and ticagrelor are alternatives to clopidogrel for patients with acute coronary syndromes managed with percutaneous coronary interventions. In angina and infarction, these drugs are often used in conjunction with β blockers, calcium channel blockers, and fibrinolytic drugs.

DRUGS USED IN BLEEDING DISORDERS

VITAMIN K

Vitamin K confers biologic activity upon prothrombin and factors VII, IX, and X by participating in their postribosomal modification. Two natural forms exist: vitamins K1 and K2. Vitamin K1 is available clinically in oral and parenteral forms. Onset of effect is delayed for 6 hours but the effect is

reason, recombinant clotting factor

complete by 24 hours when activity by excess warfarin or vitamin K deficiency. Vitamin K1 is currently administered to all newborns to prevent the hemorrhagic disease of vitamin K deficiency, which is especially common in premature infants.

PLASMA FRACTIONS

Sources & Preparations

Deficiencies in plasma coagulation factors can cause bleeding. Spontaneous bleeding occurs when factor activity is less than 5–10% of normal. Factor VIII deficiency (classic hemophilia, or hemophilia A) and factor IX deficiency (Christmas disease, or hemophilia B) account for most of the heritable coagulation defects. Concentrated plasma fractions and recombinant protein preparations are available for the treatment of these deficiencies. Lyophilized factor VIII concentrates are prepared from large pools of plasma. However, there is potential causes of transmissible diseases such as prions. For this reason, recombinant clotting factor

preparations are recommended containing prothrombin, factors IX and X, and varied amounts of factor VII (Proplex, etc) whenever possible for factor replacement. The best use of these therapeutic materials requires diagnostic specificity of the deficient factor and quantitation of its activity in plasma. Humate-P is a factor VIII concentrate that is approved by the FDA for the treatment of bleeding associated with von Willebrand disease. Fresh frozen plasma is used for factor deficiencies for which no recombinant form of the protein is available. A four-factor plasma replacement preparation containing vitamin K-dependent factors II VII, IX, and X is available for rapid reversal of warfarin in bleeding patients.

Clinical Uses

Hemophilia A and B patients are given factor VIII and IX replacement, respectively, as prophylaxis to prevent bleeding, and in higher doses to treat bleeding events or to prepare for surgery. Desmopressin acetate increases the factor VIII activity of patients with mild hemophilia A or von Willebrand disease. Freeze-dried concentrates of plasma

Are commercially available for treating deficiencies of these factors. Some preparations of factor IX concentrate contain activated clotting factors, which has led to their use in treating patients with inhibitors or antibodies to factor VIII or factor IX. Two products are available expressly for this purpose: Autoplex (with factor VIII correctional activity) and FEIBA (Factor Eight Inhibitor Bypassing Activity). Recombinant activated factor VII (NovoSeven) is being increasingly used to treat coagulopathy associated with liver disease and major blood loss in trauma and surgery.

Cryoprecipitate is a plasma protein fraction obtainable from whole blood. It is used to treat deficiencies or qualitative abnormalities of fibrinogen. A single unit of cryoprecipitate contains 300 mg of fibrinogen. Cryoprecipitate may also be used for patients with factor VIII deficiency and von Willebrand

disease if desmopressin is not indicated and a pathogen-inactivated, recombinant, or plasma-derived product is not available. Rh-negative women with potential for childbearing should receive only Rh-negative cryoprecipitate because of possible contamination of the product with Rh-positive blood cells.

RECOMBINANT FACTOR VIIa

Recombinant factor VIIa is approved for treatment of inherited or acquired hemophilia A or B with inhibitors, treatment of bleeding associated with invasive procedures in congenital or acquired hemophilia, or factor VII deficiency. In the European Union, the drug is also approved for treatment of Glanzmann's thrombasthenia.

FIBRINOLYTIC INHIBITORS: AMINOCAPROIC ACID

Aminocaproic acid (EACA), which is chemically similar to the amino acid lysine, is a synthetic inhibitor of fibrinolysis. It competitively inhibits plasminogen activation. Clinical uses of EACA are as adjunctive therapy in hemophilia, as therapy for bleeding from fibrinolytic therapy, and as prophylaxis for rebleeding from intracranial aneurysms. Treatment success has also been reported in patients with postsurgical gastrointestinal bleeding and postprostatectomy bleeding and bladder hemorrhage secondary to radiation- and drug-induced cystitis. Adverse effects of the drug include intravascular thrombosis from inhibition of plasminogen activator, hypotension, myopathy, abdominal discomfort, diarrhea, and nasal stuffiness. The drug should not be used in patients with disseminated intravascular coagulation or genitourinary bleeding of the upper tract, eg, kidney and ureters, because of the potential for excessive clotting.

SERINE PROTEASE INHIBITORS: APROTININ

Aprotinin is a serine protease inhibitor (serpin) that inhibits fibrinolysis by free plasmin and may have other antihemorrhagic effects as well. It also inhibits the plasmin-streptokinase complex in patients who have received that thrombolytic agent. Use of the

drug was associated with an increased risk of renal failure, heart attack, and stroke.

The drug was removed from the market in 2007.

Ch35: Dyslipidemia

Plasma lipids are transported in complexes called lipoproteins. Elevations in any lipoprotein species are termed hyperlipoproteinemias or hyperlipidemias. Hyperlipemia denotes increased levels of

triglycerides. The two major clinical sequelae of hyperlipidemias are acute pancreatitis and atherosclerosis. Cellular components in atherosclerotic plaques include foam cells, which are transformed macrophages, and smooth muscle cells filled with cholestryl esters. High-density lipoproteins (HDL) exert several antiatherogenic effects which participate in retrieval of cholesterol from the artery wall and inhibit the oxidation of atherogenic lipoproteins. Low levels of HDL (hypoalphalipoproteinemia)

are a risk factor for atherosclerotic disease . Cigarette smoking and diabetes are a major risk factors for coronary disease. Because atherogenesis is multifactorial, therapy should be directed toward all modifiable risk factors. Primary and secondary prevention trials have shown significant reduction in mortality from new coronary events and in all-cause mortality.

PATHOPHYSIOLOGY of HYPERLIPOPROTEINE

MIA

NORMAL LIPOPROTEIN METABOLISM Structure

Lipoproteins have hydrophobic core regions containing cholestryl esters and triglycerides surrounded by unesterified cholesterol, phospholipids, and apoproteins. Certain lipoproteins contain very high-molecular-weight B proteins that exist in two forms:

B-48, formed in the intestine and found in chylomicrons; and **B-100**, synthesized in liver and found in **VLDL, VLDL remnants (IDL), LDL, and Lp(a) lipoproteins**. HDL consist of at least 20 discrete molecular species containing a polipoprotein A-I (apo A-I).

Synthesis & Catabolism

A. Chylomicrons

Chylomicrons are formed in the intestine and carry triglycerides of dietary origin, unesterified cholesterol, and cholestryl esters. Triglycerides are removed in extrahepatic tissues through a pathway shared with VLDL that involves hydrolysis by the lipoprotein lipase (LPL) system.

B. Very-Low-Density Lipoproteins

VLDL are secreted by liver and export triglycerides to peripheral tissues. VLDL triglycerides are hydrolyzed by LPL, yielding free fatty acids for storage in adipose tissue and for oxidation in tissues. Depletion of triglycerides produces remnants (IDL), some of which undergo endocytosis directly into hepatocytes.

C. Low-Density Lipoproteins

LDL are catabolized chiefly in hepatocytes and other cells by receptor-mediated endocytosis. Cholesteryl esters from LDL are hydrolyzed, yielding free cholesterol for the synthesis of cell membranes. Even more cholesterol is delivered to the liver via IDL and chylomicrons. Unlike other cells, hepatocytes can eliminate cholesterol by secretion in bile and by conversion to bile acids.

D. Lp(a) Lipoprotein

Lp(a) lipoprotein is formed from LDL and the (a) protein, linked by a disulfide bridge.

E. High-Density Lipoproteins

The apoproteins of HDL are secreted by the liver and intestine. HDL acquires cholesterol from peripheral tissues, protecting the cholesterol homeostasis of cells. Free cholesterol is transported from the cell membrane chiefly by a transporter, ABCA1, leading to the formation of larger HDL species. Cholesterol is also exported from macrophages by the ABCG1 transporter and the docking Scavenger receptors

(A Docking Receptor for HDL).

(Scavenger receptors are a group of receptors that recognize modified low-density lipoprotein (LDL) by oxidation or acetylation), SR-BI, to large HDL particles.

LIPOPROTEIN DISORDERS

Lipoprotein disorders are detected by measuring lipids in serum after a 10-hour fast.

Current blood lipid guidelines.

THE PRIMARY

LDL cholesterol	
Optimal	< 100
Near optimal/borderline	100–129
Borderline high	130–159
High	160–189
Very high	≥ 190
Total cholesterol	
Desirable	≤ 200
Borderline high	200–239
High	≥ 240
HDL cholesterol	
Low	≤ 40
High	≥ 60

LYC-ERIDEMIAS

Hypertriglyceridemia is associated with increased risk of coronary disease. VLDL and IDL have been found in atherosclerotic plaques.

Patients with triglycerides above 700 mg/dL should be treated to prevent acute pancreatitis because the LPL clearance mechanism is saturated at about this level. The severity of hypertriglyceridemia of any cause is increased in the presence of the metabolic syndrome or type 2 diabetes.

Hypertriglyceridemia is an important component of the metabolic syndrome, which also includes low levels of HDL-C, insulin resistance, hypertension, and abdominal obesity.

Primary Chylomicronemia

Chylomicrons are not present in the serum of normal individuals who have fasted 10 hours. The recessive traits of deficiency of LPL is usually associated with severe lipemia. Although these patients have a predominant chylomicronemia, they may also have moderately elevated VLDL, presenting with a pattern called mixed lipemia. LPL deficiency is diagnosed by assay of lipolytic activity after intravenous injection of heparin.

Familial Hypertriglyceridemia

A. Severe (Usually Mixed Lipemia)

Mixed lipemia usually results from impaired removal of triglyceride-rich lipoproteins.

Factors that increase VLDL production aggravate the lipemia because VLDL and chylomicrons are competing substrates for LPL. Treatment is primarily dietary, with restriction of total fat.

B. Moderate

Increased levels of VLDL can also reflect a genetic predisposition and are worsened by factors that increase the rate of VLDL secretion from

liver. Treatment includes addressing these issues and the use of fibrates or niacin.

- **Familial Combined Hyperlipoproteinemia (FCH)**

Familial combined hyperlipoproteinemia involves an approximate doubling in VLDL secretion and appears to be transmitted as a dominant trait. Elevations of cholesterol and triglycerides are generally moderate. A reductase inhibitor alone, or in combination with niacin or fenofibrate, is usually required to treat these patients.

Familial Dysbetalipoproteinemia

In this disorder, remnants of chylomicrons and VLDL accumulate and levels of LDL are decreased.

Weight loss, together with decreased fat, cholesterol, and alcohol consumption, may be sufficient, but a fibrate or niacin is usually needed to control the condition.

THE

PRIMARY HYPERCHOLESTEROLEMIAS

Familial Hypercholesterolemia (FH)

Familial hypercholesterolemia is an autosomal dominant trait. Although levels of LDL tend to increase throughout childhood, the diagnosis can often be made on the basis of elevated umbilical cord blood cholesterol. In heterozygous patients, LDL can be normalized with reductase inhibitors or combined drug regimens. Homozygotes and those with combined heterozygosity whose receptors retain even minimal function may partially respond to niacin, ezetimibe, and reductase inhibitors.

Familial Ligand-Defective Apolipoprotein B-100

Defects in the domain of apo B-100 that binds to the LDL receptor impair the endocytosis of LDL, leading to hypercholesterolemia of moderate severity. Up-regulation of LDL receptors in liver increases endocytosis of LDL precursors but does not increase uptake of ligand-defective LDL particles. Niacin often has beneficial effects by reducing VLDL production.

Familial Combined Hyperlipoproteinemia (FCH)

some persons with familial combined hyperlipoproteinemia have only an elevation in LDL. Serum cholesterol is often less than 350 mg/dL. Dietary and drug treatment, usually with a reductase inhibitor, is indicated.

Lp(a) Hyperlipoproteinemia

This familial disorder, which is associated with increased atherosclerosis and arterial thrombus formation,

Is determined chiefly by alleles that dictate increased production of the (a) protein moiety (moiety: as a portion of a molecule). Niacin reduces levels of Lp(a) in many patients.

Cholesteryl Ester Storage Disease

Individuals lacking activity of lysosomal acid lipase (LAL), accumulate cholesteryl esters in liver and certain other cell types leading to hepatomegaly with subsequent fibrosis, elevated levels of LDL-C, low levels of HDL-C. A recombinant replacement enzyme therapy, Sebelipase alfa, is in clinical

trials.

• Other Disorders:

HDL Deficiency

Rare genetic disorders, including Tangier disease and LCAT (lecithin:cholesterolacyltransferase) deficiency, are associated with extremely low levels of HDL.

Familial hypoalphalipoproteinemia is a more common disorder with levels of HDL cholesterol usually below 35 mg/dL in men and 45 mg/dL in women. Niacin increases HDL in many of these patients. Reductase inhibitors and fibric acid derivatives exert lesser effects.

The primary hyperlipoproteinemias and their treatment.

SECONDARY

Disorder	Manifestations	Diet + Single Drug ¹	Drug Combination
Primary chylomicronemia (familial lipoprotein lipase or cofactor deficiency; others)	Chylomicrons, VLDL increased	Dietary management (omega-3 fatty acids, fibrate or niacin)	Fibrate plus niacin
Familial hypertriglyceridemia- Severe	VLDL, chylomicrons increased	Omega-3 fatty acids, fibrate, or niacin	Fibrate plus niacin
Moderate	VLDL increased; chylomicrons may be increased	Omega-3 fatty acids, fibrate, or niacin	Fibrate plus niacin
Familial combined hyperlipoproteinemia	VLDL predominantly increased	Omega-3 fatty acids, fibrate, niacin, or reductase inhibitor	Two or three of the single agents
	LDL predominantly increased	reductase inhibitor, ezetimibe, or niacin	Two or three of the single agents
	VLDL, LDL increased	Omega-3 fatty acids, reductase inhibitor, or niacin	Niacin or fibrate plus reductase inhibitor ²
Familial dysbetalipoproteinemia	VLDL remnants, chylomicron remnants increased	Omega-3 fatty acids, fibrate, reductase inhibitor, or niacin	Reductase inhibitor plus fibrate or niacin
Familial hypercholesterolemia			
Heterozygous	LDL increased	Reductase inhibitor, resin, niacin, or ezetimibe	Two or three of the individual drugs
Homozygous	LDL increased	Niacin, atorvastatin, rosuvastatin, ezetimibe, mipomersen, or lomitapide	Combinations of some of the single agents
Familial ligand-defective apo B	LDL increased	Reductase inhibitor, niacin, or ezetimibe	Two or three of the single agents
Lp(a) hyperlipoproteinemia	Lp(a) increased	Niacin	

HYPERLIPOPROTEINMIA

Before primary disorders can be diagnosed, secondary causes of the phenotype (phenotype is the composite of an organism's observable characteristics or traits, such as its morphology, development, biochemical or physiological properties) must be considered.

DIETARY MANAGEMENT OF HYPERLIPOPROTEINEMIA

General recommendations include limiting total calories from fat to 20–25% of daily intake, saturated fats to less than 7%, and cholesterol to less than 200 mg/d. Reductions in serum cholesterol range from 10% to 20% on this regimen. Use of complex carbohydrates and fiber is recommended, and *cis*-monounsaturated fats should predominate. Weight reduction, caloric restriction, and avoidance of alcohol are especially important for patients with elevated VLDL and IDL.

BASIC & CLINICAL PHARMACOLOGY OF DRUGS USED IN

HYPERLIPIDEMIA

Diet should be continued to achieve the full potential of the drug regimen. These drugs should be avoided in pregnant and lactating women and those likely to become pregnant. All drugs that alter plasma lipo-protein concentrations potentially require adjustment of doses of warfarin and indandione anticoagulants. Drugs are rarely indicated before age 16 in the absence of multiple risk factors or compound genetic dyslipidemias.

COMPETITIVE INHIBITORS OF HMG-COA REDUCTASE (REDUCTASE INHIBITORS: “STATINS”)

These compounds are structural analogs of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A). **Lovastatin, atorvastatin, fluvastatin, pravastatin, simvastatin, rosuvastatin, and pitavastatin** belong to this class. They are most effective in reducing LDL.

FIBRIC ACID DERIVATIVES (FIBRATES)

Gemfibroziland fenofibratedecrease levels of VLDL and, in some patients, LDL

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
STATINS • Atorvastatin, simvastatin, rosuvastatin, pitavastatin	Inhibit HMG-CoA reductase	Reduce cholesterol synthesis and up-regulate low-density lipoprotein (LDL) receptors on hepatocytes • modest reduction in triglycerides	Atherosclerotic vascular disease (primary and secondary prevention) • acute coronary syndromes	Oral • duration 12–24 h • Toxicity: Myopathy, hepatic dysfunction • Interactions: CYP-dependent metabolism (3A4, 2C9) interacts with CYP inhibitors/competitors
<i>• Fluvastatin, pravastatin, lovastatin: Similar but somewhat less efficacious</i>				
FIBRATES • Fenofibrate, gemfibrozil	Peroxisome proliferator-activated receptor-alpha (PPAR- α) agonists	Decrease secretion of very-low-density lipoproteins (VLDL) • increase lipoprotein lipase activity • increase high-density lipoproteins (HDL)	Hypertriglyceridemia, low HDL	Oral • duration 3–24 h • Toxicity: Myopathy, hepatic dysfunction
BILE ACID SEQUESTRANTS • Colestipol	Binds bile acids in gut • prevents reabsorption • increases cholesterol catabolism • up-regulates LDL receptors	Decreases LDL	Elevated LDL, digitalis toxicity, pruritus	Oral • taken with meals • not absorbed • Toxicity: Constipation, bloating • interferes with absorption of some drugs and vitamins
<i>• Cholestyramine, colestevam: Similar to colesterol</i>				
STEROL ABSORPTION INHIBITOR • Ezetimibe	Blocks sterol transporter NPC1L1 in intestine brush border	Inhibits reabsorption of cholesterol excreted in bile • decreases LDL and phytosterols	Elevated LDL, phytosterolemia	Oral • duration 24 h • Toxicity: Low incidence of hepatic dysfunction, myositis
NIACIN	Decreases catabolism of apo AI • reduces VLDL secretion from liver	Increases HDL • decreases lipoprotein(a) [Lp(a)], LDL	Low HDL • elevated VLDL, Lp(a); elevated LDL in statin-unresponsive or intolerant patients	Oral • large doses • Toxicity: Gastric irritation, flushing, low incidence of hepatic toxicity • may reduce glucose tolerance
<i>• Extended-release niacin: Similar to regular niacin • Sustained-release niacin (not the same as extended-release product): Should be avoided</i>				

as well.

NIACIN (NICOTINIC ACID)

Niacin (but not niacinamide) decreases triglycerides and LDL levels, and Lp(a) in most patients. It often increases HDL levels significantly.

BILE ACID-BINDING RESINS

Colestipol, cholestyramine, and colestevam are useful only for isolated increases in LDL. In patients who also have

hypertriglyceridemia, VLDL levels may be further increased during treatment with resins.

INHIBITORS OF INTESTINAL STEROL ABSORPTION

Ezetimibe inhibits intestinal absorption of phytosterols and cholesterol. Its primary clinical effect is reduction of LDL levels.

NEWER AGENTS FOR TREATMENT OF DYSLIPIDEMIA

INHIBITION OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN

Microsomal triglyceride transfer protein (MTP) plays an essential role in the accretion of triglycerides to nascent VLDL in liver, and to chylomicrons in the intestine. Its inhibition decreases VLDL secretion and consequently the accumulation of LDL in plasma.

An MTP inhibitor, **lomitapide**, is available but is currently restricted to patients with homozygous familial hypercholesterolemia.

ANTISENSE INHIBITION

OF APO B-100 SYNTHESIS

Mipomersen is an apo B 20-mer antisense oligonucleotide that targets apo B-100, mainly in the liver. Subcutaneous injections of mipomersen reduce levels of LDL and Lp(a). The drug is available only for use in homozygous familial hypercholesterolemia.

CETP INHIBITION

Cholesteryl ester transfer protein (CETP) inhibitors are under active investigation.

The first drug in this class, **torcetrapib**, aroused great interest because it markedly increased HDL and reduced LDL.

Anacetrapib and **evacetrapib** are analogs currently in phase 3 clinical trials.

PCSK9 INHIBITION

Development of inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) follows on the observation that loss of function mutations result in very low levels of LDL-C and no apparent morbidity. Therapeutic agents currently include antibodies (eg, evolocumab, alirocumab) and antisense oligonucleotides.

AMP KINASE ACTIVATION

AMP-activated protein kinase acts as a sensor of energy status in cells. When increased ATP availability is required, AMP kinase

increases fatty acid oxidation and insulin sensitivity, and inhibits cholesterol and triglyceride biosynthesis.

TREATMENT WITH DRUG COMBINATIONS

Combined drug therapy is useful (1) when VLDL levels are significantly increased during treatment of hypercholesterolemia with a resin; (2) when LDL and VLDL levels are both elevated initially; (3) when LDL or VLDL levels are not normalized with a single agent, or (4) when an elevated level of Lp(a) or an HDL deficiency coexists with other hyperlipidemias.

FIBRIC ACID DERIVATIVES

& BILE ACID-BINDING RESINS

This combination is sometimes useful in treating patients with familial combined hyperlipidemia who are intolerant of niacin or statins.

HMG-COA REDUCTASE INHIBITORS & BILE ACID-BINDING RESINS

This synergistic combination is useful in the treatment of familial hypercholesterolemia but may not control levels of VLDL in some patients with familial combined hyperlipoproteinemia. Statins should be given 1 hour before or at least 2 hours after the resin to ensure their absorption.

NIACIN & BILE ACID-BINDING RESINS

This combination effectively controls VLDL levels during resin therapy of familial combined hyperlipoproteinemia or other disorders involving both increased VLDL and LDL levels.

NIACIN & REDUCTASE INHIBITORS

This combination may be useful in the treatment of familial combined hyperlipoproteinemia.

REDUCTASE INHIBITORS & EZETIMIBE

This combination is highly synergistic in treating primary hypercholesterolemia and has some use in the treatment of patients with homozygous familial hypercholesterolemia

REDUCTASE INHIBITORS & FENOFIBRATE

Fenofibrate appears to be complementary with most statins

in the treatment of familial combined hyperlipoproteinemia and other conditions involving elevations of both LDL and VLDL. The combination of fenofibrate with rosuvastatin appears to be well tolerated.

COMBINATIONS OF RESINS, EZETIMIBE, NIACIN, & REDUCTASE INHIBITORS

These agents act in a complementary fashion to normalize cholesterol in patients with severe disorders involving elevated LDL.

Ch.36 Nonsteroidal antiInflammatory Drugs, Disease-Modifyingantirheumatic

Drugs, Nonopioidanalgesics& Drugs Used in Gout

THE IMMUNE RESPONSE

The immune response occurs when immunologically competent cells are activated in response to foreign organisms or antigenic substances liberated during the acute or chronic inflammatory response. The cell damage associated with inflammation acts on cell membranes to release leukocyte lysosomal enzymes; arachidonic acid is then liberated from precursor compounds. The lipoxygenase pathway of arachidonate metabolism yields leukotrienes, which have a powerful chemotactic effect on eosinophils, neutrophils, and macrophages and promote bronchoconstriction and alterations in vascular permeability. During inflammation, stimulation of the neutrophil membranes produces oxygen-derived free radicals and other reactive molecules such as hydrogen peroxide and hydroxyl radicals.

THERAPEUTIC STRATEGIES

The treatment of patients with inflammation involves two primary goals: first, the relief of symptoms and the maintenance of function and second, the slowing or arrest of the tissue-damaging process. Reduction of inflammation with **NSAIDs** often results in relief of pain for significant periods. Aspirin has anti-inflammatory effects, so it is appropriate for the treatment of both acute and chronic inflammatory conditions. The **glucocorticoids** also have powerful anti-inflammatory effects. **DMARDs** including **biologics** (a subset of the DMARDs). They decrease inflammation and improve symptoms.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Salicylates and other similar agents used to treat rheumatic disease share the capacity to suppress the signs and symptoms of inflammation including pain. These drugs also exert antipyretic effects.

Chemistry & Pharmacokinetics

Most of these drugs are well absorbed, and food does not substantially change their bioavailability. Most of the NSAIDs are highly metabolized. Renal excretion is the most important route for final elimination

Pharmacodynamics

NSAID anti-inflammatory activity is mediated chiefly through inhibition of prostaglandin biosynthesis. Various NSAIDs have additional possible mechanisms of action, including inhibition of chemotaxis, down-regulation of IL-1 production, decreased production of free radicals and

superoxide (A **superoxide**, also known by the obsolete name **hyperoxide**), and interference with calcium-mediated intracellular events.

Aspirin irreversibly acetylates and blocks platelet COX, while the non-COX-selective NSAIDs are reversible inhibitors. Selectivity for COX-1 versus COX-2 is variable and incomplete for the older NSAIDs. NSAIDs are all gastric irritants and can be associated with GI ulcers and bleeds. Nephrotoxicity and Hepatotoxicity can also occur with any NSAID.

ASPIRIN

Aspirin is now rarely used as an anti-inflammatory medication and will be reviewed only in terms of its antiplatelet effects (ie, doses of 81–325 mg once daily).

Pharmacokinetics:

Aspirin (acetylsalicylic acid; ASA) has a pKa of 3.5.

It is absorbed as such and is rapidly hydrolyzed (serum half-life 15 minutes) to acetic acid salicylate by esterases in tissue and blood.

Mechanisms of Action:

Aspirin irreversibly inhibits platelet COX so that aspirin's antiplatelet effect lasts 8–10 days.

Clinical Uses:

Aspirin decreases the incidence of transient ischemic attacks, unstable angina, coronary artery thrombosis with myocardial infarction .

Adverse Effects:

aspirin's main adverse effects at antithrombotic doses are gastric

upset and gastric and duodenal ulcers. Hepatotoxicity, asthma, rashes, GI bleeding, and renal toxicity rarely if ever occur at antithrombotic doses.

5. The antiplatelet action of aspirin contraindicates its use by patients with hemophilia. Also, it is not recommended during pregnancy.

NONACETYLATED SALICYLATES

These drugs include magnesium choline salicylate, sodium salicylate, and salicyl salicylate. All nonacetylated salicylates are effective anti-inflammatory drugs. The nonacetylated salicylates are administered in doses up to 3–4 g of salicylate a day.

COX-2 SELECTIVE INHIBITORS

COX-2 selective inhibitors, or coxibs, were developed in an attempt to inhibit prostaglandin synthesis by the COX-2 isozyme induced at sites of inflammation without affecting the action of the constitutively active “housekeeping” COX-1 isozyme found in the GI tract, kidneys, and

platelets. COX-2 inhibitors at usual doses have no impact on platelet aggregation, which is mediated by thromboxane produced by the COX-1 isozyme.

Celecoxib

Celecoxib is a selective COX-2 inhibitor—about 10–20 times more selective for COX-2 than for COX-1. It does not affect platelet aggregation at usual doses.

Meloxicam

Meloxicam is an enolcarboxamide related to piroxicam that preferentially inhibits COX-2 over COX-1, particularly at its lowest therapeutic dose of 7.5 mg/d.

NONSELECTIVE COX INHIBITORS

Diclofenac

Diclofenac is a phenylacetic acid derivative that is relatively non-selective as a COX inhibitor. Gastrointestinal ulceration may occur less frequently than with some other NSAIDs. Diclofenac, 150 mg/d, appears to impair renal blood flow and glomerular filtration rate. It has many different dosage forms such as

ophthalmic preparation, topical gel, rectal suppository, oral mouthwash and for intramuscular administration.

Diflunisal

Although diflunisal is derived from salicylic acid, it is not metabolized to salicylic acid or salicylate. It undergoes an enterohepatic cycle with reabsorption of its glucuronide metabolite followed by cleavage of the glucuronide to again release the active moiety. A 2% diflunisal oral ointment is a clinically useful analgesic for painful oral lesions. Diflunisal's dosage should be limited in patients with significant renal impairment.

Etodolac

Etodolac is a racemic acetic acid derivative with an intermediate half-life. The analgesic dosage of etodolac is 200– 400 mg three to four times daily.

Flurbiprofen

Flurbiprofen is a propionic acid derivative with a possibly more complex mechanism of action than other NSAIDs. Flurbiprofen is available in a topical ophthalmic formulation for inhibition of intraoperative miosis (it this is common in cataract surgery after the intraocular lens is inserted in the posterior chamber of the eye (which is behind the il) to keep the lens in place so to speak.).

Flurbiprofen intravenously is effective for perioperative analgesia and in lozenge form for sore throat.

Ibuprofen

Ibuprofen is a simple derivative of phenylpropionic acid. In doses of about 2400 mg daily, ibuprofen is equivalent to 4 g of aspirin in anti-inflammatory effect. It is available over the counter in low-dose forms under several trade names.

Ibuprofen has many different dosage form such as oral, IV, topical cream preparation and liquid gel preparation. He drug is relatively contraindicated in individuals with nasal polyps (fleshy swellings that develop in the lining of the nose and paranasal sinuses), angioedema, and bronchospastic reactivity to aspirin. The concomitant administration of

ibuprofen and aspirin antagonizes the irreversible platelet inhibition induced by aspirin. Furthermore, the use of ibuprofen concomitantly with aspirin may decrease the total antiinflammatory effect.

Indomethacin

Indomethacin is an indole derivative. It is a potent nonselective COX inhibitor and may also inhibit phospholipase A and C, reduce neutrophil migration, and decrease T-cell and B-cell proliferation. It has been used to accelerate closure of patent ductus arteriosus("patent" means open. The ductus arteriosus is a blood vessel that allows blood to go around the baby's lungs before birth.). Indomethacin has many different dosage forms such as ophthalmic preparation, Epidural injections(it injects spinal cord in the lower back) and oral rinse. The common side effects may include pancreatitis. Headache is experienced by 15–25% of patients and may be associated with dizziness, confusion, and depression.

Ketoprofen

Ketoprofen is a propionic acid derivative that inhibits both COX (nonselectively) and lipoxygenase.

The effectiveness of ketoprofen at dosages of 100–300 mg/d is equivalent to that of other NSAIDs. Its major adverse effects are on the GI tract and the central nervous system.

Nabumetone

Nabumetone is the only nonacid NSAID in current use; it is given as a ketone prodrug and resembles naproxen in structure. Its half-life of more than 24 hours permits once-daily dosing. Like naproxen, Nabumetone has been associated with pseudoporphyria (bullos photosensitivity that clinically and histologically mimics porphyria cutanea tarda) and photosensitivity in some patients.

Naproxen

Naproxen is a naphthalene derivative. It is the only NSAID presently marketed as a single enantiomer. Naproxen is effective for the usual rheumatologic indications and is available in a slow-release formulation, as an oral suspension, and over the counter. A topical preparation and an ophthalmic solution are also available.

Oxaprozin

Oxaprozin is another propionic

acid derivative NSAID. The major difference from the other members of this subgroup is a very long half-life (50–60 hours).

Piroxicam

Piroxicam, an oxicam is a nonselective COX inhibitor that at high concentrations also inhibits polymorphonuclear leukocyte migration, decreases oxygen radical production, and inhibits lymphocyte function. Piroxicam can be used for the usual rheumatic indications. When piroxicam is used in dosages higher than 20 mg/d, an increased incidence of peptic ulcer and bleeding.

Sulindac

Sulindac is a sulfoxide prodrug. It is reversibly metabolized to the active sulfide metabolite, which is excreted in bile and then reabsorbed from the intestine. The enterohepatic cycling prolongs the duration of action to 12–16 hours. In addition to its rheumatic disease indications, sulindac suppresses familial intestinal polyposis and it may inhibit the development of colon, Breast, and prostate cancer in humans.

Tolmetin

Tolmetin is a nonselective COX inhibitor with a short half-life (1–2 hours) and is not often used. It is ineffective in the treatment of gout.

CHOICE OF NSAID

All NSAIDs, including aspirin, are about equally efficacious with a few exceptions-tolmetin seems not to be effective for gout . Some surveys suggest that indomethacin and tolmetin are the NSAIDs associated with the greatest toxicity, while salsalate, aspirin, and ibuprofen are least toxic. Diclofenac and sulindac are associated with more liver function test abnormalities than other NSAIDs. Elecoxib is probably safest for patients at high risk for GI bleeding but may have a higher risk of cardiovascular toxicity. Celecoxib or a nonselective NSAID plus omeprazole or misoprostol may be appropriate in patients at highest risk for GI bleeding. Elecoxib is probably safest for patients at high risk for GI bleeding but may have a higher risk of cardiovascular toxicity. Celecoxib or a nonselective NSAID plus omeprazole or misoprostol may be appropriate in patients at highest risk for GI bleeding,

so that there is no best NSAID for all patients.

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

RA rheumatoid arthritis is a progressive immunologic disease that causes significant systemic effects, shortens life, and reduces mobility and quality of life. The effects of disease-modifying therapies may take 2 weeks to 6 months to become clinically evident. These therapies include nonbiologic and biologic disease-modifying antirheumatic drugs (usually designated "DMARDs").

ABATACEPT

1. Mechanism of action:

Abatacept is a co-stimulation modulator biologic that inhibits the activation of T cells. After a T cell has engaged an antigen-presenting cell (APC), a second signal is produced by CD28 on the T cell that interacts with CD80 or CD86 on the APC, leading to T-cell activation.

2. Pharmacokinetics:

The recommended dose of abatacept for the treatment of adult patients with RA is three

intravenous infusion "induction" doses (day 0, week 2, and week 4), followed by monthly infusions. The dose is based on body weight.

3. Indications:

It can be used as monotherapy or in combination with methotrexate or other DMARDs in patients with moderate to severe RA severe PJIA (Polyarticular juvenile idiopathic arthritis).

4. Adverse Effects:

there is a slightly increased risk of infection of the upper respiratory tract.

AZATHIOPRINE

1. Mechanism of action:

Azathioprine is a synthetic nonbiologic DMARD that acts through its major metabolite, 6-thioguanine. 6-Thioguanine suppresses inosinic acid synthesis, B-cell and T-cell function, immunoglobulin production, and IL-2 secretion.

2. Pharmacokinetics:

Can be given orally or parenterally.

3. Indications:

Azathioprine is approved for use in RA at a dosage of 2 mg/kg/d. It is also used for the prevention of kidney transplant rejection in combination with other immune suppressants. Also used in scleroderma (skleros = hard or indurated and derma = skin).

4. Adverse Effects:

Bone marrow suppression, GI disturbances, and some increase in infection risk.

CHLOROQUINE & HYDROXYCHLOROQUINE

1. Mechanism of action:

Suppression of T-lymphocyte responses to mitogens, inhibition of leukocyte chemotaxis, stabilization of lysosomal enzymes, processing through the Fc-receptor, inhibition of DNA and RNA synthesis, and the trapping of free radicals.

2. Pharmacokinetics:

Antimalarials are rapidly absorbed and 50% protein-bound in the plasma. The drugs are deaminated in the liver and have blood elimination half-lives of up to 45 days.

3. Indications:

Antimalarials are approved for RA, but they are not considered very effective DMARDs.

4. Adverse Effects:

Ocular toxicity may occur at dosages greater than 250 mg/d for chloroquine and greater than 6.4 mg/kg/d for hydroxychloroquine. These toxicities include dyspepsia, nausea, vomiting, abdominal pain.

These drugs are safe in pregnancy.

CYCLOPHOSPHAMIDE

1. Mechanism of action:

It is synthetic non- biologic DMARD. Its major active metabolite is phosphoramide mustard, which cross-links DNA to prevent cell replication. It suppresses T-cell and B-cell function by 30–40%; T-cell suppression correlates with clinical response in the rheumatic diseases.

2. Indications:

It is used regularly at 2 mg/kg/d to treat SLE, vasculitis, Wegener's granulomatosis, and other severe rheumatic diseases.

CYCLOSPORINE

1. Mechanism of action:

It is a peptide antibiotic but is considered a nonbiologic DMARD. Through regulation of gene transcription, it inhibits IL-1 and IL-2 receptor production and secondarily inhibits macrophage-T-cell interaction and T-cell responsiveness.

2. Pharmacokinetics:

Cyclosporine is metabolized by CYP3A and consequently is subject to a large number of drug interactions.

3. Indications:

Cyclosporine is approved for use in RA and retards the appearance of new bony erosions. Its usual dosage is 3–5 mg/kg/d divided into two doses. Also it may be useful in SLE, polymyositis and dermatomyositis and Wegener's granulomatosis.

4. Adverse Effects:

Leukopenia, thrombocytopenia, and to a lesser extent, anemia are predictable.

LEFLUNOMIDE

1. Mechanism of action:

Leflunomide, another nonbiologic DMARD, undergoes rapid conversion, both in the intestine and in the plasma, to its active metabolite, A77-1726. This metabolite inhibits dihydroorotate dehydrogenase,

Leading to a decrease in ribonucleotide synthesis and the arrest of stimulated cells in the G1 phase of cell growth.

2. Pharmacokinetics:

It is completely absorbed from the gut and has a mean plasma half-life of 19 days.

3. Indications:

Is as effective as methotrexate in RA, including inhibition of bony damage.

4. Adverse Effects:

Diarrhea occurs in approximately 25% of patients given leflunomide. Other adverse effects associated with leflunomide are mild alopecia, weight gain, and increased blood pressure.

METHOTREXATE

Methotrexate, a synthetic nonbiologic antimetabolite, is the

first-line DMARD for treating RA.

1. Mechanism of action:

Inhibition of amino-imidazolecarboxamideribonucleotide (AICAR) transformylase and thymidylatesynthetase. AICAR, which accumulates intracellularly, competitively inhibits AMP deaminase, leading to an accumulation of AMP. The AMP is released and converted extracellularly to adenosine, which is a potent inhibitor of inflammation.

2. Pharmacokinetics:

Methotrexate's serum half-life is usually only 6–9 hours.

3. Indications:

The most common methotrexate dosing regimen for the treatment of RA is 15–25 mg weekly, there is an increased effect up to 30–35 mg weekly.

4. Adverse Effects:

Nausea and mucosal ulcers are the most common toxicities.

MYCOPHENOLATE MOFETIL

1. Mechanism of action:

Mycophenolate mofetil (MMF), a semisynthetic DMARD, is converted to mycophenolic acid, the active form of the drug. The active product inhibits inosine monophosphate dehydrogenase, leading to suppression of T- and B-lymphocyte proliferation.

2. Indications:

MMF is effective for the treatment of renal disease due to SLE and may be useful in vasculitis and Wegener's granulomatosis.

3. Adverse Effects:

MMF is associated with nausea, dyspepsia, and abdominal pain. MMF is associated with an increased incidence of

Infections.

RITUXIMAB

1. Mechanism of action:

Rituximab is a chimeric monoclonal antibody biologic agent that targets CD20 B lymphocytes. Depletion of these cells takes place through cell mediated and complement-dependent cytotoxicity and stimulation of cell apoptosis. Depletion of B

lymphocytes reduces inflammation by decreasing the presentation of antigens to T lymphocytes and inhibiting the secretion of proinflammatory cytokines.

2. Pharmacokinetics:

Rituximab is given as two intravenous infusions of 1000 mg, separated by 2 weeks. It may be repeated every 6–9 months, as needed.

3. Indications:

For the treatment of moderately to severely active RA in combination with methotrexate in patients with an inadequate response to one or more TNF- α antagonists.

4. Adverse Effects:

About 30% of patients develop rash with the first 1000 mg treatment; this incidence decreases to about 10% with the second infusion and progressively decreases with each course of therapy thereafter.

SULFASALAZINE

1. Mechanism of action:

Sulfasalazine, a synthetic nonbiologic DMARD, is metabolized to sulfapyridine and 5-aminosalicylic acid. The sulfapyridine is probably the active moiety when treating RA. Sulfasalazine or its metabolites inhibit the release of inflammatory cytokines produced by monocytes or macrophages, eg, IL-1, -6, and -12, and TNF- α .

2. Pharmacokinetics:

Only 10–20% of orally administered sulfasalazine is absorbed. Sulfasalazine's half-life is 6–17 hours.

3. Indications:

Sulfasalazine is effective in RA and reduces radiologic disease progression. It has also been used in juvenile chronic arthritis, inflammatory bowel disease. The usual regimen is 2–3 g/d.

4. Adverse Effects:

Common adverse effects include nausea, vomiting, headache, and rash. Hemolytic anemia and methemoglobinemia also occur, but rarely. Reversible infertility occurs in men, but sulfasalazine does not affect fertility women.

elevated liver enzymes.

TOCILIZUMAB

1. Mechanism of action:

Tocilizumab, a newer biologic humanized antibody, binds to soluble and membrane-bound IL-6 receptors, and inhibits the IL-6-mediated signaling via these receptors.

2. Pharmacokinetics:

His half-life of tocilizumab is dose dependent, approximately 11 days for the 4 mg/kg dose and 13 days for the 8 mg/kg dose.

3. Indications:

Tocilizumab is indicated for adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs.

It is also indicated in patients who are older than 2 years with active SJIA or active PJIA.

4. Adverse Effects:

Serious infections including tuberculosis, fungal, viral, and other opportunistic infections have occurred. The most common adverse reactions are upper respiratory tract infections, headache, hypertension, and

TNF- α BLOCKING AGENTS:

Cytokines play a central role in the immune response and in RA. Five biologic DMARDs interfering with TNF- α have been approved for the treatment of RA and other rheumatic diseases.

Adalimumab

1. Mechanism of action:

Adalimumab is a fully human IgG1 anti-TNF monoclonal antibody. This compound complexes with soluble TNF- α and prevents its interaction with p55 and p75 cell surface receptors. This results in down-regulation of macrophage and T-cell function.

2. Pharmacokinetics:

Adalimumab is given subcutaneously and has a half-life of 10–20 days. The usual dose in RA is 40 mg every other week, but dosing is frequently increased to 40 mg weekly.

3. Indications:

The compound is approved for RA, AS, PA, JIA, plaque psoriasis, Crohn's disease, and ulcerative colitis.

Certolizumab

1. Mechanism of action:

Certolizumab is a recombinant, humanized antibody Fab fragment conjugated to a polyethyl- ene glycol (PEG) with specificity for human TNF- α . Certolizumab neutralizes membrane-bound and soluble TNF- α in a dose-dependent manner.

2. Pharmacokinetics:

Certolizumab is given subcutaneously and has a half-life of 14 days. The usual dose for RA is 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week, or 400 mg every 4 weeks.

3. Indications:

Certolizumab is indicated for the treatment of adults with moderately to severely active RA. It can be used as monotherapy or in combination with nonbiologic DMARDs.

Etanercept

1. Mechanism of action:

Etanercept is a recombinant fusion protein consisting of two soluble TNF p75 receptor moieties linked to the Fc portion of human IgG1;

it binds TNF- α molecules and also inhibits lymphotxin- α .

2. Pharmacokinetics:

Etanercept is given subcutaneously as 25 mg twice weekly or 50 mg weekly. Etanercept has a mean serum elimination half-life of 4.5 days.

3. Indications:

Etanercept is approved for the treatment of RA, juvenile chronic arthritis, psoriasis, PA, and AS.

Golimumab

1. Mechanism of action:

Golimumab is a human monoclonal antibody with a high affinity for soluble and membrane-bound TNF- α . Golimumab effectively neutralizes the inflammatory effects produced by TNF- α seen in diseases such as RA.

2. Pharmacokinetics:

Golimumab is administered subcutaneously and has a half-life of approximately 14 days. The recommended dose for the treatment of RA, PA, and AS is 50 mg given every 4 weeks.

3. Indications:

Golimumab with methotrexate is indicated for the treatment of moderately to severely active RA in adult patients.

Infliximab

1. Mechanism of action:

Infliximab is a chimeric IgG1 monoclonal antibody that binds with high affinity to soluble and possibly membrane-bound TNF- α . Its mechanism of action probably is the same as that of adalimumab.

2. Pharmacokinetics:

Infliximab is given as an intravenous infusion with “induction” at 0, 2, and 6 weeks and maintenance every 8 weeks thereafter. Dosing is 3–10 mg/kg, and the usual dose is 3–5 mg/kg every 8 weeks. The terminal half-life is 9–12 days

3. Indications:

Infliximab is approved for use in RA, AS, PA, Crohn’s disease, ulcerative colitis, pediatric inflammatory bowel disease, and psoriasis.

Adverse Effects of TNF- α Blocking Agents

The risk of bacterial infections and macrophage-dependent infection (including tuberculosis, fungal, and other opportunistic infections) is increased, although it remains very low.

TOFACITINIB

1. Mechanism of action:

Tofacitinib is a synthetic small molecule that selectively inhibits all members of the Janus kinase family to varying degrees. At therapeutic doses, tofacitinib exerts its effect mainly by inhibiting JAK3, and to a lesser extent JAK1, hence interrupting the JAK-STAT signaling pathway. This pathway plays a major role in the pathogenesis of autoimmune diseases including RA.

2. Pharmacokinetics:

Tofacitinib is an oral, targeted DMARD. The recommended dose in the treatment of RA is 5 mg twice daily. The elimination half-life is about 3 hours.

3. Indications:

Tofacitinib was originally developed to prevent solid organ allograft rejection. It has been tested for the treatment of

inflammatory bowel disease, spondyloarthritis, psoriasis, and dry eyes. Tofacitinib is approved in the USA for the treatment of adult patients with moderately to severely active RA who have failed or are intolerant to methotrexate.

4. Adverse Effects:

Tofacitinib slightly increases the risk of infection, and it should not be used with potent immunosuppressants or biologic DMARDs. Upper respiratory tract infection and urinary tract infection represent the most common infections.

INTERLEUKIN-1 INHIBITORS

IL-1 α plays a major role in the pathogenesis of several inflammatory and autoimmune diseases including RA. IL-1 β and IL-1 receptor antagonist (IL-1RA) are other members of the IL-1 family. IL-1RA acts as a competitive inhibitor of the proinflammatory IL-1 α and IL-1 β .

Anakinra

1. Mechanism of action:

Anakinra is a recombinant IL-1RA; it blocks the effect of IL-1 α and IL-1 β on IL-1 receptors, hence decreasing the immune response in inflammatory diseases.

2. Pharmacokinetics:

Anakinra is administered subcutaneously and reaches a maximum plasma concentration after 3–7 hours. It has a 4- to 6-hour terminal half-life. The recommended dose in the treatment of RA is 100 mg daily.

3. Indications:

Anakinra is approved for the treatment of moderately to severely active RA in adult patients, but it is not very effective, and it is the drug of choice for CAPS, particularly the neonatal-onset multisystem inflammatory disease (NOMID).

Canakinumab

1. Mechanism of action:

Canakinumab is a human IgG1/k monoclonal antibody against IL-1 β . It forms a complex with IL-1 β , preventing its binding to IL-1 receptors.

2. Pharmacokinetics:

It is given as subcutaneous injections. A 26-day mean terminal half-life.

3. Indications:

It is indicated for active SJIA in children 2 years or older. It is also used to treat CAPS.

Rilonacept

1. Mechanism of action:

It binds mainly to IL-1 β and binds with lower affinity to IL-1 α and IL-1RA. Rilonacept neutralizes IL-1 β and prevents its attachment to IL-1 receptors.

2. Pharmacokinetics:

The subcutaneous dose of rilonacept for CAPS is age-dependent (12–17 years of age 4.4 mg/kg)

3. Indications:

It is approved to treat CAPS subtypes: familial cold autoinflammatory syndrome and Muckle-Wells syndrome in patients 12 years or older. Rilonacept is also used to treat gout.

Adverse Effects of Interleukin-1 Inhibitors

The most common adverse effects are injection site reactions and upper respiratory tract infections.

BELIMUMAB

Belimumab is an antibody that specifically inhibits B-lymphocyte stimulator (BLyS). It is administered as an intravenous infusion. The recommended dose is 10 mg/kg at weeks 0, 2, 4, and every 4 weeks thereafter.

Belimumab has a distribution half-life of 1.75 days and a terminal half-life of 19.4 days. It is approved only for the treatment of adult patients with active, seropositive SLE who are receiving standard treatment. The most common adverse effects are nausea, diarrhea, and respiratory tract infection.

COMBINATION THERAPY WITH

DMARDs

When added to methotrexate background therapy, cyclosporine, chloroquine, hydroxychloroquine, leflunomide, infliximab, adalimumab, rituximab, and etanercept have all shown improved efficacy. Triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine appears to be as effective as etanercept and methotrexate.

GLUCOCORTICOID DRUGS

Indications

Corticosteroids have been used in 60–70% of RA patients. Corticosteroids may be administered for certain serious extra-articular manifestations of RA such as pericarditis or eye involvement or during periods of exacerbation. When prednisone is required for long-term therapy, the dosage should not exceed 7.5 mg daily. A recent approach uses **delayed-release prednisone** for

the treatment of early morning stiffness and pain in RA.

Adverse Effects

Prolonged use of corticosteroids leads to serious and disabling toxic effects as described in Chapter 39.

OTHER ANALGESICS

ACETAMINOPHEN

Acetaminophen is the active metabolite of phenacetin and is responsible for its analgesic effect. It is a weak COX-1 and COX-2 inhibitor in peripheral tissues and possesses no significant anti-inflammatory effects.

1. Pharmacokinetics:

Acetaminophen is administered orally. The half-life of acetaminophen is 2–3 hours.

2. Indications:

The drug is useful in mild to moderate pain such as headache, myalgia, postpartum pain. Acetaminophen alone is

inadequate therapy for inflammatory conditions such as RA. For mild analgesia, acetaminophen is the preferred drug in patients allergic to aspirin, when salicylates are poorly tolerated

3. Adverse Effects:

In therapeutic doses, a mild reversible increase in hepatic enzymes may occasionally occur. With larger doses, dizziness, excitement, and disorientation may occur.

4. Dosage:

Acute pain and fever may be effectively treated with 325–500 mg four times daily. Dosing in adults is now recommended not to exceed 4 g/d, in most cases.

KETOROLAC

Ketorolac is an NSAID promoted for systemic use mainly as a short-term analgesic, not as an anti-inflammatory drug. The drug is an effective analgesic and has been used to replace morphine in some situations involving mild to moderate postsurgical pain. It is often given intramuscularly or intravenously.

TRAMADOL

Tramadol is a centrally acting synthetic analgesic, structurally related to opioids.

The drug may exert part of its analgesic effect by enhancing 5-hydroxytryptamine (5-HT) release and inhibiting the reuptake of norepinephrine and 5-HT.

DRUGS USED IN GOUT

Gout is a metabolic disease characterized by recurrent episodes of acute arthritis due to deposits of monosodium urate in joints and cartilage. Gout is usually associated with a high serum uric acid level (hyperuricemia), a poorly soluble substance that is the major end product of purine metabolism. The treatment of gout aims to relieve acute gouty attacks and prevent recurrent gouty episodes and urate lithiasis. Clinical gout is dependent on a macromolecular complex of proteins, called NLRP3, which regulates the activation of IL-1.

COLCHICINE

Although NSAIDs, corticosteroids, or colchicines are first-line drugs for acute gout, colchicines was the primary treatment for many years.

1. Pharmacokinetics:

Colchicine is eliminated with a serum half-life of 9 hours.

2. Pharmacodynamics:

Colchicine relieves the pain and inflammation of gouty arthritis in 12–24 hours without altering the metabolism or excretion of urates and without other analgesic effects. Colchicine produces its anti-inflammatory effects by binding to the intracellular protein tubulin, thereby preventing its polymerization into microtubules and leading to the inhibition of leukocyte migration and phagocytosis.

3. Indications: Colchicine is indicated for gout.

It prevents attacks of acute Mediterranean fever and may have a mild beneficial effect in sarcoid

arthritis (Sarcoidosis is an inflammatory disease that affects multiple organs in the body, but mostly the lungs and lymph gland) and in hepatic cirrhosis.

Colchicine is also used to treat and prevent pericarditis, pleurisy, and coronary artery disease.

4. Adverse Effects:

Colchicine often causes diarrhea and may occasionally cause nausea, vomiting, and abdominal pain. Hepatic necrosis, acute renal failure, disseminated intravascular coagulation, and seizures.

5. Dosage:

In prophylaxis (the most common use), the dosage of colchicine is 0.6 mg one to three times daily.

NSAIDS IN GOUT

In addition to inhibiting prostaglandin synthase, NSAIDs inhibit urate crystal phagocytosis. Aspirin is not used because it causes renal retention of uric acid at low doses (≤ 2.6 g/d). All other NSAIDs except aspirin, salicylates, and tolmetin have been successfully used to treat acute gouty episodes.

URICOSURIC AGENTS

Probenecid and **sulfinpyrazone** are uricosuric drugs employed to decrease the body pool of urate in patients with tophaceous gout or in those with increasingly frequent gouty attacks.

1. Pharmacokinetics:

The terminal serum half-life is 5–8 hours.

2. Pharmacodynamics:

It inhibits active transport sites for reabsorption and secretion in the proximal renal tubule so that net reabsorption of uric acid in the proximal tubule is decreased.

3. Indications:

Uricosuric therapy should be initiated in gouty patients with underexcretion of uric acid when allopurinol or febuxostat is contraindicated.

4. Adverse Effects: Nephrotic syndrome has occurred after the use of probenecid.

5. Dosage:

Probenecid is usually started at a dosage of 0.5 g orally daily in divided doses.

1. Pharmacokinetics:

The terminal serum half-life is 1–2 hours.

2. Indications:

Allopurinol is often the first-line agent for the treatment of chronic gout in the period between attacks and it tends to prolong the intercritical period.

3. Adverse Effects:

GI intolerance (including nausea, vomiting, and diarrhea), peripheral neuritis and necrotizing vasculitis, bone marrow suppression, and aplastic anemia may rarely occur. Hepatic toxicity and interstitial nephritis have been reported.

4. Interactions and Cautions:

When chemotherapeutic purines (eg, azathioprine) are given concomitantly with allopurinol, their dosage must be reduced by about 75%. Allopurinol may also increase the effect of cyclophosphamide.

5. Dosage:

The initial dosage of allopurinol is 50–100 mg/d.

ALLOPURINOL

FEBUXOSTAT

Febuxostat is a non-purine xanthine oxidase inhibitor

1. Pharmacokinetics:

Febuxostat is more than 80% absorbed following oral administration and a half-life of 4–18 hours.

2. Pharmacodynamics:

Febuxostat is a potent and selective inhibitor of xanthine oxidase,

Thereby reducing the formation of xanthine and uric acid without affecting other enzymes in the purine or pyrimidine metabolic pathway.

3. Indications:

Febuxostat is approved for the treatment of chronic hyperuricemia in gout patients.

4. Adverse Effects:

As with allopurinol, prophylactic treatment with colchicine or NSAIDs should be started at the beginning of therapy to avoid gout flares. The most frequent treatment-related adverse events are liver function abnormalities, diarrhea, headache, and nausea.

5. Dosage:

The recommended starting dose of febuxostat is 40 mg daily.

PEGLOTICASE

Pegloticase is the newest urate-lowering therapy to be approved for the treatment of refractory chronic gout.

1. Pharmacokinetics and Dosage:

The recommended dose for pegloticase is 8 mg every 2 weeks administered as an intravenous infusion.

2. Pharmacodynamics:

Urate oxidase enzyme, absent in humans and some higher primates, converts uric acid to allantoin. This product is highly soluble and can be easily eliminated by the kidney.

3. Adverse Effects:

Nephrolithiasis, arthralgia, muscle spasm, headache, anemia, and nausea may occur.

GLUCOCORTICOIDS

Corticosteroids are sometimes used in the treatment of severe symptomatic gout, by intra-

articular, systemic, or subcutaneous routes, depending on such as anakinra, canakinumab, and rilonacept, are used for the treatment of gout.

Drugs targeting the IL-1 pathway, the degree of pain and inflammation. The most commonly used oral corticosteroid is prednisone. The recommended oral dose is 30–50 mg/d for 1–2 days, tapered over 7–10 days. Triamcinolone acetonide can be given if the patient is unable to take oral medications.

INTERLEUKIN-1 INHIBITORS



section 7

ENDOCRINE DRUGS

37 - Hypothalamic & Pituitary Hormones .

38 - Thyroid &Antithyroid Drugs .

39 - Adrenocorticosteroids& Adrenocortical Antagonists .

40 - The Gonadal Hormones & Inhibitors .

41 - Pancreatic Hormones & Antidiabetic Drugs .



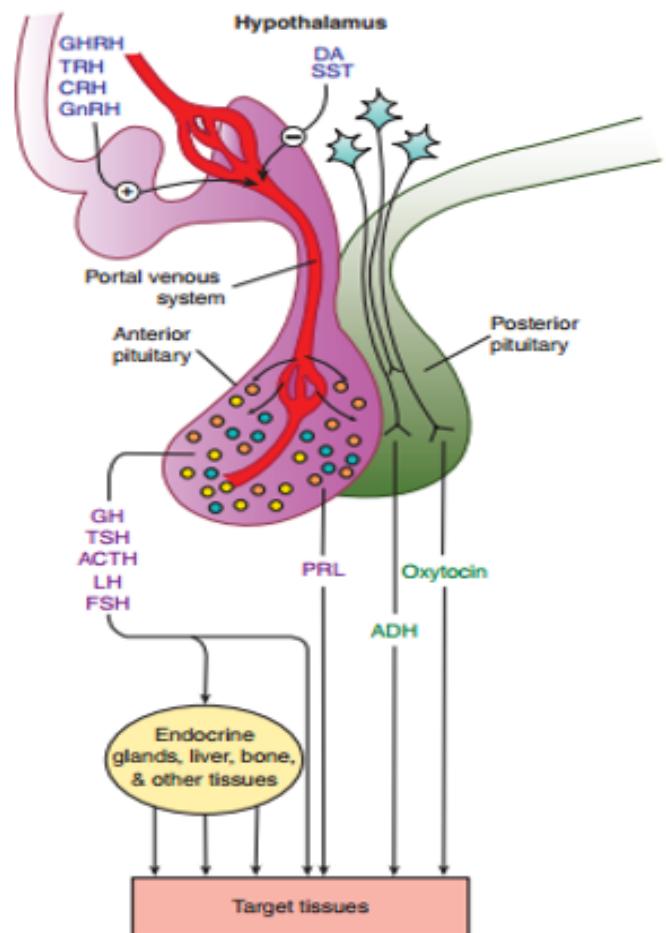
37. Hypothalamic & pituitary hormones



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Introduction

- Metabolism, reproduction, and growth in the body are regulated by neural and endocrine system.
- Pituitary and hypothalamus are the most important glands of endocrine system.
- The pituitary consists of an anterior lobe (adenohypophysis) and a posterior lobe (neurohypophysis).
- It is located under the hypothalamus in the brain.
- Pituitary gland is connected with hypothalamus by neurosecretory fibers or blood vessel.
- Portal venous system transports the hormones from hypothalamus to anterior pituitary. Neurosecretory fibers transport hormones from hypothalamus to posterior pituitary.



The hypothalamic-pituitary endocrine system

- The drugs that act on hypothalamus or pituitary can be for replacement therapy due to deficiencies of hormones, antagonists for diseases caused by increase hormone production, or for diagnosis to detect the abnormalities.
- Anterior pituitary hormones stimulate the production of hormones by a peripheral endocrine gland, the liver, or other tissues, or act directly on target tissues.
- Prolactin, vasopressin, and oxytocin are hormones of posterior pituitary gland, which act directly on target tissue.

TABLE 37-1 Links between hypothalamic, anterior pituitary, and target organ hormone or mediator.¹

Anterior Pituitary Hormone	Hypothalamic Hormone	Target Organ	Primary Target Organ Hormone or Mediator
Growth hormone (GH, somatotropin)	Growth hormone-releasing hormone (GHRH) (+), Somatostatin (-)	Liver, bone, muscle, kidney, and others	Insulin-like growth factor-I (IGF-I)
Thyroid-stimulating hormone (TSH)	Thyrotropin-releasing hormone (TRH) (+)	Thyroid	Thyroxine, triiodothyronine
Adrenocorticotropin (ACTH)	Corticotropin-releasing hormone (CRH) (+)	Adrenal cortex	Cortisol
Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)	Gonadotropin-releasing hormone (GnRH) (+) ²	Gonads	Estrogen, progesterone, testosterone
Prolactin (PRL)	Dopamine (-)	Breast	—

¹All of these hormones act through G protein-coupled receptors except GH and PRL, which act through JAK/STAT receptors.

²Endogenous GnRH, which is released in pulses, stimulates LH and FSH release. When administered continuously as a drug, GnRH and its analogs inhibit LH and FSH release through down-regulation of GnRH receptors.

(+), stimulant; (-), inhibitor.

TABLE 37–2 Clinical uses of hypothalamic hormones and their analogs.

Hypothalamic Hormone	Clinical Uses
Growth hormone-releasing hormone (GHRH)	Used rarely as a diagnostic test for GH and GHRH sufficiency
Thyrotropin-releasing hormone (TRH, protirelin)	May be used to diagnose TRH or TSH deficiencies; not currently available for clinical use
Corticotropin-releasing hormone (CRH)	Used rarely to distinguish Cushing's disease from ectopic ACTH secretion
Gonadotropin-releasing hormone (GnRH)	May be used in pulses to treat infertility caused by GnRH deficiency Analogues used in long-acting formulations to inhibit gonadal function in children with precocious puberty, in some transgender/gender variant early pubertal adolescents (to block endogenous puberty), in men with prostate cancer and women undergoing assisted reproductive technology (ART) or women who require ovarian suppression for a gynecologic disorder
Dopamine	Dopamine agonists (eg, bromocriptine, cabergoline) used for treatment of hyperprolactinemia

TABLE 37–3 Diagnostic uses of thyroid-stimulating hormone and adrenocorticotropic hormone.

Hormone	Diagnostic Use
Thyroid-stimulating hormone (TSH; thyrotropin)	In patients who have been treated surgically for thyroid carcinoma, to test for recurrence by assessing TSH-stimulated whole-body radioactive iodine scans and serum thyroglobulin determinations (see Chapter 38)
Adrenocorticotropic hormone (ACTH)	In patients suspected of adrenal insufficiency, either central (CRH/ACTH deficiency) or peripheral (cortisol deficiency), in particular in suspected cases of congenital adrenal hyperplasia. (See Figure 39–1 and Chapter 39.)

GROWTH HORMONE (SOMATOTROPIN):

- One of the anterior pituitary hormones is growth hormone (GW).
- Growth hormone is important during childhood and adolescence.
- Growth hormone is responsible for metabolism and growth like muscle and bone growth.

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
GROWTH HORMONE (GH)				
• Somatropin	Recombinant form of human GH • acts through GH receptors to increase production of IGF-I	Restores normal growth and metabolic GH effects in GH-deficient individuals • increases final adult height in some children with short stature not due to GH deficiency	Replacement in GH deficiency • increased final adult height in children with certain conditions associated with short stature (see Table 37-4) • wasting in HIV infection • short bowel syndrome	SC injection • Toxicity: Pseudotumor cerebri, slipped capital femoral epiphysis, edema, hyperglycemia, progression of scoliosis, risk of asphyxia in severely obese patients with Prader-Willi syndrome and upper airway obstruction or sleep apnea



TABLE 37–4 Clinical uses of recombinant human growth hormone.

Primary Therapeutic Objective	Clinical Condition
Growth	Growth failure in pediatric patients associated with:
	Growth hormone deficiency
	Chronic renal insufficiency pre-transplant
	Noonan syndrome
	Prader-Willi syndrome
	Short stature homeobox-containing gene (SHOX) deficiency
	Turner syndrome
	Small-for-gestational-age with failure to catch up by age 2 years
	Idiopathic short stature
	Improved metabolic state, increased lean body mass, sense of well-being
Improved metabolic state, increased lean body mass, weight, and physical endurance	Growth hormone deficiency in adults
Increased lean body mass, weight, and physical endurance	Wasting in patients with HIV infection
Improved gastrointestinal function	Short bowel syndrome in patients who are also receiving specialized nutritional support

***Additional information about Pharmacokinetics of growth hormone:**

- 1-GH has a half-life of around 20 minutes.
- 2- GH is predominantly cleared by the liver.

- **Pseudotumor cerebri = (false brain tumor) is a disease that increases the pressure around brain leading to headache, and vision problems.**
- **Slipped capital femoral epiphysis= is hip disorder**
- **Scoliosis=curvature of the spine.**
- **Edema= swelling due to accumulation of fluid.**

MECASERMIN:

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
IGF-I AGONIST				
• Mecasermin	Recombinant form of IGF-I that stimulates IGF-I receptors	Improves growth and metabolic IGF-I effects in individuals with IGF-I deficiency due to severe GH resistance	Replacement in IGF-I deficiency that is not responsive to exogenous GH	SC injection • Toxicity: Hypoglycemia, intracranial hypertension, increased liver enzymes

- Mecasermin and mecasermin tinfabate are two forms of recombinant human IGF-I.
- Mecasermin is only rhIGF-I, whereas mecasermin tinfabate is a complex of rhIGF-I and recombinant human insulin-like growth factor-binding protein-3 (rhIGFBP-3).

Antagonists of GH:

- GH-producing cells (somatotrophs) can cause GH-secreting tumors.
- *Acromegaly* (abnormal growth due to overproduction of GH) or *gigantism* (abnormal growth in children) can be caused by hormone-secreting pituitary adenomas.
- Visual problems and impaired function of central nervous system function can also be caused by hormone-secreting pituitary adenomas.

- To treat this condition, transsphenoidal surgery is recommended.
- However, antagonists of GH like somatostatin analogs and dopamine receptor agonists can be used if the surgery failed to treat GH hypersecretion.

Somatostatin Analog (Octreotide)

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
SOMATOSTATIN ANALOGS				
• Octreotide	Agonist at somatostatin receptors	Inhibits production of GH and, to a lesser extent, of TSH, glucagon, insulin, and gastrin	Acromegaly and several other hormone-secreting tumors • acute control of bleeding from esophageal varices	SC or IV injection • long-acting formulation injected IM monthly • Toxicity: Gastrointestinal disturbances, gallstones, bradycardia, cardiac conduction problems
• Lanreotide: Similar to octreotide; available as a long-acting formulation for acromegaly				

Pegvisomant

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
GH RECEPTOR ANTAGONIST				
• Pegvisomant	Blocks GH receptors	Ameliorates effects of excess GH production	Acromegaly	SC injection • Toxicity: Increased liver enzymes

THE GONADOTROPINS (FOLLICLE-STIMULATING HORMONE & LUTEINIZING HORMONE) & HUMAN CHORIONIC

GONADOTROPIN

- Gonadotroph cells secrete gonadotropins, which are essential for reproductive process.
- FSH and LH both are required for ovarian follicle development.

- In the ovary, LH stimulates androgen production by theca cells in the follicular stage of the menstrual cycle, whereas FSH stimulates the conversion of androgens to estrogens by granulosa cells.
- FSH regulates spermatogenesis in men, but LH stimulates testosterone synthesis.

- **Gynecomastia= enlargement of breast in men.**

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
GONADOTROPINS: FOLLICLE-STIMULATING HORMONE (FSH) ANALOGS				
<ul style="list-style-type: none"> Follitropin alfa 	Activates FSH receptors	Mimics effects of endogenous FSH	Controlled ovarian stimulation • infertility due to hypogonadotropic hypogonadism in men	SC injection • Toxicity: Ovarian hyperstimulation syndrome and multiple pregnancies in women • gynecomastia in men • headache, depression, edema in both sexes
<ul style="list-style-type: none"> Follitropin beta: A recombinant product with the same peptide sequence as follitropin alfa but differs in its carbohydrate side chains Urofollitropin: Human FSH purified from the urine of postmenopausal women Menotropins (hMG): Extract of the urine of postmenopausal women; contains both FSH and LH activity 				
GONADOTROPINS: LUTEINIZING HORMONE (LH) ANALOGS				
<ul style="list-style-type: none"> Human chorionic gonadotropin (hCG) 	Agonist at LH receptors	Mimics effects of endogenous LH	Initiation of final oocyte maturation and ovulation during controlled ovarian stimulation • male hypogonadotropic hypogonadism	IM or SC injection • Toxicity: Ovarian hyperstimulation syndrome • headache, depression, edema in both sexes
<ul style="list-style-type: none"> Choriogonadotropin alfa: Recombinant form of hCG Lutropin: Recombinant form of human LH Menotropins (hMG): Extract of the urine of postmenopausal women that contains both FSH and LH activity 				

GONADOTROPIN-RELEASING HORMONE & ITS ANALOGS

- Neurons in the hypothalamus produce gonadotropin-releasing hormone.
- By venous portal plexus, it goes to anterior pituitary.

- LH and FSH require Pulsatile GnRH secretion to be activated, whereas non-pulsatile GnRH or GnRH analogs inhibits the LH and FSH secretion.
- *Pulsatile secretion*= is a biochemical phenomenon in which a chemical, such as a hormone, is secreted in an episodic manner rather than constantly.





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A- GnRH analogs can be used as stimulation in male or female infertility and diagnosis of LH responsiveness.

1- Female infertility

- Gonadorelin or a GnRH agonist analog stimulates an LH surge and ovulation in women with infertility.
- Although hCG has the same function, there is some evidence that gonadorelin or a GnRH agonist is less likely than hCG to cause OHSS.
- OHSS= Ovarian hyper-stimulation syndrome.
- hCG= Human chorionic gonadotropin.

2- Male infertility

- Pulsatile gonadorelin can be used in male infertility.

3- Diagnosis of LH responsiveness

- GnRH can be used to detect the cause of delayed puberty.

B- GnRH analogs can be used as suppression of gonadotropin production.

1- Controlled ovarian stimulation:

- Leuprolide or nafarelin can be used to suppress an endogenous LH surge could prematurely trigger ovulation.

2- Endometriosis:

- Endometriosis is a painful disorder in which tissue that lines inside the uterus grows outside of it.
- Reducing estrogen and progesterone concentrations and preventing cyclical changes for treatment of endometriosis can be achieved by GnRH agonist.

3- Uterine leiomyomata (uterine fibroids):

- Uterine leiomyomata is benign tumor in uterus causing menorrhagia, anemia, and pelvic pain.
- GnRH agonist treats this condition by reducing fibroid size.
- For anemia, patient should take iron supplement.
- However, the effect of GnRH agonist is temporary, so myomectomy and hysterectomy are required.

4- Prostate cancer:

- Using GnRH agonist in combination with antiandrogen therapy reduces testosterone or androgen concentrations.

5- Central precocious puberty:

- Central precocious puberty is abnormal condition that results early onset of puberty and early development of pubertal secondary sexual characteristics. GnRH agonist treats central precocious puberty.

6- Other:

- GnRH agonist has been shown to manage advanced breast or ovarian cancer and block endogenous puberty in some transgender.

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
GONADOTROPIN-RELEASING HORMONE (GnRH) ANALOGS				
<ul style="list-style-type: none"> Leuprorelin 	Agonist at GnRH receptors	<ul style="list-style-type: none"> Increased LH and FSH secretion with intermittent administration reduced LH and FSH secretion with prolonged continuous administration 	<ul style="list-style-type: none"> Ovarian suppression controlled ovarian stimulation central precocious puberty block of endogenous puberty in some transgender/gender variant early pubertal adolescents advanced prostate cancer 	<ul style="list-style-type: none"> Administered IV, SC, IM, or intranasally • depot formulations are available Toxicity: Headache, light-headedness, nausea, injection site reactions • symptoms of hypogonadism with continuous treatment

GNRH RECEPTOR ANTAGONISTS:

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
GONADOTROPIN-RELEASING HORMONE (GnRH) RECEPTOR ANTAGONISTS				
<ul style="list-style-type: none"> Ganirelix 	Blocks GnRH receptors	Reduces endogenous production of LH and FSH	Prevention of premature LH surge during controlled ovarian stimulation	<ul style="list-style-type: none"> SC injection • Toxicity: Nausea, headache

PROLACTIN

- Prolactin is a hormone in anterior pituitary gland that is responsible for lactation and milk production.
- There is no medication to treat

DOPAMINE AGONISTS

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DOPAMINE AGONISTS				
Bromocriptine	Activates dopamine D ₂ receptors	Suppresses pituitary secretion of prolactin and, less effectively, GH • dopaminergic effects on CNS motor control and behavior	Treatment of hyperprolactinemia • acromegaly • Parkinson's disease (see Chapter 28)	Administered orally or, for hyperprolactinemia, vaginally • Toxicity: Gastrointestinal disturbances, orthostatic hypotension, headache, psychiatric disturbances, vasospasm and pulmonary infiltrates in high doses
• Cabergoline: Another ergot derivative with similar effects				

- **Hyper-prolactinemia:** dopamine is a drug of choice for hyper-prolactinemia. Dopamine agonist reduces the prolactin secretion in pituitary gland.

- **Physiologic Lactation:** Dopamine agonists were used in the past to prevent breast engorgement when breast-feeding was not desired.
- **Acromegaly:** dopamine agonist treats acromegaly, and requires high doses.

OXYTOCIN

- Oxytocin is one of the posterior pituitary hormones that stimulates the contraction during labor, promotes lactation for breast-feeding, and reduces bleeding after delivery.

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
OXYTOCIN	Activates oxytocin receptors	Increased uterine contractions	Induction and augmentation of labor • control of uterine hemorrhage after delivery	IV infusion or IM injection • Toxicity: Fetal distress, placental abruption, uterine rupture, fluid retention, hypotension

OXYTOCIN ANTAGONIST:

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
OXYTOCIN RECEPTOR ANTAGONIST				
Atosiban	Blocks oxytocin receptors	Decreased uterine contractions	Tocolysis for preterm labor	IV infusion • Toxicity: Concern about increased rates of infant death; not FDA approved

- Tocolysis = suppress premature labor.

VASOPRESSIN

(ANTIDIURETIC HORMONE, ADH)

- Vasopressin is a posterior pituitary hormone that increases blood pressure. Vasopressin treats diabetes insipidus.

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
VASOPRESSIN RECEPTOR AGONISTS				
• Desmopressin	Relatively selective vasopressin V ₁ receptor agonist	Acts in the kidney collecting duct cells to decrease the excretion of water • acts on extrarenal V ₁ receptors to increase factor VIII and von Willebrand factor	Pituitary diabetes insipidus • pediatric primary nocturnal enuresis • hemophilia A and von Willebrand disease	Oral, IV, SC, or intranasal • Toxicity: Gastrointestinal disturbances, headache, hyponatremia, allergic reactions

• Vasopressin: Available for treatment of diabetes insipidus and sometimes used to control bleeding from esophageal varices

VASOPRESSIN ANTAGONISTS

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
VASOPRESSIN RECEPTOR ANTAGONIST				
• Conivaptan	Antagonist of vasopressin V _{1a} and V ₂ receptors	Reduced renal excretion of water in conditions associated with increased vasopressin	Hyponatremia in hospitalized patients	IV infusion • Toxicity: Infusion site reactions

• Tolvaptan: Similar but more selective for vasopressin V₂ receptors; oral administration; treatment course limited to 30 days due to risk of hepatotoxicity

38. THYROID & ANTITHYROID DRUG

INTRODUCTION:

- Triiodothyronine (T₃) and tetraiodothyronine (T₄, thyroxine) are thyroid hormones that control growth and development, body temperature, and energy levels.

- Calcium metabolism is regulated by Calcitonin, the second type of thyroid hormone.
- Thyroxine and T₃ in plasma are reversibly bound to protein, primarily thyroxine-binding globulin (TBG). Only about 0.04% of total T₄ and 0.4% of T₃ exist in the free form (as FT₄ and FT₃).

TABLE 38-2 Typical values for thyroid function tests.

Name of Test	Normal Value ¹	Results in Hypothyroidism	Results in Hyperthyroidism
Total thyroxine (T ₄)	4.8–10.4 mcg/dL (62–134 nmol/L)	Low	High
Total triiodothyronine (T ₃)	59–156 ng/dL (0.9–2.4 nmol/L)	Normal or low	High
Free T ₄ (FT ₄)	0.8–1.4 ng/dL (10–18 pmol/L)	Low	High
Free T ₃ (FT ₃)	169–371 ng/dL (2.6–5.7 pmol/L)	Low	High
Thyrotropic hormone (TSH)	0.45–4.12 μIU/mL (0.45–4.12 mIU/L)	High ²	Low
¹²³ I uptake at 24 hours	5–35%	Low	High
Antithyroglobulin antibodies (Tg-Ab)	< 4.11 IU/mL	Often present	Usually present
Thyroid peroxidase antibodies (TPA)	< 60 U/mL	Often present	Usually present
Isotope scan with ¹²³ I or ^{99m} TcO ₄	Normal pattern	Test not indicated	Diffusely enlarged gland
Fine-needle aspiration biopsy (FNA)	Normal pattern	Test not indicated	Test not indicated
Serum thyroglobulin	Women: 1.5–38.5 mcg/L Men: 1.4–29.2 mcg/L	Test not indicated	Test not indicated
TSH receptor-stimulating antibody or thyroid-stimulating immunoglobulin (TSI)	Negative is < 140% of baseline	Test not indicated	Elevated in Graves' disease

¹Results may vary with different laboratories.

²Exception is central hypothyroidism.

THYROID

Subclass, Drug	Mechanism of Action and Effects	Indications	Pharmacokinetics, Toxicities, Interactions
<i>Thyroid Preparations</i>			
• Levothyroxine (T_4) • Liothyronine (T_3)	Activation of nuclear receptors results in gene expression with RNA formation and protein synthesis	Hypothyroidism	See Table 38-1 • maximum effect seen after 6–8 weeks of therapy • Toxicity: See Table 38-4 for symptoms of thyroid excess

HORMONES:

- Thyroxine(T_4) should be administered on an empty stomach.

TABLE 38-1 Summary of thyroid hormone kinetics.

Variable	T_4	T_3
Volume of distribution	10 L	40 L
Extrathyroidal pool	800 mcg	54 mcg
Daily production	75 mcg	25 mcg
Fractional turnover per day	10%	60%
Metabolic clearance per day	1.1 L	24 L
Half-life (biologic)	7 days	1 day
Serum levels		
Total	4.8–10.4 mcg/dL (62–134 nmol/L)	60–181 ng/dL (0.92–2.79 nmol/L)
Free	0.8–2.7 ng/dL (10.3–34.7 pmol/L)	230–420 pg/dL (3.5–6.47 pmol/L)
Amount bound	99.96%	99.6%
Biologic potency	1	4
Oral absorption	70%	95%



TABLE 38-3 Drug effects and thyroid function.

Drug Effect	Drugs
Change in thyroid hormone synthesis	
Inhibition of TRH or TSH secretion without induction of hypothyroidism or hyperthyroidism	Bexarotene, dopamine, bromocriptine, cabergoline, levodopa, corticosteroids, somatostatin, octreotide, metformin, interleukin-6, heroin
Inhibition of thyroid hormone synthesis or release with the induction of hypothyroidism (or occasionally hyperthyroidism)	Iodides (including amiodarone), lithium, aminoglutethimide, thioamides, ethionamide, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib), HIV protease inhibitors
Alteration of thyroid hormone transport and serum total T_3 and T_4 levels, but usually no modification of FT_3 or TSH	
Increased TBG	Estrogens, tamoxifen, raloxifene, heroin, methadone, mitotane, 5-fluorouracil, perphenazine
Decreased TBG	Androgens, anabolic steroids, glucocorticoids, danazol, L-asparaginase, nicotinic acid
Displacement of T_3 and T_4 from TBG with transient hyperthyroxinemia	Salicylates, fenclofenac, mefenamic acid, intravenous furosemide, heparin
Alteration of T_3 and T_4 metabolism with modified serum T_3 and T_4 levels but not TSH levels (unless receiving thyroxine replacement therapy)	
Increased hepatic metabolism, enhanced degradation of thyroid hormone	Nicardipine, phenytoin, carbamazepine, primidone, phenobarbital, rifampin, rifabutin, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib), sertraline, quetiapine
Inhibition of 5'-deiodinase with decreased T_3 , increased FT_3	Iopanoic acid, ipodate, amiodarone, β blockers, corticosteroids, propylthiouracil, flavonoids, interleukin-6
Other interactions	
Interference with T_4 absorption from the gut	Oral bisphosphonates, cholestyramine, colestevam, colestipol, chromium picolinate, charcoal, ciprofloxacin, proton pump inhibitors, sucralose, Kayexalate, raloxifene, sevelamer hydrochloride, aluminum hydroxide, ferrous sulfate, calcium carbonate, bran/fiber, soy, coffee, orlistat
Induction of autoimmune thyroid disease with hypothyroidism or hyperthyroidism	Interferon- α , interleukin-2, interferon- β , lithium, amiodarone, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib)
Effect of thyroid function on drug effects	
Anticoagulation	Lower doses of warfarin required in hyperthyroidism; higher doses in hypothyroidism
Glucose control	Increased hepatic glucose production and glucose intolerance in hyperthyroidism; impaired insulin action and glucose disposal in hypothyroidism
Cardiac drugs	Higher doses of digoxin required in hyperthyroidism; lower doses in hypothyroidism
Sedatives; analgesics	Increased sedative and respiratory depressant effects from sedatives and opioids in hypothyroidism; converse in hyperthyroidism

TABLE 38-4 Manifestations of thyrotoxicosis and hypothyroidism.

System	Thyrotoxicosis	Hypothyroidism
Skin and appendages	Warm, moist skin; sweating; heat intolerance; fine, thin hair; Plummer's nails; pretibial dermopathy (Graves' disease)	Pale, cool, puffy, yellowish skin, face, and hands; dry and brittle hair; brittle nails
Eyes, face	Retraction of upper lid with wide stare; periorbital edema; exophthalmos; diplopia (Graves' disease)	Drooping of eyelids; periorbital edema; loss of temporal aspects of eyebrows; puffy, nonpitting facies; large tongue, hoarseness
Cardiovascular system	Decreased peripheral vascular resistance; increased heart rate, stroke volume, cardiac output, pulse pressure; high-output heart failure; increased inotropic and chronotropic effects; arrhythmias; angina	Increased peripheral vascular resistance; decreased heart rate, stroke volume, cardiac output, pulse pressure; low-output heart failure; ECG: bradycardia, prolonged PR interval, flat T wave, low voltage; pericardial effusion
Respiratory system	Dyspnea; hypoventilation; decreased vital capacity	Pleural effusions; hypoventilation and CO ₂ retention; sleep apnea
Gastrointestinal system	Increased appetite; increased frequency of bowel movements; hypoproteinemia	Decreased appetite; decreased frequency of bowel movements, constipation; ascites
Central nervous system	Nervousness; hyperkinesia; emotional lability, agitation	Lethargy/fatigue; general slowing of mental processes; neuropathies; weakness and muscle cramps
Musculoskeletal system	Weakness and muscle fatigue; increased deep tendon reflexes; tremors; hypercalcemia; osteoporosis	Stiffness and muscle fatigue; carpal tunnel syndrome; decreased deep tendon reflexes; increased alkaline phosphatase, LDH, AST
Renal system	Mild polyuria; increased renal blood flow; increased glomerular filtration rate	Impaired water excretion; decreased renal blood flow; decreased glomerular filtration rate
Hematopoietic system	Increased erythropoiesis; anemia ¹	Decreased erythropoiesis; anemia ¹
Reproductive system	Menstrual irregularities; amenorrhea; infertility; increased gonadal steroid metabolism	Menorrhagia; infertility; decreased libido; impotence; oligospermia; decreased gonadal steroid metabolism
Metabolic system	Increased basal metabolic rate; negative nitrogen balance; hyperglycemia; increased free fatty acids; decreased total cholesterol and triglycerides; increased hormone degradation; increased requirements for fat- and water-soluble vitamins; increased drug metabolism; decreased warfarin requirement	Decreased basal metabolic rate; slight positive nitrogen balance; delayed degradation of insulin with increased sensitivity; increased total cholesterol and triglycerides; hyponatremia; decreased hormone degradation; decreased requirements for fat- and water-soluble vitamins; decreased drug metabolism; increased warfarin requirement

¹The anemia of hyperthyroidism is usually normochromic and caused by increased red blood cell turnover. The anemia of hypothyroidism may be normochromic, hyperchromic, or hypochromic and may be due to decreased production rate, decreased iron absorption, decreased folic acid absorption, or to autoimmune pernicious anemia. LDH, lactic dehydrogenase; AST, aspartate aminotransferase.

ANTITHYROID AGENTS:

- Antithyroid agents are used to reduce the production of thyroid hormones to prevent hyperthyroidism.
- Thioamides, iodides, and radioactive iodine are examples of antithyroid agents.



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THIOAMIDES:

- The thioamides methimazole and propylthiouracil are used to treat thyrotoxicosis.
- Methimazole is more effective than propylthiouracil for adults and children.
- Both thioamides cross the placental barrier and are concentrated by the fetal thyroid, category D.

ANION INHIBITORS:

Subclass, Drug	Mechanism of Action and Effects	Indications	Pharmacokinetics, Toxicities, Interactions
<i>Antithyroid Agents</i>			
THIOAMIDES <ul style="list-style-type: none">• Methimazole• Propylthiouracil (PTU)	Inhibit thyroid peroxidase reactions • block iodine organification • inhibit peripheral deiodination of T_4 and T_3 (primarily PTU)	Hyperthyroidism	Oral • duration of action: 24 h (methimazole), 6–8 h (PTU) <ul style="list-style-type: none">• delayed onset of action• Toxicity: Nausea, gastrointestinal distress, rash, agranulocytosis, hepatitis (PTU black box), hypothyroidism

- Potassium perchlorate blocks thyroidal reuptake of I- in patients with iodide-induced hyperthyroidism).
- Potassium perchlorate is not commonly used because it can cause aplastic anemia.

IODIDES:

Subclass, Drug	Mechanism of Action and Effects	Indications	Pharmacokinetics, Toxicities, Interactions
IODIDES			
• Lugol's solution • Potassium iodide	Inhibit organification and hormone release • reduce the size and vascularity of the gland	Preparation for surgical thyroidectomy	Oral • acute onset within 2-7 days • Toxicity: Rare (see text)

- Adverse reactions of iodides are acneiform rash (similar to that of bromism), swollen salivary glands, mucous membrane ulcerations, conjunctivitis, rhinorrhea, drug fever, metallic taste, bleeding disorders, and rarely, anaphylactoid reactions.

RADIOACTIVE IODINE:

- ^{131}I is the only isotope used for treatment of thyrotoxicosis (others are used in diagnosis).

Subclass, Drug	Mechanism of Action and Effects	Indications	Pharmacokinetics, Toxicities, Interactions
RADIOACTIVE IODINE ^{131}I (RAI)			
	Radiation destruction of thyroid parenchyma	Hyperthyroidism • patients should be euthyroid or on β blockers before RAI • avoid in pregnancy and in nursing mothers	Oral • half-life 5 days • onset in 6-12 weeks • maximum effect in 3-6 months • Toxicity: Sore throat, sialitis, hypothyroidism

ADRENOCEPTOR-BLOCKING AGENTS:

Subclass, Drug	Mechanism of Action and Effects	Indications	Pharmacokinetics, Toxicities, Interactions
BETA BLOCKERS			
• Propranolol, other β blockers lacking partial agonist activity	Inhibition of β adrenoreceptors • inhibit T_4 to T_3 conversion (only propranolol)	Hyperthyroidism, especially thyroid storm • adjunct to control	Onset within hours • duration of 4–6 h (oral propranolol)

HYPOTHYROIDISM

TABLE 38-5 Etiology and pathogenesis of hypothyroidism.

Cause	Pathogenesis	Goiter	Degree of Hypothyroidism
Hashimoto's thyroiditis	Autoimmune destruction of thyroid	Present early, absent later	Mild to severe
Drug-induced ¹	Blocked hormone formation ²	Present	Mild to moderate
Dyshormonogenesis	Impaired synthesis of T_4 due to enzyme deficiency	Present	Mild to severe
Radiation, ^{131}I , X-ray, thyroidectomy	Destruction or removal of gland	Absent	Severe
Congenital (cretinism)	Athyreosis or ectopic thyroid, iodine deficiency; TSH receptor-blocking antibodies	Absent or present	Severe
Secondary (TSH deficit)	Pituitary or hypothalamic disease	Absent	Mild

¹Iodides, lithium, fluoride, thioamides, aminosalicylic acid, phenylbutazone, amiodarone, perchlorate, ethionamide, thiocyanate, cytokines (interferons, interleukins), bexarotene, tyrosine kinase inhibitors, etc. See Table 38-3.

²See Table 38-3 for specific pathogenesis.

Special Problems in Management of Hypothyroidism:

A. Myxedema and Coronary Artery Disease:

- Myxedema is associated with elderly.
- Therefore, myxedema can lead to coronary artery disease.
- Correction of myxedema must be done cautiously to avoid provoking these cardiac events.
- If coronary artery surgery is indicated, it should be done first, prior to correction of the myxedema by thyroxin administration.

B. Myxedema Coma:

- Myxedema come is a life-threatening condition that results progressive weakness, stupor, hypothermia, hypoventilation, hypoglycaemia, hypernatremia, water intoxication, shock, and death.

- The drug of choice for treatment of myxedema coma is taking levothyroxine intravenously.

C. Hypothyroidism and Pregnancy:

- For pregnant hypothyroid patients, the daily dose of thyroxin should be suitable and adequate because maternal thyroxin is responsible for early development of the fetal brain.

D. Subclinical Hypothyroidism:

- For TSH levels greater than 10 mIU/L, Thyroid hormone therapy should be given, whereas close TSH monitoring is recommended for lower TSH elevations.

E. Drug-Induced Hypothyroidism:

- Levothyroxine therapy is recommended.

HYPERTHYROIDISM:

GRAVES' DISEASE:

- Graves' disease is a one of autoimmune disorder that results hyperthyroidism.
- To control hyperthyroidism, antithyroid drug therapy, surgical thyroidectomy, and destruction of the gland with radioactive iodine are used.

Special problems:

1- Thyroid Storm:

- Thyroid storm is medical emergency of hyperthyroidism.
- To block synthesis, propylthiouracil is used
- To block the release of hormones, potassium iodide is recommended.
- To block the conversion of T4 to T3, hydrocortisone is used.

2- Ophthalmopathy:

- Uncommon condition that can occur due to RAI radioiodine therapy especially in those who smoke.
- Treatment of thyroid such as total surgical excision or ^{131}I ablation of the gland plus oral prednisone therapy is required.
- Local therapy may be necessary, eg, elevation of the head to diminish periorbital edema and artificial tears to relieve corneal drying due to exophthalmos.
- Smoking cessation is highly recommended.

2- Dermopathy:

- Dermopathy can be treated with corticosteroids.

3- Thyrotoxicosis during Pregnancy:

- Thyrotoxicosis should be treated with ^{131}I or subtotal thyroidectomy before the pregnancy to avoid the complications of the disease during the pregnancy or following delivery.
- RAI should be avoided because it can cross the placenta and harm fetal thyroid.
- Propylthiouracil (fewer teratogenic risks than methimazole) can be given in the first trimester, and then methimazole can be given for the remainder of the pregnancy in order to avoid potential liver damage.

4- Neonatal Graves' Disease:

- Propylthiouracil, Lugol's solution, and propranolol are used to treat neonatal Graves' disease.

5- Amiodarone-Induced Thyrotoxicosis:

- Two types of amiodarone-induced thyrotoxicosis have been reported: iodine-induced (type I), which often occurs in persons with underlying thyroid disease (eg, multinodular goiter, Graves' disease); and an inflammatory thyroiditis (type II).
- That occurs in patients without thyroid disease due to leakage of thyroid hormone into the circulation.
- Treatment of type I requires therapy with thioamides, while type II responds best to glucocorticoids.

39. Adrenocorticos teroids & Adrenocortical Antagonists

- The natural adrenocortical hormones are steroid molecules produced and released by the adrenal cortex.
- Secretion of adrenocortical steroids is controlled by the pituitary release of corticotropin (ACTH).

ADRENOCORTICOS TEROIDS:

- The hormonal steroids may be classified as those having important effects on:
- Metabolism and immune function: glucocorticoids
- Salt-retaining activity: mineralocorticoid s
- Androgenic or estrogenic activity.

- The major glucocorticoid is cortisol.
- The most important

Diffusion of glucocorticoid across the membrane of the target cell to bind to a **glucocorticoid receptor-heat-shock protein complex** in the cytoplasm

Release of the heat-shock protein and transport of the hormone receptor complex into the **nucleus**

Binding of the hormone-receptor complex to specific nucleotide sequences along the DNA, called **Glucocorticoid response elements (GREs)**

Decreased or increased accumulation of mRNA within the target cell

Decreased or increased transcription of genes coding for specific proteins

Changes in the rate of synthesis of specific proteins that carry out the biologic actions of the hormones

mineralocorticoid is aldosterone.

- Dehydroepiandrosterone (DHEA) in its sulfated form (DHEAS) is the major adrenal androgen.
- DHEA and two other adrenal androgens, androstenedione and androstanediol, are weak

androgens and androstenediol is a potent estrogen .

- Cortisol (also called hydrocortisone, compound F).

• THE NATURALLY OCCURRING GLUCOCORTICOID S; CORTISOL:

Pharmacokinetics:

- Its synthesis and secretion are tightly regulated by the central nervous system, which is very sensitive to negative feedback.
- Governed by pulses of ACTH that peak in the early morning hours and after meals.
- In plasma, cortisol is bound to circulating proteins.
- The half-life of cortisol in the circulation is normally about 60-90 minutes.
- Most cortisol is metabolized in the liver and excreted in the urine.

Pharmacodynamics:

A-Mechanism of Action.

B-Physiologic Effects :

- The glucocorticoids have widespread effects because they influence the function of most cells in the body.
- The major metabolic consequences of glucocorticoid secretion or administration are due to direct actions of these hormones in the cell.
- Homeostatic responses by insulin and glucagon.

C-Metabolic Effects:

- The glucocorticoids have important dose-related effects on carbohydrate,

phosphoenolpyruvate carboxykinase

glycogen synthase

They stimulate

glucose-6-phosphatase

gluconeogenesis

protein, and fat metabolism.

- Glucocorticoids increase serum glucose levels and thus stimulate insulin release and inhibit the uptake of glucose by muscle cells, while they stimulate hormone-sensitive lipase and thus lipolysis.
- The increased insulin secretion stimulates lipogenesis and to a lesser degree inhibits lipolysis, leading to a net increase in fat deposition combined with increased release of fatty acids and glycerol into the circulation.

b- Catabolic and Antianabolic Effects:

- Glucocorticoids stimulate RNA and protein synthesis in the liver, they have catabolic and antianabolic effects in lymphoid and connective tissue, muscle, peripheral fat, and skin.
- Catabolic and antianabolic effects on bone are the cause of osteoporosis in Cushing's syndrome
- In children, glucocorticoids reduce growth.

c-Anti-Inflammatory and Immunosuppressive Effects:

- Glucocorticoids dramatically reduce the manifestations of inflammation.

d- Other Effects:

- Adrenal insufficiency causes marked slowing of the alpha rhythm of the electroencephalogram and is associated with depression.
- Increased amounts of glucocorticoids often produce behavioral disturbances in human.
- Glucocorticoids given chronically suppress the pituitary release of ACTH, growth hormone, thyroid-stimulating hormone, and luteinizing hormone.
- Peptic ulcer promote fat redistribution in the body.
- Also have important effects on the hematopoietic system.
- Development of the fetal lungs.

Pharmacokinetics :

- The synthetic corticosteroid are in most cases rapidly and completely absorbed when given by mouth.
- In some cases, the agent given is a prodrug.

Pharmacodynamics :

- The actions of the synthetic steroids are similar to those of cortisol.

SYNTHETIC CORTICOSTEROIDS

- Glucocorticoids have become important agents for use in the treatment of many inflammatory, immunologic, hematologic, and other disorders.
- This has stimulated the development of many synthetic steroids with anti-inflammatory and immunosuppressive

activity.

CLINICAL PHARMACOLOGY:

- Diagnosis and Treatment of Disturbed Adrenal Function:

1- Adrenocortical insufficiency:

A- Chronic (Addison's disease):

- Characterized by weakness, fatigue, weight loss, hypotension, hyperpigmentation, and inability to maintain the blood glucose level during fasting.
- In primary adrenal insufficiency, about 20–30 mg of hydrocortisone must be given daily, with increased amounts during periods of stress.
- Synthetic glucocorticoids that are long acting and devoid of salt-retaining activity should not be administered to these patients.

B-Acute:

- (Treatment must be instituted immediately)
 - large amounts of parenteral hydrocortisone in addition to correction of fluid and electrolyte.
- Hydrocortisone sodium succinate or phosphate in doses of 100 mg IV is given every 8 hours until the patient is stable.
- The administration of salt-retaining hormone is resumed when the total hydrocortisone dosage has been reduced to 50 mg/d.

2-Adrenocortical hypo- and hyper function:

A-Congenital adrenal hyperplasia:

(This group of disorders is characterized by specific defects in the synthesis of cortisol.)

- In pregnancies at high risk for congenital adrenal hyperplasia, fetuses can be protected from genital abnormalities by administration of

dexamethasone to the mother.

- Oral hydrocortisone, 12–18 mg/m²/d in two unequally divided doses (two thirds in the morning, one third in late afternoon).
- Alternate day therapy with prednisone has also been used.
- Fludrocortisone, 0.05–0.2 mg/d, should also be administered by mouth, with added salt to maintain normal blood pressure, plasma renin activity, and electrolytes.

B-Primary generalized glucocorticoid resistance (Chrousos syndrome):

- This rare sporadic or familial genetic condition is usually due to inactivating mutations of the glucocorticoid receptor gene.
- The therapy of this syndrome is high doses of synthetic glucocorticoids such as dexamethasone with no inherent mineralocorticoid activity.

C-Cushing's syndrome:

(usually the result of bilateral adrenal hyperplasia secondary to an ACTH secreting pituitary adenoma

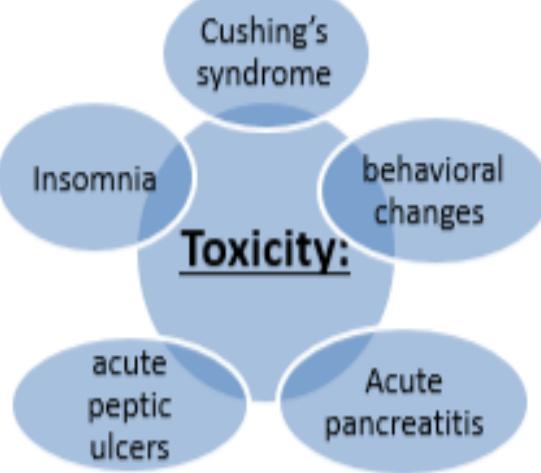
- This disorder is treated by surgical removal of the tumor producing ACTH or cortisol, irradiation of the pituitary tumor, or resection of one or both adrenals.
- These patients must receive large doses of cortisol during and after the surgical procedure.
- Doses of up to 300 mg of soluble hydrocortisone may be given as a continuous intravenous infusion on the day of surgery.

- These patients must receive large doses of cortisol during and after the surgical procedure.
- Doses of up to 300 mg of soluble hydrocortisone may be given as a continuous intravenous infusion on the day of surgery.

Some therapeutic indications for the use of glucocorticoids in nonadrenal disorders:

- Allergic reactions
- Collagen-vascular Disorders
- GIT Diseases
- Eye diseases
- Hematologic Disorders
- Systemic Inflammation
- Infections
- Inflammatory conditions of bones and joints
- Nausea and Vomiting
- Neurologic disorders
- Pulmonary Diseases
- Organ transplants
- thyroid diseases
- renal disorders
- skin diseasea
- miscellaneous: hypercalcemia, mountain sickness

Toxicity:



Contraindications & Cautions:

A- Special Precautions :

- Patients receiving glucocorticoids must be monitored carefully .
- The dosage should be kept as low as possible.

B- Contraindications :

- Glucocorticoids must be used with great caution in patients with:
 - peptic ulcer
 - heart disease or hypertension with heart failure
 - certain infectious illnesses such as varicella and tuberculosis
 - psychoses , diabetes
 - osteoporosis , glaucoma

▪ MINERALOCORTICOIDS (ALDOSTERONE, DEOXYCORTICOSTERONE, FLUDROCORTISONE)

Physiologic and Pharmacologic Effects:

- Mineralocorticoids act by binding to the mineralocorticoid receptor in the cytoplasm of target cells, especially principal cells of the distal convoluted and collecting tubules of the kidney.
- The major effect of activation of the aldosterone receptor is increased expression of Na^+/K^+ -ATPase and the epithelial sodium channel (ENaC).

B- Metabolism:

- The half-life of aldosterone injected in tracer quantities is 15–20 minutes.
- The metabolism of aldosterone is similar to that of cortisol.

Aldosterone

synthesized mainly in the zona glomerulosa of the adrenal cortex.

ACTH produces a moderate stimulation of its release.

aldosterone is no less than one third as effective as cortisol in suppressing ACTH

Without ACTH, aldosterone secretion falls to about half the normal rate.

Deoxycorticosterone (DOC)

Its half-life when injected into the human circulation is about 70 minutes.

The control of its secretion differs from that of aldosterone in that the secretion of DOC is primarily under the control of ACTH.

Although the response to ACTH is enhanced by dietary sodium restriction

Fludrocortisone

This compound, a potent steroid with both glucocorticoid and mineralocorticoid activity.

Oral doses of 0.1 mg two to seven times weekly have potent salt-retaining activity and are used in the treatment of adrenocortical insufficiency associated with mineralocorticoid deficiency

These dosages are too small to have important anti-inflammatory or antigrowth effects.

ADRENAL ANDROGENS

- The adrenal cortex secretes large amounts of DHEA and smaller amounts of androstenedione and testosterone.
- Although these androgens are thought to contribute to the normal maturation process, they do not stimulate or support major androgen-dependent pubertal changes in humans.
- Additional effects may be exerted through an interaction with the GABA and glutamate receptors in the brain or with a nuclear receptor in several central and peripheral sites.
- The androgenic or estrogenic actions of DHEA could explain the effects of the

compound in both situations.

■ ANTAGONISTS OF ADRENOCORTICAL AGENTS

SYNTHESIS INHIBITORS

GLUCOCORTICOID ANTAGONISTS

- Inhibitors of steroid synthesis act at several different steps and one glucocorticoid antagonist acts at the receptor level.

Aminoglutethimide:

- Blocks the conversion of cholesterol to pregnenolone and causes a reduction in the synthesis of all hormonally active steroids.
- Eliminates estrogen production in patients with carcinoma of the breast.
- It can be used in patients with Cushing's syndrome.

Metyrapone:

- is a relatively selective inhibitor of steroid 11-hydroxylation, interfering with cortisol and corticosterone synthesis.
- measure of the capacity of the anterior pituitary to produce ACTH.
- Metyrapone is the only adrenal-inhibiting medication that can be administered to pregnant women with Cushing's syndrome.
- The major adverse effects observed are salt and water retention and hirsutism.

Trilostane:

- Trilostane is a 3β -17-hydroxysteroid-dehydrogenase inhibitor that interferes with the synthesis of adrenal and gonadal hormones and is comparable to aminoglutethimide.
- Trilostane's adverse effects are predominantly gastrointestinal.

Abiraterone:

- Is the newest of the steroid synthesis inhibitors to be approved.
- It blocks 17 α -hydroxylase (P450c17) and 17,20-lyase and predictably reduces synthesis of cortisol.

- Abiraterone is an orally active steroid prodrug and is approved for the treatment of refractory prostate cancer.

Mifepristone (RU-486) :

- Mifepristone is a pharmacologic antagonist at the steroid receptor.
- This compound has strong antiprogestin activity and initially was proposed as a contraceptive-contragestive agent.
- Mifepristone causes generalized glucocorticoid resistance.
- Given orally to several patients with Cushing's syndrome due to ectopic ACTH production or adrenal carcinoma.

MINERALOCORTICO

ID ANTAGONISTS

Spironolactone:

- Its onset of action is slow.
- It is used in the treatment of primary aldosteronism.
- It has been useful in establishing the diagnosis in some patients and in ameliorating the signs and symptoms when surgical removal of an adenoma is delayed.
- Spironolactone is also useful in preparing these patients for surgery.
- Spironolactone is also an androgen antagonist and as such is sometimes used in the treatment of hirsutism in women.
- Adverse effects reported for spironolactone include hyperkalemia, cardiac arrhythmia, menstrual abnormalities, gynecomastia, sedation, headache, gastrointestinal

disturbances, and skin rashes.

Eplerenone:

- Another aldosterone antagonist is approved for the treatment of hypertension.
- This aldosterone receptor antagonist is somewhat more selective than spironolactone and has no reported effects on androgen receptors.
- The most common toxicity is hyperkalemia, but this is usually mild.

Drospirenone:

- A progestin, in an oral contraceptive
- Also antagonizes the effects of aldosterone.

40

the Gonadal hormones & Inhibitors

THE OVARY (ESTROGENS, PROGE STS OTHER OVARIAN HORMONES, ORAL CONTRACEPTIVES, INHIBITORS & ANTAGONISTS, & OVULATION- INDUCING AGENTS)

- The mechanism responsible for the onset of ovarian function at the time of puberty is thought to be neural in origin, because the

immature gonad can be stimulated by gonadotropins already present in the pituitary and because the pituitary is responsive to exogenous hypothalamic gonadotropin-releasing hormone.

- The change of ovarian function at puberty is called gonadarche. A year or so after gonadarche, sufficient estrogen is produced to induce endometrial changes and periodic bleeding (**menarche**).
- After the first few irregular cycles, which may be anovulatory, normal cyclic function is established.

*The ovary normally ceases its gametogenic and endocrine function with time.

- This change is accompanied by a cessation in uterine bleeding

(menopause) and occurs at a mean age of 52 years in the USA.

- Although the ovary ceases to secrete estrogen, significant levels of estrogen persist in many women as a result of conversion of adrenal and ovarian steroids such as androstenedione to estrone and estradiol in adipose and possibly other nonendocrine tissues.

periods of amenorrhea or anovulatory cycles are self-limited.

- They are often associated with emotional or physical stress and reflect temporary alterations in the stress centers in the brain that control the secretion of GnRH.

- Anovulatory cycles are also associated with eating disorders (bulimia, anorexia nervosa) and with severe exercise such as distance running and swimming.

- Normal ovarian function can be modified by androgens produced by the adrenal cortex or tumors arising from it.

- The ovary also gives rise to androgen-producing neoplasms such as arrhenoblastomas, as well as to estrogen-producing granulosa cell tumors.

Disturbances in Ovarian Function

- A minority of these result from inflammatory or neoplastic processes that influence the functions of the uterus, ovaries, or pituitary.
- Many of the minor disturbances leading to

THE ESTROGENS

- Estrogen-mimetic compounds (flavonoids) are found in many plants, including saw palmetto, and soybeans and other foods.

Natural Estrogens

- The major estrogens produced by women are **estradiol** (estradiol- 17 β , E2), **estrone** (E1), and **estriol** (E3) (Figure 40–2). Estradiol is the major secretory product of the ovary.

- Although some estrone is produced in the ovary, most estrone and estriol are formed in the liver from estradiol or in peripheral tissues from androstenedione and other androgens.

- During the first part of the menstrual cycle estrogens are produced in the ovarian follicle by the theca and

granulosa cells.

- After ovulation, the estrogens as well as progesterone are synthesized by the luteinized granulosa and theca cells of the corpus luteum, and the pathways of biosynthesis are slightly different.

- During pregnancy, a large amount of estrogen is synthesized by the fetoplacental unit—consisting of the fetal adrenal zone, secreting androgen precursor, and the placenta, which aromatize it into estrogen.
- The estriol synthesized by the fetoplacental unit is released into the maternal circulation and excreted into the urine.
- In normal women, estradiol is produced at a rate that varies during the menstrual cycle, resulting in plasma levels as low as 50 pg/mL in the early follicular

phase to as high as 350–850 pg/mL at the time of the preovulatory peak.

diffusion into cells, and it is the free fraction that is physiologically active.

- Estradiol is converted by the liver and other tissues to estrone and estriol and their hydroxylated derivatives and conjugated metabolites (which are too insoluble in lipid to cross the cell membrane readily) and excreted in the bile.

Synthetic Estrogens

- A variety of chemical alterations have been applied to the natural estrogens.

- The most important effect of these alterations has been to increase their oral effectiveness.

Pharmacokinetics

- In the circulation, estradiol binds strongly to an α_2 globulin (sex hormone-binding globulin [SHBG]) and with lower affinity to albumin.
- Bound estrogen is relatively unavailable for

Physiologic Effects

A. Mechanism

- Estrogens in the blood and interstitial fluid are bound to SHBG, from which they dissociate to cross the cell membrane, enter the nucleus, and bind to their receptor.
- Two genes code for two

estrogen receptor isoforms. Recently, all steroid receptors except the mineralocorticoid receptors were shown to have palmitoylation motifs that allow enzymatic addition of palmitate and increased localization of the receptors in the vicinity of plasma membranes.

- Such receptors are available for direct interactions with, and effects on, various membrane-associated or cytoplasmic proteins without the need for entry into the nucleus and induction of transcriptional actions.

B. Female Maturation

- Estrogens are required for the normal sexual maturation and growth of the female. They stimulate the development of the vagina,

uterus, and uterine tubes as well as the secondary sex characteristics.

C. Endometrial Effects

- Estrogen plays an important role in the development of the endometrial lining.
- When estrogen production is properly coordinated with the production of progesterone during the normal human menstrual cycle, regular periodic bleeding and shedding of the endometrial lining occur.
- Continuous exposure to estrogens for prolonged periods leads to hyperplasia of the endometrium that is usually associated with abnormal bleeding patterns.

D. Metabolic and Cardiovascular Effects

- Estrogens alter the production and activity of many other proteins in the body.
- Metabolic alterations in the liver are especially important, so that there is a higher circulating level of proteins such as transcortin (corticosteroid-binding globulin [CBG]), thyroxine-binding globulin (TBG), SHBG, transferrin, renin substrate, and fibrinogen.
- This leads to increased circulating levels of thyroxine, estrogen, testosterone, iron, copper, and other substances.
- Alterations in the composition of the plasma lipids caused by estrogens are characterized by an increase in the high-density lipoproteins (HDL), a slight reduction in the low-density lipoproteins (LDL), and a reduction in total plasma cholesterol levels.

E. Effects on Blood Coagulation

- Estrogens enhance the coagulability of blood. Many changes in factors influencing coagulation have been reported, including increased circulating levels of factors II, VII, IX, and X and decreased antithrombin III, partially as a result of the hepatic effects mentioned above.
- Increased plasminogen levels and decreased platelet adhesiveness have also been found.

F. Other Effects

- Estrogens induce the synthesis of progesterone receptors. They may influence behavior and libido in humans.
- Administration of

estrogens stimulates central components of the stress system, including the production of corticotropin-releasing hormone and the activity of the sympathetic system, and promotes a sense of well-being when given to women who are estrogen-deficient.

- They also facilitate the loss of intravascular fluid into the extracellular space, producing edema.
- The resulting decrease in plasma volume causes a compensatory retention of sodium and water by the kidney. Estrogens also modulate sympathetic nervous system control of smooth muscle function.

Clinical Uses

A. Primary

Hypogonadism

- Treatment of primary hypogonadism is usually begun at 11–13 years of age in order to stimulate the development of secondary sex characteristics and menses, to stimulate optimal growth, to prevent osteoporosis, and to avoid the psychological consequences of delayed puberty and estrogen deficiency.
- Treatment attempts to mimic the physiology of puberty.
 - It is initiated with small doses of estrogen (0.3 mg conjugated estrogens or 5–10 mcg ethinyl estradiol) on days 1–21 each month and is slowly increased to adult doses and then maintained until the age of menopause (approximately 51 years of age).

B. Postmenopausal Hormonal Therapy

- If the main indication for therapy is hot flushes and sleep disturbances, therapy with the lowest dose of estrogen required for symptomatic relief is recommended.
- Treatment may be required for only a limited period of time and the possible increased risk for breast cancer avoided.
 - In women who have undergone hysterectomy, estrogens alone can be given 5 days per week or continuously, since progestins are not required to reduce the risk for endometrial hyperplasia and cancer.
 - Hot flushes, sweating, insomnia, and atrophic vaginitis are generally relieved by estrogens; many patients experience some
- Patients at low risk of developing osteoporosis who manifest only mild atrophic vaginitis can be treated with topical preparations.
 - The vaginal route of application is also useful in the treatment of urinary tract symptoms in these patients.
 - It is important to realize, however, that although locally administered estrogens escape the first-pass effect (so that some undesirable hepatic effects are reduced), they are almost completely absorbed into the circulation, and these preparations should be given cyclically.
 - The administration of estrogen is associated with an increased risk of endometrial carcinoma.

increased sense of well-being; and climacteric depression and other psychopathologic states are improved.

- The administration of a progestational agent with the estrogen prevents endometrial hyperplasia and markedly reduces the risk of this cancer.

- Estrogens may also be administered vaginally or transdermally.

- When estrogens are given by these routes, the liver is bypassed on the first circulation, and the ratio of the liver effects to peripheral effects is reduced.

- In patients in whom estrogen replacement therapy is contraindicated, such as those with estrogen-sensitive tumors, relief of vasomotor symptoms may be obtained by the use of clonidine.

C. Other Uses

- Estrogens combined with progestins can be used to suppress ovulation in

patients with intractable dysmenorrhea or when suppression of ovarian function is used in the treatment of hirsutism and amenorrhea due to excessive secretion of androgens by the ovary.

- Under these circumstances, greater suppression may be needed, and oral contraceptives containing 50 mcg of estrogen or a combination of a low estrogen pill with GnRH suppression may be required.

Adverse Effects

A. Uterine Bleeding

- Estrogen therapy is a major cause of postmenopausal uterine

bleeding. Unfortunately, vaginal bleeding at this time of life may also be due to carcinoma of the endometrium.

- To avoid confusion, patients should be treated with the smallest amount of estrogen possible.
- It should be given cyclically so that bleeding, if it occurs, will be more likely to occur during the withdrawal period.
 - As noted above, endometrial hyperplasia can be prevented by administration of a progestational agent with estrogen in each cycle.

B. Cancer

- The relation of estrogen therapy to cancer continues to be the subject of active investigation.
- Although no adverse effect of short- term estrogen

therapy on the incidence of breast cancer has been demonstrated, a small increase in the incidence of this tumor may occur with prolonged therapy.

- Although the risk factor is small (1.25), the impact may be great since this tumor occurs in 10% of women, and addition of progesterone does not confer a protective effect.
- Studies indicate that following unilateral excision of breast cancer, women receiving tamoxifen (an estrogen partial agonist) show a 35% decrease in contralateral breast cancer compared with controls.
- These studies also demonstrate that tamoxifen is well tolerated by most patients, produces estrogen-like alterations in plasma lipid levels, and stabilizes bone mineral loss.
- Studies bearing on the

possible efficacy of tamoxifen and raloxifene in postmenopausal women at high risk for breast cancer show decreases of risk for at least 5 years, but of unknown further duration.

- A recent study shows that postmenopausal hormone replacement therapy with estrogens plus progestins was associated with greater breast epithelial cell proliferation and breast epithelial cell density than estrogens alone or no replacement therapy.
- Furthermore, with estrogens plus progestins, breast proliferation was localized to the terminal duct-lobular unit of the breast, which is the main site of development of breast cancer.
- Thus, further studies are needed to conclusively assess the possible association between

progestins and breast cancer risk.

C. Other Effects

• Nausea and breast tenderness are common and can be minimized by using the smallest effective dose of estrogen.

• Hyperpigmentation also occurs. Estrogen therapy is associated with an increase in frequency of migraine headaches as well as cholestasis, gallbladder disease, and hypertension

• Estrogens should not be used in patients with estrogen-dependent neoplasms such as carcinoma of the endometrium or in those with—or at high risk for—

carcinoma of the breast.

- They should be avoided in patients with undiagnosed genital bleeding, liver disease, or a history of thromboembolic disorder.
- In addition, the use of estrogens should be avoided

were developed to avoid this effect.

- When administered transdermally, 50–100 mcg of estradiol has effects similar to those of 0.625–1.25 mg of conjugated oral estrogens on gonadotropin concentrations, endometrium, and vaginal epithelium.

- Furthermore, the transdermal estrogen preparations do not significantly increase the concentrations of renin substrate, CBG, and TBG and do not produce the characteristic changes in serum lipids.

- Combined oral preparations containing 0.625 mg of conjugated estrogens and 2.5 mg of medroxyprogesterone acetate are available for menopausal replacement therapy.

- Tablets containing 0.625

Preparations & Dosages

- For a given level of gonadotropin suppression, oral estrogen preparations have more effect on the circulating levels of CBG, SHBG, and a host of other liver proteins, including angiotensinogen, than do transdermal preparations.
- The oral route of administration allows greater concentrations of hormone to reach the liver, thus increasing the synthesis of these proteins.
- Transdermal preparations



mg of conjugated estrogens and 5 mg of medroxyprogesterone acetate are available to be used in conjunction with conjugated estrogens in a sequential fashion.

- Estrogens alone are taken on days 1–14 and the combination on days 15–28.

Synthetic Progestins

- A variety of progestational compounds have been synthesized.
- Some are active when given by mouth.

Natural Progestins: Progesterone

- Progesterone is the most important progestin in humans.
- In addition to having important hormonal effects, it serves as a precursor to the estrogens, androgens, and adrenocortical steroids.
- It is synthesized in the ovary, testis, and adrenal cortex from circulating cholesterol.

*They are not a uniform group of compounds, and all of them differ from progesterone in one or more respects.

- Table 40–2 lists some of these compounds and their e

Pharmacokinetics

- Progesterone is rapidly absorbed following administration by any route.
- Its half-life in the plasma is approximately 5 minutes, and small amounts are stored temporarily in body fat. In the liver, progesterone is metabolized to pregnanediol and conjugated with glucuronic acid.

- It is excreted into the urine as pregnanediol glucuronide.
- The amount of pregnanediol in the urine has been used as an index of progesterone secretion.
- This measure has been very useful despite the fact that the proportion of secreted progesterone

converted to this compound varies from day to day and from individual to individual.

- In addition to progesterone, 20α - and 20β -hydroxyprogesterone (20α - and 20β -hydroxy-4-pregnene-3-one) are also found.
- These compounds have about one fifth the progestational activity of progesterone in humans and other species.
- Little is known of their physiologic role, but 20α -hydroxyprogesterone is produced in large amounts in some species and may be of some importance biologically.

Physiologic Effects

A. Mechanism

- The mechanism of action of progesterone—described in more detail above—is similar to that of other steroid hormones.
- Progestins enter the cell and bind to progesterone receptors that are distributed between the nucleus and the cytoplasm.
- The ligand-receptor complex binds to a progesterone response element (PRE) to activate gene transcription.
- The progesterone-receptor complex forms a dimer before binding to DNA. Like the estrogen receptor, it can form heterodimers as well as homodimers between two isoforms, A and B.
- These isoforms are produced by alternative splicing of the same gene.

B. Effects of Progesterone

- Progesterone has little effect on protein metabolism.
- It stimulates lipoprotein lipase activity and seems to favor fat deposition.
- The effects on carbohydrate metabolism are more marked. Progesterone increases basal insulin levels and the insulin response to glucose.
- There is usually no manifest change in carbohydrate tolerance.
- In the liver, progesterone promotes glycogen storage, possibly by facilitating the effect of insulin.
- Progesterone also promotes keto- genesis.
- Progesterone is responsible for the alveolobular development of

the secretory apparatus in the breast.

- It also participates in the preovulatory LH surge and causes the maturation and secretory changes in the endometrium that are seen following ovulation.
- Progesterone decreases the plasma levels of many amino acids and leads to increased urinary nitrogen excretion.
- It induces changes in the structure and function of smooth endoplasmic reticulum in experimental animals.

C. Synthetic Progestins

- The 21-carbon progesterone analogs antagonize aldosterone-induced sodium retention.
- The remaining compounds ("19-

nortestosterone" third-generation agents) produce a decidual change in the endometrial stroma, do not support pregnancy in test animals, are more effective gonadotropin inhibitors, and may have minimal estrogenic and androgenic or anabolic activity.

- They are sometimes referred to as "impeded androgens." Progestins without androgenic activity include desogestrel, norgestimate, and gestodene.
- The first two of these compounds are dispensed in combination with ethinyl estradiol for oral contraception in the USA.
- Oral contraceptives containing the progestins cyproterone acetate (also an antiandrogen) in combination with ethinyl

Physiologic Effects

A. Therapeutic Applications

- The major uses of progestational hormones are for hormone replacement therapy and hormonal contraception.
- In addition, they are useful in producing long-term ovarian suppression for other purposes.
 - When used alone in large doses parenterally (eg, medroxyprogesterone acetate, 150 mg intramuscularly every 90 days), prolonged anovulation and amenorrhea result.
 - This therapy has been employed in the treatment of dysmenorrhea, endometriosis, and bleeding disorders when estrogens are contraindicated, and for

contraception.

- The major problem with this regimen is the prolonged time required in some patients for ovulatory function to return after cessation of therapy.
- It should not be used for patients planning a pregnancy in the near future.
- Similar regimens will relieve hot flushes in some menopausal women and can be used if estrogen therapy is contraindicated.
- When progestational agents were administered to patients with previous abortions, a salvage rate of 80% was achieved
- It is now recognized that similar patients abort only 20% of the time even when untreated.
- On the other hand, progesterone was given experimentally to delay premature labor with encouraging results.

B. Diagnostic Uses

- Progesterone can be used as a test of estrogen secretion.
- The administration of progesterone, 150 mg/d, or medroxyprogesterone, 10 mg/d, for 5–7 days, is followed by withdrawal bleeding in amenorrheic patients only when the endometrium has been stimulated by estrogens.
- A combination of estrogen and progestin can be given to test the responsiveness of the endometrium in patients with amenorrhea.

- Studies of progestational compounds alone and with combination oral contraceptives indicate that the progestin in these agents may increase blood pressure in some patients.
- The more androgenic progestins also reduce plasma HDL levels in women.
- Two recent studies suggest that combined progestin plus estrogen replacement therapy in postmenopausal women may increase breast cancer risk significantly compared with the risk in women taking estrogen alone.
- These findings require careful examination and if confirmed will lead to important changes in postmenopausal hormone replacement practice.

exert their contraceptive effect largely through selective inhibition of pituitary function that results in inhibition of ovulation

HORMONAL CONTRACEPTION
(ORAL, PARENTERAL, & IMPLANTED)

Pharmacologic Effects

- A large number of oral contraceptives containing estrogens or progestins (or both) are now available for clinical use. These preparations vary chemically and pharmacologically and have many properties in common as well as definite differences important for the correct selection of the optimum agent.

- The combination agents also produce a change in the cervical mucus, in the uterine endometrium, and in motility and secretion in the uterine tubes, all of which decrease the likelihood of conception and implantation.
- The continuous use of progestins alone does not always inhibit ovulation.

A. Mechanism of Action

- The combinations of estrogens and progestins

B. Effects on the Ovary

- Chronic use of

combination agents depresses ovarian function. Follicular development is minimal, and corpora lutea, larger follicles, stromal edema, and other morphologic features normally seen in ovulating women are absent.

- The ovaries usually become smaller even when enlarged before therapy.
- The great majority of patients return to normal menstrual patterns when these drugs are discontinued.
- About 75% will ovulate in the first posttreatment cycle and 97% by the third posttreatment cycle.
- About 2% of patients remain amenorrheic for periods of up to several years after administration is stopped.
- The cytologic findings on vaginal smears vary depending on the preparation used.

- However, with almost all of the combined drugs, a low maturation index is found because of the presence of progestational agents.

C. Effects on the Uterus

- After prolonged use, the cervix may show some hypertrophy and polyp formation.
- There are also important effects on the cervical mucus, making it more like postovulation mucus, ie, thicker and less copious.
- Agents containing both estrogens and progestins produce further morphologic and biochemical changes of the endometrial stroma under the influence of the progestin, which also stimulates glandular secretion throughout the luteal phase.
- The agents containing

“19-nor” progestins—particularly those with the smaller amounts of estrogen—tend to produce more glandular atrophy and usually less bleeding.

D. Effects on the Breast

- Stimulation of the breasts occurs in most patients receiving estrogen-containing agents.

- Some enlargement is generally noted.
- The administration of estrogens and combinations of estrogens and progestins tends to suppress lactation.
- When the doses are small, the effects on breast-feeding are not appreciable.
- Studies of the transport of the oral contraceptives into breast milk suggest that only small amounts of these compounds cross into the milk, and they have not been

considered to be of importance.

E. Other Effects of Oral Contraceptives

1. Effects on the central nervous system

- The central nervous system effects of the oral contraceptives have not been well studied in humans.
- A variety of effects of estrogen and progesterone have been noted in animals.
- Estrogens tend to increase excitability in the brain, whereas progesterone tends to decrease it.
- The thermogenic action of progesterone and some of the synthetic progestins is also thought to occur in the central nervous system

2. Effects on endocrine function

- The inhibition of pituitary gonadotropin secretion has been mentioned.
- Estrogens also alter adrenal structure and function.
- Estrogens given orally or at high doses increase the plasma concentration of the α globulin that binds cortisol (corticosteroid-binding globulin).
- Plasma concentrations may be more than double the levels found in untreated individuals, and urinary excretion of free cortisol is elevated.

3. Effects on blood

- Serious thromboembolic phenomena occurring in women taking oral contraceptives gave rise to a

great many studies of the effects of these compounds on blood coagulation.

- A clear picture of such effects has not yet emerged.
- The oral contraceptives do not consistently alter bleeding or clotting times.
- The changes that have been observed are similar to those reported in pregnancy.

4. Effects on the liver

- These hormones also have profound effects on the function of the liver.
- Some of these effects are deleterious and will be considered below in the section on adverse effects.
- The effects on serum proteins result from the effects of the estrogens on the synthesis of the various α_2 globulins and fibrinogen.
- Serum haptoglobins produced in the liver are depressed rather than increased by estrogen.

- Some of the effects on carbohydrate and lipid metabolism are probably influenced by changes in liver metabolism.
- Important alterations in hepatic drug excretion and metabolism also occur.

5. Effects on lipid metabolism

- As noted above, estrogens increase serum triglycerides and free and esterified cholesterol.
- Phospholipids are also increased, as are HDL; levels of LDL usually decrease.
- Although the effects are marked with doses of 100 mcg of mestranol or ethinyl estradiol, doses of 50 mcg or less have minimal effects.
- The progestins (particularly the “19-nortestosterone” derivatives) tend to antagonize these

effects of estrogen.

- Preparations containing small amounts of estrogen and a progestin may slightly decrease triglycerides and HDL.

6. Effects on carbohydrate metabolism

- The administration of oral contraceptives produces alterations in carbohydrate metabolism similar to those observed in pregnancy.
- There is a reduction in the rate of absorption of carbohydrates from the gastrointestinal tract.
- Progesterone increases the basal insulin level and the rise in insulin induced by carbohydrate ingestion.
- Preparations with more potent progestins such as norgestrel may cause progressive decreases in carbohydrate tolerance over

several years.

- However, the changes in glucose tolerance are reversible on discontinuing medication.

7. Effects on the cardiovascular system

- These agents cause small increases in cardiac output associated with higher systolic and diastolic blood pressure and heart rate.
 - The pressure returns to normal when treatment is terminated.
 - Although the magnitude of the pressure change is small in most patients, it is marked in a few.
 - It is important that blood pressure be followed in each patient.
 - An increase in blood pressure has been reported to occur in a few postmenopausal women treated with estrogens alone.

8. Effects on the skin

- The oral contraceptives have been noted to increase pigmentation of the skin (chloasma).
 - This effect seems to be enhanced in women with dark complexions and by exposure to ultraviolet light.
 - Some of the androgen-like progestins might increase the production of sebum, causing acne in some patients.
 - However, since ovarian androgen is suppressed, many patients note decreased sebum production, acne, and terminal hair growth.
 - The sequential oral contraceptive preparations as well as estrogens alone often decrease sebum production.

Clinical Uses

- The most important use of combined estrogens and progestins is for oral contraception.
- A large number of preparations are available for this specific purpose. They are specially packaged for ease of administration.
- In general, they are very effective; when these agents are taken according to directions, the risk of conception is extremely small.
 - The pregnancy rate with combination agents is estimated to be about 5–12 per 100 woman years at risk.
 - (Under conditions of perfect adherence, the pregnancy rate would be 0.5–1 per 100 woman years.)
 - Contraceptive failure has been observed in some patients when one or more doses are missed, if phenytoin is also being used

(which may increase catabolism of the compounds), or if antibiotics are taken that alter enterohepatic cycling of metabolites

- The incidence of serious known toxicities associated with the use of these drugs is low—far lower than the risks associated with pregnancy.
- There are a number of reversible changes in intermediary metabolism.
 - Minor adverse effects are frequent, but most are mild and many are transient.
 - Continuing problems may respond to simple changes in pill formulation.
 - Although it is not often necessary to discontinue medication for these reasons, as many as one third of all

patients started on oral contraception discontinue use for reasons other than a desire to become pregnant.

1. Nausea, mastalgia, breakthrough bleeding, and edema

2. Changes in serum proteins and other effects on endocrine function

3. Headache is mild and often transient.

4. Withdrawal bleeding sometimes fails to occur—most often with combination preparations—and may cause confusion with regard to pregnancy.

• Any of the following may require discontinuance of oral contraceptives:

1. Breakthrough bleeding is the most common problem in using progestational agents alone for

contraception.

2. Weight gain is more common with the combination agents containing androgen-like progestins.

3. Increased skin pigmentation may occur, especially in dark-skinned women. It is thought to be exacerbated by vitamin B deficiency. It is often reversible upon discontinuance of medication but may disappear very slowly.

4. Acne may be exacerbated by agents containing androgen-like progestins, whereas agents containing large amounts of estrogen usually cause marked improvement in acne.

5. Hirsutism may also be aggravated by the “19-nortestosterone” derivatives, and combinations containing nonandrogenic progestins are preferred in

these patients.

6. Ureteral dilation similar to that observed in pregnancy has been reported.

7. Vaginal infections are more common and more difficult to treat in patients who are using oral contraceptives.

8. Amenorrhea occurs in some patients. Patients who have had menstrual irregularities before taking oral contraceptives are particularly susceptible to prolonged amenorrhea

the serious unanticipated effects to be reported and has been the most thoroughly studied

a. Venous thromboembolic disease

- Superficial or deep thromboembolic disease in women not taking oral contraceptives occurs in about 1 patient per 1000 woman years.
- The overall incidence of these disorders in patients taking low-dose oral contraceptives is about threefold higher.
- The risk for this disorder is increased during the first month of contraceptive use and remains constant for several years or more.

C. Severe Adverse Effects

1. Vascular disorders

- Thromboembolism was one of the earliest of

b. Myocardial infarction

- The use of oral

contraceptives is associated with a slightly higher risk of myocardial infarction in women who are obese, have a history of preeclampsia or hypertension, have hyperlipoproteinemia or diabetes.

- There is a much higher risk in women who smoke.
- The risk attributable to oral contraceptives in women 30–40 years of age who do not smoke is about 4 cases per 100,000 users per year, as compared with 185 cases per 100,000 among women 40–44 who smoke heavily.

c. Cerebrovascular disease

- The risk of stroke is concentrated in women over age 35.
- It is increased in

current users of oral contraceptives but not in past users.

- However, subarachnoid hemorrhages have been found to be increased among both current and past users and may increase with time.
- The risk of thrombotic or hemorrhagic stroke attributable to oral contraceptives (based on older, higher-dose preparations) has been estimated to about 37 cases per 100,000 users per year.

2. Gastrointestinal disorders

- Many cases of cholestatic jaundice have been reported in patients taking progestin-containing drugs.

- The differences in incidence of these disorders from one population to another suggest that genetic factors may be involved.

- The jaundice caused by these agents is similar to that produced by other 17-alkyl-substituted steroids.

- It is most often observed in the first three cycles and is particularly common in women with a history of cholestatic jaundice during pregnancy.

- Jaundice and pruritus disappear 1–8 weeks after the drug is discontinued.

3. Depression

- Depression of sufficient degree to require cessation of therapy occurs in about

6% of patients treated with some preparations.

4. Cancer

- The occurrence of malignant tumors in patients taking oral contraceptives has been studied extensively.

- It is now clear that these compounds reduce the risk of endometrial and ovarian cancer.

- The lifetime risk of breast cancer in the population as a whole does not seem to be affected by oral contraceptive use.

- Some studies have shown an increased risk in younger women, and it is possible that tumors that develop in younger women become clinically apparent sooner.

5. Other

- In addition to the above effects, a number of other adverse reactions have been reported for which a causal relation has not been established.
 - These include alopecia, erythema multiforme, erythema nodosum, and other skin disorders.

- They should not be used to treat vaginal bleeding when the cause is unknown.
- They should be avoided in patients with known or suspected tumors of the breast or other estrogen-dependent neoplasms.
- Since these preparations have caused aggravation of preexisting disorders, they should be avoided or used with caution in patients with liver disease, asthma, eczema, migraine, diabetes, hypertension, optic neuritis, retrobulbar neuritis, or convulsive disorders.
- The oral contraceptives may produce edema, and for that reason they should be used with great caution in patients in heart failure or

Contraindications & Cautions

- These drugs are contraindicated in patients with thrombophlebitis, thromboembolic phenomena, and cardiovascular and cerebrovascular disorders or a past history of these conditions.



in whom edema is otherwise undesirable or dangerous.

- Estrogens may increase the rate of growth of fibroids.
- Therefore, for women with these tumors, agents with the smallest amounts of estrogen and the most androgenic progestins should be selected.
- The use of progestational agents alone for contraception might be especially useful in such patient.

suited for use in patients for whom estrogen administration is undesirable.

- They are about as effective as intrauterine devices or combination pills containing 20–30 mcg of ethinyl estradiol.

• There is a high incidence of abnormal bleeding.

- Contraception with progestins is useful in patients with hepatic disease, hypertension, psychosis or mental retardation, or prior thromboembolism.

- The side effects include headache, dizziness, bloating and weight gain of 1–2 kg, and a reversible reduction of glucose tolerance.

Contraception with Progestins Alone

- Small doses of progestins administered orally or by implantation under the skin can be used for contraception.

- They are particularly

Beneficial Effects of Oral Contraceptives

- It has become apparent that reduction in the dose of the constituents of oral contraceptives has markedly reduced mild and severe adverse effects, providing a relatively safe and convenient method of contraception for many young women.

- Treatment with oral contraceptives has also been shown to be associated with many benefits unrelated to contraception.
 - These include a reduced risk of ovarian cysts, ovarian and endometrial cancer, and

benign breast disease.

- There is a lower incidence of ectopic pregnancy.

ESTROGEN & PROGESTERONE INHIBITORS & ANTAGONISTS

TAMOXIFEN & RELATED PARTIAL AGONIST ESTROGENS

- Tamoxifen a competitive partial agonist inhibitor of estradiol at the estrogen receptor.
- It was the first selective estrogen receptor modulator to be

introduced.

- The mechanism of its mixed 4 agonist/antagonist relations to the estrogen receptor has been intensively studied but is still not completely understood.
- Tamoxifen is extensively used in the palliative treatment of breast cancer in postmenopausal women and is approved for chemoprevention of breast cancer in high-risk women.
- It is a nonsteroidal agent that is given orally.
- Peak plasma levels are reached in a few hours.
- Tamoxifen has an initial half-life of 7–14 hours in the circulation and is predominantly excreted

by the liver.

- It is used in doses of 10–20 mg twice daily.
- Hot flushes and nausea and vomiting occur in 25% of patients, and many other minor adverse effects are observed.
- **Toremifene** is a structurally similar compound with very similar properties, indications, and toxicities.
- **Raloxifene** is another partial estrogen agonist-antagonist at some but not all target tissues.
- Although subject to a high first-pass effect, raloxifene has a very large volume of distribution and a long half life (>24 hours), so it can be taken once a day.
- Newer SERMs have

been developed and one, **Bazedoxifene**, in combination with conjugated estrogens, is approved for treatment of menopausal symptoms and prophylaxis of postmenopausal osteoporosis.

MIFEPRISTONE

- Mifepristone is a “19-norsteroid” that binds strongly to the progesterone receptor and inhibits the activity of progesterone.
- The drug has luteolytic (Degradation of the corpus luteum) properties in 80% of women when given in the mid-luteal period.
- The mechanism of this effect is unknown, but it may provide the basis for using mifepristone as a contraceptive.
- However, because the compound has a long half-life, large doses may prolong the follicular phase of the subsequent cycle and so make it difficult to use continuously for this purpose.
- A single dose of 600 mg is an effective emergency postcoital contraceptive, though it may result in delayed ovulation in the following cycle
- Mifepristone’s major use thus far has been to terminate early pregnancies.
- Doses of 400–600 mg/d for 4 days or 800 mg/d for 2 days successfully terminated pregnancy in over 85% of the women studied.
- The adverse effects of the

medications included vomiting, diarrhea, and abdominal or pelvic pain.

- As many as 5% of patients have vaginal bleeding requiring intervention.
- Because of these adverse effects, mifepristone is administered only by physicians at family planning centers.

surge of LH and FSH and can prevent the compensatory increase in LH and FSH following castration in animals, but it does not significantly lower or suppress basal LH or FSH levels in normal women.

- Danazol binds to androgen, progesterone, and glucocorticoid receptors and can translocate the androgen receptor into the nucleus to initiate androgen-specific RNA synthesis.

• It does not bind to intracellular estrogen receptors, but it does bind to sex

hormone-binding and corticosteroid-binding globulins.

- It inhibits P450scc (the cholesterol side chain-cleaving enzyme), 3 β -hydroxysteroid dehydrogenase, 17 α -hydroxysteroid dehydrogenase, P450c17 (17 α -hydroxylase),

DANAZOL

- Danazol, an isoxazole derivative of ethisterone (17 α -ethinyl-testosterone) with weak progestational, androgenic, and glucocorticoid activities, is used to suppress ovarian function.
- Danazol inhibits the midcycle

P450c11 (11 β -hydroxylase), and P450c21 (21 β -hydroxylase).

- However, it does not inhibit aromatase, the enzyme required for estrogen synthesis.
- It increases the mean clearance

of progesterone, probably by competing with the hormone for binding proteins, and may have similar effects on other active steroid hormones.

- Ethisterone, a major metabolite of danazol, has both progestational and mild androgenic effects.
- Danazol is slowly metabolized

in humans, having a half-life of over 15 hours.

- This results in stable circulating levels when the drug is administered twice daily.
- It is highly concentrated in the

liver, adrenals, and kidneys and is excreted in both feces and urine.

- Danazol has been employed as an inhibitor of gonadal function and has found its major use in the treatment of endometriosis.
 - For this purpose, it can be given in a dosage of 600 mg/d.
 - The dosage is reduced to 400 mg/d after 1 month and to 200 mg/d in 2 months.
 - About 85% of patients show marked improvement in 3–12 months.

OTHER INHIBITORS

- **Anastrozole** and **Letrazole** are selective nonsteroidal inhibitor of aromatase (the enzyme required for estrogen

synthesis) is effective in some women whose breast tumors have become resistant to tamoxifen.

- **Exemestane**, a steroid molecule, is an irreversible inhibitor of aromatase.

Like anastrozole and letrozole, it is approved for use in women with advanced breast cancer.

- **Fulvestrant** is a pure estrogen receptor antagonist that has been somewhat more effective than those with partial agonist effects in some patients who have become resistant to tamoxifen.

OVULATION-INDUCING AGENTS

CLOMIPHENE

- Clomiphene citrate, a partial estrogen agonist.

This compound is well absorbed when taken orally. It has a half-life of 5–7 days and is excreted primarily in the urine.

Pharmacologic Effects

A. Mechanisms of Action.

- In humans it leads to an increase in the secretion of gonadotropins and estrogens by inhibiting estradiol's negative feedback effect on the gonadotropins.

B. Effects

- The pharmacologic importance of this compound rests on its ability to stimulate ovulation in women with oligomenorrhea or

amenorrhea and ovulatory dysfunction.

- The majority of patients suffer from polycystic ovary syndrome, a common disorder affecting about 7% of women of reproductive age.
- The syndrome is characterized by gonadotropin-dependent ovarian hyperandrogenism associated with anovulation and infertility.
- Clomiphene probably blocks the feedback inhibitory influence of estrogens on the hypothalamus, causing a surge of gonadotropins, which leads to ovulation.

Clinical Use

Clomiphene is used in the treatment of disorders of ovulation in patients who wish to become pregnant.

Usually, a single ovulation is induced by a single course of therapy, and the patient must be treated repeatedly until pregnancy is achieved. The compound is of no value in patients with ovarian or pituitary failure.

Adverse Effects

- The most common adverse effects in patients treated with this drug are hot flushes, which resemble those experienced by menopausal patients.
- They tend to be mild, and disappear when the drug is discontinued. There have been occasional

reports of eye symptoms due to intensification and prolongation of afterimages. These are generally of short duration.

- Headache, constipation, allergic skin reactions, and reversible hair loss have been reported occasionally.
- The effective use of clomiphene is associated with some stimulation of the ovaries and usually with ovarian enlargement.
- The degree of enlargement tends to be greater and its incidence higher in patients who have enlarged ovaries at the beginning of therapy.

- Special precautions should be observed in patients with enlarged ovaries.
- These women are thought to be more sensitive to this drug and should receive small doses.
- Any patient who complains of abdominal symptoms should be examined carefully.
- Maximum ovarian enlargement occurs after the 5-day course has been completed, and many patients can be shown to have a palpable increase in ovarian size by the seventh to tenth days.

Special precautions must also be taken in patients who have visual symptoms associated with clomiphene therapy, since these symptoms may make activities such as driving more hazardous

Contraindications & Cautions

THE TESTIS

(ANDROGENS & ANABOLIC STEROIDS, ANTIANDROGENS, & MALE CONTRACEPTION)

- The testis, like the ovary, has both gametogenic and endocrine functions.
- The onset of gametogenic function of the testes is controlled largely by the secretion of FSH by the pituitary.
- High concentrations of testosterone locally are also required for continuing sperm production in the seminiferous tubules. With LH stimulation, testosterone is produced by the interstitial or Leydig cells found in the spaces between the seminiferous tubules

ANDROGENS & ANABOLIC STEROIDS

- In humans, the most important androgen secreted by the testis is testosterone.
- In men, approximately 8 mg of testosterone is produced daily.
- About 95% is produced by the Leydig cells and only 5% by the adrenals.
- The testis also secretes small amounts of another potent androgen, dihydrotestosterone, as well as androstenedione and dehydroepiandrosterone, which are weak androgens.
- Plasma levels of testosterone in males are about 0.6

mcg/dL after puberty and appear to decline after age 50.

- Testosterone is also present in the plasma of women in concentrations of approximately 0.03 mcg/dL and is derived in approximately equal parts from the ovaries and adrenals and by the peripheral conversion of other hormones.

- Changes in the skin include the appearance of pubic, axillary, and beard hair.
- The sebaceous glands become more active, and the skin tends to become thicker and oilier.
- The larynx grows and the vocal cords become thicker, leading to a lower-pitched voice.
- Skeletal growth is stimulated and epiphyseal closure accelerated.
- Androgens play an important role in stimulating and maintaining sexual function in men.
- Metabolic effects include the reduction of hormone binding and other carrier proteins and increased liver synthesis of clotting factors, triglyceride lipase, α 1- antitrypsin,

Physiologic Effects

- In the normal male, testosterone or its active metabolite 5 α -dihydrotestosterone is responsible for the many changes that occur in puberty.
- In addition to the general growth-promoting properties of androgens on body tissues, these hormones are responsible for penile and scrotal growth.

haptoglobin, and sialic acid.

- They also stimulate renal erythropoietin secretion and decrease HDL levels.

Synthetic Steroids with Androgenic & Anabolic Action

- Testosterone, when administered by mouth, is rapidly absorbed.
- However, it is largely converted to inactive metabolites, and only about one sixth of the dose administered is available in active form
- Testosterone and its derivatives

have been used for their anabolic effects as well as in the treatment of testosterone deficiency

Pharmacologic

A. Mechanism of Action

- Like other steroids, testosterone acts intracellularly in target cells.
- In tissues, dihydrotestosterone is the dominant androgen.
- Testosterone and dihydrotestosterone bind to the intracellular androgen receptor, initiating a series of events leading to growth, differentiation, and synthesis of a variety of enzymes and other functional proteins.

B. Effects

- In the male at puberty, androgens cause development of the secondary sex characteristics.

- In the adult male, large doses of testosterone—when given alone—or its derivatives suppress the secretion of gonadotropins and result in some atrophy of the interstitial tissue and the tubules of the testes.
- Since fairly large doses of androgens are required to suppress gonadotropin secretion, it has been postulated that Inhibit (Gonadal hormone), in combination with androgens, is responsible for the feedback control of secretion.
- In women, androgens are capable of producing changes similar to those observed in the prepubertal male.
- These include growth of facial and body hair, deepening of the voice, enlargement of the clitoris, frontal

baldness, and prominent musculature.

- The natural androgens stimulate erythrocyte production.

Clinical Uses

A. Androgen Replacement Therapy in Men

- Androgens are used to replace or augment endogenous androgen secretion in hypogonadal men (Table 40–6).
- Even in the presence of pituitary deficiency, androgens are used rather than gonadotropin except when normal

spermatogenesis is to be achieved.

- In patients with hypopituitarism, androgens are not added to the treatment regimen until puberty, at which time they are instituted in gradually increasing doses to achieve the growth spurt and the

Finally, it is changed to the adult replacement dose of 200 mg at 2-week intervals.

TABLE 40–6 Androgen preparations for replacement therapy.

Drug	Route of Administration	Dosage
Methyltestosterone	Oral	25–50 mg/d
	Sublingual (buccal)	5–10 mg/d
Fluoxymesterone	Oral	2–10 mg/d
Testosterone enanthate	Intramuscular	See text
Testosterone cypionate	Intramuscular	See text
Testosterone	Transdermal	2.5–10 mg/d
	Topical gel (1%)	5–10 g/d

each change-taking place at 3-month intervals.

- The dose is then doubled to 100 mg every 2 weeks until maturation is complete.

B. Gynecologic Disorder

- Androgens are used occasionally in the

treatment of certain gynecologic disorders, but the undesirable effects in women are such that they must be used with great caution.

- Androgens have been used to reduce breast engorgement (Filled with excess) during the postpartum period, usually in conjunction

danazol is used in the treatment of endometriosis.

- They have been used for chemotherapy of breast tumors in premenopausal women.

C. Use as Protein Anabolic Agents

- Androgens and anabolic steroids have been used in conjunction with dietary measures and exercises in an attempt to reverse protein loss after trauma, surgery, or prolonged immobilization and in patients with debilitating diseases.

D. Osteoporosis

- The weak androgen with estrogens.
- Androgens and anabolic agents have been used in the treatment of osteoporosis, either

alone or in conjunction with estrogens.

- With the exception of substitution therapy in hypogonadism, bisphosphonates have largely replaced androgen use for this purpose.

E. Use as Growth Stimulators

- These agents have been used to stimulate growth in boys with delayed puberty.
- If the drugs are used carefully, these children will probably achieve their expected adult height.
- If treatment is too vigorous, the patient may grow rapidly at first but will not achieve full predicted final stature because of the accelerated epiphyseal

closure that occurs.

- It is difficult to control this type of therapy adequately since the action of the hormones on epiphyseal centers may continue for many months after therapy is discontinued.

F. Anabolic Steroid and Androgen Abuse in Sports

- Many athletes and their coaches believe that anabolic steroids in doses 10–200 times larger than the daily normal physiologic production increase strength and aggressiveness, thereby improving competitive performance.
- Such effects have been unequivocally demonstrated only in women.
 - Furthermore, the adverse effects of these drugs clearly make their use inadvisable.

G. Aging

- Androgen production falls with age in men and may contribute to the decline in muscle mass, strength, and libido.
- Preliminary studies of androgen replacement in aging males with low androgen levels show an increase in lean body mass and hematocrit and a decrease in bone turnover.
- Longer studies will be required to assess the usefulness of this therapy.

Adverse Effects

- The adverse effects of these compounds are due largely to their masculinizing actions and are most noticeable in women and prepubertal children.
- In women, the administration of more than 200–300 mg of testosterone per month is usually associated with hirsutism, acne, amenorrhea, clitoral enlargement, and deepening of the voice.
- These effects may occur with even smaller doses in some women.
- Some of the androgenic steroids exert progestational activity, leading to endometrial bleeding upon discontinuation.
- These hormones also alter serum lipids and could conceivably increase susceptibility to atherosclerotic disease in women.
- Except under the most unusual circumstances, androgens should not be used in infants.
- Recent studies in animals suggest that

administration of androgens in early life may have profound effects on maturation of central nervous system centers governing sexual development, particularly in the female.

- Administration of these drugs to pregnant women may lead to masculinization of the external genitalia in the female fetus, or under masculinization of the external genitalia in the male fetus.
- Although the above-mentioned effects may be less marked with the anabolic agents, they do occur. Sodium retention and edema are not common but must be carefully watched for in patients with heart and kidney disease.

- Most of the synthetic androgens and anabolic agents are 17-alkyl-substituted steroids.
- Administration of drugs with this structure is often associated with evidence of hepatic dysfunction.
- Hepatic dysfunction usually occurs early in the course of treatment, and the degree is proportionate to the dose.
- Replacement therapy in men may cause acne, sleep apnea, erythrocytosis, gynecomastia, and azoospermia.

Contraindications & Cautions

- The use of androgenic steroids is contraindicated in pregnant women or women who may

become pregnant during the course of therapy.

- Androgens should not be administered to male patients with carcinoma of the prostate or breast.
- Until more is known about the effects of these hormones on the central nervous system in developing children, they should be avoided in infants and young children.
- Special caution is required in giving these drugs to children to produce a growth spurt. In most patients, the use of somatotropin is more appropriate.
- Care should be exercised in the administration of these drugs to patients with renal or cardiac disease predisposed to edema.

- If sodium and water retention occurs, it will respond to diuretic therapy.

ANDROGEN SUPPRESSION & ANTIANDROGEN

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ANDROGEN SUPPRESSION

- The treatment of advanced prostatic carcinoma often requires orchectomy or large doses of estrogens to reduce available endogenous androgen.
- The psychological effects of the former and gynecomastia produced by the latter make these approaches undesirable.
- The GnRH analogs such as goserelin, nafarelin, buserelin, and leuprolide acetate produce effective gonadal suppression when blood levels are continuous rather than pulsatile.

ANTIANDROGENS

- The potential usefulness of antiandrogens in the treatment of patients producing excessive amounts of testosterone has led to the search for effective drugs that can be used for this purpose.
- Several approaches to the problem, especially inhibition of synthesis and receptor antagonism, have met with some success.

placental aromatase activity.

- It displaces estradiol and dihydrotestosterone from sex hormone-binding protein in vitro and increases the estradiol: testosterone ratio in plasma in vivo by a different mechanism.
- However, it does not appear to be clinically useful in women with increased androgen levels because of the toxicity associated with prolonged use of the 400–800 mg/d required.
- Men treated with ketoconazole often develop reversible gynecomastia during therapy; this may be due to the demonstrated increase in the estradiol: testosterone ratio.

Steroid Synthesis Inhibitors

- **Ketoconazole**, used primarily in the treatment of fungal disease, is an inhibitor of adrenal and gonadal steroid synthesis.
- It does not affect ovarian aromatase, but it reduces human

Conversion of Steroid Precursors

to Androgens

- Several compounds have been developed that inhibit the 17-hydroxylation of progesterone or pregnenolone, thereby preventing the action of the side chain-splitting enzyme and the further transformation of these steroid precursors to active androgens.
- **Abiraterone**, a newer 17 α -hydroxylase inhibitor, has been approved for use in metastatic prostate cancer.
- Since dihydrotestosterone—not testosterone—appears to be the essential androgen in the prostate, androgen effects in this and similar dihydrotestosterone-dependent tissues can be reduced by an inhibitor of 5 α - reductase.
- **Finasteride**, a steroidlike inhibitor of this enzyme, is orally active and causes a reduction in dihydrotestosterone levels that begins within 8 hours after administration and lasts for about 24 hours.
- The half-life is about 8 hours (longer in elderly individuals).
- Finasteride has been reported to be moderately effective in reducing prostate size in men with benign prostatic hyperplasia and is approved for this use.
- The dosage is 5 mg/d.
- **Dutasteride** is a similar orally active steroid derivative with a slow onset of action and a much longer half-life than finasteride.
- It is approved for treatment of benign prostatic hyperplasia at a dosage of 0.5 mg daily.

- These drugs are not approved for use in women or children, although finasteride has been used successfully in the treatment of hirsutism in women and is approved for treatment of early male pattern baldness in men (1 mg/d).

hirsutism and in men to decrease excessive sexual drive and are being studied in other conditions in which the reduction of androgenic effects would be useful.

- Cyproterone acetate in a dosage of 2 mg/d administered concurrently with an estrogen is used in the treatment of hirsutism in women, doubling as a contraceptive pill.
- **Flutamide** is a potent antiandrogen that has been used in the treatment of prostatic carcinoma.
 - It is rapidly metabolized in humans.
 - It frequently causes mild gynecomastia (probably by increasing testicular estrogen production) and occasionally causes mild

Receptor Inhibitors

- **Cyproterone** and **cyproterone acetate** are effective antiandrogens that inhibit the action of androgens at the target organ.
- The acetate form has a marked progestational effect that suppresses the feedback enhancement of LH and FSH, leading to a more effective antiandrogen effect.
- These compounds have been used in women to treat

reversible hepatic toxicity.

- Administration of this compound causes some improvement in most patients with prostatic carcinoma who have not had prior endocrine therapy.
- Preliminary studies indicate that flutamide is also useful in management of excess androgen effect in women.

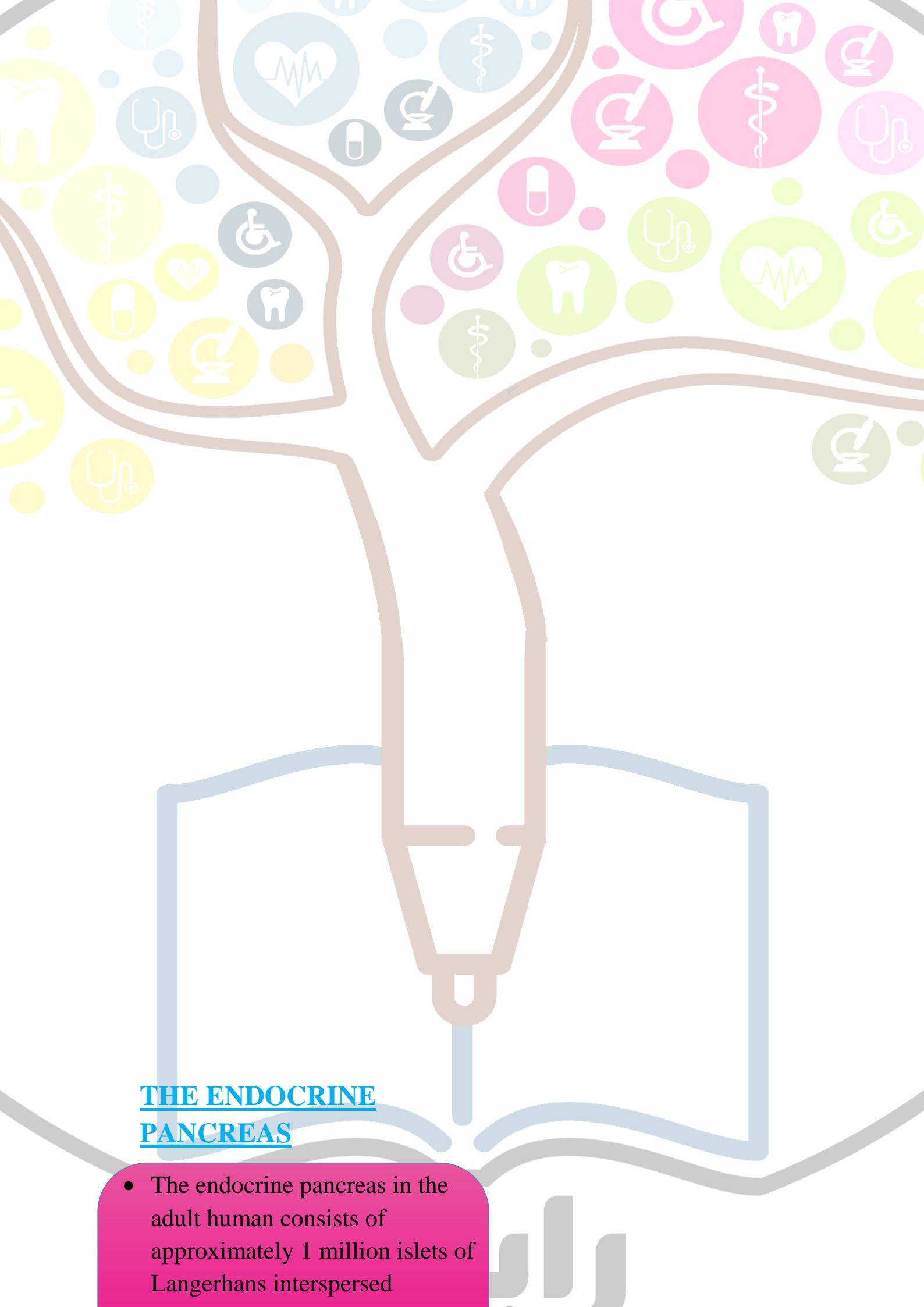
Sicalutamide, nilutamide, enzalutamide and are potent orally active antiandrogens that can be administered as a single daily dose and are used in patients with metastatic carcinoma of the prostate.

- It is used in dosages of 50–200 mg/d in the treatment of hirsutism in women

and appears to be as effective as finasteride, flutamide, cyproterone or this condition.

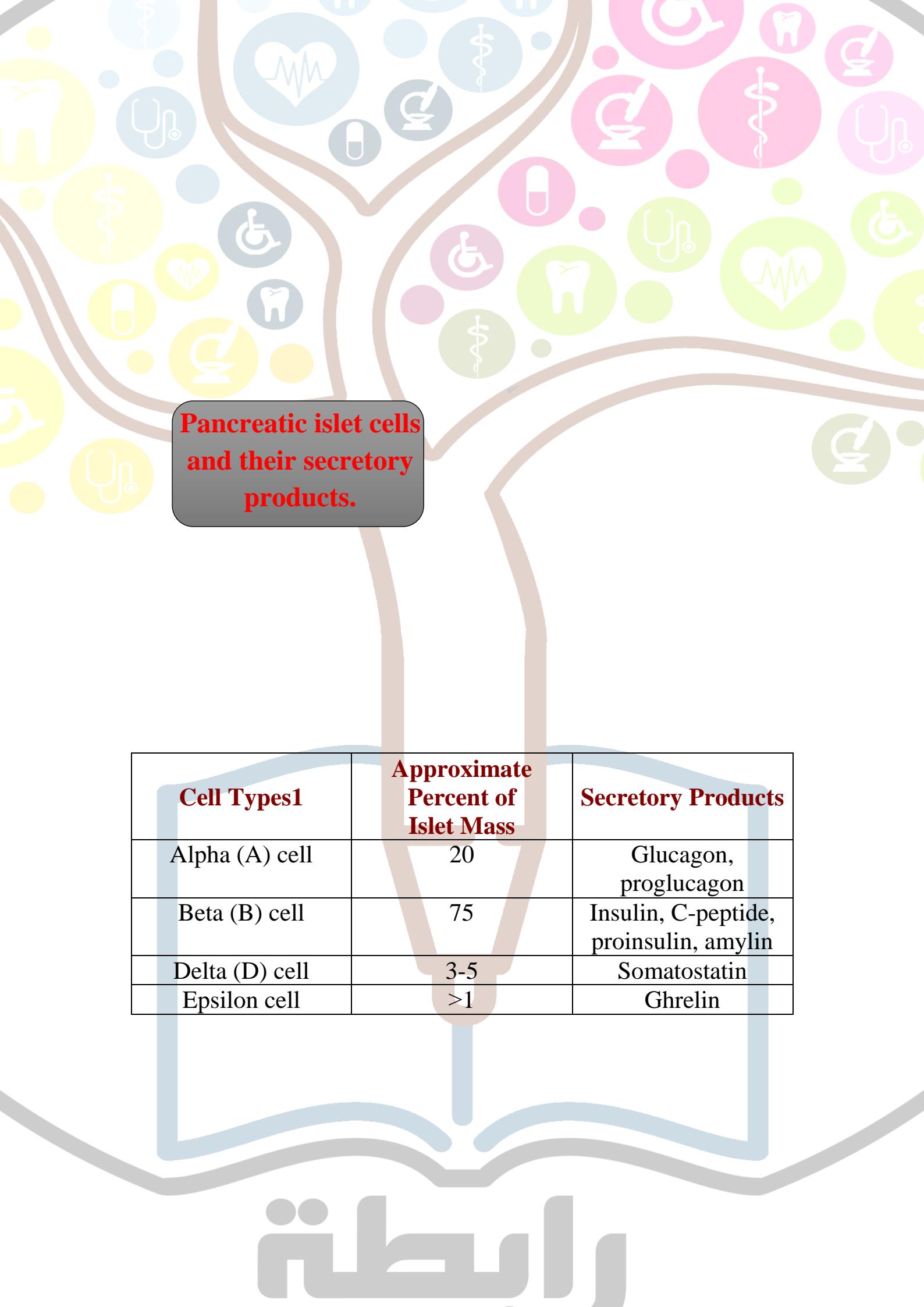
chapter 41

Pancreatic Hormones & Antidiabetic Drugs



THE ENDOCRINE PANCREAS

- The endocrine pancreas in the adult human consists of approximately 1 million islets of Langerhans interspersed



Pancreatic islet cells and their secretory products.

Cell Types ¹	Approximate Percent of Islet Mass	Secretory Products
Alpha (A) cell	20	Glucagon, proglucagon
Beta (B) cell	75	Insulin, C-peptide, proinsulin, amylin
Delta (D) cell	3-5	Somatostatin
Epsilon cell	>1	Ghrelin

Diabetes mellitus

- Is defined as an elevated blood glucose associated with absent or inadequate pancreatic insulin secretion, with or without concurrent impairment of insulin action.
- The disease states underlying the diagnosis of diabetes mellitus are now classified into four categories: -
 - Type 1.
 - Type 2.
 - Other and gestational diabetes mellitus.

- The immune form is the most common form of type 1 diabetes.
- Most patients with type 1 diabetes have one or more circulating antibodies.
- These antibodies facilitate the diagnosis of type 1a diabetes.
- For persons with type 1 diabetes, insulin replacement therapy is necessary to sustain life.
- Pharmacologic insulin is administered by injection into the subcutaneous tissue using a manual injection device or an insulin pump that continuously infuses insulin under the skin.
- Interruption of the insulin replacement therapy can be life-threatening and can result in diabetic ketoacidosis or death.
- Diabetic ketoacidosis is caused by insufficient or absent insulin and results from excess release of fatty acids and subsequent formation of toxic levels of ketoacids.

Type 1 Diabetes Mellitus

- The hallmark of type 1 diabetes is selective beta cell (B cell) destruction and *severe or absolute*insulin deficiency.
- Type 1 diabetes is further subdivided into immune-mediated (type 1a) and idiopathic causes (type 1b).



- Some patients with type 1 diabetes have a more indolent autoimmune process and initially retain enough beta cell function to avoid ketosis.
- They can be treated at first with oral hypoglycemic agents but then need insulin as their beta cell function declines.

Type 2 Diabetes Mellitus

- Type 2 diabetes is characterized by tissue resistance to the action of insulin combined with a *relative* deficiency in insulin secretion.
- Although insulin is produced by the beta cells in these patients, it is inadequate to overcome the resistance, and the blood glucose rises.
- The impaired insulin action also affects fat metabolism, resulting in increased free fatty acid flux and triglyceride levels and reciprocally low levels of high-density lipoprotein (HDL).

- Individuals with type 2 diabetes may not require insulin to survive, but 30% or more will benefit from insulin therapy to control blood glucose.
- Dehydration in individuals with untreated or poorly controlled type 2 diabetes can lead to a lifethreatening condition called nonketotic hyperosmolar coma.
- In this condition, the blood glucose may rise to 6–20 times the normal range and an altered mental state develops or the person loses consciousness.
- Urgent medical care and rehydration are required.

Other Specific Types of Diabetes Mellitus

- The “other” designation refers to multiple *other* specific causes of an elevated blood glucose: pancreatectomy, pancreatitis, nonpancreatic diseases, drug therapy, etc.



Gestational Diabetes Mellitus

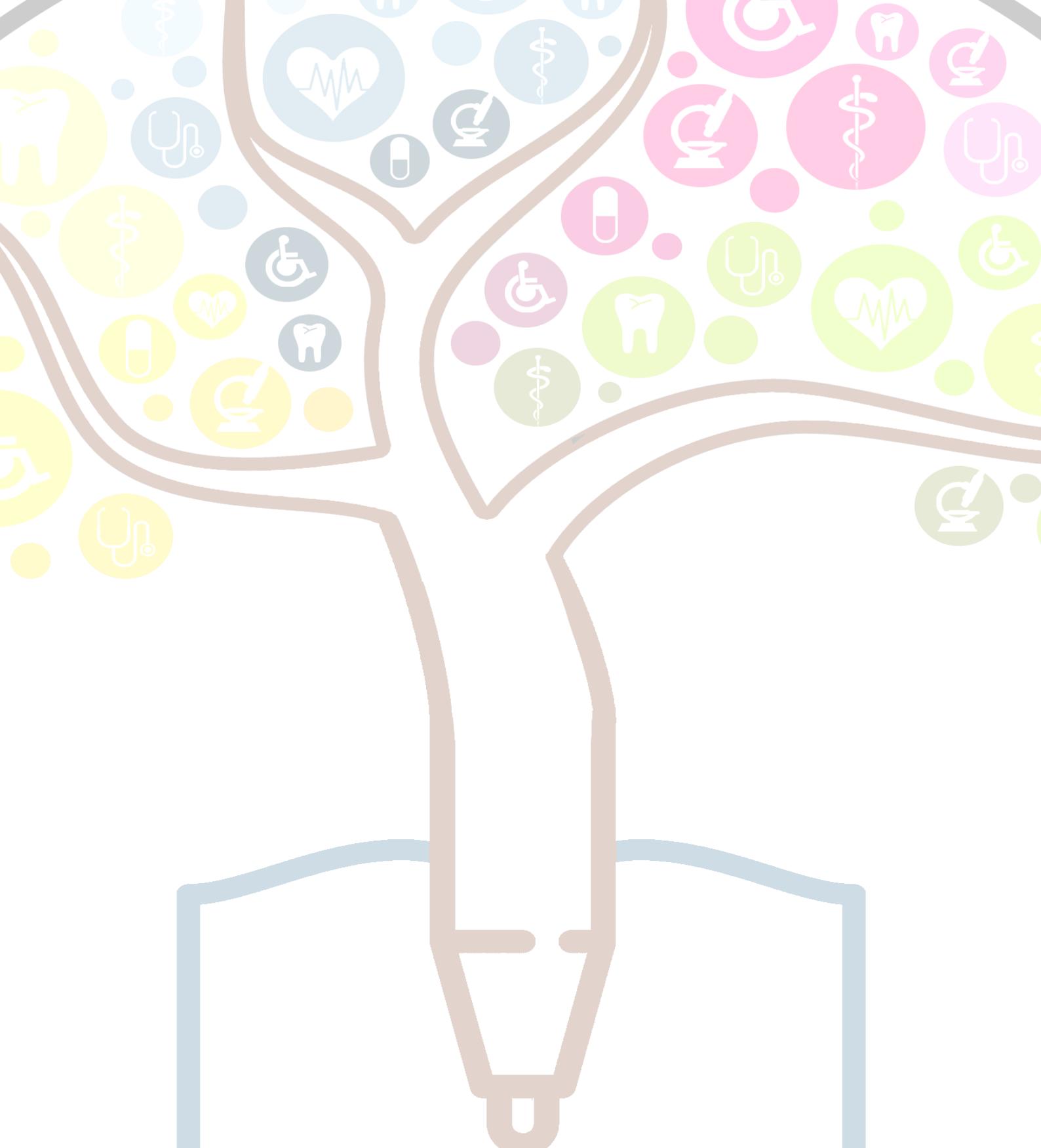
- Gestational diabetes (GDM) is defined as any abnormality in glucose levels noted for the first time during pregnancy.
- During pregnancy, the placenta and placental hormones create an insulin resistance Risk assessment for diabetes is suggested starting at the first prenatal visit.
- High-risk women should be screened immediately.

INSULIN

- With improved purification techniques, the unit is presently defined on the basis of weight, and present insulin standards used for assay purposes contain 28 units per milligram.

Insulin Secretion

- Insulin is released from pancreatic beta cells at a low basal rate and at a much higher stimulated rate in response to a variety of stimuli, especially glucose and other stimulants.
- Stimulatory drugs are



Insulin Degradation

- The liver and kidney are the two main organs that remove insulin from the circulation.
- The half-life of circulating

Endocrine effects of insulin

Effect on liver:

- Reversal of catabolic features of insulin deficiency
 - Inhibits glycogenolysis
 - Inhibits conversion of fatty acids and amino acids to keto acids
 - Inhibits conversion of amino acids to glucose
- Anabolic action
- Promotes glucose storage as glycogen (induces glucokinase and glycogen synthase, inhibits phosphorylase)
 - Increases triglyceride synthesis and very-low-density lipoprotein formation

Effect on muscle:

- Increased protein synthesis
- Increases amino acid transport
- Increases ribosomal protein synthesis
- Increased glycogen synthesis
- Increases glucose transport
- Induces glycogen synthase and inhibits phosphorylase

Effect on adipose tissue:

- Increased triglyceride storage
- Lipoprotein lipase is induced and activated by insulin to hydrolyze triglycerides from lipoproteins
- Glucose transport into cell provides glycerol phosphate to permit esterification of fatty acids supplied by lipoprotein transport
- Intracellular lipase is inhibited by insulin



Insulin Delivery Systems

A. Standard Delivery

The standard mode of insulin therapy is subcutaneous injection.

B. Portable Pen Injectors

To facilitate multiple subcutaneous injections of insulin, particularly during intensive insulin therapy, portable pen-sized injectors have been developed.

C. Continuous Subcutaneous Insulin Infusion Devices.

- Bolus amounts are either dynamically programmed or use preprogrammed algorithms.
- When the boluses are dynamically programmed, the user and the current blood glucose level.
- The user calculates the dose based on the amount of carbohydrate consumed and the current blood glucose level.

(CSII, Insulin Pumps)

- Continuous subcutaneous insulin infusion devices are external.

Treatment with Insulin

- The current classification of



Insulin Regimens

A- Intensive Insulin Therapy

- Intensive insulin regimens are prescribed for almost everyone with type 1 diabetes—diabetes as well as many with type 2.
- The patient uses the formulas to calculate the rapid-acting insulin bolus dose by considering how much carbohydrate is in the

B-Conventional Insulin Therapy

- Conventional insulin therapy is usually prescribed only for certain people with type 2 diabetes. The insulin regimen ranges from one injection per day to many injections per day. Referred to as sliding-scale regimens.

Insulin Treatment of Special Circumstances

A- Diabetic Ketoacidosis

- Diabetic ketoacidosis (DKA) is a life-threatening medical emergency caused by inadequate or absent insulin replacement.

- Signs and symptoms include nausea, vomiting, abdominal pain, deep slow (Kussmaul) breathing, change in mental status, elevated blood and urinary ketones and glucose, an arterial blood pH lower than 7.3, and low bicarbonate ($< 15 \text{ mmol/L}$).
- Close attention has to be given to hydration and renal status, the sodium and potassium levels, and the rate of correction of plasma glucose and plasma osmolality.
- Fluid therapy generally begins with normal saline. Regular human insulin should be used for intravenous therapy with a usual starting dosage of about 0.1



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- the most common cause is insulin therapy.
- They usually occur after skipping a meal or after physical exertion without enough insulin.
- Rapid development of symptoms in persons with diabetes include altered awareness, confusion, hyperactivity, and tachycardia.

B- Hyperosmolar Hyperglycemic Syndrome

- Hyperosmolar hyperglycemic syndrome (HHS) is diagnosed in persons with type 2 diabetes and is characterized by profound hyperglycemia and dehydration.
- The diagnostic hallmarks are declining mental status and even seizures, a plasma glucose of over 600 mg/dL, and a calculated serum osmolality higher than 320 mmol/L.
- Persons with HHS are not acidotic unless DKA is also present.



B. In of In

- In persons exposed to frequent hypoglycemic episodes during tight glycemic control, autonomic warning signals of hypoglycemia are less common or even absent.
- This dangerous acquired condition is termed “hypoglycemic unawareness.”
- When patients lack the early

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2. Immune insulin

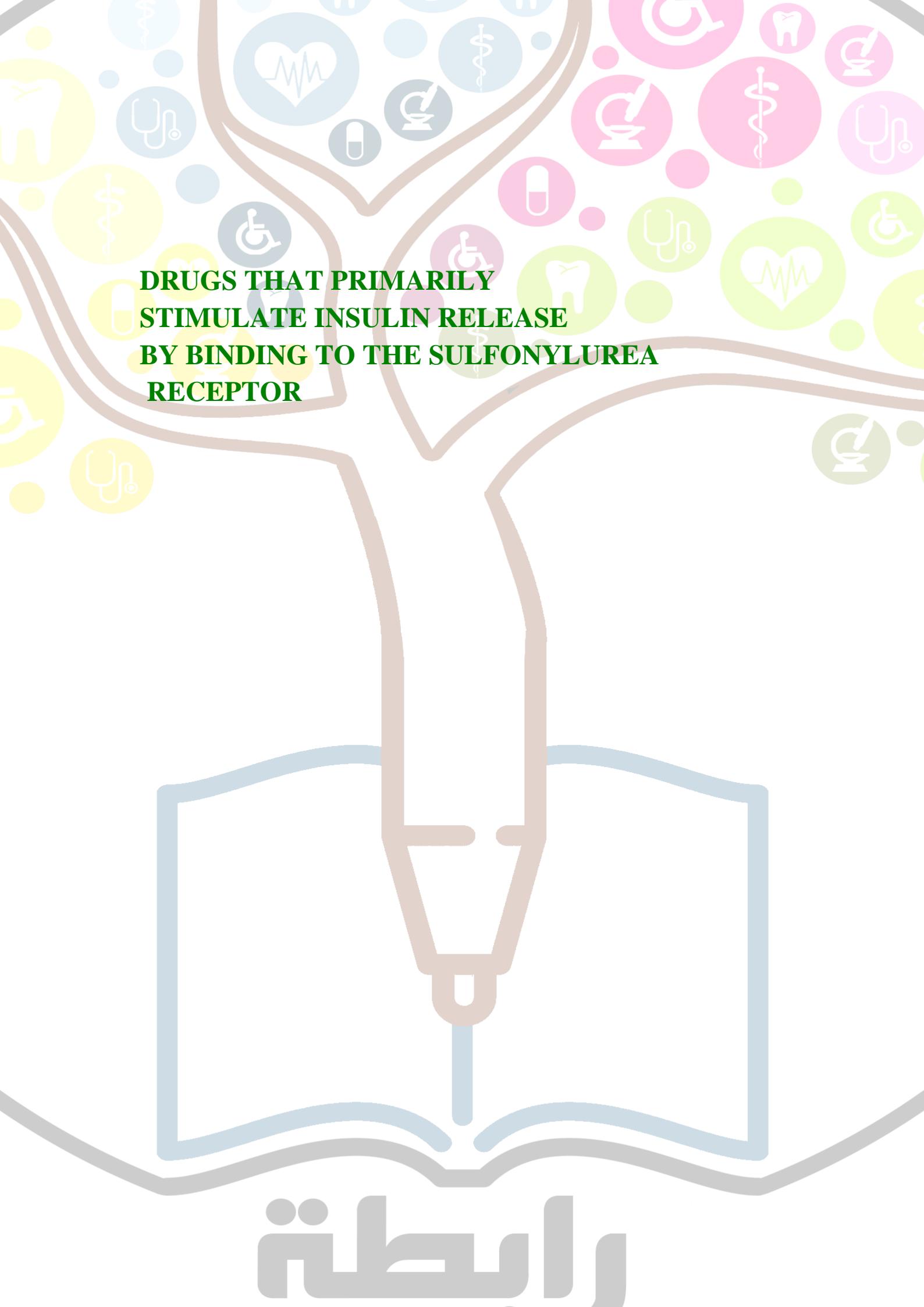
- A low titer of circulating IgG anti-insulin antibodies that neutralize the action of insulin to a negligible extent develops in most insulin-treated patients.

D.Lipodystrophy at Injection Sites

- Injection of animal insulin preparations sometimes led to atrophy of subcutaneous fatty tissue at the site of injection.

C.Increased Cancer Risk

- An increased risk of cancer attributed to insulin resistance and hyperinsulinemia has been reported in individuals with insulin resistance, prediabetes, and type 2 diabetes.



DRUGS THAT PRIMARILY STIMULATE INSULIN RELEASE BY BINDING TO THE SULFONYLUREA RECEPTOR

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SULFONYLUREAS

Mechanism of Action

The major action of sulfonylureas is to increase insulin release from the pancreas.

Regulation of insulin release in humans.

Stimulants of insulin release

Humoral: Glucose, mannose, leucine, arginine, other amino acids, fatty acids (high concentrations)

Hormonal: Glucagon, glucagon-like peptide 1(7–37), glucose-dependent insulinotropic polypeptide, cholecystokinin, gastrin

Neural: β -Adrenergic stimulation, vagal stimulation

Drugs: Sulfonylureas, meglitinide, nateglinide, isoproterenol, acetylcholine

Inhibitors of insulin release

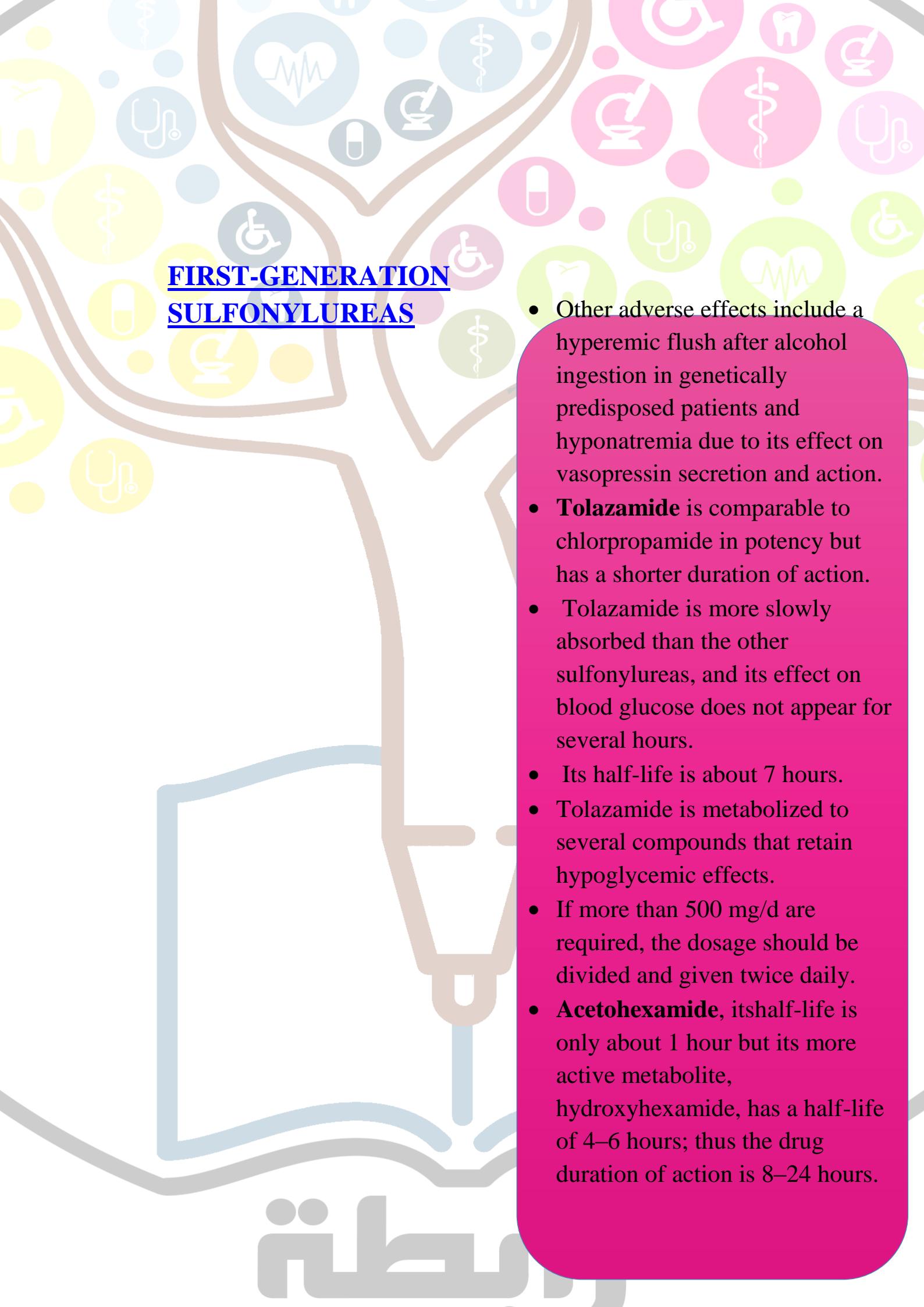
Hormonal: Somatostatin, insulin, leptin

Neural: α -Sympathomimetic effect of catecholamines

Drugs: Diazoxide, phenytoin, vinblastine, colchicine

Efficacy & Safety of the Sulfonylureas

- Sulfonylureas are metabolized by the liver and excreted by the kidney. With the exception of acetohexamide, the metabolites are either weakly active or inactive.
- Idiosyncratic reactions are rare, with skin rashes or hematologic toxicity (leukopenia, thrombocytopenia) occurring in less than 0.1% of cases.
- The second-generation sulfonylureas have greater affinity for their receptor compared with the first generation agents.



FIRST-GENERATION SULFONYLUREAS

- Other adverse effects include a hyperemic flush after alcohol ingestion in genetically predisposed patients and hyponatremia due to its effect on vasopressin secretion and action.
- **Tolazamide** is comparable to chlorpropamide in potency but has a shorter duration of action.
- Tolazamide is more slowly absorbed than the other sulfonylureas, and its effect on blood glucose does not appear for several hours.
- Its half-life is about 7 hours.
- Tolazamide is metabolized to several compounds that retain hypoglycemic effects.
- If more than 500 mg/d are required, the dosage should be divided and given twice daily.
- **Acetohexamide**, its half-life is only about 1 hour but its more active metabolite, hydroxyhexamide, has a half-life of 4–6 hours; thus the drug duration of action is 8–24 hours.

- **Tolbutamide** is well absorbed but rapidly metabolized in the liver.
- Its duration of effect is relatively short (6–10 hours), with an elimination half-life of 4–5 hours.
- Tolbutamide is best administered in divided doses (eg, 500 mg before each meal).
- The maximum dosage is 3000 mg daily.
- **Chlorpropamide** has a half-life of 32 hours and is slowly metabolized in the liver to products that retain some biologic activity.
- The average maintenance dosage is 250 mg daily, given as a single dose in the morning.
- Prolonged hypoglycemic reactions are more common in elderly patients, and the drug is contraindicated in this group.
- Glyburide, Glipizide, Gliclazide, and glimepiride are 100–200 times more potent than tolbutamide.
- They should be used with caution in patients with cardiovascular disease or in elderly patients, in whom hypoglycemia would be especially dangerous.
- **Glyburide** is metabolized in the liver into products with very low hypoglycemic activity.

- The usual starting dosage is 2.5 mg/d or less, and the average maintenance dosage is 5–10 mg/d given as a single morning dose; maintenance dosages higher than 20 mg/dare not recommended.
- Glyburide is contraindicated in the presence of hepatic impairment and in patients with renal insufficiency.
- **Glipizide**has the shortest half-life (2–4 hours) of the more potent agents.

Its dosage is 0.25–1.5 g/d as single dose or in two divided doses. Chlorpropamide, tolazamide, and acetohexamide are now rarely used in clinical practice.

SECOND- GENERATION SULFONYLUREAS

- **Glimepiride** is approved for once-daily use as monotherapy or in combination with insulin.
- A single daily dose of 1 mg has been shown to be effective, and the recommended maximal daily dosage is 8 mg.
- Its half-life under multidose conditions is 5–9 hours. It is completely metabolized by the liver to metabolites with weak or no activity.
- **Gliclazide** has a half-life of 10 hours.
- The recommended starting dosage is 40–80 mg daily with a maximum dosage of 320 mg daily.
- Higher dosages are usually divided and given twice a day.
- It is completely metabolized by the liver to inactive metabolites.

- For maximum effect in reducing postprandial hyperglycemia, this agent should be ingested 30 minutes before breakfast because absorption is delayed when the drug is taken with food.
- The recommended starting dosage is 5 mg/d, with up to 15 mg/d given as a single dose.
- The maximum total daily dosage recommended by the manufacturer is 40 mg/d, although some studies indicate that the maximum therapeutic effect is achieved by 15–20 mg of the drug. At least 90% of glipizide is metabolized in the liver to inactive products, and the remainder is excreted unchanged in the urine.
- Glipizide therapy is therefore contraindicated in patients with significant hepatic impairment. Because of its lower potency and shorter duration for action, it is preferable to glyburide in the elderly.

MEGLITINIDE ANALOGS

- It can be used in patients with renal impairment and in the elderly.
- Repaglinide is approved as monotherapy or in combination with biguanides.
- Mitiglinide is similar to repaglinide in its clinical effects. These drugs modulate beta-cell insulin release by regulating potassium efflux through the potassium channels.
- There is overlap with the sulfonylureas in their molecular sites of action.
- Repaglinide has a fast onset of action, with a peak concentration and peak effect within approximately 1 hour after ingestion, but the duration of action is 4–7 hours. It is cleared by hepatic enzyme with a plasma half-life of 1 hour.
- Because of its rapid onset, repaglinide is indicated for use in controlling postprandial glucose excursions.
- The drug should be taken just before each meal in doses of 0.25–4 mg (maximum 16 mg/d) hypoglycemia is a risk if the meal is delayed or skipped or contains inadequate carbohydrate.

D-PHENYLALANINE

DERIVATIVE

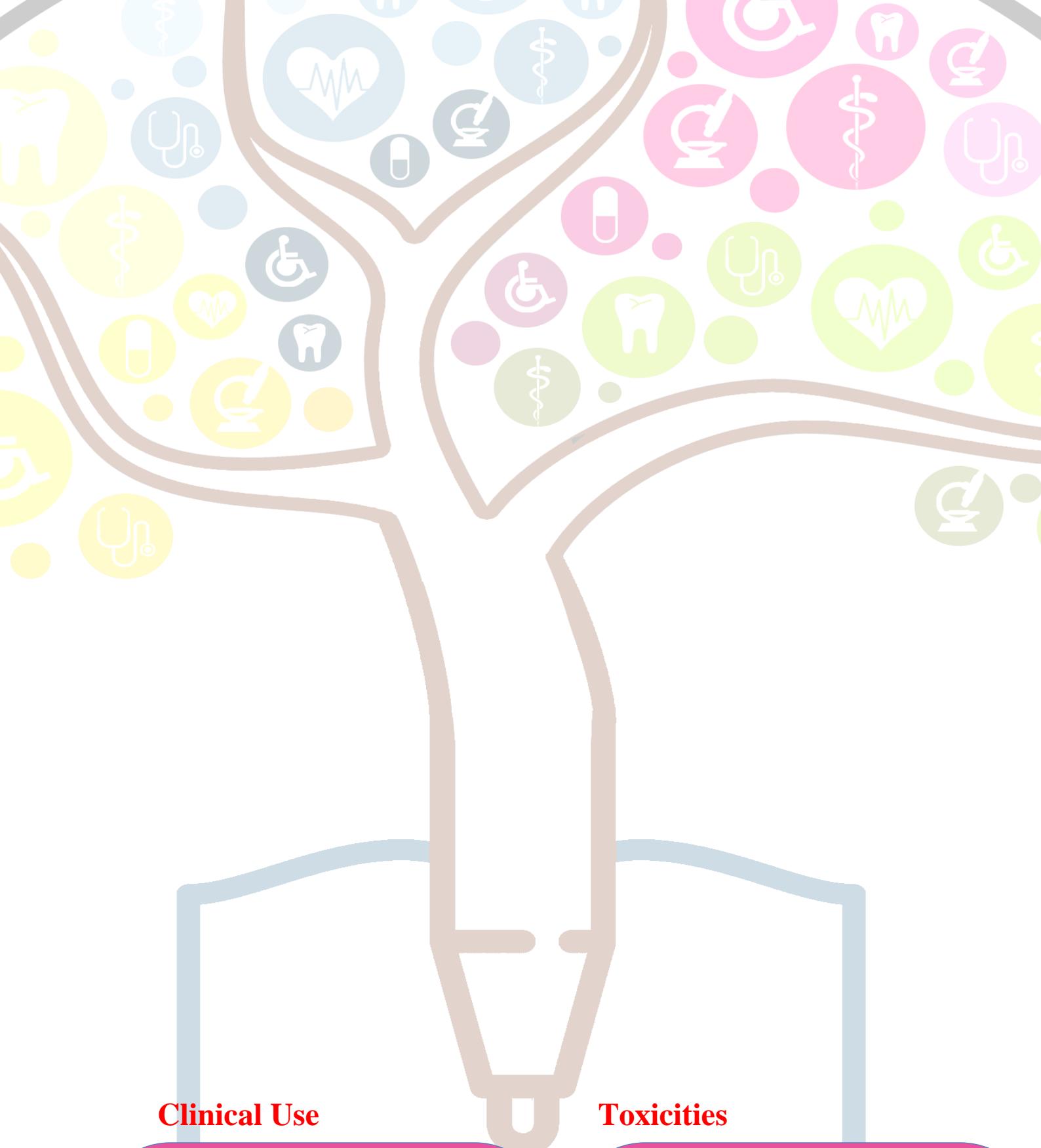
- Nateglinide, stimulates rapid and transient release of insulin from beta cells through closure of the ATP-sensitive K⁺ channel.
- It is absorbed within 20 minutes after oral (for postprandial) administration with a time to peak concentration of less than one hour and is metabolized in the liver and with a half-life of about 1 hour.
- The overall duration of action is about 4 hours. It can be used in patients with renal impairment and in the elderly.

DRUGS THAT PRIMARILY LOWER GLUCOSE LEVELS BY THEIR ACTIONS ON THE LIVER, MUSCLE, & ADIPOSE TISSUE.

BIGUANIDES

- Metformin is the only biguanide currently available in the United States.
- Their primary effect is to activate the enzyme AMP-activated protein kinase (AMPK) and reduce hepatic gluconeogenesis.

- As a consequence of metformin's blockade of gluconeogenesis, the drug may impair the hepatic metabolism of lactic acid.
- In patients with renal insufficiency, biguanides



Clinical Use

- Biguanides are recommended as first-line therapy for type 2 diabetes.
- Because metformin is an insulin-sparing agent and does not increase body weight or provoke hypoglycemia, it offers obvious advantages over insulin or

Toxicities

- The most common toxic effects of metformin are gastrointestinal (anorexia, nausea, vomiting, abdominal discomfort, and diarrhea).
- They are dose related, tend to occur at the onset of therapy, and are often transient.

THIAZOLIDINEDIONES

- Thiazolidinediones act to decrease insulin resistance.
- They are ligands of peroxisome proliferator-activated receptor-gamma.

- It is metabolized by CYP2C8 and CYP3A4 to active metabolites.
- The bioavailability of numerous other drugs also degraded by



- These drugs also have some additional effects apart from Glucose lowering.
- ### DRUGS WITH OTHER ACTIONS ON GLUCOSE

- Pioglitazone lowers triglycerides and increases HDL cholesterol without affecting total cholesterol and low-density lipoprotein (LDL) cholesterol.
- Rosiglitazone increases total cholesterol, HDL cholesterol, and LDL cholesterol but does not have significant effect on triglycerides.
- Fluid retention occurs in about 3–4 % patients on thiazolidinedione monotherapy and occurs more frequently (10–15%) in patients on concomitant insulin therapy.
- Heart failure can occur, and the drugs are contraindicated in patients with New York Heart Association class III and IV cardiac status.
- **Troglitazone**, the first medication in this class, was withdrawn because of cases of fatal liver failure.

- The **alpha-glucosidase inhibitors** competitively inhibit the intestinal alpha-glucosidase enzymes and reduce postmeal glucose excursions by delaying the digestion and absorption of starch and disaccharides.
- **Acarbose** and **miglitol** are available in the United States.
- **Voglibose** is available in Japan, Korea, and India.
- Acarbose treatment is initiated at a dosage of 50 mg twice daily with gradual increase to 100 mg three times a day.
- Miglitol therapy is initiated at a dosage of 25 mg three times a day.
- The usual maintenance dosage is 50 mg three times a day but some patients may need 100 mg three times a day.
- The drug is not metabolized and is cleared by the kidney.

- It should not be used in renal failure.
- Prominent adverse effects of α -glucosidase inhibitors include flatulence, diarrhea, and abdominal pain and result from the appearance of undigested carbohydrate in the colon that is then fermented into short-chain fatty acids, releasing gas.
- These adverse effects tend to diminish with ongoing use because;
 - Chronic exposure to carbohydrate induces the expression of α glucosidase in the jejunum and ileum.
 - Increasing distal small intestine glucose absorption.
- Minimizing the passage of carbohydrate into the colon.
- Hypoglycemia should be treated with glucose (dextrose) and not sucrose, whose breakdown may be blocked.

- Hypoglycemia should be treated with glucose (dextrose) and not sucrose, whose breakdown may be blocked.
- An increase in hepatic aminotransferases has been noted in clinical trials with acarbose, especially with dosages greater than 300 mg/d.
- The abnormalities resolve on stopping the drug.

DRUGS THAT MIMIC INCRETIN EFFECT OR PROLONG INCRETIN ACTION

- **Exenatide**, has a 53% homology with native GLP-1, and a glycine substitution to reduce degradation by DPP-4.
- It is approved as an injectable, adjunctive therapy in persons with type 2 diabetes treated with metformin or metformin plus sulfonylureas who still have suboptimal glycemic control.
- Exenatide is dispensed as fixed-dose pens (5 mcg and 10 mcg).
- It is injected subcutaneously within 60 minutes before breakfast and dinner.
- It reaches a peak concentration in approximately 2 hours with a duration of action of up to 10 hours.
- Therapy is initiated at 5 mcg twice daily for the first month and if tolerated can be increased to 10 mcg twice daily.

- When exenatide is added to preexisting sulfonylurea therapy, the oral hypoglycemic dosage may need to be decreased to prevent hypoglycemia.
- The major adverse effect is nausea.
- Exenatide undergoes glomerular filtration, and the drug is not approved for use in patients with estimated GFR of less than 30 mL/min.
- **Liraglutide** is a soluble fatty acid-acylated GLP-1 analog.
- Its half-life is approximately 12 hours permitting once-daily dosing.
- It is approved in patients with type 2 diabetes who achieve inadequate control with diet and exercise and are receiving concurrent treatment with metformin, sulfonylureas, or thiazolidinediones.

- If needed the dosage can be increased to 1.8 mg daily.
 - The most frequent side effects are nausea and vomiting.
 - **Albiglutide** is a human GLP-1 dimer fused to human albumin.
 - Its half-life is about 5 days state is reached after 4–5 weeks of once weekly administration.
 - The usual dose is 30 mg weekly by subcutaneous injection.
 - The most frequent adverse effects were nausea and injection site erythema.
- Dulaglutide** consists of two GLP-1 analog molecules covalently linked to an Fc fragment of human IgG4.
- The usual dose is 0.75 mg weekly by subcutaneous injection.
 - The half-life of dulaglutide is

- The usual dose is 0.75 mg weekly by subcutaneous injection. The maximum recommended dose is 1.5 mg weekly.
- Patients on these drugs should be counseled to seek immediate medical care if they experience unexplained persistent severe abdominal pain.
- Cases of renal impairment and acute renal injury have been reported in patients taking exenatide.
- Both exenatide and liraglutide stimulate thyroïdal C-cell (parafollicular) tumors in rodents.
- Human thyroïdal C-cells express very few GLP-1 receptors and the relevance to human therapy

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

- **Sitagliptin** is given orally as 100 mg once daily, has an oral bioavailability of over 85%, and has a half-life of approximately 12 hours.
- It is primarily excreted in the urine, in part by active tubular secretion of the drug.
- Dosage should be reduced in patients with impaired renal function (50 mg if estimated GFR is 30–50 mL/min and 25 mg if less than 30 mL/min).
- Therapy with sitagliptin has resulted in HbA1c reductions of 0.5–1.0%.
- Hypoglycemia can occur when

- Sitagliptin should be immediately discontinued if pancreatitis or allergic and hypersensitivity reactions occur.
- **Saxagliptin** is given orally as 2.5–5 mg daily.
- The drug reaches maximal concentrations within 2 hours (4 hours for its active metabolite).
- It is minimally protein bound and undergoes hepatic metabolism by CYP3A4/5.
- The major metabolite is active, and excretion is by both renal and hepatic pathways.
- The terminal plasma half-life is 2.5 hours for saxagliptin and 3.1 hours for its active metabolite.
- Dosage adjustment is recommended for individuals with renal impairment and concurrent use of strong CYP3A4/5 inhibitors such as antiviral, antifungal, and certain antibacterial agents.

- Saxagliptin resulted in an HbA1c reduction of 0.4–0.9%.
- **Linagliptin** lowers HbA1c by 0.4–0.6% when added to the therapeutic regimen.
- The dosage is 5 mg daily and since it is primarily excreted via the bile, no dosage adjustment is needed in renal failure.
GLP-1 RECEPTOR AGONISTS (SGLT2 INHIBITORS)
- The risk of pancreatitis may be increased.
- **Vildagliptin** lowers HbA1c levels by 0.5–1% when added to the therapeutic regimen.

- The relevance to human therapy is unclear and currently there is no evidence that these drugs cause pancreatic cancer in humans.

- Sodium-glucose transporter 2 (SGLT2) accounts for 90% of glucose reabsorption, and its inhibition causes glycosuria and lowers glucose levels in patients with type 2 diabetes.
- **Canagliflozin** reduces the threshold for glycosuria from a plasma glucose threshold of approximately 180 mg/dL to 70–90 mg/dL.
- The usual dosage is 100 mg daily.

- Increasing the dosage to 300 mg daily in patients with normal renal function can lower the HbA1c by an additional 0.5%.
- **Dapagliflozin** reduces HbA1c by 0.5–0.8% when used alone or in combination with other oral agents or insulin.
- The usual dosage is 10 mg daily but 5 mg daily is recommended initially in patients with hepatic failure.
- **Empagliflozin** reduces HbA1c

- The main side effects are increased incidence of genital infections and urinary tract infections affecting about 8–9% of patients.
- The osmotic diuresis can also cause intravascular volume contraction and hypotension.
- Canagliflozin and empagliflozin caused a modest increase in LDL cholesterol levels (4–8%).
- In clinical trials patients



OTHER HYPOGLYCEMIC DRUGS

- **Pramlintide** is an islet amyloid polypeptide (IAPP, amylin) analog.
- IAPP physiologically acts as a negative feedback on insulin secretion.
- At pharmacologic doses, IAPP reduces glucagon secretion, slows gastric emptying and centrally

- Pramlintide is injected immediately before eating; dosages range from 15 to 60 mcg subcutaneously for type 1 patients and from 60 to 120 mcg for type 2 patients.
- Therapy with this agent should be initiated at the lowest dosage and titrated upward. Because of the

- The drug is not that useful in type 2 patients who can instead use the GLP-1 receptor agonists.
- **Colesevelam hydrochloride**, the bile acid sequestrant and cholesterol-lowering drug, is approved as an antihyperglycemic therapy for persons with type 2 diabetes who are taking other medications or have not achieved adequate control with diet and exercise.
- The exact mechanism of action is

- It can also exacerbate the hypertriglyceridemia that commonly occurs in people with type 2 diabetes.
- **Bromocriptine**, the dopamine agonist, lowers HbA1c by 0–0.2% compared with baseline.
- The mechanism by which it lowers glucose levels is not known.
- The main adverse events are nausea, fatigue, dizziness, vomiting, and headache.
- Colesevelam and bromocriptine have very modest efficacy in lowering glucose levels and their use for this purpose is questionable.



COMBINATION THERAPY IN TYPE 2 DIABETES

- Failure to maintain a good response to therapy remains a disconcerting problem in the management of type 2 diabetes.
- Multiple medications may be

Weight loss + exercise + metformin

*

Metformin + another agent

*

Metformin + two other agents

- Pioglitazone can be used with insulin, but this combination is associated with more weight gain and peripheral edema.
- Continuing with sulfonylureas, GLP-1receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors can be of benefit in selected patients.
- Cost, complexity, and risk for adverse events should be considered when deciding which drugs to continue once the patient starts on insulin therapy.

GLUCAGON



Clinical Uses

B. Severe Hypoglycemia

The major use of glucagon is for emergency treatment of severe hypoglycemic reactions in patients with type 1 diabetes when unconsciousness precludes oral feedings and intravenous glucose treatment is not possible.

A. Beta-Adrenoceptor Blocker Overdose

Glucagon is sometimes useful for reversing the cardiac effects of an overdose of β -blocking agents because of its ability to increase cAMP production in the heart. However, it is not clinically useful in the treatment of cardiac failure.

C. Endocrine Diagnosis

Several tests use glucagon to diagnose endocrine disorders.

D. Radiology of the Bowel

Glucagon has been used extensively in radiology as an aid to X-ray visualization of the bowel because of its ability to relax the intestine.

Adverse Reactions

Transient nausea and occasional vomiting can result from glucagon administration. These are generally mild, and glucagon is relatively free of severe adverse reactions. It should not be used in a patient with pheochromocytoma.

SUMMARY Drugs Used for Diabetes

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
INSULINS				
<ul style="list-style-type: none"> Rapid-acting: Lispro, aspart, glulisine, inhaled regular Short-acting: Regular Intermediate-acting: NPH Long-acting: Detemir, glargine 	Activate insulin receptor	Reduce circulating glucose	Type 1 and type 2 diabetes	Parenteral (SC or IV) • duration varies (see text) • Toxicity: Hypoglycemia, weight gain, lipodystrophy (rare)
SULFONYLUREAS				
<ul style="list-style-type: none"> Glipizide Glyburide Glimepiride Gliclazide (not available in USA) Tolazamide, tolbutamide, chlorpropamide, acetohexamide: Older sulfonylureas, lower potency, greater toxicity; rarely used 	Insulin secretagogues: Close K ⁺ channels in beta cells • increase insulin release	Reduce circulating glucose in patients with functioning beta cells	Type 2 diabetes	Orally active • duration 10–24 h • Toxicity: Hypoglycemia, weight gain
MEGLITINIDE ANALOGS; D-PHENYLALANINE DERIVATIVE				
<ul style="list-style-type: none"> Repaglinide, nateglinide Mitiglinide¹ 	Insulin secretagogue: Similar to sulfonylureas with some overlap in binding sites	In patients with functioning beta cells, reduce circulating glucose	Type 2 diabetes	Oral • very fast onset of action • duration 5–8 h, nateglinide < 4 h • Toxicity: Hypoglycemia
BIGUANIDES				
<ul style="list-style-type: none"> Metformin 	Activates AMP kinase • reduces hepatic and renal gluconeogenesis	Decreases circulating glucose	Type 2 diabetes	Oral • maximal plasma concentration in 2–3 h • Toxicity: Gastrointestinal symptoms, lactic acidosis (rare) • cannot use if impaired renal/hepatic function • congestive heart failure (CHF), hypoxic/acidotic states, alcoholism
ALPHA-GLUCOSIDASE INHIBITORS				
<ul style="list-style-type: none"> Acarbose, miglitol Voglibose¹ 	Inhibit intestinal α-glucosidases	Reduce conversion of starch and disaccharides to monosaccharides • reduce postprandial hyperglycemia	Type 2 diabetes	Oral • rapid onset • Toxicity: Gastrointestinal symptoms • cannot use if impaired renal/hepatic function, intestinal disorders
THIAZOLIDINEDIONES				
<ul style="list-style-type: none"> Pioglitazone, rosiglitazone 	Regulate gene expression by binding to PPAR-γ and PPAR-α	Reduce insulin resistance	Type 2 diabetes	Oral • long-acting (> 24 h) • Toxicity: Fluid retention, edema, anemia, weight gain, macular edema, bone fractures in women • cannot use if CHF, hepatic disease
GLUCAGON-LIKE POLYPEPTIDE-1 (GLP-1) RECEPTOR AGONISTS				
<ul style="list-style-type: none"> Exenatide, liraglutide, albiglutide, dulaglutide 	Analog of GLP-1: Binds to GLP-1 receptors	Reduce post-meal glucose excursions: Increase glucose-mediated insulin release, lower glucagon levels, slow gastric emptying, decrease appetite	Type 2 diabetes	Parenteral (SC) • Toxicity: Nausea, headache, vomiting, anorexia, mild weight loss, pancreatitis, C-cell tumors in rodents

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS				
• Sitagliptin, saxagliptin, linagliptin, alogliptin, vildagliptin	Blocks degradation of GLP-1, raises circulating GLP-1 levels	Reduces post-meal glucose excursions: Increases glucose-mediated insulin release, lowers glucagon levels, slows gastric emptying, decreases appetite	Type 2 diabetes	Oral • half-life ~12 h • 24-h duration of action • Toxicity: Rhinitis, upper respiratory infections, headaches, pancreatitis, rare allergic reactions
SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS				
• Canagliflozin, dapagliflozin, empagliflozin	Block renal glucose resorption	Increase glucosuria, lower plasma glucose levels	Type 2 diabetes	Oral • half-life ~10–14 h • Toxicity: Genital and urinary tract infections, polyuria, pruritus, thirst, osmotic diuresis, constipation
ISLET AMYLOID POLYPEPTIDE ANALOG				
• Pramlintide	Analog of amylin: Binds to amylin receptors	Reduces post-meal glucose excursions: Lowers glucagon levels, slows gastric emptying, decreases appetite	Type 1 and type 2 diabetes	Parenteral (SC) • rapid onset • half-life ~48 min • Toxicity: Nausea, anorexia, hypoglycemia, headache
BILE ACID SEQUESTRANT				
• Colesevelam hydrochloride	Bile acid binder: Lowers glucose through unknown mechanisms	Reduces glucose levels	Type 2 diabetes	Oral • 24-h duration of action • Toxicity: Constipation, indigestion, flatulence
DOPAMINE AGONIST				
• Bromocriptine	D ₂ receptor agonist: Lowers glucose through unknown mechanism	Reduces glucose levels	Type 2 diabetes	Oral • 24-h action • Toxicity: Nausea, vomiting, dizziness, headache





Agents That Affect Bone Mineral Homeostasis

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fractures) and loss of hematopoietic capacity (eg, infantile osteopetrosis).

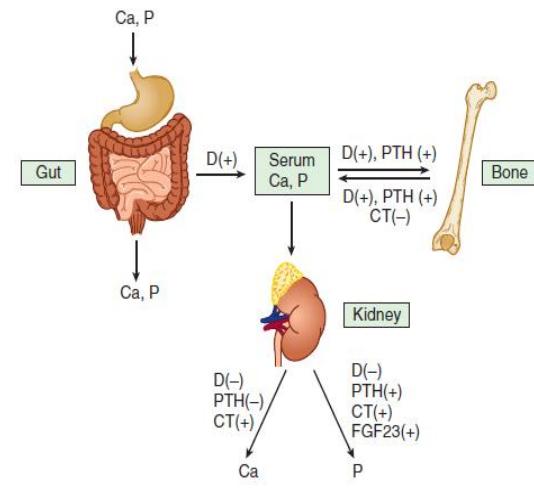
- Calcium and phosphate, the major mineral constituents of bone, are also two of the most important minerals for general cellular function.
- Accordingly, the body has evolved complex mechanisms to carefully maintain calcium and phosphate homeostasis (Figure 42–1).
- Abnormalities in bone mineral homeostasis can lead to a wide variety of cellular dysfunctions (eg, tetany, coma, muscle weakness), and to disturbances in structural support of the body (eg, osteoporosis with

hormones that regulate Calcium and Phosphorus homeostasis

parathyroid hormone (PTH),

vitamin D

fibroblast growth factor 23 (FGF23)



- **FIGURE (42–1) Mechanisms contributing to bone mineral homeostasis.**
- Serum calcium (Ca) and phosphorus (P) concentrations are controlled principally by three hormones, 1,25-dihydroxyvitamin D (D), fibroblast growth factor 23 (FGF23), and parathyroid hormone (PTH), through their action on absorption from the gut and from bone and on renal excretion.
- PTH and 1,25(OH)2D increase the input of calcium and phosphorus from bone into the serum and stimulate bone formation.
- 1,25(OH)2D also increases calcium and phosphate absorption from the gut. In the kidney, 1,25(OH)2D decreases excretion of both calcium and phosphorus, whereas PTH reduces calcium but increases phosphorus excretion.
- FGF23 stimulates renal excretion of phosphate.
- Calcitonin (CT) is a less critical regulator of calcium homeostasis, but in pharmacologic concentrations can reduce serum calcium and phosphorus by inhibiting bone resorption and stimulating their renal excretion.
- Feedback may alter the effects shown; for example, 1,25(OH)2D increases urinary calcium excretion indirectly through increased calcium absorption from the gut and inhibition of PTH secretion and may increase urinary phosphate

excretion because of increased phosphate absorption from the gut and stimulation of FGF23 production.

half-time of disappearance measured in minutes.

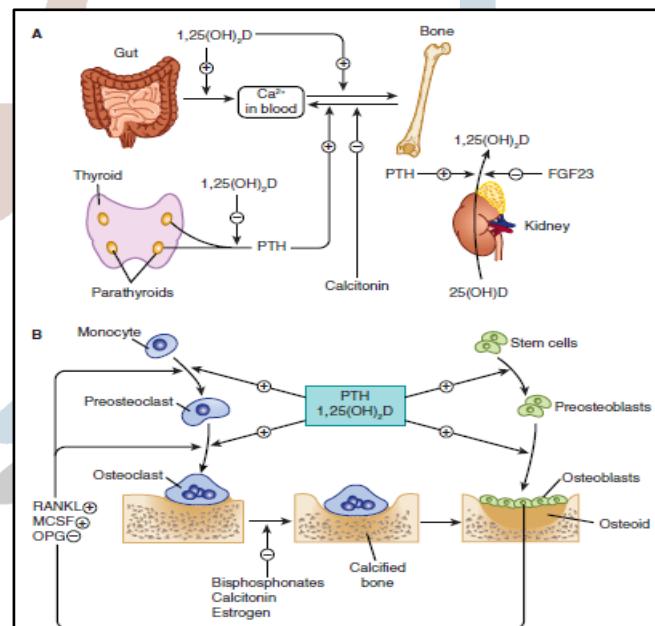
- Most of the clearance occurs in the liver and kidney.

PRINCIPAL HORMONAL REGULATORS OF BONE MINERAL HOMEOSTASIS

1- PARATHYROID HORMONE:

- TH regulates calcium and phosphate flux across cellular membranes in bone and kidney, resulting in increased serum calcium and decreased serum phosphate (Figure 42–1).
- In bone, PTH increases the activity and number of osteoclasts, the cells responsible for bone resorption (Figure 42–2).
- The metabolic clearance of intact PTH is rapid, with a

- The inactive carboxyl terminal fragments produced by metabolism of the intact hormone have a much lower clearance, especially in renal failure.
- (FIGURE 42–2)
The hormonal interactions controlling



bone mineral homeostasis)

capable of stimulating both processes.

- In the body (A), 1,25-dihydroxyvitamin D ($1,25[\text{OH}]_2\text{D}$) is produced by the kidney under the control of parathyroid hormone (PTH), which stimulates its production, and fibroblast growth factor 23 (FGF23), which inhibits its production.
- $1,25(\text{OH})_2\text{D}$ in turn inhibits the production of PTH by the parathyroid glands and stimulates FGF23 release from bone.
- $1,25(\text{OH})_2\text{D}$ is the principal regulator of intestinal calcium and phosphate absorption.
- At the level of the bone (B), both PTH and $1,25(\text{OH})_2\text{D}$ regulate bone formation and resorption, with each
- This is accomplished by their stimulation of preosteoblast proliferation and differentiation into osteoblasts, the bone-forming cell.
- PTH also stimulates osteoblast formation indirectly by inhibiting the osteocyte's production of sclerostin, a protein that blocks osteoblast proliferation by inhibiting the wnt pathway (not shown).
- PTH and $1,25(\text{OH})_2\text{D}$ stimulate the expression of RANKL by the osteoblast, which, with mCSF, stimulates the differentiation and subsequent activation of

osteoclasts, the bone-resorbing cell.

- OPG blocks RANKL action, and may be inhibited by PTH and 1,25(OH)2D. FGF23 in excess leads to osteomalacia indirectly by inhibiting 1,25(OH)2D production and lowering phosphate levels.
- mCSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; RANKL, ligand for receptor for activation of nuclear factor- κ B.

2- VITAMIN D:

- Vitamin D is a secosteroid produced in the skin from 7-dehydrocholesterol under the influence of ultraviolet radiation.
- Vitamin D is a precursor to a number of biologically

active metabolites (Figure 42-3).

- Vitamin D is first hydroxylated in the liver and other tissues to form 25(OH)D(calcifediol). The regulation of vitamin D metabolism is complex, involving calcium, phosphate, and a variety of hormones, the most important of which are PTH, which stimulates, and FGF23, which inhibits the production of 1,25(OH)2D by the kidney while reciprocally inhibiting or promoting the production of 24,25(OH)2D.
- Of the natural metabolites, only vitamin D and

TABLE 42-1 Vitamin D and its major metabolites and analogs.

Chemical and Generic Names	Abbreviation
Vitamin D ₃ ; cholecalciferol	D ₃
Vitamin D ₂ ; ergocalciferol	D ₂
25-Hydroxyvitamin D ₃ ; calcifediol	25(OH)D ₃
1,25-Dihydroxyvitamin D ₃ ; calcitriol	1,25(OH) ₂ D ₃
24,25-Dihydroxyvitamin D ₃ ; secalciferol	24,25(OH) ₂ D ₃
Dihydrotachysterol	DHT
Calcipotriene (calcipotriol)	None
1 α -Hydroxyvitamin D ₂ ; doxercalciferol	1 α (OH)D ₂
19-nor-1,25-Dihydroxyvitamin D ₂ ; paricalcitol	19-nor-1,25(OH)D ₂

Vitamin D metabolites	Use
Calcipotriene (Calcipotriol)	Used to treat psoriasis, a hyperproliferative skin disorder.
Doxercalciferol and paricalcitol	Used for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease.
Eldecalcitol	Used in treatment of osteoporosis.

1,25(OH)2D (ascalcitriol) are available for clinical use (Table 42-1).

3- FIBROBLAST GROWTH FACTOR 23:

- (FGF23) inhibits 1,25(OH)2D production and phosphate reabsorption (via the sodium phosphate co-transporters NaPi 2a and 2c) in the kidney, and can lead to both hypophosphatemia and inappropriately low levels of circulating 1,25(OH)2D.

- FGF23 production is stimulated by 1,25(OH)2D and phosphate and directly or indirectly inhibited by the dentin matrix protein DMP1 found in osteocytes.
- Mutations in DMP1 lead to increased FGF23 levels and osteomalacia.

4- INTERACTION OF PTH, FGF23, & VITAMIN D :

- A summary of the principal actions of PTH, FGF23, and vitamin D on the three main target tissues—intestine, kidney, and bone—is presented in (Table 42-2.)

TABLE 42-2 Actions of parathyroid hormone (PTH), vitamin D, and FGF23 on gut, bone, and kidney.

	PTH	Vitamin D	FGF23
Intestine	Increased calcium and phosphate absorption (by increased $1,25(\text{OH})_2\text{D}$ production)	Increased calcium and phosphate absorption by $1,25(\text{OH})_2\text{D}$	Decreased calcium and phosphate absorption by decreased $1,25(\text{OH})_2\text{D}$ production
Kidney	Decreased calcium excretion, increased phosphate excretion, stimulation of $1,25(\text{OH})_2\text{D}$ production	Calcium and phosphate excretion may be decreased by $25(\text{OH})\text{D}$ and $1,25(\text{OH})_2\text{D}^1$	Increased phosphate excretion, decreased $1,25(\text{OH})_2\text{D}$ production
Bone	Calcium and phosphate resorption increased by high doses. Low doses increase bone formation.	Increased calcium and phosphate resorption by $1,25(\text{OH})_2\text{D}$; bone formation may be increased by $1,25(\text{OH})_2\text{D}$	Decreased mineralization due to hypophosphatemia and low $1,25(\text{OH})_2\text{D}$ levels.
Net effect on serum levels	Serum calcium increased, serum phosphate decreased	Serum calcium and phosphate both increased	Decreased serum phosphate

¹Direct effect. Vitamin D also indirectly increases urine calcium owing to increased calcium absorption from the intestine and decreased PTH.

SECONDARY HORMONAL REGULATORS OF BONE MINERAL HOMEOSTASIS:

- A number of hormones modulate the actions of PTH, FGF23, and vitamin D in regulating bone mineral homeostasis.

1- CALCITONIN :

- The calcitonin secreted by the parafollicular cells of the mammalian Thyroid.

- The principal effects of calcitonin are to lower serum calcium and phosphate by actions on bone and kidney.
- The ability of calcitonin to block bone resorption and lower serum calcium makes it a useful drug for the treatment of Paget's disease, hypercalcemia, and osteoporosis, albeit a less efficacious drug than other available agents.

2- GLUCOCORTICOIDS:

- Glucocorticoid hormones alter bone mineral homeostasis by antagonizing vitamin D-stimulated intestinal calcium transport, stimulating renal calcium excretion, and blocking bone formation.
- Prolonged administration of glucocorticoids is a common cause of osteoporosis in adults and can cause stunted skeletal development in children.

- Estrogens also increase DBP production by the liver, which increases the total concentrations of the vitamin D metabolites in circulation without necessarily increasing the free levels.
- Estrogen administration in disorders of bone mineral homeostasis is the treatment or prevention of postmenopausal osteoporosis.

3- ESTROGENS

- Estrogens can prevent accelerated bone loss during the immediate postmenopausal period and at least transiently increase bone in postmenopausal women.

NONHORMONAL AGENTS AFFECTING BONE MINERAL HOMEOSTASIS:

1- BISPHOSPHONATES

- Available bisphosphonates include:
Etidronate, Pamidronate, Alendronate, Risedronate, Tiludronate, Ibandronate, and Zoledronate.
- A major adverse effect of oral forms of the bisphosphonates (Risedronate, Alendronate, Ibandronate) is esophageal and gastric irritation.
- Amino bisphosphonates such as Alendronate and Risedronate inhibit farnesyl pyrophosphate synthase.

2-DENOSUMAB

- Denosumab is a fully human monoclonal antibody that binds to and prevents the action of RANKL.

- (RANKL is produced by osteoblasts and other cells, including T lymphocytes).
- Denosumab is administered subcutaneously every 6 months.

3- CALCIMIMETICS

- Cinacalcet is the first representative of a new class of drugs that activates the calcium-sensing receptor (CaSR). By activating the parathyroid gland CaSR, cinacalcet inhibits PTH secretion.
- Cinacalcet is approved for the treatment of secondary hyperparathyroidism in chronic kidney disease and for the treatment of parathyroid carcinoma.
- CaSR antagonists are also being developed, and may be useful in conditions of hyperparathyroidism or as a means to stimulate intermittent PTH secretion in the treatment of osteoporosis.

4- PLICAMYCIN (MITHRAMYCIN)

- Plicamycin is a cytotoxic antibiotic that has been used clinically for two disorders of bone mineral metabolism: Paget's disease and hypercalcemia.
- The doses required to treat Paget's disease and hypercalcemia are about onetenth the amount required to achieve cytotoxic effects.

5- THIAZIDE DIURETICS

- Thiazides may increase the effectiveness of PTH in stimulating reabsorption of calcium by the renal tubules or may act on calcium reabsorption secondarily by increasing sodium reabsorption in the proximal tubule.

- In the distal tubule, thiazides block sodium reabsorption at the luminal surface, increasing the calcium-sodium exchange at the basolateral membrane and thus enhancing calcium reabsorption into the blood at this site.
- Thiazides have proved to be useful in reducing the hypercalciuria and incidence of urinary stone formation in subjects with idiopathic hypercalciuria.

6- FLUORIDE

- Fluoride is well established as effective for the prophylaxis of dental caries and has previously been investigated for the treatment of osteoporosis.
- Fluoride accumulates in bones and teeth, where it may stabilize the hydroxyapatite crystal.

CLINICAL PHARMACOLOGY

➤ ABNORMAL SERUM CALCIUM & PHOSPHATE LEVELS:

• HYPERCALCEMIA

- Hypercalcemia causes central nervous system depression, including coma, and is potentially lethal. Its major causes (other than thiazide therapy) are hyperparathyroidism and cancer, with or without bone metastases.
- Less common causes are hypervitaminosis D, sarcoidosis, thyrotoxicosis, milk-alkali syndrome, adrenal insufficiency, and immobilization.

➤ Drugs used in Hypercalcemia:

- Adverse effects observed—at the higher doses used for testing fluoride's effect on bone—include nausea and vomiting, gastrointestinal blood loss, arthralgias, and arthritis in a substantial proportion of patients.

7- STRONTIUM RANELATE

- Strontium ranelate appears to block differentiation of osteoclasts while promoting their apoptosis, thus inhibiting bone resorption.

- Saline Diuresis,
Bisphosphonates,
Calcitonin, Gallium
Nitrate, Plicamycin
(Mithramycin),
Phosphate,
Glucocorticoids.

• HYPOCALCEMIA

- The main features of hypocalcaemia are neuromuscular—tetany, paresthesias, laryngospasm, muscle cramps, and seizures. The major causes of hypocalcaemia in the adult are hyperparathyroidism, vitamin D deficiency, chronic kidney disease, and malabsorption.
- Neonatal hypocalcaemia is a common disorder that usually resolves without therapy large infusions of citrated blood can produce hypocalcaemia secondary to the formation of citrate-calcium complexes.

➤ **Drugs used in hypocalcaemia:**

- Calcium
- Vitamin D

• HYPERPHOSPHATEMIA

- Hypophosphatemia is a common complication of renal failure and is also found in all types of hyperparathyroidism (idiopathic, surgical and pseudohypoparathyroidism), vitamin D intoxication, and the rare syndrome of tumoral calcinosis (usually due to insufficient bioactive FGF23).
- Emergency treatment of hypophosphatemia is seldom necessary but can be achieved by dialysis or glucose and insulin infusions.
- Control of hypophosphatemia involves restriction of dietary phosphate plus phosphate-binding gels such as sevelamer, or lanthanum carbonate and calcium supplements.

- In patients with chronic kidney disease enthusiasm for the use of large doses of calcium to control hypophosphatemia has waned because of the risk of ectopic calcification.

- **HYPOPHOSPHATEMIA**

- Hypophosphatemia is associated with a variety of conditions, including primary hyperparathyroidism, vitamin D deficiency, idiopathic hypercalciuria, conditions associated with increased bioactive FGF23.
- Hypophosphatemia should be avoided when using forms of therapy that can lead to it (eg, phosphate binders, certain types of parenteral nutrition) and treated in conditions that cause it, such as the various forms of hypophosphatemic rickets.

SPECIFIC DISORDERS INVOLVING BONE MINERAL REGULATING HORMONES:

- **PRIMARY HYPERPARATHYROIDISM**

- Oral phosphate and bisphosphonates have been tried but cannot be recommended.
- The calcimimetic agent cinacalcet has been approved for secondary hyperparathyroidism
- Primary hyperparathyroidism is often associated with low levels of 25(OH)D, suggesting that mild vitamin D deficiency may be contributing to the elevated PTH levels.

- **HYPOPARATHYROIDISM**

- In PTH deficiency (idiopathic or surgical hyperparathyroidism) or an abnormal target tissue response to PTH (pseudohypoparathyroidism), serum calcium falls and serum phosphate rises.
- Vitamin D and dietary calcium supplements have been used in the past.

- **NUTRITIONAL VITAMIN D DEFICIENCY OR INSUFFICIENCY**

- A level of 25(OH)D above 10 ng/mL is necessary for preventing rickets or osteomalacia.

- **CHRONIC KIDNEY DISEASE**

- The major sequelae of chronic kidney disease that impact bone mineral homeostasis are deficient 1,25(OH)₂D production, retention of phosphate with an associated reduction in ionized calcium levels, and the secondary hyperparathyroidism that results from the parathyroid gland response to lowered serum ionized calcium and low 1,25(OH)₂D.
- In the absence of kidney function, any calcium absorbed from the intestine accumulates in the blood.
- Deferoxamine, an agent used to chelate iron also binds aluminum and is being used to treat this disorder.

• INTESTINAL OSTEODYSTROPHY

- The malabsorption of vitamin D is probably not limited to exogenous vitamin D as the liver secretes into bile a substantial number of vitamin D metabolites and conjugates that are normally reabsorbed in the distal jejunum and ileum. Interference with this process could deplete the body of endogenous vitamin D metabolites in addition to limiting absorption of dietary vitamin D.
- In mild forms of malabsorption, high doses of vitamin D should suffice to raise serum levels of 25(OH)D into the normal range.
- Calcifediol should be the drug of choice.

• OSTEOPOROSIS

- Osteoporosis is defined as abnormal loss of bone predisposing to fractures. It is most common in postmenopausal women but also occurs in men.

➤ Used in Osteoporosis :

- Bisphosphonates are potent inhibitors of bone resorption.
- Alendronate, Risedronate, Ibandronate and zoledronate.
- The SERM Raloxifene.
- Teriparatide.
- Calcitonin and Denosumab use in the treatment of postmenopausal osteoporosis.

• PSEUDOVITAMIN D DEFICIENCY RICKETS & HEREDITARY VITAMIN D-RESISTANT RICKETS

- These distinctly different autosomal recessive diseases present as childhood rickets that do not respond to conventional doses of vitamin D.
- Pseudovitamin D deficiency rickets is due to an isolated deficiency of 1,25(OH)₂D production caused by mutations in 25(OH)-D-1 α -hydroxylase (CYP27B1).

- This condition is treated with calcitriol (0.25–0.5 mcg daily).

- **NEPHROTIC SYNDROME**

- Patients with nephrotic syndrome can lose vitamin D metabolites in the urine, presumably by loss of the vitamin D-binding protein.
- **OTHER DISORDERS OF BONE MINERAL HOMEOSTASIS**

- **PAGET'S DISEASE OF BONE**

- Paget's disease is a localized bone disorder characterized by uncontrolled osteoplastic bone resorption with secondary

increases in poorly organized bone formation.

- Calcitonin and bisphosphonates are the first-line agents for this disease.
- Sodium etidronate, alendronate, risedronate, and tiludronate are the bisphosphonates currently approved for clinical use in Paget's disease of bone.
- The use of a potentially lethal cytotoxic drugs such as Plicamycin in a generally benign disorder such as Paget's disease is recommended only when other less toxic agents (calcitonin, alendronate) have failed and the symptoms are debilitating.

SUMMARY Major Drugs Used in Diseases of Bone Mineral Homeostasis

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Toxicities
VITAMIN D, METABOLITES, ANALOGS				
<ul style="list-style-type: none"> • Cholecalciferol (D₃) • Ergocalciferol (D₂) • Calcitriol • Doxercalciferol • Paricalcitol • Calcipotriene 	Regulate gene transcription via the vitamin D receptor	<p>Stimulate intestinal calcium absorption, bone resorption, renal calcium and phosphate reabsorption • decrease parathyroid hormone (PTH)</p> <ul style="list-style-type: none"> • promote innate immunity • inhibit adaptive immunity 	Osteoporosis, osteomalacia, renal failure, malabsorption, psoriasis	<p>Hypercalcemia, hypercalciuria</p> <ul style="list-style-type: none"> • the vitamin D preparations have much longer half-lives than the metabolites and analogs
BISPHOSPHONATES				
<ul style="list-style-type: none"> • Alendronate • Risedronate • Ibandronate • Pamidronate • Zoledronate 	Suppress the activity of osteoclasts in part via inhibition of farnesyl pyrophosphate synthesis	Inhibit bone resorption and secondarily bone formation	Osteoporosis, bone metastases, hypercalcemia	Adynamic bone, possible renal failure, rare osteonecrosis of the jaw, rare subtrochanteric (femur) fractures
HORMONES				
<ul style="list-style-type: none"> • Teriparatide • Calcitonin 	These hormones act via their cognate G protein-coupled receptors	Teriparatide stimulates bone turnover • calcitonin suppresses bone resorption	Both are used in osteoporosis • calcitonin is used for hypercalcemia	Teriparatide may cause hypercalcemia and hypercalciuria
SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)				
<ul style="list-style-type: none"> • Raloxifene 	Interacts selectively with estrogen receptors	Inhibits bone resorption without stimulating breast or endometrial hyperplasia	Osteoporosis	<p>Does not prevent hot flashes</p> <ul style="list-style-type: none"> • increased risk of venous thromboembolism



section 8

CHEMOTHERAPEUTIC DRUGS

43 - Beta-Lactam & Other Cell Wall- & Membrane -Active Antibiotics .

44 - Tetracyclines, Macrolides, Clindamycin Chloramphenicol, Streptogramins, & Oxazolidinones .

45 - Aminoglycosides & Spectinomycin .

46 - Sulfonamides, Trimethoprim, & Quinolones .

47 - Antimycobacterial Drugs .

48 - Antifungal Agents .

49 - Antiviral Agents .

50 - Miscellaneous Antimicrobial Agents; Disinfectants,



43. BETA-LACTAM COMPOUNDS.43 Beta-Lactam & Other cell Wall- & Membrane-active antibiotics

The penicillins share similar:

- features of chemistry
- mechanism of action.
- pharmacologic and immunologic characteristics

with: cephalosporins, monobactams, carbapenems, and β -lactamase inhibitors

Their name originate from the four membered β -lactamring in their structure.

PENICILLINS



Classification:

2. Antistaphylococcal penicillins (eg, nafcillin)

1. Penicillins (eg, penicillin G)

3. Extended-spectrum penicillins (aminopenicillins and antipseudomonal penicillins)

Mechanisms of Resistance:

Resistance to penicillins and other β -lactams is due to one of four general mechanisms:

- **inactivation of antibiotic by β -lactamase**
 - ❖ most important and most common.
 - ❖ hydrolyzes beta-lactam ring causing inactivation.
 - ❖ β -lactamase produced by bacteria such as *Staphylococcus aureus*, *Haemophilus influenzae*, and *Escherichia coli*, are relatively narrow in substrate specificity, preferring penicillins to cephalosporins.
- **modification of target PBPs (Penicillin-binding protein, An enzyme)**
 - ❖ responsible for methicillin resistance in staphylococci and penicillin resistance in pneumococci and enterococci. (These resistant organisms produce PBPs that have low affinity for binding β -lactam).
- **impaired penetration of drug to target PBPs**
 - ❖ which occurs only in G-negative species, is due to impermeability of the outer membrane that is present in G-negative but not in G-positive bacteria.

Subclass, drug	Mechanism of action	Effect	Clinical application	Adverse effect	Pharmacokinetic, Interaction
PENICILLINS					
PenicillinG (Narrow spectrum penicillin)	Inhibit bacterial growth through Preventing bacterial cell wall synthesis by binding to and inhibiting cell wall	Rapid bactericidal activity against susceptible bacteria, gram-positive organisms, gram-negative cocci, and non- β -lactamase-producing anaerobes. and little activity against gram-negative rods	Streptococcal infections, meningococcal infections, neurosyphilis	*Immediate hypersensitivity, Rash. *In patients with renal failure; penicillin in high doses can cause seizures. * Secondary infections such as vaginal candidiasis may occur.	*IV administration of PenicillinGis preferred to the IM route because of irritation and local pain from IM injection of large doses. *rapid renal clearance($t_{1/2}$ is 30 min, so requires dosing every 4 hrs). In renal failure, it may be as long as 10 hours.

Penicillin V (Narrow spectrum penicillin)	Transpeptidases		indicated only in minor infections due relatively poor bioavailability, the need for dosing four times a day, and its narrow antibacterial spectrum.	Large doses of penicillins given orally : gastrointestinal upset, particularly nausea, vomiting, and diarrhea	Oral administration, low systemic levels limit widespread use
Ampicillin, amoxicillin, ticarcillin, piperacillin (broad - spectrum penicillins)	Greater activity versus gram-negative bacteria; addition of β-lactamase inhibitor (such as clavulanic acid, sulbactam, or tazobactam) restores activity against many β-lactamase-producing bacteria		<p>Amoxicillin is given orally to treat urinary tract infections, sinusitis, otitis, and lower respiratory tract infections.</p> <p>Ampicillin and Amoxicillin are the most active of the oral β-lactam antibiotics against pneumococci with elevated MICs to penicillin and are the preferred β-lactam antibiotics for treating infections suspected to be caused by these strains.</p> <p>Ampicillin is effective for shigellosis.</p>	<p>*Ampicillin has been associated with pseudomembranous Colitis.</p> <p>*Ampicillin and amoxicillin can be associated with skin rashes when prescribed in the setting of viral illnesses, particularly noted during acute Epstein-Barr virus infection.</p>	<p>* secreted more slowly than penicillin G and have t_{1/2} of 1 hour.</p> <p>*ampicillin, and amoxicillin are acid-stable and relatively well absorbed.</p>



Benzathine penicillin, Procaine penicillinG			treatment for β -hemolytic streptococcal pharyngitis, syphilis		IM administration, long-acting formulations
Nafcillin oxacillin Methicillin <Dicloxacillin Cloxacillin> (isoxazolyl penicillin) (Penicillinase-Resistant penicillins)		These semisynthetic penicillins are resistant to staphylococcal β lactamases. They are active against staphylococci and streptococci but not against enterococci, anaerobic bacteria, and gram-negative cocci and rods.	serious systemic staphylococcal infections.	*Nafcillin associated with neutropenia. *Oxacillin can cause hepatitis. * Methicillin causes interstitial nephritis (and is no longer used for this reason).	*Gastrointestinal absorption of Nafcillin is erratic, so it is not suitable for oral administration > only IV,IM form . *Isoxazolypenicillins are relatively acid-stable and can be given orally . *Nafcillin is primarily cleared by biliary excretion * Oxacillin, dicloxacillin, and cloxacillin are eliminated by both the kidney and biliary excretion.

Side notes about Penicillins :

1. Administration: is determined by the stability of drug
Absorption: most oral penicillins (amoxicillin being an exception) is impaired by food, and the drugs should be administered at least 1–2 hours before or after a meal.
2. Distribution: Penicillin are widely distributed in body fluids and tissues with a few exceptions.
3. Penicillins concentrations in most tissues are equal to those in serum. Penicillin is also excreted into sputum and breast milk to levels 3–15% of those in the serum.
4. Except for amoxicillin, oral penicillins should be given 1–2 hours before or after a meal; they should not be given with food to minimize binding to food proteins and acid inactivation.
5. Allergic reactions include anaphylactic shock (very rare—0.05% of recipients); serum sickness-type reactions (now rare—urticaria, fever, joint swelling, angioneurotic edema, intense pruritus, and respiratory compromise occurring 7–12 days after exposure); and a variety of skin rashes. Oral lesions, fever, interstitial nephritis (an autoimmune reaction to a penicillin-protein complex), eosinophilia, hemolytic anemia and other hematologic disturbances, and vasculitis may also occur.

TABLE 43–1 Guidelines for dosing of some commonly used penicillins.

Antibiotic (Route of Administration)	Adult Dose	Pediatric Dose ¹	Neonatal Dose ²	Adjusted Dose as a Percentage of Normal Dose for Renal Failure Based on Creatinine Clearance (Cl_{cr})	
				Cl_{cr} Approx 50 mL/min	Cl_{cr} Approx 10 mL/min
Penicillins					
Penicillin G (IV)	$1\text{--}4 \times 10^6$ units q4–6h	25,000–400,000 units/kg/d in 4–6 doses	75,000–150,000 units/kg/d in 2 or 3 doses	50–75%	25%
Penicillin V (PO)	0.25–0.5 g qid	25–50 mg/kg/d in 4 doses		None	None
Antistaphylococcal penicillins					
Cloxacillin, dicloxacillin (PO)	0.25–0.5 g qid	15–25 mg/kg/d in 4 doses		100%	100%
Nafcillin (IV)	1–2 g q4–6h	50–100 mg/kg/d in 4–6 doses	50–75 mg/kg/d in 2 or 3 doses	100%	100%
Oxacillin (IV)	1–2 g q4–6h	50–100 mg/kg/d in 4–6 doses	50–75 mg/kg/d in 2 or 3 doses	100%	100%
Extended-spectrum penicillins					
Amoxicillin (PO)	0.25–0.5 g tid	20–40 mg/kg/d in 3 doses		66%	33%
Amoxicillin/potassium clavulanate (PO)	500/125 mg tid–875/125 mg bid	20–40 mg/kg/d in 3 doses		66%	33%
Piperacillin (IV)	3–4 g q4–6h	300 mg/kg/d in 4–6 doses	150 mg/kg/d in 2 doses	50–75%	25–33%
Ticarcillin (IV)	3 g q4–6h	200–300 mg/kg/d in 4–6 doses	150–200 mg/kg/d in 2 or 3 doses	50–75%	25–33%

¹The total dose should not exceed the adult dose.

²The dose shown is during the first week of life. The daily dose should be increased by approximately 33–50% after the first week of life. The lower dosage range should be used for neonates weighing less than 2 kg. After the first month of life, pediatric doses may be used.

CEPHALOSPORINS

Drug	Mechanism of action	Effect	Clinical use	Adverse effect	Pharmacokinetics
Cefazolin	Prevents bacterial cell wall synthesis by binding to and inhibiting cell wall Transpeptidases	Rapid bactericidal activity against susceptible bacteria	Skin and soft tissue infections, urinary tract infections, drug of a choice for surgical prophylaxis.	A. Allergy (because the structure similarity to the penicillin ,some patient allergic to penicillin may be allergic to cephalosporin) anaphylaxis, fever, skin rashes, nephritis *, granulocytopenia *, and hemolytic anemia*	*IV , IM administration renal clearance (half-life1.5 h) • given every 8 h • poor penetration into the central nervous system (CNS)
Cephalexin			Active against gram-positive cocci , skin and soft tissue infections such as cellulitis or soft tissue abscess. and urinary tract infections	B. Toxicity: Local irritation after IM injection and Thrombophlebitis *after IV injection. Renal toxicity, including interstitial nephritis*and tubular necrosis*.	*absorbed from the gut to a variable extent. *Excretion is mainly by glomerular filtration and tubular secretion into the urine
Cefuroxime		improved activity versus pneumococcus and Haemophilus influenza	treat community-acquired pneumonia, sinusitis, otitis. Although cefuroxime crosses the BBB, it is less effective in treatment of meningitis than ceftriaxone or cefotaxime and should not be used.	Cephalosporins that contain a methylthiotetrazole group may cause hypoprothrombinemia and bleeding disorders, severe disulfiram-like reactions.	*oral administration * It is excreted by the kidney
Cefotetan, cefoxitin		mixed anaerobic infections active againstBacteroidesfragilis.	abdominal/pelvic infections(peritonitis, diverticulitis, and pelvic inflammatory disease)		It is excreted by the kidney

Ceftriaxone		the drug of choice for treating gonococcal infections.	meningitis, pyelonephritis, and gonorrhea	* mixed clearance with long half-life (6 hours) can be injected once every 24 hours *good CNS penetration.
Ceftazidime , cefoperazone		only two drugs with useful activity against <i>P aeruginosa</i>		It is excreted by the kidney and (half-life 1–1.7 hours)
Cefepime		broad activity with improved stability to chromosomal β lactamase *good activity against <i>P aeruginosa</i> , Enterobacteriaceae, <i>S aureus</i> , and <i>S pneumoniae</i> . * It is highly active against <i>Haemophilus</i> and <i>Neisseria</i> sp.		Intravenous administration. It penetrates well into cerebrospinal fluid. It is cleared by the kidneys and has a half-life of 2 hours, and its pharmacokinetic properties are very similar to those of ceftazidime.

CEPHALOSPORIN ACCORDING TO SPECTRUM ACTIITY

st 1 Generation	(cefaZolin, cefadroxil, cephalexin, cephalothin, cephapirin, and cephadrine) active against gram-positive cocci, such as streptococci and staphylococci , <i>E coli</i> , <i>K pneumoniae</i>
nd 2 Generation	(cefaclor, cefamandole, cefonicid, cefuroxime, cefprozil, loracarbef, and ceforanide; cefoxitin, cefmetazole, and cefotetan) extended gram-negative coverage. <i>Klebsiella</i> sp, <i>H influenza</i>
rd 3 Generation	(cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, cefixime, cefpodoxime proxetil, cefdinir, cefditoren pivoxil, ceftibuten, and moxalactam.) expanded gram-negative coverage, against <i>Citrobacter</i> , <i>S marcescens</i> , and <i>Providencia</i> . They are also effective against β -lactamase-producing strains of <i>haemophilus</i> and <i>Neisseria</i>
th 4 Generation	(Cefepime) good activity against <i>P aeruginosa</i> , Enterobacteriaceae, <i>S aureus</i> , and <i>S pneumoniae</i> . It is highly active against <i>Haemophilus</i> and <i>Neisseria</i> sp, and good activity against most penicillin-non-susceptible strains of streptococci, enterobacter infections, these are comparable to third generation but more resistance to some β -lactamse.

Cephalosporins Active against



Methicillin-Resistant Staphylococci

- currently under development range of antibiotics .
- **Ceftaroline and fosamil**, the prodrug of the active metabolite ceftaroline, has increased binding to penicillin-binding protein 2a, which mediates methicillin resistance in staphylococci, resulting in bactericidal activity against these strains.
- It has some activity against enterococci and a broad gram-negative spectrum
- It is not active against AmpC or extended-spectrum -lactamase-producing organisms.
- Ceftaroline is currently approved for the treatment of skin and soft tissue infections and community-acquired pneumonia.

MONOBACTAMS					
Drug	Mechanism of action	Effect	Clinical application	Adverse effect	Pharmacokinetic, Interaction
Aztreonam	The bactericidal*action of aztreonam results from the inhibition of bacterial cell wall synthesis	The activity is limited to aerobic gram-negative rods (including <i>P aeruginosa</i>).	In patients with a history of penicillin anaphylaxis, aztreonam may be used to treat serious infections such as Pneumonia*, Meningitis*and sepsis*	skin rashes and elevations of serum aminotransferases , No cross allergenicity with penicillins	*IV administration. * penetrates well into the cerebrospinal fluid. • renal clearance half-life 1-2 hrs and is greatly prolonged in renal failure • dosed every 8 h .

BETA-LACTAMASE INHIBITORS

(CLAVULANIC ACID, SULBACTAM, & TAZOBACTAM)	A beta-lactamase inhibitor is a molecule used in conjunction with a beta-lactam antibiotic to extend its spectrum of activity.	staphylococci, H influenzae, N gonorrhoeae, salmonella, shigella, E coli, and K pneumoniae.	empirical therapy for infections caused by a wide range of potential pathogens in both immunocompromised and immunocompetent patients and treatment of mixed aerobic and anaerobic infections, such as intra-abdominal infections.		Doses are the same as those used for the single agents except that the recommended dosage of piperacillin in the piperacillin-tazobactam combination is 3–4 g every 6 hours.
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CARBAPENEMS					
Drug	Mechanism of Action	Effect	Clinical Uses	Adverse effect	Pharmacokinetics
Imipenem-cilastatin	Prevents bacterial cell wall synthesis by binding to and inhibiting cell wall transpeptidases	Rapid bactericidal Activity wide spectrum with good activity against many gram-negative rods, including <i>P aeruginosa</i> , gram-positive organisms, and anaerobes.	Serious infections such as pneumonia and sepsis. carbapenem is indicated for infections caused by susceptible organisms that are resistant to other available drugs, eg, <i>P aeruginosa</i> , and for treatment of mixed aerobic and anaerobic infections	Seizures especially in renal failure or with high doses (>2 g/d nausea, vomiting diarrhea, skin rashes, and reactions at the infusion sites.)	IV administration renal clearance (half-life 1 h), dosed every 6–8 h, cilastatin added to prevent hydrolysis by renal dehydropeptidase
Meropenem, doripenem		Similar to imipenem		Less produse seizures and less side effects.	IV administration. renal clearance. Not metabolized by renal dehydropeptidase and do not

require an inhibitor.

Ertapenem	Similar to meropenem, less active than the other carbapenems against <i>P aeruginosa</i> and <i>Acinetobacter</i> . Intravenously or intramuscular Administration . Has the longest half-life (4 hours).				



GLYCOPEPTIDE

Vancomycin	<p>Inhibits cell wall synthesis by binding to the d-Ala-d-Ala terminus of nascent peptidoglycan. This inhibits preventing further elongation of peptidoglycan and cross-linking. The peptidoglycan is thus weakened, and the cell becomes susceptible to lysis.</p>	<p>Bactericidal activity against susceptible bacteria, slower kill than β-lactam antibiotics.</p> <p>*It is active only against gram-positive bacteria including <i>C difficile</i>.</p>	<p>parenteral vancomycin are bloodstream infections and endocarditis caused by methicillin-resistant staphylococci, Infections caused by gram-positive bacteria including sepsis, endocarditis, and meningitis <i>C difficile</i> colitis (oral formulation)</p> <p>Vancomycin in combination with gentamicin is an alternative regimen for treatment of enterococcal endocarditis in a patient with serious penicillin allergy.</p>	<p>"Red man" syndrome * and Ototoxicity*</p>	<p>Oral, IV administration Vancomycin is poorly absorbed from the intestinal tract and is administered orally only for the treatment of colitis caused by <i>C difficile</i></p> <ul style="list-style-type: none"> • renal clearance (halflife 6 h)
Teicoplanin	<p>Intravenous, similar to vancomycin except that it can be given as IM and IV .long half-life (45–70 h) permits once-daily dosing</p>	Dalbavancin	<p>Dalbavancin shares the same mechanism of action as vancomycin and teicoplanin but has improved activity against many gram-positive bacteria including methicillin-resistant and vancomycin-intermediate <i>S aureus</i>.</p> <p>It is not active against most strains of vancomycin-resistant enterococci.</p> <p>Intravenous, very long half-life (6–11 days) permits once-weekly dosing, more active than vancomycin.</p>		



Telavancin	<p>active against gram-positive bacteria.</p> <p>Intravenous, dual mechanism of action(Telavancin has two mechanisms of action. Like vancomycin, telavancin inhibits cell wall synthesis by binding to the d-Ala-d-Ala terminus of peptidoglycan in the growing cell wall. In addition, it disrupts the bacterial cell membrane potential and increases membrane permeability)results in improved activity against bacteria with reduced susceptibility to vancomycin, once-daily dosing</p> <p>The half-life of telavancin is approximately 8 hours.</p> <p>Telavancin is potentially teratogenic, so administration to pregnant women must be avoided.</p>				
LIPOPEPTIDE					
Daptomycin	Binds to cell membrane, causing depolarization and rapid cell death	More rapidly bactericidal than vancomycin <p>Its spectrum of activity is similar to that of vancomycin except that it may be active against vancomycin-resistant strains of enterococci and <i>S aureus</i>.</p>	Infections caused by gram-positive bacteria including sepsis and endocarditis, skin and soft tissue infections, bacteremia.	Myopathy* monitoring of weekly creatine phosphokinase levels <p>*recommended allergic pneumonitis in patients receiving prolonged therapy (>2 weeks).</p>	IV administration renal clearance (half-life 8 h) • dosed once daily • inactivated by pulmonary surfactant so cannot be used to treat pneumonia
FOSFOMYCIN	Inhibits cell wall synthesis by inhabiting enolpyruvate transferase (MurA), which prevents the formation of N-acetylmuramic acid, an essential element of the	gram-positive and gram negative organisms	treatment of uncomplicated lower urinary tract infections in women. <p>The drug appears to be safe for use in</p>		*oral and IV The half-life is approximately 4 hours. The active drug is excreted by the kidney



	peptidoglycan cell wall.		<u>pregnancy.</u>		
CYCLOSERINE	is a structural analog of d-alanine and inhibits the incorporation of d-alanine into peptidoglycan pentapeptide by inhibiting alanine racemase, which converts l-alanine to d-alanine, and d-alanyl-d-alanine ligase	inhibits many gram-positive and gram-negative organisms, but it is used almost exclusively for <i>Mycobacterium tuberculosis</i>	tuberculosis caused by strains of <i>Mycobacterium tuberculosis</i> resistant to first-line agent as a second line therapy.	serious dose-related central nervous system toxicity with headaches, tremors, acute psychosis, and convulsions*	The drug is widely distributed in tissues Most of the drug is excreted in active form into the urine.
BACITRACIN	inhibits cell wall formation by interfering with dephosphorylation in cycling of the lipid carrier that transfers peptidoglycan subunits to the growing cell wall	It is active against gram-positive microorganisms.	(often combined with polymyxin or neomycin) suppression of mixed bacterial flora in surface lesions of the skin, in wounds, or on mucous membranes. Solutions of bacitracin in saline can be used for irrigation of joints, wounds, or the pleural cavity.	Nephrotoxic when administered systemically	Topical application only



TABLE 43-2 Guidelines for dosing of some commonly used cephalosporins and other cell-wall inhibitor antibiotics.

Antibiotic (Route of Administration)	Adult Dose	Pediatric Dose ¹	Neonatal Dose ²	Clcr Approx 50 mL/min	Clcr Approx 10 mL/min
Adjusted Dose as a Percentage of Normal Dose for Renal Failure Based on Creatinine Clearance (Cl_{cr})					
First-generation cephalosporins					
Cefadroxil (PO)	0.5–1 g qd–bid	30 mg/kg/d in 2 doses		50%	25%
Cephalexin, cephadrine (PO)	0.25–0.5 g qid	25–50 mg/kg/d in 4 doses		50%	25%
Cefazolin (IV)	0.5–2 g q8h	25–100 mg/kg/d in 3 or 4 doses		50%	25%
Second-generation cephalosporins					
Cefoxitin (IV)	1–2 g q6–8h	75–150 mg/kg/d in 3 or 4 doses		50–75%	25%
Cefotetan (IV)	1–2 g q12h			50%	25%
Cefuroxime (IV)	0.75–1.5 g q8h	50–100 mg/kg/d in 3 or 4 doses		66%	25–33%
Third- and fourth-generation cephalosporins including ceftaroline fosamil					
Cefotaxime (IV)	1–2 g q6–12h	50–200 mg/kg/d in 4–6 doses	100 mg/kg/d in 2 doses	50%	25%
Ceftazidime (IV)	1–2 g q8–12h	75–150 mg/kg/d in 3 doses	100–150 mg/kg/d in 2 or 3 doses	50%	25%
Ceftriaxone (IV)	1–4 g q24h	50–100 mg/kg/d in 1 or 2 doses	50 mg/kg/d qd	None	None
Cefepime (IV)	0.5–2 g q12h	75–120 mg/kg/d in 2 or 3 divided doses		50%	25%
Ceftaroline fosamil (IV)	600 mg q12h			50–66%	33%
Carbapenems					
Ertapenem (IM or IV)	1 g q24h			100% ³	50%
Doripenem	500 mg q8h			50%	33%
Imipenem (IV)	0.25–0.5 g q6–8h			75%	50%
Meropenem (IV)	1 g q8h (2 g q8h for meningitis)	60–120 mg/kg/d in 3 doses (maximum of 2 g q8h)		66%	50%
Glycopeptides					
Vancomycin (IV)	30–60 mg/kg/d in 2–3 doses	40 mg/kg/d in 3 or 4 doses	15 mg/kg load, then 20 mg/kg/d in 2 doses	40%	10%
Lipopeptides (IV)					
Daptomycin	4–6 mg/kg IV daily			None	50%
Telavancin	10 mg/kg IV daily			75%	50%

¹The total dose should not exceed the adult dose.

²The dose shown is during the first week of life. The daily dose should be increased by approximately 33–50% after the first week of life. The lower dosage range should be used for neonates weighing less than 2 kg. After the first month of life, pediatric doses may be used.

³50% of dose for Cl_{cr}< 30 mL/min.

: مصطلحات

bactericidal *(Causing the death of bacteria)

seizures*(is a sudden surge of electrical activity in the brain)

neutropenia*(low number of cells called neutrophils)

hepatitis*(is an inflammation of the liver)

Colitis*(is inflammation of the colon associated with an overgrowth of the bacterium Clostridium difficile (C. diff)).

nephritis *(inflammation of the kidneys and may involve the glomeruli, tubules, or interstitial tissue surrounding the glomeruli and tubules),

granulocytopenia* (a decrease in the number of white blood cells, also referred to as granulocytes)

hemolytic anemia*(condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over)

Thrombophlebitis*(superficial thrombophlebitis is an inflammatory condition of the veins due to a blood clot below the surface of the skin)

interstitial nephritis*(is a form of nephritis affecting the interstitium of the kidneys surrounding the tubules)

Pneumonia*(lung infection caused by bacteria, a virus or fungi)

Meningitis*(infection that affects the delicate membranes called meninges that cover the brain and spinal cord),

tubular necrosis*(Involving the death of tubular epithelial cells that form the renal tubules of the kidneys)

sepsis*(the presence of pathogenic organisms or their toxins in the blood and tissues)

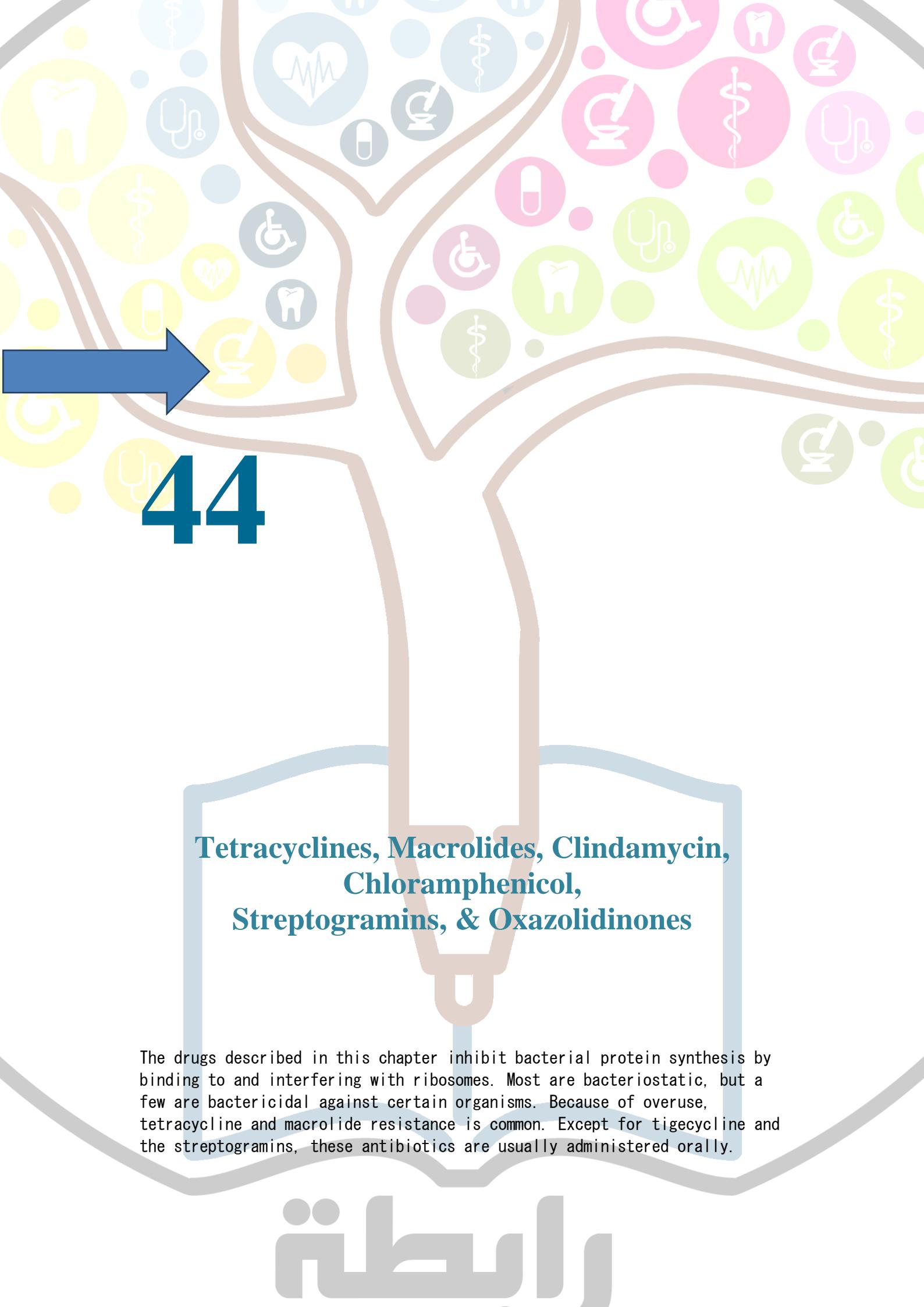
"Red man" syndrome *(**negative reaction that can occur when the antibiotic vancomycin is administered intravenously**)

Ototoxicity*(damage to the hearing or balance functions of the ear by drugs or chemicals)

Myopathy*(a group of disorders characterized by a primary structural or functional impairment of skeletal muscle).

creatine phosphokinase levels (measures the amount of creatine phosphokinase (CPK) present in the blood) convulsions* (medical condition where body muscles contract and relax rapidly and repeatedly, resulting in an uncontrolled shaking of the body)





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Tetracyclines, Macrolides, Clindamycin, Chloramphenicol, Streptogramins, & Oxazolidinones

The drugs described in this chapter inhibit bacterial protein synthesis by binding to and interfering with ribosomes. Most are bacteriostatic, but a few are bactericidal against certain organisms. Because of overuse, tetracycline and macrolide resistance is common. Except for tigecycline and the streptogramins, these antibiotics are usually administered orally.



Tetracyclines :

Tetracyclines are classified as short-acting (chlortetracycline, tetracycline, oxytetracycline), intermediate-acting (demeclocycline and methacycline), or long-acting (doxycycline and minocycline) based on serum half-lives of 6–8 hours, 12 hours, and 16–18 hours, respectively.

Subclass, drug	Mechanism of action	Effect	Clinical application	Adverse effect	Pharmacokinetic, Interaction
TETRACYCLINES					
Tetracycline	<p>Mechanism of Action: Prevents bacterial protein synthesis by binding reversibly to the 30S ribosomal subunit blocking the binding of aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex. This prevents addition of amino acids to the growing peptide.</p> <p>Mechanism of resistance: * impaired influx or increased efflux by an active transport protein pump. * ribosome protection due to production of proteins that interfere with tetracycline binding to the</p>	<p>Bacteriostatic activity against susceptible bacteria (gram-positive and gram-negative bacteria, including certain anaerobes, rickettsiae, chlamydiae, and mycoplasmas)</p> <p>tetracycline-resistant strains may be susceptible to doxycycline, minocycline, and tigecycline, all of which are poor substrates for the efflux pump, if that is the mechanism of resistance.</p>	<p>Infections caused by mycoplasma, chlamydiae, rickettsiae, some spirochetes • malaria • used in combination regimens to treat gastric and duodenal ulcer disease caused by <i>H pylori</i> • acne</p>	<p>Gastrointestinal upset, Hepatotoxicity, photosensitivity, deposition in bone and teeth As a result of chelation with calcium.</p>	<ul style="list-style-type: none"> Oral Administration <ul style="list-style-type: none"> mixed clearance (half-life 8 h) dosed every 6 h Absorption occurs mainly in the upper small intestine. Impaired by food by multivalent cations (Ca²⁺, Mg²⁺, Fe²⁺, Al³⁺); by dairy products and antacids, which contain multivalent cations; and by alkaline pH
Doxycycline			<p>Community acquired pneumonia and exacerbations of bronchitis. Doxycycline, in combination with ceftriaxone, is an alternative treatment for gonococcal disease</p>	<p>reversible vestibular toxicity, higher doses of doxycycline cause Dizziness, vertigo, nausea, and vomiting</p>	<p>Oral and IV Administration, longer half-life (18 h) so dosed twice daily; nonrenal elimination; absorption is minimally affected by divalent cations Carbamazepine, phenytoin, barbiturates, and chronic alcohol ingestion may shorten the half-life of doxycycline by 50% due to induction of hepatic</p>



	ribosome. *enzymatic inactivation.				enzymes
Minocycline			Very high concentrations in tears and saliva, which makes it useful for eradication of the meningococcal carrier state.	Dizziness, vertigo, nausea, and vomiting	Oral Administration. The almost complete absorption and slow excretion of doxycycline and minocycline allow for once-daily dosing for certain indications, but, by convention, these two drugs are usually dosed twice daily. longer half-life (16 h) so dosed twice daily.
Tigecycline		very broad spectrum of activity against gram positive, gram-negative, and anaerobic bacteria; (methicillin-Resistant <i>S. aureus</i> (MRSA), Vancomycin-Resistant Enterococci (VRE). Many tetracycline-resistant strains are susceptible to tigecycline	skin and skin structure infection, intra-abdominal infections, and community acquired pneumonia. tigecycline may not be effective for urinary tract infections and has no indication for this use.	nausea and vomiting, doesn't require discontinuation of drug. tigecycline was associated with a small but significant increase in the risk of death. This has led the FDA to issue a black box warning that tigecycline should be reserved for situations where alternative treatments are not suitable.	IV Administration, eliminated by nonrenal mechanisms. half-life of 36 hours.

Notes on Tetracyclines:



- ❖ Tetracyclines are excreted mainly in bile and urine.
- ❖ Tetracyclines cross the placenta to reach the fetus and are also excreted in breast milk.
- ❖ A tetracycline—in combination with other antibiotics—is indicated for plague, tularemia, and brucellosis.
- ❖ sometimes used in the treatment or prophylaxis of protozoal infections, eg, those due to *Plasmodiumfalciparum*.
- ❖ Other uses include treatment of , Lyme disease, relapsing fever, leptospirosis, and some nontuberculous mycobacterial infections (eg, *Mycobacterium marinum*).
- ❖ **Demeclocycline** inhibits the action of antidiuretic hormone and has been used in the treatment of inappropriate secretion of antidiuretic hormone or similar peptides by certain tumors
- ❖ Most adverse effects are due to direct toxicity of the drug or to alteration of microbial flora such as intestinal functional disturbances, anal pruritus, vaginal or oral candidiasis, or *Clostridium difficile*-associated colitis.
- ❖ Nausea, vomiting, and diarrhea are the most common reasons for discontinuing tetracyclines and can usually be controlled by administering the drug with food or carboxymethylcellulose, reducing drug dosage, or discontinuing the drug.
- ❖ Intravenous injection can lead to venous thrombosis.
- ❖ Intramuscular injection produces painful local irritation and should be avoided.
- ❖ Systemically administered tetracycline, especially demeclocycline, can induce sensitivity to sunlight or ultraviolet light, particularly in fair-skinned persons.
- ❖ Dosage : IV: 0.1–0.5 g every 6–12 hours., but doxycycline dosage of 100 mg every 12–24 hours.
Oral : 0.25–0.5 g four times daily for adults and 20–40 mg/kg/d for children (8 years of age and older)
600 mg for demeclocycline or methacycline, 100 mg once or twice daily for doxycycline,
and 100 mg twice daily for minocycline.

MACROLIDES

Erythromycin	<p>Mechanism of action : Prevents bacterial protein synthesis by binding to the 50S ribosomal subunitRNA.</p> <p>Mechanism of resistance:</p> <ul style="list-style-type: none"> * reduced permeability of the cell membrane or active efflux. * production (byEnterobacteria ceae) of esterases that hydrolyze macrolides. * modification of the ribosomal binding site (so-called ribosomal protection) by chromosomal mutation or by a macrolide-inducible or constitutive methylase. 	<p>Bacteriostatic against gram positive bacteria including pneumococci, streptococci, staphylococci, and <i>Mycoplasma pneumoniae</i>, <i>Chlamydial H pylori</i>, <i>Listeria</i>, certain mycobacteria</p> <p>Gram-negative organisms such as <i>Neisseria</i> sp., <i>Bordetella</i>, <i>Bartonella</i>, <i>Rickettsia</i> species.</p>	<p>traditional drug of choice in corynebacterial infections (diphtheria, corynebacterial sepsis, erythrasma) and in respiratory, neonatal, ocular, or genital chlamydial infections. Community-acquired pneumonia • pertussis</p>	<p>Gastrointestinal upset, Anorexia, nausea, vomiting, and diarrhea hepatotoxicity, acute cholestatic hepatitis (fever, jaundice, impaired liver function), QTcprolongation</p>	<p>Oral, IV administration</p> <ul style="list-style-type: none"> • hepatic clearance (half-life 1.5 h,5 hours in patients with anuria). •dosed every 6 h <p>It traverses the placenta and reaches the fetus.</p> <ul style="list-style-type: none"> • cytochrome P450 inhibitor. *Erythromycin is destroyed by stomach acid and must be administered with enteric coating. Food interferes with absorption. <p>Cross-resistance is complete between erythromycin and the other macrolides</p> <p>0.5–1.0 g every 6 hours for adults and 20–40 mg/kg/d for children.</p>
Clarithromycin	<p>Its mechanism of action is the same as that of erythromycin.</p>	<p>added activity versus <i>M avium</i> complex, toxoplasma, and <i>M leprae</i> and <i>H influenzae</i>.</p>	<p>The advantages of clarithromycin compared with erythromycin are lower incidence of gastrointestinal intolerance and less frequent dosing.</p>	<p>Oral administration, longer half-life (6 h)</p> <p>500 mg loading dose, then 250 mg once or twice daily</p> <p>Clarithromycin is metabolized in the liver.</p>	



Azithromycin	Its spectrum of activity, mechanism of action, and clinical uses are similar to those of clarithromycin. Slightly more active against <i>H influenzae</i>. And highly active against <i>Chlamydia</i> sp.	Community-acquired pneumonia, chlamydial cervicitis and urethritis	prolong the QT interval can lead to the torsades de pointes arrhythmia. azithromycin may be associated with a small increased risk of cardiac death.	Oral ,IV administration, very long half-life (68 h) 500 mg loading dose, followed by a 250 mg single daily dose for the next 4 –5 days course of therapy of community-acquired pneumonia; does not inhibit cytochrome P450 enzymes, It should be administered 1 hour before or 2 hours after meals
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KETOLIDES

Telithromycin	Similar to erythromycin	<i>Streptococcus pyogenes</i> , <i>S pneumoniae</i> , <i>S aureus</i> , <i>H influenzae</i> , <i>Moraxella</i> s, <i>Mycoplasma</i> sp, <i>Chlamydia</i> sp, <i>H pylori</i> , <i>Neisseria gonorrhoeae</i> , <i>T gondii</i> , many erythromycin-resistant strains of pneumococci; rare cases of fulminant hepatic failure	community-acquired bacterial pneumonia	prolong the QT interval, hepatitis and liver failure. contraindicated in patients with myasthenia gravis because it may exacerbate this condition.	Oral administration, metabolized in the liver. eliminated by a combination of biliary and urinary routes of excretion. reversible inhibitor of the CYP3A4 enzyme system. Once daily dose of 800 mg.
Clindamycin	bacterial protein synthesis by binding to the 50S	Bacteriostatic activity against susceptible	Skin and soft tissue Infections caused by streptococci and	Gastrointestinal upset, diarrhea, nausea, and	Oral, IV administration 90% protein bound.

	<p>ribosomal subunit.</p> <p>Mechanism of resistance:</p> <ul style="list-style-type: none"> *mutation of the ribosomal receptor site. *modification of the receptor by a constitutively expressed methylase. *enzymatic inactivation of clindamycin 	<p>bacteria. <i>Bacteroides</i> spp and other anaerobes, both gram-positive and gram-negative, are usually susceptible.</p> <p>Gram-negative aerobic species are intrinsically resistant because of poor permeability of the outer membrane.</p>	<p>staphylococci, and community-acquired strains of methicillin-resistant <i>S. aureus</i>.</p> <p>Clindamycin, sometimes in combination with an aminoglycoside or cephalosporin, is used to treat penetrating wounds of the abdomen and the gut; infections originating in the female genital tract, eg, septic abortion, pelvic abscesses, or pelvic inflammatory disease; and lung abscesses.</p> <p>prophylaxis of endocarditis in patients with specific valvular heart disease who are undergoing certain dental procedures and have</p>	<p>skin rashes. Impaired liver function (with or without jaundice) and neutropenia (low number of cells called neutrophils.) sometimes occur</p> <p><i>C. difficile</i> colitis</p>	<p>Clindamycin penetrates well into abscesses, phagocytic cells and most tissues, with exceptions of brain and cerebrospinal fluid.</p> <ul style="list-style-type: none"> • hepatic clearance (half-life 2.5 h) excreted in bile and urine. • 0.15–0.3 g every 8 hours (10–20 mg/kg/d for children)
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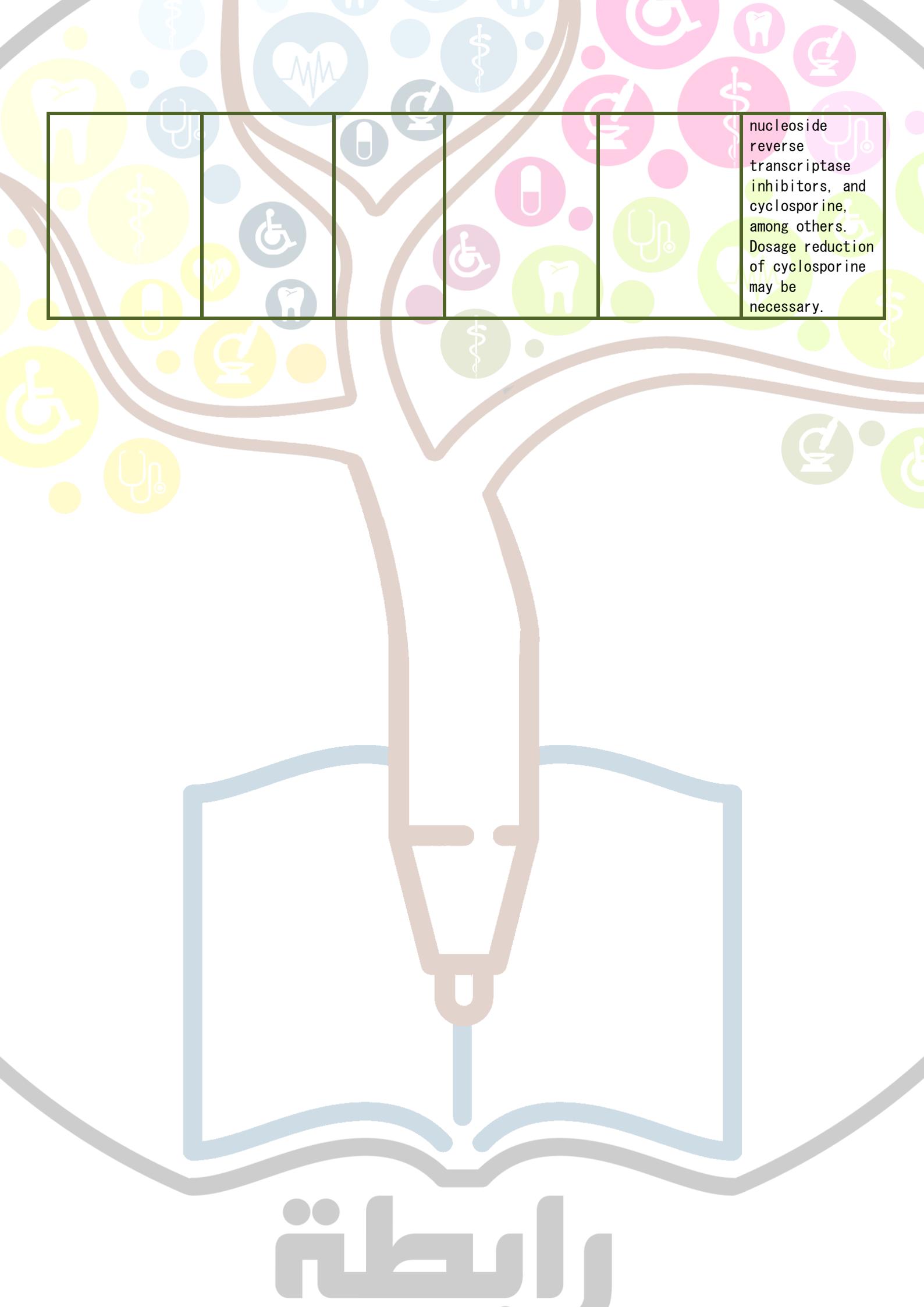
significant penicillin allergies.

Clindamycin + primaquine is an effective alternative to trimethoprim-sulfamethoxazole for moderate to moderately severe pneumonia in AIDS patients. It is also used in combination with pyrimethamine for AIDS-related toxoplasmosis of the brain.

STREPTOGRAMINS

Quinupristin-dalfopristin	Prevents bacterial protein synthesis by binding to the 50S ribosomal subunit. Mechanism of resistance: *modification of the quinupristin binding site (MLS-B type resistance). *enzymatic inactivation of dalfopristin. * efflux.	Rapid bactericidal activity against most susceptible bacteria	Infections caused by staphylococci or vancomycin resistant strains of <i>E faecium</i>	pain at the infusion site, Severe infusion-related myalgias (muscle pain) and arthralgias (pain in joint)	IV administration • hepatic clearance Elimination is principally by the fecal route 7.5 mg/kg every 8–12 hours inhibitor cytochrome P450 which metabolizes warfarin, diazepam, astemizole, terfenadine, cisapride, non-
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nucleoside reverse transcriptase inhibitors, and cyclosporine, among others. Dosage reduction of cyclosporine may be necessary.

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CHLORAMPHENICOL

CHLORAMPHENICOL	<p>Prevents bacterial protein synthesis by binding to the 50S ribosomal subunit.</p> <p>Mechanism of resistance:</p> <ul style="list-style-type: none"> *production of chloramphenicol acetyl transferase, a plasmid-encoded enzyme that inactivates the drug. *decrease permeability to the drug. 	<p>Bacteriostatic activity broad-spectrum antibiotic that is active against both aerobic and anaerobic gram-positive and gram-negative organisms. It is active also against <i>Rickettsiae</i></p> <p><i>H influenzae, Neisseria meningitidis, are highly susceptible, and for these organisms, chloramphenicol may be bactericidal.</i></p>	<p>Use is rare in the developed world because of serious toxicities. rickettsial infections , bacterial meningitis occurring in patients who have major hypersensitivity reactions to penicillin, , eye infections.</p>	<p>nausea, vomiting, and diarrhea , Oral or vaginal candidiasis, Dose-related anemia, idiosyncratic aplastic anemia (condition that occurs when your body stops producing enough new blood cells.), gray baby syndrome (syndrome due to toxicity of the antibiotic chloramphenicol in the newborn, especially the premature newborn)</p>	<p>Oral , topical, IV administration.</p> <p>widely distributed to virtually all tissues and body fluids, including the central nervous system and cerebrospinal fluid</p> <p>*Metabolism conjugated in liver with glucuronic acid.</p> <ul style="list-style-type: none"> • hepatic clearance (half-life 2.5 h) • dosage is 50–100 mg/kg/d in four divided doses <p>inhibits hepatic microsomal enzymes</p>
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Dose :

- ❖ To avoid this toxic effect in infants and the dosage limited to 50 less during the first week of life) in full-term infants more than 1 25 mg/kg/d in premature infants.
- ❖ Adult : The dosage is 50–100 mg/kg/d in four divided doses.



OXAZOLIDINONES

Linezolid	Prevents bacterial protein synthesis by binding to the 23S ribosomal RNA of 50S subunit. Resistance is caused by mutation of the linezolid binding site on 23S ribosomal RNA.	Bacteriostatic activity against susceptible bacteria, it is active against gram-positive organisms including staphylococci, streptococci, enterococci, grampositive anaerobic cocci, and It corynebacteria, <i>Nocardiasp</i> , and <i>L monocytogenes</i> <i>Mycobacterium tuberculosis</i> . bactericidal against streptococci.	Infections caused by methicillin-resistant staphylococci and vancomycin-resistant enterococci. community-acquired pneumonia, and both complicated and uncomplicated skin and soft tissue infections.	Duration dependent bone marrow suppression, neuropathy, and optic neuritis(inflammation of the optic nerve, the bundle of nerve fibers that transmits visual information from your eye to your brain), Thrombocytopenia , lactic acidosis • serotonin syndrome may occur when co-administered with other serotonergic drugs (eg, selective serotonin reuptake inhibitors)	100% Oral bioavailability IV administration. <ul style="list-style-type: none"> • hepatic clearance (half-life 4–6 hrs) • 600 mg twice daily, either orally or intravenously
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45. Aminoglycosides & Spectinomycin ...

The drugs described in this chapter are bactericidal inhibitors of protein synthesis that interfere with ribosomal function. These agents are useful mainly against aerobic gram-negative microorganisms.

- AMINOGLYCOSIDES : The aminoglycosides include : streptomycin, neomycin, kanamycin , amikacin, gentamicin, tobramycin, sisomicin, netilmicin, and others.

#General Properties of Aminoglycosides:

A_ Mechanism of Action and Mechanism of Resistance :

Aminoglycosides are irreversible inhibitors of protein synthesis by binding to 30s ribosomal subunit , but the precise mechanism for bactericidal activity is not known.. it accours through 3 activities that leads to cell death :

- (1) interference with the initiation complex of peptide formation
- (2) misreading of mRNA
- (3) breakup of polysomes into nonfunctional monosomes.

Resistance may occur through one of three principal mechanisms:

- (1) inactivation of aminoglycosides through adenylylation, acetylation, or phosphorylation by transferase enzyme or other enzymes
- (2) impaired entry of aminoglycoside into the cell that result from either genotypic mutation or deletion of a porin protein or proteins involved in transport and maintenance of the electrochemical gradient; or phenotypic, eg, resulting from growth conditions under which the oxygen-dependent transport.
- (3) The receptor protein on the 30S ribosomal subunit may be deleted or altered as a result of a mutation.

Spectrum of activity :

Aminoglycosides are mostly used against aerobic gram-negative bacteria , generally aminoglycosides is active against many gram positive and negative bacteria

used most widely in combination with a β -lactam antibiotic in serious infections with gram-negative bacteria

in combination with vancomycin or a β -lactam antibiotic for gram-positive endocarditis,

Gentamicin is slightly more active against *S marcescens*, whereas tobramycin is slightly more active against *P aeruginosa*; *Enterococcus faecalis* is susceptible to both gentamicin and tobramycin,

Amikacin Many gram-negative bacteria, including many strains of *Proteus*, *Pseudomonas*, *Enterobacter*, and *Serratia*,

B. Pharmacokinetics :

- Aminoglycosides are absorbed very poorly from the intact gastrointestinal tract with exception the drugs may be absorbed if ulcerations are present.
- Aminoglycosides are cleared by the kidney, and excretion is directly proportional to creatinine clearance.
- Aminoglycosides are usually administered intravenously or intramuscular injection.
- Intrathecal or intraventricular injection is required for high levels in cerebrospinal fluid for treatment of neonatal meningitis .
- The half-life of aminoglycosides in serum is 2–3 hours, 24–48 hours in patients with significant renal impairment.
- traditionally, aminoglycosides have been administered in two or three equally divided doses per day . However, may have better efficacy when administered as a single large dose than when administered as multiple smaller doses

for two reasons:

- 1- Aminoglycosides have **concentration-dependent killing**; that is, higher concentrations kill a larger proportion of bacteria and at a more rapid rate.
 - 2- They also have a significant **postantibiotic effect**, such that the antibacterial activity persists beyond the time during which measurable drug is present for several hours.
- If the creatinine clearance is $> 60 \text{ mL/min}$, then a single daily dose of 5–7 mg/kg of gentamicin or tobramycin is recommended (15 mg/kg for amikacin).
For patients with creatinine clearance $< 60 \text{ mL/min}$, traditional dosing of

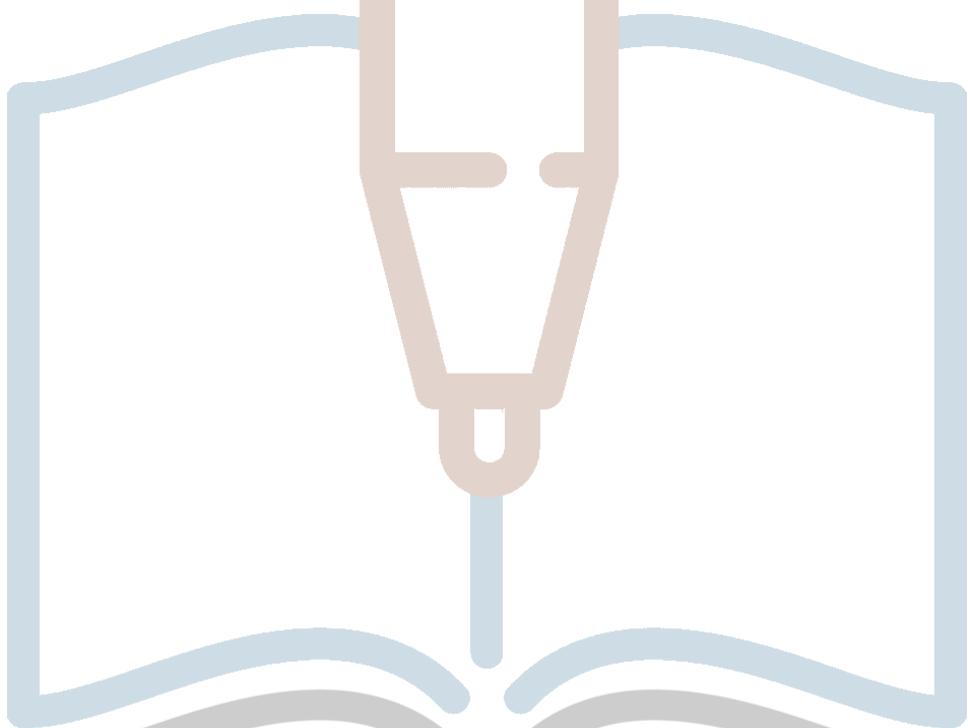
- With traditional dosing, adjustments must be made to prevent accumulation of drug and toxicity in patients with renal insufficiency. Either the dose of drug is kept constant and the interval between doses is increased, or the interval is kept constant and the dose is reduced.
- aminoglycosides exhibit synergistic killing When administered with a cell wall-active antibiotic (a β lactam or vancomycin) specially in treatment of endocarditis.

C. Adverse Effects :

- All aminoglycosides are ototoxic manifested in form of auditory damage, resulting in tinnitus and high-frequency hearing loss initially, or as vestibular damage with vertigo, ataxia, and loss of balance.
 - also nephrotoxic when therapy is continued for more than 5 days, at higher doses, in the elderly, and in the setting of renal insufficiency.
 - Use of aminoglycoside with loop diuretics or other nephrotoxic antimicrobial agents (eg, vancomycin or amphotericin) can potentiate nephrotoxicity and should be avoided if possible.
 - In very high doses, aminoglycosides can produce a curare-like effect with neuromuscular blockade that results in respiratory paralysis.
This paralysis is usually reversible by calcium gluconate (given promptly) or neostigmine.
 - Neomycin, kanamycin, and amikacin are the most ototoxic agents. Streptomycin and gentamicin are the most vestibulotoxic.
- Neomycin, tobramycin, and gentamicin are the most nephrotoxic.



DRUG AMINOGLYCOSIDES & SPECTINOMYCIN



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Drug	Clinical Applications	Adverse Effects	Pharmacokinetics, Toxicities, Interactions
STREPTOMYCIN	<p>Mainly used as a second-line agent for treatment of tuberculosis and used only in combination with other agents to prevent emergence of resistance.</p> <p>Plague, tularemia, and sometimes brucellosis.</p> <p>Penicillin plus streptomycin is effective for enterococcal endocarditis and 2-week therapy of viridans streptococcal endocarditis.</p>	<p>Fever, skin rashes may result from hypersensitivity or prolonged course of treatment (eg, for tuberculosis).</p> <p>Most serious toxicity is irreversible disturbance of vestibular function—vertigo and loss of balance. The frequency and severity of this disturbance are in proportion to the age of the patient, the blood levels of the drug, and the duration of administration</p> <p>Pain at the injection site is common but usually not severe.</p> <p>Streptomycin is contraindicated during pregnancy as it can cause deafness in the newborn</p>	<p>The dosage is 0.5–1 g/d (7.5–15 mg/kg/d meant for children), which is given intramuscularly or intravenously.</p> <p>In plague, streptomycin, 1 g/d (15 mg/kg/d for children), is given intramuscularly in combination with an oral tetracycline</p>
GENTAMICIN	<p>used mainly in severe infections caused by gram negative bacteria especially <i>P aeruginosa</i>, <i>Enterobacter</i> sp, <i>Serratiamarcescens</i>, <i>Acinetobacter</i> sp, and <i>Klebsiella</i> sp. It usually is used in combination with a second agent because an aminoglycoside alone may cause resistance.</p> <p>In combination with a cell wall-active antibiotic, its indicated in the treatment of endocarditis caused by gram positive bacteria (streptococci,</p>	<p>Nephrotoxicity (reversible), ototoxicity (irreversible), mainly as vestibular dysfunction.</p> <p>Loss of hearing can also occur.</p> <p>And neuromuscular blockade</p>	<p>IV,IM. Intrathecal , topical administration</p> <p>Resistance of Streptococci and enterococci due to failure of the drug to penetrate into the cell. However, gentamicin in combination with vancomycin or a penicillin enhance uptake of drug and result potent bactericidal effect.</p>

	<p>staphylococci, and enterococci).</p> <p>Creams, ointments, and solutions containing 0.1–0.3% gentamicin sulfate have been used for the treatment of infected burns, wounds, or skin lesions and in attempts to prevent intravenous catheter infections And treatment of ocular infection</p> <p>Meningitis caused by gram-negative bacteria has been treated by the intrathecal injection of gentamicin sulfate, 1–10 mg/d.</p>		
TOBRAMYCI	<p>inhalation (300 mg in 5 mL twice daily in repeated cycles of 28 days on therapy, followed by 28 days off therapy) for treatment of <i>P aeruginosa</i> lower respiratory tract infections complicating cystic fibrosis.</p>	<p>Nephrotoxicity and ototoxicity.</p> <p>Caution should be used when administering tobramycin to patients with preexisting renal, vestibular, or hearing disorders.</p>	<p>Inhalation ,IV,IM</p> <p>The daily dose of tobramycin is 5–6 mg/kg intramuscularly or intravenously, traditionally divided into three equal amounts and given every 8 hour.</p>
AMIKACIN	<p>Infections caused by Many gram-negative bacteria, including many strains of <i>Proteus</i>, <i>Pseudomonas</i>, <i>Enterobacter</i>, and <i>Serratia</i>.</p> <p>Used in treatment of TB</p>	<p>amikacin is nephrotoxic and ototoxic</p>	<p>After injection of 500 mg of amikacin every 12 hours (15 mg/kg/d) intramuscularly,</p> <p>The dosage of amikacin for tuberculosis is 7.5–15 mg/kg/d as a once-daily or two to three times weekly</p>
NEOMYCIN KANAMYCIN And Paromomycin	<p>Solutions containing 1–5 mg/mL are used on infected</p>	<p>neomycin group have significant nephrotoxicity and ototoxicity</p>	<p>Topical and oral use only</p> <p>Neomycin is too toxic</p>



	<p>surfaces or injected into joints, the pleural cavity, tissue spaces, or abscess cavities.</p> <p>Used In preparation for elective bowel surgery, 1 g of neomycin is given orally every 6–8 hours for 1–2 days, often combined with 1 g of erythromycin base.</p> <p><i>. Use of neomycin for hepatic encephalopathy has been largely supplanted by lactulose and other medications that are less toxic.</i></p> <p>Paromomycin has effective against visceral leishmaniasis</p> <p><i>Entamoeba histolytica</i> infection and is sometimes used for intestinal infections with other parasites.</p>	<p><i>. Auditory function is affected more than vestibular function</i></p> <p><i>. neomycin-containing ointments to skin and eyes has resulted in severe allergic reactions.</i></p> <p>The sudden absorption of postoperatively instilled kanamycin from the peritoneal cavity (3–5 g) has resulted in curare-like neuromuscular blockade and respiratory arrest. Calcium gluconate and neostigmine can act as antidotes.</p>	<p>for parenteral use.</p> <p><i>After oral administration, the intestinal flora is suppressed or modified, and the drug is excreted in the feces. Excretion of any absorbed drug is mainly through glomerular filtration into the urine.</i></p>
SPECTINOMYCI N	it is used almost solely as an alternative treatment for drug-resistant gonorrhea or gonorrhea in penicillin-allergic patients	pain at the injection site and, occasionally, fever and nausea. Nephrotoxicity and anemia have been observed rarely.	A single dose of 40 mg/kg up to a maximum of 2 g is given

46.

Sulfonamide·Trimethoprim&Quinolones

ANTIFOLATE DRUGS;

Folic acid one of the vitamins of the B complex. is involved in the synthesis of amino acids and DNA. is essential for normal cell growth and replication.

	Mechanism of Action	Antimicrobial Activity	Resistance	Pharmacokinetics	Clinical Uses	Adverse Reactions
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SULFONAMIDES	<p>As structural analogs of PABA, inhibit dihydropteroate synthase and folate production that is essential for production DNA.</p> <p>-inhibit both gram-positive and gram-negative bacteria, Nocardia sp, Chlamydia trachomatis, some protozoa and Some enteric bacteria.</p> <p>-Activity is poor against anaerobes.</p> <p>- Pseudomonas aeruginosa is intrinsically resistant to sulfonamide antibiotics</p>	<p>-inhibit both gram-positive and gram-negative bacteria, Nocardia sp, Chlamydia trachomatis, some protozoa and Some enteric bacteria.</p> <p>-Activity is poor against anaerobes.</p> <p>- Pseudomonas aeruginosa is intrinsically resistant to sulfonamide antibiotics</p>	<p>may occur as a result of mutations that (1) cause overproduction of PABA, (2) cause production of a folic acid synthesizing enzyme that has low affinity for sulfonamides, or (3) impair permeability to the sulfonamide.</p>	<p>Oral, Topical</p> <ul style="list-style-type: none"> - Therapeutic concentrations are in the range of 40–100 mcg/mL of blood. -Blood levels generally peak 2–6 hours after oral administration. -renal clearance - In significant renal failure, the dosage must be reduced. 	<p>-urinary tract infections</p> <p>-acute toxoplasmosis.</p> <p>- inflammatory bowel disease</p> <p>-bacterial conjunctivitis and as adjunctive therapy for trachoma.</p> <p>- prevention of infection of burn wounds.</p>	<p>fever, skin rashes, exfoliative dermatitis, photosensitivity, urticaria, nausea, vomiting, diarrhea, and difficulties referable to the urinary tract . Stevens-Johnson syndrome stomatitis, arthritis, hematopoietic disturbances hepatitis and, rarely, polyarteritis nodosa and psychosis.</p>
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	Mechanism of Action	Antimicrobial Activity	Resistance	Pharmacokinetics	Clinical Uses	Adverse Reactions
TRIMETHOPRIM & TRIMETHOPRIM - SULFAMETHOXAZOLE MIXTURES	selectively inhibits bacterial dihydrofolic acid reductase, which converts dihydrofolic acid to tetrahydrofolic acid, a step leading to the synthesis of purines and ultimately to DNA	- Bactericidal activity against susceptible bacteria - trimethoprim or pyrimethamine in combination with a sulfonamide blocks sequential steps in folate synthesis, resulting in marked synergism of the activity of both drugs.	can result from 1-reduced cell permeability, 2-overproduction of dihydrofolate reductase, or 3-production of an altered reductase with reduced drug binding.	- Oral, IV - renal clearance (half-life 8 h) dosed every 8–12 h formulated in a 5:1 ratio of sulfamethoxazole to trimethoprim -The dose should be reduced by half for patients with creatinine clearances of 15–30 mL/min.	urinary tract infections. Pneumonia, shigellosis, systemic salmonella toxoplasmosis.	- megaloblastic anemia - leukopenia - granulocytopenia - Nausea - vomiting - fever - vasculitis - renal damage - central nervous system disturbances

	Mechanism of Action	Antimicrobial Activity	Resistance	Pharmacokinetics	Clinical Uses	Adverse Reactions
Fluoroquinolones	block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV.	- Bactericidal activity against susceptible bacteria	<ul style="list-style-type: none"> - Resistance is due to one or more point mutations in the quinolone binding region of the target enzyme or to a change in the permeability of the organism. - Resistance to one fluoroquinolone, particularly if it is of high level, generally confers cross-resistance to all other members of this class. 	<ul style="list-style-type: none"> -half-lives range from 3 to 10 hours. -Oral absorption is impaired by divalent and trivalent cations -renal clearance -Dosage adjustment is required for patients with creatinine clearances less than 50 mL/min -Dosage adjustment for renal failure is not necessary for moxifloxacin. - contraindicated in patients with hepatic failure 	<ul style="list-style-type: none"> -urinary tract infections - infections of soft tissues, bones and joints and in intra-abdominal and respiratory tract infections. - prophylaxis and treatment of anthrax - chlamydial urethritis or cervicitis. - tuberculosis and atypical mycobacterial infections. 	<ul style="list-style-type: none"> nausea, vomiting, and diarrhea. headache, dizziness, insomnia, skin rash, or abnormal liver function tests develop. Photosensitivity Prolongation of the QTc interval arthropathy peripheral neuropathy. <p>Fluoroquinolones should be avoided during pregnancy</p>

Exfoliative dermatitis

is characterized by generalized erythema with scaling or desquamation affecting at least 90% of the body surface area.

Stevens-Johnson syndrome

is an immune-complex-mediated hypersensitivity complex that typically involves the skin and the mucous membranes.

47.Antimycobacterial Drugs

First line drug of TB



Drug	MOA	EFFECT	CLINICAL APPLICATION	PHARMACOKINETICS TOXICITIES INTERACTIONS
Isoniazid	Inhibits synthesis of mycolic acids, an essential component of mycobacterial cell walls , Isoniazid is a prodrug that is activated by KatG , the mycobacterial catalase-peroxidase.	Bactericidal activity against susceptible strains of M tuberculosis	First-line agent against mycobacteria	Isoniazid is readily absorbed from the gastrointestinal tract Oral or IV. Hepatic clearance(half life 1 hour) . reduces level of phenytoin Isoniazid metabolites and a small amount of unchanged drug are excreted mainly in the urine Toxicity: Hepatotoxic, peripheral neuropathy (give pyridoxine to prevent)
RIFAMYCINS Refampine	Inhibits DNA-dependent RNA polymerase, thereby blocking production of RNA	Bactericidal activity against susceptible bacteria and rapidly emerges when used as a single drug in the treatment of active infection	First-line agent for mycobacterial infections colonization, staphylococcal infections	Rifampin is well absorbed after oral administration and excreted mainly through the liver into bile The drug is relatively highly protein-bound and adequate cerebrospinal fluid concentrations are achieved only in the presence of meningeal inflammation. Cytochrome P450 inducer Toxicity: Rash, nephritis, thrombocytopenia, cholestasis, flu-like



				syndrome with intermittent dosing , Rifampin imparts a harmless orange color to urine, sweat, and tears
ETHAMBUTOL	Ethambutol inhibits mycobacterial arabinosyl transferases, which are encoded by the embCAB operon. Arabinosyl transferases are involved in the polymerization reaction of	Bacteriostatic activity against susceptible mycobacteria	Given in four-drug initial combination therapy for tuberculosis until drug used for atypical mycobacterial infections	Ethambutol is well absorbed from the gut ,drug is excreted in feces and urine in unchanged form. Ethambutol crosses the blood-brain barrier only when the meninges are inflamed. Oral. Mixed clearance (half life 4h). dose must be reduced in renal failure Toxicity: retrobulbar neuritis, resulting in loss of visual acuity
Pyrazinamide	Pyrazinamide is converted to pyrazinoic acid—the active form of the drug—by mycobacterial pyrazinamidase. Pyrazinoic acid disrupts mycobacterial cell membrane metabolism and	Bacteriostatic activity against susceptible strains of <i>M tuberculosis</i> bactericidal against actively dividing organism	“Sterilizing” agent used during first 2 months of duration of therapy to be shortened to 6 months	9 h), but metabolites are renally cleared so use 3 doses weekly if creatinine clearance < 30 mL/ Toxicity: Hepatotoxic, hyperuricemia



	transport functions.			
STREPTOMYCIN	Prevents bacterial protein synthesis by binding to the ribosomal subunit	Bactericidal activity against susceptible mycobacteria	Used in tuberculosis when an injectable drug is needed and in treatment of drug- resistant strains	IM, IV. Renal clearance (half life 2.5h). administered daily initially . <i>Toxicity:</i> Nephrotoxic, ototoxic

TABLE 47-2 Recommended duration of therapy for tuberculosis.

Regimen (In Approximate Order of Preference)	Duration in Months
Isoniazid, rifampin, pyrazinamide	6
Isoniazid, rifampin	9
Rifampin, ethambutol, pyrazinamide	6
Rifampin, ethambutol	12
Isoniazid, ethambutol	18
All others	≥ 24

Second-line agents for TB

DRUG	MOA	EFFECT	CLINICAL APPLICATION	PHARMACOKINATIKS TOXICITY INTERACTION
ETHIONAMIDE	It blocks the synthesis of mycolic acid	Bactericidal against M TB	Second line to treat TB	Gastric irritation and neurologic symptoms, Ethionamide is also

				hepatotoxic. Neurologic symptoms may be alleviated by pyridoxine.
Capreomycin	Inhibit the peptide protein synthesis	bacteriostatic	Treat TB It is given 2 or 3 times weakly to reduce toxicity	I.M. nephrotoxic and ototoxic Tinnitus, deafness, and vestibular disturbance occur
Cycloserine	Inhibit the cell wall synthesis	Bactericidal or bacteriostatic	TB peak serum concentration(2-4h) help to minimize side effect	ORALLY. Peripheral neuropathy and central nervous system dysfunction
Kanamycin & Amikacin	The aminoglycoside antibiotics are discussed in Chapter 45.	Bactericidal	Kanamycin had been used for treatment of tuberculosis caused by streptomycin-resistant strains Amikacin is playing a greater role in the treatment of tuberculosis due to the prevalence of multidrug-resistant strains	I.V. must be used with other drugs
Aminosalicylic Acid (PAS)	Aminosalicylic acid is a folate synthesis antagonist that is active on MTB		Orally Not well tolerated	May be diminished by giving the drug with meals and with antacids. Peptic ulceration and hemorrhage may occur. Hypersensitivity reactions manifested by fever, joint pains, skin rashes,



				hepatosplenomegaly, hepatitis, adenopathy, and granulocytopenia
Fluoroquinolones	Inhibit the strains of TB in con of less than 2 mcg/mL		Taken if tb strains are resistant to first line	May develop rash if taken alone Orally twice daily
Linezolid	Inhibit the TB strains in con of 4-8 mcg/mL		Taken with combination of drugs	It effects bone marrow suppression and irreversible peripheral and optic neuropathy, have been reported with the prolonged courses of therapy that are necessary for treatment of tuberculosis
Revabutin	it is a bacterial RNA polymerase inhibitor		TB	Rifabutin is indicated in place of rifampin for treatment of tuberculosis in patients with HIV infection who are receiving antiretroviral therapy with a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor If receiving protease inhibitor dose should be reduced

Rifabutin	it is a bacterial RNA polymerase inhibitor		TB	25-desacetylrifapentine, have an elimination half-life of 13 hours. Same as refamycin Rifapentine, given once weekly for 3 months in combination with isoniazid
Bedaquiline	Bedaquiline inhibits adenosine 5'-triphosphate (ATP) synthase in mycobacteria, has in vitro activity against both replicating and nonreplicating bacilli	Bacteriocidal	TB	Bedaquiline has been associated with both hepatotoxicity and cardiac toxicity (prolongation of the QTc interval), so patients must be closely monitored during treatment Taken orally

SECO (The most prominent untoward effect is discoloration of the skin and conjunctivae. Gastrointestinal side effects are also common)

Drugs for other mycobacterial infection (leprosy)

Dapsone :

MOA:

Inhibit folate synthesis

PHARMACOKINETICS+TOXICITY+INTERACTION:

Develop hemolysis, erythema nodosum leprosum often develops

RIFAMPIN

CLOFAZIMINE

Clofazimine is stored widely in reticuloendothelial tissues and skin

The half life (2months)



48. Antifungal Agents

Human fungal infections have increased dramatically in incidence and severity in recent years.

- Causes increased numbers of patients at risk for fungal infections include :
Advances in surgery, cancer treatment, treatment of patients with solid organ and bone marrow transplantation, the HIV epidemic, and increasing use of broad-spectrum antimicrobial therapy in critically ill patients.
- These changes have resulted in The antifungal drugs presently available fall into the following categories: systemic drugs (oral or parenteral) for systemic infections, oral systemic drugs for mucocutaneous infections, and topical drugs for mucocutaneous infections.

Drugs of anti fungal

drug	MOA	effect	clinical app	pharmacokinetics toxicity and interaction

Amphotericin B	Attacking the ergosol forming pores in the membrane	loss of intracellular component. bactericidal have soared spectrum	Localized and systemic . <i>Candida</i> . <i>Cryptococcus</i> , <i>histoplasma</i> , <i>blastomycetes</i> , <i>coccidioids</i> , <i>aspergillus</i> <i>The lipid formulation=lower the toxicity and can be taken in higher doses</i>	Oral but not absorbed. I.V for systemic use. intrathecal for fungal meningitis . Topical for ocular and bladder infections <i>Toxicity:</i> Infusion reactions <i>Interactions:</i> Additive with other renal toxic drug
flucytocine	interfere with DNA and RNA in fungi	Synergistic with toxicity in host due to DNA and RNA effec	<i>Cryptococcus</i> and chromoblastomycosis infections	Oral-duration,high renal excretion <i>Toxicity:</i> Myelosuppression
Echinocandins**	Inhibit the formation of cell	Prevent the synthesis of	Candida and aspigillus	IV.duration 11-15H <i>Toxicity:</i> Minor



	was by inhibiting the synthesis of $\beta(1\rightarrow 3)$ -glucan	cells wall		gastrointestinal effects, flushing <i>Interactions:</i> Increases cyclosporine levels (avoid combination)
azole	Inhibition of fungal cytochrome P450	Reduce ergosterol synthesis	Broad spectrum	The most common adverse reaction is relatively minor gastrointestinal upset.

**mecafungin.anidulafungin(mecafungin increases levels of nifedipin)



Aazole

ketoconazole	orally	it has greater propensity to inhibit mammalian cytochrome P450 enzymes
itraconazole	orally and IV	An important drug interaction is reduced bioavailability of itraconazole when taken with rifa- mycins (rifampin, rifabutin, rifapentine)
fluconazole	good oral bioavailability	lead side effect (widest therapeutic index)
voriconazole	IV and orally	Photosensitivity dermatitis, rash and elevate hepatic enzymes

poaconazole

orally only

Drug interactions with increased levels of CYP3A4 substrates such as tacrolimus and cyclosporine have been documented.

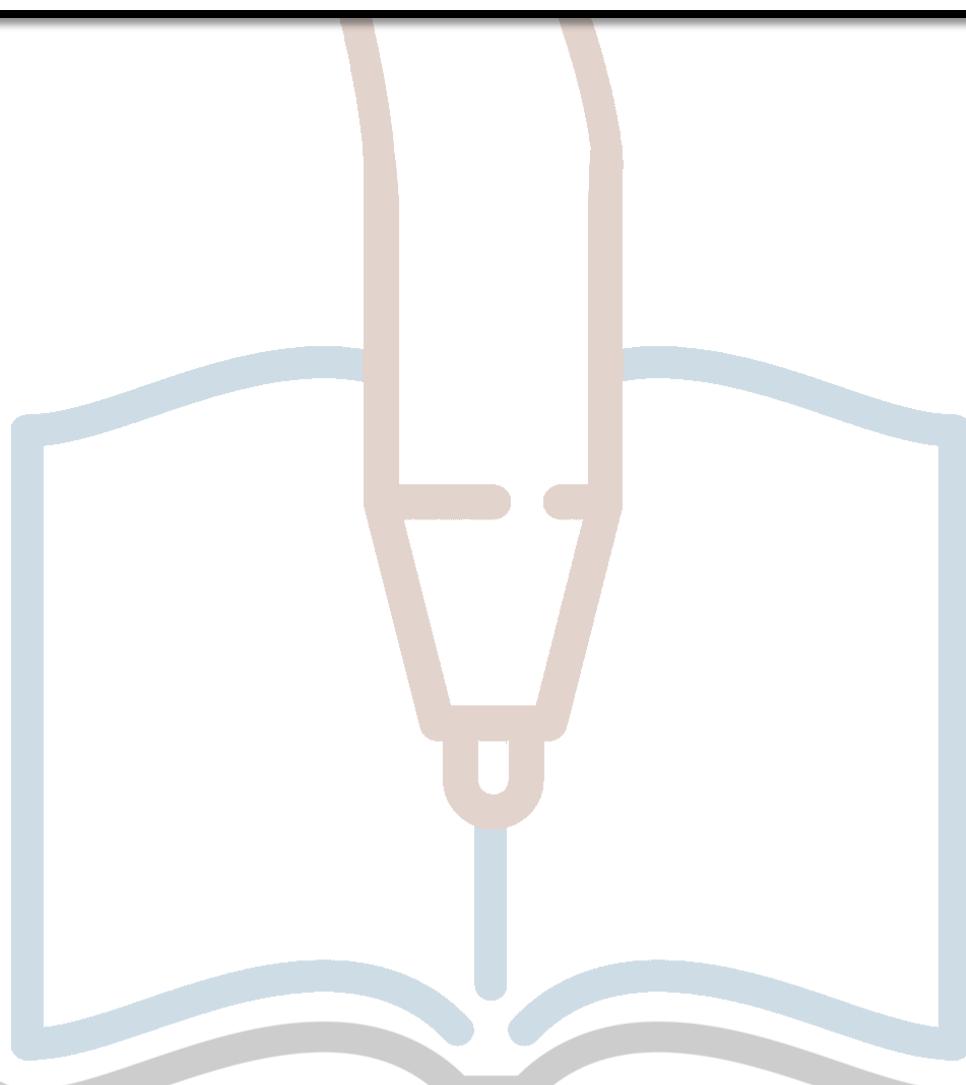
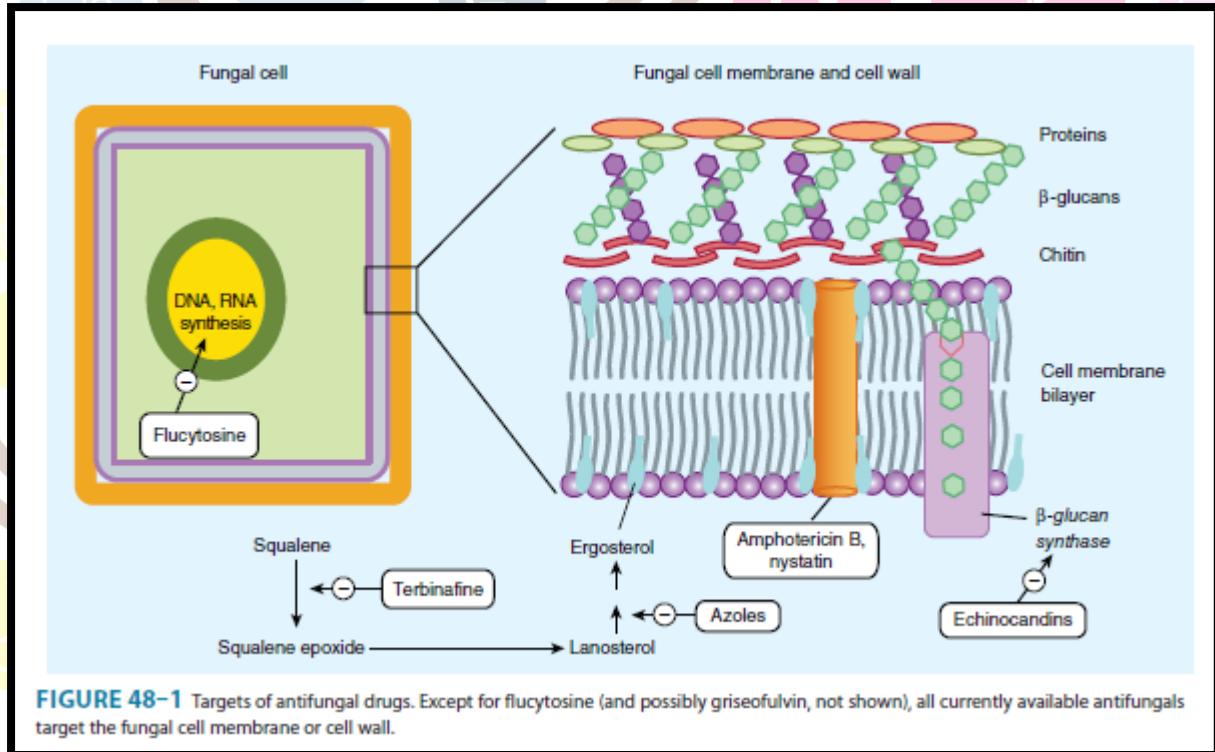
Oral systemic antifungal drug of mucocutaneous infection

drug	MOA	Effect	toxicity-interaction
GRISEOFULVIN	It is deposited in newly forming skin where it binds to keratin, protecting the skin from new infection.	Bacteriostatic	Adverse effects include an allergic syndrome much like serum sickness, hepatitis, and drug interactions with warfarin and phenobarbital
TERBINAFINE	It inhibits the fungal enzyme squalene epoxidase	Bactericidal	taken orally . adverse effects :consisting primarily of gastrointestinal upset and headache

Topical anti fungal agents

Nystatin	too toxic for parenteral administration	Used for oropharyngeal thrush, vaginal candidiasis, and intertriginous candidal infections.
Topical azole	clotrimazole and miconazole	It is useful for dermatophytic infections, including tinea corporis, tinea pedis, and tinea cruris.
Topical allylamide	Terbinafine and naftifine	Tinea cruris and tinea corporis

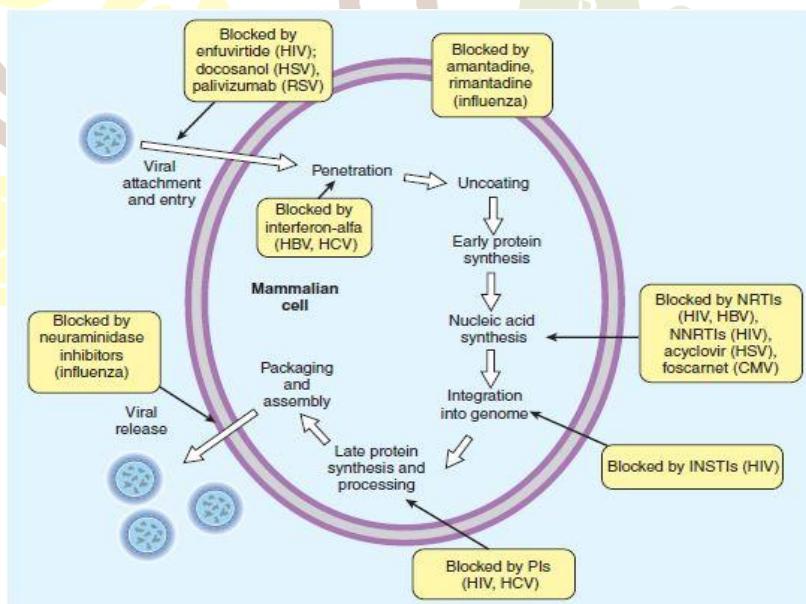




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49. Antivirus

Introduction:



Viruses are obligate intracellular parasites; their replication depends primarily on synthetic processes of the host cell. Therefore, to be effective, antiviral agents must either block viral entry into or exit from the cell or be active inside the host cell.

The two first-generation antiviral agents, 5-iododeoxyuridine and trifluorothymidine, had poor specificity (ie, they inhibited host cell DNA as well as viral DNA) that rendered them too toxic for systemic use. However, both agents are effective when used topically for the treatment of herpes keratitis (تسيل العين بالدموع وتصبح مؤلمة جداً وتتغير الرؤية).

Antiviral therapy is now available for herpes viruses, hepatitis C virus (HCV), hepatitis B virus (HBV), papillomavirus, influenza, human immunodeficiency virus (HIV), and respiratory syncytial virus (RSV).

*The major sites of antiviral drug action. Note: Interferon alfas are speculated to have multiple sites of action.

Viral replication requires several steps (Fig_1): (1) attachment of the virus to receptors on the host cell surface; (2) entry of the virus through the host cell membrane; (3) uncoating of viral nucleic acid; (4) synthesis of early regulatory proteins, eg: nucleic acid polymerases; (5) synthesis of new viral RNA or DNA; (6) integration into the nuclear genome;(7)

synthesis of late, structural proteins; (8) assembly (maturation) of viral particles; and (9) release from the cell. Antiviral agents can potentially target any of these steps.

► AGENTS TO TREAT HERPESSIMPLEX VIRUS (HSV) & VARICELLA-ZOSTER VIRUS (VZV) INFECTIONS:

Three oral nucleoside analogs are licensed for the treatment of HSV and VZV infections: **acyclovir**, **valacyclovir**, and **famciclovir**. They have similar mechanisms of action and comparable indications for clinical use; all are well tolerated.

There are other trials have been demonstrated with similar efficacies to the three agents for the treatment of HSV but modest superiority of famciclovir and valacyclovir for the treatment of herpes zoster infections.

♦**ACYCLOVIR: (attachment of the virus to receptors on the host cell surface)**

-Is an acyclic guanosine derivative with clinical activity against HSV-1, HSV-2, and VZV, but it is approximately 10 times more potent against HSV-1 and HSV-2 than against VZV.

-The bioavailability of oral acyclovir is low (15–20%) and is unaffected by food. An intravenous formulation is available. Topical formulations produce high concentrations in herpetic lesions, but systemic concentrations are undetectable by this route.

-Acyclovir is cleared primarily by glomerular filtration and tubular secretion. The half-life is 2.5–3 hours in patients with normal renal function and 20 hours in patients with anuria (**فشل الكليتين في انتاج البول**), and it diffuses readily into most tissues and body fluids, Cerebrospinal fluid concentrations are 20–50% of serum values.

-Long-term suppression with oral acyclovir in patients decreases the frequency of symptomatic recurrences and of asymptomatic viral shedding, thus decreasing the rate of sexual transmission.

-acyclovir therapy significantly decreases the total number of lesions, duration of symptoms, and viral shedding in patients with varicella (**if begun within 24 hours after the onset of rash**) or cutaneous zoster (**if begun within 72 hours**).

-The risk of post-herpetic neuralgia is also reduced if treatment is initiated early. However, because VZV is less susceptible to acyclovir than HSV, **higher doses are required**

-In organ transplantation it's given for prophylactic proposes to prevents reactivation of HSV and VZV.

-**Intravenous acyclovir** is the treatment of choice for herpes simplex encephalitis, neonatal HSV infection, and serious HSV or VZV infections

- In neonates with central nervous system HSV, oral acyclovir suppression for 6 months following acute treatment improves neurodevelopment outcomes.
- In immunocompromised patients with VZV infection, intravenous acyclovir reduces the incidence of cutaneous and visceral dissemination.
- Topical acyclovir cream is substantially less effective than oral therapy for primary HSV infection. It is of no benefit in treating recurrent genital herpes.

Resistance to acyclovir can develop in HSV or VZV through alteration in either the viral thymidine kinase or the DNA polymerase, and clinically resistant infections have been reported in immune compromised hosts. Most clinical isolates are resistant on the basis of deficient thymidine kinase activity and thus are cross resistant to valacyclovir, famciclovir, and ganciclovir. Agents such as **foscarnet**, **cidofovir**, and **trifluridine** do not require activation by viral thymidine kinase and thus have preserved activity against the most prevalent acyclovir-resistant strains (Fig_2).

*Mechanism of action
of antiherpetic agents.

Side effects: nausea, diarrhea, and headache may occur

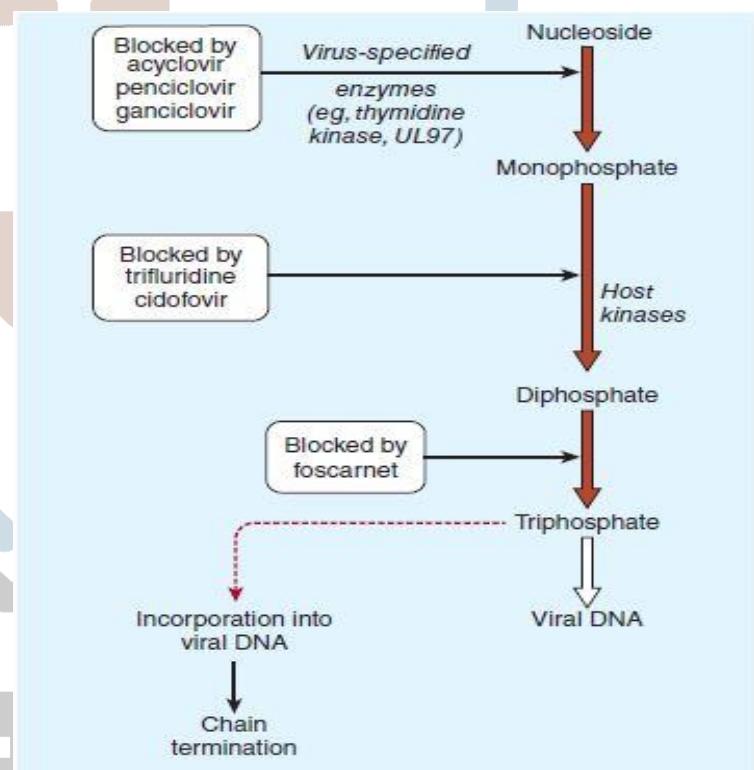
Intravenous infusion may be associated with reversible renal toxicity or neurologic effects

-However, these are uncommon with adequate hydration and avoidance of rapid infusion rates.

High doses-cause chromosomal damage and testicular atrophy in rats, but there has been no evidence of teratogenicity, reduction in sperm production, or cytogenetic alterations in peripheral blood lymphocytes in patients receiving daily suppression of genital herpes for more than 10 years.

Drug Drug interactions:

-Concurrent use of nephrotoxic agents may enhance the potential for nephrotoxicity. **Probenecid** and **cimetidine** decrease acyclovir clearance and increase exposure. **Somnolence**



and **lethargy** (بلادة جسدية و ذهنية: حالة من ضعف الاستجابة و الفعالية على حافة فقد الوعي) may occur in patients receiving concomitant **zidovudine** and **acyclovir**.

♦**VALACYCLOVIR: (prodrug)**

-Is the L-valyl ester of acyclovir. It is rapidly converted to acyclovir after oral administration via first-pass enzymatic hydrolysis in the liver and intestine, resulting in serum levels that are three to five times greater than those achieved with oral acyclovir and approximate those achieved with intravenous acyclovir.

-Oral bioavailability is 54–70%, and cerebrospinal fluid levels are about 50% of those in serum. Elimination half-life is 2.5–3.3 hours.

-Drug regimen and treatments:

-Twice-dailyvalacyclovir is effective for treatment of first or recurrent genital herpes and varicella and zoster infections; it is approved for use as a 1-day treatment for orolabial herpes and as suppression of frequently recurring genital herpes.

-Once-daily dosing of valacyclovir for chronic suppression in persons with recurrent genital herpes has been shown to markedly decrease the risk of sexual transmission. In comparative trials with acyclovir for the treatment of patients with zoster, rates of cutaneous healing were similar, but valacyclovir was associated with a shorter duration of zoster-associated pain.

-Higher doses:

are effective in preventing CMV disease after organ transplantation and suppressive valacyclovir prevents VZV reactivation after hematopoietic stem cell transplantation.

Side effects:

nausea, headache, vomiting, or rash may occur.

At high doses, confusion, hallucinations, and seizures have been reported.

In **AIDS patients** who received high-dosage valacyclovir chronically (ie, 8 g/d) had increased gastrointestinal intolerance as well as thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome; this dose has also been associated with confusion and hallucinations in transplant patients.

♦**FAMCICLOVIR: (prodrug)**

-Is the diacetyl ester prodrug of 6-deoxypenciclovir, an acyclic guanosine analog.

-Oral administration,

famciclovir is rapidly deacetylated and oxidized by first-pass metabolism to **penciclovir**.

-It is active in vitro against HSV-1, HSV-2, VZV, EBV, and HBV.

-As with acyclovir, activation by phosphorylation is catalyzed by the virus-specified thymidine kinase in infected cells, followed by competitive inhibition of the viral DNA polymerase to block DNA synthesis.

however, penciclovir does not cause chain termination. Penciclovir

triphosphate has lower affinity for the viral DNA polymerase than acyclovir triphosphate, but it achieves higher intracellular concentrations.

-The bioavailability of penciclovir from orally administered famciclovir is 70%. half-life of penciclovir triphosphate is prolonged, at 7–20 hours.

Penciclovir is excreted primarily in the urine.

Treatments:

-Oral famciclovir is effective for the treatment of first and recurrent genital herpes, for chronic daily suppression of genital herpes, for treatment of herpes labialis, and for the treatment of acute zoster.

-One-day usage of famciclovir significantly accelerates time to healing of recurrent genital herpes and of herpes labialis.

-Comparison of famciclovir to valacyclovir for treatment of herpes zoster in immunocompetent patients showed similar rates of cutaneous healing and pain resolution; both agents shortened the duration of zoster-associated pain compared with acyclovir.

Side effects: ☹

-Headache, nausea, or diarrhea may occur. As with acyclovir, testicular toxicity has been demonstrated in animals receiving repeated doses.

- However, men receiving daily famciclovir (250 mg every 12 hours) for 18 weeks had no changes in sperm morphology or motility.

♦PENCICLOVIR:

-The guanosine analog penciclovir, the active metabolite of famciclovir, is available for topical use.

-Penciclovir cream (1%) shortened the median duration of recurrent herpes labialis by ~ 17 hours compared to placebo when applied within 1 hour of the onset of prodromal symptoms and continued every 2 hours during waking hours for 4 days.

-Adverse effects are uncommon, other than application site reactions in ~1%.

♦DOCOSANOL: (preventing viral entry into cells and subsequent viral replication.)

-Is a saturated 22-carbon aliphatic alcohol that inhibits fusion between the host cell plasma membrane and the HSV envelope,

-Topical docosanol 10% cream is available without a prescription. When applied within 12 hours of the onset of prodromal symptoms, five times daily, median healing time was shortened by 18 hours compared with placebo in recurrent orolabial herpes. Application site reactions occur in ~2%.

♦**TRIFLURIDINE: ((trifluorothymidine))**

-Is a fluorinated pyrimidine nucleoside that inhibits viral DNA synthesis in HSV-1, HSV-2, CMV, vaccinia, and some adenoviruses.

Mechanism of action:

-It is phosphorylated intracellularly by host cell enzymes, and then competes with thymidine triphosphate for incorporation by the viral DNA polymerase.

-Incorporation of trifluridine triphosphate into both viral and host DNA prevents its systemic use.

Application of a 1% solution is effective in treating keratoconjunctivitis and recurrent epithelial keratitis due to HSV-1 or HSV-2. Cutaneous application of trifluridine solution, alone or in combination with interferon alfa, has been used successfully in the treatment of acyclovir-resistant HSV infections.

♦**INVESTIGATIONAL AGENTS:**

Valomaciclovirus is an inhibitor of the viral DNA polymerase; it is currently under clinical evaluation for the treatment of patients with acute zoster and acute EBV infection (infectious mononucleosis).

To sum up, Agents that used to treat or prevent herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections shown below as route of administration, uses and recommended adult dosage and regimen:

	Route of Administration	Use	Recommended Adult Dosage and Regimen
Acyclovir ¹	Oral	First episode genital herpes treatment	400 mg tid × 7–10 days
		Recurrent genital herpes treatment	800 mg tid × 2 days or 800 mg bid × 5 days
		Genital herpes suppression	400–800 mg bid ²
		Herpes proctitis treatment	400 mg 5 times daily until healed
		First episode orolabial herpes treatment	400 mg tid × 7–10 days
		Recurrent orolabial herpes treatment	400 mg 5 times daily × 5 days
		Orolabial herpes suppression	400–800 mg bid–tid ²
		Varicella treatment (age ≥ 2 years)	800 mg qid × 5 days
		Zoster treatment	800 mg 5 times daily × 7–10 days
	Intravenous	Severe HSV treatment	5 mg/kg q8h × 7–10 days
		Mucocutaneous herpes in the immunocompromised host treatment	10 mg/kg q8h × 7–14 days
		Herpes encephalitis treatment	10–15 mg/kg q8h × 14–21 days
		Neonatal HSV infection treatment	10–20 mg/kg q8h × 14–21 days
		Varicella or zoster in the immunosuppressed host treatment	10 mg/kg q8h × 7 days
	Topical (5% cream)	Herpes labialis treatment	5 times daily × 4 days
Famciclovir ¹	Oral	First episode genital herpes treatment	250 mg tid × 7–10 days
		Recurrent genital herpes treatment	1000 mg bid × 1 day
		Genital herpes in the HIV-infected host treatment	500 mg bid × 5–10 days
		Genital herpes suppression	250–500 mg bid ²
		First episode orolabial herpes treatment	1500 mg bid–tid × 7–10 days
		Recurrent orolabial herpes treatment	1500 mg once
		Orolabial herpes suppression	500 mg bid
		Zoster	500 mg tid × 7 days
Valacyclovir ¹	Oral	First episode genital herpes treatment	1000 mg bid × 7–10 days
		Recurrent genital herpes treatment	500 mg bid × 3 days or 1 g qd × 5 days
		Genital herpes suppression	500–1000 mg qd–bid ²
		First episode orolabial herpes treatment	1 g bid × 7–10 days
		Recurrent orolabial herpes treatment	2 g bid × 1 day
		Orolabial herpes suppression	500–1000 mg qd
		Varicella (age > 2 years)	20 mg/kg tid × 5 days (maximum, 1 g tid)
		Zoster	1 g tid × 7 days
Foscarnet ¹	Intravenous	Acyclovir-resistant HSV and VZV infections	40–60 mg/kg q8h until healed
Docusanol	Topical (10% cream)	Recurrent herpes labialis	Every 2 h while awake
Ganciclovir	Topical (0.15% gel)	Keratitis	Every 3 h while awake
Penciclovir	Topical (1% cream)	Herpes labialis or herpes genitalis	Every 2 h while awake
Trifluridine	Topical (1% solution)	Acyclovir-resistant HSV infection	5 times daily

¹Dosage must be reduced in patients with renal insufficiency.

²The higher doses are recommended for immunocompromised patients.

HIV, human immunodeficiency virus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

► AGENTS TO TREAT CYTOMEGALOVIRUS (CMV) INFECTIONS:

-CMV infections occur primarily in the setting of advanced immune suppression and are typically due to reactivation of latent infection. Dissemination of infection results in end-organ disease, including retinitis, colitis, esophagitis, central nervous system disease, and pneumonitis. Although the incidence in HIV infected patients has markedly decreased with the advent of potent anti-retroviral therapy, clinical reactivation of CMV infection after organ transplantation is still prevalent.

-The availability of oral valganciclovir has decreased the use of intravenous ganciclovir, intravenous foscarnet, and intravenous cidofovir for the prophylaxis and treatment of end-organ CMV disease.



-Oral valganciclovir has replaced oral ganciclovir because of its lower pill burden.

ریکارڈ

♦GANCICLOVIR:

-Is an acyclic guanosine analog that requires activation by triphosphorylation before inhibiting the viral DNA polymerase.

Mechanism of action :

Initial phosphorylation is catalyzed by the virus-specified protein kinase phosphotransferase UL97 in CMV-infected cells. The activated compound competitively inhibits viral DNA polymerase and causes termination of viral DNA elongation.

- Ganciclovir has in vitro activity against CMV is up to 100 times greater than that of acyclovir.
- Ganciclovir is administered intravenously; the bioavailability of oral ganciclovir is poor, and it is no longer available in the US.
- Cerebrospinal fluid concentrations are approximately 50% of serum concentrations.

Treatment:

- Ganciclovir gel is available for the treatment of acute herpetic keratitis.
- is also used to treat CMV colitis, esophagitis, and pneumonitis (the latter often in combination with intravenous cytomegalovirus immunoglobulin) in immunocompromised patients.
- Intravenous ganciclovir, followed by either oral ganciclovir or high-dose oral acyclovir, reduced the risk of CMV infection in transplant recipients. Limited data in infants with symptomatic congenital neurologic CMV disease suggest that treatment with IV ganciclovir may reduce hearing loss.

-**ورم خبيث من الاوعية الدموية في الجلد و يظهر كلطخات ارجوانية الى** (The risk of Kaposi's sarcoma is reduced in AIDS patients receiving long-term ganciclovir, presumably because of activity against HHV-8.)

- The elimination half-life is 4 hours, and the intracellular half-life is prolonged at 16–24 hours.
- Clearance of the drug is linearly related to creatinine clearance. Ganciclovir is readily cleared by hemodialysis.
- Intravenous ganciclovir has been shown to delay progression of CMV retinitis in immune compromised patients. Dual therapy with foscarnet and ganciclovir is more effective in delaying progression of retinitis than either drug alone in patients with AIDS, although adverse effects are compounded.

-Intravitreal injections of ganciclovir may be used to treat CMV retinitis. Concurrent therapy with a systemic anti-CMV agent is necessary to prevent other sites of end-organ CMV disease.

-The intraocular ganciclovir implant is no longer available in the USA.

-Resistance to ganciclovir increases with duration of use.

The most common adverse effect of intravenous ganciclovir treatment is myelosuppression, which although reversible may be dose-limiting.

-Myelosuppression (انخفاض في انتاج الكريات الدموية من نخاع العظام) may be additive in patients receiving concurrent zidovudine, azathioprine, or mycophenolate mofetil.

-Other potential adverse effects are nausea, diarrhea, fever, rash, headache, insomnia, and peripheral neuropathy.

Central nervous system toxicity (confusion, seizures, psychiatric disturbance) and hepatotoxicity have been rarely reported. Intravitreal ganciclovir has been associated with vitreous hemorrhage and retinal detachment.

- Ganciclovir is mutagenic in mammalian cells and carcinogenic and embryotoxic at high doses in animals and causes aspermatogenesis; the clinical significance of these preclinical data is unclear.

Drug Drug interactions:

Levels of ganciclovir may rise in patients concurrently taking **probenecid** or **trimethoprim**. Concurrent use of ganciclovir with **didanosine** may result in increased levels of **didanosine**.

◆VALGANCICLOVIR:

- Is an L-valyl ester prodrug of ganciclovir that exists as a mixture of two diastereomers. After oral administration, both diastereomers are rapidly hydrolyzed to ganciclovir by esterases in the intestinal wall and liver.

-the bioavailability of oral valganciclovir is 60% and it is recommended that the drug be taken with food.

-The major route of elimination is renal

-Is effective as intravenous ganciclovir for the treatment of CMV retinitis and is also indicated for the prevention of CMV disease in high-risk solid organ and bone marrow transplant recipients.

♦**FOSCARNET: (phosphonoformic acid)**

-Is an inorganic pyrophosphate analog that inhibits herpesvirus DNA polymerase, RNA polymerase, and HIV reverse transcriptase directly without requiring activation by phosphorylation.

Mechanism of actions

Foscarnet blocks the pyrophosphate binding site of these enzymes and inhibits cleavage of pyrophosphate from deoxy nucleotide triphosphates. It has in vitro activity against HSV, VZV, CMV, EBV, HHV-6, HHV-8, HIV-1, and HIV-2.

-Foscarnet is available in an intravenous formulation only; poor oral bioavailability and gastrointestinal intolerance preclude oral use.

- Cerebrospinal fluid concentrations are 43–67% of steady-state serum concentrations. Although the mean plasma half-life is 3–7 hours, up to 30% of foscarnet may be deposited in bone, with a half-life of several months.

- The clinical repercussions of this are unknown.

-Clearance of foscarnet is primarily renal and is directly proportional to creatinine clearance.

Treatment:

-Is effective in the treatment of end-organ CMV disease (ie, retinitis, colitis, and esophagitis), including ganciclovir-resistant disease;
- It is also effective against acyclovir-resistant HSV and VZV infections.

-Foscarnet has been administered intravitreally for the treatment of CMV retinitis in patients with AIDS, but data regarding efficacy and safety are incomplete.

The combination of

ganciclovir and **foscarnet** is synergistic in vitro against CMV and has been shown to be superior to either agent alone in delaying progression of retinitis;

- However, toxicity is also increased when these agents are administered concurrently.

Side effects:

-Potential adverse effects of foscarnet include renal impairment, hypo- or hypercalcemia, hypo- or hyperphosphatemia, hypokalemia, and hypomagnesemia. Saline preloading helps prevent nephrotoxicity, as does avoidance of concomitant administration of drugs with nephrotoxic potential (eg, amphotericin B, pentamidine, aminoglycosides).

-The risk of severe hypocalcemia, caused by chelation of divalent cations, is increased with concomitant use of **pentamidine**.

-Genital ulcerations associated with foscarnet therapy may be due to high levels of ionized drug in the urine.

-Nausea, vomiting, anemia, elevation of liver enzymes, and fatigue have been reported; the risk of anemia may be additive in patients receiving concurrent zidovudine.

-Central nervous system toxicity includes headache, hallucinations, and seizures; the risk of seizures may be increased with concurrent use of imipenem.

♦CIDOFOVIR:

-Is a cytosine nucleotide analog with in vitro activity against CMV, HSV-1, HSV-2, VZV, EBV, HHV-6, HHV-8, adenovirus, poxviruses, polyomaviruses, and human papillomavirus.

-In contrast to ganciclovir, phosphorylation of cidofovir to the active diphosphate is independent of viral enzymes; thus activity is maintained against thymidine kinase-deficient or -altered strains of CMV or HSV.

Mechanism of action:

Cidofovir diphosphate acts both as a potent inhibitor of and as an alternative substrate for viral DNA polymerase, competitively inhibiting DNA synthesis and becoming incorporated into the viral DNA chain.

-The terminal half-life of cidofovir is approximately 2.6 hours.

-Cerebrospinal fluid penetration is poor.

-Elimination is by active renal tubular secretion.

Treatment

-Intravenous cidofovir is effective for the treatment of CMV retinitis and is used experimentally to treat adenovirus, human papillomavirus, BK polyomavirus, vaccinia, and poxvirus infections.

-Intravenous cidofovir must be administered with high-dose probenecid (**2 g at 3 hours before the infusion and 1 g at 2 and 8 hours after**), which blocks active tubular secretion and decreases nephrotoxicity.

-Initiation of cidofovir therapy is contraindicated in patients with existing renal insufficiency.

-Direct intravitreal administration of cidofovir is not recommended because of ocular toxicity.

Side effects:

- The primary adverse effect of intravenous cidofovir is a dose dependent proximal tubular nephrotoxicity, which may be reduced with prehydration using normal saline.
- Proteinuria, azotemia, metabolic acidosis, and Fanconi's syndrome may occur.
- Other potential adverse effects include uveitis, ocular hypotony, and neutropenia (15–24%).
- Concurrent probenecid use may result in other toxicities or drug-drug interactions (see Chapter 36).
- Cidofovir is mutagenic, gonadotoxic, and embryotoxic, and causes hypospermia and mammary adenocarcinomas in animals.

► ANTIRETROVIRAL AGENTS:

#Six classes of antiretroviral agents are currently available for use:

- 1-nucleoside/nucleotide reverse transcriptase inhibitors (**NRTIs**),
- 2-non-nucleoside reverse transcriptase inhibitors (**NNRTIs**),
- 3-proteaseinhibitors (**PIs**),
- 4-fusion inhibitors,
- 5-CCR5 co-receptor antagonists (also called **entry inhibitors**),
- 6-HIV integrase strand transfer inhibitors (**INSTIs**)

- Administration of combination antiretroviral therapy, typically including at least three antiretroviral agents with differing susceptibility patterns, has become the standard of care.
 - Such combinations must be chosen with care and tailored to the individual, as must changes to a given regimen.
 - Decrease of the circulating viral load by antiretroviral therapy is correlated with enhanced survival as well as decreased morbidity.
- 1-NUCLEOSIDE & NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs):**
- NRTIs are considered the “backbone” of antiretroviral therapy and are generally used in combination with other classes of agents, such as: **NNRTI**, **PI**, or **integrase inhibitor**.
 - Certain NRTI combinations should be avoided, due to either drug-drug interactions (eg, didanosine + tenofovir), similar resistance patterns (eg, lamivudine + emtricitabine) or overlapping toxicities (eg, stavudine + didanosine).



Mechanism of action:

Act by competitive inhibition of HIV-1 reverse transcriptase; incorporation into the growing viral DNA chain causes premature chain termination due to inhibition of binding with the incoming nucleotide.

-Each agent requires intracytoplasmic activation via phosphorylation by cellular enzymes to the triphosphate form.

Side reactions:

All NRTIs may be associated with mitochondrial toxicity, probably owing to inhibition of mitochondrial DNA polymerase gamma. Less commonly, lactic acidosis with hepatic steatosis may occur, which can be fatal.

-The thymidine analogs zidovudine and stavudine may be particularly associated with dyslipidemia and insulin resistance. Also, some evidence suggests an increased risk of myocardial infarction in patients receiving abacavir; this remains unproven.

♦**ABACAVIR:**

-Abacavir is a guanosine analog that is well absorbed following oral administration (83%) and is unaffected by food.

-The serum half-life is 1.5 hours.

-serum levels of abacavir may be increased with concurrent alcohol (ie, ethanol) ingestion.

-Cerebrospinal fluid levels are approximately one-third those of plasma.

- Abacavir is available in a fixed dose formulation with lamivudine and also with zidovudine + lamivudine.

Side effects:

-Hypersensitivity reactions, occasionally fatal, have been reported in up to 8% of patients

-Symptoms, which generally occur within the first 6 weeks of therapy, include fever, fatigue,

nausea, vomiting, diarrhea, and abdominal pain. Respiratory symptoms such as dyspnea, pharyngitis, and cough may also be present, and skin rash occurs in about 50% of patients.

-The syndrome tends to resolve quickly with discontinuation of medication.

-Other potential adverse events are rash, fever, nausea, vomiting, diarrhea, headache, dyspnea, fatigue, and pancreatitis (rare).

-Abacavir has been associated with a higher risk of myocardial infarction.

◆ DIDANOSINE:

Is a synthetic analog of deoxyadenosine.

- Oral bioavailability is approximately 40%. Dosing on an empty stomach is optimal, but buffered formulations are necessary to prevent inactivation by gastric acid.

- Cerebrospinal fluid concentrations of the drug are approximately 20% of serum concentrations.

- Serum half-life is 1.5 hours, but the intracellular half-life of the activated compound is as long as 20–24 hours.

- The drug is eliminated by both cellular metabolism and renal excretion.

- The major clinical toxicity associated with didanosine therapy is dose-dependent pancreatitis

- Due to an increased risk of lactic acidosis and hepatic steatosis when combined with stavudine, this combination **should be avoided**, especially during **pregnancy**.

- The buffer in didanosine tablets interferes with absorption of indinavir, delavirdine, atazanavir, dapsone, itraconazole, and fluoroquinolone agents; therefore, administration should be **separated in time**.

Currently available antiretroviral agents.

Agent	Class of Agent	Recommended Adult Dosage	Administration Recommendation	Characteristic Adverse Effects	Comments
Abacavir	NRTI ¹	300 mg bid or 600 mg qd	Testing to rule out the presence of the HLA-B5701 allele is recommended prior to the initiation of therapy	Rash, hypersensitivity reaction, nausea. Possible increase in myocardial infarction	Avoid alcohol.
Atazanavir	PI ²	400 mg qd or 300 mg qd with ritonavir 100 mg qd. Adjust dose in hepatic insufficiency	Take with food. Separate dosing from ddI or antacids by 1 h. Separate dosing from cimetidine and other acid-reducing agents by 12 h	Nausea, vomiting, diarrhea, abdominal pain, headache, peripheral neuropathy, skin rash, indirect hyperbilirubinemia, prolonged PR and/or QTc interval	See footnote 4 for contraindicated medications. Also avoid etravirine, fosamprenavir, nevirapine, and proton pump inhibitors. Avoid in severe hepatic insufficiency
Darunavir	PI ²	Treatment-experienced: 600 mg bid with ritonavir 100 mg bid. Treatment-naïve: 800 mg qd with ritonavir 100 mg qd. Tablets can be dissolved in water	Take with food	Diarrhea, headache, nausea, rash, hyperlipidemia, ↑ liver enzymes, ↑ serum amylase	Avoid in patients with sulfa allergy. See footnote 4 for contraindicated medications
Delavirdine	NNRTI	400 mg tid	Separate dosing from ddI or antacids by 1 h	Rash, ↑ liver enzymes, headache, nausea, diarrhea	See footnote 4 for contraindicated medications. Also avoid concurrent fosamprenavir and rifabutin. Teratogenic in rats
Didanosine (ddI)	NRTI ¹	Tablets, 400 mg qd or 200 mg bid ³ adjusted for weight. Buffered powder, 250 mg bid ³	30 min before or 2 h after meals. Separate dosing from fluoroquinolones and tetracyclines by 2 h	Peripheral neuropathy, pancreatitis, diarrhea, nausea, hyperuricemia.	Avoid concurrent neuropathic drugs (eg, stavudine, zalcitabine, isoniazid), ribavirin, and alcohol. Do not administer with tenofovir
Dolutegravir	INSTI	50 mg qd	Separate dosing from antacids by 2 h	Insomnia, headache, hypersensitivity reaction, ↑ liver enzymes.	See footnote 4 for contraindicated medications. Dofetilide is also contraindicated.
Efavirenz	NNRTI	600 mg qd	Take on an empty stomach. Bedtime dosing recommended initially to minimize central nervous system side effects	Central nervous system effects, rash, ↑ liver enzymes, headache, nausea	See footnote 4 for contraindicated medications. Teratogenic in primates
Elvitegravir	INSTI	150 mg qd. Available only in combined formulation with cobicistat, tenofovir, and emtricitabine	Take with food.	Under investigation	Should not be initiated if CrCl < 70 mL/min and should be discontinued if CrCl < 50 mL/min
Emtricitabine	NRTI ¹	200 mg qd. ³ Tablets can be dissolved in water	Oral solution should be refrigerated	Headache, diarrhea, nausea, asthenia, skin hyperpigmentation	Do not administer concurrent lamivudine. Avoid disulfiram and metronidazole with oral solution
Enfuvirtide	Fusion inhibitor	90 mg subcutaneously bid	Store at room temperature as a powder; refrigerate once reconstituted	Local injection site reactions, hypersensitivity reaction	
Etravirine	NNRTI	200 mg bid	Take after a full meal	Rash, nausea, diarrhea	See footnote 4 for contraindicated medications. Do not administer with other NNRTIs, indinavir, atazanavir-ritonavir, fosamprenavir-ritonavir, tipranavir-ritonavir, or any unboosted PI

Agent	Class of Agent	Recommended Adult Dosage	Administration Recommendation	Characteristic Adverse Effects	Comments
Fosamprenavir	PI ²	1400 mg bid or 700 mg bid with ritonavir 100 mg bid or 1400 mg daily with ritonavir 100–200 mg qd. Adjust dose in hepatic insufficiency	Separate dosing from antacids or didanosine by > 1 h. Avoid concurrent high-fat meals	Diarrhea, nausea, vomiting, hypertriglyceridemia, rash, headache, perioral paresthesias, ↑ liver enzymes	See footnote 4 for contraindicated medications. Do not administer with etravirine; do not administer with lopinavir/ritonavir or in severe hepatic insufficiency. Also avoid cimetidine, disulfiram, metronidazole, vitamin E, ritonavir oral solution, and alcohol when using the oral solution
Indinavir	PI ²	800 mg tid or 800 mg bid with ritonavir 100–200 mg bid. Adjust dose in hepatic insufficiency	Best on an empty stomach. Drink at least 48 oz liquid daily. Separate dosing from ddl by 1 h. Store in original container, which contains desiccant	Nephrolithiasis, nausea, indirect hyperbilirubinemia, headache, asthenia, blurred vision	See footnote 4 for contraindicated medications. Do not administer with etravirine
Lamivudine	NRTI ¹	150 mg bid or 300 mg qd ³		Nausea, headache, dizziness, fatigue	Do not administer with zalcitabine
Lopinavir/ritonavir	PI/PI ²	Treatment-experienced: 400 mg/100 mg bid. Treatment-naïve: 800 mg/200 mg qd. May need dose adjustment in hepatic insufficiency	Take with food. Separate dosing from ddl by 1 h. Store capsules and solution in refrigerator	Diarrhea, abdominal pain, nausea, hypertriglyceridemia, headache, ↑ liver enzymes	See footnote 4 for contraindicated medications. Also avoid fosamprenavir. Avoid disulfiram and metronidazole with oral solution
Maraviroc	CCR5 inhibitor	300 mg bid; 150 bid with CYP3A inhibitors; 600 mg bid with CYP3A inducers ³		Cough, muscle pain, diarrhea, sleep disturbance, ↑ liver enzymes	See footnote 4 for medications that must be co-administered with caution.
Nelfinavir	PI ²	750 mg tid or 1250 mg bid	Take with food	Diarrhea, nausea, flatulence	See footnote 4 for contraindicated medications. Do not administer with efavirenz
Nevirapine	NNRTI	200 mg bid. Adjust dose in hepatic insufficiency	Dose-escalate from 200 mg daily over 14 days to decrease frequency of rash	Rash, hepatitis (occasionally fulminant), nausea, headache	See footnote 4 for contraindicated medications. Do not administer with atazanavir
Raltegravir	INSTI	400 mg bid. Increase dose to 800 mg bid if administered with ddI	Separate dosing from antacids by ≥ 4 h	Insomnia, headache, diarrhea, nausea, dizziness, muscle aches, ↑ liver enzymes, ↑ creatine kinase, hypersensitivity reaction	
rifampin					
Rilpivirine	NNRTI	25 mg qd	Take with food. Avoid concurrent proton pump inhibitors. Separate dosing from antacids by ≥ 4 h	Insomnia, depression, rash, ↑ liver enzymes	See footnote 4 for contraindicated medications
Ritonavir	PI ²	600 mg bid	Take with food. Separate dosing with ddl by 2 h. Dose-escalate from 300 mg bid over 1–2 weeks to improve tolerance. Refrigerate capsules but not oral solution	Nausea, diarrhea, paresthesias, hepatitis	See footnote 4 for contraindicated medications. Avoid disulfiram and metronidazole with oral solution
Saquinavir	PI ²	1000 mg bid with ritonavir 100 mg bid	Take within 2 h of a full meal. Refrigeration recommended	Nausea, diarrhea, rhinitis, abdominal pain, dyspepsia, rash	See footnote 4 for contraindicated medications. Avoid in severe hepatic insufficiency. Use sunscreen owing to an increase in photosensitivity. Avoid concomitant garlic capsules

Agent	Class of Agent	Recommended Adult Dosage	Administration Recommendation	Characteristic Adverse Effects	Comments
Stavudine	NRTI ¹	30–40 mg bid, depending on weight ³		Peripheral neuropathy, lipodystrophy, hyperlipidemia, rapidly progressive ascending neuromuscular weakness (rare), pancreatitis	Avoid concurrent zidovudine and neuropathic drugs (eg, ddl, zalcitabine, isoniazid)
Tenofovir	NRTI ¹	300 mg qd ³	Take with food	Nausea, diarrhea, vomiting, flatulence, headache, renal insufficiency	Avoid concurrent atazanavir, probenecid, didanosine
Tipranavir	PI ²	500 mg bid with ritonavir 200 mg bid. Avoid use in hepatic insufficiency	Take with food. Separate from ddl by at least 2 h. Avoid antacids. Avoid in patients with sulfa allergy. Refrigeration required	Diarrhea, nausea, vomiting, abdominal pain, rash, ↑ liver enzymes, hypercholesterolemia, hypertriglyceridemia	See footnote 4 for contraindicated medications. Avoid concurrent fosamprenavir, saquinavir, etravirine. Do not administer to patients at risk for bleeding
Zidovudine	NRTI ¹	200 mg tid or 300 mg bid ³		Macrocytic anemia, neutropenia, nausea, headache, insomnia, asthenia	Avoid concurrent stavudine and myelosuppressive drugs (eg, ganciclovir, ribavirin)

1All NRTI agents, including tenofovir, carry the risk of lactic acidosis with hepatic steatosis as a potential adverse event.

2All PI agents, with the possible exception of fosamprenavir, carry the risk of hyperlipidemia, fat maldistribution, hyperglycemia, and insulin resistance as potential adverse events.

3Adjust dose in renal insufficiency.

INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.

Clinically significant drug-drug interactions pertaining to two-drug antiretroviral

Agent	Drugs That Increase Its Serum Levels	Drugs That Decrease Its Serum Levels
Atazanavir	Ritonavir	Didanosine, efavirenz, etravirine, nevirapine, stavudine, tenofovir, tipranavir
Darunavir	Indinavir	Lopinavir/ritonavir, saquinavir
Delavirdine		Amprenavir, didanosine, fosamprenavir
Didanosine	Tenofovir	Atazanavir, ritonavir
Dolutegravir		Efavirenz, etravirine
Efavirenz	Darunavir	Etravirine, nevirapine
Etravirine	Atazanavir, lopinavir/ritonavir	Darunavir, efavirenz, nevirapine, ritonavir, saquinavir, tenofovir, tipranavir
Fosamprenavir	Atazanavir, delavirdine, etravirine, ritonavir	Didanosine, efavirenz, lopinavir/ritonavir, nevirapine, tipranavir
Indinavir	Darunavir, delavirdine, nelfinavir, ritonavir	Didanosine, efavirenz, etravirine, nevirapine
Lopinavir/ritonavir	Darunavir, delavirdine	Didanosine, efavirenz, nelfinavir, nevirapine, tipranavir
Maraviroc	Atazanavir, darunavir, lopinavir/ritonavir, nevirapine, saquinavir, ritonavir	Efavirenz, etravirine, tipranavir
Nelfinavir	Delavirdine, indinavir, ritonavir	
Nevirapine		Etravirine
Raltegravir	Atazanavir	Etravirine, tipranavir
Saquinavir	Atazanavir, delavirdine, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir	Efavirenz, nevirapine, tipranavir
Tenofovir	Atazanavir	
Tipranavir		Efavirenz

¹Dose adjustment may be necessary if co-administered.

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sis.

Vomiting and diarrhea .
The drug should be avoided in pregnancy because of its teratogenic

Is a fluorinated analog of lamivudine with a long intracellular half-life (> 24 hours), allowing for once daily dosing. Oral bioavailability of the capsules is 93% and is unaffected by food, but penetration into the cerebrospinal fluid is low. Elimination is by both glomerular filtration and active tubular secretion. The serum half-life is about 10 hours.

The oral solution, which contains propylene glycol, is contraindicated in young children, pregnant women, patients with renal or hepatic failure, and those using metronidazole or disulfiram. Also, because of its activity against HBV, patients co-infected with HIV and HBV should be closely monitored if treatment with emtricitabine is interrupted or discontinued, owing to the likelihood of hepatitis flare.

Emtricitabine is available with tenofovir, either alone or in combination with efavirenz, rilpivirine, or elvitegravir + cobicistat.

The most common adverse effects observed in patients receiving emtricitabine are headache, insomnia,

nausea, and rash. In addition, hyperpigmentation of the palms or soles may be observed (~ 3%), particularly in African Americans (up to 13%).

LAMIVUDINE

Lamivudine (3TC) is a cytosine analog with in vitro activity against HIV-1 that is synergistic with a variety of antiretroviral nucleoside analogs—including zidovudine and stavudine—against both zidovudine-sensitive and zidovudineresistant HIV-1 strains. lamivudine has activity against HBV; therefore, discontinuation in patients that

are co-infected with HIV and HBV may be associated with a flare of hepatitis.

Oral bioavailability exceeds 80% and is not food-dependent. In children, the average cerebrospinal fluid:plasma ratio of lamivudine was 0.2. Serum half-life is 2.5 hours, and its elimination unchaned in urine.

Lamivudine still one of the recommended antiretroviral agents in pregnant women.

And is available in combination with zidovudine and also with abacavir. adverse effects are headache, dizziness, insomnia, fatigue, dry mouth, and gastrointestinal discomfort, although these are typically mild and infrequent. Co administration of lamivudine with trimethoprim-sulfamethoxazole to increase its bioavailability, Either with zalcitabine to inhibit the intracellular phosphorylation of each other,

Their concurrent use should be avoided if possible.

STAVUDINE

The thymidine analog stavudine (d4T) has high oral bioavailability (86%) that is not food-dependent. The serum half-life is 1.1 hours, the intracellular half-life is 3.0–3.5 hours, and mean cerebrospinal fluid concentrations are 55% of those of plasma. Excretion is by active tubular secretion and glomerular filtration.

Administration of stavudine may cause nephropathy and its increase if administered with potentially neurotoxin drugs. Or in patient with immunosuppression, and Symptoms well resolve if discontinued.

Other potential adverse effects are pancreatitis, arthralgias, and elevation in serum aminotransferases. Lactic acidosis with hepatic steatosis, as well as lipodystrophy, appear to occur more frequently in patients receiving stavudine than in those receiving other NRTI agents.

Moreover, because the co-administration of stavudine and didanosine may increase the incidence of lactic acidosis and pancreatitis, concurrent use should be avoided. This combination has been implicated in several deaths in HIV-infected pregnant women. A rare adverse effect is a rapidly progressive ascending neuromuscular weakness. Since zidovudine may reduce the phosphorylation of stavudine, these two drugs should not be used together.

TENOFOVIR

Is an acyclic nucleoside phosphonate (ie, nucleotide) analog of adenosine. Tenofovir competitively inhibits HIV reverse transcriptase and causes chain

termination after incorporation into DNA.

Also approved for the treatment of patients with HBV infection.

Tenofovir disoproxil fumarate is a water-soluble prodrug of active tenofovir. The oral bioavailability in fasted patients is approximately 25% and increases to 39% after a high-fat meal. The prolonged serum (12–17 hours) and intracellular half-lives allow once-daily dosing. Elimination occurs by both glomerular filtration and active tubular secretion, and dosage adjustment in patients with renal insufficiency is recommended.

Tenofovir is available in several fixed-dose formulations. the combination of tenofovir and emtricitabine is now recommended as pre-exposure prophylaxis to reduce HIV acquisition, and in injection drug users.

Gastrointestinal complaints are the most common adverse effects but rarely require discontinuation of therapy.

Other potential adverse effects include headache, rash, dizziness, and asthenia. Cumulative loss of renal function has been observed, possibly increased with concurrent use of boosted PI regimens. Acute renal failure and Fanconi's syndrome have also been reported. And it should have used with cautions and monitorings.

Tenofovir-associated proximal renal tubulopathy causes excessive renal phosphate and calcium losses and 1-hydroxylation defects of vitamin D.

Concurrent use of atazanavir or lopinavir/ritonavir may increase serum levels of tenofovir.

ZIDOVUDINE

Is a deoxythymidine analog that is well absorbed (63%) and distributed to most body tissues and fluids, including the cerebrospinal fluid, where drug levels are 60–65% of those in serum.

Although the serum half-life averages 1 hour, the intracellular half-life of the phosphorylated compound is 3–4 hours, allowing twice-daily dosing.

Zidovudine is eliminated primarily by renal excretion following glucuronidation in the liver.

Zidovudine is available with lamivudine, either alone or in combination with abacavir.

The drug has been shown to decrease the rate of clinical disease progression and prolong survival in HIV-infected individuals. Efficacy has also been demonstrated in the treatment of HIV-associated dementia and thrombocytopenia.

And it's remains one of the first-line agents for use in pregnant women.

High-level zidovudine resistance is generally seen in strains with three or more of the five most common mutations: M41L, D67N, K70R, T215F, and K219Q. However, the emergence of certain mutations that confer decreased susceptibility to one drug may enhance zidovudine susceptibility in previously zidovudine-resistant strains.

The most common adverse effect of zidovudine is myelosuppression, resulting in macrocytic anemia or neutropenia, Gastrointestinal intolerance, headaches, and insomnia

may occur but tend to resolve during therapy.

Less common toxicities include thrombocytopenia, hyperpigmentation of the nails, and myopathy. High doses can cause anxiety, confusion, and tremulousness.

There are drugs that increase zidovudine level through inhibition of first-pass metabolism or through decreased clearance. And it's may decrease phenytoin level. co-administration with myelosuppressive drugs can cause hematologic toxicity.

Combination with stavudine should be avoided due to in vitro antagonism.

The use of antiretroviral agent's in pregnancy.1

Recommended Agents	Alternate Agents
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	
Lamivudine, zidovudine	Abacavir, emtricitabine, tenofovir
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	
Nevirapine	
Protease inhibitors (PIs)	
Lopinavir/ritonavir, atazanavir/ ritonavir	Darunavir, saquinavir

¹Data are insufficient to recommend the use of entry inhibitors or integrase inhibitors in pregnancy at the present time.

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

The NNRTIs bind directly to HIV-1 reverse transcriptase, resulting in allosteric inhibition of RNA- and DNA-dependent DNA polymerase activity. The binding site of NNRTIs is near to but distinct from that of NRTIs. Unlike the NRTI agents, NNRTIs neither compete with nucleoside

triphosphates nor require phosphorylation to be active.

Baseline genotypic testing is recommended prior to initiating NNRTI treatment.

NNRTI agents tend to be associated with varying levels of gastrointestinal intolerance and skin rash, the latter of which may infrequently be serious. A further limitation to use of NNRTI agents as a component of antiretroviral therapy is their metabolism by the CYP450 system, leading to innumerable potential drug-drug interactions.

All NNRTI agents are substrates for CYP3A4 and can act as inducers (nevirapine), inhibitors (delavirdine), or mixed inducers and inhibitors (efavirenz, etravirine).

DELAVIDINE

Delavirdine has an oral bioavailability of about 85%, but this is reduced by antacids or H₂-blockers. It is extensively bound (~ 98%) to plasma proteins and has correspondingly low cerebrospinal fluid levels. Serum half-life is approximately 6 hours.

Skin rash occurs in up to 38% of patients receiving delavirdine; However, severe rash such as erythema multiform and Stevens-Johnson syndrome have rarely been reported. Other possible adverse effects are headache, fatigue, nausea, diarrhea, and increased serum aminotransferase levels. pregnancy should be avoided when taking delavirdine.

Delavirdine is extensively metabolized by the CYP3A and CYP2D6 enzymes and also inhibits CYP3A4 and 2C9. Therefore, there are

numerous potential drug-drug interactions to consider.

fosamprenavir and rifabutin is not recommended with it because of decreased delavirdine levels.

Co-administration of delavirdine with indinavir or saquinavir prolongs the elimination half-life of these protease inhibitors, thus allowing them to be dosed twice rather than three times daily.

EFAVIRENZ

It's have the longest half life between other antiviral agents.

Its moderately well absorbed following oral administration (45%). Since toxicity may increase owing to increased bioavailability after a high-fat meal, efavirenz should be taken on an empty stomach.

Efavirenz Is Metabolized by CYP3A4 and CYP2B6 to inactive hydroxylated metabolites; the remainder is eliminated in the feces as unchanged drug.

It is highly bound to albumin (~ 99%), and cerebrospinal fluid levels range from 0.3% to 1.2% of plasma levels.

The principal adverse effects involve the central nervous system. Dizziness, drowsiness, insomnia, nightmares, and headache tend to diminish with continued therapy; And some psychiatric symptoms have been observed, skin rash in different level of severity, nausea, vomiting, diarrhea, crystalluria, elevated liver enzymes, and an increase in total serum cholesterol by 10–20%.

High rates of fetal abnormalities are observed in pregnant monkeys exposed in doses roughly equivalent to the

human dosage; several cases of congenital anomalies have been reported in humans; therefore, should be avoided in pregnant women specially in 1st trimester.

Since efavirenz may lower methadone levels, patients receiving these two agents concurrently should be monitored for signs of opioid withdrawal and may require an increased dose of methadone.

ETRAVIRINE

Etravirine was designed to be effective against strains of HIV that had developed resistance to first-generation NNRTIs, due to mutations such as K103N and Y181C, and is recommended for treatment-experienced patients that have resistance to other NNRTIs.

should be taken with a meal to increase systemic exposure, it is highly protein-bound and is primarily metabolized by the liver. Mean terminal half-life is ~41 hours.

The most common adverse effects of etravirine are rash, nausea, and diarrhea. The rash is typically mild and usually resolves after 1–2 weeks without discontinuation of therapy. And there are elevations in serum cholesterol, triglyceride, glucose, and hepatic transaminase levels (HBV or HCV co-infection).

Etravirine is a substrate as well as an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19; it has many therapeutically significant drug-drug interactions, some of the interactions are difficult to predict.

This drug should be given alone to prevent that interactions.

NEVIRAPINE

It has excellent oral bioavailability. The drug is highly lipophilic and achieves cerebrospinal fluid levels that are 45% of those in plasma. Serum half-life is 25–30 hours.

It is extensively metabolized by the CYP3A isoform to hydroxylated metabolites and then excreted, primarily in the urine.

A single dose (200 mg) is effective in the prevention of transmission of HIV from mother to newborn when administered to women at the onset of labor and followed by a 2 mg/kg oral dose to the neonate within 3 days after delivery, and nevirapine remains one of the recommended agents in pregnant women.

Rash, usually a maculopapular eruption that spares the palms and soles, usually in the first 4–6 weeks of therapy.

When initiating therapy, gradual dose escalation over 14 days is recommended to decrease the incidence of rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Patients with accompanying constitutional symptoms and severe rash should not be taken this medicine; because it increases the severity of that symptoms.

Symptomatic liver toxicity may occur in some patients, may be severe, and is more frequent in those with higher pretherapy CD4 cell counts. in women, and in those with HBV or HCV co-infection.

life-threatening hepatitis has been reported. Other adverse effects include fever, nausea, headache, and somnolence. Nevirapine is a moderate inducer of CYP3A metabolism,

resulting in decreased levels of amprenavir, indinavir, lopinavir, saquinavir, efavirenz, and methadone. therefore; there some drugs act as inducer for same enzyme results in decrease nevirapine levels in plasma, and as well as there some drugs have inhibiting activity for the same enzyme that well increase nevirapine.

Since nevirapine may lower methadone levels, patients receiving these two agents concurrently should be monitored for signs of opioid withdrawal and may require an increased dose of methadone.

RILPIVIRINE

Rilpivirine is recommended only in treatment-naive patients with HIV-1 RNA $\leq 100,000$ copies/mL, and only in combination with at least 2 other antiretroviral agents. It is available in a fixed dose formulation with emtricitabine and tenofovir.

Rilpivirine must be administered with a meal. Its oral bioavailability can be significantly reduced in the presence of acid lowering agents. It should be used with caution with antacids and H2-receptor antagonists. Rilpivirine is contraindicated with proton-pump inhibitors (PPIs). The drug is highly protein bound and the terminal elimination half-life is 50 hours.

There is cross-resistance with other NNRTIs, and the combination of rilpivirine with other NNRTIs is not recommended.

Rilpivirine is primarily metabolized by CYP3A4, and drugs that induce or inhibit CYP3A4 may thus affect the clearance of rilpivirine.

Drug drug interactions with other antiretroviral agents are not identified yet.

Concurrent use of carbamazepine, dexamethasone, phenobarbital, phenytoin, proton pump inhibitors, rifabutin, rifampin, rifapentine, and St John's wort is contraindicated. Methadone withdrawal may be precipitated with concurrent usage.

The most common adverse effects are rash, depression, headache, insomnia, and increased serum aminotransferases. Increased serum cholesterol, and fat redistribution syndrome has been reported. Higher doses have been associated with QTc prolongation.

PROTEASE INHIBITORS (PIs)

The HIV protease is responsible for cleaving these precursor molecules (the gag and gag-pol gene products) to produce the final structural proteins of the mature virion core. By preventing posttranslational cleavage of the Gag-Pol polyprotein, protease inhibitors (PIs) prevent the processing of viral proteins into functional conformations, resulting in the production of immature, noninfectious viral particles.

Unlike the NRTIs, PIs do not need intracellular activation.

Specific genotypic alterations that confer phenotypic resistance are fairly common with these agents, thus contraindicating monotherapy.

The I50L substitution emerging during atazanavir therapy has been associated with increased susceptibility to other PIs. Darunavir and tipranavir appear to have improved virologic activity in

patients harboring HIV-1 resistant to other PIs.

All PIs may be associated with cardiac conduction abnormalities, including PR or QT interval prolongation or both.

Drug-induced hepatitis and rare severe hepatotoxicity have been reported to varying degrees with all PIs; the frequency of hepatic events is higher with tipranavir/ ritonavir than with other PIs.

All of the antiretroviral PIs are extensively metabolized by CYP3A4, with ritonavir having the most pronounced inhibitory effect and saquinavir the least.

Expert resources about drug-drug interactions should be consulted, as dosage adjustments are frequently required and some combinations are contraindicated.

ATAZANAVIR

Atazanavir is an azapeptide PI with a pharmacokinetic profile that allows once-daily dosing. Atazanavir requires an acidic medium for absorption; therefore, it should be taken with meals and separation of ingestion from acid-reducing agents by at least 12 hours is recommended; concurrent proton pump inhibitors are contraindicated.

The plasma half-life is 6–7 hours, which increases to approximately 11 hours when co-administered with ritonavir. The primary route of elimination is biliary; it should not be given to patients with severe hepatic insufficiency.

Atazanavir is one of the recommended antiretroviral agents for pregnant women.

Resistance to atazanavir has been associated with various known PI mutations as well as with the novel I50L substitution. Whereas some atazanavir resistance mutations have been associated in vitro with decreased susceptibility to other PIs, the I50L mutation has been associated with increased susceptibility to other PIs.

The most common adverse effects in patients receiving atazanavir are diarrhea and nausea; vomiting, abdominal pain, headache, peripheral neuropathy, and skin rash may also occur. As with indinavir, indirect hyperbilirubinemia with overt jaundice may occur.

patients with underlying HBV or HCV co-infection are observed with them an elevation in hepatic enzymes. Nephrolithiasis has been described in association with atazanavir use, and prolonged use of boosted atazanavir is associated with cumulative loss of renal function.

atazanavir does not appear to be associated with dyslipidemia, fat redistribution, or the metabolic syndrome.

As an inhibitor of CYP3A4 and CYP2C9, the potential for drug-drug interactions with atazanavir is great.

The combination with proton pump inhibitors should be avoided. when it co-administered with other drugs that inhibit UGT1A1 increase its levels.

DARUNAVIR

Darunavir should be taken with meals to improve bioavailability. It is highly protein-bound and primarily metabolized by the liver.

Most common adverse effects of darunavir include diarrhea, nausea, headache, and rash, hepatotoxicity may be higher for persons with HBV, HCV, or other chronic liver disease.

Laboratory abnormalities include dyslipidemia and increases in amylase and hepatic transaminase levels.

Darunavir both inhibits and is metabolized by the CYP3A enzyme system, conferring many possible drug-drug interactions. In addition, the co-administered ritonavir is a potent inhibitor of CYP3A and CYP2D6, and an inducer of other hepatic enzyme systems.

FOSAMPRENAVIR

Fosamprenavir is a prodrug of amprenavir that is rapidly hydrolyzed by enzymes in the intestinal epithelium. It is most often administered in combination with low-dose ritonavir.

After hydrolysis of fosamprenavir, amprenavir is rapidly absorbed from the GI tract, and its prodrug can be taken with or without food. It should be avoided with fat meals.

Amprenavir must be used with caution in case of hepatic insufficiency.

The most common adverse effects of fosamprenavir are headache, nausea, diarrhea, perioral paresthesias, depression.

Amprenavir is both an inducer and an inhibitor of CYP3A4 and is contraindicated with numerous drugs.

The oral solution, which contains propylene glycol, is contraindicated in young children, pregnant women, patients with renal or hepatic failure,

and those using metronidazole or disulfiram, should not be administered with ritonavir, and patients with sulfa allergy. Supplemental vitamin E should be avoided, because it is already in it. Lopinavir/ritonavir should not be coadministered with it, because it decreases amprenavir levels and altered lopinavir exposures.

Recommendations when it is co-administered with efavirenz Increase dose level.

INDINAVIR

Indinavir requires an acidic environment for optimum solubility and therefore must be consumed on an empty stomach or with a small, low-fat, low-protein meal for maximal absorption. The serum half-life is 1.5–2 hours, protein binding is approximately 60%, and the drug has a high level of cerebrospinal fluid penetration.

The most common adverse effects of indinavir are indirect hyperbilirubinemia and nephrolithiasis due to urinary crystallization of the drug. Nephrolithiasis can occur within days after initiating therapy.

Thrombocytopenia, elevations of serum aminotransferase levels, nausea, diarrhea, insomnia, dry throat, dry skin. Insulin resistance may be more common with indinavir than with the other PIs, occurring in 3–5% of patients. There have also been rare cases of acute hemolytic anemia. Since indinavir is an inhibitor of CYP3A4, numerous and complex drug interactions can occur. Combination with ritonavir allows for

2 times daily rather than 3 times daily dosing and eliminates the food restriction associated with use of indinavir.

High fluid intake is advised.

LOPINAVIR

Lopinavir is currently available only in combination with ritonavir, which inhibits the CYP3A-mediated metabolism of lopinavir, thereby resulting in increased exposure to lopinavir. Lopinavir/ritonavir is generally well tolerated, and recommended in pregnant women. Lopinavir is highly protein bound, and its half-life is 5–6 hours. It is extensively metabolized by CYP3A, which is inhibited by ritonavir. Serum levels of lopinavir may be increased in patients with hepatic impairment.

The most common adverse effects of lopinavir are diarrhea, abdominal pain, nausea, vomiting, and asthenia. Ritonavir boosted lopinavir may be more commonly associated with gastrointestinal adverse events than other PIs. Elevations in serum cholesterol and triglycerides are common.

Prolonged use of boosted lopinavir is associated with cumulative loss of renal function. Concomitant use of lopinavir/ritonavir and rifampin is contraindicated due to an increased risk for hepatotoxicity. Since the oral solution of lopinavir/ ritonavir contains alcohol, concurrent disulfiram and metronidazole are contraindicated.

NELFINAVIR

Nelfinavir has high absorption in the fed state, metabolized by CYP3A, and

is excreted primarily in the feces. The plasma half-life in humans is 3.5–5 hours, and is Highly protein-bound. The most common adverse effects associated with nelfinavir are diarrhea and flatulence. Diarrhea often responds to antidiarrheal medications but can be dose-limiting. multiple drug interactions may occur.

RITONAVIR

Ritonavir has a high bioavailability that increases with food. It is highly protein-bound and has a serum half-life of 3–5 hours. Metabolism to an active metabolite occurs via the CYP3A and CYP2D6 isoforms; excretion is primarily in the feces. Caution is advised when administering the drug to Persons with impaired hepatic function.

adverse effects of ritonavir, particularly when administered at full dosage, are gastrointestinal disturbances, paresthesias, elevated serum aminotransferase levels, altered taste, headache, and elevations in serum creatine kinase. GI disturbance diminish over time or if the drug is taken with meals. Dose escalation over 1–2 weeks is recommended to decrease the dose limiting side effects.

Therapeutic levels of digoxin and theophylline should be monitored when co-administered with ritonavir owing to a likely increase in their concentrations. The concurrent use of saquinavir and ritonavir is contraindicated due to an increased risk of QT prolongation and PR interval prolongation.

SAQUINAVIR

oral saquinavir was poorly bioavailable However, reformulation of saquinavir

for once-daily dosing in combination with low-dose ritonavir has both improved antiviral efficacy and decreased gastrointestinal adverse effects.

Saquinavir should be taken within 2 hours after a fatty meal for enhanced absorption. It is highly protein-bound, and serum half-life is approximately 2 hours. Saquinavir has a large volume of distribution. Excretion is primarily in the feces.

Adverse effects include gastrointestinal discomfort and rhinitis.

When administered in combination with low-dose ritonavir, there appears to be less dyslipidemia or GI toxicity than with some of the other boosted PI regimens. However, the concurrent use of saquinavir and ritonavir may confer an increased risk of QT prolongation and PR interval prolongation.

Saquinavir is subject to extensive first-pass metabolism by CYP3A4 and functions as a CYP3A4 inhibitor as well as a substrate; thus, there are many potential drug-drug interactions. Liver tests should be monitored if saquinavir is co-administered with delavirdine or rifampin.

TIPRANAVIR

Tipranavir is a newer PI indicated for use in treatment-experienced patients who harbor strains resistant to other PI agents.

Bioavailability is poor but is increased when taken with a highfat meal. The drug is metabolized by the liver microsomal system and is contraindicated in patients with hepatic

insufficiency. It's should not be used in patients with sulfa allergy.

The most common adverse effects of tipranavir are GI discomfort. An urticarial or maculopapular rash is more common in women and may be accompanied by systemic symptoms or desquamation.

Liver toxicity, including life-threatening hepatic de-compensation, has been observed and may be more common than with other PIs, particularly in patients with chronic HBV or HCV infection.

Tipranavir should be discontinued in patients who have increased serum transaminase levels.

the drug should be avoided in patients with head trauma or bleeding diathesis. Other potential adverse effects include depression, elevation in amylase, and decreased white blood cell count.

Tipranavir both inhibits and induces the CYP3A4 system.

Is also induce P-glycoprotein transporter and thus may alter the disposition of many other drugs.

ENTRY INHIBITORS

The process of HIV-1 entry into host cells is complex; each step presents a potential target for inhibition. Viral attachment to the host cell entails binding of the viral envelope glycoprotein complex gp160 to its cellular receptor CD4.

This binding induces conformational changes in gp120 that enable access to the chemokine receptors CCR5 or CXCR4. Chemokine receptor binding induces further conformational changes in gp120, allowing exposure to gp41 and leading to fusion of the

viral envelope with the host cell membrane and subsequent entry of the viral core into the cellular cytoplasm.

ENFUVIRTIDE

Enfuvirtide is a synthetic 36-amino-acid peptide fusion inhibitor that blocks HIV entry into the cell.

Enfuvirtide binds to the gp41 subunit of the viral envelope glycoprotein, preventing the fusion of the viral and cellular membranes.

It is administered in combination with other antiretroviral agents in treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral therapy.

Enfuvirtide is the only parenterally administered antiretroviral agent.

Metabolized by proteolytic hydrolysis, Elimination half-life is 3.8 hours.

Enfuvirtide lacks cross-resistance with the other currently approved antiretroviral drug classes.

The most common adverse effects associated with enfuvirtide therapy are local injection site reactions, consisting of painful erythematous nodules. Although frequent, these are typically mild-to-moderate and rarely lead to discontinuation. Other side effects may include insomnia, headache, dizziness, and nausea. Hypersensitivity reactions may rarely occur, are of varying severity, and may recur on rechallenge.

No drug-drug interactions have been identified that would require the alteration of the dosage of concomitant antiretroviral or other drugs.

MARAVIROC

Maraviroc is approved for use in combination with other antiretroviral agents in treatment-experienced adult

patients infected with only CCR5-tropic HIV-1 detectable who are resistant to other antiretroviral agents.

Maraviroc binds specifically and selectively to the host protein CCR5, one of two chemokine receptors necessary for entrance of HIV into CD4+ cells.

Since maraviroc is active against HIV that uses the CCR5 co-receptor exclusively, and not against HIV strains with CXCR4, dual, or mixed tropism, co-receptor tropism should be determined by specific testing before maraviroc is started, using the enhanced sensitivity tropism assay.

The absorption of maraviroc is rapid but variable. Most of the drug (~75%) is excreted in the feces, whereas approximately 20% is excreted in urine.

The recommended dose varies according to renal function and the concomitant use of CYP3A inducers or inhibitors.

And Is contraindicated in patients with severe or end-stage renal impairment who are taking concurrent CYP3A inhibitors or inducers, and caution is advised when used in patients with preexisting hepatic impairment and in those co-infected with HBV or HCV.

Emergence of CXCR4 virus appears to be a more common cause of virologic failure than the development of resistance mutations.

Maraviroc is a substrate for CYP3A4 and therefore requires adjustment in the presence of drugs that interact with these

enzymes. It is also a substrate for P-glycoprotein, which limits intracellular concentrations of the drug.

The dosage of maraviroc must be decreased if it is co-administered with strong CYP3A inhibitors and must be increased if co-administered with CYP3A.

Potential adverse effects of maraviroc include cough, upper respiratory tract infections, muscle and joint pain, diarrhea, sleep disturbance, and elevations in serum aminotransferases. Hepatotoxicity has been reported, discontinuation of maraviroc should be started if this constellation occurs.

Caution should be used in patients with pre-existing liver dysfunction or co-infected with HBV or HCV. Myocardial ischemia and infarction have been observed in patients receiving maraviroc; therefore, caution is advised in patients at increased cardiovascular risk.

there has been no evidence of an increased risk of either malignancy or infection in patients receiving maraviroc.

INTEGRASE STRAND TRANSFER INHIBITORS (INSTIs)

This class of agents binds integrase, a viral enzyme essential to the replication of both HIV-1 and HIV-2. By doing so, it inhibits strand transfer, the third and final step of provirus integration, thus interfering with the integration of reverse-transcribed HIV DNA into the chromosomes of host cells.

Limited data suggest that effects upon lipid metabolism are favorable compared with efavirenz and PIs.

Rare and severe events include systemic hypersensitivity reactions and rhabdomyolysis.

DOLUTEGRAVIR

Dolutegravir may be taken with or without food. It should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.

It is primarily metabolized via UGT1A1 with some contribution from CYP3A. Therefore, drug-drug interactions may occur.

Dolutegravir inhibits the renal organic cation transporter OCT2, thereby increasing plasma concentrations of drugs eliminated via OCT2 such as dofetilide (C/I) and metformin (D/A). The most common adverse reactions are insomnia and headache.

Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported and may be life-threatening.

Other reported side effects include elevations in serum aminotransferases and the fat redistribution syndrome.

ELVITEGRAVIR

Elvitegravir requires boosting with cobicistat or ritonavir, and others. The combined formulation should be taken with food.

Cobicistat can inhibit renal tubular secretion of creatinine,

causing increases in serum creatinine that may not be clinically significant; in the fixed-dose formulation it may be difficult to distinguish between cobicistat effect and tenofovir-induced nephrotoxicity.

The recommendation is that the fixed-dose combination elvitegravir/cobicistat/tenofovir/emtricitabine should not be initiated in patients with calculated creatinine clearance < 70 mL/min and should be discontinued in those with creatinine clearance < 50 mL/min; discontinuation should be considered if the serum creatinine increases by 0.4 mg/dL or more.

Raltegravir

Absolute bioavailability of the pyrimidinone analog raltegravir has not been established but does not appear to be food-dependent. The drug does not interact with the cytochrome P450 system but is metabolized by glucuronidation, particularly UGT1A1. Inducers or inhibitors of UGT1A1 may affect serum levels of raltegravir.

The chewable tablets may contain phenylalanine, which can be harmful to patients with phenylketonuria.

Potential adverse effects of raltegravir include insomnia, headache, dizziness, diarrhea, nausea, fatigue, and muscle aches. Increases in pancreatic amylase, serum aminotransferases, and creatine kinase may occur. Severe, potentially life-threatening and fatal skin reactions have been reported, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis.

ANTIEPATITIS AGENTS

INTERFERON ALFA

Interferons are host cytokines that exert complex antiviral, immunomodulatory, and antiproliferative actions (see Ch-55) and some have proven useful in both HBV and HCV.

appears to function by induction of intracellular signals following binding to specific cell membrane receptors, resulting in inhibition of viral penetration, translation, transcription, protein processing, maturation, and release, as well as increased host expression of major histo-compatibility complex antigens, enhanced phagocytic activity of macrophages, and augmentation of the proliferation and survival of cytotoxic T cells.

*Drugs used to treat viral hepatitis.

Agent	Indication	Recommended Adult Dosage	Route of Administration
Nucleoside/nucleotide analogs			
Adefovir dipivoxil ¹	Chronic hepatitis B	10 mg qd	Oral
Entecavir ¹	Chronic hepatitis B	500 mg qd	Oral
Lamivudine ¹	Chronic hepatitis B	100 mg qd (150 mg qd if co-infection with HIV is present)	Oral
Tenofovir ¹	Chronic hepatitis B	300 mg qd	Oral
Telbivudine ¹	Chronic hepatitis B	600 mg qd	Oral
Interferons			
Interferon alfa-2b	Chronic hepatitis B	5 million units qd or 10 million units three times weekly	Subcutaneous or intramuscular
Interferon alfa-2b ¹	Acute hepatitis C	5 million units qd for 3–4 weeks, then 5 million units three times weekly	Subcutaneous or intramuscular
Pegylated interferon alfa-2a ¹	Chronic hepatitis B	180 mcg once weekly	Subcutaneous
Pegylated interferon alfa-2a ¹	Chronic hepatitis C	180 mcg once weekly plus ribavirin (800–1200 mg/d)	Subcutaneous
Pegylated interferon alfa-2b ¹	Chronic hepatitis C	1.5 mcg/kg once weekly with ribavirin (800–1200 mg/d)	Subcutaneous
Protease inhibitors			
Boceprevir	Chronic hepatitis C	800 mg tid × 24–44 weeks with peg-interferon alfa-2a or peg-interferon alfa-2b	Oral
Telaprevir	Chronic hepatitis C	750 mg tid × 12 weeks with peg-interferon alfa-2a or peg-interferon alfa-2b	Oral
Polymerase inhibitor			
Sofosbuvir	Chronic hepatitis C	400 mg qd (see text)	Oral

¹Dose must be reduced in patients with renal insufficiency.

Interferon alfa-2a and interferon alfa-2b may be administered either subcutaneously or intramuscularly; half-life is 2–5 hours, depending on the route of administration.

Alfa interferons are filtered at the glomerulus and undergo rapid proteolytic degradation. Liver metabolism and subsequent biliary excretion are considered minor pathways.

The adverse effects of interferon alfa include a flu-like syndrome that typically occurs within 6 hours after dosing; this syndrome occurs during the first week of therapy and tends to resolve upon continued administration. Transient hepatic enzyme elevations may occur in the first 8–12 weeks of therapy and appear to be more common in responders. Potential adverse effects during chronic therapy include neuro-toxicities, myelo-suppression, profound fatigue, weight loss, rash, cough, myalgia, alopecia, tinnitus, reversible hearing loss, retinopathy, pneumonitis, and possibly cardio-toxicity. Induction of auto-antibodies may occur, causing exacerbation or unmasking of autoimmune disease. C/Is to interferon alfa therapy include hepatic decompensation, autoimmune disease, and history of cardiac arrhythmia. Caution is advised in the setting of psychiatric disease, epilepsy, thyroid disease, ischemic cardiac disease, severe renal insufficiency, and cytopenia, and in case of pregnancy.

Potential drug-drug interactions include increased theophylline and methadone levels. Co-administration with didanosine is not recommended because of a risk of hepatic failure, and co-administration with zidovudine may exacerbate cytopenias.

TREATMENT OF HEPATITIS B VIRUS INFECTION

TREATMENT OF HEPATITIS B VIRUS INFECTION

The goals are the suppression of HBV DNA to undetectable levels, seroconversion of HBeAg and HBsAg from positive to negative, and reduction in elevated hepatic transaminase levels.

Current therapies suppress HBV replication without eradicating the virus, initial responses may not be durable. The covalently closed circular

(ccc) viral DNA exists in stable form indefinitely within the cell, serving as a reservoir for HBV throughout the life of the cell and resulting in the capacity to reactivate.

There some drugs were approved for treatment of chronic HBV infection in US: five oral nucleoside/nucleotide analogs and two injectable interferon drugs.

nucleoside/nucleotide analog therapies have better tolerability and produce a higher response rate than the interferons and are now considered the first line of therapy. Combination therapies may reduce the development of resistance.

Agents with dual HBV and HIV activity are particularly useful as part of a first-line regimen in co-infected patients.

However, it is important to note that acute exacerbation of hepatitis may occur upon discontinuation or interruption of these agents; this may be severe or even fatal.

ADEFOVIR DIPIVOXIL

Adefovir dipivoxil is the diester prodrug of adefovir, an acyclic phosphonated adenine nucleotide analog. It is phosphorylated by cellular kinases to the active diphosphate metabolite and then competitively inhibits HBV DNA polymerase and causes chain termination after incorporation into viral DNA.

Adefovir is active in vitro against a wide range of DNA and RNA viruses, including HBV, HIV, and herpesviruses.

It's had highly Oral bioavailability and is unaffected by meals; it is rapidly and completely hydrolyzed by intestinal and blood esterases. Protein

binding is low (< 5%). The intracellular half-life is prolonged (5-18 H), this makes once-daily dosing feasible.

Adefovir is excreted by a combination of glomerular filtration and active tubular secretion and requires dose adjustment for renal dysfunction; however, it may be administered to patients with decompensated liver disease.

Adefovir is well tolerated. A dose-dependent nephrotoxicity, manifested by ↑ serum creatinine and ↓ serum phosphorous, may occur and is more common with use of higher doses or pre-existing azotemia.

Other potential adverse effects are headache, diarrhea, asthenia, and abdominal pain. As with other NRTI agents, lactic acidosis and hepatic steatosis are considered a risk owing to mitochondrial dysfunction.

Adefovir is embryotoxic in rats at high doses and is genotoxic in preclinical studies.

ENTECAVIR

Is an orally administered guanosine nucleoside analog that competitively inhibits all three functions of HBV DNA polymerase, including base priming, reverse transcription of the negative strand, and synthesis of the positive strand of HBV DNA.

It's should be taken on an empty stomach. The intracellular half-life is 15 hours and plasma half-life is prolonged at 128-149 H, allowing once-daily dosing. It is excreted by the kidney, undergoing both glomerular filtration and net tubular secretion.

Entecavir has weak anti-HIV activity and can induce development of the M184V variant in HBV/HIV co-infected patients, resulting in resistance to emtricitabine and lamivudine.

Potential adverse events are headache, fatigue, dizziness, nausea, rash, and fever. Lung adenomas and carcinomas in mice, hepatic adenomas and carcinomas in rats and mice, vascular tumors in mice, and brain gliomas and skin fibromas in rats have been observed at varying exposures.

LAMIVUDINE (see NNRTIs)

Lamivudine can be safely administered to patients with decompensated liver disease.

Prolonged treatment has been shown to decrease clinical progression of HBV, as well as development of hepatocellular cancer by approximately 50%.

Lamivudine inhibits HBV DNA polymerase and HIV reverse transcriptase by competing with deoxycytidine triphosphate for incorporation into the viral DNA, resulting in chain termination.

Resistance has been associated with flares of hepatitis and progressive liver disease. Cross-resistance between lamivudine and emtricitabine or entecavir may occur.

TELBIVUDINE

Is a thymidine nucleoside analog with activity against HBV DNA polymerase. It is phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours. The phosphorylated compound competitively inhibits HBV DNA polymerase, resulting in incorporation into viral DNA and chain termination.

The serum half-life is approximately 15 hours and excretion is renal. There are no known metabolites and no known interactions with the CYP450 system or other drugs.

Adverse effects are mild; they include fatigue, headache, cough, nausea, diarrhea, rash, and fever. Both uncomplicated myalgia and myopathy have been reported, concurrent with increased creatine kinase levels, as has peripheral neuropathy.

TENOFOVIR (see NNRTIs)

Tenofovir maintains activity against lamivudine- and entecavir-resistant hepatitis virus isolates but has reduced activity against adefovir resistant strains.

The most common adverse effects of tenofovir in patients with HBV infection are nausea, abdominal pain, diarrhea, dizziness, fatigue, and rash.

TREATMENT OF HEPATITIS C INFECTION

The primary goal of treatment is viral eradication.

the primary efficacy end point is typically achievement of sustained viral response (SVR), defined as the absence of detectable viremia 24 weeks after completion of therapy. In acute hepatitis C, the rate of clearance of the virus without therapy is estimated at 15–30%. In one (uncontrolled) study, treatment of acute infection with interferon alfa-2b, in doses higher than those used for chronic hepatitis C, resulted in a sustained rate of clearance of 95% at 6 months.

the traditional standard treatment is once-weekly pegylated interferon alfa in combination with daily oral ribavirin.

Pegylated interferon alfa-2a and -2b have replaced their unmodified interferon alfa counterparts because of superior efficacy in combination with ribavirin, regardless of genotype. monotherapy with pegylated interferon alfa is recommended only in patients who cannot tolerate ribavirin. Administration of boceprevir, simeprevir, or telaprevir, in combination with peg-interferon and ribavirin, dramatically increased the rate of viral clearance in patients with HCV genotype 1; sofosbuvir is effective against HCV genotypes 1, 2, 3, and 4.

POLYMERASE INHIBITORS

Sofosbuvir

Sofosbuvir is a nucleotide analog that inhibits the HCV NS5B RNA-dependent RNA polymerase in patients infected with HCV genotype 1, 2, 3, or 4.

It is administered once daily, with or without food, in combination with peg-interferon alfa and ribavirin, for a total of 12–24 weeks.

Sofosbuvir is metabolized in the liver to form the active nucleoside analog triphosphate GS-461203. Elimination is by renal clearance, and safety has not been established in patients with severe renal insufficiency.

PROTEASE INHIBITORS

Three oral protease NS3/4A inhibitors have recently become available for the treatment of HCV genotype 1 infection, in combination with peg-interferon and ribavirin: boceprevir, simeprevir, and telaprevir.

Of concern is the enhanced toxicity when used in combination with peg-interferon and ribavirin, the high potential for drug-drug interactions,

and the low genetic barrier to resistance, which may develop as early as 4 days after initiation of therapy when administered as monotherapy. All three agents are inhibitors and substrates of CYP3A inhibitors. Drug-drug interactions are to be expected with many concurrent agents, particularly the NNRTIs and PIs in patients with HIV/HCV co-infection. Co-administration with strong CYP3A4 inducers is contraindicated due to potential decrease in serum levels of the anti-HCV agent, and co-administration with statin agents is contraindicated due to increased serum levels of the statin agent.

The effectiveness of hormonal contraceptives may be reduced by co-administration with boceprevir or telaprevir.

Boceprevir

Boceprevir therapy is initiated after the administration of peg-interferon and ribavirin therapy for 4 weeks.

Boceprevir should be taken with food to maximize absorption.

It is ~75% protein-bound and has a mean plasma half-life of ~ 3.4 h. Boceprevir is metabolized by the aldo-keto-reductase and CYP3A4/5 pathways and is an inhibitor of CYP3A4/5 and P-glycoprotein transporter.

Co-administration of boceprevir with numerous drugs is contraindicated. The most common adverse effects are fatigue, anemia, neutropenia, nausea, headache, and dysgeusia.

Rates of anemia are higher in patients taking boceprevir with peginterferon and ribavirin than in those taking peginterferon and ribavirin; rates of neutropenia are also higher.

Simeprevir

Simeprevir is administered in combination with peg-interferon and ribavirin for a total of 12 weeks in patients with compensated liver disease that are infected with HCV genotype 1.

metabolized in the liver by CYP3A pathways, and undergoes biliary excretion. Its safety in patients with moderate to severe liver insufficiency has not been established.

Simeprevir is a substrate and mild inhibitor of CYP3A and a substrate and inhibitor of P-gp and OATP1B1/3. Co-administration with moderate or strong inhibitors or inducers of CYP3A may significantly ↑ or ↓ the plasma concentration of simeprevir.

Reported adverse events include photosensitivity reaction and rash. Since simeprevir contains a sulfa moiety, caution should be used in patients with a history of sulfa allergy.

Telaprevir

Therapy with telaprevir + peg-interferon and ribavirin is administered for at least 12 weeks in treatment-naïve patients with HCV infection.

It is 59–76% bound to plasma proteins and the effective half-life at steady state is 9–11 hours. Telaprevir is metabolized by the CYP pathways in the liver and is an inhibitor of CYP3A4 and P-glycoprotein.

Co-administration of telaprevir with numerous drugs is contraindicated. The dosage of telaprevir must be increased when co-administered with efavirenz, due to lowered levels of telaprevir.

The most common adverse effects are rash (30–55%), anemia, fatigue, pruritus, nausea, and anorectal

discomfort. Severe rash or Stevens-Johnson syndrome has been reported; in these patients, the drug should be stopped and not restarted.

Rates of anemia are higher in patients taking telaprevir with peg-interferon and ribavirin than in those taking peg-interferon and ribavirin alone.

Leukopenia, thrombocytopenia, increased serum bilirubin levels, hyperuricemia, and anorectal burning may also occur.

RIBAVIRIN

Ribavirin is a guanosine analog that is phosphorylated intracellularly by host cell enzymes. Although its mechanism of action has not been fully elucidated, it appears to interfere with the synthesis of guanosine triphosphate, to inhibit capping of viral messenger RNA, and to inhibit the viral RNA-dependent polymerase of certain viruses.

Ribavirin triphosphate inhibits the replication of a wide range of DNA and RNA viruses, including influenza A and

B, parainfluenza, respiratory syncytial virus, para-myxoviruses, HCV, and HIV-1.

The oral bioavailability is 45–64%, ↑ with high-fat meals, and ↓ with co-administration of antacids. Plasma protein binding is negligible. Ribavirin elimination is primarily through the urine; therefore, clearance is ↓ in patients with creatinine clearances ≤ 30 mL/min.

Higher doses of ribavirin or a longer duration of therapy or both may be more efficacious in those with a lower likelihood of response to therapy or in those who have relapsed. This must be

balanced with an increased likelihood of toxicity.

Other potential adverse effects are depression, fatigue, irritability, rash, cough, insomnia, nausea, and pruritus. Contraindications to ribavirin therapy include anemia, end-stage renal failure, ischemic vascular disease, and pregnancy. Ribavirin is teratogenic and embryotoxic in animals as well as mutagenic in mammalian cells.

Patients exposed to the drug should not conceive children for at least 6 months thereafter.

ANTI-INFLUENZA AGENTS

Influenza virus strains are classified by their core proteins, species of origin, and geographic site of isolation.

Influenza **A**, the only strain that causes pandemics, is classified into 16 H (hemagglutinin) and 9 N (neuraminidase) known subtypes based on surface proteins.

Influenza **B** viruses usually infect only people; influenza A virus can infect a variety of animal hosts.

Current influenza A subtypes include H1N1, H1N2, and H3N2.

OSELTAMIVIR & ZANAMIVIR

The neuraminidase inhibitors oseltamivir and zanamivir, analogs of sialic acid, interfere with release of progeny influenza virus from infected host cells, thus halting the spread of infection within the respiratory tract.

These agents competitively and reversibly interact with the active enzyme site to inhibit viral neuraminidase activity at low nanomolar concentrations.

Oseltamivir is an orally administered prodrug that is activated by hepatic esterases and widely distributed

throughout the body. Oral bioavailability is approximately 80%, plasma protein binding is low, and concentrations in the middle ear and sinus fluid are similar to those in plasma. The half-life of oseltamivir is 6–10 hours, and excretion is by glomerular filtration and tubular secretion.

Probenecid reduces renal clearance of oseltamivir by 50%. Serum concentrations of oseltamivir carboxylate, the active metabolite of oseltamivir, increase with declining renal function; therefore, dosage should be adjusted in patients with renal insufficiency.

Potential adverse effects include nausea, vomiting, and headache. Taking oseltamivir with food does not interfere with absorption and may decrease nausea and vomiting. Fatigue and diarrhea have also been reported and appear to be more common with prophylactic use.

Neuropsychiatric events (self-injury or delirium) have been reported, particularly in adolescents and adults living in Japan.

Zanamivir is administered directly to the respiratory tract via inhalation. 10 to 20 % of the active compound reaches the lungs, and the remainder is deposited in the oropharynx.

5 to 15 % of the total dose is absorbed and excreted in the urine with minimal metabolism. Potential adverse effects include cough, bronchospasm (severe), reversible decrease in pulmonary function, and transient nasal and throat discomfort. Zanamivir administration is not recommended

for patients with underlying airway disease.

AMANTADINE & RIMANTADINE

Amantadine and its α -methyl derivative, rimantadine, are tricyclic amines of the adamantine family that block the M2 proton ion channel of the virus particle and inhibit uncoating of the viral RNA within infected host cells, thus preventing its replication. They are active against influenza A only.

Rimantadine is about 40% protein-bound and has a half-life of 24–36 h. Nasal secretion and salivary levels approximate those in the serum, and cerebrospinal fluid levels are 52–96% of those in the serum; nasal mucus concentrations of rimantadine average 50% higher than those in plasma.

Amantadine is excreted unchanged in the urine, whereas rimantadine undergoes extensive metabolism by hydroxylation, conjugation, and glucuronidation before urinary excretion.

When begun within 1–2 days after the onset of illness, the duration of fever and systemic symptoms is reduced by 1–2 days. However, due to high rates of resistance in both H1N1 and H3N2 viruses, these agents are no longer recommended for the prevention or treatment of influenza.

The most common adverse effects are gastrointestinal and central nervous system. More serious side effects may be due to alteration of dopamine neurotransmission (see Ch28); are less frequent with rimantadine than with amantadine; are associated with high plasma concentrations; may occur more frequently in patients with renal

insufficiency, seizure disorders, or advanced age; and may increase with concomitant antihistamines, anticholinergic drugs, hydrochlorothiazide, and trimethoprim-sulfamethoxazole.

Clinical manifestations of anticholinergic activity tend to be present in acute amantadine overdose. Both agents are teratogenic and embryotoxic in rodents, and birth defects have been reported after exposure during pregnancy.

OTHER ANTIVIRAL AGENTS INTERFERONS

Interferons have been studied for numerous clinical indications. In addition to HBV and HCV infections, intralesional injection of interferon alfa-2b or alfa-n3 may be used for treatment of condylomataacuminata (see Ch 61).

RIBAVIRIN

In addition to oral administration for HCV infection in combination with interferon alfa, aerosolized ribavirin is administered by nebulizer to children and infants with severe respiratory syncytial virus (RSV) bronchiolitis or pneumonia to reduce the severity and duration of illness. Aerosolized ribavirin has also been used to treat influenza A and B infections but has not gained widespread use. Systemic absorption is low (< 1%).

Aerosolized ribavirin can cause conjunctival or bronchial irritation. Ribavirin is teratogenic and embryotoxic. Health care workers and pregnant women should be protected against extended inhalation exposure. Intravenous ribavirin decreases mortality in patients with Lassa fever

and other viral hemorrhagic fevers if started early.

Clinical benefit has been reported in cases of severe measles pneumonitis and certain encephalitides, and continuous infusion of ribavirin has decreased virus shedding in several patients with severe lower respiratory tract influenza or parainfluenza infections.

PALIVIZUMAB

Is a humanized monoclonal antibody directed against an epitope in the A antigen site on the F surface protein of RSV. It is licensed for the prevention of RSV infection in high-risk infants and children, such as premature infants and those with bronchopulmonary dysplasia or congenital heart disease.

Potential adverse effects include upper respiratory tract infection, fever, rhinitis, rash, diarrhea, vomiting, cough, otitis media, and elevation in serum aminotransferase levels.

IMIQUIMOD

Imiquimod is an immune response modifier shown to be effective in the topical treatment of external genital and perianal warts.

Recurrences appear to be less common than after ablative therapies. Imiquimod may also be effective against molluscumcontagiosum but is not licensed in the United States for this indication.

Local skin reactions are the most common adverse effect; these tend to resolve within weeks after therapy. However, pigmentary skin changes may persist. Systemic adverse effects

such as fatigue and influenza-like syndrome have occasionally been reported.



50. Miscellaneous Antimicrobial Agents; Disinfectants, Antiseptics, & Sterilants

URINARY ANTISEPTICS

Urinary antiseptics are oral agents that exert antibacterial activity in the urine but have little or no systemic antibacterial effect. Their usefulness is limited to lower urinary tract infections

	MOA	Effect	clinical apps	pharmacokinetics toxicity



Nitrofrantron	Not fully understood disrupt the synthesis of proteins, RNA, DNA, and metabolic processes	bactericidal activity against susceptible bacteria	Uncomplicated urinary tract prophylaxis	Oral , rapid renal clearance ($t_{1/2} 0.5$ h) • blood levels are negligible • contraindicated in renal Failure Toxicity: Gastrointestinal upset, pneumonitis Neuropathies and hemolytic anemia occur in patients with glucose-6-phosphate dehydrogenase deficiency
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DISINFECTANTS,ANTISEPTICS, STERILANTS



METRONIDAZOLE	Disruption of electron transport chain	bactericidal	for anaerobic bacteria or mixed intra-abdominal infections and sensitive protozoa (C difficile colitis)	oral or IV , The drug penetrates well into the cerebrospinal fluid and brain hepatic clearance every 8h, disulfiram like reaction when given with alcohol. oxicity: Gastrointestinal upset ,metallic taste, neuropathy, seizures
MUPIROCIN	Mupirocin inhibits protein synthesis By reversibly binding to isoleucyltRNA synthetase	bactericidal	Mupirocin is active against gram-positive cocci, including methicillin-susceptible and methicillin-resistant strains of <i>Staphylococcus aureus</i> .	Ointment for topical application.

POLYMYXINS polymyxin B and polymyxin E (colistin)	It act as cationic detergents. They attach to and disrupt bacterial cell membranes & They also bind and inactivate endotoxin	bactericidal	active against gram negative bacteria	Ointment Anaphylactic reaction with dyspnea and tachycardia
FIDAXOMICIN	Inhibits bacterial RNA polymerase	Bactericidal in gram-positive bacteria	<i>C difficile</i> colitis	Oral , blood level negligible. Toxicity: Nonspecific gastrointestinal upset

(disulfiram reaction is a very uncomfortable **reaction** characterized by severe flushing, and may be accompanied by tachycardia and hypotension)

(detergents a water-soluble cleansing agent which combines with impurities and dirt to make them more soluble)

- Tinidazole: Oral; similar to metronidazole but dosed once daily; approved for trichomonas, giardiasis, and amebiasis

- Methenamine hippurate and methenamine mandelate: Oral; release formaldehyde at acidic pH in the urine; used only for suppression, not treatment, of urinary tract infections

agent	MOA	Effect	Toxicity
Alcohol (ethanol and isopropyl alcohol (isopropanol).	They are rapidly active, killing bacteria, Mycobacterium tuberculosis, and many fungi by Denaturation of protein	gram+and-bacteria	Alcoholbased hand rubs are ineffective against spores of C difficile, and assiduous handwashing with soap and water is still required for Alcohols damages corneal tissue if applied directly.

CHLORHEXIDINE	<p>It strongly adsorbs to bacterial membranes, causing leakage of small molecules and precipitation of cytoplasmic proteins</p>	<p>It is active against vegetative bacteria and mycobacteria and has variable activity against fungi and viruses.</p>	<p>Chlorhexidine has a very low skin-sensitizing or irritating capacity. Oral toxicity is low because it is poorly absorbed from the alimentary tract. Chlorhexidine must not be used during surgery on the middle ear because it causes sensorineural deafness. Similar neural toxicity may be encountered during neurosurgery</p>
Halogens(iodine)	bactericidal	bacteria and spores	serious hypersensitivity reactions that may occur and because of its staining of clothing and



			dressings.
phenol	Phenolic compounds disrupt cell walls and membranes, precipitate proteins, and inactivate enzymes.	used for hard surface decontamination	corrosive effect on tissue its toxicity when absorbed, and its carcinogenic effect.
Quaternary Ammonium Compounds	The bactericidal action of quaternary compounds has been attributed to inactivation of energy-producing enzymes, denaturation of proteins, and disruption of the cell membrane.	used for sanitation of noncritical surfaces (floors, bench tops, etc). Their low toxicity has led to their use as sanitizers in food production facilities	quaternary ammonium compounds such as benzalkonium chloride not be used as antiseptics because several outbreaks of infections have occurred that were due to growth of Pseudomonas



			and other gram-negative bacteria in quaternary ammonium antiseptic solutions.
Aldehydes (Formaldehyde . Glutaraldehyde , Ortho-phthalaldehyde OPA)	<p>hey act by alkylation of chemical groups in proteins and nucleic acids. Failures of disinfection or sterilization can occur as a result of dilution below the known effective concentration, the presence of organic material, and the failure of liquid to penetrate into small channels in the instruments</p>	<p>have a broad spectrum of activity against microorganisms.</p>	<p>cannot withstand exposure to the high temperatures of steam sterilization. They are not corrosive for metal, plastic, or rubber.</p>

Ortho-phthalaldehyde (OPA) is a phenolic dialdehyde chemical sterilant with a spectrum of activity comparable to glutaraldehyde, it is less irritating to mucous membranes, and does not require exposure monitoring.



OPA is useful for disinfection or sterilization of endoscopes, surgical instruments, and other medical devices.

Agent	MOA	Effect	Toxicity
Superoxidized Water	Potent disinfectant and sterilant properties	Bactericidal, fungicidal, tuberculocidal, and sporicidal	The solution is nontoxic and nonirritating and requires no special disposal precautions.
Peroxygen Compounds (hydrogenperoxide and peracetic acid)	Broad spectrum against bacteria, spores, viruses, and fungi when used in appropriate concentration	Disinfectants and sterilants.	Organisms with the enzymes catalase and peroxidase rapidly degrade hydrogen peroxide. Products are not toxic and do not injure the environment
Heavy Metals (mercury and silver)	Are now rarely used as disinfectants	silver salts are strongly bactericidal & used as a preventive for gonococcal ophthalmitis in newborns	- Mercury is an environmental hazard, and pathogenic bacteria have developed plasmid-mediated resistance

			to mercurials -Causative link to autism
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Sterilants :

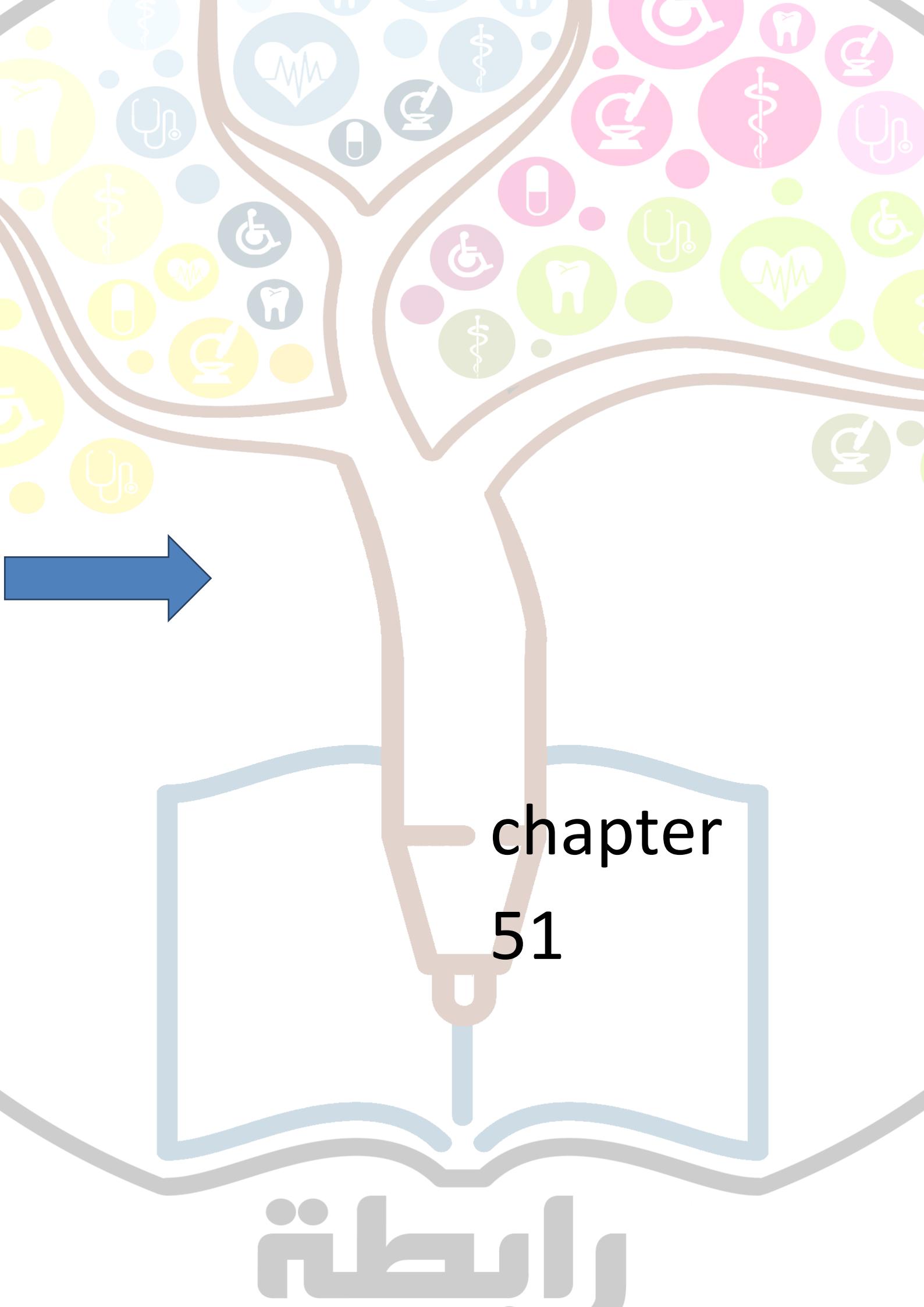
For many years, pressurized steam (autoclaving) at 120°C for 30 minutes has been the basic method for sterilizing instruments and other heat-resistant materials.

- When autoclaving is not possible, as with lensed instruments and materials containing plastic and rubber, ethylene oxide diluted with either fluorocarbon or carbon dioxide to diminish explosive hazard—has been used at 440–1200 mg/L at 45–60°C with 30–60% relative humidity.

Preservatives :

Disinfectants are used as preservatives to prevent the overgrowth of bacteria and fungi in pharmaceutical products, laboratory sera and reagents, cosmetic products, and contact lenses.

- Preservatives should not be irritating or toxic to tissues to which they will be applied, they must be effective in preventing growth of microorganisms likely to contaminate solutions, and they must have sufficient solubility and stability to remain active.
- Commonly used preservative agents include organic acids such as benzoic acid and salts .



chapter 51

رالطب

Clinical Use of

Antimicrobial Agents

EMPIRIC ANTIMICROBIAL THERAPY

رالطب

Antimicrobial agents are frequently used before the pathogen responsible for a particular illness or the susceptibility to a particular antimicrobial agent is known.

This use is called empiric therapy and is based on experience with a particular clinical entity. The usual justification for empiric therapy is the hope that early intervention will improve the outcome;

there are many clinical entities, in which it is difficult to identify a specific pathogen. In such cases, a clinical response to empiric therapy may be an important clue to the likely pathogen.

Frequently, the signs and symptoms of infection diminish as a result of empiric therapy, and microbiologic test results become available that establish a specific microbiologic diagnosis.

At the time that the pathogenic organism responsible is identified, empiric therapy is optimally modified to definitive therapy

Approach to Empiric Therapy

Initiation of empiric therapy should follow a specific and systematic approach.

- .A. Formulate a Clinical Diagnosis of Microbial Infection
- B. Obtain Specimens for Laboratory Examination
- C. Formulate a Microbiologic Diagnosis
- D. Determine the Necessity for Empiric Therapy
- E. Institute Treatment

Choice of Antimicrobial Agent

depends on

A- host factors that include the following:

- 1-concomitant disease states or the use of immunosuppressive medications
- 2- prior adverse drug effects,
- 3-impaired elimination or detoxification of the drug



4-age of the patient

5-pregnancy status

6-epidemiologic exposure

B-Pharmacologic factors include

1-the kinetics of absorption, distribution, and elimination-

2-the ability of the drug to be delivered to the site of infection

3-the potential toxicity of an agent

4-pharmacokinetic or pharmacodynamic interactions with other drugs.

C- knowledge of the susceptibility of an organism to a specific agent in a hospital or community setting is important in the selection of empiric therapy.

Pharmacokinetic differences among agents with similar antimicrobial spectrums may be exploited to reduce the frequency of dosing

Finally, increasing consideration is being given to the cost of antimicrobial therapy, especially when multiple agents with comparable efficacy and toxicity are available for a specific infection. Changing from intravenous to oral antibiotics for prolonged administration can be particularly cost-effective.

ANTIMICROBIAL THERAPY OF INFECTIONS WITH KNOWN ETIOLOGY

INTERPRETATION OF CULTURE RESULTS

Properly obtained specimens for culture frequently

Yield reliable information about the cause of infection

The lack of a confirmatory microbiologic diagnosis may be due to the following:



1. Sample error.

2. Non Cultivable or slow-growing organisms

3. Requesting *bacterial* cultures when infection is due to other organisms

4. Not recognizing the need for special media or isolation techniques

Even in the setting of a classic infectious disease for which isolation techniques have been established for decades ,the sensitivity of the culture technique may be inadequate to identify all cases of the .disease

GUIDING ANTIMICROBIAL THERAPY OF ESTABLISHED INFECTIONS

Susceptibility Testing

Testing bacterial pathogens for their susceptibility to antimicrobial agents is extremely valuable in confirming susceptibility, ideally to a narrow-spectrum nontoxic antimicrobial drug. Tests measure the concentration of drug required to inhibit growth of the organism (minimal inhibitory concentration [MIC]) or to kill the organism (minimal bactericidal concentration [MBC]).

Only MICs are routinely measured in most infections, whereas in infections in which bactericidal therapy .is required MBC measurements occasionally may be useful

Specialized Assay Methods

A. Beta-Lactamase Assay

For some bacteria , the susceptibility patterns of strains are similar except for the production of β lactamase. In these cases, extensive susceptibility testing may not be required, and a direct test for β lactamase may be substituted.

B. Synergy Studies

Synergy studies are in vitro tests that attempt to measure synergistic, additive, indifferent, or antagonistic drug interactions which have not correlated well with clinical outcomes .

MONITORING THERAPEUTIC RESPONSE: DURATION OF THERAPY

The therapeutic response may be monitored microbiologically or clinically. Cultures of specimens taken from infected sites should eventually become sterile or demonstrate eradication of the pathogen and are useful for documenting recurrence or relapse.

Follow-up cultures may also be useful for detecting superinfections or the development of resistance.

The duration of definitive therapy required for cure depends on the pathogen, the site of infection, and host factors

Precise data on duration of therapy exist for some infections ,In other situations, duration of therapy is determined empirically

For recurrence infections (eg, sinusitis,uti) longer courses of antimicrobial therapy or surgical intervention are frequently necessary for eradication.

Clinical Failure of Antimicrobial Therapy

When the patient has an inadequate clinical or microbiologic response to antimicrobial therapy selected by in vitro susceptibility testing, systematic investigation should be undertaken to determine the cause of failure.

ANTIMICROBIAL PHARMACODYNAMIC

The time course of drug concentration is closely related to the antimicrobial effect at the site of infection and to any toxic effects. Pharmacodynamic factors with pharmacokinetics information permits the selection of optimal antimicrobial dosage regimens.

Bacteriostatic versus Bactericidal Activity

Antibacterial agents may be classified as bacteriostatic or bactericidal . inhibitory drug concentrations are much lower in bacteriostatic than bactericidal drug . In general, cell wall-active agents are bactericidal, and drugs that inhibit protein synthesis are bacteriostatic.

the classification has limitations. Some agents that are considered to be bacteriostatic may be bactericidal against selected organisms.



Bactericidal agents should be selected over bacteriostatic ones in circumstances in which local or systemic host defenses are impaired.

Bactericidal agents can be divided into two groups: agents that exhibit concentration-dependent killing and agents that exhibit time-dependent killing.

For drugs whose killing action is concentration-dependent, the rate and extent of killing increase with increasing drug concentrations.

For drugs whose killing action is time-dependent, bactericidal activity continues as long as serum concentrations are greater than the MBC

Postantibiotic Effect

It is the persistent suppression of bacterial growth after limited exposure to an antimicrobial agent.

Proposed mechanisms include (1) slow recovery after reversible nonlethal damage to cell structures; (2) persistence of the drug at a binding site or within the periplasmic space; and (3) the need to synthesize new enzymes before growth can resume.

Usually In vivo PAEs much longer than in vitro PAEs, this is thought to be due to postantibiotic leukocyte enhancement (PALE) and exposure of bacteria to subinhibitory antibiotic concentration.

PHARMACOKINETIC CONSIDERATIONS

Route of Administration

Many antimicrobial agents have similar pharmacokinetic properties when given orally or parenterally

oral therapy with these drugs is equally effective, less costly, and results in fewer complications than parenteral therapy.

The intravenous route is preferred in the following situations: (1) for critically ill patients; (2) for patients with bacterial meningitis or endocarditis; (3) for patients with nausea, vomiting, gastrectomy, ileus, or diseases that may impair oral absorption; and (4) when giving antimicrobials that are poorly absorbed following oral administration.

Conditions That Alter Antimicrobial Pharmacokinetics

Various diseases and physiologic states alter the pharmacokinetics of antimicrobial agents. Impairment of renal or hepatic function may result in decreased elimination.

Failure to reduce antimicrobial agent dosage in such patients may cause toxic effects. Conversely, patients with burns, cystic fibrosis, or trauma may have increased dosage requirements for selected agents. The pharmacokinetics of antimicrobials is also altered in the elderly, in neonates, and in pregnancy.

Drug Concentrations in Body Fluids

Most antimicrobial agents are well distributed to most body tissues and fluids. Penetration into the cerebrospinal fluid is an exception.

Monitoring Serum Concentrations of Antimicrobial Agents

For most antimicrobial agents, the relation between dose and therapeutic outcome is well established, and serum concentration monitoring is unnecessary for these drugs.

To justify routine serum concentration monitoring, it should be established (1) that a direct relationship exists between drug concentrations and efficacy or toxicity; (2) that substantial inter patient variability exists in serum concentrations on standard doses; (3) that a small difference exists between therapeutic and toxic serum concentrations; (4) that the clinical efficacy or toxicity of the drug is delayed or difficult to measure; and (5) that an accurate assay is available.

■ MANAGEMENT OF ANTIMICROBIAL DRUG TOXICITY

Owing to the large number of antimicrobials available, it is usually possible to select an effective alternative in patients who develop serious drug toxicity. However, for some infections there are no effective alternatives to the drug of choice.

For mild reactions, it may be possible to continue therapy with use of adjunctive agents or dosage reduction.

Adverse reactions to antimicrobials occur with increased frequency in several groups, including neonates, geriatric patients, renal failure patients, and AIDS patients. Dosage adjustment of the drugs is essential for the prevention of adverse effects in patients with renal failure. In addition, several agents are contraindicated in patients with renal impairment because of increased rates of serious toxicity.

■ ANTIMICROBIAL DRUG COMBINATIONS

RATIONALE FOR COMBINATION ANTIMICROBIAL THERAPY

Most infections should be treated with a single antimicrobial agent. Although indications for combination therapy exist.

The unnecessary use of antimicrobial combinations increases toxicity and costs and may occasionally result in reduced efficacy due to antagonism of one drug by another. Antimicrobial combinations should be selected for one or more of the following reasons:

1. To provide broad-spectrum empiric therapy in seriously ill patients.
2. To treat polymicrobial infections
3. To decrease the emergence of resistant strains.
4. To decrease dose-related toxicity
5. To obtain enhanced inhibition or killing.

SYNERGISM & ANTAGONISM

Synergism is when the inhibitory or killing effects of two or more antimicrobials used together are significantly greater than expected from their effects when used individually.

Antagonism occurs when the combined inhibitory or killing effects of two or more antimicrobial drugs are significantly less than observed when the drugs are used individually.



Mechanisms of Synergistic Action

1. Blockade of sequential steps in a metabolic sequence
2. Inhibition of enzymatic inactivation
3. Enhancement of antimicrobial agent uptake

Mechanisms of Antagonistic Action

1. Inhibition of cidal activity by static agents
2. Induction of enzymatic inactivation

■ ANTIMICROBIAL PROPHYLAXIS

Antimicrobial agents are effective in preventing infections in many settings. Antimicrobial prophylaxis may be divided into surgical prophylaxis and nonsurgical prophylaxis.

Surgical Prophylaxis

surgical procedures that necessitate the use of antimicrobial prophylaxis include contaminated and clean-contaminated operations, selected operations in which postoperative infection may be catastrophic ,clean procedures that involve placement of prosthetic materials, and any procedure in an immunocompromised host.

General principles of antimicrobial surgical prophylaxis include the following:

1. The antibiotic should be active against common surgical wound pathogens.
2. The antibiotic should have proved efficacy in clinical trials.
3. The antibiotic must achieve concentrations greater than the MIC of suspected pathogens, and these concentrations must be present at the time of incision.

-
4. The shortest possible course—ideally a single dose—of the most effective and least toxic antibiotic should be used.
 5. The newer broad-spectrum antibiotics should be reserved for therapy of resistant infections.
 6. If all other factors are equal, the least expensive agent should be used.

The antibiotic should be present in adequate concentrations at the operative site before incision and throughout the procedure; initial dosing is dependent on the volume of distribution, peak levels, clearance, protein binding, and bioavailability.

For many antimicrobial agents, doses should be repeated if the procedure exceeds 2–6 hours in duration. Single-dose prophylaxis is effective for most procedures and results in decreased toxicity and antimicrobial resistance.

Improper administration of antimicrobial prophylaxis leads to excessive surgical wound infection rates.

Common errors in antibiotic prophylaxis include selection of the wrong antibiotic, administering the first dose too early or too late, failure to repeat doses during prolonged procedures, excessive duration of prophylaxis, and inappropriate use of broad-spectrum antibiotics.

Nonsurgical Prophylaxis

Nonsurgical prophylaxis includes the administration of antimicrobials to prevent colonization or asymptomatic infection as well as the administration of drugs following colonization by or inoculation of pathogens but before the development of disease. Nonsurgical prophylaxis is indicated in individuals who are at high risk for temporary exposure to selected virulent pathogens and in patients who are at increased risk for developing infection because of underlying disease

Prophylaxis is most effective when directed against organisms that are predictably susceptible to antimicrobial agents.

52. Antiprotozoal Drugs

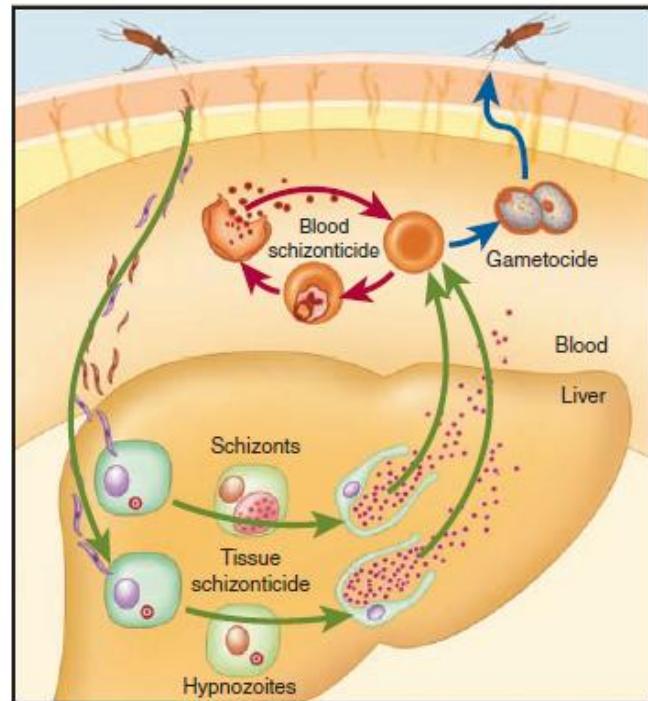
MALARIA;



Malaria is the most important parasitic disease of humans and causes hundreds of millions of illnesses per year. Five species of plasmodium typically cause human malaria: *Plasmodium falciparum*, *P vivax*, *P malariae*, *P ovale* and *P knowlesi*.

PARASITE LIFE CYCLE

1-An anopheline mosquito inoculates plasmodium sporozoites to initiate human infection .



2- Circulating sporozoites rapidly invade liver cells, and exoerythrocytic stage tissue schizonts mature in the liver (Only erythrocytic parasites cause clinical illness)

3-Merozoites are subsequently released from the liver and invade erythrocytes.

4- Sexual stage gametocytes develop in erythrocytes before being taken up by mosquitoes, where they develop into infective sporozoites.

Antimalarial drugs:

- In *P falciparum* and *P malariae* infection, treatment that eliminates erythrocytic parasites will cure these infections.
- In *P vivax* and *P ovale* infections, a dormant hepatic stage, the hypnozoite, is not eradicated by most drugs, and relapses can occur after therapy
 - directed against erythrocytic parasites. Eradication of both erythrocytic and hepatic parasites is required to cure these infections.

DRUG CLASSIFICATION

Tissue schizonticides : Drugs that eliminate developing or dormant liver forms .

Blood schizonticides : Drugs that act on erythrocytic parasites

Gametocides : Drugs that kill sexual stages and prevent transmission to mosquitoes .

	mechanism	Antimalarial Action	Pharmacokinetics	Resistance	Clinical Uses	Adverse Effects	Contraindications & Cautions
(1) CHLOROQUINE	acts by concentrating in parasite food vacuoles, preventing the biocrystallization of the hemoglobin breakdown product, heme, into hemozoin, and thus eliciting parasite toxicity due to the buildup of free heme.	-is a highly effective blood schizonticide. -Moderate effective against gametocytes of P vivax, P ovale, and P malariae but not against those of P falciparum. - not active against liver stage parasites.	-Renal clearance with initial half-life of 3–5 days and terminal elimination half-life of 1–2 months.	Resistance to among strains of P falciparum and P vivax. resistance can be reversed by certain agents, including verapamil, desipramine, and chlorpheniramine. the clinical value of resistance-reversing drugs is not established.	1-uncomplicated nonfalciparum and sensitive falciparum malaria. 2- Chemoprophylaxis in malarious regions without resistant falciparum malaria. 3- Amebic liver abscess	Pruritus, Nausea, vomiting, abdominal pain, headache, anorexia, malaise, blurring of vision, impaired hearing, confusion, psychosis, seizures, agranulocytosis, exfoliative dermatitis, alopecia, bleaching of hair, hypotension, and electrocardiographic changes.	is contraindicated in patients with psoriasis or porphyria. The antidiarrheal agent kaolin and calcium- and magnesium-containing antacids interfere with the absorption of chloroquine and should not be co-administered.

	mechanism	Antimalarial Action	Pharmacokinetics	Resistance	Clinical Uses	Adverse Effects
(2) ARTEMISININ & ITS DERIVATIVES	production of free radicals that follows the iron-catalyzed cleavage of the artemisinin endoperoxide bridge.	-are very rapidly acting blood schizonticides against all human malaria parasites. -Haveno effect on hepatic stages.	-Half-lives are 30–60 minutes for artesunate and dihydroartemisinini -Half-lives are 2–3 hours for artemether. Artemisinin, artesunate, and artemether.	delayed clearance of P falciparum infections and decreased treatment efficacy.	falciparum malaria	nausea, vomiting, diarrhea, dizziness neutropenia, anemia, hemolysis, elevated liver enzymes, and allergic reactions.

	mechanism	Antimalarial Action	Pharmacokinetics	Resistance	Clinical Uses	Adverse Effects	Cautions
(3) QUININE & QUINIDINE	unknown	is gametocidal against <i>P vivax</i> and <i>P ovale</i> but not <i>P falciparum</i> . It is not active against liver stage parasites.	The half-life of quinine is 11 hours. Quinidine has a shorter half-life than quinine. metabolized in the liver and excreted in the urine.	common but still provides a partial therapeutic effect in most patients.	falciparum malaria Malarial chemoprophylaxis Babesiosis	tinnitus, headache, nausea, dizziness, flushing, visual disturbances, cinchonism, Hypersensitivity reactions, Hematologic Abnormalities, Hypoglycemia, uterine contractions, Severe hypotension, Blackwater fever,	Absorption may be blocked by aluminum containing antacids. Quinine can raise plasma levels of warfarin and digoxin. Dosage must be reduced in renal insufficiency.

cinchonism

(toxicity due to overdosage of cinchona alkaloids; symptoms are tinnitus and slight deafness, photophobia and other visual disturbances, mental dullness, depression, confusion, headache, and nausea. Called also quininism.)

psoriasis

(is a chronic, non-contagious disease characterized by inflamed lesions covered with silvery-white scabs of dead skin.)

Porphyria

(a genetic disorder characterized by a disturbance in porphyrin metabolism with resultant increase in the formation and excretion of porphyrins) or their precursors; called also hematoporphyria)

Nausea, vomiting, dizziness, sleep and behavioral disturbances, diarrhea, abdominal pain, headache,

2. Treating uncomplicated falciparum malaria.

Adverse Effects

Antimalarial Action

- strong blood schizonticidal activity against *P falciparum* and *P vivax*.
- it is not active against hepatic stages or gametocytes.

Pharmacokinetics

Oral

The terminal elimination half-life is about 20 day.

Weekly dosing for chemoprophylaxis.

Resistance

associated with resistance to quinine and halofantrine, but not with resistance to chloroquine.

Clinical Uses

1 .Chemoprophylaxis

4-Gametocidal action

and dizziness.

Neuropsychiatric toxicities

Leukocytosis, thrombocytopenia (low platelet count) arrhythmias and bradycardia.

Contraindications & Cautions

contraindicated in a patient with a history of epilepsy, psychiatric disorders, arrhythmia, cardiac conduction defects, or sensitivity to related drugs.

safe for children weighing less than 5 kg and pregnancy.

5-PRIMAQUINE

Mechanism:unknown

4-Mefloquine

mechanism

Unknown

antimalarial action

- active against hepatic stages of all human malaria parasites and the dormant hypnozoite stages of *P vivax* and *P ovale*.
- gametocidal against the four human malaria species .
- weak activity against erythrocytic stage parasites.

Resistance

- Some strains of *P vivax* are relatively resistant.
- Liver forms of these strains may not be eradicated by a single standard treatment and may require repeated therapy.

Clinical Uses

- .Therapy (radical cure) of acute vivax and ovale Malaria.
- 2 Terminal prophylaxis of vivax and ovale malaria.
- .3 Chemoprophylaxis of malaria.

5-Pneumocystis jiroveci infection.

Adverse Effects

nausea, epigastric pain, headache, leukopenia, agranulocytosis (bone marrow does not make enough of a neutrophils (leukocytosis, cardiac arrhythmias and methemoglobinemia (increased quantities of hemoglobin in which the iron of heme is oxidized to the ferric (Fe^{3+}) form)

Contraindications & Cautions

- It is never given parenterally because it may cause marked hypotension.
- Patients should be tested for G6PD deficiency before primaquine is prescribed.
- should be discontinued if there is evidence of hemolysis or anemia.
- avoided in pregnancy

6-ATOVAQUONE

mechanism

inhibition of nucleic acid and ATP synthesis

antimalarial action

It is active against tissue and erythrocytic schizonts

Pharmacokinetics

Oral

absorption is increased by fatty food.

half-life of 2–3 days.

Resistance

Initial use of atovaquone to treat malaria led to disappointing results, with frequent failures due to the selection of resistant parasites during therapy.

Clinical Uses

treatment of mild to moderate *P jiroveci* pneumonia.

treatment and chemoprophylaxis of falciparummalaria.

immunocompromised patients with toxoplasmosis unresponsive to other agents.

Adverse Effects

fever, rash, nausea, vomiting, diarrhea, headache, and insomnia ((الارق))

Contraindications & Cautions

-It is considered safe for use in children with body weight above 5 kg.

-not advised in pregnant women

7-INHIBITORS OF FOLATE SYNTHESIS

mechanism

4. Toxoplasmosis

Pyrimethamine and Proguanil:

selective inhibition of plasmodial dihydrofolate reductase a key enzyme in the pathway for synthesis of folate.

Sulfonamides:

Inhibit dihydropteroate synthase and folate production that is essential for production DNA.

antimalarial action

Pyrimethamine and Proguanil:

Not effective against the persistent liver stages of *P. vivax* or *P. ovale*.

Sulfonamides:

weakly active against erythrocytic schizonts but not against liver stages or gametocytes.

Pharmacokinetics

Pyrimethamine :

Proguanil:

- prodrug; only its triazine metabolite, cycloguanil, is active.

- elimination half-life of about 16 hours

Sulfonamides:

Fansidar: fixed combination of the sulfonamide sulfadoxine and pyrimethamine.

The average half-life of sulfadoxine is about 170 hours.

Resistance

P. falciparum and less common for *P. vivax*.

Clinical Uses

1. Chemoprophylaxis
2. Intermittent preventive therapy
3. Treatment of chloroquine-resistant *falciparum*

Malaria.

5. Pneumocystosis(fungal infection of the respiratory system).

Adverse Effects

Gastrointestinal symptoms, skin rashes, itching, Mouth ulcers and alopecia(الثعلبة). Stevens-Johnson syndrome, andrenal toxicity.

Contraindications & Cautions

should be used cautiously in the presence of renal orhepatic dysfunction.

Fansidar and Proguanil are safely used in pregnancy

8-HALOFANTRINE

Mechanism

unknown.

antimalarial action

effectiveagainst erythrocyticstages of all four humanmalaria species.

elimination half-life of about 3.5 days.

Oralabsorption is variable and enhanced by food. And should not be taken with meals.

half-life is about4 days.

Clinical Uses

P falciparum, but its use is limited by cardiac toxicity.

Adverse Effects

abdominal pain, diarrhea,vomiting, cough, rash, headache, pruritus (حكة)elevated liverenzymes. andprolongation of QT and PR intervals

Contraindications & Cautions

should notbe used for chemoprophylaxis.

contraindicated in patients who have cardiac conduction defectsor who have recently taken mefloquine .

contraindicated in pregnancy.

Pharmacokinetics

9-LUMEFANTRINE mechanism

unknown

antimalarial action

highly effective in the treatment of falciparum malaria when administered twice daily for 3 days.

Pharmacokinetics

- available only as a fixed-dose combination with artemether.

- The half-life of lumefantrine, when used in combination, is 3–4 days.

- oral absorption is variable and improved when the drug is taken with food.

- should be administered with fatty food to maximize antimalarial efficacy.

Pharmacokinetics

Adverse Effects

gastrointestinal disturbances, headache, dizziness, rash, and pruritus (حكة)

-AMEBIASIS

Amebiasis is infection with *Entamoeba histolytica*. This organism can cause asymptomatic intestinal infection.

1-METRONIDAZOLE & TINIDAZOLE

Mechanism

Produce free radicals can interact with DNA leading to inhibition of DNA synthesis and DNA degradation.

Antiamoebic action

It kills trophozoites but not cysts of *E histolytica* and effectively eradicates intestinal and extra-intestinal tissue infections.

intestinal wall
orextraintestinal tissues.

Adverse Effects

diarrhea—which usually

the half-life is 7.5 hours for metronidazole and 12–14 hours for tinidazole.

Clinical Uses

1 .Amebiasis(infection with Entamoeba histolytica. It is commonly asymptomatic, but symptoms ranging from mild diarrhea to severe dysentery)

2 .Giardiasis(diarrheal disease caused by the microscopic parasite Giardia)

3. Trichomoniasis(is infection of the vagina or male genital tract with Trichomonas vaginalis)

Adverse Effects

Nausea, headache, dry mouth, metallic taste in the mouth,vomiting·diarrhea,

Clinical Uses

first-line therapy for uncomplicated falciparum malaria

Cautions

The dosage should be adjusted for patients with severe liver or renal disease.

avoided in pregnant.

2-IODOQUINOL

Mechanism

unknown.

Antiamoebic action

effective luminal amebicide.

Pharmacokinetics

half-life of 11–14 hour.

should be taken with meals to limit gastrointestinal toxicity.

Clinical Uses

effective against organisms in the bowel lumen but not against trophozoites in the

Intravenous

half-life is 2–3 hours.

clinical use

treat visceral leishmaniasis

Adverse Effects

stops after several days—
anorexia (فقد الشهية), nausea,
vomiting, abdominal pain,
headache, rash, and
pruritus (حكة.)

Cautions

used with caution in patients
with optic neuropathy, renal
or thyroid disease, or
nonamebic hepatic disease.

It is contraindicated in
patients with intolerance to
iodine.

3-DILOXANIDE FUROATE

Mechanism

unknown.

Antiamoebic action

insomnia (الارق), weakness,
dizziness, thrush, rash,
dysuria (dark urine, vertigo),
neutropenia (abnormally low
concentration of neutrophils
in the blood) and disulfiram-
like effect

treat serious intestinal and
extraintestinal infections.

Adverse Effects

Flatulence (تجشؤ), nausea,
abdominal cramps and
rashes.

Cautions

not recommended in
pregnancy.

4-PAROMOMYCIN SULFATE

Mechanism

irreversible inhibitors of
protein synthesis **Antiamoebic action**

luminal amebicide and has
no effect against
extraintestinal organisms.

Pharmacokinetics

has activity against trypanosomatid protozoans and against *P. jiroveci*, but toxicity is significant.

Pharmacokinetics

parenteral.

inhaled as

Abdominal distress and diarrhea.

5- EMETINE & DEHYDROEMETINE

Mechanism

blocking protein synthesis

Antiamebic action

effective against tissue trophozoites of *E. histolytica*

Pharmacokinetics

subcutaneously (preferred) or intramuscularly in a supervised setting.

clinical use

unusual circumstances in which severe amebiasis

It is an effective luminal amebicide but is not active against tissue trophozoites.

Pharmacokinetics

oral

clinical use

changes. Serious toxicities include cardiac arrhythmias, heart failure, and hypotension

Cautions

should be used for the minimum period needed to relieve

severe symptoms (usually 3–5 days)

OTHER ANTIPROTOZOAL DRUGS

1-PENTAMIDINE

Mechanism

unknown.

Action

Adverse Effects

Gastrointestinal symptoms, fever, headache, myalgia(muscle pain), arthralgias(joint pain) , rash and T-wave changes and QT prolongation.

a nebulized powder for the prevention of pneumocystosis.

trace amounts of pentamidine appear in the central nervous system, so it is not effective against CNS African trypanosomiasis
Initial half-life of about 6 hours.

clinical use

1. Pneumocystosis
2. African trypanosomiasis (sleeping sickness) Pentamidine should not be used to treat late trypanosomiasis with central nervous system involvement.
3. Leishmaniasis(is caused by species of Leishmania)

Adverse Effects

requires effective therapy and metronidazole cannot be used.

Adverse Effects

pain, tenderness, and sterile abscesses at the injection site, diarrhea, nausea, and vomiting; muscle weakness and discomfort; and minor electrocardiographic

be recumbent and monitored closely during treatment

2- SODIUM STIBOGLUCONATE

Mechanism

unknown.

Pharmacokinetics

Intravenous (preferred) or Intramuscular short initial (about 2-hour) half-life and a much longer terminal (<24-hour) half-life.

clinical use

first-line agents for cutaneous and visceral leishmaniasis.

Cautions

electrocardiogram should be monitored during therapy.

Intramuscular injections can be very painful and lead to sterile abscesses.

hypotension, tachycardia, dizziness, and dyspnea, Pancreatic toxicity, Hypoglycemia, metallic taste, hallucinations, and cardiac arrhythmias

Cautions

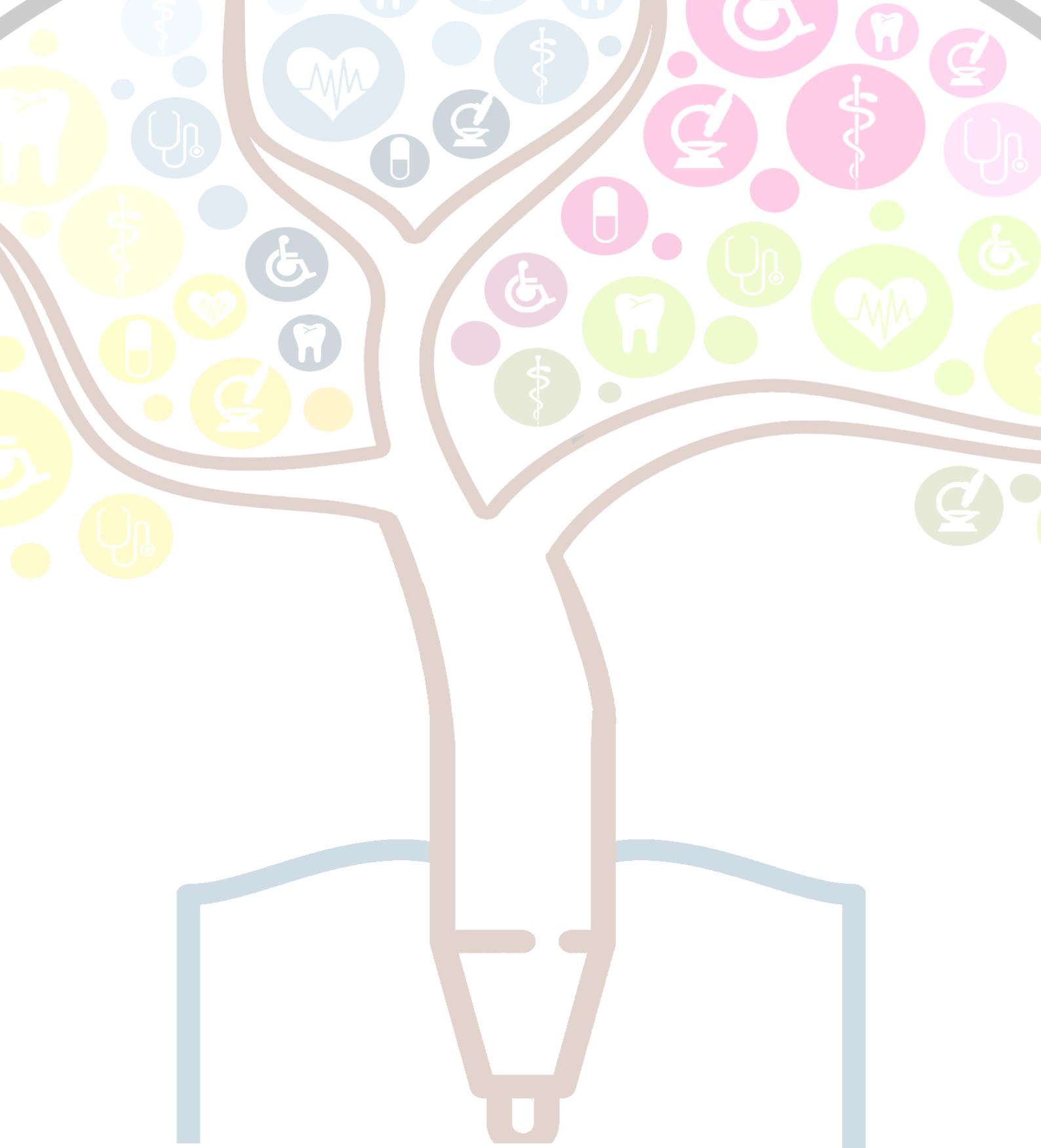
the drug should be administered slowly (over 2 hours), and patients should

3- NITAZOXANIDE

-Prodrug and converted to tizoxanide and tioxanide conjugates.

-have activity against metronidazole-resistant protozoal strains, against Giardia lamblia and Cryptosporidium parvum.

4- OTHER DRUGS FOR TRYPANOSOMIASIS & LEISHMANIASIS



slow intravenous infusion	first-line therapy for advanced central nervous system East African trypanosomiasis (sleeping sickness), and second-line therapy (after eflornithine) for advanced West African trypanosomiasis	fever, vomiting, abdominal pain, and arthralgias(joint pain). The most important toxicity is a reactive encephalopathy. (a disease that affects the function or structure of your brain) Other serious side effects include: peripheral neuropathy, optic neuritis, and peripheral edema.	Pharmacokinetics	Clinical use
It is administered in propylene glycol by slow intravenous infusion			Intravenous with very tight protein binding short initial half-life but a terminal	chemoprophylaxis against African trypanosomiasis because it does not enter the CNS



<p>Paromomycin aminoglycoside antibiotic</p>	<p>Oral topical</p>	<p>cutaneous leishmaniasis. visceral leishmaniasis</p>	<p>mild injection pain, uncommon ototoxicity and reversible liver enzyme elevations</p>
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Chapter 53

Clinical pharmacology of the antihelminthic Drugs

CHEMOTHERAPY OF HELMINTHIC INFECTIONS

Helminths (worms) are multicellular organisms that infect very large numbers of humans and cause a broad range of diseases.

Many drugs, directed against a number of different targets, are available to treat helminthic infections.

The goal is control of infection, with elimination of most parasites, alleviating disease symptoms, and decreasing the transmission of infection. In other cases, complete elimination of parasites is the goal of therapy, although this goal can be challenging with certain helminthic infections, because of both limited efficacy of drugs and frequent reinfection after therapy in endemic areas.

Parasites should be identified before treatment is started.

Adverse Reactions, Contraindication & Cautions	clinical uses	basic pharmacology		subclass, drug
When used for 1–3 days, it is nearly free of significant adverse effects. Mild and transient epigastric distress, diarrhea, headache, nausea, dizziness, lassitude, and insomnia	Administered on an empty stomach when used against intraluminal parasites but with a fatty meal when used against tissue parasites. -Ascariasis (single dose)	After oral administration, it is erratically absorbed and rapidly undergoes first-pass metabolism in the liver to the active metabolite albendazole sulfoxide.	a broad-spectrum orally the drug of choice and is approved in the USA for treatment of hydatid disease and cysticercosis . It is also used in the treatment of	ALBENDAZOLE

<p>can occur.</p> <p>In long-term use for hydatid disease, albendazole is well tolerated, but it can cause abdominal distress, headaches, fever, fatigue, alopecia, increases in liver enzymes, and pancytopenia.</p>	<p>of 400 mg orally repeated for 2–3 days for heavy infections and in 2 weeks for pinworm infections)</p> <p>trichuriasis, and hookworm (400mg orally once daily for 3 days).</p> <p>albendazole showing improved efficacy over mebendazole. In addition, combination of either mebendazole or albendazole with ivermectin to treat trichuriasis markedly improved treatment</p>	<p>Half-life is 8–12 hours.</p> <p>Mostly protein-bound, distributes well to tissues, and enters bile, cerebrospinal fluid, and hydatid cysts.</p> <p>Excreted in the urine.</p>	<p>pinworm and hookworm infections, ascariasis, trichuriasis, and strongyloidiasis.</p>	
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<p>hypersensitivity to other benzimidazole drugs or to those with cirrhosis. The safety in pregnancy and in children younger than 2 years has not been established.</p>	<p>outcomes.</p> <ul style="list-style-type: none"> -Hydatid disease (400 mg twice daily with meals for 1 month or longer). -Neurocysticercosis (Corticosteroids are usually given with the antihelminthic drug to decrease inflammation caused by dying organisms. Given in a dosage of 400 mg twice daily for up to 21 days). cutaneous larva migrans (400 mg daily for 3 days). 			
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		Visceral larva migrans (400 mg twice daily for 5 days). Intestinal capillariasis (400 mg daily for 10 days).		
		microsporidial infections (400 mg Twice daily for 2 weeks or longer).		
		gnathostomiasis (400 mg twice daily for 3 weeks).		



taeniasis
(400 mg
daily for 3
days)

trichinosis
(400 mg
twice daily
for 1–2
weeks)

clonorchiiasis
(400 mg
twice daily
for 1 week).

Albendazole
has been
recommended as empiric
therapy to
treat those
who return
from the
tropics with
persistent
unexplained
eosinophilia.

similar
efficacy
to that of

	metronidazole, with less toxicity, against giardiasis.			
<p>Adverse effects, are generally mild and transient, but occasionally their severity requires interruption of therapy</p> <p>Include diarrhea, abdominal cramps, anorexia, nausea, vomiting, dizziness, and headache.</p> <p>Skin rashes may occur after a week or more of therapy</p> <p>Bithionol should be</p>	<p>paragonimiasis and fascioliasis, 30–50 mg/kg in two or three)</p> <p>Divided doses, given orally after meals on alternate days for 10–15 (doses.</p> <p>pulmonary paragonimiasis,</p> <p>Cerebral paragonimiasis(repeat courses may be necessary).</p>	<p>After ingestion, bithionol reaches peak blood levels in 4–8 hours.</p> <p>Excretion appears to be mainly via the kidney.</p> <p>Excretion appears to be mainly via the kidney.</p>	<p>Bithionol is an alternative to triclabendazole for the treatment of fascioliasis (sheep liver fluke) and an alternative to praziquantel for the treatment of paragonimiasis.</p>	<p>BITHIONOL</p>

used with caution in children younger than 8 years because there has been limited experience in this age group.

Drug of

<p>Generally mild and transient, include headache, malaise, anorexia, weakness, nausea, vomiting, and dizziness.</p> <p>Reactions are particularly severe with onchocerciasis.</p> <p>Caution is advised when using diethylcarbamazine in patients with hypertension or renal disease.</p>	<p>Lymphatic filariasis (2 mg/kg three times a day for 12 days)</p> <p>Loiasis is treated with the same regimen for 2–3 weeks</p> <p>Antihistamines may be given for the first few days of therapy to limit allergic reactions, and corticosteroids should be started and doses of diethylcarbamazine lowered or interrupted if severe reactions occur.</p> <p>For patients with high <i>L. loa</i>worm burdens,</p>	<p>Rapidly absorbed from the gastrointestinal tract</p> <p>The half-life is 2–3 hours in acidic urine but about 10 hours if the urine is alkaline.</p> <p>Excreted, principally in the urine, as unchanged drug and the N-oxide metabolite.</p> <p>Dosage should be reduced in patients with renal impairment.</p> <p>It immobilizes microfilariae and alters their surface structure,</p>	<p>choice in the treatment of filariasis, loiasis, and tropical eosinophilia. It has been replaced by ivermectin for the treatment of onchocerciasis.</p>	<p>DIETHYLCARBAMAZINE CITRATE</p> <p>Snowwhite</p>
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	<p>strategies to decrease risks of severe toxicity include (a) apheresis, if available, to remove microfilariae before treatment with diethylcarbamazine, or (b) therapy with albendazole, which is slower acting and better tolerated, followed by therapy with diethylcarbamazine or ivermectin</p> <p>Chemoprophylaxis against filarial infections (300 mg weekly or 300 mg on 3 successive</p>	<p>displacing them from tissues and making them more susceptible to destruction by host defense mechanisms.</p> <p>The drug should be taken after meals.</p>		



	<p>days each month for loiasis; 50 mg monthly for bancroftian and Malayan filariasis).</p> <p>For tropical eosinophilia, (orally at a dosage of 2 mg/kg three times (daily for 2–3 weeks.</p>			
	<p>significant macrofilaricidal activity against <i>W bancrofti</i>, And onchocerciasis.</p> <p>Drug for filariasis, both for treatment of active disease and in mass chemotherapy campaigns.</p>	<p>acts indirectly, by killing <i>Wolbachia</i>,</p>	<p>‘suggesting better activity than any other available drug against adult worms</p>	<p>DOXYCYC LINE</p>

<p>In strongyloidiasis treatment, infrequent adverse effects include fatigue, dizziness, nausea, vomiting, abdominal pain, and rashes.</p> <p>In onchocerciasis treatment, adverse effects are principally from the killing of microfilariae and can include fever, headache, dizziness, somnolence, weakness, rash, increased pruritus,</p>	<p>Onchocerciasis:</p> <p>Single oral dose of ivermectin, 150 mcg/kg, with water on an empty stomach. Doses are repeated; regimens vary from monthly to less frequent (every 6–12 months) dosing schedules. After acute therapy, treatment is repeated at 12-month intervals until the adult worms die</p> <p>:Strongyloidiasis</p> <p>200mcg/kg once daily for 2 days. In immunosup</p>	<p>available only for oral administration, rapidly absorbed with wide tissue distribution</p> <p>half-life is about 16 hours</p> <p>Excretion of the drug and its metabolites is almost exclusively in the feces.</p> <p>Ivermectin appears to paralyze nematodes and arthropods by intensifying γ-aminobutyric acid (GABA)-</p>	<p>Drug of choice in strongyloidiasis and onchocerciasis.</p>	<p>IVERMECTIN</p>

<p>diarrhea, joint and muscle pains, hypotension, tachycardia, lymphadenitis, lymphangitis, and peripheral edema.</p>	<p>ressed patients with disseminated infection, repeated treatment is often needed</p>	<p>mediated transmission of signals in peripheral nerves.</p>		
<p>It is best to avoid concomitant use of ivermectin with other drugs that enhance GABA activity</p>	<p>It has been used with diethylcarbamazine and albendazole for the control of <i>W. bancrofti</i>,</p>	<p>With repeated doses of ivermectin, the drug appears to have a low-level macrofilaricidal action and to permanently reduce microfilarial production.</p>		
<p>Ivermectin should not be used during pregnancy. Safety in children younger than 5 years has not been established.</p>	<p>Effective in controlling scabies, lice, and cutaneous larva migrans and in eliminating a large proportion of ascarid</p>			

worms.			
<p>Short-term mebendazole therapy for intestinal nematodes is nearly free of adverse effects. Mild nausea, vomiting, diarrhea, and abdominal pain have been reported infrequently. Rare side effects, usually with high-dose therapy, are hypersensitivity reactions (rash, urticaria), agranulocytosis, alopecia, and elevation of liver enzymes.</p> <p>Mebendazol</p>	<p>Pinworm infection, 100 mg once, repeated at 2 weeks.</p> <p>ascariasis, trichuriasis, hookworm, and trichostrongylus infections, a dosage of 100 mg twice daily for 3 days is used for adults and for children older than 2 years.</p> <p>Intestinal capillariasis, mebendazole is used at a dosage of 200 mg twice daily for 21 or more days.</p>	<p>Less than 10% of orally administered mebendazole is absorbed. The absorbed drug is protein-bound is rapidly converted to inactive metabolites</p> <p>A half-life of 2–6 hours. It is excreted mostly in the urine and the bile.</p> <p>Absorption is increased if the drug is ingested with a fatty meal.</p> <p>The drug acts by inhibiting</p>	<p>Has a wide spectrum of antihelminthic activity and a low incidence of adverse effects.</p> <p>MEBENDAZOLE</p>

<p>It is teratogenic in animals and therefore contraindicated in pregnancy. It should be used with caution in children younger than 2 years. Plasma levels may be decreased by concomitant use of carbamazepine or phenytoin and increased by cimetidine. Mebendazole should be used with caution in patients with cirrhosis.</p>	<p>Corticosteroids should be co-administered for severe infections.</p> <p>It can be taken before or after meals; the tablets should be chewed before swallowing.</p>	<p>microtubule synthesis.</p>		
<p>Mild and transient</p>	<p><i>S. haematobium</i>, an oral</p>	<p>Rapidly absorbed after oral</p>	<p>Metrifonate is a safe, low-cost alternative</p>	<p>METRIFONATE</p>

<p>cholinergic symptoms, including nausea and vomiting, diarrhea, abdominal pain, bronchospasm, headache, sweating, fatigue, weakness, dizziness, and vertigo.</p> <p>Metrifonate should not be used after recent exposure to insecticides or drugs that might potentiate cholinesterase inhibition. Metrifonate is contraindicated in pregnancy.</p>	<p>dose of 7.5–10 mg/kg is given three times at 14-day intervals.</p> <p>Effective as a prophylactic agent when given monthly to children in a highly endemic area.</p>	<p>administration. The half-life is about 1.5 hours.</p> <p>Clearance appears to be Through nonenzymatic transformation to dichlorvos, its active metabolite.</p> <p>The mode of action is thought to be cholinesterase inhibition.</p>	<p>drug for the treatment of <i>Schistosoma haematobium</i> infections</p> <p>It is not active against <i>Schistosoma mansoni</i> or <i>Schistosoma japonicum</i>.</p>	
<p>infrequent, mild, and</p>	<p>The adult</p>	<p>It appears to</p>	<p>second-line drug for the</p>	<p>NICLOSAM</p>

<p>transitory adverse events include nausea, vomiting, diarrhea, and abdominal discomfort.</p>	<p>dose of niclosamide is 2 g once, given in the morning on an empty stomach. The tablets must be chewed thoroughly and then swallowed with water</p>	<p>be minimally absorbed from the gastrointestinal tract—neither the drug nor its metabolites have been recovered from the blood or urine. Adult worms are rapidly killed, presumably due to inhibition of oxidative phosphorylation or stimulation of ATPase activity.</p>	<p>treatment of most tape-worm infections</p>	<p>IDE</p>
<p>The consumption of alcohol should be avoided on the day of Treatment and for 1 day afterward.</p>	<p>D latum and T saginata (A single 2 g dose)</p>			
<p>The safety of the drug has not been established in pregnancy or for children younger than 2 years.</p>	<p>It is probably equally effective against T solium.</p>			
<p>The drug is given in the morning on an empty stomach.</p>	<p>For Hymenolepsis diminuta and Dipylidium caninum infections are cured with a 7-day course of treatment.</p>			

The tablets must be chewed thoroughly and then swallowed with water.

A few require a second course. As an alternative drug in the treatment of *Fasciolopsis buski*, *Heterophyes heterophyes*, and *Metagonimus yokogawai* infections. The standard dose is given every other day for three doses.

				OXAMNIQUE
<p>Mild symptoms, starting about 3 hours after a dose and lasting for several hours</p> <p>Central nervous system symptoms (dizziness, headache, drowsiness) are most common; nausea and vomiting, diarrhea, colic, pruritus, and urticaria also occur.</p> <p>Since the drug makes many patients dizzy or drowsy, it should be</p>	<p>It's safe and effective in all stages of <i>S. mansoni</i>.</p> <p>Optimal dosage schedules vary for different regions of the world. In the western hemisphere and western Africa, the adult oxamniquine dosage is 12–15 mg/kg given once. In northern and southern Africa, standard schedules are 15 mg/kg twice daily for 2 days. In eastern Africa and the Arabian peninsula, standard dosage is 15–20 mg/kg</p>	<p>It is readily absorbed orally; it should be taken with food.</p> <p>Its half-life is about 2.5 hours.</p> <p>The drug is metabolized to inactive metabolites and excreted in the urine</p> <p>The mechanism of action is unknown.</p>	<p>Is an alternative to praziquantel for the treatment of <i>S. mansoni</i> infections. It has also been used extensively for mass treatment. It is not effective against <i>S. haematobium</i> or <i>S. japonicum</i>.</p>	

<p>used with caution in patients whose work or activity requires mental alertness</p> <p>It should be used with caution in those with a history of epilepsy.</p> <p>Oxamniquine is contraindicated in pregnancy.</p>	<p>twice in 1 day. Cure rates are 70–95%, with marked reduction in egg excretion in those not cured. In mixed schistosome infections, oxamniquine has been successfully used in combination with metrifonate.</p>			
<p>Occasional mild adverse effects include nausea, vomiting, diarrhea, abdominal pain, dizziness,</p>	<p>Piperazine is an alternative for the treatment of ascariasis</p> <p>The dosage</p>	<p>It is readily absorbed</p> <p>Most of the drug is excreted unchanged in the urine in 2–6 hours.</p> <p>Paralysis of</p>	<p>Is an alternative for the treatment of ascariasis, with cure rates over 90% when taken for 2 days, but it is not recommended for</p>	<p>PIPERAZINE</p>

<p>and headache.</p> <p>Piperazine compounds should not be given to pregnant women, patients with impaired renal or hepatic function, or those with a history of epilepsy or chronic neurologic disease.</p>	<p>of piperazine (as the hexahydrate) is 75 mg/kg (maximum dose, 3.5 g) orally once daily for 2 days.</p> <p>For heavy infections, treatment should be continued for 3–4 days or repeated after 1 week.</p>	<p>ascaris by blocking acetylcholine at the myoneural junction.</p>	<p>other helminth infections.</p>
<p>The drug is effective in adults and children and is generally well tolerated by patients in the hepatosplenic stage of advanced</p>	<p>Schistosomiasis The dosage is 20 mg/kg per dose for two or three doses at intervals of 4–6 hours.</p> <p>Clonorchiasis, opisthorchiasis</p>	<p>It is rapidly absorbed, with a bioavailability of about 80% after oral administration.</p> <p>The half-life</p>	<p>Is effective in the treatment of schistosome infections of all species and most other trematode and cestode infections, including cysticercosis. The drug's</p> <p>PRAZIQUANTEL</p>

<p>disease.</p> <p>Mild and transient adverse effects are common.</p>	<p>is, and paragonimiasis</p> <p>Standard dosing is 25 mg/kg three times daily for 2 days for each of these fluke infections.</p>	<p>is 0.8–1.5 hours.</p> <p>Excretion is mainly via the kidneys and bile</p>	<p>safety and effectiveness as a single oral dose have also made it useful in mass treatment of several infections.</p>	
<p>Most common are headache, dizziness, drowsiness, and lassitude; others include nausea, vomiting, abdominal pain, loose stools, pruritus, urticaria, arthralgia, myalgia, and low-grade fever.</p> <p>The intensity</p>	<p>Taeniasis and diphyllobothriasis</p> <p>A single dose of praziquantel, 5–10 mg/kg</p> <p>Neurocysticercosis</p> <p>Dosage is 100 mg/kg/d in three divided doses for 1 day, then 50 mg/kg/d to complete a 2- to 4-week</p>	<p>Plasma concentrations increase when the drug is taken with a high carbohydrate meal or with cimetidine;</p> <p>Bioavailability is markedly reduced with some antiepileptics (phenytoin, carbamazepine) or with corticosteroids.</p> <p>It appears to increase the permeability of trematode and cestode cell</p>		

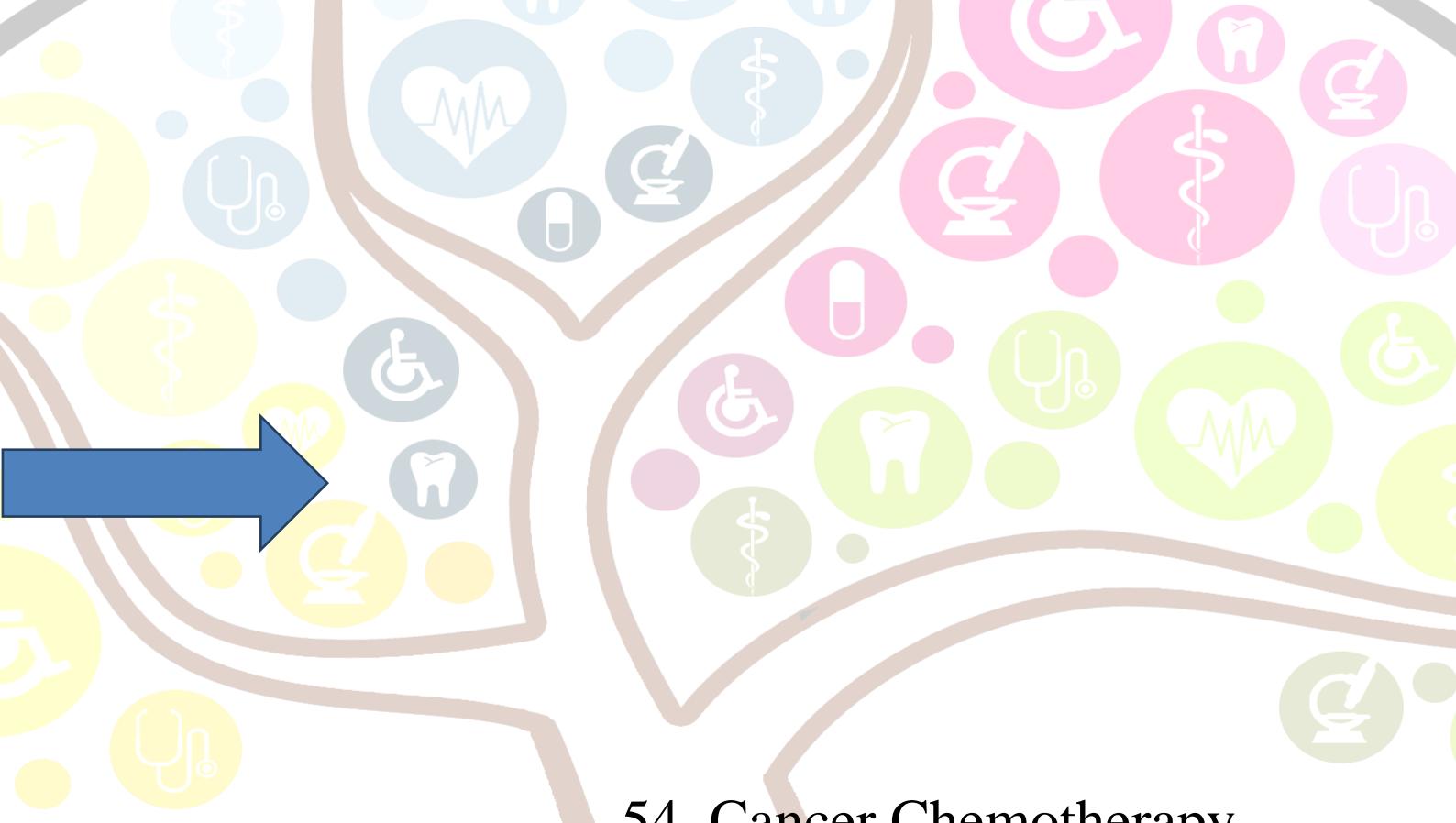
<p>and frequency of adverse effects increase with dosage</p>	<p>course.</p> <p>Hymenolepis nana</p> <p>A single dose of 25 mg/kg is taken initially and repeated in 1 week.</p>	<p>membranes to calcium, resulting in paralysis, dislodgement, and death.</p>		
<p>it is contraindicated in ocular cysticercosis,</p> <p>Spinal neurocysticercosis.</p>	<p>Hydatid disease</p>	<p>fasciolopsiasis, metagonimiasis, and other forms of heterophyiasis</p> <p>at a dosage of 25 mg/kg three times daily for 1–2 days</p>		
<p>Praziquantel is safe and well tolerated in children.</p> <p>The drug should be avoided in pregnancy if possible.</p> <p>Because the drug induces dizziness and drowsiness, patients should not drive during therapy and</p>				

should be warned regarding activities requiring particular physical coordination or alertness.				
<p>Adverse effects are infrequent, mild, and transient. They may include nausea, vomiting, diarrhea, abdominal cramps, dizziness, drowsiness, headache, insomnia, rash, fever, and weakness.</p> <p>Pyrantel should be used with caution in</p>	<p>For ascariasis, and hookworm infections, a single dose is effective against light infections; but for heavy infection a 3-day course is necessary</p> <p>The standard dose is 11mg/kg maximum (1g). Given orally once with or without food.</p>	<p>It is poorly absorbed from the gastrointestinal tract</p> <p>Over half of the administered dose is recovered unchanged in the feces.</p> <p>The drug is a neuromuscular blocking agent that causes release of acetylcholine and inhibition of</p>	<p>Is a broad-spectrum antihelminthic highly effective for the treatment of pinworm, ascaris, and Trichostrongylusorientalis infections.</p> <p>It is moderately effective against both species of hookworm.</p> <p>It is not effective in trichuriasis or strongyloidiasis.</p>	PYRANTEL PAMOATE

<p>patients with liver dysfunction,</p> <p>Experience with the drug in pregnant women and children younger than 2 years is limited.</p>		<p>cholinesterase; this results in paralysis of worms, followed by expulsion.</p>		
<p>Thiabendazole is much more toxic than other benzimidazoles. So other agents are now preferred for most indications.</p> <p>Common adverse effects include dizziness, anorexia, nausea, and</p>	<p>The standard dosage, 25 mg/kg (maximum 1.5 g) twice daily, should be given after meals. Tablets should be chewed. For strongyloidiasis infection, treatment is for 2 days.</p>	<p>It is rapidly absorbed after ingestion. The half-life is 1.2 hours. It is excreted in the urine in 48 hours.</p> <p>Thiabendazole can also be absorbed from the skin.</p>	<p>Alternative to ivermectin or albendazole for the treatment of strongyloidiasis and cutaneous larva migrans.</p>	<p>THIABENDAZOLE</p>



vomiting.				
<p>Less common problems are epigastric pain, abdominal cramps, diarrhea, pruritus, headache, drowsiness, and neuropsychiatric symptoms. Irreversible liver failure and fatal Stevens-Johnson syndrome have been reported.</p> <p>The drug should not be used in pregnancy or in the presence of hepatic or renal disease</p>	<p>patients with hyperinfection syndrome, the standard dose is continued twice daily for 5–7 days</p> <p>For cutaneous larva migrans, thiabendazole cream can be applied topically, or the oral drug can be given for 2 days</p>	<p>The mechanism of action of thiabendazole is the same as that of other benzimidazoles (inhibition of microtubule synthesis).</p> <p>The drug has ovicidal effects against some parasites.</p>		



54. Cancer Chemotherapy

Cancer

It is a disease characterized by a defect in the normal control mechanisms that govern cell survival, proliferation, and differentiation. Cells that have undergone neoplastic transformation usually express cell surface antigens that may be of normal fetal type, and they may display other signs of apparent immaturity, and may exhibit qualitative or quantitative chromosomal abnormalities, including various translocations and the appearance of amplified gene sequences. They retain the ability to undergo repeated cycles of proliferation as well as to migrate to distant sites in the body to colonize various organs in the process called metastasis

CAUSES OF CANCER

The incidence, geographic distribution, and behavior of specific types of cancer are related to multiple factors, including sex, age, race, genetic predisposition, and exposure to environmental carcinogens. Of these factors, *environmental exposure* is probably most important. Exposure to *ionizing radiation* has been well documented as a significant risk factor for a number of cancers. Also *Chemical carcinogens* have been well documented as leading to a wide range of human cancer. *Several viruses* have been implicated in the etiology of various human cancers.



CANCER TREATMENT MODALITIES

Localized tumor	About one-third of patients are cured with local treatment strategies, such as surgery or radiotherapy. Earlier diagnosis might lead to increased cure rates with such local treatment.
Early micrometastasis	Early micrometastasis is a characteristic feature, indicating that a systemic approach with chemotherapy is required for effective cancer management.
Locally advanced disease	Chemotherapy is often combined with radiotherapy to allow for subsequent surgical resection to take place, and such a combined modality approach has led to improved clinical outcomes
Advanced stage	Chemotherapy alone is able to cure less than 10% of all cancer patients

Chemotherapy is presently used in three main clinical settings:

Primary chemotherapy	Neoadjuvant chemotherapy	Adjuvant chemotherapy
<ul style="list-style-type: none"> -Refers to chemotherapy administered as the primary treatment in patients who present with advanced <i>metastatic</i> cancer for which no alternative treatment exists. -The goals of therapy are to relieve tumor related symptoms, improve overall quality of life, and 	<ul style="list-style-type: none"> -Refers to the use of chemotherapy in patients who present with localized cancer for which alternative local therapies, such as surgery, exist but which are less than completely effective. -The goal of the <u>neoadjuvant approach</u> is to reduce the size of the primary tumor so that surgical resection 	<ul style="list-style-type: none"> -Refers to local treatment modalities In this setting, chemotherapy is administered after surgery has been performed. -<u>The goal of chemotherapy</u> is to reduce the incidence of both local and systemic recurrence and to improve the overall survival of

prolong time to tumor progression.	can then be made easier.	patients.
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ROLE OF CELL CYCLE KINETICS & ANTI-CANCER EFFECT

The cardinal rule of chemotherapy the invariable inverse relation between cell number and curability was established with this model, and this relationship is applicable to other hematologic malignancies. Information on cell and population kinetics of cancer cells explains, in part, the limited effectiveness of most available anticancer drugs. This information is relevant to the mode of action, indications, and scheduling of **cell cycle-specific (CCS) and cell cycle-nonspecific (CCNS) drugs**. Agents falling into these two major classes are summarized in table 1.

TABLE 1 Cell cycle effects of major classes of anti-cancer drugs

Cell Cycle-Specific (CCS) Agents	Cell Cycle-Nonspecific (CCNS) Agents
Antimetabolites (S phase)	Alkylating agents
Capcitabine Cladribine Clofarabine Cytarabine (ara-C) Fludarabine 5-Fluorouracil (5-FU) Gemcitabine 6-Mercaptopurine (6-MP) Methotrexate (MTX) Nelarabine Pralatrexate 6-Thioguanine (6-TG)	Altretamine Bendamustine Busulfan Carmustine Chlorambucil Cyclophosphamide Dacarbazine Lomustine Mechlorethamine Melphalan Temozolamide Thiotepa
Topoisomerase II inhibitor (G₁-S phase)	Antitumor antibiotics
Etoposide	Dactinomycin Mitomycin
Topoisomerase I inhibitors (Camptothecins, G₂-M)	Platinum analogs
Irinotecan Topotecan	Carboplatin Cisplatin Oxaliplatin
Taxanes (M phase)	Anthracyclines
Albumin-bound paclitaxel Cabazitaxel Docetaxel Paclitaxel	Daunorubicin Doxorubicin Epirubicin Idarubicin Mitomantrome
Vinca alkaloids (M phase)	
Vinblastine Vincristine Vinorelbine	
Antimicrotubule inhibitor (M phase)	
Docetaxel Eribulin	
Antitumor antibiotics (G₂-M phase)	
Bleomycin	

The Role of Drug Combinations

The use of combination chemotherapy is important for several reasons.

First, it provides maximal cell kill within the range of toxicity tolerated by the host for each drug as long as dosing is not compromised.

Second, it provides a broader range of interaction between drugs and tumor cells with different genetic abnormalities in a heterogeneous tumor population.

Finally, it may prevent or slow the subsequent development of cellular drug resistance.

Certain principles have guided the selection of drugs in the most effective drug combinations, and they provide a paradigm for the development of new drug therapeutic programs.

1- Efficacy: Only drugs known to be somewhat effective when used alone against a given tumor should be selected for use in combination.

2-Toxicity: When several drugs of a given class are available and are equally effective, a drug should be selected on the basis of toxicity that does not overlap with the toxicity of other drugs in the combination.

3-Optimum scheduling: Drugs should be used in their optimal dose and schedule, and drug combinations should be given at consistent intervals.

4-Mechanism of interaction: There should be a clear understanding of the biochemical, molecular, and pharmacokinetic mechanisms of interaction between the individual drugs in a given combination, to allow for maximal effect.

5-Avoidance of arbitrary dose changes: An arbitrary reduction in the dose of an effective drug in order to add other less effective drugs may reduce the dose of the most effective agent below the threshold of effectiveness and destroy the ability of the combination to cure disease in a given patient.

Dosage Factors

Dose intensity is one of the main factors limiting the ability of chemotherapy or radiation therapy to achieve cure. For

chemotherapy, therapeutic selectivity is dependent on the difference between the dose-response curves of normal and tumor tissues. A positive relationship between dose intensity and clinical efficacy has been documented in several solid tumors. At present, there are three main approaches to **dose-intense delivery of chemotherapy:**

1. **Dose escalation**, involves increasing the doses of the respective anti-cancer agents.
2. Administration of anti-cancer agents in a dose-intens manner by **reducing the interval** between treatment cycles.
3. **Sequential scheduling** of either single agents or of combination regimens.

DRUG RESISTANCE

A fundamental problem in cancer chemotherapy is the development of cellular drug resistance. ***Primary, or inherent resistance*** refers to drug resistance in the absence of prior exposure to available standard agents. In contrast to primary resistance, ***acquired resistance*** develops in response to exposure to a given anti-cancer agent.

BASIC PHARMACOLOGY OF CANCER CHEMOTHERAPEUTIC DRUGS

- **Alkylating Agents:** this book classifies Alkylating agents into:



CLASSIC ALKYLATING AGENTS

Examples of classic:

Cyclophosphamide,
Chlorambucil and
Mechlorethamine

* major alkylating
agents are in this
category

NITROSOUREAS

These drugs appear to be
non-cross-resistant with
other alkylating agents.

They are highly lipid-
soluble and are able to
readily cross the blood-
brain barrier, making them

Examples of nitrosoureas:

Lomustine, Carmustine and
streptozocin

NONCLASSIC ALKYLATING AGENTS

Several other compounds
have mechanisms of

Examples of non-classic:
procarbazine, dacarbazine,
bendamustine and temozolomide

- PLATINUM ANALOGS: Three platinum analogs are currently used in clinical practice: cisplatin, carboplatin, and oxaliplatin. The platinum complexes appear to **synergize** with certain other anti-cancer drugs, including alkylating agents, fluoropyrimidines and taxanes.

TABLE 2 Alkylating agents and platinum analogs: Clinical activity and toxicities.

Alkylating Agent	Mechanism of Action	Clinical Applications	Acute Toxicity	Delayed Toxicity	Note (pharmacokinetics , route of administration, ...)
Mechlorethamine	Forms DNA cross-links, resulting in inhibition of DNA synthesis and function	Hodgkin's and non-Hodgkin's lymphoma	Nausea and vomiting	Moderate depression of peripheral blood count; excessive doses produce severe bone marrow	
Chlorambucil	Same as above	CLL and non-Hodgkin's lymphoma	Nausea and vomiting		
Cyclophosphamide	Same as above	Breast cancer, ovarian cancer, non-Hodgkin's lymphoma, CLL, soft tissue sarcoma, neuroblastoma, Wilms' tumor, rhabdomyosarcoma	Nausea and vomiting	depression with leukopenia, thrombocytopenia, and bleeding; alopecia and hemorrhagic cystitis occasionally occur with cyclophosphamide; cystitis can be	- most widely used alkylating agents. One of the potential advantages of this compound relates to its high oral bioavailability. it can be administered via the oral and intravenous routes with equal clinical efficacy

Bendamustine	Same as above	CLL, non-Hodgkin's lymphoma	Nausea and vomiting	prevented with adequate hydration; busulfan is associated with skin pigmentation, pulmonary fibrosis, and adrenal insufficiency	the cross-resistance between bendamustine and other alkylating agents is only partial, thereby providing a rationale for its clinical activity despite the development of resistance to other alkylating agents.
Procarbazine	Same as above	Hodgkin's and non-Hodgkin's lymphoma, brain tumors	Central nervous system depression	Myelosuppression, hypersensitivity reactions	One metabolite is a weak monoamine oxidase (MAO) inhibitor, and adverse events can occur when procarbazine is given with other MAO inhibitors as well as with sympathomimetic agents, tricyclic antidepressants, antihistamines, central nervous system depressants, antidiabetic agents, alcohol, and tyramine-containing foods.
Dacarbazine	Same as above	Hodgkin's lymphoma, melanoma, soft tissue sarcoma and neuroblastoma.	Nausea and vomiting	Myelosuppression, central nervous system toxicity with neuropathy, ataxia, lethargy, and confusion	It is administered parenterally and this agent is a potent vesicant, and care must be taken to avoid extravasation during drug administration.
Melphalan	Same as above	Multiple myeloma, breast cancer, ovarian cancer	Nausea and vomiting		
Thiotepa	Same as above	Breast cancer, ovarian cancer, superficial bladder cancer	Nausea and vomiting		
Busulfan	Same as above	CML	Nausea and vomiting		
Carmustine	Same as above	Brain cancer, Hodgkin's and non-Hodgkin's lymphoma	Nausea and vomiting	Myelosuppression; rarely interstitial lung disease and interstitial nephritis	
Lomustine	Same as above	Brain cancer	Nausea and vomiting		After oral administration, Peak plasma levels of metabolites appear



					within 1–4 hours; central nervous system concentrations reach 30–40% of the activity present in the plasma. Urinary excretion appears to be the major route of elimination from the body
<u>streptozocin</u>	Same as above	This agent has activity in the treatment of insulin-secreting islet cell carcinoma of the pancreas.			This drug is interesting because it has minimal bone marrow toxicity.
Altretamine	Same as above	Ovarian cancer	Nausea and vomiting	Myelosuppression, peripheral neuropathy, flu-like syndrome	
Temozolomide	Methylates DNA and inhibits DNA synthesis and function	Brain cancer, melanoma	Nausea and vomiting, headache and fatigue	Myelosuppression, mild elevation in liver function tests, photosensitivity	
Cisplatin	Forms intrastrand and interstrand DNA cross-links; binding to nuclear and cytoplasmic proteins	Non-small cell and small cell lung cancer, breast cancer, bladder cancer, cholangiocarcinoma, gastroesophageal cancer, head and neck cancer, ovarian cancer, germ cell cancer	Nausea and vomiting	Nephrotoxicity, peripheral sensory neuropathy, ototoxicity, nerve dysfunction	Cisplatin and the other platinum analogs are extensively cleared by the kidneys and excreted in the urine. as a result, dose modification is required in patients with renal dysfunction
Carboplatin	Same as cisplatin	Non-small cell and small cell lung cancer, breast cancer, bladder cancer, head and neck cancer, ovarian cancer	Nausea and vomiting	Myelosuppression; peripheral neuropathy, renal toxicity, hepatic dysfunction	used in transplant regimens to treat refractory hematologic malignancies. It is viewed as an easier agent to administer to patients
Oxaliplatin	Same as cisplatin	Colorectal cancer, gastroesophageal cancer, pancreatic cancer	Nausea and vomiting, laryngopharyngeal dysesthesias and Neurotoxicity triggered and worsened by exposure to cold.	Myelosuppression, peripheral sensory, diarrhea and Neurotoxicity; chronic form is dependent on the cumulative dose of drug administered, it tends to be reversible, in contrast to cisplatin-induced	Tumors that are resistant to cisplatin or carboplatin on the basis of mismatch repair defects are not cross-resistant to oxaliplatin.



					neurotoxicity	
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CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia.

Resistance of alkylating agents:

The mechanism of acquired resistance to alkylating agents may involve increased capability to repair DNA lesions through increased expression and activity of DNA repair enzymes, decreased transport of the alkylating drug into the cell, and increased expression or activity of glutathione and glutathione-associated proteins, which are needed to conjugate the alkylating agent, or increased glutathione S-transferase activity, which catalyzes the conjugation.

ANTIMETABOLITES: this book classify anti-metabolites into four categories:

ANTIFOLATES

- Ex: - Methotrexate
- Pemetrexed
- Pralatrexate

FLUOROPYRIMIDINES

- Ex: - 5-Fluorouracil
- Capecitabine

DEOXYCYTIDINE ANALOGS

- Ex: - Cytarabine
- Gemcitabine

PURINE ANTAGONISTS

- Ex: - 6-Thiopurines
- Fludarabine
- Cladribine

TABLE 3 Antimetabolites: Clinical activity and toxicities.

Drug name	Mechanism of Action	Clinical Applications	Toxicity	Note (pharmacokinetics , Drug-drug interactions, route of administration, ...)
Capecitabine	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Breast cancer, colorectal cancer, gastroesophageal cancer, hepatocellular cancer, pancreatic cancer	Diarrhea, hand-foot syndrome, myelosuppression, nausea and vomiting	The oral bioavailability of this drug is 70-80%
5-Fluorouracil	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Colorectal cancer, anal cancer, breast cancer, gastroesophageal cancer, head and neck	Nausea, mucositis, diarrhea, bone marrow depression, neurotoxicity and	It is administered IV and the clinical activity of this drug is highly schedule-dependent. Because of its extremely

		cancer,hepatocellular carcinoma	hand-foot syndrome	short half-life, on the order of 10–15 minutes, infusional schedules of administration have been generally favored over bolus schedules. Up to 80–85% of an administered dose of 5-FU is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD).
Methotrexate (MTX)	Inhibits DHFR; inhibits TS; inhibits de novo purine nucleotide synthesis	Breast cancer, head and neck cancer, osteogenic sarcoma, primary central nervous system lymphoma, non-Hodgkin's lymphoma, bladder cancer, choriocarcinoma	Mucositis, diarrhea, myelosuppression with neutropenia and thrombocytopenia	MTX is administered by IV, intrathecal, or oral route. However, oral bioavailability is saturable and erratic at doses greater than 25 mg/m². Renal excretion is the main route of elimination. As a result, dose modification is required in the setting of renal dysfunction. Care must also be taken when MTX is used in the presence of drugs such as aspirin, nonsteroidal anti-inflammatory agents, penicillin, and cephalosporins, as these agents inhibit the renal excretion of MTX. The effects of MTX can be reversed by administration of the reduced folate leucovorin or by L-leucovorin, which is the active enantiomer.
Pemetrexed	Inhibits TS, DHFR, and purine nucleotide synthesis	Mesothelioma, non-small cell lung cancer	Myelosuppression, skin rash, mucositis, diarrhea, fatigue, hand-foot syndrome	Excreted in the urine, and dose modification is required in patients with renal dysfunction. Vitamin supplementation with folic acid and vitamin B₁₂ appears to reduce the toxicities associated with pemetrexed, while not interfering with clinical efficacy. The <u>hand-foot syndrome</u> is manifested by painful erythema and swelling of the hands and feet, and <u>dexamethasone</u> treatment has been shown to be effective in reducing the incidence and severity of this toxicity
Pralatrexate	Same as above	NSCLC, refractory peripheral T-cell lymphoma	Same as above	As with the other antifolate analogs, mainly excreted in the urine, and dose modification is required in renal dysfunction.
Cytarabine	Inhibits DNA chain elongation, DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs;	AML, ALL, CML in blast crisis	Nausea and vomiting, myelosuppression with neutropenia and	The clinical activity of this drug is highly schedule-dependent and because of its rapid degradation, it is usually



	incorporation of cytarabine triphosphate into DNA		thrombocytopenia, cerebellar ataxia	administered via continuous infusion over a 5–7 day period. This agent has absolutely no activity in solid tumors.
Gemcitabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of gemcitabine triphosphate into DNA resulting in inhibition of DNA synthesis and function	Pancreatic cancer, bladder cancer, breast cancer, non-small cell lung cancer, ovarian cancer, non-Hodgkin's lymphoma, soft tissue sarcoma	Nausea, vomiting occur in 70% of patients, diarrhea, Myelosuppression and flu-like syndrome.	In contrast to cytarabine, gemcitabine has broad-spectrum activity against solid tumors and hematologic malignancies.
Fludarabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of fludarabine triphosphate into DNA; induction of apoptosis	Non-Hodgkin's lymphoma, CLL	Myelosuppression, immunosuppression, nausea and vomiting, fever, myalgias, arthralgias	It is given parenterally, and up to 25–30% of parent drug is excreted in the urine. Patients are at increased risk for opportunistic infections thus, patients should receive PCP prophylaxis with trimethoprim-sulfamethoxazole (double strength) at least three times a week, and this should continue for up to 1 year after stopping fludarabine therapy
Cladribine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of cladribine triphosphate into DNA; induction of apoptosis	Hairy cell leukemia, CLL, non-Hodgkin's lymphoma	Myelosuppression, nausea and vomiting, and immunosuppression	It is normally administered as a single continuous 7-day infusion; under these conditions, it has a very manageable safety profile with the main toxicity consisting of transient myelosuppression.
6-Mercaptopurine (6-MP)	Inhibits de novo purine nucleotide synthesis; incorporation of triphosphate into RNA; incorporation of triphosphate into DNA	AML	Myelosuppression, immunosuppression, and hepatotoxicity	6-MP is converted to an inactive (6-thiouric acid) by an oxidation reaction catalyzed by xanthine oxidase, This is an important issue because the purine analog allopurinol, a potent xanthine oxidase inhibitor, is frequently used as a supportive care measure in the treatment of acute leukemias to prevent the development of hyperuricemia, .as a result, simultaneous therapy with allopurinol and 6-MP would result in increased levels of 6-MP, thereby leading to excessive toxicity. In this setting, the dose of mercaptopurine must be reduced by 50–75%.
6-Thioguanine (6-TG)	Same as 6-MP	ALL, AML	Same as above	6-TG has a synergistic action when used together with cytarabine in the treatment of adult acute leukemia. in contrast with (6-

(MP), it can be used in full doses with allopurinol

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DHFR, dihydrofolate reductase; dNTP, deoxyribonucleotide triphosphate; FdUTP, 5-fluorodeoxyuridine-5'-triphosphate; FUTP, 5-fluorouridine-5'-triphosphate; TS, thymidylate synthase. IV; intravenously, (PCP):Pneumocystis jiroveci pneumonia

NATURAL PRODUCT CANCER CHEMOTHERAPY

DRUGS: : this book classify Natural product cancer chemotherapy drugs into four categories:

VINCA ALKALOIDS

Ex: - Vinblastine , Vincristine and Vinorelbine

TAXANES DRUG

Ex: - Paclitaxel,Docetaxel, Cabazitaxel.

ANTI-MICROTUBULE DRUG

Ex: - ixabepilon,Eribulin.

EPIPODOPHYLLO TOXINS:

Ex: Etoposide.

CAMPTOTHECINS

Ex: Topotecan and irinotecan

ANTITUMOR ANTIBIOTICS:

ANTHACYCLINES

Ex: Daunorubicin, Doxorubicin and Idarubicin

- notes: the free radical mechanism is the cause of the cardiotoxicity associated with the anthracyclines. They are administered via the iv route and metabolized extensively in the liver. Up to 50% of drug is eliminated in the feces via biliary excretion, and dose reduction is required in patients with liver dysfunction.

Although anthracyclines are usually

MITOMYCIN

BLEOMYCIN

TABLE 4 Natural product cancer chemotherapy drugs & ANTITUMOR ANTIBIOTICS: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications	Acute Toxicity	Delayed Toxicity	Note (pharmacokinetics , Drug-drug interactions, route of administration, ...)
Bleomycin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks	Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, head and neck cancer	Allergic reactions, fever, hypotension	Skin toxicity, pulmonary fibrosis, mucositis, alopecia.	The incidence of pulmonary toxicity is increased in patients older than 70 years of age, in those who receive cumulative doses greater than 400 units, in those with underlying pulmonary disease
Daunorubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	AML, ALL	Nausea and vomiting, fever, red urine (not hematuria)	Cardiotoxicity, alopecia, myelosuppression	its efficacy in solid tumors is limited.
Doxorubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	Breast cancer, Hodgkin's and non-Hodgkin's lymphoma, soft tissue sarcoma, ovarian cancer, non-small cell and small cell lung cancer, thyroid cancer, Wilms' tumor, neuroblastoma	Nausea, red urine (not hematuria)	Cardiotoxicity, alopecia, myelosuppression, stomatitis	Use of lower weekly doses or continuous infusions of doxorubicin appear to reduce the incidence of cardiac toxicity.
Idarubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	AML, ALL, CML in blast crisis	Nausea and vomiting	Myelosuppression, mucositis, cardiotoxicity	

Mitoxantrone	inhibits both DNA and RNA synthesis.	prostate cancer, non-Hodgkin's lymphoma, breast cancer and acute myeloid leukemias	nausea and vomiting, mucositis, and alopecia also	Myelosuppression with leukopenia and cardiac toxicities	blue discoloration of the fingernails, sclera, and urine is observed 1–2 days after drug administration.
Etoposide	Inhibits topoisomerase II	Non-small cell and small cell lung cancer; non-Hodgkin's lymphoma,gastric cancer	Nausea, vomiting, hypotension	Alopecia, myelosuppression	<p>-Intravenous and oral formulations of etoposide are approved. The oral bioavailability is about 50% requiring the oral dose to be twice that of an intravenous dose.</p> <p>Up to 30–50% of drug is excreted in the urine, and dose reduction is required in patients with renal dysfunction.</p>
Irinotecan	Inhibits topoisomerase I	Colorectal cancer, gastroesophageal cancer, non-small cell and small cell lung cancer	Diarrhea, nausea, vomiting	Diarrhea, myelosuppression, nausea and vomiting	It is prodrug that is converted mainly in the liver and eliminated in bile and feces, and dose reduction is required in the setting of liver dysfunction
Mitomycin	Acts as an alkylating agent and forms cross-links with DNA; formation of oxygen free radicals,which target DNA	Superficial bladder cancer, gastric cancer, breast cancer, non-small cell lung cancer, head and neck cancer (in combination with radiotherapy)	Nausea and vomiting	Myelosuppression, mucositis, anorexia and fatigue, hemolytic-uremic syndrome SIADH	
Paclitaxel	Inhibits mitosis	Breast cancer, non-small cell and small cell lung cancer, ovarian cancer, gastroesophageal cancer, prostate cancer, bladder cancer, head and neck cancer	Nausea, vomiting, hypotension, arrhythmias, hypersensitivity	Myelosuppression, peripheral sensory neuropathy	It is metabolized by the liver P450 system, and nearly 80% of the drug is excreted in feces. Dose reduction is required in patients with liver dysfunction.
Docetaxel	Inhibits mitosis	Breast cancer, non-small cell lung cancer, prostate cancer, gastric cancer, head and neck cancer,ovarian cancer, bladder cancer	Hypersensitivity	Neurotoxicity, fluid retention, myelosuppression with neutropenia	

Cabazitaxel	Inhibits mitosis	prostate cancer	-	myelosuppression, neurotoxicity, and allergic reactions.	cabazitaxel is a poor substrate for the multidrug and may therefore be useful for treating multidrug-resistant tumors.
Ixabepilone	inhibition of normal microtubule dynamics	breast cancer	-	myelosuppression, hypersensitivity reactions, and neurotoxicity	this agent continues to have activity in drug-resistant tumors
Eribulin	inhibition of normal microtubule dynamics	breast cancer	-	-	less sensitive to the multidrug resistance and continues to have activity in drug-resistant tumors
Topotecan	Inhibits topoisomerase I	Small cell lung cancer, ovarian cancer	Nausea and vomiting	Myelosuppression	The main route of elimination is renal excretion, and dosage must be adjusted in patients with renal impairment.
Vinblastine	Inhibits mitosis	Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, breast cancer, Kaposi's sarcoma	Nausea and vomiting	Myelosuppression, mucositis, alopecia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), vascular events	This drug and other vinca alkaloids are metabolized by the liver P450 system. the majority excreted in feces via the hepatobiliary system. So dose modification is required in case of liver dysfunction.
Vincristine	Inhibits mitosis	ALL, Hodgkin's and non-Hodgkin's lymphoma, rhabdomyosarcoma, neuroblastoma, Wilms' tumor	None	Neurotoxicity with peripheral neuropathy, paralytic ileus, myelosuppression, alopecia,	myelosuppression is generally milder and much less significant than with vinblastine.
Vinorelbine	Inhibits mitosis	Non-small cell lung cancer, breast cancer, ovarian cancer	Nausea and vomiting	Myelosuppression, Neutropenia, transient elevations in liver function tests, constipation, SIADH	

syndrome of inappropriate secretion of antidiuretic hormone (SIADH) ;
for other See Table 3 for acronyms.



MISCELLANEOUS ANTI-CANCER DRUGS: A large number of anti-cancer drugs that do not fit traditional categories have been approved for clinical use; they are listed in Table 5.

MISCELLANEOUS ANTI-CANCER DRUGS

TABLE 5 Miscellaneous anti-cancer drugs: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications	Acute Toxicity	Delayed Toxicity	
Bortezomib	Inhibitor of the 26S proteosome; results in down-regulation of the NF- kB signaling pathway	Multiple myeloma, mantle cell lymphoma	Nausea and vomiting, fever	Peripheral sensory neuropathy, diarrhea, orthostatic hypotension, fever, pulmonary toxicity, reversible posterior leukoencephalopathy (RPLS), congestive heart failure (CHF), rare cases of QT prolongation	
Carfilzomib	Inhibitor of the 26S proteosome; results in down-regulation of the NF-kB signaling pathway; maintains activity in bortezomibresistant tumors	Multiple myeloma	Fever	Fatigue, cardiac toxicity with CHF and myocardial infarction, myelosuppression, pulmonary toxicity, hepatotoxicity, orthostatic hypotension	
Erlotinib	Inhibits EGFR tyrosine kinase leading to inhibition of EGFR signaling	Non-small cell lung cancer, pancreatic cancer	Diarrhea	Skin rash, diarrhea, anorexia, interstitial lung disease	It is metabolized in the liver by the CYP3A4 enzyme system, and elimination is mainly hepatic with excretion in feces. Caution must be taken when using these agents with drugs that are also metabolized by the liver CYP3A4 system, such as phenytoin and warfarin, and the use of grapefruit products

					should be avoided.
Imatinib	Inhibits Bcr-Abl tyrosine kinase and other receptor tyrosine kinases, including PDGFR, and c-kit	CML, gastrointestinal stromal tumor (GIST), Philadelphia chromosome-positive ALL	Nausea and vomiting	Fluid retention with ankle and periorbital edema, diarrhea, myalgias, congestive heart failure	Imatinib is well absorbed orally. Imatinib and the other TKIs are metabolized in the liver, mainly by the CYP3A4 liver microsomal enzyme. It is important to review the patient's current list of prescription and nonprescription drugs because these agents have potential drug-drug interactions, especially with those that are also metabolized by the CYP3A4 system.
Dasatinib	inhibitor of several tyrosine kinases including Bcr-Abl, Src, c-kit, and PDGFR- α	CML, Philadelphia (Ph) chromosome-positive (ALL) with resistance or intolerance to imatinib therapy.	-	-	
Nilotinib	inhibits Bcr-Abl, c-kit, and PDGFR- α tyrosine kinases	CML with resistance or intolerance to imatinib	-	-	
Bosutinib	Inhibits Bcr-Abl tyrosine kinase and retains activity in imatinib-resistant Bcr-Abl mutations except for the T315I and V299L mutations. Inhibits Src family tyrosine kinases.	CML	Nausea and vomiting	Diarrhea, fluid retention, myelosuppression, skin rash, hepatotoxicity	
Cetuximab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy	Colorectal cancer, head and neck cancer (used in combination with radiotherapy), non-small cell lung cancer	Infusion reaction	Skin rash, hypomagnesemia, fatigue, interstitial lung disease	only effective in patients whose tumors express wild-type KRAS mutations. approved to be administered on a weekly schedule, pharmacokinetic studies have shown that an every-2-week schedule provides the same level of clinical activity as the weekly schedule.
Panitumumab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy	Colorectal cancer	Infusion reaction (rarely)	Skin rash, hypomagnesemia, fatigue, interstitial lung disease	only effective in patients whose tumors express wild-type KRAS mutations.
Bevacizumab	Inhibits binding of VEGF-A to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery	Colorectal cancer, breast cancer, nonsmall cell lung cancer, renal cell cancer, glioblastoma multiformae	Hypertension, infusion reaction	Arterial thromboembolic events, gastrointestinal perforations, wound healing complications, bleeding complications, proteinuria	One potential advantage of this antibody is that it does not appear to exacerbate the toxicities typically observed with cytotoxic chemotherapy



Ziv-aflibercept	Inhibits binding of VEGF-A, VEGF-B, and PI GF to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery	Colorectal cancer	Hypertension	Arterial thromboembolic events, gastrointestinal perforations, wound healing complications, bleeding complications, diarrhea, mucositis, proteinuria	
Asparaginase	It hydrolyzes circulating l-asparagine to aspartic acid and ammonia.	childhood (ALL).	hypersensitivity reaction manifested by fever, chills, nausea and vomiting, skin rash, urticaria.	Severe cases can present with bronchospasm, respiratory failure, and hypotension.	
Sorafenib	Inhibits multiple RTKs, including raf kinase, VEGF-R2, VEGF-R3, and PDGFR- β leading to inhibition of angiogenesis, invasion, and metastasis	Renal cell cancer, hepatocellular cancer	Nausea, hypertension	Skin rash, fatigue and asthenia, bleeding complications, hypophosphatemia	metabolized in the liver by the CYP3A4 system, and elimination is primarily hepatic with excretion in feces. Therefore, each of these agents has potential interactions with drugs that are also metabolized by the CYP3A4 system, especially warfarin.
Sunitinib, pazopanib	Inhibits multiple RTKs, including VEGF-R1, VEGF-R2, VEGF-R3, PDGFR- α and PDGFR- β leading to inhibition of angiogenesis, invasion, and metastasis	Renal cell cancer, GIST	Hypertension	Skin rash, fatigue and asthenia, bleeding complications, cardiac toxicity leading to congestive heart failure in rare cases	

Epidermal growth factor receptor (EGFR), reversible posterior leukoencephalopathy (RPLS), congestive heart failure (CHF), gastrointestinal stromal tumor (GIST), platelet-derived growth factor receptor (PDGFR), placental growth factor (PIGF), acute lymphoblastic leukemia (ALL), vascular endothelial growth factor (VEGF) receptor

CLINICAL PHARMACOLOGY OF CANCER CHEMOTHERAPEUTIC DRUGS

A complete knowledge of the kinetics of tumor cell proliferation along with an understanding of the pharmacology and mechanism of action of cancer chemotherapeutic agents is important in designing optimal regimens for patients with cancer.

THE LEUKEMIAS

	ACUTE LEUKEMIA	CHRONIC MYELOGENOUS LEUKEMIA CML	CHRONIC LYMPHOCYTIC LEUKEMIA CLL
Childhood Leukemia	<p>Acute lymphoblastic leukemia (ALL) is the main form of leukemia in childhood, Treatments: corticosteroids, 6-mercaptopurine, cyclophosphamide, vincristine, daunorubicin, and asparaginase have all been found to be active against this disease. A combination of vincristine and prednisone plus other agents is currently used to induce remission. The value of prophylactic intrathecal methotrexate therapy for prevention of central nervous system leukemia (a major mechanism of relapse) has been clearly demonstrated.</p>	<p>CML arises from a chromosomally abnormal hematopoietic stem cell in which a balanced translocation between the long arms of chromosomes 9 and 22. The clinical symptoms and course are related to the white blood cell count and its rate of increase. Most patients with white cell counts over 50,000/μL should be treated. The goals of treatment are to reduce the granulocytes to normal levels, to raise the hemoglobin concentration to normal, and to relieve disease-related symptoms. The tyrosine kinase inhibitor TKI imatinib is considered as standard first-line therapy in previously untreated patients with chronic phase CML. Nearly all patients treated with imatinib exhibit a complete hematologic response. Initially, dasatinib and nilotinib were approved for patients who were intolerant or resistant to imatinib; each shows clinical activity, and both are now also indicated as first-line treatment of chronic phase CML. In addition to these TKI, other treatment options include interferon-α, busulfan, other oral alkylating agents, and hydroxyurea.</p>	<p>Patients with early-stage CLL have a relatively good prognosis, and therapy has not changed the course of the disease. However, in the setting of high-risk disease or in the presence of disease-related symptoms, treatment is indicated. Chlorambucil and cyclophosphamide are the two most widely used alkylating agents for this disease. Chlorambucil is frequently combined with prednisone. In most cases, cyclophosphamide is combined with vincristine and prednisone (COP), or it can also be given with these same drugs along with doxorubicin (CHOP). Bendamustine is the newest alkylating agent to be approved for use in this disease, either as monotherapy or in combination with prednisone. Rituximab is an anti-CD20 antibody that has documented clinical activity in this setting. This chimeric antibody appears to enhance the antitumor effects of cytotoxic chemotherapy and is also effective in settings in which resistance to chemotherapy has developed. Ofatumumab is a fully human IgG1 antibody that binds to a different CD20 epitope than rituximab. Of note, it maintains activity in rituximab-resistant tumors, and it is presently approved for CLL that is refractory to fludarabine and alemtuzumab therapy.</p>
Adult Leukemia	<p>Acute myelogenous leukemia (AML) is the most common leukemia in adults. Treatment: The single most active agent for AML is cytarabine; however, it is best used in combination with an anthracycline. While there are several anthracyclines that can be effectively combined with cytarabine, idarubicin is preferred. Patients often require intensive supportive care during the period of induction chemotherapy. Such care includes platelet transfusions to prevent bleeding, the granulocyte colony-stimulating factor filgrastim to shorten periods of neutropenia, and antibiotics to combat infections.</p>		

HODGKIN'S & NON-HODGKIN'S LYMPHOMAS

HODGKIN'S LYMPHOMA		NON-HODGKIN'S LYMPHOMA
<p>This lymphoma is now widely recognized as a B-cell neoplasm in which the malignant Reed-Sternberg cells have rearranged <i>VH</i> genes. Complete staging evaluation is required before a definitive treatment plan can be made.</p>		<p>It is a heterogeneous disease, and the clinical characteristics are related to the underlying histopathologic features and the extent of disease involvement. In general, the nodular lymphomas have a far better prognosis, with a median survival up to 7 years, compared with the diffuse lymphomas, which have a median survival of about 1–2 years.</p> <p>Combination chemotherapy is the treatment standard for patients with diffuse non-Hodgkin's lymphoma. The anthracycline containing regimen CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) has been considered the best treatment in terms of initial therapy. Randomized phase III clinical studies have now shown that the combination of CHOP with rituximab results in improved response rates, disease-free survival, and overall survival compared with CHOP chemotherapy alone. The nodular follicular lymphomas are low-grade, relatively slow-growing tumors that tend to present in an advanced stage and are usually confined to lymph nodes, bone marrow, and spleen.</p> <p>This form of non-Hodgkin's lymphomas, when presenting at an advanced stage, is considered incurable, and treatment is generally palliative.</p>
stage I and stage II A	stages III and IV	
<p>Initially, these patients were treated with extended-field radiation therapy. However, given the well-documented late effects of radiation therapy, which include hypothyroidism, an increased risk of secondary cancers, and coronary artery disease, combined modality therapy with a brief course of combination chemotherapy and involved field radiation therapy is now the recommended approach.</p>	<p>More recently, the anthracycline-containing regimen termed ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) has been shown to be more effective and less toxic than MOPP (mechlorethamine, vincristine, procarbazine, and prednisone), especially with regard to the incidence of infertility and secondary malignancies. In general, four cycles of ABVD are given to patients. An alternative regimen, termed Stanford V, utilizes a 12-week course of combination chemotherapy (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone), followed by involved radiation therapy.</p>	

MULTIPLE MYELOMA

Plasma cell malignancy is one of the models of neoplastic disease in humans as it arises from a single tumor stem cell. Moreover, the tumor cells produce a marker protein (myeloma immunoglobulin) that allows the total body burden of tumor cells to be quantified. Multiple myeloma principally involves the bone marrow and bone, causing bone pain, lytic lesions, bone fractures, and anemia as well as an increased susceptibility to infection. Most patients with multiple myeloma are symptomatic at the time of initial diagnosis and require treatment with cytotoxic chemotherapy. Treatment with the

combination of the alkylating agent melphalan and prednisone (MP protocol) has been a standard regimen for nearly 30 years.

In patients who are considered candidates for high-dose therapy with stem cell transplantation, melphalan and other alkylating agents are to be avoided, as they can affect the success of stem cell harvesting.

-Thalidomide is a well-established agent for treating refractory or relapsed disease. More recently, thalidomide has been used in combination with dexamethasone. Lenalidomide and pomalidomide are two immunomodulatory analogs (IMiDs) of thalidomide. Lenalidomide is approved in combination with dexamethasone for multiple myeloma patients who have received at least one prior therapy, and clinical data show that this combination is effective as first-line therapy. Pomalidomide is the most recent IMid to receive approval and this drug may be able to overcome resistance to thalidomide and lenalidomide.

The side effect profiles of these IMids appear to be similar although neurotoxicity is observed more commonly with thalidomide, somewhat less often with pomalidomide, and rarely with lenalidomide.

-Bortezomib was first approved for use in relapsing or refractory multiple myeloma and is now widely used as first-line therapy.

Carfilzomib is approved for patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent. This agent is important as it is able to overcome resistance to bortezomib, and preclinical and clinical studies suggest that it has broad-spectrum activity in hematologic malignancies as well as in solid tumors.

BREAST CANCER

STAGE I & STAGE II DISEASE

STAGE III & STAGE IV DISEASE

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-Women with stage I disease (small primary tumors and negative axillary lymph node dissections) are currently treated with surgery alone, and they have an 80% chance of cure.

-Women with node-positive disease have a high risk of both local and systemic recurrence. Thus, lymph node status directly indicates the risk of occult distant micrometastasis. In this situation, postoperative use of systemic adjuvant chemotherapy with six cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF protocol) or of fluorouracil, doxorubicin, and cyclophosphamide (FAC) has been shown to significantly reduce the relapse rate and prolong survival. Alternative regimens with equivalent clinical benefit include four cycles of doxorubicin and cyclophosphamide and six cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). Each of these chemotherapy regimens has benefited women with stage II breast cancer with one to three involved lymph nodes.

-Women with four or more involved nodes have had limited benefit thus far from adjuvant chemotherapy. Long-term analysis has clearly shown improved survival rates in node-positive premenopausal women who have been treated aggressively with multiagent combination chemotherapy. The results from three randomized clinical trials clearly show that the addition of **trastuzumab**, a monoclonal antibody directed against the HER-2/neureceptor, to anthracycline- and taxane-containing adjuvant chemotherapy benefits women with HER-2-overexpressing breast cancer with respect to disease-free and overall survival.

Tamoxifen is beneficial in postmenopausal women when used alone or in combination with cytotoxic chemotherapy. The present recommendation is to administer tamoxifen for 5 years of continuous therapy after surgical resection. Then after complete 5 years of tamoxifen therapy should be placed on an aromatase inhibitor such as **anastrozole** for at least 2.5 years. In women who have completed 2–3 years of tamoxifen therapy, treatment with an aromatase inhibitor for a total of 5 years of hormonal therapy is now recommended.

Current treatment options for advanced breast cancer are only palliative. Breast cancers expressing estrogen receptors(ER) or progesterone receptors (PR) retain the intrinsic hormonal sensitivities of the normal breast—including the growth-stimulatory response to ovarian, adrenal, and pituitary hormones.

-Patients who show improvement with hormonal ablative procedures also respond to the addition of tamoxifen. The aromatase inhibitors anastrozole and letrozole are now approved as first-line therapy in women with advanced breast cancer whose tumors are hormone-receptor positive. In addition, these agents and exemestane are approved as second-line therapy following treatment with tamoxifen.

-Patients with significant involvement of the lung, liver, or brain and those with rapidly progressive disease rarely benefit from hormonal maneuvers, and initial systemic chemotherapy is indicated in such cases. The humanized monoclonal anti-HER-2/neu antibody, trastuzumab, is available for therapeutic use alone or in combination with cytotoxic chemotherapy.

-A broad range of anti-cancer agents have activity in this disease, including the anthracyclines (doxorubicin, mitoxantrone, and epirubicin), the taxanes (docetaxel, paclitaxel, and albumin-bound paclitaxel) along with the microtubule inhibitor ixabepilone, navelbine, capecitabine, gemcitabine, cyclophosphamide, methotrexate, and cisplatin. The anthracyclines and the taxanes are two of the most active classes of cytotoxic drugs.

PROSTATE CANCER



Prostate cancer was the second cancer shown to be responsive to hormonal manipulation. The treatment of choice for patients with metastatic prostate cancer is elimination of testosterone production by the testes through either surgical or chemical castration. Bilateral orchectomy or estrogen therapy in the form of diethylstilbestrol was previously used as first-line therapy. Presently, the use of luteinizing hormone-releasing hormone (LHRH) agonists including leuprolide and goserelin agonists, alone or in combination with an antiandrogen (eg, flutamide, bicalutamide, or nilutamide)—is the preferred approach.

Abiraterone, an inhibitor of steroid synthesis, has recently been approved. Hormonal treatment reduces symptoms and may cause a significant reduction in the prostate-specific antigen (PSA) level, which is now widely accepted as a surrogate marker for response to treatment in prostate cancer. Although initial hormonal manipulation is able to control symptoms for up to 2 years, patients usually develop progressive disease. Second-line hormonal therapies include aminoglutethimide plus

hydrocortisone, the antifungal agent ketoconazole plus hydrocortisone, or hydrocortisone alone. Unfortunately, nearly all patients with advanced prostate cancer eventually become refractory to hormone therapy. A regimen of mitoxantrone and prednisone is approved in patients with hormone-refractory prostate cancer because it provides effective palliation in those

who experience significant bone pain. Estramustine is an antimicrotubule agent that produces an almost 20% response rate as a single agent. However, when used in combination with either etoposide or a taxane such as docetaxel or paclitaxel, response rates are more than doubled to 40–50%. The combination of docetaxel and prednisone was recently shown to confer survival advantage when compared with the mitoxantrone-prednisone regimen, and this combination has now

become the standard of care for hormone-refractory prostate cancer.

Other types of cancers

GASTROINTESTINAL CANCERS	LUNG CANCER
<p>Colorectal cancer (CRC) is the most common type of gastrointestinal malignancy. At the time of initial presentation patients are potentially curable with surgery. Patients presenting with high-risk stage II disease and stage III disease are candidates for adjuvant chemotherapy with an oxaliplatin-based regimen in combination with 5-FU plus leucovorin (FOLFOX or FLOX) or with oral capecitabine (XELOX) and are generally treated for 6 months following surgical resection. Significant advances have been made over the past 10 years with respect to treatment of metastatic CRC. There are four active cytotoxic agents—5-FU, the oral fluoropyrimidine capecitabine, oxaliplatin, and irinotecan; and 5 active biologic agents—the anti-VEGF antibody bevacizumab; the recombinant fusion protein ziv-aflibercept that targets VEGF-A, VEGF-B, and PIGF; the anti- EGFR antibodies cetuximab and panitumumab; and the smallmolecule TKI inhibitor regorafenib.</p> <p>The incidence of gastric cancer, esophageal cancer, and pancreatic cancer is much lower than for CRC, but these malignancies tend to be more aggressive and result in greater tumor-related symptoms. In most cases, they cannot be completely resected surgically, as most patients present with either locally advanced or metastatic disease at the time of their initial diagnosis. 5-FU-based chemotherapy, using either intravenous 5-FU or oral capecitabine, is generally considered the main backbone for regimens targeting gastroesophageal cancers. In addition, cisplatin-based regimens in combination with either irinotecan or one of the taxanes (paclitaxel or docetaxel) also exhibit clinical activity. Recent studies have shown that the addition of the biologic agent trastuzumab to cisplatincontaining chemotherapy regimens provides significant clinical benefit in gastric cancer patients whose tumors overexpress the HER-2/neureceptor. Although gemcitabine is approved for use as a single agent in metastatic pancreatic</p>	<p>Lung cancer is divided into two main histopathologic subtypes, non-small cell(NSCLC) and small cell(SCLC). Non-small cell lung cancer includes adenocarcinoma, squamous cell cancer, and large cell cancer. The incidence of NSCLC more than SCLC. When NSCLC is diagnosed in an advanced stage with metastatic disease, the prognosis is extremely poor, with a median survival of about 8 months. It is clear that prevention (primarily through avoidance of cigarette smoking) and early detection remain the most important means of control. When diagnosed at an early stage, surgical resection results in patient cure. Adjuvant platinum-based chemotherapy provides a survival benefit in patients with pathologic stage IB, II, and IIIA disease. However, in most cases, distant metastases have occurred at the time of diagnosis. In certain instances, radiation therapy can be offered for palliation of pain, airway obstruction, or bleeding and to treat patients whose performance status would not allow for more aggressive treatments. In patients with advanced disease, systemic chemotherapy is generally recommended. Combination regimens that include a platinum agent (“platinum doublets”) appear superior to nonplatinum doublets, and either cisplatin or carboplatin are appropriate platinum agents for such regimens. For the second drug, paclitaxel and vinorelbine appear to have activity independent ofhistology, while the antifolate pemetrexed should be used for nonsquamous cell cancer, and gemcitabine for squamous cell cancer. For patients with good performance status and those with nonsquamous histology, the combination of the anti-VEGF antibody bevacizumab with carboplatin and paclitaxel is a standard treatment option. In patients deemed not to be appropriate candidates for bevacizumab therapy and those with squamous cell histology, a platinum-based chemotherapy regimen in combination with the anti-EGFR antibody cetuximab is a reasonable treatment strategy. Maintenance chemotherapy with pemetrexed is now used in patients with non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. Finally, first-line therapy with erlotinib significantly improves outcomes in NSCLC patients with sensitizing EGFR mutations.</p> <p>SCLC is usually exquisitely sensitive, at least initially, to</p>

<p>cancer. Intense efforts continue to be placed on incorporating gemcitabine into various combination regimens and on identifying novel agents that target signal transduction pathways thought to be critical for the growth of pancreatic cancer. One such agent is erlotinib. This agent is now approved for use in combination with gemcitabine in locally advanced or metastatic pancreatic cancer</p>	<p>platinum-based combination regimens, including cisplatin and etoposide or cisplatin and irinotecan. Unfortunately, drug resistance eventually develops in nearly all patients with extensive disease. When diagnosed at an early stage, this disease is potentially curable using a combined modality approach of chemotherapy and radiation therapy. Topotecan is used as second-line monotherapy in patients who have failed a platinum-based regimen.</p>
<p>OVARIAN CANCER</p>	<p>TESTICULAR CANCER</p>
<p>Ovarian cancer remains occult and becomes symptomatic only after it has already metastasized to the peritoneal cavity. At this stage, it usually presents with malignant ascites. It is important to accurately stage this cancer with laparoscopy, ultrasound, and CT scanning. Patients with stage I disease appear to benefit from whole-abdomen radiotherapy and may receive additional benefit from combination chemotherapy with cisplatin and cyclophosphamide. Combination chemotherapy is the standard approach to stage III and stage IV disease. More recently, carboplatin plus paclitaxel has become the treatment of choice. In patients who present with recurrent disease, topotecan, altretamine, or liposomal doxorubicin are used as single agent monotherapy.</p>	<p>The introduction of platinum-based combination chemotherapy has made an impressive change in the treatment of patients with advanced testicular cancer. Presently, chemotherapy is recommended for patients with stage IIC or stage III seminomas and nonseminomatous disease. In patients with good risk features, three cycles of cisplatin, etoposide, and bleomycin (PEB protocol) or four cycles of cisplatin and etoposide yield virtually identical results. In patients with high-risk disease, the combination of cisplatin, etoposide, and ifosfamide can be used as well as etoposide and bleomycin with high-dose cisplatin.</p>
<p>MALIGNANT MELANOMA</p>	<p>BRAIN CANCER</p>
<p>Malignant melanoma is curable with surgical resection when it presents locally. However, once metastasis has occurred, it is one of the most difficult cancers to treat because of drug resistance. While dacarbazine, temozolamide, and cisplatin are the most active cytotoxic agents for this disease, the overall response rates to these agents remain low. Biologic agents, including interferon-α and interleukin-2 (IL-2), have greater activity than traditional cytotoxic agents, and treatment with high-dose IL-2 has led to cures. Ipilimumab is the most recent biologic agent to have been approved for metastatic melanoma. Vemurafenib, dabrafenib and trametinib have also been approved for metastatic melanoma.</p>	<p>Chemotherapy has had only limited efficacy in the treatment of malignant gliomas. Given their ability to cross the blood-brain barrier, the nitrosoureas have historically been the most active agents in this disease. Carmustine (BCNU) has been used as a single agent, or lomustine (CCNU) can be used in combination with procarbazine and vincristine (PCV regimen). In addition, the alkylating agent temozolamide is active when combined with radiotherapy and is also used in patients with newly diagnosed glioblastoma multiforme (GBM) as well as in those with recurrent disease. The histopathologic subtype oligodendrogloma has been shown to be especially chemosensitive, and the PCV combination regimen is the treatment of choice for this disease. It is now well-established that the anti-VEGF antibody bevacizumab alone or in combination with chemotherapy has documented clinical activity in adult GBM. Bevacizumab is presently approved as a single agent for adult GBM in the setting of progressive disease following first-line chemotherapy.</p>

SECONDARY MALIGNANCIES & CANCER CHEMOTHERAPY

The development of secondary malignancies is a late complication of the alkylating agents and the epipodophyllotoxin etoposide. For both drug classes, the most frequent secondary malignancy is acute myelogenous leukemia (AML). In general, AML develops in up to 15% of patients with Hodgkin's lymphoma who have received radiotherapy plus MOPP chemotherapy and in patients with multiple myeloma, ovarian carcinoma, or breast carcinoma treated with melphalan. The increased risk of AML is observed as early as 2–4 years after the initiation of chemotherapy and typically peaks at 5 and 9 years. With improvements in the clinical efficacy of various combination chemotherapy regimens resulting in prolonged survival and in some cases actual cure of cancer, the issue of how second cancers may affect long-term survival assumes greater importance. There is already evidence that certain alkylating agents (eg, cyclophosphamide) may be less carcinogenic than others (eg, melphalan). In addition to AML, other secondary malignancies have been well-described, including non-Hodgkin's lymphoma and bladder cancer, the latter most typically associated with cyclophosphamide therapy.

Terminology::

- Ability to undergo repeated cycles of proliferation as well as to migrate to distant sites in the body to colonize various organs in the process called *metastasis*.
- anti-cancer drugs exert their action on cells traversing the cell cycle and are called cell **cycle-specific (CCS) drugs** “more sensitive”

- **CCNS** drugs can kill both G0 and cycling cells.
- ***inherent resistance*** refers to drug resistance in the absence of prior exposure to available standard agents.
- ***acquired resistance*** develops in response to exposure to a given anti-cancer agent.
- ***cross-resistant*:** tolerance (as of a virus) to a usually toxic substance (as an antibiotic) that is acquired not as a result of direct exposure but by exposure to a related substance
- ***Synergies*** : the interaction of two or more agents so that their combined effect is greater than sum of their individual effects.



55. Immunopharmacology

Agents that suppress the immune system play an important role in preventing the rejection of organ or tissue grafts and in the treatment of certain diseases that arise from dysregulation of the immune response.

Agents that augment the immune response or selectively alter the balance of various components of the immune system are also becoming important in the management of certain diseases such as cancer, AIDS, and autoimmune or inflammatory diseases. A growing number of other conditions (infections, cardiovascular diseases, organ transplantation) may also be candidates for immune manipulation.

Immunosuppressive therapy

GLUCOCORTICOIDS

Class of drug	Mechanism of action	Uses
IMMUNOSUPPRESSIVE THERAPY	Not direct cytotoxic , it modify cellular functions , interfere with the cell cycle of activated	idiopathic thrombocytopenic purpura



lymphoid cells and cytotoxic to certain subsets of T cells.

Reduction of the size and lymphoid content of the lymph nodes and spleen.
no toxic effect on proliferating myeloid or erythroid stem cells in the bone marrow.

and rheumatoid arthritis.

Glucocorticoids modulate allergic reactions and are useful in the treatment of diseases like asthma or as premedication for other agents (eg, blood products, chemotherapy) that might cause undesirable immune responses.

CALCINEURIN INHIBITORS

Drug	Mechanism of Action	Adverse Effects	Uses
Cyclosporine	Cyclosporine is a peptide antibiotic that appears to act at an early stage in the antigen receptor-induced differentiation of T cells and blocks their activation by binding to cyclophilin, a member of a class of	nephrotoxicity, hypertension, hyperglycemia, liver dysfunction, hyperkalemia, altered mental status, seizures, and hirsutism. Cyclosporine causes very little bone marrow toxicity. While an increased incidence of	intravenously or orally for treatment of graft-versus-host (GVH) disease after hematopoietic stem cell transplantation, and in the treatment of selected autoimmune disorders. Cyclosporine ophthalmic solution is now

Tacrolimus

tacrolimus binds to the immunophilin FK-binding protein (FKBP which inhibit calcineurin, which is necessary for the activation of the T-cell-specific transcription factor NF-AT).

On a weight basis, tacrolimus is 10–100 times more potent than cyclosporine in inhibiting immune responses.

Pharmacokinetics:
orally or

intracellular proteins called immunophilins.

Cyclosporine and cyclophilin form a complex that inhibits the cytoplasmic phosphatase, calcineurin, which is necessary for the activation of a T-cell-specific transcription factor.

lymphoma and other cancers (Kaposi's sarcoma, skin cancer) have been observed in transplant recipients receiving cyclosporine, other immunosuppressive agents may also predispose recipients to cancer

Its toxic effects are similar to those of cyclosporine and include nephrotoxicity, neurotoxicity, hyperglycemia, hypertension, hyperkalemia, and gastrointestinal complaints.

available for severe dry eye syndrome, as well as ocular GVH disease.

Inhaled cyclosporine is being investigated for use in lung transplantation

. Tacrolimus is utilized for the same indications as cyclosporine, particularly in organ and stem cell transplantation.

Effective therapy for preventing rejection in solid-organ transplant patients even after failure of standard rejection therapy, including anti-T cell antibodies.

A standard prophylactic agent (usually in combination with

	<p>intravenously. The half-life of the intravenous form is approximately 9–12 hours.</p> <p>Like cyclosporine, tacrolimus is metabolized primarily by P450 enzymes in the liver, and there is potential for drug interactions.</p> <p>The dosage is determined by trough blood level at steady state.</p>	<p>methotrexate or mycophenolate mofetil) for GVHD disease.</p> <p>Tacrolimus ointment is currently used in the therapy of atopic dermatitis and psoriasis.</p>
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PROLIFERATION SIGNAL INHIBITORS

<i>Drugs</i>	<i>Mechanism of action</i>	<i>Uses</i>	<i>Adverse Effects</i>	<i>Pharmacokinetics</i>
Sirolimus (rapamycin) and its derivative Everolimus.	PSIs bind the circulating immunophilin FK506-binding protein 12, resulting in an active complex that blocks the molecular target of rapamycin (mTOR).	Sirolimus has been used effectively alone and in combination with other immunosuppressants to prevent rejection of solid organ allografts.	profound myelosuppression (especially thrombocytopenia), hepatotoxicity, diarrhea, hypertriglyceridemia, pneumonitis, and headache . increased use in stem	Sirolimus is available only as an oral drug. Its half-life is about 60 hours. everolimus is about 43 hours. Substrates for

	<p>The mTOR is a key component of a complex intracellular signaling pathway involved in cellular processes such as cell growth and proliferation, angiogenesis, and metabolism. Thus, blockade of mTOR ultimately can lead to inhibition of interleukin-driven T-cell proliferation. may inhibit B-cell proliferation and immunoglobulin production.</p>	<p>It is used as prophylaxis and as therapy for steroid refractory acute and chronic GVH disease in hematopoietic stem cell transplant recipients</p> <p>Topical sirolimus is also used in some dermatologic disorders and, in combination with cyclosporine, in the management of uveoretinitis</p>	<p>cell transplantation regimens as GVH disease prophylaxis, particularly when combined with tacrolimus, has revealed an increased incidence of hemolytic-uremic syndrome.</p>	<p>both cytochrome P450 3A and P-glycoprotein. Hence, significant drug interactions can occur.</p>
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MYCOPHENOLATE MOFETIL

Mechanism of Actions	Adverse Effects	Uses
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it inhibits T- and B-lymphocyte responses probably by inhibition of de novo synthesis of purines. Mycophenolate mofetil is hydrolyzed to mycophenolic acid, the active immunosuppressive moiety.

Mycophenolate mofetil is available in both oral and intravenous forms.

Toxicities include gastrointestinal disturbances (nausea and vomiting, diarrhea, abdominal pain) headache, hypertension, and reversible myelosuppression (primarily neutropenia).

the first-line drug for preventing or reducing chronic allograft vasculopathy in cardiac transplant recipients.

used as prophylaxis for and treatment of both acute and chronic GVH disease in hematopoietic stem cell transplant patient.

Lupus nephritis, rheumatoid arthritis, inflammatory bowel disease, and somedermatologic disorders.

THALIDOMIDE

Mechanism of action

It inhibits tumor necrosis factor-alpha (TNF- α), reduces phagocytosis by neutrophils, increases production of IL-10, alters adhesion molecule expression, and enhances cell-mediated immunity via interactions with T cells.

Used in the treatment of multiple myeloma at initial diagnosis and for relapsed-refractory disease. Treatment of some manifestations of leprosy and has been for erythema nodosum leprosum; it is also useful in management of the skin manifestations of lupus erythematosus.

Lenalidomide to treat multiple myeloma.

Use

Adverse Effects

The most important toxicity is teratogenesis.

Other adverse effects of thalidomide include peripheral neuropathy, constipation, rash, fatigue, hypothyroidism, and increased risk of deep vein thrombosis.

CYTOTOXIC AGENTS

Drugs	Mechanism of action	Clinical Uses	Adverse Effects
Azathioprine	<p>Prodrug of mercaptopurine and, like mercaptopurine, functions as an antimetabolite.</p> <p>interfering with purine nucleic acid metabolism at steps that are required for the wave of lymphoid cell proliferation that follows antigenic stimulation.</p> <p>The purine analogs are thus cytotoxic agents that destroy stimulated lymphoid cells.</p>	<p>management of acute glomerulonephritis, in the renal component of systemic lupus erythematosus, and in some cases of rheumatoid arthritis, Crohn's disease, and multiple sclerosis.</p> <p>Use in prednisone-resistant antibody-mediated idiopathic thrombocytopenic purpura and autoimmune hemolytic anemias.</p>	<p>bone marrow suppression, usually manifested as leukopenia, although anemia and thrombocytopenia may occur.</p> <p>gastrointestinal symptoms such as Skin rashes, fever, nausea and vomiting, and sometimes diarrhea.</p>
Cyclophosphamide	<p>destroys proliferating lymphoid cells but also appears to alkylate some resting cells</p>	<p>In smaller doses, it has been effective against autoimmune disorders (including systemic lupus erythematosus) and in patients with acquired factor XIII antibodies and bleeding syndromes, autoimmune hemolytic anemia, antibody-induced pure red cell aplasia, and Wegener's granulomatosis.</p>	<p>Induce considerable risk of pancytopenia and therefore is generally combined with stem cell rescue (transplant) procedures.</p> <p>may also cause hemorrhagic cystitis, which can be prevented or treated with mesna.</p> <p>Other adverse effects include nausea, vomiting, cardiac toxicity, and electrolyte disturbances.</p> <p>Elevation of liver enzymes with some risk of liver damage.</p>
Pyrimidine Synthesis Inhibitors (Leflunomide, Teriflunomide)	<p>inhibit the mitochondrial enzyme dihydroorotate dehydrogenase, which is involved in pyrimidine synthesis and ultimately results in decreased</p>	<p>Use rheumatoid arthritis at present</p> <p>Leflunomide with Mycophenolate Mofetil combined can be used for a</p>	<p>Renal impairment</p>



Hydroxychloroquine

lymphocyte activation.

They have anti-inflammatory activity in addition to immunomodulatory properties.

Pharmacokinetics :

Leflunomide is orally active, and the active metabolite has a long half-life of several weeks. Thus, the drug should be started with a loading dose, but it can be taken once daily after reaching steady state.

Leflunomide also appears to have antiviral activity.

an antimalarial agent with immunosuppressant properties.

suppress intracellular antigen processing and loading of peptides onto MHC class II molecules by increasing the pH of lysosomal and endosomal compartments, thereby decreasing T-cell activation.

Other Cytotoxic Agents(methotrexate, vincristine, Cytarabine and Pentostatin)

Pentostatin an adenosine deaminase inhibitor

variety of autoimmune and inflammatory skin disorders, as well as preservation of allografts in solid organ transplantation.

This drug is teratogenic and contraindicated in pregnancy

Teriflunomide is Used for treatment of relapsing-remitting multiple sclerosis (decrease the number of activated lymphocytes in the central nervous system)

used to treat some autoimmune disorders(eg, Rheumatoid Arthritis and Systemic Lupus Erythematosus)

It has also been used to both treat and prevent GVH disease after allogeneic stem cell transplantation.

Methotrexate has been used extensively in rheumatoid arthritis and in the treatment of GVH disease specially in patient idiosyncratic reactions to purine antagonists.

Vincristine is quite useful in idiopathic thrombocytopenic

purpura refractory to prednisone.

Pentostatin used mainly as an antineoplastic agent for lymphoid malignancies; it produces a profound lymphopenia, and now frequently used for steroid-resistant GVH disease after allogeneic stem cell transplantation, as well as in preparative regimens prior to those transplants to provide severe immunosuppression to prevent allograft rejection.

Miscellaneous Agents: all following agents used exclusively in the treatment of relapsing remitting multiple sclerosis.

- **Dimethylfumarate (DMF)** used orally and Its exact mechanism of action is unknown, though it appears to activate the nuclear factor (erythroid-derived)-like-2 (NFR-2) transcriptional pathway. it also appears to help protect the nerve cells from inflammation.
Adverse effects : Lymphopenia, Flushing is common. Other less common adverse effects include nausea, diarrhea, abdominal pain , increased hepatic enzymes, and eosinophilia.
- **Glatiramer acetate (GA)** is given as a subcutaneous injection and its mechanism is unknown but Studies suggest that GA downregulates the immune response to myelin antigens by induction and activation of suppressor T-cells that migrate to the central nervous system. Adverse effects: skin hypersensitivity, flushing, chest pain, dyspnea, throat constriction, and palpitations, all of which are usually mild and self-limited.
 - **Fingolimod hydrochloride (FH)** is an orally active sphingosine 1-phosphate (S1P) receptor modulator which controls the release of lymphocytes from lymph nodes and the thymus. drug is metabolized primarily by the cytochrome P450 system; thus caution is needed when it is used in combination with other drugs metabolized in the same manner. Adverse effects : including bradycardia, prolongation of the QT interval, and other arrhythmias. FH is contraindicated in patients with preexisting conditions such as type II or III heart block, prolonged QTc, recent myocardial infarction, or heart failure. Less common adverse effects include macular edema, elevated hepatic enzymes, headache, diarrhea, and cough.

IMMUNOSUPPRESSIVE ANTIBODIES

Drugs	Mechanism of Action	Uses	Adverse effects
Antilymphocyte & Antithymocyte Antibodies, & Chimeric Molecules	<p>Antilymphocyte globulin (ALG) and antithymocyte globulin (ATG) are now in clinical use in especially in transplantation programs.</p> <p>ALG acts primarily on the small, long-lived peripheral lymphocytes and T lymphocytes that circulate between the blood and lymph which result of the destruction or inactivation of T cells..</p>	<p>Management of solid organ and bone marrow transplantation .</p> <p>used in the induction of immunosuppression, in the treatment of initial rejection, and in the treatment of steroid-resistant rejection</p>	<p>Local pain and erythema often occur at the injection site (type III hypersensitivity).</p> <p>Anaphylactic and serum sickness reactions.</p> <p>kidney damage may occur due to complexes of host antibodies with horse ALG may precipitate and localize in the glomeruli.</p>
Immune Globulin Intravenous (IGIV)	<p>intravenous use of polyclonal human immunoglobulin (usually IgG)</p> <p>mechanism of action is still unknown, Possible mechanisms are a reduction of T helper cells, increase of regulatory T cells, decreased spontaneous immunoglobulin production, Fc receptor blockade, increased antibody catabolism, and idiotypic-anti-idiotypic interactions with “pathologic antibodies.”</p>	<p>variety of different applications ranging from immunoglobulin deficiencies to autoimmune disorders to HIV disease to bone marrow transplantation.</p> <p>Also used for treatment of Kawasaki’s disease, systemic lupus erythematosus and refractory idiopathic thrombocytopenic purpura.</p>	-



Rho(D) Immune Globulin	An injection of Rho(D) antibody is administered to the Rh-negative mother within 24–72 hours after the birth of an Rh-positive infant, the mother's own antibody response to the foreign Rho(D)-positive cells is suppressed because the infant's red cells are cleared from circulation before the mother can generate a B-cell response against Rho(D). Therefore she has no memory B cells that can activate upon subsequent pregnancies with an Rho(D)-positive fetus.	<i>Treatment is for Rh-negative mothers antepartum at 26–28 weeks' gestation who have had miscarriages, ectopic pregnancies, or abortions, when the blood type of the fetus is unknown.</i>	Infrequent and consist of local discomfort at the injection site or, rarely, a slight temperature elevation.
Hyperimmune Immunoglobulins	Intravenous administration of the hyper immune globulins is a passive transfer of high titer antibodies that either reduces risk or reduces the severity of infection.	Treatment of respiratory syncytial virus, cytomegalovirus, varicella zoster, human herpesvirus 3, hepatitis B virus, rabies, tetanus, and digoxin overdose. Rattlesnake and coral snake hyperimmune globulins (antivenoms)	

MONOCLONAL ANTIBODIES (MABS)

Antitumor MABs

<i>Drugs</i>	<i>Mechanism of Action</i>	<i>Clinical Uses</i>	<i>Adverse effect</i>
Alemtuzumab	-	Treatment of B-cell chronic lymphocytic leukemia (CLL) in patients who have been treated with alkylating agents and have failed fludarabine therapy by	Lymphopenia , neutropenia, anemia, and thrombocytopenia.

		causing the leukemic and normal cells to direct antibody-dependent lysis.	
		Relapsing remitting multiple sclerosis by depleting autoimmune inflammatory T and B cells while the drug is in the circulation.	
Bevacizumab	Binds to vascular endothelial growth factor (VEGF) and inhibits VEGF from binding to its receptor, especially on endothelial cells therefore inhibit growth of blood vessels (angiogenesis) in tumors	treatment of patients with metastatic colorectal cancer alone or in combination with appropriate chemotherapy treatment of non-small cell lung cancer, glioblastoma multiforme that has progressed after prior treatment, and metastatic kidney cancer when used with interferon-alfa. Off label use : intravitreal injection to slow progression of neovascular macular degeneration	Possible AE Include : hemorrhage, gastrointestinal perforations, and wound healing problems
Catumaxomab	IgG hybrid monoclonal antibody that targets the epithelial cell adhesion molecule (EpCAM) on tumor cells and the CD3 protein on T cells.	treating abdominal ascites in ovarian and gastric cancers	-
Cetuximab	Its chimeric monoclonal antibody that targets , bind and inhabit epidermal growth factor receptor (EGFR) which result inhabiting tumor cell growth by a variety of mechanisms, including decreases in kinase activity, matrix metalloproteinase activity, and growth factor production, and increased apoptosis.	used in patients with EGFR-positive head and neck squamous cell carcinoma in combination with radiotherapy or appropriate chemotherapy. It is also approved for treatment of kRas-negative, EGFR-positive metastatic colorectal cancer in combination with radiotherapy or appropriate chemo- therapy, or as a single agent in patients who cannot tolerate certain chemotherapies	-
Ofatumumab	Binds and lysis all B cells including B-CLL along with antibody-dependent cellular	Use patients with CLL who are refractory to fludarabine and alemtuzumab.	Risk of hepatitis B virus reactivation



Panitumumab	<p>cytotoxicity.</p> <p>binds to EGFR inhibiting epidermal growth factor from binding to its receptor, and prevents ligand-induced receptor autophosphorylation and activation of receptor-associated kinases , which result inhibition cell growth, induces apoptosis, decreases vascular growth factor production, and suppresses internalization of the EGFR.</p>	<p><i>treatment of EGFR-expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan- containing chemotherapy regimens.</i></p>	infusion-related toxicities are common
Pertuzumab	<p>suppresses tumor growth by preventing of the human epidermal growth factor receptor HER-2/neu with other HER family members, thus inhibiting ligand-mediated intracellular signaling through MAP kinase and PI3 kinase pathways , also mediates antibody-dependent cell-mediated cytotoxicity on HER-2/neu-positive tumor cells.</p>	<p><i>treatment of metastatic or locally advanced HER-2/neu-positive breast cancer in combination with trastuzumab (see below) and docetaxel as neoadjuvant therapy</i></p>	
Rituximab	<p>Complement-mediated lysis, antibody-dependent cellular cytotoxicity, and induction of</p>	<p>CD20-positive large-B-cell diffuse non-Hodgkin's lymphoma, and relapsed or refractory low-grade or follicular B-cell non-</p>	Anemia , neutropenia, Hypotension, rash, gastrointestinal disturbance, fever and fatigue.

	<p>apoptosis in malignant lymphoma cells and in B cells involved in the pathogenesis.</p>	<p>Hodgkin's lymphoma as a single agent or in combination with appropriate chemotherapy</p> <p>treatment of CLL in combination with chemotherapy.</p> <p>treatment of rheumatoid arthritis in combination with methotrexate in patients for whom anti-TNF-α therapy has failed.</p> <p>Treatment of Wegener's granulomatosis and microscopic polyangiitis.</p>	
Trastuzumab	<p>binds to the extracellular domain of HER-2/neu and blocks the natural ligand from binding and down-regulates the receptor.</p>	<p>treatment of HER-2/neu-positive tumors in patients with breast cancer and patients with metastatic gastric or gastroesophageal junction adenocarcinoma.</p>	Potential cardiomyopathy

❖ MABs Used to Deliver Isotopes & Toxins to Tumors

Drugs	Mechanism of Action	Uses	Adverse Effects
Ado-trastuzumab emtansine	<p>antibody-drug conjugate in which the anti-HER-2/neu antibody, and trastuzumab is the drug.</p>	<p>Use patients with HER-2/neu-positive breast cancer who have previously received trastuzumab and a taxane separately or in combination, and whose disease recurred or progressed during prior treatment</p>	<p>identical to trastuzumab alone, also include hepatotoxicity due to emtansine.</p>

Arcitumomab	Fab fragment from an anti-carcinoembryonic antigen (CEA) antibody.	used for imaging patients with metastatic colorectal carcinoma (immonoscintigraphy) to determine extent of disease. CEA is often upregulated in patients with gastrointestinal carcinomas
Brentuximab vedotin	antibody-drug conjugate that binds CD30 (a cell surface marker in the TNF receptor superfamily that is expressed lymphomas and on activated leukocytes) and induce cell cycle arrest and apoptosis.	Hodgkin's lymphoma after failure of autologous stem cell transplantation or after failure of at least two previous chemotherapy regimens. systemic anaplastic large cell lymphoma after failure of at least one previous multiagent chemotherapy regimen
Capromab pendetide	murine monoclonal antibody specific for prostate specific membrane antigen.	used in immonoscintigraphy for patients with biopsy-confirmed prostate cancer and post-prosta- tectomy in patients with rising prostate specific antibody level to determine extent of disease.
Ibritumomab tiuxetan	an anti-CD20 murine monoclonal antibody. The	relapsed or refractory low-grade, follicular, or B-cell non-Hodgkin's lymphoma, including patients with rituximab-



radiation of the isotope coupled to the antibody provides the major antitumor activity of this drug.

refractory follicular disease.
used in conjunction with rituximab in a two-step therapeutic regimen.

❖ MABs Used as *Immunosuppressants & Anti-Inflammatory Agents*

<i>Drugs</i>	<i>Mechanism of Action</i>	<i>Uses</i>
<i>Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab</i>	Antibodies bind TNF- α , a proinflammatory Cytokine	<i>for Rheumatoid arthritis and similar inflammatory diseases</i>
<i>Alefacept</i>	It inhibits activation of T cells by binding to cell surface CD2, inhibiting the normal CD2/LFA-3 interaction.	<i>Treatment of plaque psoriasis</i>
<i>Basiliximab</i>	IgG1 that binds to CD25, the IL-2 receptor alpha chain on activated lymphocytes.	rheumatoid and other forms of arthritis
<i>Daclizumab</i>	IgG1 that also binds to the α subunit of the IL-2 receptor. Both agents function as IL-2 antagonists,	Prophylaxis of acute organ rejection in renal transplant patients <i>used as part of an immunosuppressive regimen that also includes</i>



		blocking IL-2 from binding to activated lymphocytes, and IgG kappa chain monoclonal antibody that prevents IL-1 β from binding to its receptor.	<i>glucocorticoids and cyclosporine.</i>
Canakinumab			cryopyrin-associated periodic syndromes (CAPS) in adults and children 4 years old and older. CAPS includes familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and systemic juvenile idiopathic arthritis in children 2 years old or older.
Natalizumab		binds to α 7 integrins expressed on the surfaces of all leukocytes except neutrophils, and inhibits the α 4-mediated adhesion of leukocytes to their cognate receptor.	multiple sclerosis and Crohn's disease
Omalizumab		Antibody blocks the binding of IgE on basophils and mast cells, which suppresses IgE-mediated release of type I allergy mediators such as histamine and leukotrienes.	Allergic asthma in adult and adolescent patients whose symptoms are refractory to inhaled corticosteroids. The drug is also approved for chronic urticaria.
Ustekinumab		It blocks IL-12 and IL-23 from binding to their receptors, therefore inhibiting receptor-mediated signaling in lymphocytes.	adult patients with moderate to severe plaque psoriasis either alone or with methotrexate
Vedolizumab		antibody that targets the α 4 β 7 integrin in the gastrointestinal tract	<i>treatment of Crohn's disease and ulcerative colitis.</i>

Other MABs

<i>Drugs</i>	<i>Mechanism of Action</i>	<i>Uses</i>
Abciximab	Monoclonal antibody that binds to the integrin receptor on activated platelets and inhibits fibrinogen, von Willebrand factor, and other adhesion molecules from binding to activated platelets, thus preventing their aggregation	adjunct to percutaneous coronary intervention in combination with aspirin and heparin for the prevention of cardiac ischemic complications.
Denosumab	IgG2 monoclonal antibody that binds to RANKL and inhibits the maturation of osteoclasts, the cells responsible for bone resorption.	treatment of postmenopausal women with osteoporosis at high risk for fracture During treatment, patients should receive supplements of calcium and vitamin D.
Eculizumab	IgG monoclonal antibody that binds the C5 complement component, inhibiting its cleavage into C5a and C5b thereby inhibiting the terminal pore-forming lytic activity of complement.	paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). It dramatically reduces the need for red blood cell transfusions. It prevents PNH symptoms of anemia, fatigue, thrombosis, and hemoglobinemia by inhibiting intravascular hemolysis.
Palivizumab	IgG1 monoclonal antibody that binds to the fusion protein of respiratory syncytial virus (RSV).	neonates at risk for this viral infection and reduces the frequency of infection and hospitalization by about 50%
Ranibizumab	recombinant human IgG1 Fab that binds to VEGF-A. It prevents new blood vessel formation by blocking VEGF from binding to its receptor.	intravitreal injection in patients with neovascular age-related macular degeneration, diabetic macular edema, and sudden blurring or vision loss secondary to macular edema following retinal vein occlusion.
Raxibacumab	IgG1 chain monoclonal antibody that binds to the PA protein of <i>Bacillus anthracis</i> , preventing cellular entry of the anthrax toxins	treatment or prophylaxis of adults and children with inhalational anthrax in combination with appropriate antibacterial drugs.



■ CLINICAL USES OF IMMUNOSUPPRESSIVE DRUGS

Immunosuppressive agents are commonly used in two clinical circumstances: transplantation and autoimmune disorders.

SOLID ORGAN & BONE MARROW TRANSPLANTATION

Prior to transplant, patients may receive an immunosuppressive regimen, including antithymocyte globulin, daclizumab, or basiliximab.

Four types of rejection can occur in a solid organ transplant recipient: **hyperacute**, **accelerated**, **acute**, and **chronic**.

- Hyperacute rejection is due to preformed antibodies against the donor organ and cause rapid necrosis and failure of the transplanted organ , such as anti-blood group antibodies. Hyperacute rejection occurs within hours of the transplant and cannot be stopped with immunosuppressive drugs.
- Accelerated rejection is mediated by both antibodies and T cells, and it also cannot be stopped by immunosuppressive drugs.
- Acute rejection of an organoccurs within days to months and involves mainly cellular immunity.Reversal of acute rejection is usually possible with general immunosuppressive drugs such as azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, glucocorticoids, cyclophosphamide, methotrexate, and sirolimus.
- Chronic rejection usually occurs months or even yearsafter transplantation. It is characterized by thickening and fibrosisof the vasculature of the transplanted organ, involving both cellularand humoral immunity. Chronic rejection is treated with the samedrugs as those used for acute rejection.

Allogeneic hematopoietic stem cell transplantation is a well-established treatment for many malignant and nonmalignant diseases. An HLA-matched donor, usually a family member, is located, patients are conditioned with high-dose chemotherapy or radiation therapy, and then donor stem cells are infused.

GVH disease occurs even with administration of immunosuppressive therapy occurs because donor T cells fail to recognize the patient's skin, liver, and gut (usually) as self and attack those tissues.

Acute GVH disease occurs within the first 100 days, and is usually manifested as a skin rash, severe diarrhea, or hepatotoxicity.

Additional medications are added, invariably starting with high-dose corticosteroids, and adding drugs such as mycophenolate mofetil, sirolimus, tacrolimus, daclizumab, and others, with variable success rates.

Autoimmune Disorders

The use of immunosuppressive remissions can be obtained in many instances of autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, type 1 diabetes, Hashimoto's thyroiditis, and temporal arteritis.

Improvement is also often seen in patients with systemic lupus erythematosus, acute glomerulonephritis, acquired factor VIII inhibitors (antibodies), rheumatoid arthritis, inflammatory myopathy, scleroderma, and certain other autoimmune states.

■ IMMUNOMODULATION THERAPY

Cytokines : The cytokines are a large and heterogeneous group of proteins with diverse functions. In most instances, cytokines mediate their effects through receptors on relevant target cells with similar mechanism of action of hormones. In other instances, cytokines may have antiproliferative, antimicrobial, and antitumor effects.

- ❖ Groups of cytokines : interferons (IFNs), colony-stimulating factors (CSFs), interleukins (ILs).

Most cytokines have very short serum half-lives (minutes).

Interferons are proteins that are currently grouped into three families: IFN- γ , IFN- α , and IFN- β . The IFN- γ and IFN- α families IFNs interact with cell receptors to produce a wide variety of effects that depend on the cell and IFN types.

- IFN- α is approved for the treatment of several neoplasms, including hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma, and Kaposi's sarcoma, and for use in hepatitis B and C infections.
- IFN- β is approved for use in relapsing-type multiple sclerosis. IFN- γ is approved for the treatment of chronic granulomatous disease and IL-2, for metastatic renal cell carcinoma and malignant melanoma. Toxicities includes : fever, flu-like symptoms, anorexia, fatigue, and malaise.

Cytokines inhibitors :

Drugs	Mechanism of Action	Uses
Anakinra	Recombinant form of the naturally occurring IL-1 receptor antagonist that prevents IL-1 from binding to its receptor.	adult rheumatoid arthritis patients who have failed treatment with one or more disease-modifying antirheumatic drugs



Rilonacept

portions of the human interleukin-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) fused to the Fc portion of human IgG1.

treatment of cryopyrin-associated periodic syndromes.

■ IMMUNOLOGIC REACTIONS TO DRUGS & DRUG ALLERGY

Allergic drug reactions Includes :

❖ IMMEDIATE (TYPE I) DRUG ALLERGY

IgE-mediated acute allergic reactions to stings, pollens, and drugs, including anaphylaxis, urticaria, and angioedema. IgE is fixed to tissue mast cells and blood basophils, and after interaction with antigen the cells release potent mediators.

Drug treatment for immediate reaction :

One can test an individual for possible sensitivity to a drug by a simple scratch test,

Prednisone : it blocks proliferation of the IgE-producing clones and inhibits IL-4 production by T helper cells in the IgE response.

Epinephrine : opposes histamine; it relaxes bronchiolar smooth muscle and contracts vascular muscle, relieving both bronchospasm and hypotension. *epinephrine is the drug of choice in anaphylactic reactions.*

The antihistamines : competitively inhibit histamine, which would otherwise produce bronchoconstriction and increased capillary permeability in end organs.

Glucocorticoids: may also act to reduce tissue injury and edema in the inflamed tissue, as well as facilitating the actions of catecholamines in cells that may have become refractory to epinephrine or isoproterenol.

Desensitization to Drugs

When reasonable alternatives are not available, certain drugs (eg, penicillin, insulin) must be used for life-threatening illnesses even in the presence of known allergic sensitivity. In such cases, desensitization (also called hyposensitization) can sometimes be accomplished by starting with very small doses of the drug and gradually increasing the dose over a period of hours or days to the full therapeutic range .

It is thought that slow and progressive administration of the drug gradually binds all available IgE on mast cells, triggering a gradual release of granules.

❖ AUTOIMMUNE (TYPE II) REACTIONS TO DRUGS

These allergic responses involve IgG or IgM in which the antibody becomes fixed to a host cell, which is then subject to complement dependent lysis or to antibody-dependent cellular cytotoxicity.

Certain autoimmune syndromes can be induced by drugs. Examples include

- systemic lupus erythematosus following hydralazine or procainamide therapy
- “lupoid hepatitis” due to cathartic sensitivity,
- autoimmune hemolytic anemia resulting from methyldopa administration.
- thrombocytopenic purpura due to quinidine
- agranulocytosis due to a variety of drugs

Fortunately, autoimmune reactions to drugs usually subside within several months after the offending drug is withdrawn. Immunosuppressive therapy is warranted only when the autoimmune response is unusually severe.

❖ SERUM SICKNESS & VASCULITIC (TYPE III) REACTIONS

- Drugs may cause serum sickness, which involves immune complexes containing IgG complexed with a foreign antigen and is a multisystem complement-dependent vasculitis that may also result in urticaria.
- The clinical features of serum sickness include urticarial and erythematous skin eruptions, arthralgia or arthritis, lymphadenopathy, glomerulonephritis, peripheral edema, and fever.
- The reactions generally last 6–12 days and usually subside once the offending drug is eliminated.
- Stevens–Johnson syndrome is probably a more severe form of this hypersensitivity reaction and consists of erythema multiforme, arthritis, nephritis, central nervous system abnormalities, and myocarditis. It has frequently been associated with sulfonamide therapy.
- Administration of nonhuman monoclonal or polyclonal antibodies such as rattlesnake antivenom may cause serum sickness.
- Glucocorticoids are useful in attenuating severe serum sickness reactions to drugs. In severe cases

plasmapheresis can be used to remove the offending drug and immune complexes from circulation.

- ❖ **Type IV:** Cell-mediated allergy is the mechanism involved in allergic contact dermatitis from topically applied drugs or induration of the skin at the site of an antigen injected intradermally.

section 9

TOXICOLOGY

56 - Introduction to Toxicology: Occupational & Environmental .

57 - Heavy Metal Intoxication &Chelators .

58 - Management of the Poisoned Patient

Section IX: Toxicology

Chapter 56: Introduction to Occupational & Environmental

The occupational- environmental toxicologist is primarily concerned with adverse effects in humans resulting from exposure to chemicals encountered in the environment. He must identify and treat hazards associated with chemicals. Occupational and environmental exposure is rarely limited to single type of molecule.

Occupational toxicology:

The major emphasis is to identify the agent of concern, identify the acute and chronic disease that they cause, define the conditions under which they may be used safely and prevent absorption of harmful amounts.

Toxicologists may also carry out programs for surveillance of exposed workers. They frequently work hand in hand with occupational hygienists and certified professionals in their activities.

Occupational safety and healthadmiration (OSHA) promulgates standards for specific materials of particularly serious toxicity. Such standards have the force of law and employers who use these materials are obligated to comply with the standards.

Voluntary organizations such as American Conference Of Governmental Industrial Hygienists (ACGHI) prepare lists of recommended **threshold limit values (TLVs)** for many chemicals. The ACGHI TLV guidelines are useful as reference points in the evaluation of potential work-place exposures.

Environmental toxicology:

It deals with the potentially deleterious impact of chemicals, present as pollutants. The term environment includes all the surrounding of an individual organism. Air pollution is usually a product of

industrialization, technologic development. The United Nations Food And Agriculture Organization And The World Health Organization (FAO\WHO) Joint Expert Commission Of Food Additives adopted the term acceptable daily intake (ADI) to denote the daily intake of a chemical form food.

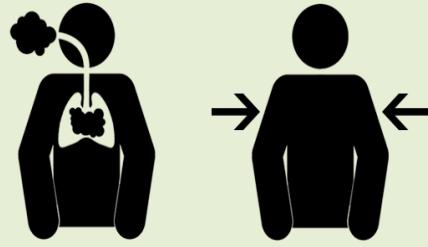
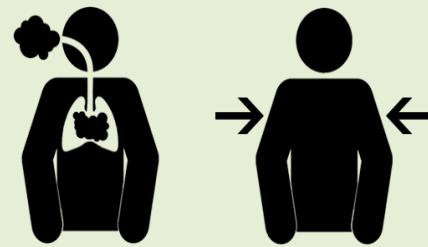
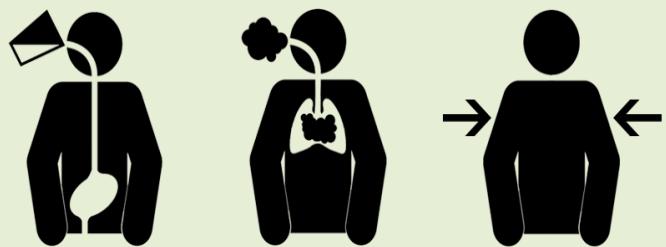
Ecotoxicology:

Ecotoxicology is concerned with the impact on population of living organisms or on ecosystems.

Toxicological terms and definitions

Hazard & Risk:

- ❖ Hazard is the ability of a chemical agent to cause injury in a given situation. To assess hazard, one needs to have knowledge about:
 - 1- The inherent toxicity of the substance
 - 2- The amounts to which individuals are liable to be exposed.
- ❖ Hazard is based on subjective estimates rather than objective evaluation.
- ❖ Risk is defined as the expected frequency of the occurrence of an undesirable effect arising from exposure to a chemical or physical agent. Estimation of risk makes use of dose-response data and extrapolation from the observed relationships to the expected responses at doses occurring in actual exposure situations. The quality and suitability of the biologic data are major limiting factors. Only long-term observation of population causes and outcomes will provide the basis for validation of newer risk assessment technologies.

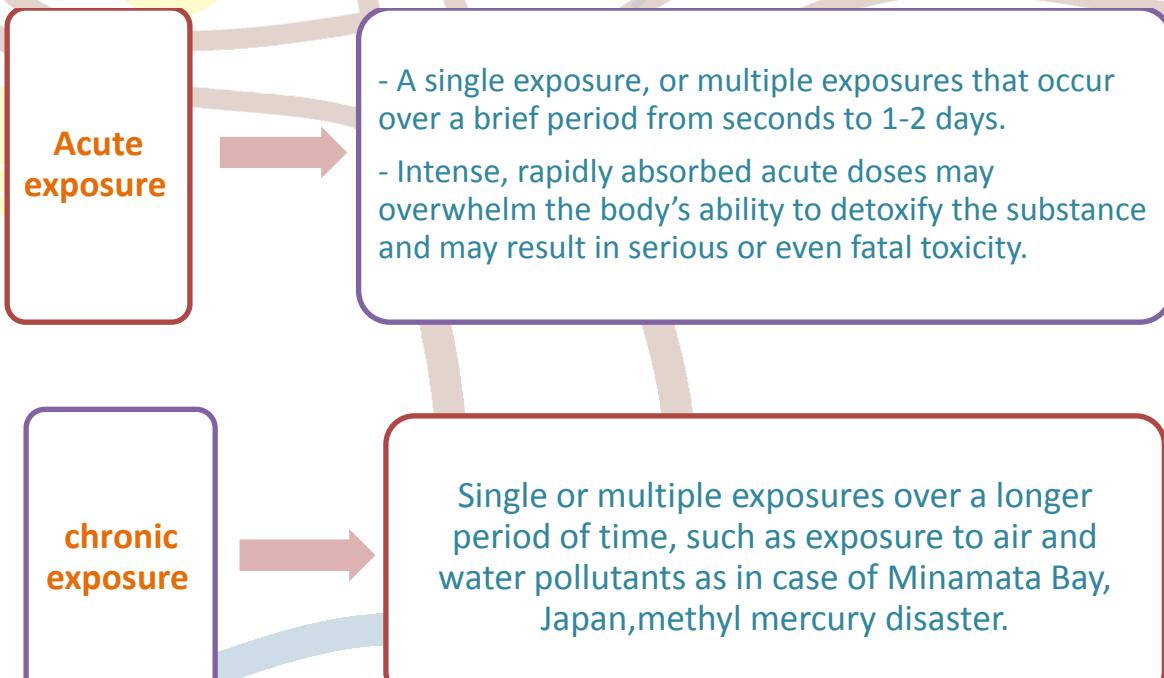
<u>Rout of Exposure</u>	Industrial	
	Atmospheric	
	Water & soil pollutants	

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Quantity, Duration, & Intensity of Exposure

Toxic reactions depend on:

- 1- quantity of exposure,
- 2- duration
- 3- rate at which the exposure takes place



Environmental considerations:

- Certain chemical and physical characteristics are important for the estimation of the potential hazard of environmental toxicants.
- Poorly degraded chemicals exhibit environmental persistence and can accumulate. Such as organic pollutants (POPs), polychlorinated biphenyls, dioxins and furans.
- Lipophilic substances such as organochlorine pesticides tend to bioaccumulate in body fat.

When the toxicant is incorporated into the food chain, biomagnification occurs.

What are Bioaccumulation and Biomagnification?

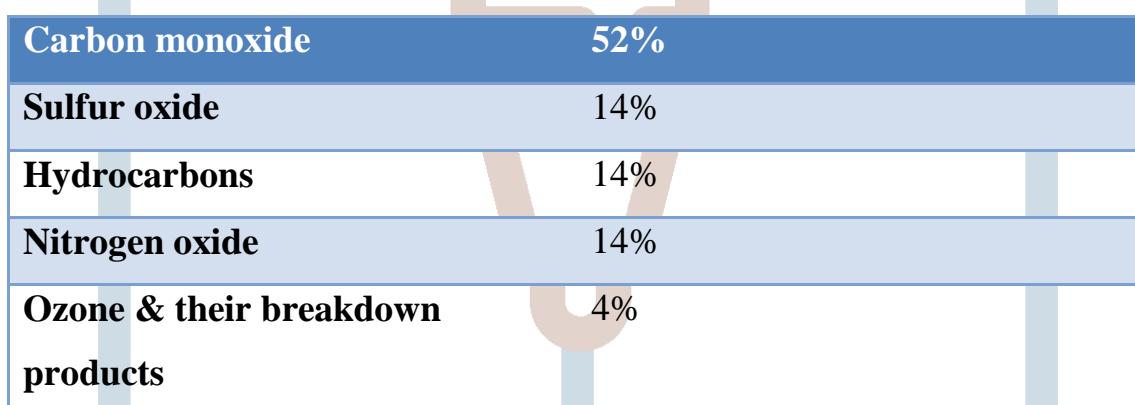
- If the intake of a long-lasting contaminant by an organism exceeds the latter's ability to metabolize or excrete the substance, the chemical accumulates within the tissues of the organism. This is called **bioaccumulation**.
- The concentration of a contaminant may be virtually undetectable in water; it may be magnified hundreds or thousands of times as the contaminant passes up the food chain. This is called **biomagnification**.

SPECIFIC CHEMICALS

AIR POLLUTANTS:

- Result from vapors, aerosols, smokes, particulates, and individual chemicals.

About 98% of air pollution:



- ✓ Sources of pollutants include fossil fuel burning, transportation, manufacturing, and other industrial activities.

- ✓ The introduction of “clean, low-sulfur” diesel fuels is helping to reduce urban and highway pollutants such as sulfur oxides.
- ✓ In addition, the ban on tetraethyl lead in gasoline has eliminated a major source of lead contamination.

A) Carbon Monoxide	B) Sulfur Dioxide
<ul style="list-style-type: none"> Carbon monoxide (CO) is a colorless, tasteless, odorless, and nonirritating gas, a byproduct of incomplete combustion. The average concentration of CO in the atmosphere is about 0.1 ppm; 	<ul style="list-style-type: none"> Sulfur dioxide (SO₂) is a colorless irritant gas generated primarily by the combustion of sulfur-containing fossil fuels.
<u>The mechanism of action</u>	<p>1- CO combines tightly but reversibly in high affinity with the oxygen-binding sites of hemoglobin.</p> <p>2- The presence of carboxyhemoglobin interferes with the dissociation of oxygen from the remaining oxyhemoglobin as a result of the Bohr Effect, which will result in damaging the brain, heart and kidneys.</p> <ul style="list-style-type: none"> A person who breathes air that contains 0.1% CO (1000 ppm) would have a carboxyhemoglobin level of about 50% in a short period of time.
<u>Clinical</u>	<p>The signs are: 1- hypoxia, 2-</p> <p>-The signs and symptoms of</p>



<u>effects</u>	<p>psychomotor impairment, 3-headache, 4- confusion and loss of visual acuity, 5- deep coma, convulsions, shock, and respiratory failure.</p> <ul style="list-style-type: none"> ✓ Carboxyhemoglobin levels below 15% may produce headache. ✓ Collapse and syncope may appear at around 40% ✓ At 60% and above death may result. ✓ The clinical effects may be aggravated by heavy labor, high altitudes, and high ambient temperatures. ✓ Exposure of a pregnant woman may cause fetal death 	<p>intoxication include irritation of the eyes, nose, and throat, reflex bronchoconstriction, and increased bronchial secretions.</p> <p>-Cumulative effects have been associated with aggravation of chronic cardiopulmonary disease.</p>
<u>Treatment</u>	<ul style="list-style-type: none"> -Patients must be removed from the exposure source immediately. -Respiration, high flow and concentration of oxygen must be administered. -High concentrations of oxygen may cause acute respiratory distress syndrome, so it should be used for short period of time. -Hypothermic therapy is also used to reduce the metabolic demand of the 	<p>Treatment is not specific for SO₂ but depends on therapeutic maneuvers used to treat irritation of the respiratory tract and asthma.</p>



	<p>brain.</p> <p>-Patients manifest neuropsychological and motor dysfunction for a long time after recovery.</p>	
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	<p>C) Nitrogen Oxides</p> <ul style="list-style-type: none"> • Nitrogen dioxide (NO₂) is a brownish irritant gas. • It is formed from fresh silage; exposure of farmers to NO₂ in the confines of a silo can lead to silo-filler's disease, a severe and potentially lethal form of acute respiratory distress syndrome. 	<p>D) Ozone & Other Oxides</p> <ul style="list-style-type: none"> • Ozone (O₃) is a bluish irritant gas. It absorbs the UV light at high altitude. • At ground level it is an air pollutant. Atmospheric ozone is derived from photolysis of oxides of nitrogen, volatile organic compounds, and CO that are resulting from burning, fossil fuels and motor vehicles.
MOA	<p>1- It is relatively insoluble deep lung irritant. It is capable of producing pulmonary edema and acute adult respiratory distress syndrome (ARDS).</p> <p>2- Inhalation damages the lung infrastructure that produces the surfactant necessary for lung</p>	<p>1- Ozone penetration in the lung depends on tidal volume; consequently, exercise can increase the amount of ozone reaching the distal lung.</p> <p>2- O₃ toxicity may result from the formation of reactive free radicals.</p>



	<p>expansion.</p> <p>3- The type I cells of the alveoli appear to be the cells chiefly affected by acute low to moderate inhalation exposure.</p> <p>4- Some patients develop non-allergic asthma, or “twitchy airway” disease.</p> <p>5- If severe damage to the type I and type II alveolar cells occurs, replacement of the cells is impaired; progressive fibrosis may ensue which leads to bronchial ablation and alveolar collapse.</p> <p>6- Long-term exposure has been linked to cardiovascular disease.</p>	
<u>Clinical effects</u>	<ul style="list-style-type: none"> ✓ Irritation of the eyes and nose, cough, mucoid or frothy sputum production, dyspnea, and chest pain. 	<ul style="list-style-type: none"> ✓ Ozone is an irritant of mucous membranes. ✓ Mild exposure produces upper respiratory tract irritation. ✓ Severe exposure can cause deep lung irritation, with pulmonary edema.

	<ul style="list-style-type: none"> ✓ Chronic exposure has resulted in emphysematous changes in the tested animals. 	<ul style="list-style-type: none"> ✓ The gas causes shallow, rapid breathing and a decrease in pulmonary compliance. ✓ Airway hyper-responsiveness and airway inflammation.
Treatments	<ul style="list-style-type: none"> ✓ There is no specific treatment for the acute intoxication NO₂; therapeutic measures for the management of deep lung irritation and non-cardiogenic pulmonary edema are used. ✓ Drug therapy may include bronchodilators, sedatives, and antibiotics. 	<ul style="list-style-type: none"> ✓ There is no specific treatment for acute O₃ intoxication. ✓ Management depends on therapeutic measures used for deep lung irritation and non-cardiogenic pulmonary edema.

Solvents

A) Halogenated Aliphatic Hydrocarbons

- These “halohydrocarbon” agents once found wide use as industrial solvents, degreasing and cleaning agents.
- The substances include:
 - 1- Carbon tetrachloride,
 - 2- Chloroform
 - 3- Methyl chloroform.

B) Aromatic Hydrocarbons

Benzene is used for its solvent properties and as an intermediate in the synthesis of other chemicals such as gasoline. The current PEL is 1.0 ppm in the air and a 5 ppm limit is recommended for skin exposure and the recommendation is to reduce it to 0.1 ppm.



- Dry cleaning as an occupation is listed as a class 2B carcinogenic activity by the International Agency for Research on Cancer (IARC).
- Fluorinated aliphatic such as the freons can cause severe damage to the ozone layer.

MOA and clinical effects: In laboratory animals, the halogenated hydrocarbons cause central nervous system (CNS) depression, hepatotoxicity, and nephrotoxicity.

Trichloroethylene and tetrachloroethylene are listed as “reasonably anticipated to be a human carcinogen” by the U.S. National Toxicology Program, and as class 2A probable human carcinogens by IARC.

The acute toxic effect of benzene is depression of the CNS. Exposure to 7500 ppm for 30 minutes can be fatal.

Chronic exposure to benzene can result in bone marrow injury. The pluri-potent bone marrow stem cells appear to be targets of benzene.

Benzene has long been known to be a potent clastogen, i.e., a mutagen that acts by causing chromosomal breakage

Toluene (methylbenzene) is not carcinogenic and is listed as class 3 by IARC. It is, however, a CNS depressant and a skin and eye irritant. Exposure to 800 ppm can lead to severe fatigue and ataxia; 10,000 ppm can produce rapid loss of consciousness.

Xylene (dimethylbenzene) has been substituted for benzene in many solvent degreasing operations. Like toluene, the three xylenes do not possess the myelotoxicity properties of benzene. Estimated TLV-TWA

and TLV-STEL are 100 and 150 ppm, respectively.

Treatments: There is no specific treatment for the acute intoxication.

No specific treatment exists for the acute toxic effect of benzene.

PESTICIDES

1- Organochlorine Pesticides

- These agents are usually classified into four groups: DDT (chlorophenothane) and its analogs, benzene hexachlorides, cyclodienes, and Toxaphenes.
- They are aryl, carbocyclic, or heterocyclic compounds containing chlorine substituents.
- They can be absorbed through the skin, inhalation or oral ingestion.
- They are now known to be endocrine disrupters in animals and humans.

1- Human toxicology

2- Environmental toxicology

These agents interfere with inactivation of the sodium channel in excitable membranes and cause rapid repetitive firing in most neurons.

Calcium ion transport is inhibited. These events affect repolarization and enhance the excitability of neurons. The major effect is CNS stimulation.

There is no specific treatment for the acute intoxicated state, and management is symptomatic.

Chronic administration to laboratory animals over long periods results in enhanced carcinogenesis. Endocrine pathway disruption is the postulated mechanism.

Brain cancer, non-Hodgkin's lymphoma and testicular cancer can be resulted from the exposure.

Non-cancer end points such as cryptorchidism and hypospadias in newborns can happen.

Degradation is quite slow when compared with other pesticides, and bioaccumulation is well documented.

These compounds induce significant abnormalities in the endocrine balance of sensitive animal and bird species, in addition to their adverse impact on humans.

2- Organophosphorus Pesticides

They are useful pesticides when in direct contact with insects or when used as plant systemics, where the agent is translocated within the plant and exerts its effects on insects that feed on the plant.

The organophosphate pesticides are based on compounds such as soman, sarin and tabun which were once used as war gases.

Some of the less toxic organophosphorus compounds are used in human and veterinary medicine as local or systemic antiparasitics.

Absorption is via the direct contact with skin, ingestion, and inhalation.

A) Human toxicology

- The major effect of these agents is inhibition of acetylcholinesterase through phosphorylation of the esteratic site.
- Acute intoxication is due to inhibition of this enzyme and accumulation of acetylcholine; some of the agents also possess direct cholinergic activity.
- Pretreatment with physostigmine and other short-acting compounds may provide protection against these pesticides.
- Some of these agents are capable of phosphorylating another enzyme present in neural tissue, the so-called neuropathy target esterase (NTE), (which has no specific treatment), which results in progressive demyelination of the longest nerves. Associated with paralysis and axonal degeneration, this lesion is sometimes called organophosphorus ester-induced delayed polyneuropathy (OPIDP).
- Progressive chronic axonal neurotoxicity has been observed with triorthocresyl phosphate (TOCP), a noninsecticidal organophosphorus compound.

- The polyneuropathy usually begins as burning and tingling sensations. Gait is affected, and ataxia may be present.
There is no specific treatment for this form of delayed neurotoxicity.
- Neuromuscular transmission failure and cardiac failure more typical of nicotinic than muscarinic poisoning is an intermediate syndrome that has been observed.

B) Environmental toxicology

- They are not considered to be persistent pesticides. They are relatively unstable and break down in the environment.

3- Carbamate Pesticides

4- Botanical Pesticides



- ✓ These compounds inhibit acetylcholinesterase by carbamoylation of the esteratic site.
- ✓ The binding is relatively weak, dissociation occurs after minutes to hours, and clinical effects are of shorter duration than those observed with organophosphorus compounds.
- ✓ Spontaneous reactivation of cholinesterase is more rapid after inhibition by the carbamates.
- ✓ they have large therapeutic index but using them is not recommended
- ✓ They are considered non-persistent pesticides.
- ✓ Pesticides derived from natural sources include nicotine, rotenone, and pyrethrum.
- ✓ Nicotine is rapidly absorbed from the mucosal surface, and the free alkaloid is absorbed from the skin.
- ✓ Nicotine reacts with the acetylcholine receptor of the postsynaptic membrane (sympathetic and parasympathetic ganglia, neuromuscular junction), resulting in depolarization of the membrane.
- ✓ Toxic doses cause stimulation rapidly followed by blockade of transmission. Treatment is directed toward maintenance of vital signs and suppression of convulsions.
- ✓ The oral ingestion of rotenone produces gastrointestinal irritation and conjunctivitis.
- ✓ Pyrethrum consists of six known insecticidal esters: pyrethrin I, pyrethrin II, cinerin I, cinerin II, jasmolin I, and jasmolin II. The major site of toxic action is the CNS; convulsions and tetanic

paralysis can occur. Voltage-gated sodium, calcium, and chloride channels, peripheral-type benzodiazepine receptors are considered targets.

- ✓ The chloride channel agonist, ivermectin, is of use, as are pentobarbital and mephenesin.
- ✓ The pyrethroids are highly irritating to the eyes and they may cause irritant asthma and, potentially, reactive airways dysfunction syndrome (RADS) and even anaphylaxis.

HERBICIDES

1- Chlorophenoxy Herbicides

2,4-Dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and their salts are used for the destruction of weeds. In humans, 2,4-D in large doses can cause coma and generalized muscle hypotonia.

In laboratory animals, signs of liver and kidney dysfunction have also been reported with chlorophenoxy herbicides, and there is a link between 2,4D and non-Hodgkin's lymphoma.

The dichlorophenoxy and related herbicides have been found to contain and to generate dimethylnitrosamine (*N*-nitrosodimethylamine; NDMA), a potent human carcinogen

2- Glyphosate

Glyphosate (N-[phosphonomethyl] glycine, Figure 56–1), the principle ingredient in Roundup, It functions as a contact herbicide and it is absorbed through the leaves and roots of plants.

Genetically modified plants such as soybean, corn, and cotton that are glyphosate-resistant.

Glyphosate is a significant eye and skin irritant. When ingested it can cause mild to moderate esophageal erosion. It also causes aspiration pneumonia and renal failure.

Treatment is symptomatic and no specific protocol is indicated.

Hemodialysis has been used with success in cases of renal failure.

3- Bipyridyl Herbicides

The mechanism of action of Paraquat involves single-electron reduction of the herbicide to free radical species.

Paraquat accumulates slowly in the lung by an active process and causes lung edema, alveolitis, and progressive fibrosis.

It probably inhibits superoxide dismutase, resulting in intracellular free-radical oxygen toxicity.

First signs and symptoms after oral exposure are hematemesis and bloody stools.

During the acute period, oxygen should be used cautiously to combat dyspnea or cyanosis because it may aggravate the pulmonary lesions.

Because of the delayed pulmonary toxicity, prompt immobilization of the paraquat to prevent absorption is important by using adsorbents such as activated charcoal and Fuller's earth.

Gastric lavage is not recommended as it may promote aspiration from the stomach into the lungs.

The pulmonary proliferative phase begins 1–2 weeks after paraquat ingestion.

Immunosuppression and corticosteroids have weak efficacy.

Antioxidants such as acetylcysteine and salicylate might be beneficial through free radical-scavenging, anti-inflammatory, and nuclear factor kappa-B inhibitory actions.

However, there are no published human trials.

ENVIRONMENTAL POLLUTANTS

1- Polychlorinated & Polybrominated Biphenyls

- Highly halogenated biphenyl compounds, which have desirable properties for insulation and fire retardancy.
- The polychlorinated biphenyls (PCBs, coplanar biphenyls) were used as dielectric and heat transfer fluid.
- The chlorinated products used commercially were actually mixtures of PCB isomers and homologs containing 12–68% chlorine. These chemicals are very stable, highly lipophilic, poorly metabolized, and very resistant to environmental degradation; thus they bioaccumulate in food chains which is the major source of PCB residues in humans
- It has effects on the fetus and on the development of the offspring of poisoned women.
- It is now known that the contaminated cooking oil contained not only PCBs but also polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs) and their exposure will develop dermatologic problems that include chloracne, folliculitis and erythema.
- The halogenated pesticides are potent endocrine disrupters.

- the IARC has classify some co-planar PCBs as class 1, carcinogenic to humans, in volume 100 of the IARC monographs
- The biphenyls are no longer produced but the biphenyl esters remain in use as fire retardants in plastics for bedding and in automobile upholstery.
- PBBs are considered IARC class 2a: probable human carcinogens.
- The polychlorinated dibenzo-*p*-dioxins (PCDDs), or *dioxins*, are dioxin-like compounds, including polychlorinated dibenzofurans (PCDFs) and coplanar biphenyls.
- Like PCBs, these chemicals are very stable and highly lipophilic. They are poorly metabolized and very resistant to environmental degradation.
- Wasting syndrome (severe weight loss accompanied by reduction of muscle mass and adipose tissue), thymic atrophy, epidermal changes, hepatotoxicity, immunotoxicity, effects on reproduction and development, teratogenicity, and carcinogenicity have been produced.
- There is epidemiologic evidence for an association between occupational exposure to the phenoxy herbicides and an excess incidence of non-Hodgkin's lymphoma.
- TCDD is considered an IARC class 1, known human carcinogen. Other halogenated compounds of this type are not currently classifiable as to carcinogenicity; they are listed as IARC class 3.

2- Perfluorinated Compounds (PFCs)

Fluorinated hydrocarbon chemicals have been used in coolant materials in air conditioning systems; artificial oxygen-carrying substances in experimental clinical studies

The higher molecular weight, more highly fluorinated compounds, now called *perfluorinated substances* (eg, Teflon)

A) Human toxicology

- ❖ PFCs have estrogenic properties and accumulation and persistence in humans.
- ❖ Exposure is either via ingestion which is the major source of contamination, or inhalation.
- ❖ The human half-life of PFOA is about 3 years.
- ❖ It has some long-term adverse impact on reproductive function, cellular proliferation, and other cellular homeostatic mechanisms. Several PFCs (but not perfluoro compounds derived from PFOA) have been found to act as proliferators of breast cancer cells.

B) Environmental toxicology

- ❖ Now found widely in water, soil, and many terrestrial and avian species. Aquatic organisms have accumulated significant loads of PFCs.

- ❖ Kidney cancer, prostate cancer, cholesterol elevation, and uric acid abnormalities are resulted from this exposure.
- ❖ Finally, an acute pulmonary disorder, polymer fume fever, is caused by the pyrolysis of PFOA.
- ❖ Like metal fume fever, seen in welders as a result of cadmium vaporization, polymer fume fever has an acute onset several hours after exposure to the vaporized PFOA and may cause severe respiratory distress.
- ❖ While polymer fume fever is usually mild and self-limited, non-cardiogenic pulmonary edema has occurred.
- ❖ Whenever PFOA is heated above 350–400° C, toxic fumes capable of causing polymer fume fever are emitted.

3- Endocrine Disruptors

- ✓ They have anti-androgenic properties.
- ✓ These chemicals mimic, enhance, or inhibit a hormonal action.
- ✓ They include a number of plant constituents (phytoestrogens) and some mycoestrogens as well as industrial chemicals, persistent organochlorine agents (eg, DDT), PCBs, and brominated flame retardants.
- ✓ Modified endocrine responses in reptiles and marine invertebrates have been observed.
- ✓ Epidemiologic studies of populations exposed to higher concentrations of endocrine-disrupting environmental chemicals are underway.
- ✓ There are indications that breast and other reproductive cancers are increased in these patients.

4- Asbestos

- ❖ All forms of asbestos have been shown to cause progressive fibrotic lung disease (asbestosis), lung cancer, and mesothelioma.
- ❖ Lung cancer occurs in people exposed at fiber concentrations well below concentrations that produce asbestosis.
- ❖ All forms of asbestos cause mesothelioma of the pleura or peritoneum at very low doses.



METALS

Beryllium

- ❖ Beryllium (Be) is a light alkaline metal
- ❖ Beryllium-copper alloys find use as components of computers and in the encasement of the first stage of nuclear weapons.
- ❖ Because of the use of beryllium in dental appliances, dentists and dental appliance makers are often exposed to beryllium dust in toxic concentrations and may develop beryllium disease.
- ❖ Beryllium is highly toxic by inhalation and is classified by the IARC as a class 1, known human carcinogen.
- ❖ Inhalation of beryllium particles produces both acute beryllium disease and chronic disease characterized by progressive pulmonary fibrosis.
- ❖ Skin disease also develops in workers exposed to beryllium.

Cadmium

- ✓ Cadmium (Cd) is a transition metal found in the manufacture of nickel and cadmium batteries.
- ✓ Cadmium smelter workers often face both lead and cadmium toxicity.
- ✓ Cadmium is toxic by inhalation and by ingestion.
- ✓ Fine dust and fumes released produce an acute respiratory disorder called cadmium fume fever. This disorder, common in welders, is usually characterized by shaking chills, cough, and fever.
- ✓ Cadmium is a human carcinogen and is listed as a class 1, known human carcinogen by the IARC.

The pulmonary disease is called chronic beryllium disease (CBD) and is a chronic granulomatous pulmonary fibrosis.

- ❖ Prognosis in CBD is poor.

Nanomaterials

- ✓ Nanomaterials are defined as any material, natural or manufactured, that has at least one dimension that lies between 1 and 100 nanometers (nm) in size.
- ✓ In the pharmaceutical manufacturing industry, nanoparticles are being tested and used to deliver cancer chemotherapeutic and other drugs.
- ✓ Currently produced nanomaterials include gold, silver, cadmium, germanium, and ceramic.
- ✓ Because nanomaterials behave in unique patterns of chemical and physical reactivity, their toxicology is often novel.

Human toxicology	Environmental toxicology
1- Inhalation, oral ingestion, dermal absorption, and parenteral administration of nanomaterials have been the sources of human exposure.	<ul style="list-style-type: none">✓ Nanomaterials can enter the environment at all stages of their industrial life cycle, including manufacturing, delivery, use, and disposal.✓ When nanomaterials are



- 2- Nanomaterials can cross cellular membranes, penetrate nuclear material and genetic information, and may impact cellular response at a nanoscale.
- 3- Silica nanoparticles have been demonstrated to produce kidney toxicity in humans
- 4- Zinc oxide nanoparticles are toxic to human liver cells.
- 5- Titanium dioxide nanoparticles that are widely used in sunscreens, other cosmetics are toxic to the lungs.

placed into waste streams they may enter water systems, or be carried by wind or soils, and enter the food chain.

Chapter 57: Heavy Metal Intoxication & Chelators

Some metals are essential for life, whereas others serve no useful biologic purpose. Toxic heavy metals interfere with the function of essential cations, cause enzyme inhibition, generate oxidative stress, and alter gene expression. As a result, multisystem signs and symptoms are a hallmark of heavy metal intoxication. Chelator molecules may be used to bind the metal and facilitate its excretion from the body.

TOXICOLOGY OF HEAVY METALS:

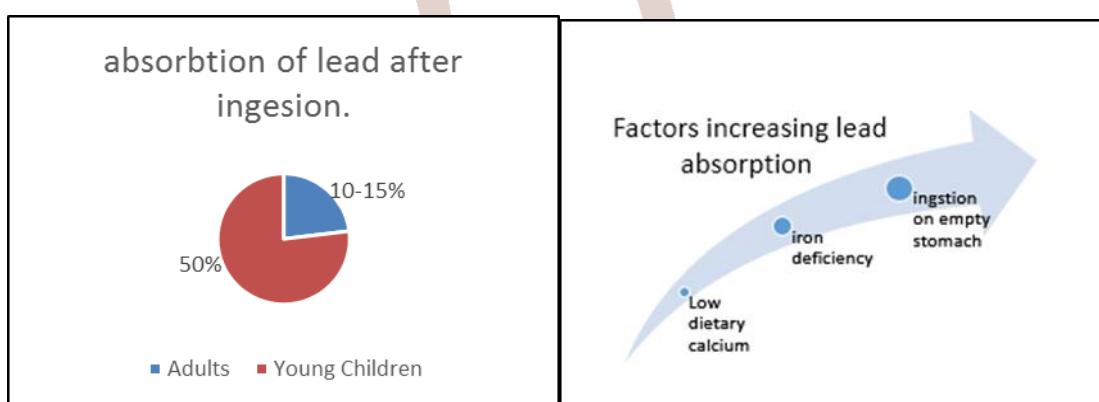
1- Lead

- Source and presence of metal

Commercial application; storage batteries, ammunition, glass, plastics, pigments, and ceramics, lead plumbing, certain folk medicines, cosmetics.

- Pharmacokinetics

Absorbed via the respiratory and gastrointestinal tracts, and it's poorly absorbed through the skin.



*Once absorbed, lead enters the bloodstream, where approximately 99% is bound to erythrocytes and 1% is present in the plasma. Lead is subsequently distributed to soft tissues, then to the subperiosteal (the normal investment of bone e of bone) surface and later to bone matrix. Lead also crosses the placenta and poses a potential hazard to the fetus.

*The kinetics of lead clearance from the body follows a multicompartment model; half-life of 1–2 months in case of blood and soft tissue, and the skeleton with a half-life of years to decades. Approximately 70% of the lead that is eliminated appears in the urine.

*slow release from the skeleton may elevate blood lead concentrations, and pathologic high bone turnover states such as hyperthyroidism or prolonged immobilization may result in frank lead intoxication.

Pharmacodynamics

Lead exerts multisystemic toxic effects that are mediated by multiple modes of action:

1. inhibition of enzymatic function
2. interference with the action of essential cations
3. generation of oxidative stress
4. changes in gene expression
5. alterations in cell signaling
6. disruption of the integrity of membranes

A. Nervous System

*The developing central nervous system of the fetus and young child is the most sensitive target organ for lead's toxicity.

*Adults are less sensitive to the CNS effects of lead, but blood lead concentrations in the range of 10–30 mcg/dL may be associated with subclinical effects on neurocognitive function. At blood lead concentrations higher than 30 mcg/dL, behavioral and neurocognitive signs or symptoms may gradually emerge; irritability, fatigue, decreased libido, sleep disturbance.

* Lead encephalopathy, usually occurring at blood lead concentrations higher than 100 mcg/dL, is typically accompanied by increased intracranial pressure and may cause ataxia, stupor, coma, convulsions, and death.

*Overt peripheral neuropathy may occur at blood lead concentrations higher than 100 mcg/dL.

B. Blood

Lead can induce an anemia that may be either normocytic or microcytic and hypochromic. Lead interferes with heme synthesis by blocking the incorporation of iron into protoporphyrin IX and by inhibiting the function of enzymes in the heme synthesis pathway, including aminolevulinic acid dehydratase and ferrochelatase. Also contributes to anemia by increasing erythrocyte membrane fragility and decreasing red cell survival time.

C. Kidneys

Chronic high-dose lead exposure greater than 80 mcg/dL, result in renal interstitial fibrosis and nephrosclerosis. Lead may alter uric acid excretion by the kidney, resulting in recurrent bouts of gouty arthritis. Acute high-dose lead produces transient azotemia.

D. Reproductive Organs

High-dose lead exposure is a recognized risk factor for stillbirth or spontaneous abortion. Prenatal exposure to low levels of lead to decrements in physical and cognitive development. In males, blood lead concentrations higher than 40 mcg/dL have been associated with diminished or aberrant sperm production.

E. Gastrointestinal Tract

Moderate lead poisoning may cause loss of appetite, constipation, and, less commonly, diarrhea. At high dosage, intermittent bouts of severe colicky abdominal pain. The mechanism of lead colic is unclear but is believed to involve spastic contraction of the smooth muscles of the intestinal wall, mediated by alteration in synaptic transmission at the smooth muscle-neuromuscular junction.

F. Cardiovascular System

Lead exposure elevates blood pressure in experimental animals and in susceptible humans. The pressor effect of lead may be mediated by an interaction with calcium-mediated contraction of vascular smooth muscle, as well as generation of oxidative stress and an associated interference in nitric oxide signaling pathways. High blood lead concentration is linked with increases in systolic and diastolic blood pressure, has also been associated with prolongation of the QTc interval on the electrocardiogram.

Major forms of lead intoxication

A. Inorganic lead poisoning

1 – Acute

It results from industrial inhalation of large quantities of lead oxide fumes or, in small children, from ingestion of a large oral dose of lead eg, toys coated or fabricated from lead. The onset of severe symptoms usually requires recurrent exposure as signs and symptoms of encephalopathy or colic. Evidence of hemolytic anemia and elevated hepatic aminotransferases may be present. The diagnosis of acute inorganic lead poisoning may be difficult, the condition has sometimes been mistaken for appendicitis, pancreatitis, or infectious meningitis. When there has been recent ingestion of lead-containing material, radiopacities may be visible on abdominal radiographs.

2 – Chronic

*patient with symptomatic chronic lead intoxication typically presents with multisystemic findings; anorexia, fatigue; neurologic complaints; headache, difficulty in concentrating, and irritability,weakness, arthralgias; and gastrointestinal symptoms.

* Lead poisoning strongly suspected in patients presenting with headache, abdominal pain, and anemia; and less commonly with motor neuropathy, gout, and renal insufficiency. Also it should be considered in any child with neurocognitive deficits, growth retardation, or developmental delay.

*The diagnosis of lead intoxication is best confirmed by measuring lead in whole blood.the concentration of lead in bone assessed bynoninvasive K X-ray fluorescence measurement of lead has been correlated with long-term cumulative lead exposure.

*Measurement of lead excretion in the urine after a single dose of a chelating agent reflects the lead content of soft tissues and may not be a reliable marker of long-term lead exposure, remote past exposure, or skeletal lead burden. the finding of a blood lead concentration of 30 mcg/dL or more with no concurrent increase in zinc protoporphyrin suggests that the lead exposure was of recent onset.

B. Organolead Poisoning

Because of their volatility or lipid solubility, organolead compounds tend to be well absorbed through either the respiratory tract or the skin. Organolead compounds predominantly target the CNS, producing dose-dependent effects; neurocognitive deficits, insomnia, delirium, hallucinations, tremor, convulsions, and death.

Treatment

A. Inorganic Lead Poisoning

Treatment of inorganic lead poisoning		
immediate termination of exposure	supportive care	judicious use of chelation therapy
Lead encephalopathy	Intensive supportive care.	
Cerebral edema	Corticosteroids and mannitol	
Seizures	Anticonvulsant	

*Intravenous **edetate calcium disodium (CaNa₂EDTA)** is administered at a dosage of 1000–1500 mg/m²/d (approximately 30–50 mg/kg/d) by continuous infusion for up to 5 days.treatment for lead encephalopathy initiated with an intramuscular injection of **dimercaprol**, followed in 4 hours by concurrent administration of dimercaprol and EDTA. Parenteral chelation is limited to 5 or fewer days, at which time oral treatment with another chelator, **succimer**, may be instituted. In symptomatic lead intoxication without encephalopathy, treatment may sometimes be initiated with succimer.

*Prophylactic use of chelating agents in the workplace should never be a substitute for reduction or prevention of excessive exposure.

*The longer-term goal should be for workers to maintain blood lead levels less than 10 mcg/dL, and for pregnant women to avoid occupational or avocational exposure that would result in blood lead levels higher than 5 mcg/dL.

B. Organic Lead Poisoning

Initial treatment consists of



- decontaminating the skin and preventing further exposure.
- appropriate anticonvulsants to treat seizures
- Empiric chelation for high blood lead concentration

2- Arsenic

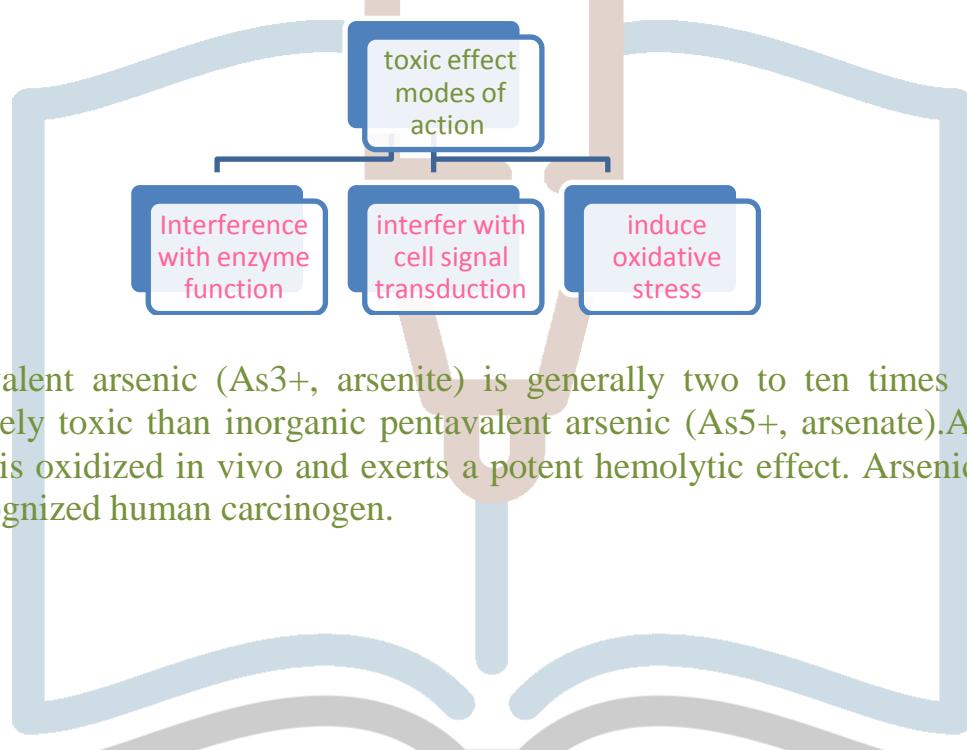
Arsenic is a naturally occurring element in the earth's crust. is an agent of deliberate poisoning, commercial applications of arsenic include its use in the manufacture of semiconductors, glass, herbicides, and marine timbers or utility poles. Organic arsenicals were the first pharmaceutical antimicrobial

- Pharmacokinetics

*Soluble arsenic compounds are well absorbed through the respiratory and gastrointestinal tracts. Percutaneous absorption may be clinically significant after heavy exposure to concentrated arsenic.

*Absorbed inorganic arsenic undergoes methylation, mainly in the liver, to monomethyl-arsionic acid and dimethylarsinic acid, which are excreted in the urine. When daily absorption is less than 1000 mcg of soluble inorganic arsenic, two thirds of the absorbed dose is excreted in the urine within 2–3 days. Arsenic binds to sulfhydryl groups present in keratinized tissue, and following cessation of exposure, hair, nails, and skin may contain elevated levels.

- Pharmacodynamics



Trivalent arsenic (As³⁺, arsenite) is generally two to ten times more acutely toxic than inorganic pentavalent arsenic (As⁵⁺, arsenate). Arsine gas is oxidized in vivo and exerts a potent hemolytic effect. Arsenic is a recognized human carcinogen.

Major Forms of Arsenic Intoxication

A. Acute Inorganic Arsenic Poisoning

*Within minutes to hours after exposure to high doses of soluble inorganic arsenic compounds, many systems are affected. Initial gastrointestinal signs and symptoms include nausea, vomiting, diarrhea, and abdominal pain. Diffuse capillary leak, combined with gastrointestinal fluid loss, may result in hypotension, shock, and death. Cardiopulmonary toxicity, including congestive cardiomyopathy, cardiogenic or noncardiogenic pulmonary edema, ventricular arrhythmias, and pancytopenia.

*Central nervous system effects, including delirium, encephalopathy, and coma. An ascending sensorimotor peripheral neuropathy may begin to develop after a delay of 2–6 weeks.

* Months after an acute poisoning, transverse white striae (Aldrich-Mees lines) may be visible in the nails.

*arsenic poisoning should be considered in an individual presenting with abrupt onset of gastroenteritis in combination with hypotension and metabolic acidosis.

*Blood arsenic levels should not be used for diagnostic purposes, the diagnosis may be confirmed by demonstration of elevated amounts in the urine.

*Treatment is based on appropriate gut decontamination, intensive supportive care, and prompt chelation with **unithiol**, 3–5 mg/kg intravenously every 4–6 hours, or **dimercaprol**, 3–5 mg/kg intramuscularly every 4–6 hours.

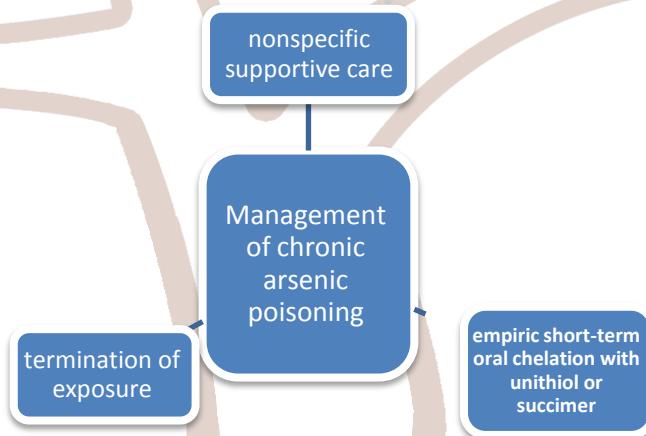
*if diagnostic suspicion is high, treatment should not be withheld.

B. Chronic Inorganic Arsenic Poisoning

*Overt noncarcinogenic effects may be evident after chronic absorption of more than 0.01 mg/kg/d. Constitutional symptoms of fatigue, weight loss, and weakness may be present, along with anemia, nonspecific gastrointestinal complaints, and a sensorimotor peripheral neuropathy, peripheral vascular disease and noncirrhotic portal hypertension. Cancer of the lung, skin, bladder, and possibly other sites.

*Administration of arsenite in cancer chemotherapy regimens, often at a daily dose of 10–20 mg for weeks to a few months, has been associated with prolongation of the QT interval on the electrocardiogram and occasionally has resulted in malignant ventricular arrhythmias.

* The diagnosis of chronic arsenic poisoning involves integration of the clinical findings with confirmation of exposure. All seafood should be avoided for at least 3 days before submission of a urine sample for diagnostic purposes. Preliminary studies suggest that dietary supplementation of folate—thought to be a cofactor in arsenic methylation—might be of value in arsenic-exposed individuals.



C. Arsine Gas Poisoning

A distinctive pattern of intoxication dominated by profound hemolytic effects. After a latent period that may range from 2 to 24 hours postinhalation (depending on the magnitude of exposure), massive intravascular hemolysis may occur. Initial symptoms may include malaise, headache, dyspnea, weakness, nausea, vomiting, abdominal pain, jaundice, and hemoglobinuria and oliguric renal failure. Intensive supportive care—including exchange transfusion, vigorous hydration, and, in the case of acute renal failure, hemodialysis—is the mainstay of therapy. Currently available chelating agents have not been demonstrated to be of clinical value in arsine poisoning.

3- Mercury

Metallic mercury known as “quicksilver”—the only metal that is liquid under ordinary conditions—elemental mercury and alkylmercury, also other key mercurials include inorganic mercury salts and aryl mercury compounds, each of which exerts a relatively unique pattern of clinical toxicity. Industrial applications of mercury are found in the electrolytic production of chlorine and caustic soda, electrical equipment,

thermometers, dental amalgam and artisanal gold production. It is used in antiseptics and folk medicines.

- Pharmacokinetics

Elemental mercury absorbed from the lungs and poorly absorbed from the intact gastrointestinal tract. Organic short-chain alkylmercury compounds are volatile and potentially harmful by inhalation as well as by ingestion. Percutaneous absorption of metallic mercury and inorganic mercury can be of clinical concern following massive acute or chronic exposure. Alkylmercury appears to be well absorbed through the skin, and acute contact with a few drops of dimethylmercury has severe, delayed toxicity. Mercury is distributed to the tissues within a few hours, with the highest concentration occurring in the kidney. Inorganic mercury is excreted through the urine and feces. Most of inorganic mercury is excreted within weeks to months. After inhalation of elemental mercury, urinary mercury levels decline with a half-life of 1–3 months. Methylmercury, which has a blood and whole body half-life of 50 days, undergoes biliary excretion and enterohepatic circulation, with more than two thirds eventually excreted in the feces. Mercury binds to sulfhydryl groups in keratinized tissue, and as with lead and arsenic, traces appear in the hair and nails.

Major Forms of Mercury Intoxication

Mercury inhibits enzymes and alters cell membranes.

A. Acute

Inhalation of elemental mercury causes chemical pneumonitis and noncardiogenic pulmonary edema. Ingestion of inorganic mercury salts can result in a corrosive, potentially life-threatening hemorrhagic gastroenteritis followed within hours to days by acute tubular necrosis and oliguric renal failure.

B. Chronic

*Chronic poisoning from inhalation of mercury results in a classic triad of tremor, neuropsychiatric disturbance, and gingivostomatitis (Inflammation of the gums and the mucous membrane of the oral cavity). Recent studies suggest that low-dose exposure may produce subclinical neurologic effects.

*Acrodynia (A syndrome in children, adults and infants caused by mercury poisoning) occurs mainly in children. It is characterized by painful erythema of the extremities and may be associated with hypertension, insomnia, irritability and a miliary rash. Chronic exposure

to inorganic mercury salts, sometimes via topical cosmetic skin-lightening creams, has been associated with neurological symptoms and renal toxicity. Methylmercury intoxication affects mainly the CNS and results in paresthesias, ataxia, hearing impairment, dysarthria, and progressive constriction of the visual fields.

*High-dose prenatal exposure to methylmercury may produce mental retardation and a cerebral palsy-like syndrome in the offspring and Low-level associated with a risk of subclinical neurodevelopmental deficits. The diagnosis involves integration of the history and physical findings with confirmatory laboratory testing.

*To minimize the risk of developmental neurotoxicity from methylmercury; pregnant women, women who might become pregnant, nursing mothers, and young children should avoid consumption of fish with high mercury levels (eg, swordfish).

Treatment

A. Acute Exposure

In addition to intensive supportive care, prompt chelation with oral or intravenous **unithiol**, intramuscular **dimercaprol**, or oral **succimer** after acute exposure to inorganic mercury salts. Vigorous hydration may help to maintain urine output, but if acute renal failure ensues, days to weeks of hemodialysis or hemodiafiltration in conjunction with chelation may be necessary.

B. Chronic Exposure

Unithiol and **succimer** increase urine mercury excretion following acute or chronic elemental mercury inhalation Dimercaprol has been shown to redistribute mercury to the central nervous system from other tissue sites, so dimercaprol should not be used in treatment of exposure to elemental or organic mercury.

	Form Entering Body	Major Route of Absorption	Distribution	Major Clinical Effects	Key Aspects of Mechanism	Metabolism and Elimination
Arsenic	Inorganic arsenic salts	Gastrointestinal, respiratory (all mucosal surfaces)	Predominantly soft tissues (highest in liver, kidney). Avidly bound in skin, hair, nails	Cardiovascular: shock, arrhythmias. CNS: encephalopathy, peripheral neuropathy. Gastroenteritis; pancytopenia; cancer (many sites)	Inhibits enzymes; interferes with oxidative phosphorylation; alters cell signaling, gene expression	Methylation. Renal (major); sweat and feces (minor)
Lead	Inorganic lead oxides and salts	Gastrointestinal, respiratory	Soft tissues; redistributed to skeleton (> 90% of adult body burden)	CNS deficits; peripheral neuropathy; anemia; nephropathy; hypertension; reproductive toxicity	Inhibits enzymes; interferes with essential cations; alters membrane structure	Renal (major); feces and breast milk (minor)
	Organic (tetraethyl lead)	Skin, gastrointestinal, respiratory	Soft tissues, especially liver, CNS	Encephalopathy	Hepatic dealkylation (fast) → trialkyl metabolites (slow) → dissociation to lead	Urine and feces (major); sweat (minor)
Mercury	Elemental mercury	Respiratory tract	Soft tissues, especially kidney, CNS	CNS: tremor, behavioral (erethism); gingivo-stomatitis, peripheral neuropathy; acrodynia; pneumonitis (high-dose)	Inhibits enzymes; alters membranes	Elemental Hg converted to Hg^{2+} . Urine (major); feces (minor)
	Inorganic: Hg^+ (less toxic); Hg^{2+} (more toxic)	Gastrointestinal, skin (minor)	Soft tissues, especially kidney	Acute renal tubular necrosis; gastroenteritis; CNS effects (rare)	Inhibits enzymes; alters membranes	Urine
	Organic: alkyl, aryl	Gastrointestinal, skin, respiratory (minor)	Soft tissues	CNS effects, birth defects	Inhibits enzymes; alters microtubules, neuronal structure	Deacylation. Fecal (alkyl, major); urine (Hg^{2+} after deacylation, minor)

PHARMACOLOGY OF CHELATORS:

Chelating agents are drugs used to prevent or reverse the toxic effects of a heavy metal, or to accelerate the elimination of the metal from the body by forming a complex with the heavy metal. Chelators may also redistribute some of the metal to other vital organs, also may enhance excretion of essential cations, such as zinc in the case of calcium EDTA and (DTPA), and zinc and copper in the case of succimer. If prolonged chelation during the prenatal period or early childhood period is necessary, judicious supplementation of the diet with zinc might be considered. The longer the half-life of a metal in a particular organ, the less effectively it will be removed by chelation. For example; the metal is more effectively removed from soft tissues than from bone. The capacity of chelating agents to prevent or reduce the adverse effects of toxic metals appears to be greatest when it's administered very soon after an acute metal exposure.

DIMERCAPROL(2,3-DIMERCAPTOPROPANOL, BAL)

It's an oily, colorless liquid with a strong mercaptan-like odor. The aqueous solutions of dimercaprol are unstable, So it is dispensed in 10% solution in peanut oil and must be administered by intramuscular injection, which is often painful.it can increase the rate of excretion of arsenic and lead and may offer therapeutic benefit in the treatment of acute intoxication by arsenic, lead, and mercury.

Indications & Toxicity

FDA-approved dimercaprolas single-agent treatment of acute poisoning by arsenic and inorganic mercury and for the treatment of severe lead poisoning when used in conjunction with edetatecalcium disodium . intramuscularly administered dimercaprol appears to be excreted by the kidney within 4–8 hours.When used in therapeutic doses, dimercaprol is associated with a high incidence of adverse effects, including hypertension, tachycardia,nausea, vomiting, lacrimation, salivation, fever. Also thrombocytopenia and increased prothrombin time has reported. dimercaprol may redistribute arsenic and mercury to the central nervous system, and it is not advocated for treatment of chronic poisoning. Water soluble analogs of dimercaprol—unithiol and succimer—have higher therapeutic indices and have replaced dimercaprol in many settings.

SUCCIMER (DIMERCAPTSUCCINICACID, DMSA)

It is work by prevent and reverse metal-induced inhibition of sulfhydryl-containing enzymes and to protect against the acute lethal effects of arsenic also is associated with an increase in urinary lead excretion and a decrease in blood lead concentration.Peak blood levels of succimer occur at approximately 3 hours.

Indications & Toxicity

Succimer is currently FDA-approved for the treatment of children with blood lead concentrations greater than 45 mcg/dL, but it isalso commonly used in adults. The typical dosage is 10 mg/kg orally three times a day.It has supplanted EDTA in outpatient treatment of patients who are capable of absorbing the oral drug.It has a negligible impact on body stores of calcium, iron, and magnesium.It induces a mild increase in urinary excretion of zinc and, less consistently, copper.

Side effects

Gastrointestinal disturbances	Most common less than 10%
Rashes	less than 5%
Mild, reversible increases in liver aminotransferases	6–10%
mild to moderate neutropenia	

EDETALE CALCIUM

DISODIUM(ETHYLENEDIAMINETETRAACETICACID, EDTA)

Is an efficient chelator of many divalent and trivalent metals in vitro. To prevent potentially life-threatening depletion of calcium, treatment of metal intoxication should only be performed with the calcium disodium salt form of EDTA. EDTA penetrates cell membranes relatively poorly and therefore chelates extracellular metal ions more than intracellular ions. The highly polar ionic character of EDTA limits its oral absorption. Moreover, oral administration may increase lead absorption from the gut. Consequently, EDTA should be administered by intravenous infusion. In patients with normal renal function, EDTA is rapidly excreted (with 50% of an injected dose) by urine within 1 hour. In patients with renal insufficiency, excretion of the drug may be delayed.

Indications & Toxicity

Edetate calcium disodium is indicated chiefly for the chelation of lead, also in poisoning by zinc, manganese, and certain heavy radionuclides. The drug is relatively contraindicated in anuric patients, so the use of low doses of EDTA in combination with high-flux hemodialysis or hemofiltration has been described. Nephrotoxicity from EDTA has been reported, but can be prevented by maintenance of adequate urine flow, avoidance of excessive doses, and limitation of a treatment course to 5 or fewer consecutive days. EDTA may result in temporary zinc depletion.

UNITHIOL

(DIMERCAPTOPROPANESULFONICACID, DMPS)

Unithiol can be administered orally and intravenously. Bioavailability by the oral route is approximately 50%, with peak blood levels occurring in approximately 4 hours. Over 80% of an intravenous dose is excreted in the urine. The elimination half-time of total is approximately 20 hours. Unithiol exhibits protective effects against the toxic action of mercury and arsenic in animal models, and it increases the excretion of mercury, arsenic, and lead in humans.

Indications & Toxicity

Unithiol has no FDA-approved indications, but experimental studies suggest that intravenous unithiol offers advantages over intramuscular dimercaprol or oral succimer in the initial treatment of severe acute poisoning by inorganic mercury or arsenic. Aqueous preparations of unithiol can be administered at a dosage of 3–5 mg/kg every 4 hours by slow intravenous infusion over 20 minutes, because rapid intravenous infusion may cause vasodilation and hypotension. After stabilization of the patient's cardiovascular and gastrointestinal status, it may be possible to change to oral administration of 4–8 mg/kg every 6–8 hours. Oral unithiol may also be considered as an alternative to oral succimer in the treatment of lead intoxication. It has a low overall incidence of adverse effects (< 4%). Including: Self-limited dermatologic reactions, allergic reactions —multiforme and Stevens Johnson syndrome.

PENICILLAMINE (d DIMETHLCYSTEINE)

Is a water-soluble derivative of penicillin, and it's readily absorbed from the gut and is resistant to metabolic degradation.

Indications & Toxicity

Penicillamine is used chiefly for treatment of poisoning with copper or to prevent copper accumulation, as in Wilson's disease. It is also used occasionally in the treatment of severe rheumatoid arthritis (see Chapter 36). It increases urinary excretion of lead and mercury. But succimer, with its stronger capacity and lower adverse-effect profile, has generally replaced penicillamine for these purposes. Adverse effects have been seen in up to one third of patients receiving penicillamine; Hypersensitivity reactions and the drug should be used with extreme caution, if at all, in patients with a history of penicillin allergy, nephrotoxicity with proteinuria and Pancytopenia with a prolonged drug intake.

DEFEROXAMINE

It binds iron avidly but binds essential trace metals poorly. Furthermore, though competing for loosely bound iron in iron-carrying proteins, it fails to compete for biologically chelated iron. Consequently, it is the parenteral chelator of choice for iron poisoning (see Chapters 33 and 58). Deferoxamine plus hemodialysis may also be useful in the treatment of aluminum toxicity in renal failure. Deferoxamine is poorly absorbed orally and may increase iron absorption when given by this route. It should therefore be administered intramuscularly or, preferably,

intravenously. The iron-chelator complex is excreted in the urine, often turning the urine an orange-red color. Rapid intravenous administration may result in hypotension.

Adverse effects including; idiosyncratic responses, pulmonary complications with infusions lasting longer than 24 hours, and neurotoxicity and increased susceptibility to certain infections after long-term therapy.

DEFERASIROX

high affinity for iron and low affinity for other metals, orally active and well absorbed. It binds iron, and the complex is excreted in the bile. approved by the FDA for the oral treatment of iron overload caused by blood transfusions, a problem in the treatment of thalassemia and myelodysplastic syndrome.

Most side effects including	
mild to moderate gastrointestinal disturbances	Less than 15%
Skin rash	5%

PRUSSIAN BLUE (FERRICHEXACYANOFERRATE)

It is a chelator primarily by ion exchange, and secondarily by mechanical trapping or adsorption, the compound has high affinity for certain univalent cations, particularly cesium and thallium. Used as an oral drug, insoluble Prussian blue undergoes minimal gastrointestinal absorption (< 1%). It works by preventing their absorption or interrupts enterohepatic and enteroenteric circulation of these cations and accelerating their elimination in the feces.



Chapter 58: Management of the Poisoned Patient

Only a small number of poisoning cases are fatal. Most deaths are due to intentional suicidal overdose by an adolescent or adult. Childhood deaths due to accidental ingestion. The careful management of respiratory failure, hypotension, seizures, and thermoregulatory disturbances has resulted in improved survival of patients who reach the hospital alive.

■ TOXICOKINETICS & TOXICODYNAMICS

Toxicokinetics denotes the absorption, distribution, excretion, and metabolism of toxins, toxic doses of therapeutic agents, and their metabolites.

Toxicodynamics is used to denote the injurious effects of these substances on body functions.

SPECIAL ASPECTS OF TOXICOKINETICS

Volume of Distribution (Vd)

The apparent volume into which a substance is distributed in the body. A large Vd (> 5 L/kg) implies that the drug is not readily accessible to measures aimed at purifying the blood, such as hemodialysis. Such as antidepressants, antipsychotics. relatively small Vd (< 1 L/kg) include salicylate, ethanol and lithium.

Clearance

A measure of the volume of plasma that is cleared of drug per unit time. The total clearance is the sum of clearances via excretion by the kidneys and metabolism by the liver. Overdosage of a drug can alter the usual pharmacokinetic processes. At normal dosage, most drugs are eliminated at a rate proportional to the plasma concentration (first-order kinetics). If the plasma concentration is very high and normal metabolism is saturated, the rate of elimination may become fixed (zero-order kinetics).

SPECIAL ASPECTS OF TOXICODYNAMICS

two drugs may have the same therapeutic index but unequal safe dosing ranges if the slopes of their dose-response curves are not the same.

For many drugs, at least part of the toxic effect may be different from the therapeutic action, overdoses of drugs that depress the cardiovascular system, eg, β -blockers is not only cardiac function but all functions that are dependent on blood flow.

■ APPROACH TO THE POISONED PATIENT

HOW DOES THE POISONED PATIENT DIE?

Many toxins depress the central nervous system (CNS), resulting in obtundation or coma. Comatose patients frequently lose their airway protective reflexes and their respiratory drive. Thus, they may die as a result of airway obstruction. Common causes of death due to overdoses of narcotics and sedative-hypnotic drugs. Seizures may cause pulmonary aspiration, hypoxia, and brain damage. Drugs that cause seizures include antidepressants, isoniazid.

Toxicity type	The causative
Hypotension	depression of cardiac contractility
hypovolemia	vomiting, diarrhea, or fluid sequestration
Hypothermia or hyperthermia	exposure as well as the temperature-dysregulating effects of many drugs
Lethal arrhythmias	overdoses of cardioactive drugs such as ephedrine and not cardioactive drugs , such as tricyclic antidepressants
Cellular hypoxia	Poisoning with cyanide, hydrogen sulfide, carbon monoxide
Hyperthermia	sustained muscular hyperactivity and can lead to muscle breakdown and myoglobinuria, renal failure, lactic acidosis, and hyperkalemia.

■ INITIAL MANAGEMENT OF THE POISONED PATIENT

The initial management of a patient with coma, seizures, or altered mental status should follow the same approach regardless of the poison involved: supportive measures are the basics (“ABCs”) of poisoning treatment.

Airway should be cleared of any obstruction and an oral airway or endotracheal tube inserted if needed.

Breathing, Patients with respiratory insufficiency should be intubated and mechanically ventilated.

Circulation should be assessed by continuous monitoring. An intravenous line should be placed and blood drawn for serum glucose and other routine determinations.

At this point, every patient with altered mental status should receive a challenge with concentrated **dextrose**, unless a rapid bedside blood glucose test demonstrates that the patient is not hypoglycemic. Adults are

given 25 g (50 mL of 50% dextrose solution) intravenously, children 0.5 g/kg (2 mL/kg of 25% dextrose).

Alcoholic or malnourished patients should also receive 100 mg of thiamine intramuscularly or in the intravenous infusion solution at this time to prevent Wernicke's syndrome. The opioid antagonist naloxone may be given in a dose of 0.4–2 mg intravenously. Naloxone reverses respiratory and CNS depression therefore, if airway and breathing assistance have already been instituted, naloxone may not be necessary.

overdose of propoxyphene, codeine, and some other opioids. The benzodiazepine antagonist flumazenil may be of value in these patients, but it should not be used if there is a history of tricyclic antidepressant overdose or a seizure disorder, as it can induce convulsions in such patients.

History & Physical Examination

A. History

Oral statements about the amount and even the type of drug ingested in toxic emergencies may be unreliable. Even so, who brings the patient should be asked to describe the environment in which the toxic emergency occurred.

B. Physical Examination

Emphasizing those areas most likely to give clues to the toxicologic diagnosis;

1. Vital signs

Signs of toxicity	Causative drugs or toxins
Hypertension and tachycardia	amphetamines, cocaine, and antimuscarinic drugs
Hypotension and bradycardia	calcium channel blockers, $\beta\alpha$ blockers, clonidine, and sedative hypnotics
Hypotension with tachycardia	tricyclic antidepressants, trazodone, quetiapine, vasodilators, and $\beta\alpha$ agonists.
Rapid respirations	Salicylates, carbon monoxide
Hyperthermia	sympathomimetics
Hypothermia	CNS-depressant drug

2. Eyes

Eye's signs	Causative drugs or toxins
miosis	opioids, clonidine, phenothiazines.
mydriasis	amphetamines, cocaine, LSD, and atropine
Horizontal nystagmus	phenytoin, alcohol, barbiturates
vertical and horizontal nystagmus	strongly suggestive of phencyclidine poisoning
Ptosis and ophthalmoplegia	botulism

3. Mouth

Signs of burns due to corrosive substances, or soot from smoke inhalation. Also Typical odors may be noted.

4. Skin

Skin's signs	Causative drugs or toxins
flushed, hot, and dry skin	atropine and other antimuscarinics
Excessive sweating	organophosphates, nicotine, and sympathomimetic drugs

Cyanosis may be caused by hypoxemia or by methemoglobinemia. Icterus may suggest hepatic necrosis due to acetaminophen or *Amanita phalloides* mushroom poisoning.

5. Abdomen

Signs of toxicity	Causative drugs or toxins
Ileus	antimuscarinic, opioid
Hyperactive bowel sounds, abdominal cramping, and diarrhea	organophosphates, iron, arsenic, theophylline, <i>A phalloides</i> , and <i>A muscaria</i> .

6. Nervous system

Signs	Causative drugs or toxins
Nystagmus, dysarthria, and ataxia	phenytoin, carbamazepine, alcohol, and other sedative intoxication
Twitching and muscular hyperactivity	atropine and other anticholinergic agents, and cocaine and other sympathomimetic drugs.
Muscular rigidity	haloperidol and other antipsychotic agents
Seizures	Antidepressants, cocaine, amphetamines

Laboratory & Imaging Procedures

A. Arterial Blood Gases

Hypoventilation results in an elevated Pco_2 (hypercapnia) and a low Po_2 (hypoxia). Poor tissue oxygenation will result in metabolic acidosis. The Po_2 measures only oxygen dissolved in the plasma and not total blood oxygen content and may appear normal in patients with severe carbon monoxide poisoning. Pulse oximetry may also give falsely normal results in carbon monoxide intoxication.

B. Electrolytes

Sodium, potassium, chloride, and bicarbonate should be measured. Alterations in the serum potassium level are hazardous because they can result in cardiac arrhythmias. Drugs that may cause hyperkalemia despite normal renal function include potassium itself, $\beta\alpha$ blockers, digitalis glycosides, potassium-sparing diuretics, and fluoride. Drugs associated with hypokalemia include barium, $\beta\alpha$ agonists, caffeine, theophylline, and thiazide and loop diuretics.

C. Renal Function Tests

Some toxins have direct nephrotoxic effects; in other cases, renal failure is due to shock or myoglobinuria. Blood urea nitrogen and creatinine levels should be measured and urinalysis performed. Elevated serum creatine kinase (CK) and myoglobin in the urine suggest muscle necrosis due to seizures or muscular rigidity. Oxalate crystals in large numbers in the urine suggest ethylene glycol poisoning.

D. Serum Osmolality

The calculated serum osmolality is dependent mainly on the serum sodium and glucose and the blood urea nitrogen.

Ethanol and other alcohols may contribute significantly to the measured serum osmolality but, since they are not included in the calculation, cause an osmol gap.

Some substances that can cause an osmol gap:

Substance	Serum level (mg/dL)	Corresponding Osmol Gap (mOsm/kg)
Ethanol	350	75
Methanol	80	25
Ethylene glycol	200	35
Isopropanol	350	60

E. Electrocardiogram

Widening of the QRS complex duration	antidepressant and quinidine
QTc interval prolongation	quinidine, antidepressants and antipsychotics, lithium, and arsenic
Variable atrioventricular block	digoxin and other cardiac glycosides

F. Imaging Findings

When head trauma is suspected, a computed tomography (CT) scan is recommended.

It is a common misconception that a broad toxicology is the best way to diagnose and manage an acute poisoning.

Unfortunately, it is time consuming and expensive and results of tests may not be available for days. Moreover, many highly toxic drugs are not included in the screening process.

When a specific antidote or other treatment is under consideration, quantitative laboratory testing may be indicated.

Decontamination

Decontamination involves removing toxins from the skin or gastrointestinal tract.

A. Skin

Contaminated clothing should be completely removed. Wash contaminated skin with soap and water.

B. Gastrointestinal Tract

For most ingestions, clinical toxicologists recommend simple administration of activated charcoal to bind ingested poisons in the gut before they can be absorbed. In unusual circumstances, induced emesis or gastric lavage may also be used.

1. Emesis

Emesis can be induced with ipecac syrup.

Ipecac should not be used if the suspected intoxicant is a corrosive agent, a petroleum distillate, or a rapid-acting convulsant.

2. Gastric lavage

Performed if the patient is awake. Lavage solutions (usually 0.9% saline) should be at body temperature to prevent hypothermia.

3. Activated charcoal

Charcoal does not bind iron, lithium, or potassium, and it binds alcohols and cyanide only poorly.

Repeated doses of oral activated charcoal may enhance systemic elimination of some drugs by a mechanism referred to as “gut dialysis,”

4. Cathartics

Administration of a cathartic (laxative) agent may hasten removal of toxins from the gastrointestinal tract and reduce absorption. Whole bowel irrigation with a balanced polyethylene glycol-electrolyte solution (GoLYTELY, CoLyte) can enhance gut decontamination. The solution is administered orally at 1–2 L/h (500 mL/h in children) for several hours until the rectal effluent is clear.

Methods of Enhancing Elimination of Toxins

A. Dialysis Procedures

1. Peritoneal dialysis

peritoneal dialysis is inefficient in removing most drugs.

2. Hemodialysis

It assists in correction of fluid and electrolyte imbalance and may also enhance removal of toxic metabolites.

Hemodialysis is especially useful in overdose cases in which the precipitating drug can be removed and fluid and electrolyte imbalances are present and can be corrected.

C. Forced Diuresis and Urinary pH Manipulation

Forced diuresis may cause volume overload and electrolyte abnormalities and is not recommended.

Renal elimination of a few toxins can be enhanced by alteration of urinary pH. For example, urinary alkalinization is useful in cases of salicylate overdose. Acidification may increase the urine concentration of drugs such as phencyclidine and amphetamines but is not advised because it may worsen renal complications from rhabdomyolysis, which often accompanies the intoxication.

Hemodialysis in drug overdose and poisoning. (This listing is not comprehensive.)

Hemodialysis may be indicated depending on the severity of poisoning or the blood concentration:

Carbamazepine

Ethylene glycol

Lithium

Methanol

Metformin

Phenobarbital

Salicylate

Theophylline

Valproic acid

Hemodialysis is ineffective or is not useful:

Amphetamines

Antidepressants

Antipsychotic drugs

Benzodiazepines

Calcium channel blockers

Digoxin

Metoprolol and propranolol



Specific Antidotes

The major antidotes and their characteristics are listed below:

Antidote	Poison(s)	Comments
Acetylcysteine (Acetadote, Mucomyst)	Acetaminophen	Best results if given within 8–10 hours of overdose. Follow liver function tests and acetaminophen blood levels. Acetadote is given intravenously; Mucomyst is given orally.
Atropine	Anticholinesterase intoxication: organophosphates, carbamates	An initial dose of 1–2 mg (for children, 0.05 mg/kg) is given IV and if there is no response the dose is doubled every 10–15 minutes, with decreased wheezing and pulmonary secretions as therapeutic end points.
Atropine	Rapid-onset mushroom poisoning with predominant muscarinic excess symptoms	Useful for control of muscarinic symptoms. Note: of no value in delayed-onset mushroom poisoning.
Bicarbonate, sodium	Membrane-depressant cardiotoxic drugs (tricyclic antidepressants, quinidine, etc)	1–2 mEq/kg IV bolus usually reverses cardiotoxic effects (wide QRS, hypotension). Give cautiously in heart failure (avoid sodium overload).
Calcium	Fluoride; calcium channel blockers	Large doses may be needed in severe calcium channel blocker overdose. Start with 15 mg/kg IV.
Deferoxamine	Iron salts	If poisoning is severe, give 15 mg/kg/h IV. 100 mg of deferoxamine binds 8.5 mg of iron.
Digoxin antibodies	Digoxin and related cardiac glycosides	One vial binds 0.5 mg digoxin; indications include serious arrhythmias, hyperkalemia.
Esmolol	Theophylline, caffeine, metaproterenol	Short-acting β blocker. Infuse 25–50 mcg/kg/min IV.
Ethanol	Methanol, ethylene glycol	A loading dose is calculated so as to give a blood level of at least 100 mg/dL (42 g/70 kg in adults). Fomepizole (see below) is easier to use.
Flumazenil	Benzodiazepines	Adult dose is 0.2 mg IV, repeated as necessary to a maximum of 3 mg. Do not give to patients with seizures, benzodiazepine dependence, or tricyclic overdose.
Fomepizole	Methanol, ethylene glycol	More convenient than ethanol. Give 15 mg/kg; repeat every 12 hours.
Glucagon	β blockers	5–10 mg IV bolus may reverse hypotension and bradycardia.
Hydroxocobalamin	Cyanide	Adult dose is 5 g IV over 15 minutes. Converts cyanide to cyanocobalamin (Vitamin B12).
Naloxone	Narcotic drugs, other opioid derivatives	A specific antagonist of opioids; give 0.4–2 mg initially by IV, IM, or SC injection. Larger doses may be needed to reverse the effects of overdose with propoxyphene, codeine, or fentanyl derivatives. Duration of action (2–3 hours) may be significantly shorter than that of the opioid being antagonized.
Oxygen	Carbon monoxide	Give 100% by high-flow nonrebreathing mask; use of hyperbaric chamber is controversial but often recommended for severe poisoning.
Physostigmine	Suggested for delirium caused by anticholinergic agents	Adult dose is 0.5–1 mg IV slowly. The effects are transient (30–60 minutes), and the lowest effective dose may be repeated when symptoms return. May cause bradycardia, increased bronchial secretions, seizures. Have atropine ready to reverse excess effects. Do not use for tricyclic antidepressant overdose.
Pralidoxime (2-PAM)	Organophosphate (OP) cholinesterase inhibitors	Adult dose is 1 g IV, which should be repeated every 3–4 hours as needed or preferably as a constant infusion of 250–400 mg/h. Pediatric dose is approximately 250 mg. No proved benefit in carbamate poisoning; uncertain benefit in established OP poisoning.

Common toxic syndromes

Acetaminophen

- ❖ Acetaminophen is one of the drugs commonly involved in suicide attempts and accidental poisonings.
- ❖ Acute ingestion of more than 150–200 mg/kg (children) or 7 g total (adults) is considered potentially toxic.
- ❖ A highly toxic metabolite is produced in the liver.
- ❖ patient is asymptomatic or has mild gastrointestinal upset after 24–36 hours, evidence of liver injury appears, with elevated aminotransferase levels and hypoprothrombinemia, and then fulminant liver failure occurs, leading to hepatic encephalopathy and death.
- ❖ If the level is greater than 150–200 mg/l approximately 4 hours after ingestion, the patient is at risk for liver injury.
- ❖ The antidote acetylcysteine

Amphetamines & other stimulants

- ❖ Methamphetamine (“crank,” “crystal”), methylenedioxymethamphetamine (mdma, “ecstasy”), and cocaine (“crack”)
- ❖ Caffeine is often added to dietary supplements sold as “metabolic enhancers” or “fat-burners.”
- ❖ Euphoria and wakefulness are accompanied by a sense of power at usual doses.
- ❖ At higher doses, restlessness, agitation, and acute psychosis may occur, accompanied by hypertension and tachycardia.
- ❖ Hyperthermia can cause brain damage, hypotension, coagulopathy, and renal failure.
- ❖ Treatment includes general supportive measures .there is no specific antidote.
- ❖ Symptoms are treated with benzodiazepines for seizures; temperature is reduced with clothing, spraying with tepid water.
- ❖ For very high body temperatures (eg,

acts as a glutathione substitute, binding the toxic metabolite as it is produced .it is most effective when given early.

> 40–41°C [104–105.8°F]), neuromuscular paralysis is used to abolish muscle activity quickly.

Anticholinergic agents

- ❖ A large number of drugs can inhibit the effects of acetylcholine at muscarinic receptors. Some drugs used for other purposes (eg, antihistamines) also have anticholinergic effects, in addition to other potentially toxic actions.
- ❖ For example, antihistamines such as diphenhydramine can cause seizures; tricyclic antidepressants, which have anticholinergic, quinidine-like, and blocking effects, can cause severe cardiovascular toxicity.
- ❖ The classic anticholinergic syndrome is remembered as

Antidepressants

- ❖ Tricyclic antidepressants are in life-threatening drug overdose. Ingestion of more than 1 g of a tricyclic (or about 15–20 mg/kg) is considered potentially lethal.
- ❖ Tricyclic antidepressants are competitive antagonists at muscarinic cholinergic receptors, and anticholinergic findings (tachycardia, dilated pupils, and dry mouth) are common.
- ❖ Tricyclics are also strong α blockers which can lead to vasodilation.
- ❖ Treatment with supportive care, endotracheal intubation and assisted ventilation may be needed. Intravenous fluids are given for hypotension, and dopamine or norepinephrine is

- “red as a beet” (skin flushed)
 - “hot as a hare” (hyperthermia)
 - “dry as a bone” (dry mucous membranes, no sweating)
 - “blind as a bat” (blurred vision, cycloplegia)
 - “mad as a hatter” (confusion, delirium).
- ❖ Urinary retention is common, especially in older men.
- ❖ Treatment for anticholinergic syndrome is largely supportive.
- ❖ Agitated patients may require sedation with a benzodiazepine or an antipsychotic agent (eg, haloperidol).
- ❖ The specific antidote for peripheral and central anticholinergic syndrome is physostigmine
- ❖ Physostigmine is given in small intravenous doses (0.5–1 mg) with careful

- added if necessary.
- ❖ The antidote for quinidine-like cardiac toxicity (manifested by a wide qrs complex) is sodium bicarbonate: a bolus of 50–100 meq (or 1–2 meq/kg) provides a rapid increase in extracellular sodium that helps overcome sodium channel blockade.
- ❖ Monoamine oxidase inhibitors can interact with the selective serotonin reuptake inhibitors
- ❖ (ssris) and cause hypertensive crisis.
- ❖ Newer antidepressants are mostly ssris and are generally safer.
- ❖ Bupropion (not an ssri) has caused seizures even in therapeutic doses.
- ❖ Some antidepressants have been associated with qt prolongation and torsades de pointes arrhythmia. Ssris may interact with each other or especially with monoamine oxidase inhibitors to cause the serotonin syndrome, characterized by agitation, muscle hyperactivity, and hyperthermia.

monitoring, because it can cause bradycardia and seizures if given too rapidly.

Antipsychotics

- ❖ They can cause CNS depression, seizures, and hypotension. Some can cause QT prolongation. The potent dopamine D₂ blockers are also associated with parkinsonian movement disorders (dystonic reactions) and in rare cases with the neuroleptic malignant syndrome, characterized by "lead-pipe" rigidity, hyperthermia, and autonomic instability

Aspirin (salicylate)

- ❖ Acute ingestion of salicylate more than 200 mg/kg is likely to produce intoxication.
- ❖ Poisoning causes uncoupling of oxidative phosphorylation and disruption of normal cellular metabolism.
- ❖ The first sign of salicylate toxicity is often hyperventilation and respiratory alkalosis due to medullary stimulation.
- ❖ The first sign of salicylate toxicity is hyperventilation and respiratory alkalosis due to medullary stimulation.
- ❖ Metabolic acidosis follows, and an increased anion gap results from accumulation of lactate as well as excretion of bicarbonate by the kidney to compensate for respiratory alkalosis.
- ❖ Arterial blood gas testing often reveals a mixed respiratory alkalosis and metabolic acidosis.



	<ul style="list-style-type: none"> ❖ Body temperature may be elevated owing to uncoupling of oxidative phosphorylation. ❖ Vomiting and hyperpnea as well as hyperthermia contribute to fluid loss and dehydration. ❖ General supportive care is essential. Gastric lavage and repeated doses of activated charcoal, and consideration of whole bowel irrigation. ❖ For moderate intoxications, intravenous sodium bicarbonate is given to alkalinize the urine and promote salicylate excretion by trapping the salicylate in its ionized, polar form. ❖ For severe poisoning emergency hemodialysis is performed to remove the salicylate more quickly and restore acid base balance and fluid status.
Beta blockers	<ul style="list-style-type: none"> ❖ In overdose, β blockers inhibit both β_1 and β_2 adrenoceptors;
Calcium channel blockers	<ul style="list-style-type: none"> ❖ These channel blockers depress sinus node automaticity and



selectivity, if any, is lost at high dosage.

- ❖ The most toxic b blocker is propranolol. Because propranolol in high doses may cause sodium channel blocking effects similar to those seen with quinidine-like drugs, and it is lipophilic, allowing it to enter the cns
- ❖ Bradycardia and hypotension are the most common manifestations of toxicity.
- ❖ Agents with partial agonist activity (eg, pindolol) can cause tachycardia and hypertension.
- ❖ General supportive care and glucagon is a useful antidote that—like b agonists— acts on cardiac cells to raise intracellular camp but does so independent of b adrenoceptors.
- ❖ It can improve heart rate and blood pressure when given in high doses (5–20 mg intravenously).

slow av node conduction

- ❖ They also reduce cardiac output and blood pressure. Serious hypotension is mainly seen with nifedipine and related dihydropyridines
- ❖ Treatment requires general supportive care.
- ❖ For sustained-release form initiate whole bowel irrigation and oral activated charcoal as soon as possible, before calcium antagonist-induced ileus intervenes.
- ❖ Calcium, given intravenously in doses of 2–10 g, is a useful antidote for depressed cardiac contractility but less effective for nodal block or peripheral vascular collapse. Other treatments reported to be helpful
- ❖ In managing hypotension associated with calcium channel blocker poisoning include glucagon and high-dose insulin (0.5–1 unit/kg/h) plus glucose supplementation to

maintain euglycemia.

- ❖ Intralipid, normally used as an intravenous dietary fat supplement) for severe verapamil overdose.

Cholinesterase inhibitors

- ❖ Organophosphate and carbamate cholinesterase inhibitors stimulate muscarinic receptors cause abdominal cramps, diarrhea, excessive salivation, sweating, and urinary frequency.
- ❖ Stimulation of nicotinic receptors causes generalized ganglionic activation, which can lead to hypertension and either tachycardia or bradycardia.
- ❖ Muscle twitching and fasciculations may progress to weakness and respiratory muscle paralysis.
- ❖ The mnemonic dumbells (diarrhea, urination, mitosis and muscle weakness, bronchospasm, excitation, lacrimation, and seizures, sweating, and salivation)
- ❖ Blood testing to document

Cyanide

- ❖ Cyanide (cn^-) salts and hydrogen cyanide (hcn) are highly toxic chemicals used in chemical synthesis, as rodenticides.
- ❖ Cyanide is also released after ingestion of various plants (eg, cassava) and seeds (eg, apple, peach, and apricot).
- ❖ Cyanide binds readily to cytochrome oxidase, inhibiting oxygen utilization within the cell and leading to cellular hypoxia and lactic acidosis.
- ❖ Symptoms of cyanide poisoning include shortness of breath, agitation, and tachycardia also severe metabolic acidosis.
- ❖ The venous oxygen content may be elevated because oxygen is not being taken up by

depressed activity of red blood cell (acetylcholinesterase) and plasma (butyrylcholinesterase) enzymes, which provide an indirect estimate of synaptic cholinesterase activity.

- ❖ Antidotal treatment consists of atropine and pralidoxime. Atropine is an effective competitive inhibitor at muscarinic sites but has no effect at nicotinic sites.
- ❖ Pralidoxime given early enough may be capable of restoring the cholinesterase activity and is active at both muscarinic and nicotinic sites.

cells.

- ❖ Treatment includes rapid administration of activated charcoal (although charcoal binds cyanide poorly, it can reduce absorption) and general supportive care.
- ❖ There is an antidote kit available form of nitrite (amyl nitrite and sodium nitrite) and sodium thiosulfate.
- ❖ The nitrites induce methemoglobinemia, which binds CN^- , creating the less toxic cyanomethemoglobin; thiosulfate is a cofactor in the enzymatic conversion of CN^- to the much less toxic thiocyanate (SCN^-).
- ❖ Hydroxocobalamin (one form of vitamin b12) is a new cyanide antidote, it combines rapidly with CN^- to form nontoxic cyanocobalamin (another form of vitamin b12)

TABLE 58-5 Characteristics of poisoning with some gases.

Gas	Mechanism of Toxicity	Clinical Features and Treatment
Irritant gases (eg, chlorine, ammonia, sulfur dioxide, nitrogen oxides)	Corrosive effect on upper and lower airways	Cough, stridor, wheezing, pneumonia <i>Treatment:</i> Humidified oxygen, bronchodilators
Carbon monoxide	Binds to hemoglobin, reducing oxygen delivery to tissues	Headache, dizziness, nausea, vomiting, seizures, coma <i>Treatment:</i> 100% oxygen; consider hyperbaric oxygen
Cyanide	Binds to cytochrome, blocks cellular oxygen use	Headache, nausea, vomiting, syncope, seizures, coma <i>Treatment:</i> Conventional antidote kit consists of nitrites to induce methemoglobinemia (which binds cyanide) and thiosulfate (which hastens conversion of cyanide to less toxic thiocyanate); a newer antidote kit (Cyanokit) consists of concentrated hydroxocobalamin, which directly converts cyanide into cyanocobalamin
Hydrogen sulfide	Similar to cyanide	Similar to cyanide. Smell of rotten eggs <i>Treatment:</i> No specific antidote; some authorities recommend the nitrite portion of the conventional cyanide antidote kit.
Oxidizing agents (eg, nitrogen oxides)	Can cause methemoglobinemia	Dyspnea, cyanosis (due to brown color of methemoglobin), syncope, seizures, coma <i>Treatment:</i> Methylene blue (which hastens conversion back to normal hemoglobin)

Digoxin

- ❖ Toxicity may occur as a result of acute overdose or from accumulation of digoxin in a patient with renal insufficiency or from taking a drug that interferes with digoxin elimination.
- ❖ Patients receiving long-term digoxin treatment are often also taking diuretics, which can lead to electrolyte depletion (especially potassium).
- ❖ Vomiting is common in patients with digitalis overdose.
- ❖ Hyperkalemia may be caused by acute digitalis overdose or severe poisoning,

Ethanol & sedative-hypnotic drugs

- ❖ Patients with ethanol or other sedative-hypnotic overdose may be euphoric and rowdy ("drunk") or in a state of stupor or coma ("dead drunk").
- ❖ Comatose patients often have depressed respiratory drive which may result in pulmonary aspiration of gastric contents, leading to pneumonia.
- ❖ Hypothermia is present.
- ❖ Ethanol blood levels greater than 300 mg/dl usually cause deep coma.
- ❖ General supportive care should be provided.
- ❖ Hypotension usually responds to

whereas hypokalemia may be present in patients as a result of long-term diuretic treatment.

- ❖ (digitalis does not cause hypokalemia.)
- ❖ A variety of cardiac rhythm disturbances may occur
- ❖ Treatment with general supportive care and atropine is often effective for bradycardia or av block.
- ❖ Digoxin antibodies may also be tried in cases of poisoning by other cardiac glycosides (eg, digitoxin, oleander), although larger doses may be needed due to incomplete cross-reactivity.

intravenous fluids and dopamine if needed.

- ❖ Patients with isolated benzodiazepine overdose may awaken after intravenous flumazenil. However, this drug may precipitate seizures in patients who are addicted to benzodiazepines or who have ingested a convulsant drug (eg, a tricyclic antidepressant).

Ethylene glycol & methanol

- ❖ Ethylene glycol and methanol have highly toxic organic acids metabolites.
- ❖ They are capable of causing cns depression and a drunken state similar to ethanol overdose.
- ❖ In addition, their products of metabolism—formic acid (from methanol), oxalic, and glycolic acids (from ethylene glycol)—cause a severe metabolic acidosis and can lead to coma and blindness (in the case of formic acid) or renal failure (from oxalic acid and glycolic acid).
- ❖ Severe anion gap metabolic acidosis becomes apparent, accompanied by hyperventilation and altered mental status.
- ❖ Metabolism of ethylene glycol and methanol to their toxic products can be blocked by inhibiting the enzyme alcohol dehydrogenase with a competing drug, such as

fomepizole (4 methylpyrazole).

- ❖ Ethanol is also an effective antidote, but it can be difficult to achieve a safe and effective blood level.

Iron & other metals

Iron is a leading cause of childhood poisoning deaths. As few as 10–12 prenatal multivitamins with iron may cause serious illness in a small child.

Opioids

Opioids (opium, morphine, heroin, meperidine, methadone, etc.) Are common drugs of abuse.

Rattlesnake envenomation

- ❖ Rattlesnakes are the most common venomous reptiles. 60% of bites cause significant morbidity due to the destructive digestive enzymes found in the venom.
- ❖ Evidence of rattlesnake envenomation includes severe pain, swelling, bruising, hemorrhagic bleb formation, and obvious fang marks.
- ❖ Systemic effects include nausea, vomiting, and muscle fasciculations
- ❖ Emergency field remedies such as incision and suction,



tourniquets, and ice packs are far more damaging than useful.

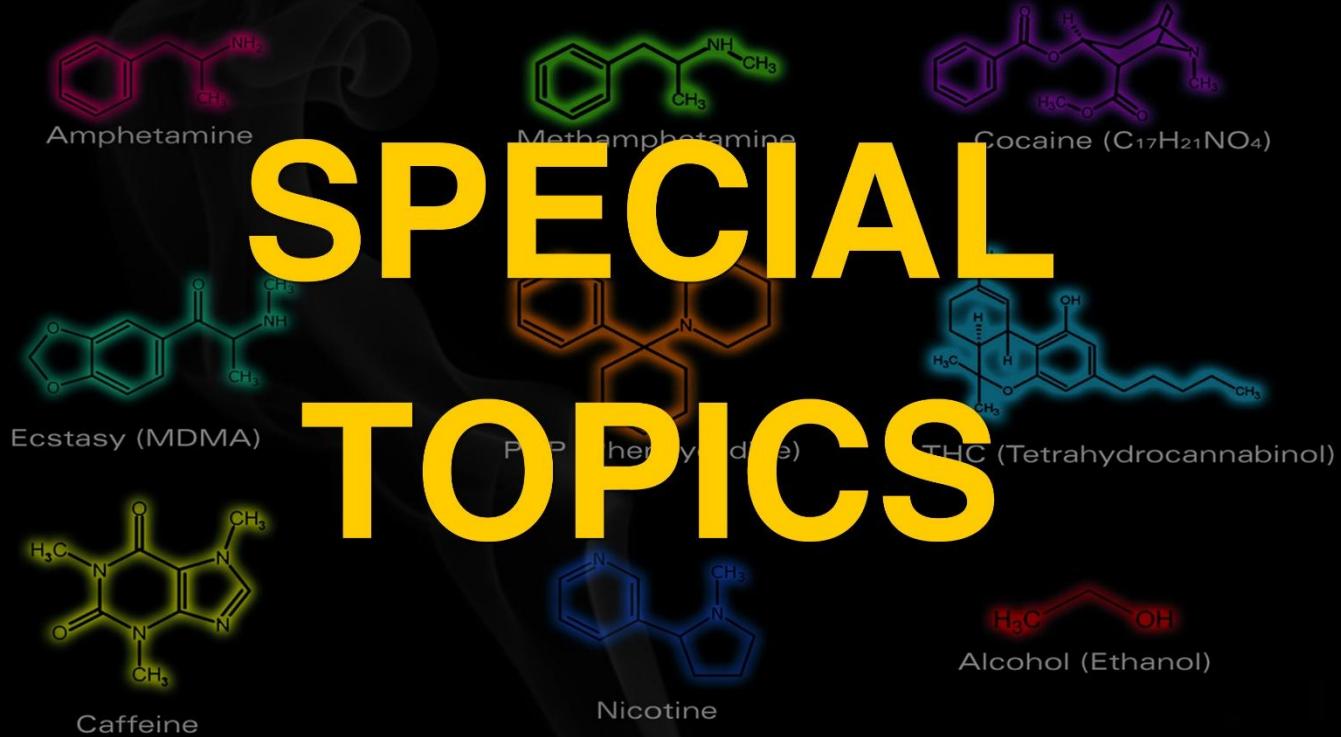
Avoidance of unnecessary motion, on the other hand, does help to limit the spread of the venom. Definitive therapy relies on intravenous antivenom (also known as antivenin)

Theophylline

- ❖ Theophylline is used for the treatment of bronchospasm by some patients with asthma and bronchitis. A dose of 20–30 tablets can cause serious or fatal poisoning.
- ❖ Chronic or subacute theophylline poisoning occur as result of accidental overmedication or use of a drug that interferes with theophylline metabolism (eg, cimetidine, ciprofloxacin)
- ❖ Symptoms are sinus tachycardia and tremor hypotension, tachycardia, hypokalemia, and hyperglycemia owing to β_2 -adrenergic activation, the effects can be ameliorated by β blockers
- ❖ In severe poisoning (eg, acute overdose with serum level > 100 mg/l), seizures often occur and are usually resistant to common anticonvulsants.
- ❖ General supportive care should be provided. Aggressive gut decontamination should be carried out using repeated doses of activated charcoal and whole bowel irrigation. Propranolol or other β blockers (eg, esmolol) are useful antidotes. Phenobarbital is preferred over phenytoin for convulsions
- ❖ Hemodialysis is indicated for serum concentrations greater than 100 mg/l and for intractable seizures in patients with lower levels.



section 10



59 - Special Aspects of Perinatal & Pediatric Pharmacology

60 - Special Aspects of Geriatric Pharmacology

61 - Dermatologic Pharmacology

62 - Drugs Used in the Treatment of Gastrointestinal Diseases

63 - Therapeutic & Toxic Potential of Over-the-Counter Agents

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Section X: SPECIAL TOPICS

Chapter 59: Special Aspects of Perinatal & Pediatric Pharmacology

DRUG THERAPY IN PREGNANCY

Pharmacokinetics

Most drugs taken by pregnant women can cross the placenta and expose the developing embryo and fetus to their pharmacologic and teratogenic effects.

Factors affecting placental drug transfer and drug effects on the fetus:

- 1) The physicochemical properties of the drug.
- 2) The rate at which the drug crosses the placenta and the amount of drug reaching the fetus.
- 3) The duration of exposure to the drug
- 4) Distribution characteristics in different fetal tissues.
- 5) The stage of placental and fetal development at the time of exposure to the drug.
- 6) The effects of drugs used in combination.

A. Lipid Solubility

Drug passage across the placenta is dependent on:

Lipid Solubility

- Lipophilic drugs tend to diffuse readily across the placenta and enter the fetal circulation.
 - e.g.: thiopental.

Degree Of Drug Ionization

- Highly ionized drugs cross the placenta slowly and achieve very low



concentrations in the fetus.

- e.g.: succinylcholine and tubocurarine.

Polarity

- Impermeability of the placenta to polar compounds is relative rather than absolute. If high enough maternal-fetal concentration gradients are achieved, polar compounds cross the placenta in measurable amounts.
 - Salicylate, which is almost completely ionized at physiologic pH, crosses the placenta rapidly. This occurs because the small amount of salicylate that is not ionized is highly lipid-soluble.

B. Molecular Size and pH

The molecular weight of the drug influences:

- 1) The rate of drug transfer
- 2) The amount of drug transferred across the placenta.

Drugs Molecular Weights	Cross The Placenta (Easily/Poorly)
250–500	<ul style="list-style-type: none">- Cross the placenta easily.- Depending upon their lipid solubility, and degree of ionization.
500–1000	Cross the placenta with more difficulty
Greater than 1000	Cross very poorly.

Important Clinical Application of This Property:

- The choice of heparin as an anticoagulant in pregnant women: Because it is a very large (and polar) molecule, heparin is unable to cross the placenta. Unlike warfarin, which is teratogenic.

- The placenta contains drug transporters, which can carry larger molecules to the fetus:

For example, a variety of maternal antibodies cross the placenta and may cause fetal morbidity, as in case of Rh incompatibility.

C. Placental Transporters

P-glycoprotein transporter:

- Encoded by the *MDRI* gene pumps back into the maternal circulation.
- Variety of drugs, including cancer drugs (e.g., vinblastine, doxorubicin) viral protease inhibitors other agents.

BCRP and MRP3 transporter:

The hypoglycemic drug glyburide has much lower plasma levels in the fetus as compared with the mother:

- Glyburide is effluxed from the fetal circulation by the BCRP and MRP3 transporter located in the placental brush border membrane.
- Very high maternal protein binding of glyburide

D. Protein Binding

The degree to which a drug is bound to plasma proteins (particularly albumin) may also affect the rate of transfer and the amount transferred.

Very lipid-soluble compound:

- It will not be affected greatly by protein binding, (eg, some anesthetic gases).
- Transfer of these more lipid-soluble drugs and their overall rates of equilibration are more dependent on placental blood flow. This is because very lipid-soluble drugs diffuse across placental membranes so rapidly that their overall rates of equilibration do not depend on the free drug concentrations becoming equal on both sides.

Poorly lipid-soluble and ionized:

Its transfer is slow and will probably be impeded by its binding to maternal plasma proteins.

Some drugs exhibit greater protein binding in maternal plasma than in fetal plasma because of a lower binding affinity of fetal proteins. This has been shown for sulfonamides, barbiturates, phenytoin, and local anesthetic agents.

E. Placental and Fetal Drug Metabolism

Two mechanisms help protect the fetus from drugs in the maternal circulation:



(1) The placenta itself plays a role both as a semipermeable barrier and as a site of metabolism of some drugs passing through it:

- Several different types of aromatic oxidation reactions (eg, hydroxylation, N-dealkylation, demethylation occur in placental tissue.
- Conversely, the metabolic capacity of the placenta may lead to creation of toxic metabolites, and the placenta may therefore augment toxicity (eg, ethanol, benzpyrenes).

(2) Drugs that have crossed the placenta enter the fetal circulation via the umbilical vein:

- About 40–60% of umbilical venous blood flow enters the fetal liver; the remainder bypasses the liver and enters the general fetal circulation. A drug that enters the liver may be partially metabolized there before it enters the fetal circulation.
- Large proportion of drug present in the umbilical artery (returning to the placenta) may be shunted through the placenta back to the umbilical vein and into the liver again.
- Metabolites of some drugs may be more active than the parent compound and may affect the fetus adversely.

Pharmacodynamics

A. Maternal Drug Actions

During pregnancy cardiac output, renal blood flow, etc. may be altered, requiring the use of drugs that are not needed by the same woman when she is not pregnant. For example, cardiac glycosides and diuretics may be needed for heart failure precipitated by the increased cardiac workload of pregnancy, or insulin may be required for control gestational diabetes.

B. Therapeutic Drug Actions in the Fetus

Fetal therapeutics is an emerging area in perinatal pharmacology, examples include:

- Corticosteroids are used to stimulate fetal lung maturation when preterm birth is expected.
- Phenobarbital, when given to pregnant women near term, can induce fetal hepatic enzymes responsible for the glucuronidation of bilirubin, decreasing the incidence of jaundice in newborns.
- Antiarrhythmic drugs have also been given to mothers for treatment of fetal cardiac arrhythmias.

- Maternal use of zidovudine decreases the transmission of HIV from the mother to the fetus, and use of combinations of three antiretroviral agents can eliminate fetal infection almost entirely.

C. Predictable Toxic Drug Actions in the Fetus

- Chronic use of opioids by the mother may produce dependence in the fetus and newborn, leading to neonatal withdrawal syndrome.
- The use of angiotensin-converting enzyme inhibitors during pregnancy can result in significant and irreversible renal damage in the fetus.
- Adverse effects may also be delayed, as in the case of female fetuses exposed to diethylstilbestrol, who may be at increased risk for adenocarcinoma of the vagina after puberty.

D. Teratogenic Drug Actions

A single intrauterine exposure to a drug can affect the fetal structures undergoing rapid development at the time of exposure. Thalidomide affects the development of the limbs after only brief exposure leading to phocomelia. The risk occurs during the fourth through the seventh weeks of gestation because it is during this time that the arms and legs develop.

1. Teratogenic mechanisms:

Drugs may have a direct effect on maternal tissues with secondary or indirect effects on fetal tissues:

Drugs may interfere with the passage of oxygen or nutrients through the placenta and therefore have effects on the most rapidly metabolizing tissues of the fetus.

Drugs may have important direct actions on the processes of differentiation in developing tissues:

Vitamin A (retinol) and its several analogs (isotretinoin, etretinate) are powerful teratogens, they alter the normal processes of differentiation.

Deficiency of a critical substance plays a role in some types of abnormalities:

Folic acid supplementation during pregnancy reduces the incidence of neural tube defects (eg, spina bifida).

Continued exposure to a teratogen may produce cumulative effects:

Chronic consumption of high doses of ethanol during pregnancy, particularly during the first and second trimesters, may result in the fetal alcohol syndrome.

2. Defining a teratogen:

Substance or process considered teratogenic if:

- 1) Result in a characteristic set of malformations, indicating selectivity for certain target organs.
- 2) Exert its effects at a particular stage of fetal development (figure 59–1).
- 3) Show a dose-dependent incidence.

Teratogenic could lead to:

Major malformations
(eg, Thalidomide)

Miscarriage
(eg, alcohol),

Intrauterine growth restriction
(eg, cigarette smoking),

Stillbirth
(eg, cigarette smoke),

Neurocognitive delay
(eg, alcohol, valproic acid).

3. Counseling women about teratogenic risk

- Every woman needs counseling about fetal exposure to drugs, chemicals, and radiation.
- Information should be up-to-date and evidence-based.
- Woman should understand that the risk of a neonatal abnormality in the absence of any known teratogenic exposure is about 3%.
- It is also critical to address the maternal-fetal risks of the untreated condition if a medication is avoided.
 - e.g.: Discontinuing selective serotonin reuptake inhibitor therapy for depression in pregnancy could lead to serious morbidity in women.

DRUG THERAPY IN INFANTS & CHILDREN

Physiologic processes that influence pharmacokinetic variables in the infant change significantly in the first year of life, particularly during the first few months. Therefore, special attention must be paid to pharmacokinetics in this age group.

Pharmacodynamic differences between pediatric and other patients have not been explored in great detail, except for those specific target tissues that mature at birth or immediately thereafter (eg, the ductus arteriosus).

Drug Distribution

Body Water: As body composition changes with development, the distribution volumes of drugs are also changed. Most neonates will experience diuresis in the first 24–48 hours of life. Since many drugs are distributed throughout the extracellular water space, the size (volume) of the extracellular water compartment may be important in determining the concentration of drug at receptor sites. This is especially important for water-soluble drugs (such as aminoglycosides) and less crucial for lipid soluble agents.

Age Groups	% of body weight as water	Extracellular Water
Full-term neonate	70%	
Small preterm neonate	85%	40%
Adult	50–60%	20%

Body Fat: Preterm infants have much less fat than full-term infants. Therefore, organs that generally accumulate high concentrations of lipid-soluble drugs in adults and older children may accumulate smaller amounts of these agents in less mature infants.

Age Groups	Total Body Fat
preterm infants	1%
full-term neonates	15%

Binding to Plasma Proteins: Another major factor determining drug distribution is drug binding to plasma proteins. Albumin is the plasma protein with the greatest binding capacity. In general, protein binding of drugs is reduced in the neonate. This has been seen with local anesthetic drugs, diazepam, phenytoin, ampicillin, and phenobarbital. Therefore, the

concentration of free (unbound) drug in plasma is increased initially. Because the free drug exerts the pharmacologic effect, this can result in greater drug effect or toxicity despite a normal or even low plasma concentration of total drug (bound plus unbound).

Serum Bilirubin:

- Some drugs compete with serum bilirubin for binding to albumin. Drugs given to a neonate with jaundice can displace bilirubin from albumin. Because of the greater permeability of the neonatal blood-brain barrier, substantial amounts of bilirubin may enter the brain and cause kernicterus. This was in fact observed when sulfonamide antibiotics were given to preterm neonates as prophylaxis against sepsis.
- Conversely, as the serum bilirubin rises for physiologic reasons or because of a blood group incompatibility, bilirubin can displace a drug from albumin and substantially raise the free drug concentration. This may occur without altering the total drug concentration and would result in greater therapeutic effect or toxicity at normal concentrations. This has been shown to happen with phenytoin.

Drug Metabolism

The metabolism of most drugs occurs in the liver. The drug-metabolizing activities of the cytochrome P450-dependent mixed-function oxidases and the conjugating enzymes are substantially lower (50–70% of adult values) in early neonatal life than later. The point in development at which enzymatic activity is maximal depends upon the specific enzyme system in question. **Glucuronide formation** reaches adult values between the third and fourth years of life.

Because of the neonate's decreased ability to metabolize drugs, many drugs have slow clearance rates and prolonged elimination half-lives. If drug doses and dosing schedules are not altered appropriately, this immaturity predisposes the neonate to adverse effects from drugs that are metabolized by the liver.

The process of maturation must be considered when administering drugs to this age group, especially in the case of drugs administered over long periods.

If the mother was receiving drugs (eg, phenobarbital) this can induce early maturation of fetal hepatic enzymes. In this case, the ability of the neonate to metabolize certain drugs will be greater than expected, less therapeutic effect and lower plasma drug concentrations when the usual neonatal dose is given. During toddlerhood (12–36 months), the metabolic rate of many drugs exceeds adult values, often necessitating larger doses per kilogram than later in life.

Drug Excretion

The glomerular filtration rate is much lower in newborns than in older infants, children, or adults, and this limitation persists during the first few days of life. Glomerular filtration in the neonate is only 30–40% of the adult value. The glomerular filtration rate is even lower in neonates born before 34 weeks of gestation. Function improves substantially during the first week of life. At the end of the first week, the glomerular filtration rate and renal plasma flow have increased 50% from the first day. By the end of the third week, glomerular filtration is 50–60% of the adult value; by 6–12 months, it reaches adult values (per unit surface area). Subsequently, during toddlerhood, it exceeds adult values.

- Therefore, drugs that depend on renal function for elimination are cleared from the body very slowly in the first weeks of life. Penicillins, for example, are cleared by preterm infants at 17% of the adult rate based on comparable surface area and 34% of the adult rate when adjusted for body weight. The dosage of ampicillin for a neonate less than 7 days old is 50–100 mg/kg/d in two doses at 12-hour intervals. The dosage for a neonate over 7 days old is 100–200 mg/kg/d in three doses at 8-hour intervals. A decreased rate of renal elimination in the neonate has also been observed with aminoglycoside antibiotics (kanamycin, gentamicin, neomycin, and streptomycin).
- Total body clearance of digoxin is directly dependent upon adequate renal function, and accumulation of digoxin can occur when glomerular filtration is decreased. Since renal function in a sick infant may not improve at the predicted rate during the first weeks and months of life, appropriate adjustments in dosage and dosing schedules may be very difficult. In this situation, adjustments are best made on the basis of plasma drug

concentrations determined at intervals throughout the course of therapy.

- It is important to remember that toddlers may have *shorter* elimination half-lives of drugs than older children and adults, due probably to *increased* renal elimination and metabolism. For example, the dose per kilogram of digoxin is much higher in toddlers than in adults.

Special Pharmacodynamics Features in the Neonate

The appropriate use of drugs has made possible the survival of neonates with severe abnormalities who would otherwise die within days or weeks after birth. For example:

- Administration of indomethacin causes the rapid closure of a patent ductus arteriosus, which would otherwise require surgical closure in an infant with a normal heart.
- Infusion of prostaglandin E1, on the other hand, causes the ductus to remain open, which can be lifesaving in an infant with transposition of the great vessels or tetralogy of Fallot. An unexpected effect of such infusion has been described when the drug caused antral hyperplasia with gastric outlet obstruction as a clinical manifestation in 6 of 74 infants who received it. This phenomenon appears to be dose-dependent.
- Neonates are also more sensitive to the central depressant effects of opioids than are older children and adults, necessitating extra caution when they are exposed to some narcotics (eg, codeine) through breastmilk.

At birth, the function of drug transporters may be very low; for example:

- P-glycoprotein, which pumps morphine from the blood-brain barrier back to the systemic circulation. Low-level function of P-glycoprotein at birth may explain why neonates are substantially more sensitive than older children to the central nervous system depressant effects of morphine.

PEDIATRIC DOSAGE FORMS & COMPLIANCE

The form in which a drug is manufactured and the way in which the parent dispenses the drug to the child determines the actual dose administered. Many drugs prepared for children are in the form of elixirs or suspensions:

- **Elixirs** are alcoholic solutions in which the drug molecules are dissolved and evenly distributed. Noshaking is required, and unless some of the vehicle has evaporated, the first dose from the bottle and the last dose should contain equivalent amounts of drug.
- **Suspensions** contain undissolved particles of drug that must be distributed throughout the vehicle by shaking. If shaking is not thorough each time a dose is given, the first doses from the bottle may contain less drug than the last doses, with the result that less than the expected plasma concentration or effect of the drug may be achieved early in the course of therapy. Conversely, toxicity may occur late in the course of therapy, when it is not expected. This uneven distribution is a potential cause of inefficacy or toxicity in children taking phenytoinsuspensions. It is thus essential that the prescriber know the form in which the drug will be dispensed and provide proper instructions to the pharmacist and patient or parent.
- **Compliance** may be more difficult to achieve in pediatric practice than otherwise, since it involves not only the parent's conscientious effort to follow directions but also such practical matters as measuring errors, spilling, and spitting out. The parents should obtain a calibrated medicine spoon or syringe from the pharmacy. These devices improve the accuracy of dose measurements and simplify administration of drugs to children.
- When **evaluating compliance**, it is often helpful to ask if an attempt has been made to give a further dose after the child has spilled half of what was offered. The parents may not always be able to say with confidence how much of a dose the child actually received. The parents must be told whether or not to wake the infant for its every-6-hour dose day or night. These matters should be discussed and made clear, and no assumptions should be made about what the parents may or may not do.
- **Noncompliance** frequently occurs when antibiotics are prescribed to treat otitis media or urinary tract infections and the child feels well after 4 or 5 days of therapy. The parents may not feel there is any reason to continue giving the medicine even though it was prescribed for 10 or 14 days. This common situation should be anticipated so the parents can be told why it is important to continue giving the

medicine for the prescribed period even if the child seems to be “cured.”

- **Practical and convenient dosage forms and dosing schedules** should be chosen to the extent possible. The easier it is to administer and take the medicine and the easier the dosing schedule is to follow, the more likely it is that compliance will be achieved.
- **Children should be given some responsibility** for their own health care and for taking medications. This should be discussed in appropriate terms both with the child and with the parents. Possible adverse effects and drug interactions with over-the-counter medicines or foods should also be discussed.
- Whenever a drug does not achieve its therapeutic effect, the possibility of noncompliance should be considered. There is ample evidence that in such cases parents’ or children’s reports may be grossly inaccurate. **Random pill counts and measurement of serum concentrations** may help disclose noncompliance. The use of **computerized pill containers**, which record each lid opening, has been shown to be very effective in measuring compliance.
- Because many pediatric doses are calculated—eg, using bodyweight—rather than simply read from a list, **major dosing errors may result from incorrect calculations**. Typically, tenfold errors due to incorrect placement of the decimal point have been described. A good rule for avoiding such “decimal point” errors is to use a leading “0” plus decimal point when dealing with doses less than “1” and to avoid using a zero after a decimal point.

DRUG USE DURING LACTATION

Most drugs are excreted into breast milk in amounts too small to adversely affect neonatal health.

Therefore, the total amount the infant would receive in a day is substantially less than what would be considered a “therapeutic dose.” If the nursing mother must take medications and the drug is a relatively safe one, she should optimally take it 30–60 minutes after nursing and 3–4 hours before the next feeding. In some cases this may allow time for drugs to be partially cleared from the mother’s blood, and the concentrations in breast milk will be relatively low.

Drug	Comments
Sedatives and	Most achieve concentrations in breast milk sufficient to

hypnotics	<p>produce a pharmacologic effect in some infants.</p> <ul style="list-style-type: none"> - Barbiturates taken in hypnotic doses by the mother can produce lethargy, sedation, and poor suck reflexes in the infant. - Chloral hydrate can produce sedation if the infant is fed at peak milk concentrations. - Diazepam can have a sedative effect on the nursing infant, but, most importantly, its long half-life can result in significant drug accumulation.
Opioids	<ul style="list-style-type: none"> - Such as heroin, methadone, and morphine enter breast milk in quantities potentially sufficient to prolong the state of neonatal narcotic dependence if the drug was taken chronically by the mother during pregnancy. - If conditions are well controlled and there is a good relationship between the mother and the physician, an infant could be breast-fed while the mother is taking methadone. She should not, however, stop taking the drug abruptly; the infant can be tapered off the methadone as the mother's dose is tapered. The infant should be watched for signs of narcotic withdrawal. Although codeine has been believed to be safe, a recent case of neonatal death from opioid toxicity revealed that the mother was an ultra rapid metabolizer of cytochrome 2D6 substrates, producing substantially higher amounts of morphine. - Hence, polymorphism in maternal drug metabolism may affect neonatal exposure and safety. A subsequent case control study has shown that this situation is not rare. The FDA has published a warning to lactating mothers to exert extra caution while using painkillers containing codeine.
Alcohol	<ul style="list-style-type: none"> - Minimal use of alcohol by the mother has not been reported to harm nursing infants. - Excessive amounts of alcohol, however, can produce alcohol effects in the infant.
Nicotine	Low in the breast milk of smoking mothers and do not



	produce effects in the infant.
Lithium	Enters breast milk in concentrations equal to those in maternal serum. Clearance of this drug is almost completely dependent upon renal elimination, and women who are receiving lithium may expose the infant to relatively large amounts of the drug.
Radioactive substances	Iodinated ^{125}I albumin and radioiodine can cause thyroid suppression in infants and may increase the risk of subsequent thyroid cancer as much as tenfold. Breast-feeding is contraindicated after large doses and should be withheld for days to weeks after small doses.
Cancer chemotherapy, Cytotoxic, Immunomodulating agents	Breast-feeding should be avoided in mothers receiving cancer chemotherapy or being treated with cytotoxic or immunomodulating agents for collagen diseases such as lupus erythematosus or after organ transplantation.

PEDIATRIC DRUG DOSAGE

Because of differences in pharmacokinetics in infants and children, simple proportionate reduction in the adult dose may not be adequate to determine a safe and effective pediatric dose. The most reliable pediatric dose information is usually that provided by the manufacturer in the package insert.

Most drugs approved for use in children have recommended pediatric doses, generally stated as milligrams per kilogram or per pound. In the absence of explicit pediatric dose recommendations, an approximation can be made by any of several methods based on age, weight, or surface area. These rules are not precise and should not be used if the manufacturer provides a pediatric dose.

When pediatric doses are calculated, the pediatric dose should never exceed the adult dose.



Studies in adults indicate that dosing based on per-kilogram body weight may constitute overdosing, because in obese subjects, drugs are distributed based on lean body weight.

Surface Area, Age, & Weight

Calculations of dosage based on age or weight are conservative and tend to underestimate the required dose. Doses based on surface area (Table 59–6) are more likely to be adequate.

In spite of these approximations, only by conducting studies in children can safe and effective doses for given a condition be determined.

Age (Young's rule):

$$\text{Dose} = \text{Adult dose} \times \frac{\text{Age (years)}}{\text{Age} + 12}$$

Weight (somewhat more precise is Clark's rule):

$$\text{Dose} = \text{Adult dose} \times \frac{\text{Weight (kg)}}{70}$$

or

$$\text{Dose} = \text{Adult dose} \times \frac{\text{Weight (lb)}}{150}$$

TABLE 59–6 Determination of drug dosage from surface area.¹

Weight (kg)	Approximate Age	Surface Area (m ²)	Percent of Adult Dose
3	6.6	Newborn	0.2
6	13.2	3 months	0.3
10	22	1 year	0.45
20	44	5.5 years	0.8
30	66	9 years	1
40	88	12 years	1.3
50	110	14 years	1.5
60	132	Adult	1.7
70	154	Adult	1.76
			103

¹For example, if adult dose is 1 mg/kg, dose for 3-month-old infant would be 0.18 mg/kg or 1.1 mg total.

CHAPTER 60:Special Aspects of Geriatric Pharmacology

Chronologic age is only one determinant of the changes pertinent to drug therapy that occur in older people. In addition to the chronic diseases in the elderly, they have an increased incidence of many conditions. As a result, the need for drug treatment is great in this age group. It has long been known that caloric restriction alone can prolong the life span of animals, including mammals. Drugs that mimic caloric restriction have been shown to increase lifespan. **Metformin** and **rapamycin** each increase life span alone and appear to have synergistic effects when given together. Sirtuins, a class of endogenous protein deacetylase enzymes, may be linked to life span in some species. General changes in the lives of older people have significant effects on the way drugs are used. In the general population, measurements of functional capacity of most of the major organ systems show a linear decrease beginning no later than age 45. The elderly do not lose specific functions at an accelerated rate compared with young and middle-aged adults. The health practitioner should be aware of the changes in pharmacologic responses that may occur in older people and should know how to deal with these changes.

Pharmacokinetic Changes

Variable	Young Adults (20–30 years)	Older Adults (60–80 years)
Body water (% of body weight)	61	53
Lean body mass (% of body weight)	19	12
Body fat (% of body weight)	26–33 (women) 18–20 (men)	38–45 36–38
Serum albumin (g/dL)	4.7	3.8
Kidney weight (% of young adult)	100	80
Hepatic blood flow (% of young adult)	100	55–60

A. Absorption

Conditions associated with age may alter the rate of drugs absorption:

- 1-Altered nutritional habits.
- 2- Greater consumption of nonprescription drugs

(eg, antacids and laxatives).

3- Changes in gastric emptying, which is often slower in older persons, especially in older diabetics.

B. Distribution

Alter the appropriate loading dose of a drug. decreased volume of distribution. The maintenance dose may have to be reduced because of reduced clearance of the drug.

C. Metabolism

The capacity of the liver to metabolize drugs does not appear to decline consistently with age for all drugs . Certain drugs are metabolized more slowly in the elderly; which may be caused by decreased liver blood flow. There is variability in the clearance of drugs that have a high hepatic extraction ratio. In addition, there is a decline with age of the liver's ability to recover from injury. Similarly, severe nutritional deficiencies, which occur moreoften in old age, may impair hepatic function.

D. Elimination

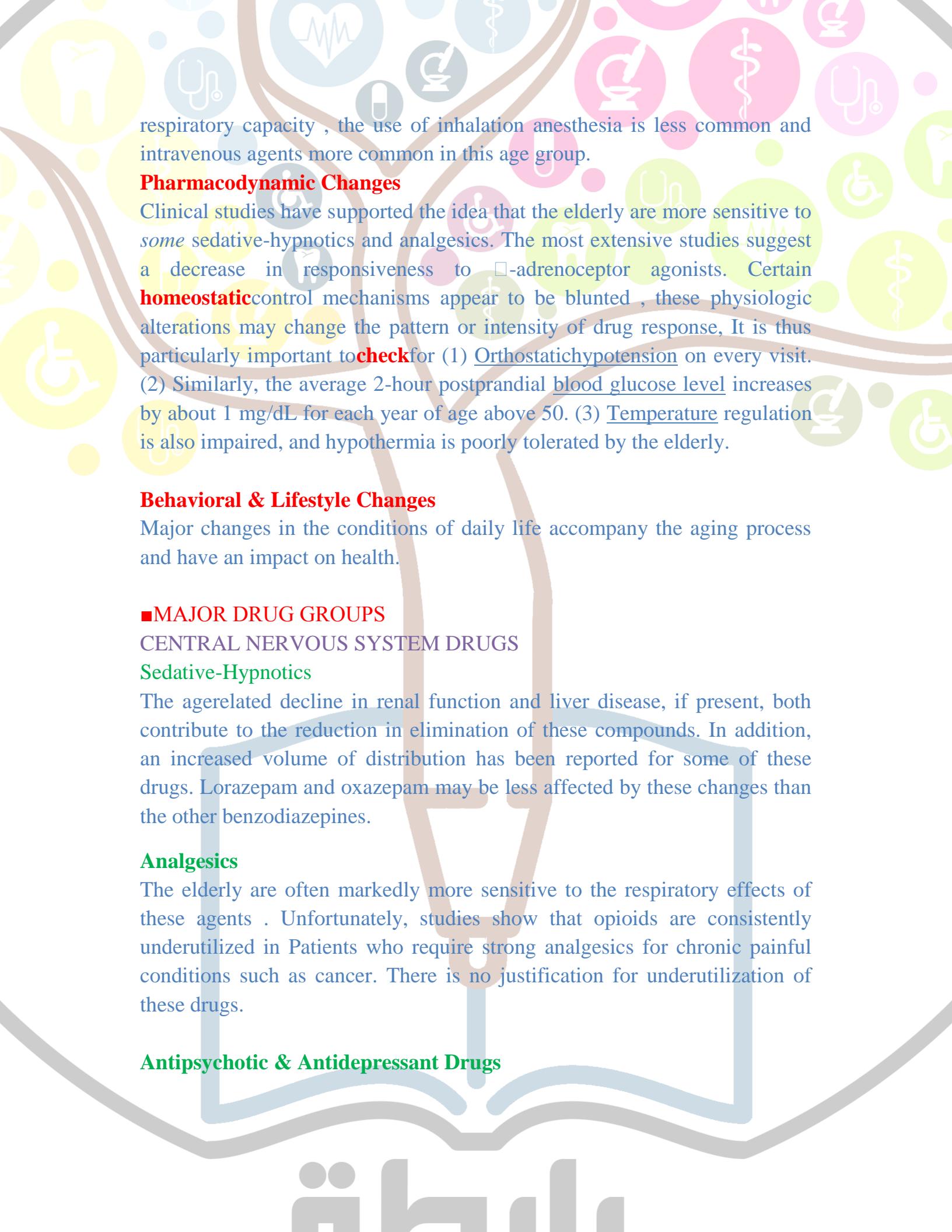
The age-related decline of **renal** functional capacity is very important. It is important to note that the decline in creatinine clearance is not reflected in an equivalent rise in serum creatinine because the production of creatinine is also reduced as muscle mass declines with age. The practical result of thischange is marked prolongation of the half-life of many drugs, and the possibility of accumulation to toxic levels if dosage is not reduced in size or frequency rough correction can be made

by using the **Cockcroft-Gault** formula, which is applicable to patients from ages 40 through 80.

Estimated creatinine clearance (mL/min)=

$$(140 - \text{Age}) \times (\text{Weight in kg}) / 72 \times \text{Serum creatinine in mg/dL}$$

For women, the result should be multiplied by 0.85. Simple online calculators using the more modern MDRD (Modification of Diet in Renal Disease) formula are available, eg,<http://nkdep.nih.gov/lab-evaluation/gfr-calculators.shtml>.Nutritional changes alter pharmacokinetic parameters. The lungs are important for the excretion of volatile drugs. As a result of reduced



respiratory capacity , the use of inhalation anesthesia is less common and intravenous agents more common in this age group.

Pharmacodynamic Changes

Clinical studies have supported the idea that the elderly are more sensitive to *some* sedative-hypnotics and analgesics. The most extensive studies suggest a decrease in responsiveness to α -adrenoceptor agonists. Certain **homeostatic** control mechanisms appear to be blunted , these physiologic alterations may change the pattern or intensity of drug response, It is thus particularly important to **check**for (1) Orthostatic hypotension on every visit. (2) Similarly, the average 2-hour postprandial blood glucose level increases by about 1 mg/dL for each year of age above 50. (3) Temperature regulation is also impaired, and hypothermia is poorly tolerated by the elderly.

Behavioral & Lifestyle Changes

Major changes in the conditions of daily life accompany the aging process and have an impact on health.

■MAJOR DRUG GROUPS

CENTRAL NERVOUS SYSTEM DRUGS

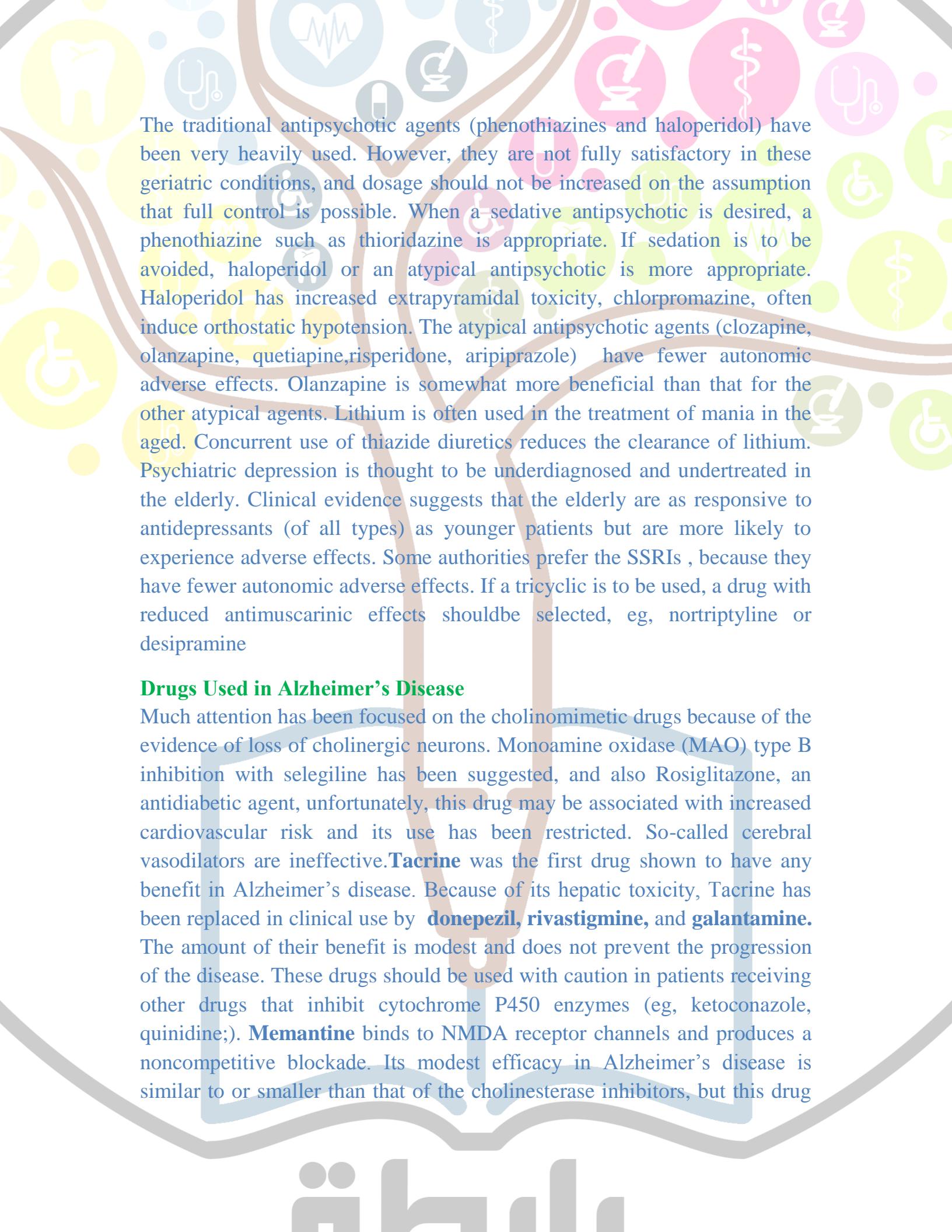
Sedative-Hypnotics

The age-related decline in renal function and liver disease, if present, both contribute to the reduction in elimination of these compounds. In addition, an increased volume of distribution has been reported for some of these drugs. Lorazepam and oxazepam may be less affected by these changes than the other benzodiazepines.

Analgesics

The elderly are often markedly more sensitive to the respiratory effects of these agents . Unfortunately, studies show that opioids are consistently underutilized in Patients who require strong analgesics for chronic painful conditions such as cancer. There is no justification for underutilization of these drugs.

Antipsychotic & Antidepressant Drugs

The background of the page is filled with a variety of medical and health-related icons in different colors (yellow, blue, green, pink) and sizes. These icons include a tooth, a stethoscope, a heart with an ECG line, a caduceus (a staff with two snakes entwined), a graduation cap, a dollar sign, a wheelchair, a hand with a bandage, a syringe, and various other symbols related to medicine and healthcare.

The traditional antipsychotic agents (phenothiazines and haloperidol) have been very heavily used. However, they are not fully satisfactory in these geriatric conditions, and dosage should not be increased on the assumption that full control is possible. When a sedative antipsychotic is desired, a phenothiazine such as thioridazine is appropriate. If sedation is to be avoided, haloperidol or an atypical antipsychotic is more appropriate. Haloperidol has increased extrapyramidal toxicity, chlorpromazine, often induce orthostatic hypotension. The atypical antipsychotic agents (clozapine, olanzapine, quetiapine, risperidone, aripiprazole) have fewer autonomic adverse effects. Olanzapine is somewhat more beneficial than that for the other atypical agents. Lithium is often used in the treatment of mania in the aged. Concurrent use of thiazide diuretics reduces the clearance of lithium. Psychiatric depression is thought to be underdiagnosed and undertreated in the elderly. Clinical evidence suggests that the elderly are as responsive to antidepressants (of all types) as younger patients but are more likely to experience adverse effects. Some authorities prefer the SSRIs, because they have fewer autonomic adverse effects. If a tricyclic is to be used, a drug with reduced antimuscarinic effects should be selected, eg, nortriptyline or desipramine

Drugs Used in Alzheimer's Disease

Much attention has been focused on the cholinomimetic drugs because of the evidence of loss of cholinergic neurons. Monoamine oxidase (MAO) type B inhibition with selegiline has been suggested, and also Rosiglitazone, an antidiabetic agent, unfortunately, this drug may be associated with increased cardiovascular risk and its use has been restricted. So-called cerebral vasodilators are ineffective. **Tacrine** was the first drug shown to have any benefit in Alzheimer's disease. Because of its hepatic toxicity, Tacrine has been replaced in clinical use by **donepezil, rivastigmine, and galantamine**. The amount of their benefit is modest and does not prevent the progression of the disease. These drugs should be used with caution in patients receiving other drugs that inhibit cytochrome P450 enzymes (eg, ketoconazole, quinidine;). **Memantine** binds to NMDA receptor channels and produces a noncompetitive blockade. Its modest efficacy in Alzheimer's disease is similar to or smaller than that of the cholinesterase inhibitors, but this drug

may be better tolerated and less toxic. Anti-amyloid antibodies, **solanezumab** and **bapineuzumab**, both failed to improve cognition or slow progression. the accumulation of filamentous tangles of tau protein is a critical component of neuronal damage in Alzheimer's and several other neurodegenerative conditions. Which is associated with dissociation from microtubules in neurons, which has stimulated interest in drugs that inhibit microtubule disassembly, such as **epothilone-D**

CARDIOVASCULAR DRUGS

Antihypertensive Drugs

Thiazides are a reasonable first step in drug therapy and they cause hypokalemia, hyperglycemia, and hyperuricemia more relevant in the elderly. Calcium channel blockers are effective and safe if titrated to the appropriate response. Beta blockers are potentially hazardous in patients with obstructive airway disease and are considered less useful than calcium channel blockers in older patients unless chronic heart failure is present. Angiotensin-converting enzyme inhibitors are also considered less useful in the elderly unless heart failure or diabetes is present. The most powerful drugs, such as minoxidil, are rarely needed.

Positive Inotropic Agents

Hypokalemia, hypomagnesemia, hypoxemia (from pulmonary disease), and coronary atherosclerosis all contribute to the high incidence of digitalis-induced arrhythmias in geriatric patients.

Antiarrhythmic Agents

Disopyramide should be avoided. anticoagulant drugs should be taken to reduce the risk of thromboembolism in chronic atrial fibrillation.

ANTIMICROBIAL THERAPY

β -lactam, aminoglycoside, and fluoroquinolone antibiotics are excreted by the kidney, important changes in half-life may be expected. This is particularly important in the case of the aminoglycosides, because they cause concentration- and time-dependent toxicity in the kidney and in other organs. The half-lives of gentamicin, kanamycin, and netilmicin are more than doubled. The increase may be less marked for tobramycin.

ANTI-INFLAMMATORY DRUGS

The (NSAIDs) must be used with special care in geriatric patients because they cause toxicities to which the elderly are very susceptible. The most important of these toxicities is gastrointestinal irritation and bleeding seen with Aspirin. In the case of the newer NSAIDs, the most important is renal damage, which may be irreversible. There is no evidence that the cyclooxygenase (COX)-2 selective NSAIDs are safer with regard to renal function. Corticosteroids are extremely useful in elderly patients who cannot tolerate full doses of NSAIDs. They cause a dose- and duration-related increase in osteoporosis, a hazardous toxic effect in the elderly. This drug-induced effect can be reduced by increased calcium and vitamin D intake, and to encourage frequent exercise.

OPHTHALMIC DRUGS

Drugs Used in Glaucoma

Glaucoma is more common in the elderly, but its treatment does not differ from that of earlier onset.

Macular Degeneration

Oral formulations of vitamins C and E, β -carotene, zinc oxide, and cupric oxide are available. Oral drugs in clinical trials include the carotenoids lutein and zeaxanthin, and n-3 long-chain polyunsaturated fatty acids. Neovascular AMD can now be treated with laser phototherapy or with antibodies against vascular endothelial growth factor (VEGF). Two antibodies are available: bevacizumab (Avastin, used off-label) and ranibizumab (Lucentis), as well as the oligopeptide pegaptanib (Macugen). Ranibizumab is extremely expensive. Fusion proteins and RNA agents are under study.

■ ADVERSE DRUG REACTIONS IN THE ELDERLY

Cimetidine, an H₂-blocking drug heavily prescribed (or recommended in its over-the-counter form) to the elderly, causes a much higher incidence of untoward effects (eg, confusion, slurred speech). It inhibits the hepatic metabolism of many drugs, including phenytoin, warfarin, β -blockers, and other agents. A patient who has been taking one of the latter agents without untoward effect may develop markedly elevated blood levels and severe toxicity if cimetidine is added to the regimen without adjustment of dosage of the other drugs. Many antihistamines have significant sedative effects and

are inherently more hazardous in patients with impaired cognitive function. Similarly, their antimuscarinic action may precipitate urinary retention in geriatric men or glaucoma in patients with a narrow anterior chamber angle. Gingko is more likely to cause bleeding while taken with low doses of aspirin.

■ PRACTICAL ASPECTS OF GERIATRIC PHARMACOLOGY

The monthly cost of arthritis therapy with newer NSAIDs may exceed \$100, whereas that for generic ibuprofen and naproxen, two older but equally effective NSAIDs, about \$20. Patients may forget instructions regarding the need to complete a fixed duration of therapy when a course of anti-infective drug is being given. The disappearance of symptoms is often regarded as the best reason to halt drug taking, especially if the prescription was expensive. A decision not to take a drug may be based on prior experience with it. Considering the patient as a participant in therapeutic decisions increases the motivation to succeed. Some errors in drug taking are caused by physical disabilities. Liquid medications that are to be measured “by the spoonful” are especially inappropriate for patients with any type of tremor or motor disability. Use of a dosing syringe may be helpful in such cases. Macular degeneration occur in a large number of patients over 70.

Chapter 61: Dermatologic Pharmacology

TABLE 61–1 Local cutaneous reactions to topical medications.

Reaction type	Mechanism	Comment
Irritation	Non-allergic	Most common local reaction
Photoirritation	Non-allergic	Phototoxicity; usually requires UVA exposure
Allergic contact dermatitis	Allergic	Type IV delayed hypersensitivity
Photoallergic contact dermatitis	Allergic	Type IV delayed hypersensitivity; usually requires UVA exposure
Immunologic contact urticaria	Allergic	IgE-mediated type I immediate hypersensitivity; may result in anaphylaxis
Non-immunologic contact urticaria	Non-allergic	Most common contact urticaria; occurs without prior sensitization

Route for treatment of skin diseases includes: Topical and systemic administration.

Human skin is a simple three-layered structure and a complex series of diffusion barriers. Quantitation of the flux of drugs and drug vehicles through these barriers is the basis for pharmacokinetic analysis of dermatologic therapy, and techniques for making such measurements are rapidly increasing in number and sensitivity.

Major variables that determine pharmacologic response to drugs applied to the skin include the following:

1. **Regional variation in drug penetration:** For example, the scrotum, face, axilla, and scalp are far more permeable than the forearm and may require less drug for equivalent effect.
2. **Concentration gradient:** Increasing the concentration gradient increases the mass of drug transferred per unit time.
3. **Dosing schedule:** Because of its physical properties, the skin acts as a reservoir for many drugs. As a result, the “local half life” may be long enough to permit once-daily application of drugs with short systemic half-lives.
4. **Vehicles and occlusion:** An appropriate vehicle maximizes the ability of the drug to penetrate the outer layers of the skin. In addition vehicles may themselves have important therapeutic effects. Occlusion is extremely effective in maximizing efficacy.

REACTIONS TO DERMATOLOGIC MEDICATIONS

Dermatologic medications cause skin reactions. The major types of reactions are summarized in Table 61–1.

DERMATOLOGIC VEHICLES

Topical medications usually consist of active ingredients incorporated in a vehicle that facilitates cutaneous application. Important considerations in vehicle selection include:

- The solubility of the active agent in the vehicle.
- The rate of release of the agent from the vehicle.
- The ability of the vehicle to hydrate the stratum corneum, thus

enhancing penetration.

- The stability of the therapeutic agent in the vehicle.
- Interactions, chemical and physical, of the vehicle, stratum corneum, and active agent.

Depending upon the vehicle, dermatologic formulations may be classified as: tinctures, wet dressings, lotions, gels, aerosols, powders, pastes, creams, foams, and ointments. The ability of the vehicle to retard evaporation from the surface of the skin is greatest in ointments and being least in tinctures and wet dressings. In general, acute inflammation is best treated with drying preparations such as tinctures, wet dressings, and lotions, whereas chronic inflammation is best treated with more lubricating preparations such as creams and ointments. Tinctures, lotions, gels, foams, and aerosols are convenient for application to the scalp and hairy areas. Emulsified vanishing-type creams may be used in intertriginous areas without causing maceration.

ANTIBACTERIAL AGENTS

TOPICAL ANTIBACTERIAL PREPARATIONS

Topical antibacterial agents may be useful in preventing infections in clean wounds, in the early treatment of infected dermatoses and wounds, in reducing colonization of the nares by staphylococci, in axillary deodorization, and in the management of acne vulgaris. The efficacy of antibiotics in these topical applications is not uniform. Some topical anti-infective contain corticosteroids in addition to antibiotics these topical corticosteroids inhibit the antibacterial effect of antibiotics when incorporated in the same preparation. In the treatment of secondarily infected dermatoses combination therapy may prove superior to corticosteroid therapy alone also, may be useful in treating diaper dermatitis, otitis externa, and impetiginized eczema. The selection of a particular antibiotic depends upon the diagnosis and, when appropriate, in vitro culture and sensitivity studies of clinical samples. The pathogens isolated from most infected dermatoses are group A β -hemolytic streptococci, staphylococcus aureus, or both and in surgical wounds will be those resident in the environment. Information about regional patterns of drug resistance is therefore important in selecting a therapeutic agent. Formulations that contain multiple

antibiotics offer the advantages of efficacy in mixed infections, broader coverage for infections due to undetermined pathogens, and delayed microbial resistance to any single component antibiotic.

Bacitracin & Gramicidin	<p>Bacitracin and gramicidin are peptide antibiotics, active against gram-positive organisms such as streptococci, pneumococci, and staphylococci. In addition, most anaerobic cocci, neisseriae, tetanus bacilli, and diphtheria bacilli are sensitive.</p> <ul style="list-style-type: none">- Bacitracin ointment either alone or in combination with neomycin, polymyxin B, or both.- The use of bacitracin in the anterior nares may temporarily decrease colonization by pathogenic staphylococci, prolonged use result in resistance.- Bacitracin-induced contact urticaria syndrome, including anaphylaxis, occurs rarely. Allergic contact dermatitis occurs frequently, and immunologic allergic contact urticaria rarely.- Bacitracin is poorly absorbed through the skin, so systemic toxicity is rare.- Gramicidin is available only for topical use, in combination with other antibiotics.- Systemic toxicity limits this drug to topical use.- The incidence of sensitization following topical application is exceedingly low in therapeutic concentrations.
Mupirocin	<ul style="list-style-type: none">- Most gram-positive bacteria, including methicillin-resistant <i>S aureus</i> (MRSA), are sensitive to mupirocin. It is effective in the treatment of impetigo caused by <i>S aureus</i> and group A β-hemolytic streptococci.- Intranasal mupirocin ointment associated with irritation of mucous membranes caused by the polyethylene glycol vehicle.- Mupirocin is not appreciably absorbed systemically after topical application to intact skin.

Retapamulin	<ul style="list-style-type: none"> - It is effective in the treatment of uncomplicated superficial skin infection caused by group A β -hemolytic streptococci and <i>S. aureus</i>, excluding MRSA. - Topical 1% ointment is indicated for use in adult and pediatric patients, 9 months or older, for the treatment of impetigo. - Recommended treatment regimen is twice-daily application for 5 days. - Retapamulin is well tolerated with only occasional local irritation of the treatment site.
Polymyxin B Sulfate	<ul style="list-style-type: none"> - Polymyxin B is a peptide antibiotic effective against gram-negative organisms, including <i>Pseudomonas aeruginosa</i>, <i>Escherichia coli</i>, <i>enterobacter</i>, and <i>klebsiella</i>. Most strains of gram-positive organisms <i>proteus</i> and <i>serratia</i> are resistant. - Detectable serum concentrations are difficult to achieve from topical application, but the total daily should not exceed 200 mg in order to reduce the risk of neurotoxicity and nephrotoxicity. - Allergic contact dermatitis to topically applied polymyxin B sulfate is uncommon.

Neomycin & Gentamicin

Neomycin and gentamicin are aminoglycoside antibiotics active against gram-negative organisms, including E coli, proteus, klebsiella, and enterobacter.

- **Gentamicin** generally shows greater activity against P aeruginosa than neomycin, Gentamicin is more active against staphylococci and group A β-hemolytic streptococci. Serum concentrations of 1–18 mcg/mL are possible if the drug is applied to large areas of denuded skin, as in burned patients.
- Widespread topical use of gentamicin should be avoided to slow the appearance of gentamicin-resistant organisms.
- **Neomycin** available alone or in combination with other antibiotics, and as a sterile powder for topical use.
- Topical application of neomycin rarely results in detectable serum concentrations.
- Neomycin frequently causes allergic contact dermatitis if applied to eczematous dermatoses or if compounded in an ointment vehicle and cross-sensitivity to streptomycin, kanamycin, paromomycin, and gentamicin is possible.

Both drugs are water-soluble and are excreted primarily in the urine. Renal failure may permit the accumulation of these antibiotics, with possible nephrotoxicity, neurotoxicity, and ototoxicity.

TOPICAL ANTIBIOTICS IN ACNE

Several systemic antibiotics that have traditionally been used in the treatment of acne vulgaris have been shown to be effective when applied topically. Currently, four antibiotics are so utilized: clindamycin phosphate, erythromycin base, metronidazole, and sulfacetamide. The effectiveness of topical therapy is less than that achieved by systemic administration of the same antibiotic.

Therefore, topical therapy is generally suitable only in mild to moderate cases of inflammatory acne.

Clindamycin	<ul style="list-style-type: none"> - Clindamycin has activity against <i>Propionibacterium acnes</i> as the mechanism of its beneficial effect in acne therapy. - 10% of an applied dose is absorbed ; rare cases of bloody diarrhea and pseudomembranous colitis have been reported following topical application and available in fixed-combination topical gels with benzoyl peroxide and with tretinoin. - The hydroalcoholic vehicle and foam formulation may cause drying and irritation of the skin, burning and stinging. - The water-based gel and lotion formulations are well tolerated and less likely to cause irritation. <p>Allergic contact dermatitis is uncommon.</p>
Erythromycin	<ul style="list-style-type: none"> - In topical preparations, erythromycin base rather than a salt is used to facilitate penetration. - The mechanism of action of topical erythromycin in inflammatory acne vulgaris is unknown but is presumed to be due to its inhibitory effects on <i>P acnes</i>. - One of the possible complications of topical therapy is the development of antibiotic-resistant strains of organisms, including staphylococci. If this occurs in association with a clinical infection, topical erythromycin should be discontinued and appropriate systemic antibiotic therapy started. - Adverse local reactions to erythromycin solution may include a burning sensation at the time of application and drying and irritation of the skin. - The topical water-based gel is less drying and may be better tolerated. - Allergic contact dermatitis is uncommon. - It is also available in a fixed combination preparation with benzoyl peroxide for topical treatment of acne vulgaris.

Metronidazole	<ul style="list-style-type: none"> - Topical metronidazole is effective in the treatment of rosacea. - The mechanism of action is unknown, but it may relate to the inhibitory effects of metronidazole on <i>Demodex brevis</i>; alternatively, the drug may act as an anti-inflammatory agent by direct effect on neutrophil cellular function. - Oral metronidazole has been shown to be a carcinogen, and topical use during pregnancy and by nursing mothers and children is therefore not recommended. - Adverse local effects of the water-based gel formulation include dryness, burning, and stinging. - Less drying formulations may be better tolerated. - Caution should be exercised when applying metronidazole near the eyes to avoid excessive tearing.
Sodium Sulfacetamide	<ul style="list-style-type: none"> - Topical sulfacetamide is available alone as a 10% lotion and as a 10% wash, and in several preparations in combination with sulfur for the treatment of <i>acne vulgaris</i> and acne rosacea. - The mechanism of action is thought to be inhibition of <i>P acnes</i> by competitive inhibition of p-aminobenzoic acid utilization. - Approximately 4% of topically applied sulfacetamide is absorbed percutaneously, and its use is contraindicated in patients having a known hypersensitivity to sulfonamides.
Dapsone	<ul style="list-style-type: none"> - Topical dapsone is available as a 5% gel for the treatment of <i>acne vulgaris</i>. - The mechanism of action is unknown. - Topical use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency has not been shown to cause clinically relevant hemolysis or anemia. However, a slight decrease in hemoglobin concentration was noted in patients with G6PD deficiency, suggestive of mild hemolysis. Adverse reactions associated with oral use have not been reported with topical use. - Adverse local side effects include mild dryness, redness, oiliness, and skin peeling. - Application of dapsone gel followed by benzoyl peroxide may result in a temporary yellow discoloration of the skin and hair.

Topical Azole Derivatives

TOPICAL ANTIFUNGAL PREPARATIONS

The treatment of superficial fungal infections caused by dermatophytic fungi may be accomplished With topical antifungal agents, eg, clotrimazole, miconazole, econazole, ketoconazole, oxiconazole,sulconazole, sertaconazole, ciclopirox olamine, naftifine, terbinafine, butenafine, and tolnaftate; Or with orally administered agents, ie, griseofulvin, terbinafine, fluconazole, and itraconazole.Superficial infections caused by candida species may be treated with topical applications of clotrimazole, miconazole, econazole, ketoconazole, oxiconazole, ciclopiroxolamine, nystatin, or amphotericin B.

- The topical imidazoles, include clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sulconazole, and sertaconazole, have a wide range of activity against dermatophytes (*epidermophyton*, *microsporum*, and *trichophyton*) and yeasts, including *Candida albicans*and*Pityrosporum orbiculare*.
 - **Miconazole** is available for a cream or lotion and as vaginal cream or suppositories for use in vulvovaginal candidiasis.
 - **Clotrimazole**is available as a cream or lotionand as vaginal cream and tablets for use in vulvovaginal candidiasis.
 - **Econazole** is available as a cream for topical application.
 - **Oxiconazole** is available as a cream and lotion for topical use.
 - **Ketoconazole** is available as a cream for topical treatment of dermatophytosis and candidiasis and as a shampoo or foam for the treatment of seborrheic dermatitis.
 - **Sulconazole**is available as a cream or solution.
 - **Sertaconazole**is available as a cream. Topical antifungal-corticosteroidfixed combinations have more rapid symptomatic improvement than an antifungal agentalone.
 - **Clotrimazole-betamethasone dipropionate cream** is one such combination.Once- or twice-daily application to the affected area will generally result in clearing of superficial dermatophyte infections in 2–3weeks,
 - Although the medication should be continued until eradicationof the organism is confirmed. Paronychial and intertriginous candidiasis can be treated effectively by any of these agents when applied three or four times daily. Seborrheic dermatitis should betreated with twice-daily applications of ketoconazole until clinicalclearing is obtained.
 - Adverse local reactions may include stinging, pruritus, erythema, and local irritation. Allergic contact dermatitis is uncommon.

Ciclopirox Olamine	<ul style="list-style-type: none"> - Ciclopirox olamine is a synthetic broad-spectrum antimycotic agent with inhibitory activity against dermatophytes, candida species, and <i>P orbiculare</i>. - This agent inhibits the uptake of precursors of macromolecular synthesis; the site of action is the fungal cell membrane. - Pharmacokinetic studies indicate that 1–2% of the dose is absorbed when applied as a solution on the back under an occlusive dressing. - It is available as a 1% cream and lotion for the topical treatment of dermatomycosis, candidiasis, and tinea versicolor. - Low incidence of adverse reactions. Pruritus and worsening of disease. The potential for allergic contact dermatitis is small. - Topical 8% has been approved for the treatment of mild to moderate onychomycosis of fingernails and toenails. - Although well tolerated with minimal side effects, the overall cure rates in clinical trials are less than 12%.
Allylamines	<ul style="list-style-type: none"> - Naftifine hydrochloride and terbinafine are allylamines, highly active against dermatophytes but less active against yeasts. - The antifungal activity derives from selective inhibition of squalene epoxidase, a key enzyme for the synthesis. - They are available as 1% creams for the topical treatment of dermatophytosis, to be applied on a twice-daily dosing schedule. - Adverse reactions include local irritation, burning sensation, and erythema. - Contact with mucous membranes should be avoided.
Butenafine	<ul style="list-style-type: none"> - Butenafine hydrochloride is a benzylamine that is structurally related to the allylamines. - As with the allylamines, butenafine inhibits the epoxidation of squalene, thus blocking the synthesis of ergosterol, an essential component of fungal cell membranes. - Butenafine is available as a 1% cream to be applied once daily for the treatment of superficial dermatophytosis.

Tolnaftate	<ul style="list-style-type: none"> - Tolnaftate is a synthetic antifungal compound that is effective topically against dermatophyte infections caused by epidermophyton, microsporum, and trichophyton. It is also active against <i>P orbiculare</i> but not against candida. - Tolnaftate is available as a cream, solution, powder, or powder aerosol for application twice daily to infected areas. - Recurrences following cessation of therapy are common, and infections of the palms, soles, and nails are usually unresponsive to tolnaftate alone. - The powder or powder aerosol may be used chronically following initial treatment in patients susceptible to tinea infections. - Tolnaftate is generally well tolerated and rarely causes irritation or allergic contact dermatitis.
Nystatin & Amphotericin B	<p>Nystatin and amphotericin B are useful in the topical therapy of <i>C albicans</i> infections but ineffective against dermatophytes.</p> <ul style="list-style-type: none"> - Nystatin is limited to topical treatment because of its narrow spectrum and low absorption from the gastrointestinal tract. <ul style="list-style-type: none"> - The recommended dosage for topical preparations of nystatin in treating paronychial and intertriginous candidiasis is application 2-3 times a day. - Oral candidiasis (thrush) is treated by holding 5 mL (infants, 2 mL) of nystatin oral suspension in the mouth for several minutes 4 times daily before swallowing, or retain a vaginal tablet in the mouth until dissolved four times daily. - Recurrent or recalcitrant perianal, vaginal, vulvar, and diaper area candidiasis may respond to oral nystatin, 0.5–1 million units in adults (100,000 units in children) 4 times daily, in addition to local therapy. Vulvovaginal candidiasis may be treated by insertion of 1 vaginal tablet twice daily for 14 days, then nightly for an additional 14–21 days. - Adverse effects associated with oral administration of nystatin include mild nausea, diarrhea, and occasional vomiting. Topical application is nonirritating, and allergic contact hypersensitivity is exceedingly uncommon. - Amphotericin B has a broader antifungal spectrum and is used intravenously in the treatment of many systemic mycoses and to a lesser extent in the treatment of cutaneous candida infections. It is available for topical use in cream and lotion form. <ul style="list-style-type: none"> - The recommended treatment of paronychial and intertriginous candidiasis is 2-4 times daily to the affected area. - Topical amphotericin B is well tolerated and only occasionally locally irritating. The drug may cause a temporary yellow staining of the skin, especially when the cream vehicle is used.

ORAL ANTIFUNGAL AGENTS

Azole derivatives currently available for oral treatment of candida and dermatophyte infections include **fluconazole and itraconazole**. They act by affecting the permeability of the cell membrane of sensitive cells through alterations of the biosynthesis of lipids, especially sterols, in the fungal cell. Fluconazole and itraconazole are effective in the therapy of cutaneous infections caused by epidermophyton, microsporum, and trichophyton species as well as candida. Tinea versicolor is responsive to short courses of oral azoles.

- **Fluconazole** is well absorbed following oral administration, with long plasma half-life of 30 hours, daily doses of 100 mg are sufficient to treat mucocutaneous candidiasis; alternate-day doses are sufficient for dermatophyte infections.
- **Itraconazole** is effective for the treatment of onychomycosis in a dosage of 200 mg daily taken with food to ensure maximum absorption for 3 months. It is not to be given for treatment of onychomycosis in patients with ventricular dysfunction. Routine evaluation of hepatic function is recommended for patients receiving **itraconazole** for onychomycosis.
- The plasma half-life of **itraconazole** is similar to that of fluconazole, and detectable therapeutic concentrations remain in the stratum corneum for up to 28 days following termination of therapy.
- Administration of oral azoles with midazolam or triazolam has resulted in elevated plasma concentrations and may potentiate and prolong hypnotic and sedative effects of these agents.
- Administration with HMG-CoA reductase inhibitors is *contraindicated* as it cause a significant risk of rhabdomyolysis.

Oral Azole Derivatives

Terbinafine

- Terbinafine is quite effective given orally for the treatment of onychomycosis.
- Recommended oral dosage is 250 mg daily for 6 weeks for fingernail infections and 12 weeks for toenail infections.
- Patients receiving terbinafine for onychomycosis should be monitored closely with periodic laboratory evaluations for possible hepatic dysfunction.

Griseofulvin

- Griseofulvin is effective orally against dermatophyte infections caused by *epidermophyton*, *microsporum*, and *trichophyton*.
- It is ineffective against *candida* and *P orbiculare*.
- Its mechanism of antifungal action is not fully understood, but it is active only against growing cells.
- Drug can be detected in the stratum corneum 4–8 hours later after oral administration of 1 g of micronized griseofulvin.
- Reducing the particle size of the medication greatly increases absorption of the drug. Formulations that contain the smallest particle size are labeled “ultramicronized.” And it achieves bioequivalent plasma levels with half the dose of micronized drug. In addition, solubilizing griseofulvin in polyethylene glycol enhances absorption even further.
- The usual adult dosage of the micronized form of the drug is 500 mg daily in single or divided doses with meals; occasionally, 1 g/d is indicated in the treatment of recalcitrant infections. The pediatric dosage is 10 mg/kg of body weight daily in single or divided doses with meals. An oral suspension is available for use in children.
- It is most effective in treating tinea infections of the scalp and glabrous (nonhairy) skin. In general, infections of the scalp respond to treatment in 4–6 weeks, and infections of glabrous skin will respond in 3–4 weeks.
- Dermatophyte infections of the nails respond only to prolonged administration of griseofulvin. Fingernails may respond to 6 months of therapy, whereas toenails are quite recalcitrant to treatment and may require 8–18 months of therapy; relapse almost invariably occurs.
- Adverse effects include: headaches, nausea, vomiting, diarrhea, photosensitivity, peripheral neuritis, and mental confusion.
- Cross-sensitivity with penicillin may occur and it is contraindicated in patients with porphyria or hepatic failure or those who have had hypersensitivity reactions to it in the past, and its safety in pregnant patients has not been established.
- Routine evaluation of the hepatic, renal, and hematopoietic systems, prolonged therapy result in Leukopenia and proteinuria,
- Coumarin anticoagulant activity may be altered by griseofulvin, and anticoagulant dosage may require adjustment.

TOPICAL ANTIVIRAL AGENTS

Acyclovir, Valacyclovir, Penciclovir, Famciclovir	<ul style="list-style-type: none">- They have inhibitory activity against members of the herpesvirus family, including herpes simplex types 1 and 2.- Topical acyclovir is available as a 5% ointment; topical penciclovir, as a 1% cream for the treatment of recurrent orolabial herpes simplex virus infection in immunocompetent adults.- Adverse reactions to acyclovir and penciclovir may include pruritus and mild pain with transient stinging or burning.
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IMMUNOMODULATORS

Imiquimod	<ul style="list-style-type: none">- Imiquimod is used for the treatment of external genital and perianal warts in adults, actinic keratoses on the face and scalp, and biopsy-proven primary basal cell carcinomas on the trunk, neck, and extremities.- The mechanism of its action is related to imiquimod's ability to stimulate peripheral mononuclear cells to release interferon alpha and to stimulate macrophages to produce interleukins-1, -6, and -8, and tumor necrosis factor-α(TNF-α).- It should be applied to the wart tissue 3 times per week and left on the skin for 6–10 hours prior to washing off.- Treatment should be continued until eradication of the warts is accomplished, but not for more than a total of 16 weeks.- Recommended treatment of actinic keratoses consists of twice-weekly applications of the cream on the contiguous area of involvement or nightly applications of the lower concentration cream.- The cream is removed after approximately 8 hours with mild soap and water.- Treatment of superficial basal cell carcinoma consists of five-times-per-week application to the tumor, including a 1 cm margin of surrounding skin, for a 6-week course of therapy.- Percutaneous absorption is minimal, with less than 0.9% absorbed following a single-dose application.- Adverse effects consist of local inflammatory reactions, including pruritus, erythema, and superficial erosion.
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Tacrolimus & Pimecrolimus

- **Tacrolimus and pimecrolimus** are macrolide immunosuppressants that have benefit in the treatment of atopic dermatitis.
- Both agents inhibit T-lymphocyte activation and prevent the release of inflammatory cytokines and mediators from mast cells in vitro after stimulation by antigen-IgE complexes.
- Both are indicated for short-term and intermittent long-term therapy for mild to moderate atopic dermatitis.
- They are approved for use in children older than 2 years of age, although all strengths are approved for adult use.
- Recommended dosing of both agents is twice-daily application to affected skin until clearing is noted.
- Neither medication should be used with occlusive dressings.
- The most common side effect of both drugs is a burning sensation in the applied area that improves with continued use.
- The FDA has added a black box warning regarding the long-term safety because of animal tumorigenicity data.

ECTOPARASITICIDES

Permethrin	<ul style="list-style-type: none">- Permethrin is toxic to <i>Pediculushumanus</i>, <i>Pthirus pubis</i>, and <i>Sarcoptesscabiei</i>.- Less than 2% of an applied dose is absorbed percutaneously and residual drug persists up to 10 days following application.- Resistance to permethrin is becoming more widespread.- It is recommended that permethrin 1% cream rinse be applied undiluted to affected areas of pediculosis for 10 minutes and then rinsed off with warm water.- For the treatment of scabies, a single application of 5% cream is applied to the body from the neck down, left on for 8–14 hours, and then washed off.- Adverse reactions to permethrin include transient burning, stinging, and pruritus.- Cross-sensitization to pyrethrins or chrysanthemum has been alleged but inadequately documented.
Spinosad	<ul style="list-style-type: none">- Spinosad suspension is approved for the topical treatment of head lice in patients 4 years of age and older.- Spinosad is toxic to <i>P. humanus</i> with no appreciable absorption from topical application.- It is recommended that the 0.9% suspension be applied to the hair and scalp for 10 minutes and then rinsed out. A repeat treatment may be applied 1 week later if live lice are present.
Ivermectin	<ul style="list-style-type: none">- Ivermectin 0.5% lotion is approved for the treatment of head lice in patients 6 months of age and older.- It is toxic to <i>P. humanus</i>, resulting in paralysis and death of the parasite.- The lotion should be applied to the hair and scalp and rinsed out after 10 minutes.- It is for single use only and should not be repeated without health care provider recommendation.

<p>Lindane (<i>Hexachlorocyclohexane</i>)</p> <ul style="list-style-type: none"> - Percutaneous absorption studies using a solution of lindane in acetone have shown that almost 10% of a dose applied to the forearm is absorbed, to be subsequently excreted in the urine over a 5-day period. After absorption, - It is concentrated in fatty tissues, including the brain. - Lindane is available as a 1% shampoo or lotion. <i>For pediculosis capitis or pubis</i>, 30 mL of shampoo is applied to dry hair on the scalp or genital area for 4 minutes and then rinsed off. - If living lice are present 1 week after treatment. Then reapplication may be required. - Its toxicity has altered treatment guidelines for its use in scabies; the current recommendation calls for a single 60 mL application to the entire body from the neck down, left on for 8–12 hours, and then washed off. - Patients should be retreated only if active mites can be demonstrated, and never within 1 week of initial treatment. - Concerns about neurotoxicity and hematotoxicity have resulted in warnings that lindane should be used with caution in infants, children, and pregnant women. - It should not be used as a scabicide in premature infants and in patients with known seizure disorders. - Local irritation may occur, and contact with the eyes and mucous membranes should be avoided.
<p>Crotamiton</p> <ul style="list-style-type: none"> - Crotamiton is a scabicide with <i>some antipruritic</i> properties. It is available as a cream or lotion. - Its mechanism of action is not known. - Percutaneous absorption results in detectable levels of <i>crotamiton</i> in the urine following a single application on the forearm. - Suggested guidelines for scabies treatment call for two applications to the entire body from the chin down at 24-hour intervals, with a cleansing bath 48 hours after the last application. - <i>Crotamiton</i> is an effective agent that can be used as an alternative to lindane. - Allergic contact dermatitis and primary irritation may occur, necessitating discontinuance of therapy. - Application to acutely inflamed skin or to the eyes or mucous membranes should be avoided.

Sulfur	<ul style="list-style-type: none"> - Sulfur used as a scabicide. Although it is <i>nonirritating</i>, it has an unpleasant odor, is staining, and is thus <i>disagreeable</i> to use. - It has been replaced by more aesthetic and effective scabicides in recent years, but it remains a possible alternative drug for use in infants and pregnant women.
Malathion	<ul style="list-style-type: none"> - Malathion is an organophosphate cholinesterase inhibitor that is hydrolyzed and inactivated by plasma <i>carboxylesterases</i> much faster in humans than in insects, thereby providing a therapeutic advantage in treating pediculosis. - Malathion is available as a 0.5% lotion that should be applied to the hair when dry; 4–6 hours later, the hair is combed to remove nits and lice.
Benzyl Alcohol	<ul style="list-style-type: none"> - Benzyl alcohol is available as a 5% lotion for the treatment of head lice in patients older than 6 months. - The lotion is applied to dry hair and left on for 10 minutes prior to rinsing off with water. - Because the drug is notovicidal, the treatment must be repeated after 7 days. - Eye irritation and allergic contact dermatitis have been reported.

AGENTS AFFECTING PIGMENTATION

Hydroquinone, Monobenzone, & Mequinol	<ul style="list-style-type: none"> - Hydroquinone, monobenzone and mequinol are used topically to reduce hyperpigmentation of the skin. - Hydroquinone and mequinol result in temporary lightening, whereas monobenzone causes irreversible depigmentation. - The mechanism of action of these compounds to involve inhibition of the enzyme tyrosinase, thus interfering with the biosynthesis of melanin. In addition, monobenzone may be toxic to melanocytes, resulting in permanent loss of these cells. - Some percutaneous absorption of these compounds takes place, because monobenzone may cause hypopigmentation at sites distant from the area of application. - Both hydroquinone and monobenzone may cause local irritation. Allergic contact dermatitis to these compounds can occur. - Prescription combinations of hydroquinone, <i>fluocinoloneacetonide</i>, and retinoic acid and mequinol and retinoic acid are more effective than their individual components.
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Trioxsalen&Methoxsalen

- Trioxsalen and methoxsalen are psoralens used for the *repigmentation of* depigmented macules of vitiligo.
- Photochemotherapy with oral methoxsalen for psoriasis and with oral trioxsalen for vitiligo has been under intensive investigation.
- Psoralens must be photoactivated by long-wavelength ultraviolet light in the range of 320–400 nm (ultraviolet A [UVA]) to produce a beneficial effect.
- Psoralens intercalate with DNA and, with subsequent UVA irradiation, cyclobutane adducts are formed with pyrimidine bases.
- The major longterm risks of psoralen photochemotherapy are cataracts and skin cancer.

Sunscreens

SUNSCREENS

- Topical medications useful in protecting against sunlight contain either chemical compounds that absorb ultraviolet light, called sunscreens, or opaque materials such as titanium dioxide that reflect light, called sunshades.
- The three classes of chemical compounds most commonly used in sunscreens are *p*-aminobenzoic acid (PABA) and its esters, the benzophenones, and the dibenzoylmethanes.
- Most sunscreen preparations are designed to absorb ultraviolet light in the ultraviolet B (UVB) *wavelength* range from 280 to 320 nm, which is the range responsible for most of the erythema and sunburn associated with sun exposure and tanning.
- Chronic exposure to light in this range induces aging of the skin and *photocarcinogenesis*.
- Para-aminobenzoic acid and its esters are the most effective available absorbers in the B region. Ultraviolet in the longer UVA range, 320–400 nm, is also associated with skin aging and cancer.
- The benzophenones include oxybenzone, dioxybenzone, and sulisobenzone. These compounds provide a broader spectrum of absorption from 250 to 360 nm, but their effectiveness in the UVB erythema range is less than that of PABA.
- The dibenzoylmethanes include Parasol and Eusolex. These compounds absorb wavelengths throughout the longer UVA range, with maximum absorption at 360 nm.
- Patients particularly sensitive to UVA wavelengths include individuals with polymorphous light eruption, cutaneous lupus erythematosus, and drug-induced photosensitivity. In these patients, *dibenzoylmethane*-containing sunscreen may provide improved photoprotection.
- Ecamsule appears to provide greater UVA protection than the dibenzoylmethanes and is less prone to photodegradation.
- The sun protection factor (SPF) of a given sunscreen is a measure of its effectiveness in absorbing erythrogenic ultraviolet light. It is determined by measuring the minimal erythema dose with and without the sunscreen in a group of normal people. The ratio of the minimal erythema dose with sunscreen to the minimal erythema dose without sunscreen is the SPF.
- Recently updated FDA regulations limit the claimed maximum SPF value on sunscreen labels to 50+ because data are insufficient to show that products with SPF values higher than 50 provide greater protection for users.
- These regulations require that sunscreens labeled “broad spectrum” pass a standard test comparing the amount of UVA radiation protection in relation to the amount of UVB protection.

Retinoic Acid & Derivatives

ACNE PREPARATIONS

- Topically applied **retinoic acid (Tretinoin)** remains chiefly in the epidermis, with less than 10% absorption into the circulation, metabolized by the liver and excreted in bile and urine.
- It has several effects on epithelial tissues. It stabilizes lysosomes, increases ribonucleic acid polymerase activity increases prostaglandin E2, cAMP, and cGMP levels, and increases the incorporation of thymidine into DNA. Its action in acne has been attributed to decreased cohesion between epidermal cells and increased epidermal cell turnover. This is thought to result in the expulsion of open comedones and the transformation of closed comedones into open ones.
- It is applied initially in a concentration sufficient to induce slight erythema with mild peeling. The concentration or frequency of application may be decreased if too much irritation occurs.
- It should be applied to dry skin only, and avoid contact with the corners of the nose, eyes, mouth, and mucous membranes.
- During the first 4–6 weeks of therapy, comedones not previously evident may appear and give the impression that the acne has been aggravated by the retinoic acid. However, with continued therapy, the lesions will clear, and in 8–12 weeks optimal clinical improvement should occur.
- A timed-release formulation of microspheres delivers the tretinoin over time and may be less irritating for sensitive patients.
- The effects of tretinoin on keratinization and desquamation offer benefits for patients with photo-damaged skin.
- Prolonged use of tretinoin promotes dermal collagen synthesis, new blood vessel formation, and thickening of the epidermis, which helps diminish fine lines and wrinkles.
- Specially formulated moisturizing 0.05% cream (Renova, Refissa) is marketed for this purpose.
- The most common adverse effects of topical retinoic acid are erythema and dryness that occur in the first few weeks of use, but these can be expected to resolve with continued therapy.
- Patients using retinoic acid should be advised to avoid or minimize sun exposure and use a protective sunscreen; it may increase the tumorigenic potential of ultraviolet radiation.
- Allergic contact dermatitis to topical retinoic acid is rare.
- **Adapalene** resembles retinoic acid in structure and effects.
- Unlike tretinoin, adapalene is photochemically stable and shows little decrease in efficacy when used in combination with benzoyl peroxide.
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Isotretinoin

- Isotretinoin is a synthetic retinoid currently restricted to the oral treatment of severe cystic acne that is recalcitrant to standard therapies.
- The precise mechanism of action of isotretinoin in cystic acne is not known, although it appears to act by inhibiting sebaceous gland size and function.
- The drug is well absorbed, extensively bound to plasma albumin, and has an elimination half-life of 10–20 hours.
- Recently, a lipid solubilized formulation, CIP-isotretinoin has been approved which provides more consistent absorption and can be taken with or without food.
- Most patients with cystic acne respond to 1–2 mg/kg, given in two divided doses daily for 4–5 months.
- If severe cystic acne persists following this initial treatment, after a period of 2 months, a second course of therapy may be initiated.
- Common adverse effects resemble hypervitaminosis A and include dryness and itching of the skin and mucous membranes.
- Less common side effects are headache, corneal opacities, pseudotumor cerebri, inflammatory bowel disease, anorexia, alopecia, and muscle and joint pains. These effects are all reversible on discontinuance of therapy.
- Skeletal hyperostosis has been observed in patients receiving isotretinoin with premature closure of epiphyses noted in children treated with this medication.
- Lipid abnormalities (triglycerides, high-density lipoproteins) are frequent.
- It is teratogen therefore; women of childbearing potential *must* use an effective form of contraception for at least 1 month before, throughout isotretinoin therapy, and for one or more menstrual cycles following discontinuance of treatment.
- A negative serum pregnancy test *must* be obtained within 2 weeks before starting therapy in these patients, and therapy should be initiated only on the second or third day of the next normal menstrual period.
- In the USA, health care professionals, pharmacists, and patients must utilize the mandatory iPledge registration and follow-up system.

Benzoyl Peroxide	<ul style="list-style-type: none"> - Benzoyl peroxide is an effective topical agent in the treatment of acne vulgaris. It penetrates the stratum corneum or follicular openings unchanged and is converted metabolically to benzoic acid within the epidermis and dermis. - Less than 5% of an applied dose is absorbed from the skin in an 8-hour period. - It has been postulated that the mechanism of action of benzoyl peroxide in acne is related to its antimicrobial activity against <i>P acnes</i> and to its peeling and comedolytic effects. Combination formulations more effective than individual agents alone. - To decrease the likelihood of irritation, application should be limited to a low concentration (2.5%) once daily for the first week of therapy and increased in frequency and strength if the preparation is well tolerated. - Benzoyl peroxide is a potent contact sensitizer this adverse effect may occur in up to 1% of acne patients. - Care should be taken to avoid contact with the eyes and mucous membranes. - Benzoyl peroxide is an oxidant and may rarely cause bleaching of the hair or colored fabrics.
Azelaic Acid	<ul style="list-style-type: none"> - Azelaic acid is effective in the treatment of acne vulgaris and acne rosacea. - Its mechanism of action has not been fully determined, but preliminary studies demonstrate antimicrobial activity against <i>P acnes</i> as well as in vitro inhibitory effects on the conversion of testosterone to dihydrotestosterone. - Initial therapy is begun with once-daily applications of the cream or gel to the affected areas for 1 week and twice-daily applications thereafter. Most patients experience mild irritation with redness and dryness of the skin during the first week. - Clinical improvement is noted in 6–8 weeks of continuous therapy.

Brimonidine	<ul style="list-style-type: none"> - Brimonidine is an α₂-adrenergic agonist indicated for the topical treatment of persistent facial erythema of rosacea in adults 18 years of age or older. - Daily topical application may reduce erythema through direct vasoconstriction. - Exacerbation of facial erythema and flushing may occur, ranging from 30 minutes to several hours after application. - It should be used with caution in patients with severe, unstable, or uncontrolled cardiovascular disease.
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DRUGS FOR PSORIASIS

Acitretin	<ul style="list-style-type: none"> - Acitretin is quite effective in the treatment of psoriasis, especially pustular forms. It is given orally at a dosage of 25–50 mg/d. - Adverse effects attributable to acitretin therapy are similar to those seen with isotretinoin and resemble hypervitaminosis A. - Elevations in cholesterol and triglycerides may be noted with acitretin, and hepatotoxicity with liver enzyme elevations has been reported. - Acitretin is more teratogenic than isotretinoin in the animal and it has a prolonged elimination time (more than 3 months) after chronic administration. So, it must not be used by women who are pregnant or may become pregnant while undergoing treatment or at any time for at least 3 years after treatment is discontinued. - Ethanol must be strictly avoided during treatment with acitretin and for 2 months after discontinuing therapy, concomitant administration of acitretin and ethanol produce etretinate which may be found in plasma and subcutaneous fat for many years. - Patients must not donate blood during treatment and for 3 years after acitretin is stopped.
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Calcipotriene & Calcitriol

- **Calcipotriene** is a synthetic vitamin D₃ derivative effective in the treatment of plaque- psoriasis vulgaris of moderate severity.
- Improvement of psoriasis was generally noted following 2 weeks of therapy, with continued improvement for up to 8 weeks of treatment. However, fewer than 10% of patients demonstrate total clearing while on calcipotriene as single-agent therapy.
- Adverse effects include burning, itching, and mild irritation, with dryness and erythema of the treatment area. Care should be taken to avoid facial contact, which may cause ocular irritation.
- A once daily application combination of calcipotriene and betamethasone dipropionate ointment is more effective than its individual ingredients and is well tolerated, with a safety profile similar to betamethasone dipropionate.
- **Calcitriol** 3 mcg/g ointment is similar in efficacy to calcipotriene 0.005% ointment for the treatment of plaque psoriasis, and is better tolerated in intertriginous and sensitive areas of the skin, with comparable safety data regarding adverse reactions

Tazarotene

- Tazarotene is a topical prodrug that is hydrolyzed to its active form by an esterase. The active metabolite, tazarotenic acid, binds to retinoic acid receptors, resulting in modified gene expression.
- The mechanism of action in psoriasis is unknown but may relate to both anti-inflammatory and antiproliferative actions.
- Tazarotene is absorbed percutaneously, and teratogenic systemic concentrations may be achieved if applied to more than 20% of total body surface area.
- Women of childbearing potential must therefore be advised of the risk prior to initiating therapy, and adequate birth control measures must be utilized while on therapy.
- It should be limited to once-daily application of either 0.05% or 0.1% gel not to exceed 20% of total body surface area.
- Adverse local effects include a burning or stinging sensation (sensory irritation) and peeling, erythema, and localized edema of the skin (irritant dermatitis). Potentiation of photosensitizing medication may occur, and patients should be cautioned to minimize sunlight exposure and to use sunscreens and protective clothing.

Alefacept

- Alefacept is an immunosuppressive dimeric fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen-3 linked to the Fc portion of human IgG1.
- It interferes with lymphocyte activation, which plays a role in the pathophysiology of psoriasis, and causes a reduction in subsets of CD2 T lymphocytes and circulating total CD4 and CD8 T-lymphocyte counts.
- The recommended dosage is 7.5 mg given once weekly as an intravenous bolus or 15 mg once weekly as an intramuscular injection for a 12-week course of treatment.
- Patients should have CD4 lymphocyte counts monitored weekly while taking alefacept, and dosing should be withheld if CD4 counts are below 250 cells/ μ L.
- The drug should be discontinued if the counts remain below 250 cells/ μ L for 1 month.
- It is an immunosuppressive agent and should not be administered to patients with clinically infection. Because of the possibility of an increased risk of malignancy, it should not be administered to patients with a history of systemic malignancy.

Tnf Inhibitors: Etanercept, Infliximab, & Adalimumab

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG1.

- It binds selectively to TNF- α and β and blocks interaction with cell surface TNF receptors that play a role in the inflammatory process of plaque psoriasis.
- The recommended dosage of etanercept in psoriasis is a 50 mg subcutaneous injection given twice weekly for 3 months followed by a maintenance dose of 50 mg weekly.

Infliximab is a chimeric IgG1 monoclonal antibody composed of human constant and murine variable regions.

- It binds to the soluble and transmembrane forms of TNF- α and inhibit binding of TNF- α with its receptors.
- The recommended dose of infliximab is 5 mg/kg given as an intravenous infusion followed by similar doses at 2 and 6 weeks after the first infusion and then every 8 weeks thereafter.

Adalimumab is a recombinant IgG1 monoclonal antibody that binds specifically to TNF- α and blocks its interaction with cell surface TNF receptors.

- The recommended dose for adalimumab in psoriasis is an initial dose of 80 mg administered subcutaneously followed by 40 mg given every other week starting 1 week after the initial dose.
- Serious life-threatening infections, including sepsis and pneumonia, have been reported with the use of TNF inhibitors.
- Patients should be evaluated for tuberculosis risk factors and tested for latent tuberculosis infection prior to starting therapy.
- Concurrent use with other immunosuppressive therapy should be avoided.
- In clinical trials of all TNF-blocking agents more cases of lymphoma were observed compared with control patients.
- Patients with a prior history of prolonged phototherapy treatment should be monitored for nonmelanoma skin cancers.

Ustekinumab	<ul style="list-style-type: none"> - Ustekinumab is a human IgG1 monoclonal antibody that binds with high affinity and specificity to interleukin (IL)-12 and IL-23 cytokines inhibiting TH1 and TH17 cell-mediated responses, which are involved in the pathogenesis of psoriasis. - The recommended treatment protocol is 45 mg for patients weighing less than 100 kg, and 90 mg for patients weighing more than 100 kg given as a subcutaneous injection initially, followed by the same dose 4 weeks later, and then once every 12 weeks. - Serious allergic reactions including angioedema and anaphylaxis have occurred and caution should be exercised in patients receiving allergy immunotherapy. Serious infections, especially from mycobacterial organisms, are possible and patients must be evaluated for tuberculosis prior to initiating therapy. Reversible posterior leukoencephalopathy syndrome has been reported. - Live vaccines, including bacillus Calmette-Guérin (BCG), should not be given with ustekinumab.
Fumaric Acid Esters	<p>Fumaric acid esters are licensed in Germany for the oral treatment of psoriasis. They are considered homeopathic treatment in the USA and are not approved or regulated by the FDA for the treatment of psoriasis.</p> <ul style="list-style-type: none"> - Dimethyl fumarate has recently been approved by the FDA for treatment of multiple sclerosis. The mechanism of action of dimethyl fumarate in psoriasis may be due to immunomodulatory effects on lymphocytes and keratinocytes resulting in a shift away from a psoriatic cytokine profile. - It should be noted that four cases of progressive multifocal leukoencephalopathy have been reported in psoriasis patients treated with fumaric acid esters.
Biologic Agents	<p>Biologic agents useful in treating adult patients with moderate to severe chronic plaque psoriasis include:</p> <ul style="list-style-type: none"> - T-cell modulator alefacept. - The TNF-α inhibitors etanercept, infliximab, and adalimumab; Cytokine inhibitor ustekinumab.

ANTI-INFLAMMATORY AGENTS

Topical Corticosteroids

The therapeutic effectiveness of topical corticosteroids is based primarily on their anti-inflammatory activity. Corticosteroids are only minimally absorbed following application to normal skin; for example, approximately 1% of a dose of hydrocortisone solution applied to the ventral forearm is absorbed.

Table 61–3

- In the first group of diseases, low- to medium-efficacy corticosteroid preparations often produce clinical remission.
- In the second group, it is often necessary to use high-efficacy preparations, occlusion therapy, or both.
- Once a remission has been achieved, every effort should be made to maintain the improvement with a low-efficacy corticosteroid.

Adverse Effects

All absorbable topical corticosteroids possess the potential to suppress the pituitary-adrenal axis. Although most patients with pituitary-adrenal axis suppression demonstrate only a laboratory test abnormality, cases of severely impaired stress response can occur. Iatrogenic Cushing's syndrome may occur as a result of protracted use of topical corticosteroids in large quantities.

Applying potent corticosteroids to extensive areas of the body for prolonged periods, with or without occlusion, increases the likelihood of systemic effects. Fewer of these factors are required to produce adverse systemic effects in children, and growth retardation is of particular concern in the pediatric age group.

Adverse local effects of topical corticosteroids include the following:

Atrophy, which may present as depressed, shiny, often wrinkled "cigarette paper"-appearing skin with prominent telangiectases and a tendency to develop purpura and ecchymosis; corticoid rosacea, with persistent erythema, telangiectatic vessels, pustules, and papules in central facial distribution; perioral dermatitis, steroid acne, alterations of cutaneous infections, hypopigmentation, hypertrichosis; increased intraocular pressure; and allergic contact dermatitis.

Allergic contact dermatitis may be confirmed by patch testing with high concentrations of corticosteroids, ie, 1% in petrolatum, because topical corticosteroids are not irritating. Screening for allergic contact dermatitis potential is performed with tixocortolpivalate, budesonide, and hydrocortisone valerate or butyrate.

Topical corticosteroids are contraindicated in individuals who demonstrate hypersensitivity to them. Some sensitized subjects develop a generalized flare when dosed with adrenocorticotropic hormone or oral prednisone.

TAR compounds	<ul style="list-style-type: none">- Tar preparations are used mainly in the treatment of psoriasis, dermatitis, and lichen simplex chronicus. The phenolic constituents endow these compounds with antipruritic properties, making them particularly valuable in the treatment of chronic lichenified dermatitis.- Acute dermatitis with vesication and oozing may be irritated by even weak tar preparations, which should be avoided. However, in the subacute and chronic stages of dermatitis and psoriasis, these preparations are quite useful and offer an alternative to the use of topical corticosteroids.- The most common adverse reaction to coal tar compounds is an irritant folliculitis, necessitating discontinuance of therapy to the affected areas for a period of 3–5 days.- Photo-irritation and allergic contact dermatitis may also occur.- Tar preparations should be avoided in patients who have previously exhibited sensitivity to them.
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TABLE 61–3 Dermatologic disorders responsive to topical corticosteroids ranked in order of sensitivity.

Very responsive
Atopic dermatitis
Seborrheic dermatitis
Lichen simplex chronicus
Pruritus ani
Later phase of allergic contact dermatitis
Later phase of irritant dermatitis
Nummular eczematous dermatitis
Stasis dermatitis
Psoriasis, especially of genitalia and face
Less responsive
Discoid lupus erythematosus
Psoriasis of palms and soles
Necrobiosis lipoidica diabetorum
Sarcoidosis
Lichen striatus
Pemphigus
Familial benign pemphigus
Vitiligo
Granuloma annulare
Least responsive: Intralesional Injection required
Keloids
Hypertrophic scars
Hypertrophic lichen planus
Alopecia areata
Acne cysts
Prurigo nodularis
Chondrodermatitis nodularis chronica helicis

KERATOLYTIC & DESTRUCTIVE AGENTS

Salicylic Acid

- Salicylic acid has been extensively used in dermatologic therapy as a keratolytic agent.
- The mechanism by which it produces its keratolytic and other therapeutic effects is poorly understood. The drug may solubilize cell surface proteins that keep the *stratum corneum* intact, thereby resulting in desquamation of keratotic debris.
- Salicylic acid is keratolytic in concentrations of 3–6%. In concentrations greater than 6%, it can be destructive to tissues.
- **Salicylism** and death have occurred following topical application. The threshold for toxicity is 30–50 mg/dL and higher serum levels are possible in children. Hemodialysis is the treatment of choice for severe intoxication.
- It is advisable to limit both the total amount of salicylic acid applied and the frequency of application.
- Urticular, anaphylactic, and erythema multiforme reactions may occur in patients who are allergic to salicylates.
- Topical use may be associated with local irritation, acute inflammation, and even ulceration with the use of high concentrations.
- Particular care must be exercised when using the drug on the extremities of patients with diabetes or peripheral vascular disease.

Propylene Glycol	<ul style="list-style-type: none"> - Propylene glycol is used extensively in topical preparations because it is an excellent vehicle for organic compounds. It has been used alone as a keratolytic agent in 40–70% concentrations, with plastic occlusion, or in gel with 6% salicylic acid. - Propylene glycol is an effective keratolytic agent for the removal of hyperkeratotic debris. It is also an effective humectant and increases the water content of the stratum corneum. - The hygroscopic characteristics of propylene glycol may help it to develop an osmotic gradient through the stratum corneum, thereby increasing hydration of the outermost layers by drawing water out from the inner layers of the skin. - Propylene glycol is used under polyethylene occlusion or with 6% salicylic acid for the treatment of ichthyosis, palmar and plantar keratodermas, psoriasis, pityriasisrubra pilaris, keratosis pilaris, and hypertrophic lichen planus. - In concentrations greater than 10%, propylene glycol may act as an irritant in some patients; those with eczematous dermatitis may be more sensitive. - Allergic contact dermatitis occurs with propylene glycol, and a 4% aqueous propylene glycol solution is recommended for the purpose of patch testing.
Aminolevulinic Acid (ALA)	<ul style="list-style-type: none"> - Aminolevulinic acid is an endogenous precursor of photosensitizing porphyrin metabolites. - Treatment consists of applying ALA 20% topical solution to individual actinic keratoses followed by blue light photodynamic illumination 14–18 hours later. - When exogenous ALA is provided to the cell through topical applications, protoporphyrin IX (PpIX) accumulates in the cell. When exposed to light of appropriate wavelength and energy, the accumulated PpIX produces a photodynamic reaction resulting in the formation of cytotoxic superoxide and hydroxyl radicals. Photosensitization of actinic keratoses using ALA (LevulanKerastick) and illumination with a blue light photodynamic therapy illuminator (BLU-U) is the basis for ALA photodynamic therapy. - Transient stinging or burning at the treatment site occurs during the period of light exposure. - Patients <i>must</i> avoid exposure to sunlight or bright indoor lights for at least 40 hours after ALA application. - Redness, swelling, and crusting of the actinic keratoses will occur and gradually resolve over a 3- to 4-week time course. <p>Allergic contact dermatitis to methyl ester may occur.</p>

Urea

- Urea in a compatible cream vehicle or ointment base has a softening and moisturizing effect on the stratum corneum. It has the ability to make creams and lotions feel less greasy, and this has been utilized in dermatologic preparations to decrease the oily feel of a preparation that otherwise might feel unpleasant.
- It increases the water content of the stratum corneum, presumably as a result of the hygroscopic characteristics of this naturally occurring molecule.
- As a humectant, urea is used in concentrations of 2–20% in creams and lotions. As a keratolytic agent, it is used in 20% concentration in diseases such as ichthyosis vulgaris, hyperkeratosis of palms and soles, xerosis, and keratosis pilaris.
- Concentrations of 30–50% applied to the nail plate have been useful in softening the nail prior to avulsion.

Podophyllum Resin & Podofilox

- Podophyllum resinis used in the treatment of condyloma acuminatum and other verrucae.
- Percutaneous absorption of podophyllum resin occurs, particularly in intertriginous areas and from applications to large moist condylomas.
- It is soluble in lipids and therefore is distributed widely throughout the body, including the central nervous system.
- Podophyllotoxin and its derivatives are active cytotoxic agents with specific affinity for the microtubule protein of the mitotic spindle. Normal assembly of the spindle is prevented ,and epidermal mitoses are arrested in metaphase.
- A 25% concentrationin compound tincture of benzoin is recommended for the treatment of condyloma acuminatum.
- Application should be restricted to wart tissue only, to limit the total amount of medication used and to prevent severe erosive changes in adjacent tissue. In treating cases of large condylomas, it is advisable to limit application to sections of the affected area to minimize systemic absorption.
- The patient is instructed to wash off the preparation 2–3hours after the initial application, because the irritant reaction is variable.Depending on the individual patient's reaction, this period canbe extended to 6–8 hours on subsequent applications. If three to five applications have not resulted in significant resolution, other methodsof treatment should be considered.
- Toxic symptoms associated with excessively large applications include nausea, vomiting, alterations in sensorium, muscle weakness,neuropathy with diminished tendon reflexes, coma, and even death. Local irritation is common, and inadvertent contact with the eye may cause severe conjunctivitis.
- Local adverse effects include inflammation ,erosions, burning pain, and itching.
- Use during pregnancy iscontraindicated in view of possible cytotoxic effects on the fetus.
- Pure podophyllotoxin is approved for use as either 0.5% solution or gel for application by the patientin the treatment of genital condylomas. The low concentration of podofilox significantly reduces the potential for systemic toxicity.
- Most men with penile warts may be treated with less than 70 μ L per application. At this dose, podofilox is not routinely detectedin the serum.
- Treatment is self-administered in treatment cycles of twice-daily application for 3 consecutive days followed by a 4-day drug-free period.

Sinecatechin S	<ul style="list-style-type: none"> - Sinecatechins 15% ointment is a prescription botanical drug product for the topical treatment of external genital and perianal warts in immunocompetent patients 18 years and older. - It should be applied three times daily to the warts until complete clearance, not to exceed 16 weeks of therapy.
Fluorouracil F	<ul style="list-style-type: none"> - Fluorouracil is antimetabolite used topically for the treatment of multiple actinic keratoses. - Approximately 6% of a topically applied dose is absorbed—an amount insufficient to produce adverse systemic effects. - Most of the absorbed drug is metabolized and excreted as carbon dioxide, urea, and α-fluoro-α-alanine. A small percentage is eliminated unchanged in the urine. - Fluorouracil inhibits thymidylate synthetase activity, interfering with the synthesis of DNA and, to a lesser extent, RNA. These effects are most marked in atypical, rapidly proliferating cells. - The response to treatment begins with erythema and progresses through vesication, erosion, superficial ulceration, necrosis, and finally reepithelialization. - Fluorouracil should be continued until the inflammatory reaction reaches the stage of ulceration and necrosis, usually in 3–4 weeks, at which time treatment should be terminated. The healing process may continue for 1–2 months after therapy is discontinued. - Local adverse reactions may include pain, pruritus, a burning sensation, tenderness, and residual post-inflammatory hyperpigmentation. - Excessive exposure to sunlight during treatment may increase the intensity of the reaction and should be avoided. - Allergic contact dermatitis to fluorouracil has been reported, and its use is contraindicated in patients with known hypersensitivity.

IngenolMebutate	<ul style="list-style-type: none"> - Ingenolmebutate recently been approved for the topical treatment of actinic keratoses. - The mechanism by which ingenolmebutate induces keratinocyte cell death is unknown. - For the treatment of actinic keratoses on the face and scalp, the 0.015% gel should be applied once daily for 3 consecutive days. For actinic keratoses on the trunk and extremities, the 0.05% gel should be applied to the affected area daily for 2 consecutive days. - Local skin reactions are to be expected with crusting, swelling, vesiculation, and possible ulceration. - Caution must be taken to prevent eye exposure. Patients must wash their hands well after applying the gel and avoid transfer of the drug to the periocular area during and after application.
Nonsteroidal Anti-Inflammatory Drugs	<ul style="list-style-type: none"> - A topical 3% gel formulation of the nonsteroidal anti-inflammatory drug diclofenac has shown moderate effectiveness in the treatment of actinic keratoses. - The mechanism of action is unknown. - As with other NSAIDs, anaphylactoid reactions may occur with diclofenac, and it should be given with caution to patients with known aspirin hypersensitivity.

ANTIPRURITIC AGENTS

Doxepin	<ul style="list-style-type: none">- Topical doxepin hydrochloride 5% cream may provide significant antipruritic activity when utilized in the treatment of pruritus associated with atopic dermatitis or lichen simplex chronicus.- The precise mechanism of action is unknown but may relate to the potent H1- and H2-receptor antagonist properties of dibenzoxepin tricyclic compounds.- Percutaneous absorption is variable and may result in significant drowsiness in some patients.- In view of the anticholinergic effect of doxepin, topical use is contraindicated in patients with untreated narrow-angle glaucoma or a tendency to urinary retention.- Plasma levels of doxepin similar to those achieved during oral therapy may be obtained with topical application; the usual drug interactions associated with tricyclic antidepressants may occur. Therefore, monoamine oxidase inhibitors must be discontinued at least 2 weeks prior to the initiation of doxepin cream.- Topical application of the cream should be performed four times daily for up to 8 days of therapy.- The safety and efficacy of chronic dosing has not been established.- Adverse local effects include marked burning and stinging of the treatment site which may necessitate discontinuation of the cream in some patients.- Allergic contact dermatitis appears to be frequent, and patients should be monitored for symptoms of hypersensitivity.
Pramoxine	<ul style="list-style-type: none">- Pramoxine hydrochloride is a topical anesthetic that can provide temporary relief from pruritus associated with mild eczematous dermatoses.- It is available as a 1% cream, lotion, or gel and in combination with hydrocortisone acetate.- Application to the affected area two to four times daily may provide short-term relief of pruritus.- Local adverse effects include transient burning and stinging. Care should be exercised to avoid contact with the eyes.

ANTISEBorrhea Agents

These are of variable efficacy and may necessitate concomitant treatment with topical corticosteroids for severe cases. Topical include Betamethasone valerate foam, Chloroxine shampoo, Coal tar shampoo, Fluocinolone acetonide shampoo, Ketoconazole shampoo and gel, Selenium sulfide shampoo, Zinc pyrithione shampoo.

TRICHOGEnIC & ANTITRICHOGEnIC AGENTS

Minoxidil	<ul style="list-style-type: none">- Topical minoxidil is effective in reversing the progressive miniaturization of terminal scalp hairs associated with androgenicalopecia. Vertex balding is more responsive to therapy than frontal balding.- The mechanism of action of minoxidil on hair follicles is unknown.- Chronic dosing studies have demonstrated that the effect of minoxidil is not permanent, and cessation of treatment will lead to hair loss in 4–6 months.- Percutaneous absorption of minoxidil in normal scalp is minimal, but possible systemic effects on blood pressure should be monitored inpatients with cardiac disease.
Finasteride	<ul style="list-style-type: none">- It is a 5α-reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone the androgen responsible for androgenic alopecia in genetically predisposed men.- Oral finasteride, 1 mg/d, promotes hair growth and prevents further hair loss in a significant proportion of men with androgenic alopecia. Treatment for at least 3–6 months is necessary to see increased hair growth or prevent further hair loss.- Continued treatment with finasteride is necessary to sustain benefit.- Reported adverse effects include decreased libido, ejaculation disorders, and erectile dysfunction, which resolve in most men who remain on therapy and in all men who discontinue finasteride.- There are no data to support the use of finasteride in women with androgenic alopecia.- Pregnant women should not be exposed to finasteride either by use or by handling crushed tablets because of the risk of hypospadias developing in a male fetus.

Bimatoprost	<ul style="list-style-type: none"> - Bimatoprost is a prostaglandin analog that is available as a 0.03% ophthalmic solution to treat hypotrichosis of the eyelashes. - The mechanism of action is unknown. - Treatment consists of nightly application to the skin of the upper eyelid margins at the base of the eyelashes using a separate disposable applicator for each eyelid. - Contact lenses should be removed prior to bimatoprost application. - Side effects include pruritus, conjunctival hyperemia, skin pigmentation, and erythema of the eyelids. Although iris darkening has not been reported with applications confined to the upper eyelid skin, increased brown iris pigmentation, which is likely to be permanent, has occurred when bimatoprost ophthalmic solution was instilled onto the eye.
Eflornithine	<ul style="list-style-type: none"> - Eflornithine is an irreversible inhibitor of ornithine decarboxylase, which catalyzes the rate-limiting step in the biosynthesis of polyamines. Polyamines are required for cell division and differentiation, and inhibition of ornithine decarboxylase affects the rate of hair growth. - Topical eflornithine has been shown to be effective in reducing facial hair growth in approximately 30% of women when applied twice daily for 6 months of therapy. - Hair growth was observed to return to pretreatment levels 8 weeks after discontinuation. - Local adverse effects include stinging, burning, and folliculitis.

AGENTS FOR MELANOMA

Braf Inhibitors	<p>BRAF inhibitors are indicated for the treatment of unresectable or metastatic melanoma with BRAF mutations as detected by an FDA-approved test. These agents are not approved for treatment of BRAF wild-type melanoma.</p> <ul style="list-style-type: none">- Vemurafenib and dabrafenib are kinase inhibitors of BRAF V600E mutation. They increase the risk for new primary cutaneous malignancies including squamous cell carcinoma, keratoacanthoma, and new primary melanomas.- Trametinib is a kinase inhibitor of BRAF V600E and V600K mutations, And it use is associated with a defined risk of cardiomyopathy. All BRAF inhibitors are associated with serious hypersensitivity reactions, including severe dermatologic reactions as well as ophthalmologic complications.
Ipilimumab	<ul style="list-style-type: none">- Ipilimumab is a cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocker antibody recently approved for the treatment of unresectable or metastatic melanoma.- It may act by increasing T-cell-mediated antitumor immune responses. And its use can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation.- The most common adverse reactions are enterocolitis, hepatitis, dermatitis, neuropathy, and endocrinopathy.
Pegylated Interferon	<ul style="list-style-type: none">- Pegylated interferon alpha-2b was recently approved by the FDA for adjuvant therapy of stage III node-positive melanoma patients.- The effectiveness of once-weekly pegylated interferon versus the standard high-dose interferon regimen is yet to be proven. The FDA did not specifically approve the use of pegylated interferon as a replacement for standard interferon therapy. Clinical trials to determine the optimum interferon treatment parameters for stage III melanoma are ongoing.

OTHER ANTINEOPLASTIC AGENTS

Alitretinoin	<ul style="list-style-type: none">- Alitretinoin is a topical formulation of 9-cis-retinoic acid which is approved for the treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma. Localized reactions may include intense erythema, edema, and vesiculation necessitating discontinuation of therapy. Patients who are applying alitretinoin should not concurrently use products containing DEET, a common component of insect repellent products.
Bexarotene	<ul style="list-style-type: none">- Bexarotene is a member of a subclass of retinoids that selectively binds and activates retinoid X receptor subtypes. It is available both in an oral formulation and as a topical gel for the treatment of cutaneous T-cell lymphoma. Teratogenicity is a significant risk for both systemic and topical treatment with bexarotene, and women of childbearing potential must avoid becoming pregnant throughout therapy and for at least 1 month following discontinuation of the drug. Bexarotene may increase levels of triglycerides and cholesterol; therefore, lipid levels must be monitored during treatment.
Vismodegib	<ul style="list-style-type: none">- Vismodegib(Erivedge) is the first hedgehog pathway inhibitor available for the oral treatment of metastatic basal cell carcinoma or locally advanced basal cell carcinoma in adults who are not candidates for surgery or radiation. The recommended dosage of vismodegib is 150 mg daily. The most common adverse effects include dysgeusia and ageusia, alopecia, fatigue, and muscle spasms. It is highly effective in patients with basal cell nevus syndrome.
Vorinostat&Romidepsin	<ul style="list-style-type: none">- VorinostatandRomidepsinarehistone deacetylase inhibitors that are approved for the treatment of cutaneous T-cell lymphoma in patients with progressive, persistent, or recurrent disease after prior systemic therapy. Adverse effects include thrombocytopenia, anemia, and gastrointestinal disturbances .Pulmonary embolism, which has occurred with vorinostat ,has not been reported to date with romidepsin.

MISCELLANEOUS

MISCELLANEOUS MEDICATIONS

- A number of drugs used primarily for other conditions also find use as oral therapeutic agents for dermatologic conditions.
- A few such preparations are listed in Table 61–5.

TABLE 61–5 Miscellaneous medications and the dermatologic conditions in which they are used.

Drug or Group	Conditions
Alitretinoin	AIDS-related Kaposi's sarcoma
Antihistamines	Pruritus (any cause), urticaria
Antimalarials	Lupus erythematosus, photosensitization
Antimetabolites	Psoriasis, pemphigus, pemphigoid
Becaplermin	Diabetic neuropathic ulcers
Belimumab	Systemic lupus erythematosus
Bexarotene	Cutaneous T-cell lymphoma
Capsaicin	Post-herpetic neuralgia
Corticosteroids	Pemphigus, pemphigoid, lupus erythematosus, allergic contact dermatoses, and certain other dermatoses
Cyclosporine	Psoriasis
Dabrafenib	Melanoma
Dapsone	Dermatitis herpetiformis, erythema elevatum diutinum, pemphigus, pemphigoid, bullous lupus erythematosus
Denileukin diftitox	Cutaneous T-cell lymphoma
Drospirenone/ethynodiol estradiol	Moderate female acne
Ipilimumab	Melanoma
Mechlorethamine gel	Cutaneous T-cell lymphoma
Mycophenolate mofetil	Bullous disease
Peginterferon alpha-2b	Melanoma
Romidepsin	Cutaneous T-cell lymphoma
Thalidomide	Erythema nodosum leprosum
Trametinib	Melanoma
Vemurafenib	Melanoma
Vorinostat	Cutaneous T-cell lymphoma

Chapter: 62 (Drugs Used in the treatment of Gastrointestinal Diseases)

■DRUGS USED IN ACID-PEPTIC DISEASES

Acid-peptic diseases include gastroesophageal reflux, peptic ulcer (gastric and duodenal), and stress-related mucosal injury.

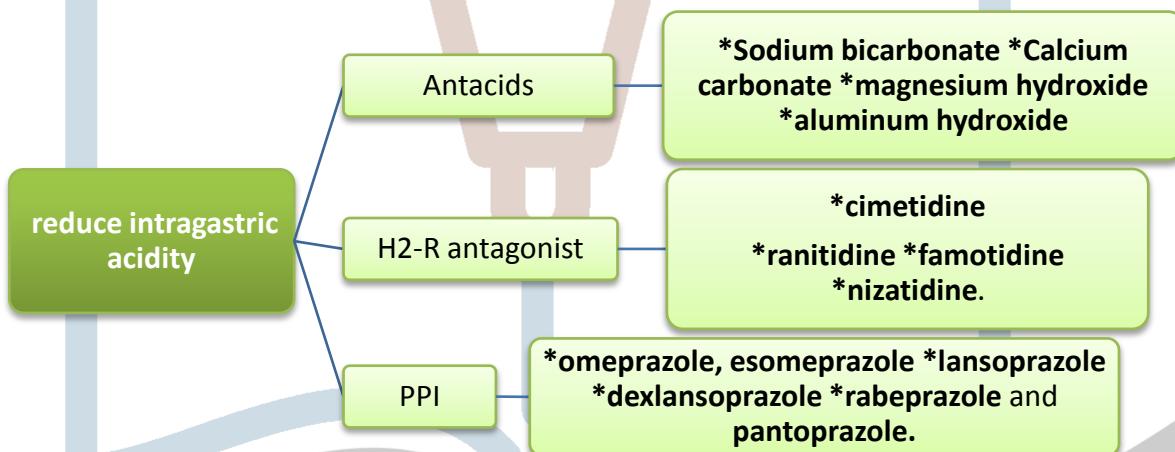
Over 90% of peptic ulcers are caused by infection with the bacterium *Helicobacter pylori* or by use of nonsteroidal anti-inflammatory drugs (NSAIDs).

The treatment may be divided into two classes: agents that reduce intragastric acidity and agents that promote mucosal defense.

AGENTS THAT REDUCE INTRAGASTRIC ACIDITY

PHYSIOLOGY OF ACID SECRETION

- 1- **The parietal cell** contains receptors for gastrin (CCK-B), histamine (H_2), and acetylcholine (muscarinic, M_3). When acetylcholine or gastrin bind to the parietal cell receptors → stimulate acid secretion H^+/K^+ -ATPase (the proton pump)
- 2- **Enterochromaffin-like (ECL) cells**. Have receptors for gastrin and acetylcholine, which stimulate histamine release. Histamine binds to the H_2 receptor on the parietal cell, → stimulate acid secretion by the H^+/K^+ ATPase.



MOA	Reduce intragastric acidity. weak bases that react with gastric hydrochloric acid to form a salt and water.	Competitive inhibition at the parietal cell H ₂ receptor and suppress basal and meal-stimulated acid secretion.	PPIs are administered as inactive prodrug. They inhibit both fasting and meal-stimulated secretion because they block the final common pathway of acid secretion, the proton pump.
Uses	Treatment of intermittent heartburn and dyspepsia.	<ul style="list-style-type: none"> Gastroesophageal reflux disease (GERD) Peptic ulcer disease Nonulcer dyspepsia Prevention of bleeding from stress-related gastritis 	<ul style="list-style-type: none"> First line for GERD Peptic ulcer: <ul style="list-style-type: none"> A) <i>H pylori</i>-associated ulcers [2AntiBiotics + PPI] B) NSAID-associated ulcers [if NSAID cant be discontinued, PPI should be taken once-twice daily] C) Prevention of rebleeding from peptic ulcers <ul style="list-style-type: none"> Nonulcer dyspepsia Prevention of stress-related mucosal bleeding Gastrinoma and other hypersecretory conditions (best treated with <u>surgical resection</u>).

Side effects	<ul style="list-style-type: none"> • Gastric distention and belching. • Metabolic acidosis • Fluid retention in patients with heart and renal problems. • Hypercalcemia with calcium-containing dairy products • Magnesium salts → osmotic diarrhea • Aluminum salts → constipation 	<ul style="list-style-type: none"> • Diarrhea, headache, fatigue, myalgias, and constipation. • ICUpatient: Mental status changes • Cemtidine long-term use: gynecomastia or impotence in men and galactorrhea in women. • Rarely: blood dyscrasias, • H2-R blockade: (bradycardia and hypotension) 	<ul style="list-style-type: none"> • <i>General:</i> Diarrhea, headache, and abdominal pain • <i>Nutrition:</i> A minor reduction in oral cyanocobalamin absorption → decrease vitamin. B12 absorption. Reduce calcium absorption or inhibit osteoclast function → increase in the risk of hip fracture (should provide Calcium supplement). • <i>Respiratory and enteric infections</i> (<i>Clostridium difficile</i> infection) • <i>Other potential problems due to decreased gastric acidity:</i> Long-term acid suppression leads to increased chronic inflammation and that may accelerate atrophic gastritis and intestinal metaplasia
ADME	Excreted by kidney. Hence, patients with renal insufficiency should not take these agents long-term	Metabolized by CYP450 enzyme	All PPIs are metabolized by hepatic P450 cytochromesThe bioavailability of all agents is decreased approximately 50% by food; hence, the drugs should be administered on an empty stomach.

DDI

Affect the absorption of other medications:

- Tetracyclines
- Fluoroquinolones
- itraconazole
- Iron.

Compete with procainamide for renal tubular secretion.

Inhibit gastric first-pass metabolism of ethanol

- Decreased gastric acidity may alter absorption of drugs for which intragastric acidity affects drug bioavailability (ketoconazole, itraconazole, digoxin, and atazanavir).
- Omeprazole → inhibit the metabolism of warfarin, diazepam, and phenytoin.
- Esomeprazole → decrease metabolism of diazepam.
- Lansoprazole → enhance clearance of theophylline
- PPIs could reduce clopidogrel activation

Sucralfate**Prostaglandin analogs****Bismuth compounds****TABLE 62-2** Pharmacokinetics of proton pump inhibitors.

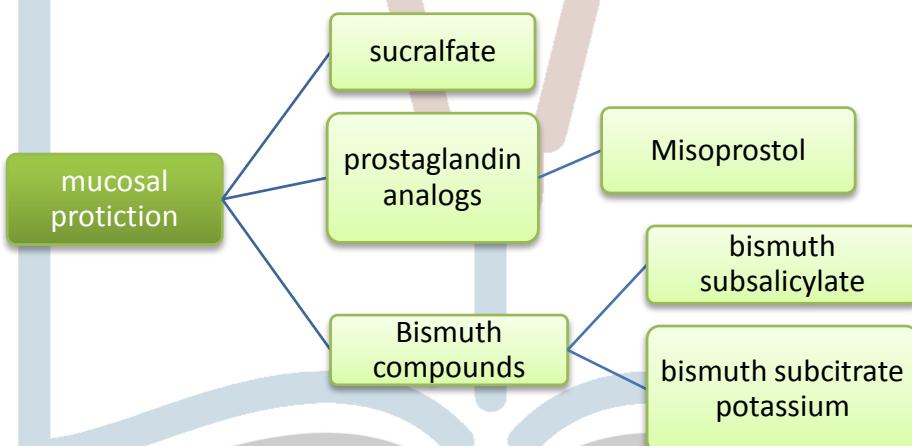
Drug	pK _a	Bioavailability (%)	t _{1/2} (h)	T _{max} (h)	Usual Dosage for Peptic Ulcer or GERD
Omeprazole	4	40–65	0.5–1.0	1–3	20–40 mg qd
Esomeprazole	4	> 80	1.5	1.6	20–40 mg qd
Lansoprazole	4	> 80	1.0–2.0	1.7	30 mg qd
Dexlansoprazole	4	NA	1.0–2.0	5.0	30–60mg qd
Pantoprazole	3.9	77	1.0–1.9	2.5–4.0	40 mg qd
Rabeprazole	5	52	1.0–2.0	3.1	20 mg qd

TABLE 62-1 Clinical comparisons of H₂-receptor blockers.

Drug	Relative Potency	Dose to Achieve > 50% Acid Inhibition for 10 Hours	Usual Dose for Acute Duodenal or Gastric Ulcer	Usual Dose for Gastroesophageal Reflux Disease	Usual Dose for Prevention of Stress-Related Bleeding
Cimetidine	1	400–800 mg	800 mg HS or 400 mg bid	800 mg bid	50 mg/h continuous infusion
Ranitidine	4–10	150 mg	300 mg HS or 150 mg bid	150 mg bid	6.25 mg/h continuous infusion or 50 mg IV every 6–8 h
Nizatidine	4–10	150 mg	300 mg HS or 150 mg bid	150 mg bid	Not available
Famotidine	20–50	20 mg	40 mg HS or 20 mg bid	20 mg bid	20 mg IV every 12 h

MUCOSAL PROTECTIVE AGENTS

Both mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin. Areas of injured epithelium are quickly repaired by restitution. Mucosal prostaglandins appear to be important in stimulating mucus and bicarbonate secretion and mucosal blood flow.



MOA	Salt of sulfated aluminum hydroxide, that binds selectively to ulcers or erosions	<ul style="list-style-type: none"> • Acid inhibitory • Mucosal protective properties 	<ul style="list-style-type: none"> • Coats ulcers and erosions. • Direct antimicrobial effects and binds enterotoxins
Uses	<ul style="list-style-type: none"> • Reduces the incidence of upper gastrointestinal bleeding for ICU patient. • Prevention of stress-related bleeding 	For prevention of NSAID-induced ulcers in high-risk patients.	<ul style="list-style-type: none"> • Eradication of <i>H pylori</i> infection. • Prevention of traveler's diarrhea
Side effect	<ul style="list-style-type: none"> • Constipation • Impair other drugs abs. 		<ul style="list-style-type: none"> • Harmless blackening of the stool • Harmless darkening of the tongue • Bismuth toxicity → encephalopathy and salicylate toxicity.
ADME		It is rapidly absorbed and metabolized to a metabolically active free acid.	It is stored in many tissues and has slow renal excretion.

■DRUGS STIMULATING GASTROINTESTINAL MOTILITY

Drugs that can selectively stimulate gut motor function (**prokinetic agents**).

- 1- Increase lower esophageal sphincter pressures → for GERD.
- 2- Improve gastric emptying → for gastroparesis and postsurgical gastric emptying delay.
- 3- Stimulate the small intestine → for postoperative ileus or chronic intestinal pseudo-obstruction.
- 4- Enhance colonic transit → treatment of constipation.

Cholinomimetic agents

Metoclopramide & Domperidone

Macrolides

PHYSIOLOGY OF THE ENTERIC NERVOUS SYSTEM

The enteric nervous system is composed of interconnected networks of ganglion cells and nerve fibers. These networks give rise to nerve fibers that connect with the mucosa and muscle. The enteric nervous system can independently regulate gastrointestinal motility and secretion.

1-Release of serotonin (5-HT) from intestinal mucosa enterochromaffin (EC) cells stimulates:

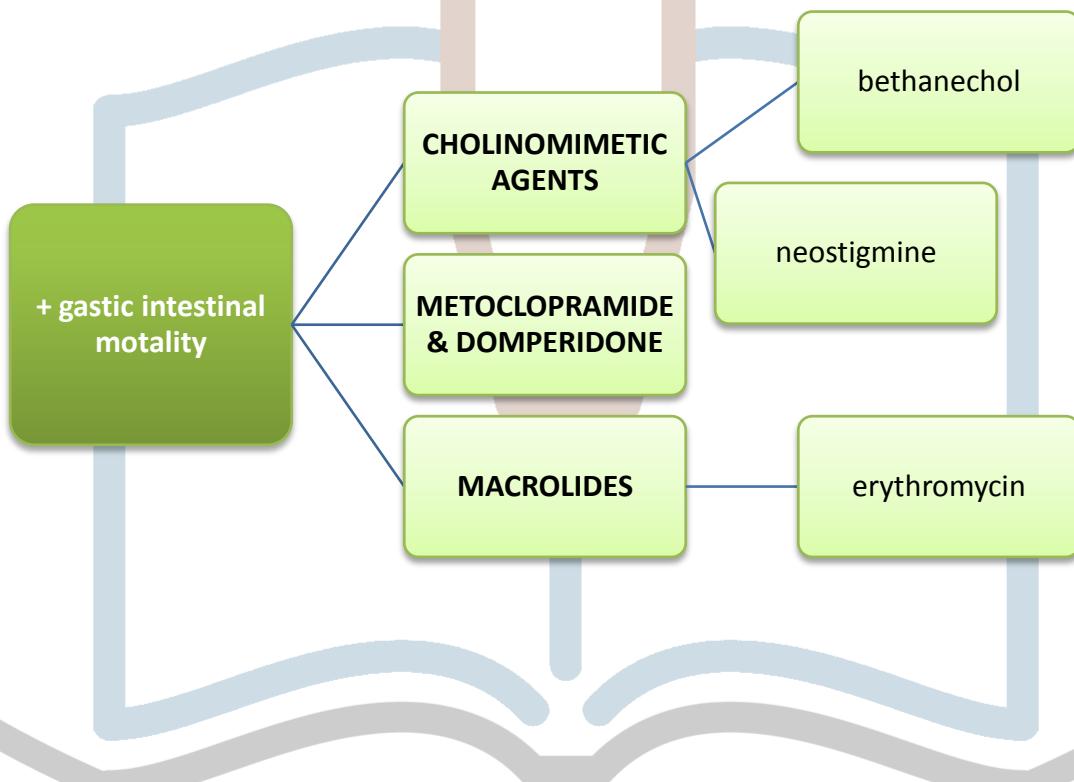
- 5-HT₃ → stimulating nausea, vomiting, or abdominal pain.
- 5-HT₄ → enhance release of CGRP or acetylcholine.

5-HT₃-receptor antagonists and 5-HT₄-receptor agonists:

Treatment of Irritable Bowel Syndrome and Antiemetic Agents.

2-Motilin → stimulates excitatory neurons or muscle cells directly.

3-Dopamine → inhibitory neurotransmitter in the gastrointestinal tract, decreasing the intensity of esophageal and gastric contractions.

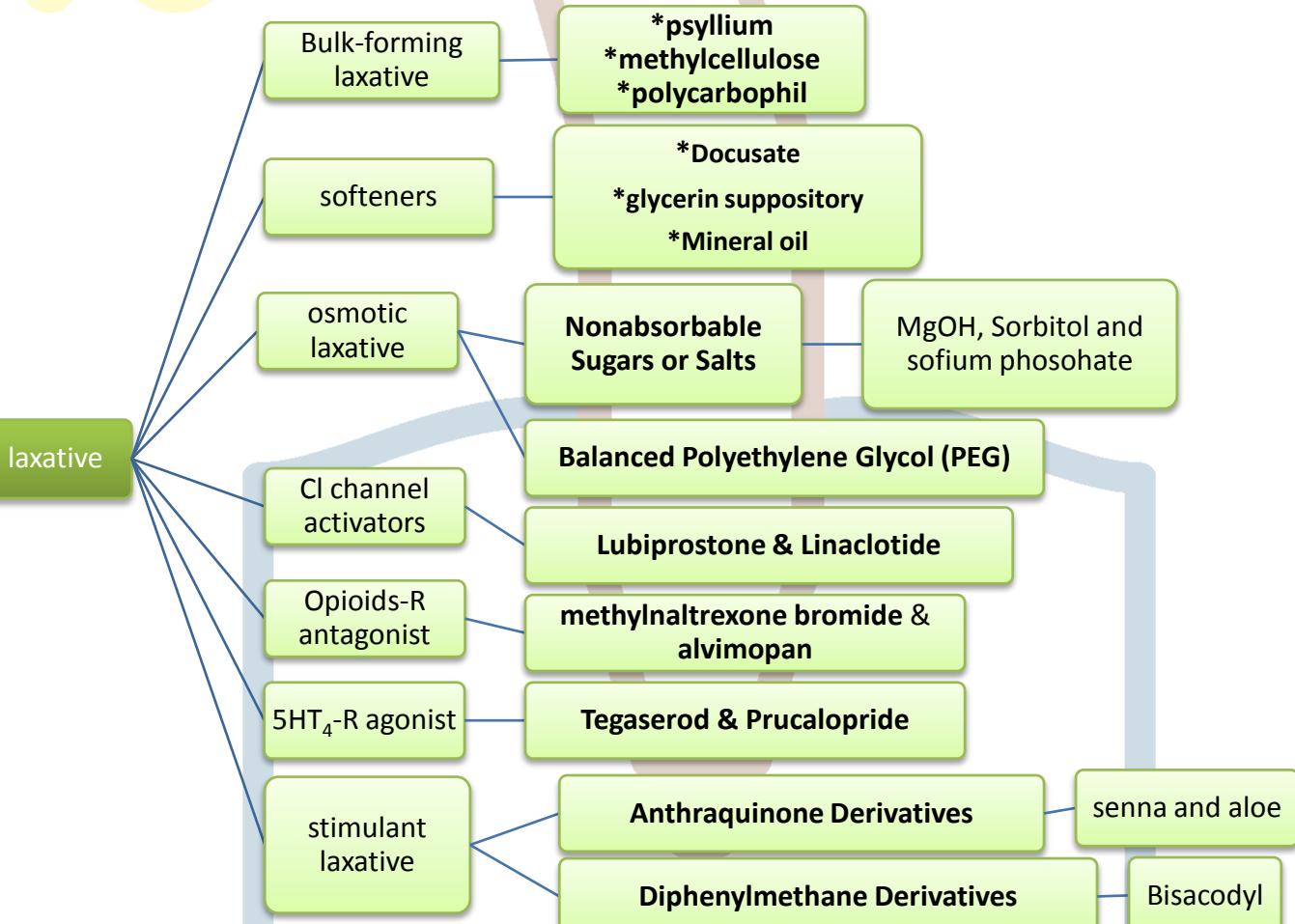


MOA	<p>Bethanechol: stimulate muscarinic M₃ receptors</p> <p>Neostigmine: acetylcholinesterase inhibitor</p>	<p>D₂-receptor antagonists. Inhibits cholinergic smooth muscle stimulation</p> <p>Increase esophageal peristaltic amplitude, increase lower esophageal sphincter pressure, and enhance gastric emptying.</p>	Directly stimulate motilin receptors.
Uses	<ul style="list-style-type: none"> GERD and gastroparesis Enhance gastric, small intestine, and colonic emptying. Treatment of hospitalized patient with colonic pseudo-obstruction 	<ul style="list-style-type: none"> GERD In combination with antisecretory agents in patients with regurgitation or refractory heartburn. Impaired gastric emptying Nonulcer dyspepsia Prevention of vomiting Block D₂ in CTZ Postpartum lactation stimulation 	<ul style="list-style-type: none"> Gastroparesis Promote gastric emptying of blood before endoscopy for acute upper gastrointestinal hemorrhage
Side effects	<ul style="list-style-type: none"> Excessive salivation, Nausea, vomiting, Diarrhea, Bradycardia. 	<p>Metoclopramide:</p> <ul style="list-style-type: none"> Restlessness, drowsiness, insomnia, anxiety, agitation Extrapyramidal effects Tardive dyskinesia, Elevated prolactin levels (long-term) 	

Bulk-forming	Softeners	Osmotic	stimulant
		While Domperidol doesn't cross BBB so it doesn't have metoclopramide-like side effects.	

LAXATIVES

Patients not responding to dietary changes or fiber supplements should undergo medical evaluation before initiating long-term laxative treatment.

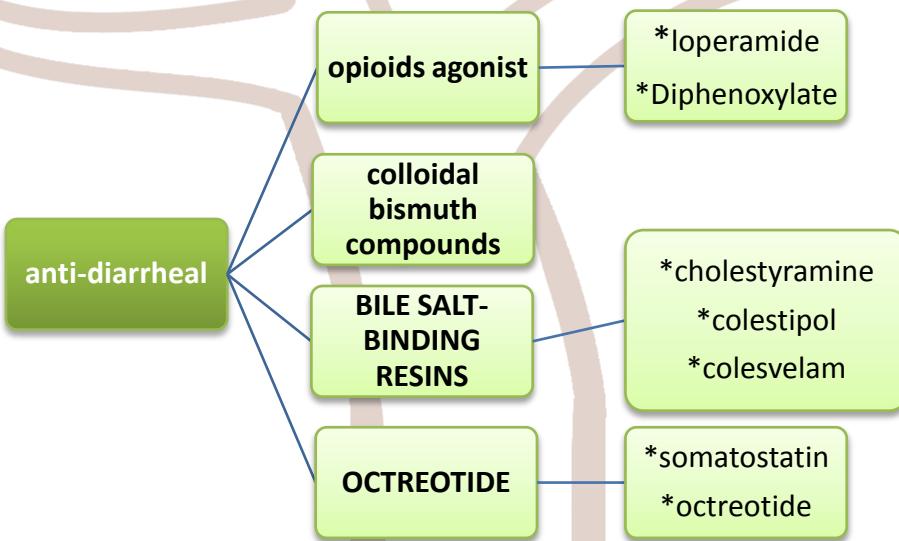


MOA	Hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis.	Permitting water and lipids to penetrate	Obligate increase in fecal fluid → increase stool liquidity.	Direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion.
Uses		<p>Docusate: prevent constipation and minimize straining.</p> <p>Mineral oil: to prevent and treat fecal impaction in young children and debilitated adults.</p>	<p>Non-absorbable sugar or salt: Treatment of acute constipation or the prevention of chronic constipation</p> <p>Purgatives: treatment of acute constipation or to cleanse the bowel prior to medical procedures</p> <p>Balanced PEG: for complete colonic cleansing before gastrointestinal endoscopic procedures.</p>	In patients who are neurologically impaired and in bed-bound patients Diphenylmethane Derivatives: treatment of acute and chronic constipation Used With PEG solutions for colonic cleansing
Side effect		Impair absorption of fat- soluble vitamins Severe lipid pneumonitis	Hypomagnesaemia, severe flatus and cramps. Hyperphosphatemia, hypocalcemia, hypernatremia, and hypokalemia. Nephrocalcinosis → cardiac arrhythmia and renal failure.	Brown pigmentation of the colon known as “melanosis coli”.

	Chloride-channel activator	Opioids-R antagonist	5HT ₄ -R agonist
MOA	<p>Lubiprostone:It acts by stimulating (ClC-2) → stimulates intestinal motility and shortens intestinal transit time.</p> <p>Linaclotide: stimulates intestinal chloride secretion</p> <p>Crofelemer: inhibition of CFTR</p>	Inhibit peripheral μ -opioid receptors without impacting analgesic effects	Stimulation of 5-HT ₄ receptors → enhance the release of calcitonin → stimulates second-order enteric neurons → stimulate peristaltic reflex and proximal bowel contraction
Uses	<p>Lubiprostone:Chronic constipation and irritable bowel syndrome (IBS)</p> <p>Linaclotide: Chronic constipation</p> <p>Crofelemer: treatment of HIV-drug-induced diarrhea.</p>	For constipation caused by opioids	Treatment of patients with chronic constipation and IBS with predominant constipation.
Side effect	<ul style="list-style-type: none"> • Category C • Nausea • Diarrhea • Linaclotide is contraindicated with pediatrics 	Cardiovascular toxicity	

■ANTIDIARRHEAL AGENTS

- Antidiarrheal agents may be used safely in patients with mild to moderate acute diarrhea
- These agents should not be used in patients with bloody diarrhea, high fever, or systemic toxicity
- Treatment of: IBS & IBD



	Opioids agonist	Bile-salt binding resins	Octreotide
MOA	Inhibition of presynaptic cholinergic nerves in the submucosal and myenteric plexuses → increased colonic transit time and fecal water absorption.		<ul style="list-style-type: none"> Inhibit numerous hormones and transmitters secretion Reduce intestinal fluid secretion and pancreatic secretion. Slows gastrointestinal motility and inhibits gallbladder contraction. Reduces portal and splanchnic blood flow. Inhibits secretion of some anterior pituitary hormones
Uses	Increase colonic phasic segmenting activity	Decrease diarrhea caused by excess fecal bile acid.	<ul style="list-style-type: none"> <i>Inhibition of endocrine tumor effects</i> <i>Other causes of diarrhea:</i> <p>High dose → treatment of diarrhea due to vagotomy or dumping syndrome, BIS and AIDS.</p> <p>Low dose → treating small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma.</p> <ul style="list-style-type: none"> Pancreatic fistula Treatment of pituitary tumors GI bleeding

Side effects	<p>Diphenoxylate: at higher dose has CNS effect and may lead to dependence.</p>	<ul style="list-style-type: none"> Bloating, Flatulence Constipation Fecal impaction. 	<p>Alter GI motility → nausea, abdominal pain, flatulence, and diarrhea.</p> <p>Gallbladder contractility inhibition → gallstone formation</p> <p>Alters the balance among insulin, glucagon, and growth hormone → hyperglycemia or hypoglycemia</p> <p>Prolong use → hypothyroidism</p> <p>Bradycardia</p>
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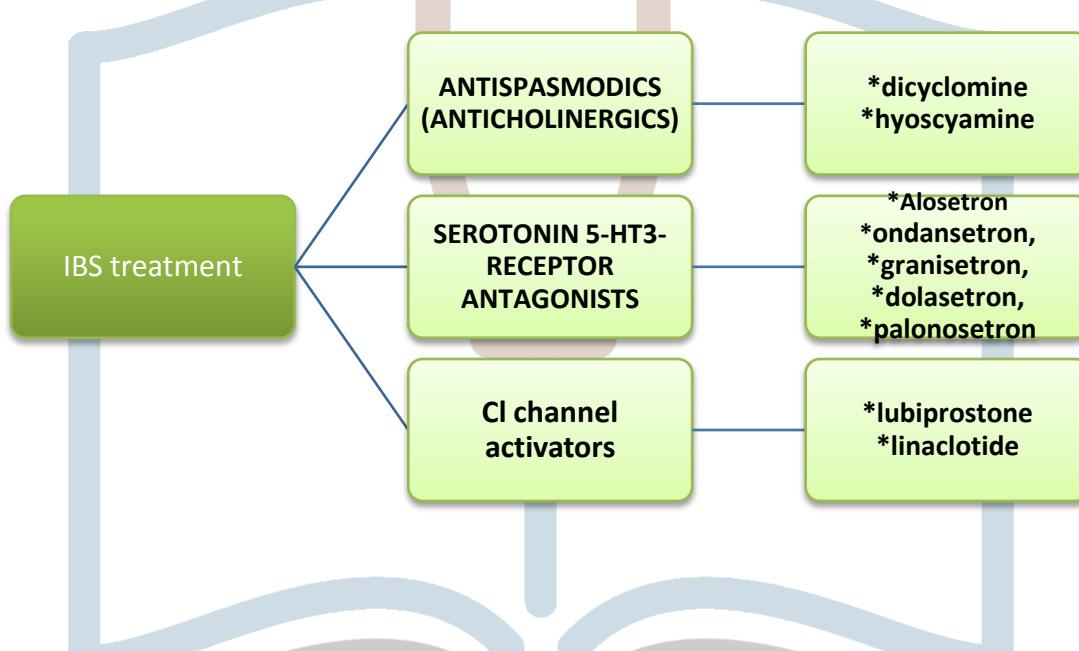
BOWEL SYNDROME (IBS)

Characterized by abdominal discomfort with alterations in bowel habits

For predominant diarrhea → antidiarrheal agents (loperamide)

For predominant constipation → fiber supplement and osmotic laxative

For chronic abdominal pain → TCA (amitriptyline or desipramine)



	Antispasmodic	5HT3-R antagonist
MOA	Inhibit muscarinic cholinergic receptors in the enteric plexus and on smooth muscle.	Inhibition of afferent gastrointestinal 5-HT ₃ receptors may reduce unpleasant visceral afferent sensation and CTZ.
Uses	Low dose: minimal autonomic effects. Higher dose: significant additional anticholinergic effects	Treatment of patients with severe IBS with diarrhea Treatment of nausea and vomiting.
Side effect	<ul style="list-style-type: none"> • Dry mouth • Visual disturbances • Urinary retention • Constipation 	<ul style="list-style-type: none"> • Rare but serious gastrointestinal toxicity. • Constipation • Ischemic colitis • Increase QT interval
ADME		Cyp450 enzyme although there is no significant drug-drug interactions.

■ ANTIEMETIC AGENTS

PATHOPHYSIOLOGY

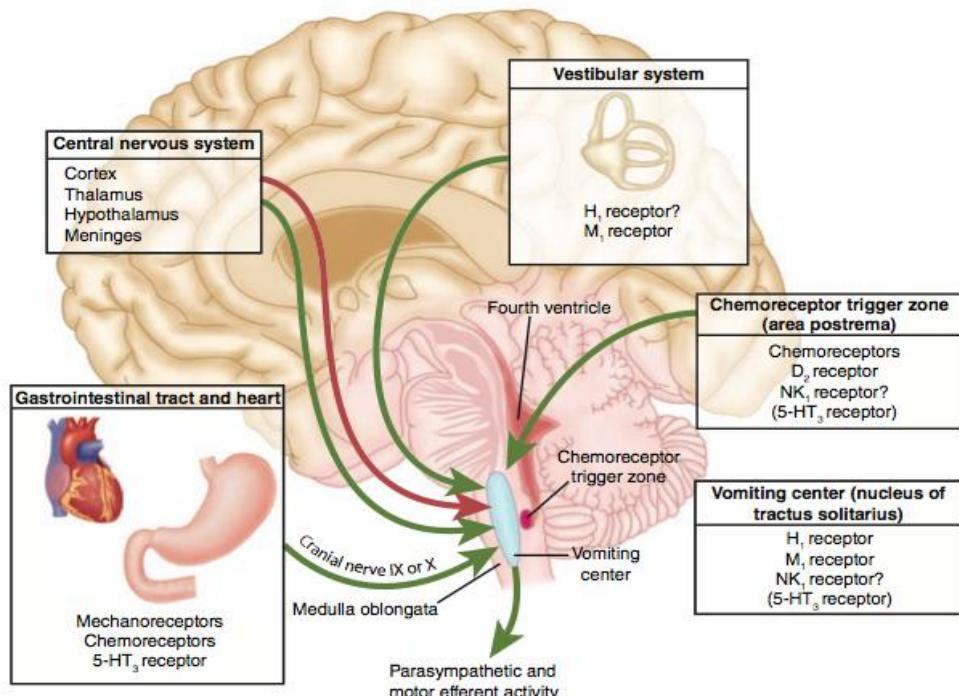


FIGURE 62–6 Neurologic pathways involved in pathogenesis of nausea and vomiting (see text). (Adapted, with permission, from Krakauer EL et al: Case records of the Massachusetts General Hospital. N Engl J Med 2005;352:817. Copyright © 2005 Massachusetts Medical Society. Reprinted, with permission, from Massachusetts Medical Society.)



5HT₃ antagonist

Nausea/Vomiting Receptor

PHENOTHIAZINES & BUTYROPHENONES

antiemetic agents

5HT₃ antagonist

corticosteroid

NK-R antagonist

PHENOTHIAZINES & BUTYROPHENONES

SUBSTITUTED BENZAMIDES

Anti-H1 & Anticholinergic

BZD

CANNABINOIDS

*dexamethasone,

*methylprednisolone

*Aprepit
*Fosaprepitant

*prochlorperazine,
*promethazine,
*thiethylperazine
*droperidol

*metoclopramide
*trimethobenzamide.

*Diphenhydramine
*dimenhydrinate,
*Meclizine *Hyoscine

*Dronabinol
*Nabilone

Lorazepam & Diazepam

MOA		Central blockade in the area postrema.	<ul style="list-style-type: none"> • Phenothiazines: Antipsychotic agents <p>Inhibition of dopamine and muscarinic receptors → antiemetic</p> <p>Antihistamine activity → sedation</p> <ul style="list-style-type: none"> • Butyrophenones: Central dopaminergic blockade → antiemetic
Uses	<i>Chemotherapy-induced nausea and vomiting</i> in combination with corticosteroid	<i>Chemotherapy-induced nausea and vomiting</i> in combination with 5HT3 antagonist and corticosteroid	For postoperative nausea and vomiting
Side effect		<ul style="list-style-type: none"> • Decrease (INR) in patients taking warfarin. • Fatigue, dizziness, and diarrhea. 	<ul style="list-style-type: none"> • Extrapyramidal effects and hypotension • Prolong the QT interval • Tachycardia
Drug-Drug Interaction		<p>Metabolized by CYP450</p> <p>Inhibit the metabolism of other drugs metabolized by the CYP3A4 pathway (docetaxel, imatinib and vincristine).</p> <p>Drugs that increase aprepitant plasma levels (ketoconazole, ciprofloxacin, ritonavir, verapamil, and quinidine)</p>	

	Substituted benzamides	Anti-H1 & Anticholinergic	Benzodiazepines	Cannabinoids
MOA	Dopamine-receptor blockade. Weak antihistaminic activity			Psychoactive agent
Uses		Treatment of motion sickness. Anti-H1:Diphenhydramine → in combination with other antiemetic treating Chemotherapy-induced nausea and vomiting Meclizine → Treatment of vertigo due to labyrinth dysfunction.	Used before the initiation of chemotherapy to reduce vomiting caused by anxiety.	Combination therapy with phenothiazines provides synergistic antiemetic action.
Side effect	Extrapyramidal effect.			<ul style="list-style-type: none"> • Euphoria • Dysphoria • Sedation hallucinations • Increased appetite • Tachycardia, • Conjunctival injection • orthostatic Hypotension

■DRUGS USED TO TREAT INFLAMMATORY BOWEL DISEASE

Aminosalicylates

Glucocorticoids

Purine analogue

- IBD comprises two distinct disorders: ulcerative colitis and Crohn's disease.
- Drugs used in IBD are chosen on the basis of disease severity, responsiveness, and drug toxicity

Disease severity	Therapy	Responsiveness to therapy
Severe	Surgery Natalizumab Cyclosporine TNF antagonists Intravenous corticosteroids	Refractory
Moderate	TNF antagonists Oral corticosteroids Methotrexate Azathioprine / 6-Mercaptopurine	
Mild	Budesonide (ileitis) Topical corticosteroids (proctitis) Antibiotics 5-Aminosalicylates	Responsive

MOA	<p>Blockade of prostaglandin synthesis by inhibition of cyclooxygenase.</p> <p>5-ASA modulates inflammatory mediators derived from both the cyclooxygenase and lipoxygenase pathways.</p> <p>Production of inflammatory cytokines.</p> <p>Inhibits the activity of nuclear factor</p> <p>Inhibit cellular functions of natural killer cells, mucosal lymphocytes, and macrophages.</p>	<p>Inhibit production of inflammatory cytokines (TNF-α, IL-1) and chemokines (IL-8).</p> <p>Reduce expression of inflammatory cell adhesion molecules.</p> <p>Inhibit gene transcription of nitric oxide synthase, phospholipase A₂, cyclooxygenase-2, and NF-κ B.</p>	<p>Antimetabolite → immunosuppressive properties.</p>
Side effects	<p>Gastrointestinal upset, arthralgias, myalgias, bone marrow suppression, and malaise.</p> <p>Hypersensitivity to sulfapyridine → exfoliative dermatitis, pancreatitis, pneumonitis, hemolytic anemia, pericarditis, or hepatitis.</p> <p>Sulfasalazine: oligospermia, and impairs folate absorption and processing → folic acid supplement is recommended.</p> <p>Olsalazine: stimulate a secretory diarrhea</p>		<ul style="list-style-type: none"> • Nausea and vomiting • Bone marrow depression • Hypersensitivity reactions • Lymphoma
Drug-Drug interaction		Potent inhibitors of CYP3A4 can increase budesonide plasma levels several-fold	Allopurinol → reduces xanthine oxidase catabolism of the purine analogs → severe leukopenia.

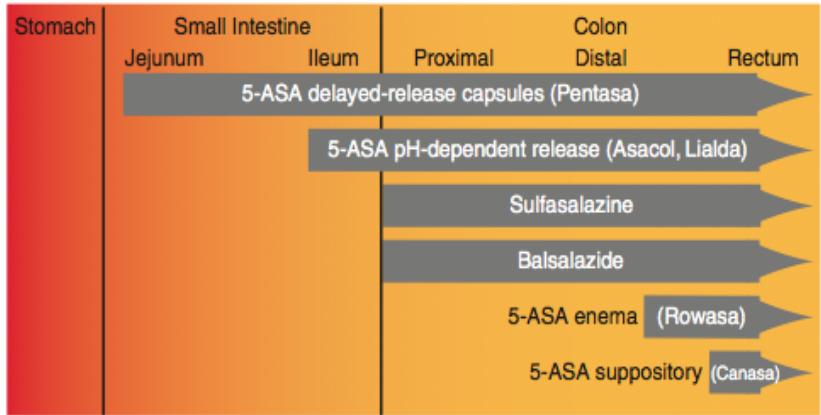


FIGURE 62-9 Sites of 5-aminosalicylic acid (5-ASA) release from different formulations in the small and large intestines.

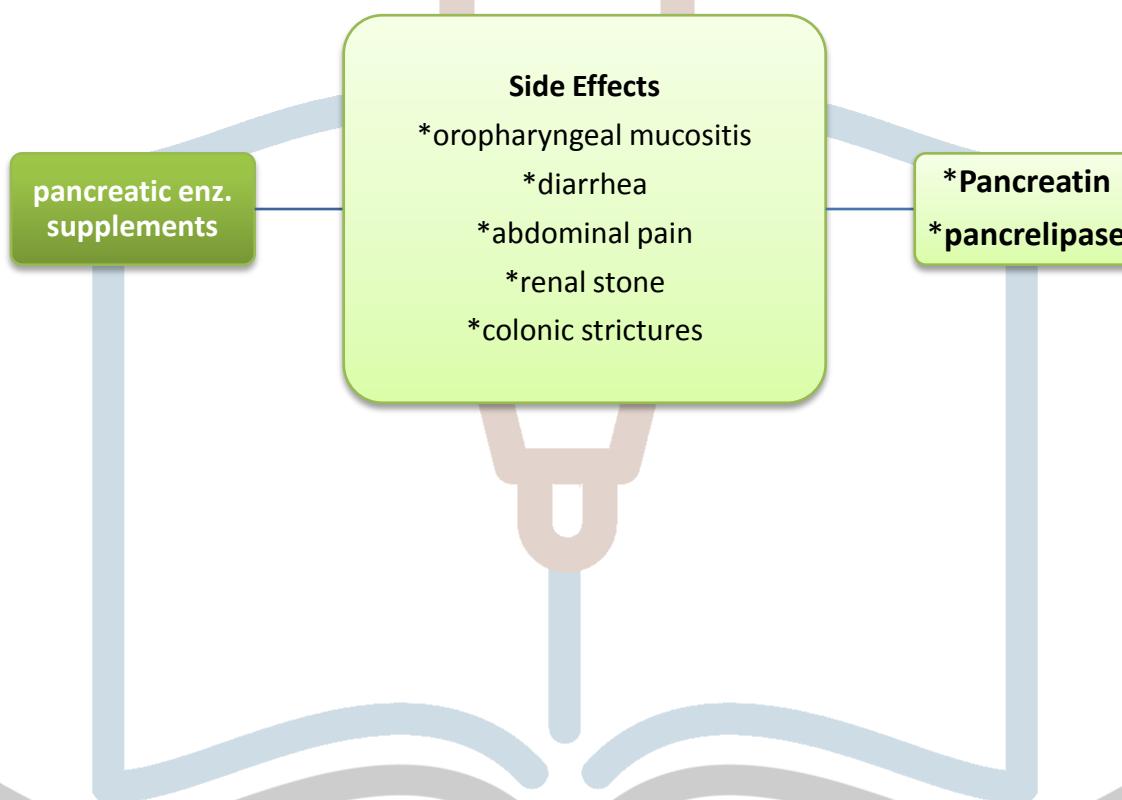
	Methotrexate	Anti-TNF	Anti-integrin therapy
MOA	Antimetabolite. Inhibition of dihydrofolate reductase.	Binding of TNF to TNFR → activates NF- κ B → stimulate transcription, growth, and expansion Activation of TNFR may later lead to apoptosis of activated cells.	Natalizumab is a humanized IgG4 monoclonal antibody targeted against the α 4 subunit → blocks several integrins on circulating inflammatory cells → prevents binding to the vascular adhesion molecules.
Uses	High dose → chemotherapy Low dose → treatment of IBD	Infliximab, adalimumab, and certolizumab → moderate to severe Crohn's disease Infliximab, adalimumab, and golimumab → treatment of moderate to severe ulcerative colitis	For patients with moderate to severe Crohn's disease who have failed other therapies.
Side Effect	<ul style="list-style-type: none"> • Bone marrow depression, • Megaloblastic anemia, • Alopecia • Mucositis, • Hepatic damage • Lymphoma 	<ul style="list-style-type: none"> • Infection • Antibodies to the antibody (ATA) • Early mild reactions • Serum sickness-like • Severe hepatic reactions 	<ul style="list-style-type: none"> • Acute infusion reactions • Risk of opportunistic infections.

TABLE 62–3 Anti-TNF antibodies used in inflammatory bowel disease.

	Infliximab	Adalimumab	Certolizumab	Golimumab
Class	Monoclonal antibody	Monoclonal antibody	Monoclonal antibody	Monoclonal antibody
% Human	75%	100%	95%	100%
Structure	IgG ₁	IgG ₁	Fab fragment attached to PEG (lacks Fc portion)	IgG ₁
Route of administration	Intravenous	Subcutaneous	Subcutaneous	Subcutaneous
Half-life	8–10 days	10–20 days	14 days	14 days
Neutralizes soluble TNF	Yes	Yes	Yes	Yes
Neutralizes membrane-bound TNF	Yes	Yes	Yes	Yes
Induces apoptosis of cells expressing membrane-bound TNF	Yes	Yes	No	Yes
Complement-mediated cytotoxicity of cells expressing membrane-bound TNF	Yes	Yes	No	Yes
Induction dose	5 mg/kg at 0, 2, and 6 weeks	160 mg, 80 mg, and 40 mg at 0, 2, and 4 weeks	400 mg at 0, 2, and 4 weeks	200 mg, 100 mg at 0, 2 weeks
Maintenance dose	5 mg/kg every 8 weeks	40 mg every 2 weeks	400 mg every 4 weeks	100 mg every 4 weeks

■ PANCREATIC ENZYME SUPPLEMENTS

- Exocrine pancreatic insufficiency is caused by cystic fibrosis, chronic pancreatitis, or pancreatic resection.
- Pancreatic enzyme supplements, which contain a mixture of amylase, lipase, and proteases.



■ GLUCAGON-LIKEPEPTIDE2 ANALOG FOR SHORT-BOWEL

SYNDROME

- Extensive surgical resection or disease of the small intestine may result in short-bowel syndrome with malabsorption of nutrients and fluids.

glucagon-like peptide 2 analog

Teduglutide

stimulating release of a number of trophic hormones (insulin-like growth)

causing neoplasia, colorectal polyps.

BILEACID THERAPY FOR GALLSTONES

ursodiol

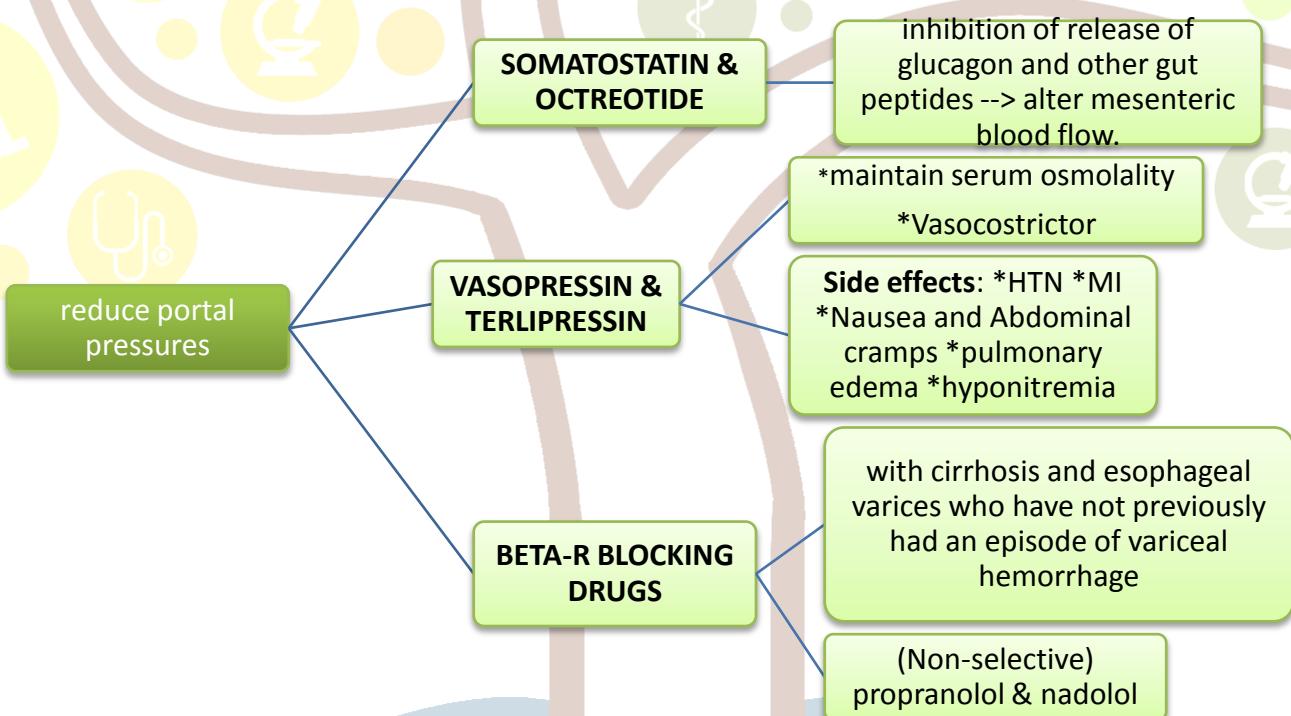
*decreases the cholesterol content of bile
*stabilize hepatocyte canalicular membranes

used for patient with:

*early- stage primary biliary cirrhosis.
*symptomatic gallbladder disease who refuse cholecystectomy
* the prevention of gallstones in obese patients undergoing rapid weight loss therapy.

DRUGS USED TO TREAT VARICEAL HEMORRHAGE

- Portal hypertension most commonly occurs as a consequence of chronic liver disease. It is caused by increased blood flow within the portal venous system and increased resistance to portal flow within the liver.
- Intrahepatic vascular resistance is increased in cirrhosis → ascites, hepatic encephalopathy, and the development of portosystemic collaterals (esophageal varices) → rupture → massive upper gastrointestinal bleeding.



CHAPTER 63: Therapeutic & Toxic Potential of Over-the-Counter Agents

In the USA, medications are divided by law into two classes:



1-Those restricted to sale by prescription only.

2- Those for which directions for safe use by the public can be written. The latter category constitutes 1-the nonprescription or 2-over-the-counter (OTC) medications. This category does not include supplements (vitamins, minerals, herbals, and botanicals) There are over100 different systemic analgesic products, almost all of which contain aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or a combination of these agents as primary ingredients. They are made different from one another by the addition of questionable ingredients such as caffeine or antihistamines; by brand names chosen to suggest a specific use or strength . There is a price attached to all of these features, and in most cases a less expensive generic product can be equally effective.

1- Ingredients designated as ineffective or unsafe for their claimed therapeutic use are being eliminated from OTC product formulations(eg, antimuscarinic agents have been eliminated from OTC sleep aids, attapulgite and polycarbophil can no longer be marketed as OTC antidiarrheal products);

2- Agents previously available by prescription only have been made available for OTC The prescription-to-OTC switch process has significantly enhanced and expanded self-care options for consumers. Some agents such as docosanol and the nicotine polacrilex lozenge have bypassed the prescription route altogether and have been released directly to the OTC market. Other prescription medications with the potential for future OTC reclassification include oral contraceptives, nicotine replacement therapy (oral inhaler, nasal spray) for smoking cessation, proton-pump inhibitors (pantoprazole) for heartburn, and second-generation nonsedating antihistamines (desloratadine, levocetirizine) for relief of allergy and cold symptoms. Cholesterol-lowering agents lovastatin and pravastatin were denied OTC status on the basis that these agents could not be used safely and effectively in an OTC setting. Oral acyclovir for OTC use in the treatment of recurrent genital herpes was not approved. Many of the active ingredients contained in OTC medications may worsen existing medical conditions or interact with prescription medications. Abuse of OTC products may actually produce significant medical

complications. Phenylpropanolamine, for example, sympathomimeticm previously found in many cold, allergy, and weight control products, was withdrawn from the US market by the FDA. The drug increased the risk of hemorrhagic stroke. Dextromethorphan, an antitussive found in many cough and cold preparations, has been increasingly abused in high doses as hallucinogen. Many dextromethorphan-containing products are formulated with other ingredients (acetaminophen, antihistamines, and sympathomimetics) that can be fatal in overdose. Pseudoephedrine,decongestant contained in numerous OTC cold preparations, has been used in the illicit manufacture of methamphetamine.

1. Select the product that is simplest in formulation with regard to ingredients and dosage form.

Acetaminophen, for example, is in many cough and cold preparations; a patient unaware of this may take separate doses of analgesic in addition to that contained in the cold preparation, potentially leading to hepatotoxicity.

2. Select a product that contains a therapeutically effective dose.

3. Consumers and providers should carefully read the “Drug Facts” label to determine which ingredients are appropriate based on the patient’s symptoms,

Multiple products (with different active ingredients) carry the Allegra name including Allegra Allergy (fexofenadine), Allegra-D (fexofenadine and pseudoephedrine), and Allegra Anti-Itch Cream (allantoin and diphenhydramine). This marketing practice of “extending a brand name” across product lines, while legal, is confusing and can lead to medication errors.

4. Recommend a generic product if one is available.

5. Be wary of “gimmicks” or advertising claims of specific superiority over similar products.

6. For children, the dose, dosage form, and palatability of the product are prime considerations.

OTC medications have standardized label formatting and content requirements that specify the indications for use, dosage, warnings, and active and inactive ingredients contained in the product, innumerable OTC products, including analgesics and allergy, cough, and cold preparations, contain sympathomimetics. These agents should be avoided or used cautiously by type 1 diabetics and patients with hypertension, angina, or hyperthyroidism. Aspirin should not be used in children and adolescents for viral infections (with or without fever) . Aspirin and other NSAIDs should be avoided by individuals with active peptic ulcer disease, certain platelet disorders, and patients taking oral anticoagulants. Cimetidine, an H₂-receptor antagonist, is a well-known inhibitor of hepatic drug metabolism and can increase the blood levels and toxicity of agents such as phenytoin, theophylline, and warfarin. Rebound congestion may be caused from the regular use of decongestant nasal sprays for more than 3 days. The improper and long-term use of some antacids (eg, aluminum hydroxide) may cause constipation and even impaction in elderly Hypophosphatemia. Laxative abuse can result in abdominal cramping and fluid and electrolyte disturbances. Insomnia, nervousness, and restlessness can result from the use of sympathomimetics or caffeine hidden in many OTC products . The long-term use of some analgesics containing large amounts of caffeine may produce rebound headaches, and long-term use of analgesics has been associated with interstitial nephritis. OTC products containing aspirin, other salicylates, acetaminophen, ibuprofen, or naproxen may increase the risk of hepatotoxicity and gastrointestinal hemorrhage in individuals who consume three or more alcoholic drinks daily. Recent evidence suggests the long-term use of certain NSAIDs may increase the risk of heart attack or stroke. Furthermore, acute ingestion of large amounts of acetaminophen by adults or children can cause serious, and often fatal, hepatotoxicity. Antihistamines may cause sedation or drowsiness, especially when taken concurrently with sedative hypnotics, tranquilizers, alcohol, or other central nervous system depressants. Antihistamines and other substances contained in OTC topical and vaginal products may induce allergic reactions. the FDA recommends that OTC cough and cold agents (eg, products containing antitussives, expectorants, decongestants, and antihistamines) not be used in infants and children younger than 2 years . There are three major drug information sources for OTC products.

Handbook of Nonprescription Drugs

Chapter 64: Dietary Supplements & Herbal Medications

The medical use of plants in their natural and unprocessed form undoubtedly began. An unbiased and regularly updated compendium of basic and clinical reports regarding botanicals is

- Pharmacist's Letter/Prescriber's Letter Natural Medicines Comprehensive Database.
- Another evidence-based resource is Natural Standard, which includes an international, multi-disciplinary collaborative website, <http://www.naturalstandard.com>. The recommendations in this database are limited by the quality of the existing research available for each dietary supplement ingredient.

For legal purposes, “dietary supplements” are distinguished from “prescription drugs” derived from plants (morphine, digitalis, atropine, etc) by virtue of being available without a prescription and, unlike “over-the-counter medications,” are legally considered dietary supplements rather than drugs.

Advantage	Disadvantage
This distinction eliminates the need for proof of efficacy and safety prior to marketing	<ul style="list-style-type: none">• places the burden of proof on the FDA to prove that a supplement is harmful before its use can be restricted or removed from the market.• marketed dietary supplements are not tested for dose response relationships or toxicity and there is a lack of adequate testing for mutagenicity, carcinogenicity, and teratogenicity.

The DSHEA defines dietary supplements as vitamins, minerals, herbs or other botanicals, amino acids or dietary supplements used to supplement the diet by increasing dietary intake, or concentrates, metabolites, constituents, extracts, or any combination of these ingredients.

CLINICAL ASPECTS OF THE USE OF BOTANICALS

Adverse effects have been documented for a variety of dietary supplements; however, under-reporting of adverse effects is likely since consumers do not routinely report, and do not know how to report an adverse effect if they suspect that the event was caused by consumption of a supplement. This leads to confusion about whether the primary ingredient or an adulterant caused the adverse effect. In some cases, the chemical constituents of the herb can clearly lead to toxicity.

An important risk factor in the use of dietary supplements is the lack of adequate testing for drug interactions. Since botanicals may contain hundreds of active and inactive ingredients, it is very difficult and costly to study potential drug interactions when they are combined with other medications. This may present significant risks to patients.

■ BOTANICAL SUBSTANCES ECHINACEA

(ECHINACEA PURPUREA)

Pharmacologic Effects

1. **Immune modulation:** In vivo human studies using commercially marketed formulations of *E purpurea* have shown increased phagocytosis, total circulating monocytes, neutrophils, and natural killer cells, indicative of general immune modulation.
2. **Anti-inflammatory effects:** Certain echinacea constituents have demonstrated anti-inflammatory properties in vitro. Inhibition of cyclooxygenase, 5-lipoxygenase, and hyaluronidase may be involved.
3. **Antibacterial, antifungal, antiviral, and antioxidant effects :**
 - Echinaforce demonstrated virucidal activity ($MIC_{100} < 1 \mu\text{g/mL}$) against influenza and herpes simplex viruses and bactericidal activity against *Streptococcus pyogenes*, *Haemophilus influenzae*, and *Legionella pneumophila* in human bronchial cells.
 - In vitro, Echinaforce inactivated both avian influenza virus (H5N1, H7N7) and swine-origin influenza virus (H1N1) at doses consistent with recommended oral consumption. The extract

blocked key steps (ie, viral hemagglutination activity and neuraminidase activity in vitro) involved in early virus replication and cellular entry.

- It was less effective against intracellular virus.
- Newer *in vitro* research in human skin fibroblasts also suggests bactericidal activity and inhibition of secretion of inflammatory cytokines produced by *Propionibacterium acnes* with Echinaforce.

Adverse Effects

Adverse effects with oral commercial formulations are minimal and most often include unpleasant taste, gastrointestinal upset, or rash. In one large clinical trial, pediatric patients using an oral echinacea product were significantly more likely to develop a rash than those taking placebo.

Drug Interactions & Precautions

Until the role of echinacea in immune modulation is better defined, this agent should be avoided in:

- Patients with immune deficiency disorders (eg, AIDS, cancer),
- Autoimmune disorders (eg, multiple sclerosis, rheumatoid arthritis).
- Persons taking immunosuppressant medications (eg, organ transplant recipients).

Dosage

It is recommended to follow the dosing on the package label, as there may be variations in dose based on the procedure used in product manufacture.

Standardized preparations made from the aerial parts of *E purpurea* (Echinaforce, Echinaguard) as an alcoholic extract or fresh pressed juice may be preferred in adults for common cold treatment if taken within the first 24 hours of cold symptoms.

It should not be used on a continuous basis for longer than 10–14 days

GARLIC (ALLIUM SATIVUM):

Pharmacologic Effects:

1. Cardiovascular effects:

In vitro, allicin and related compounds inhibit HMG-CoA reductase, which is involved in cholesterol biosynthesis, and exhibit antioxidant properties. Data suggest a small but significant benefit of garlic in lowering total cholesterol and triglycerides.

The lack of change in HDL and LDL indicate that garlic is unlikely to be clinically relevant, however, in benefiting patients with hyperlipidemia.

antiplatelet effects (possibly through inhibition of thromboxane synthesis or stimulation of nitric oxide synthesis) following garlic ingestion. A majority of human studies also suggest enhancement of fibrinolytic activity. These effects in combination with antioxidant effects

Garlic constituents may affect blood vessel elasticity and blood pressure

2. Endocrine effects:

The effect of garlic on glucose homeostasis does not appear to be significant in persons with diabetes. Certain organosulfur constituents in garlic, have demonstrated hypoglycemic effects in non diabetic animal models.

3. Antimicrobial effects:

The antimicrobial effect of garlic has not been extensively studied in clinical trials. Allicin has been reported to have in vitro activity against some gram-positive and gram-negative bacteria as well as fungi, protozoa and certain viruses. The primary mechanism involves the inhibition of thiol-containing enzymes needed by these microbes. Given the availability of safe and effective prescription antimicrobials, the usefulness of garlic in this area appears limited.

4. Antineoplastic effects:

In rodent studies, garlic inhibits procarcinogens for colon, esophageal, lung, breast, and stomach cancer, possibly by detoxification of

carcinogens and reduced carcinogen activation. Reduce incidence of stomach, esophageal, and colorectal cancers in persons with high dietary garlic consumption.

Adverse Effects

nausea (6%), hypotension (1.3%), allergy (1.1%), and bleeding (rare). Breath and body odor. Contact dermatitis may occur with the handling of raw garlic.

Drug Interactions & Precautions

- Because of reported antiplatelet effects, patients using anticoagulating medications (eg, warfarin, aspirin, ibuprofen) should use garlic cautiously.
- Additional monitoring of blood pressure and signs and symptoms of bleeding is warranted.
- May reduce the bioavailability of saquinavir, an antiviral protease inhibitor, but it does not appear to affect the bioavailability of ritonavir.

GINKGO (GINKGO BILOBA):

Pharmacologic Effects

1. Cardiovascular

effects:

increase blood flow, reduce blood viscosity, and promote vasodilation, thus enhancing tissue perfusion.	Enhancement of endogenous nitric oxide effects and antagonism of platelet-activating factor have been observed in animal models.	Has effects on mild to moderate occlusive peripheral arterial disease.
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Daily use of 240 mg/d EGb761 did not affect the incidence of hypertension or reduce blood pressure among persons with hypertension or prehypertension. No significant effects in cardiovascular disease mortality, ischemic stroke or events, or hemorrhagic stroke were observed.

2. Metabolic effects:

Antioxidant and radical-scavenging properties have been. In vitro, ginkgo have superoxide dismutase-like activity and superoxide

anion- and hydroxyl radical-scavenging properties. The flavonoid fraction has also been observed to have anti-apoptotic properties. In some studies, it has also demonstrated a protective effect in limiting free radical formation in of ischemic injury and in reducing markers of oxidative stress in patients undergoing coronary artery bypass surgery.

3. Central nervous system effects: In aged animal models, chronic administration of ginkgo for 3–4 weeks led to modifications in central nervous system receptors and neurotransmitters.

Increase	Decrease
<ul style="list-style-type: none"> Receptor densities increased for muscarinic, α_2, and 5-HT1a receptors. Increased serum levels of acetylcholine and norepinephrine and enhanced synaptosomal reuptake of serotonin 	<ul style="list-style-type: none"> Receptor densities decreased for β adrenoceptors. reduced corticosterone synthesis and inhibition of amyloid-beta fibril formation.

Additional effects include Ginkgo has been used to treat cerebral insufficiency and dementia of the Alzheimer type. The term cerebral insufficiency, however, includes a variety of manifestations ranging from poor concentration and confusion to anxiety and depression as well as physical complaints such as hearing loss and headache.

The authors concluded that the effects of ginkgo in the treatment of cognitive impairment and dementia were unpredictable and unlikely to be clinically relevant.

Adverse Effects

Nausea, headache, stomach upset, diarrhea, allergy, anxiety, and insomnia. A few case reports noted bleeding complications in patients using ginkgo

Drug Interactions & Precautions

Ginkgo may have antiplatelet properties and should not be used in combination with antiplatelet or anticoagulant medications.

Other single case reports noted

1. virologic failure when ginkgo was combined with efavirenz,
2. Sedation when combined with trazodone

- 
3. Priapism when combined with risperidone
 4. Seizure when combined with valproic acid and phenytoin

Seizures have been reported as a toxic effect of ginkgo, most likely related to seed contamination in the leaf formulations.

Uncooked ginkgo seeds are epileptogenic due to the presence of ginkgotoxin. Ginkgo formulations should be avoided in individuals with preexisting seizure disorders.

CHAPTER 65: Rational Prescribing & Prescription Writing

A written prescription is the prescriber's order to prepare or dispense a specific treatment -usually medication- for a specific patient.

RATIONAL PRESCRIBING:

Writing a prescription should be based on a series of rational steps:

1. Make a specific diagnosis.
2. Consider the pathophysiologic implications of the diagnosis.
3. Select a specific therapeutic objective.
4. Select a drug of choice.
5. Determine the appropriate dosing regimen.
6. Devise a plan for monitoring the drug's action and determine an end point for therapy.
7. Plan a program of patient education.

THE PRESCRIPTION:

1-Outpatient prescription

2- Chart order

Elements of the Prescription

1- Outpatient prescription:

- The first four elements of the outpatient prescription establish the identity of the prescriber. The pharmacist must establish the prescriber's bona fides and should be able to contact the prescriber by telephone if any questions arise.
- Element [5] is the date on which the prescription was written. The pharmacist should refuse to fill a prescription without verification by telephone if too much time has elapsed since its writing.
- Elements [6] and [7] identify the patient by name and address.
- The body of the prescription contains the elements [8] to [11] that specify the medication, the strength and quantity to be dispensed, the dosage, and complete directions for use. When writing the drug name either the brand name or the generic name

may be used. The strength of medication should be written in metric units. The quantity of medication prescribed should reflect the anticipated duration of therapy, the cost, the need for continued contact with the clinic or physician, the potential for abuse, and the potential for toxicity or overdose. The directions for use must be both drug-specific and patient-specific. The simpler the directions, the better; and the fewer the number of doses (and drugs) per day, the better. The instructions on how and when to take medications, the duration of therapy, and the purpose of the medication must be explained to each patient both by the prescriber and by the pharmacist. It is always safer to write out the direction without abbreviating. Knowledge of these abbreviations is essential for the dispensing pharmacist and often useful for the prescriber.

- Elements [12] to [14] of the prescription include refill information, waiver of the requirement for childproof containers, and additional labeling instructions (eg, warnings such as “may cause drowsiness,” “do not drink alcohol”).
- Elements [15] to [17] are the prescriber’s signature and other identification data such as National Provider Identification (NPI), Drug Enforcement Agency (DEA) number, or State License number.



①		② JOHN B. DOE, MD	③
		1234 SOUTH NORTHEAST DR	④ (234) 555-6789
FOR: ⑥		DATE: ⑤	
ADDRESS: ⑦			
RX ⑧ (DRUG NAME AND STRENGTH) ⑨ (QUANTITY) ⑩			
SIG: ⑪			
REFILL OR NO	TIMES UNTIL CHILDPROOF CONTAINER	⑫ ⑬	
WARNING: ⑭		⑮ .MD AD1234567 ⑯ STATE LICENSE NO. ⑰	

rxulr

2- Chart order:

In the hospital setting, drugs are prescribed on a particular page of the patient's hospital chart called the physician's order sheet(POS) or chart order. The patient's name is typed or written on the form; therefore, the orders consist of the name and strength of the medication, the dose, the route and frequency of administration, the date, other pertinent information, and the signature of the prescriber. Thus, the elements of the hospital chart order are equivalent to the central elements (5, 8–11, 15) of the outpatient prescription.

PRESCRIBING ERRORS:

Unfortunately, prescribing errors are common.Certain types of prescribing errors are particularly common. These include errors involving omission of needed information; poorwriting perhaps leading to errors of drug dose or timing; and prescription of drugs that are inappropriate for the specific situation.

Omission of Information:

Errors of omission are common in hospital orders and may include instructions to“continuepresent IV fluids,” which fails to state exactly what fluids are to begiven, in what volume, and over what time period; or “continue eyedrops,” which omits mention of which eye is to be treated as wellas the drug, concentration, and frequency of administration.

Poor Prescription Writing:

Poor prescription writing is traditionally exemplified by illegible handwriting. However, other types of poor writing are common and often more dangerous, for example:

- The misplaced or ambiguous decimal point.
- Use abbreviation that should never be used because it is easily misread.

Inappropriate Drug Prescriptions:

Prescribing an inappropriate drug for a particular patient often results from failure to recognize contraindications imposed by other diseases the patient may have, failure to obtain information about other drugs the patient is taking (including over-the-counter drugs), or failure to recognize possible

physicochemical incompatibilities between drugs that may react with each other.

E-PRESCRIBING:

E-prescribing provides an electronic flow of information between the prescriber, intermediary, pharmacy, and health plan . The prescriber selects the medication, strength, dosage form, quantity, and directions for use and the prescription is transmitted to the pharmacy where the appropriate data fields are populated . The pharmacist reviews the order and, if appropriate, dispenses the prescription.

COMPLIANCE:

Compliance (sometimes called adherence) is the extent to which patients follow treatment instructions. There are four types of noncompliance leading to medication errors and increased health care costs:

1. The patient fails to obtain the medication. Some patients cannot afford the medications prescribed.
2. The patient fails to take the medication as prescribed. This usually results from inadequate communication between the patient, the prescriber, and the pharmacist.
3. The patient prematurely discontinues the medication. Some patients incorrectly assume that the medication is no longer needed because the bottle is empty or symptomatic improvement has occurred.
4. The patient (or another person) takes medication inappropriately. For example, the patient may share a medication with others for any of several reasons.

Strategies for improving compliance include enhanced communication between the patient and health care team members; assessment of personal, social, and economic conditions (often reflected in the patient's lifestyle); development of a routine for taking medications (eg, at mealtimes if the patient has regular meals); provision of systems to assist taking medications (ie, containers that separate drug doses by day of the week, or medication alarm clocks that remind patients to take their medications); and mailing of refill reminders by the pharmacist to patients taking drugs chronically.

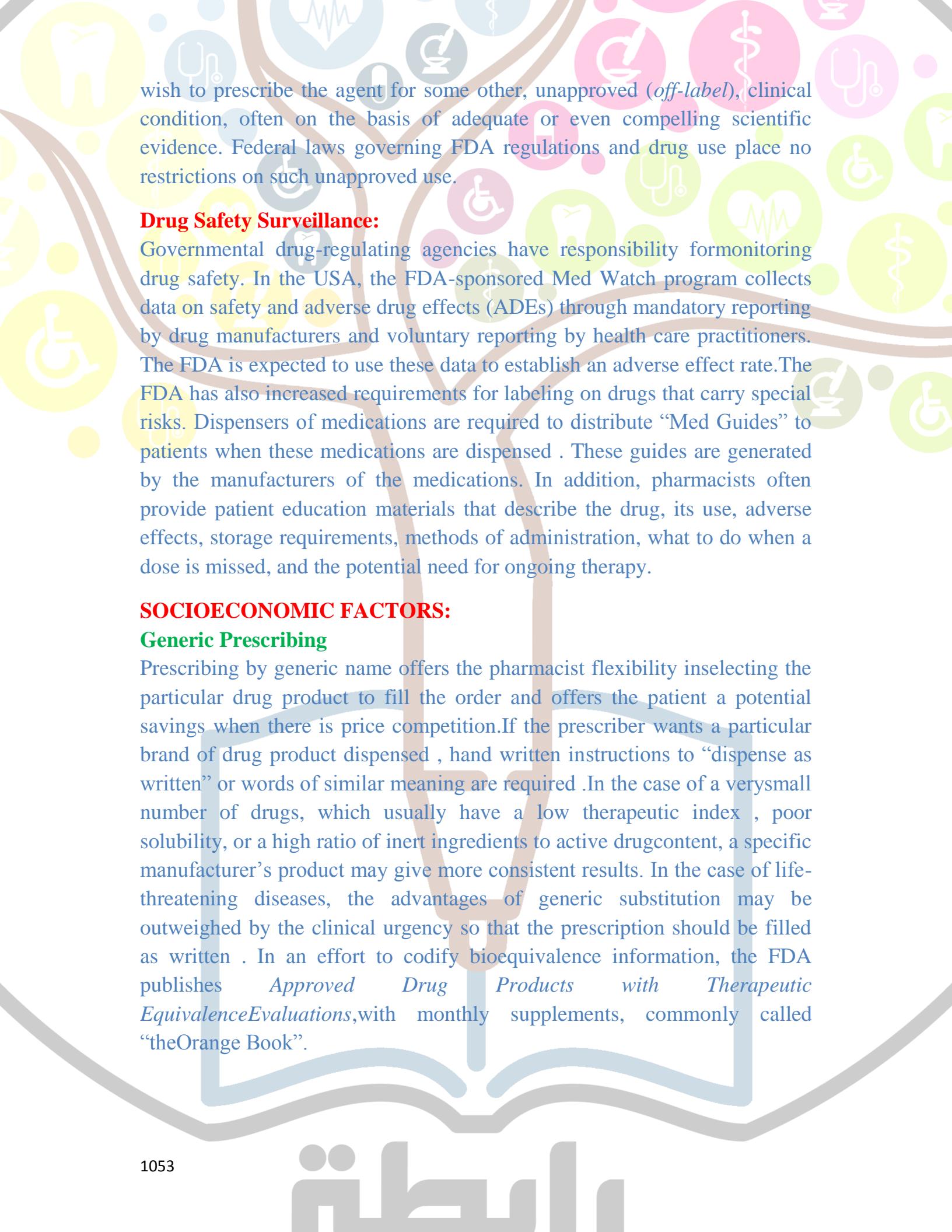
LEGAL FACTORS (USA):

There are two classes of drugs: (1) over-the-counter (OTC) drugs and (2) those that require a prescription from a licensed prescriber (Rx Only). OTC drugs are those that can be safely self-administered by the layman for self-limiting conditions and for which appropriate labels can be written for lay comprehension. Physicians, dentists, podiatrists, and veterinarians and, in many states, specialized pharmacists, nurses, physician's assistants, and optometrists—are granted authority to prescribe dangerous drugs. Pharmacists are authorized to dispense prescriptions pursuant to a prescriber's order provided that the medication order is appropriate and rational for the patient. Nurses are authorized to administer medications to patients subject to a prescriber's order. The prescriber, by writing and signing a prescription order, controls who may obtain prescription drugs. The pharmacist may purchase these drugs, but they may be dispensed only on the order of a legally qualified prescriber. Thus, a **prescription** is actually three things: the **prescriber's order in the patient's chart**, the **written order to which the pharmacist refers** when dispensing, and the **patient's medication container with a label affixed**. Prescriptions for substances with a high potential for abuse (Schedule II drugs) cannot be refilled without a new prescription.

However, multiple prescriptions for the same drug may be written with instructions not to dispense before a certain date and up to a total of 90 days. Prescriptions for Schedules III, IV, and V can be refilled if ordered, but there is a five-refill maximum, and in no case may the prescription be refilled after 6 months from the date of writing.

Labeled & Off-Labeled Uses of Drugs:

In the USA, the FDA approves a drug only for the specific uses. These approved (*labeled*) uses or indications are set forth in the package insert that accompanies the drug. These labeled indications may not include all the conditions in which the drug might be useful. Therefore, a clinician may



wish to prescribe the agent for some other, unapproved (*off-label*), clinical condition, often on the basis of adequate or even compelling scientific evidence. Federal laws governing FDA regulations and drug use place no restrictions on such unapproved use.

Drug Safety Surveillance:

Governmental drug-regulating agencies have responsibility for monitoring drug safety. In the USA, the FDA-sponsored Med Watch program collects data on safety and adverse drug effects (ADEs) through mandatory reporting by drug manufacturers and voluntary reporting by health care practitioners. The FDA is expected to use these data to establish an adverse effect rate. The FDA has also increased requirements for labeling on drugs that carry special risks. Dispensers of medications are required to distribute "Med Guides" to patients when these medications are dispensed. These guides are generated by the manufacturers of the medications. In addition, pharmacists often provide patient education materials that describe the drug, its use, adverse effects, storage requirements, methods of administration, what to do when a dose is missed, and the potential need for ongoing therapy.

SOCIOECONOMIC FACTORS:

Generic Prescribing

Prescribing by generic name offers the pharmacist flexibility in selecting the particular drug product to fill the order and offers the patient a potential savings when there is price competition. If the prescriber wants a particular brand of drug product dispensed, hand written instructions to "dispense as written" or words of similar meaning are required. In the case of a very small number of drugs, which usually have a low therapeutic index, poor solubility, or a high ratio of inert ingredients to active drug content, a specific manufacturer's product may give more consistent results. In the case of life-threatening diseases, the advantages of generic substitution may be outweighed by the clinical urgency so that the prescription should be filled as written. In an effort to codify bioequivalence information, the FDA publishes *Approved Drug Products with Therapeutic Equivalence Evaluations*, with monthly supplements, commonly called "the Orange Book".

Chapter 66: Important Drug Interactions & Their Mechanisms

One of the factors that can alter the response to drugs is the concurrent administration of other drugs. There are several mechanisms by which drugs may interact, but most can be categorized as

- pharmacokinetic (absorption, distribution, metabolism, excretion),
- pharmacodynamic (additive, synergistic, or antagonistic effects),
- or combined interactions.

Botanical medications (“herbals”) may interact with each other or with conventional drugs. Unfortunately, botanicals are much less well studied than other drugs, so information about their interactions is scanty.

Knowledge of the mechanism by which a given drug interaction occurs is often clinically useful, since the mechanism may influence both the time course and the methods of circumventing the interaction.

Some important drug interactions occur as a result of two or more mechanisms.

PREDICTABILITY OF DRUG INTERACTIONS

Interaction does not always produce an adverse effect.

Adverse effect depends on both patient- and drug specific factors.

- Patient factors can include intrinsic drug clearance, genetics, gender, concurrent diseases, and diet.
- Drug-specific factors include dose, route of administration, drug formulation, and the sequence of drug administration.

Drug or drug Group

- Alcohol

Properties Promoting Drug Interaction

- Chronic alcoholism results in enzyme induction.
- Acute alcoholic intoxication tends to inhibit drug metabolism (whether person is alcoholic or not).
- Severe alcohol-induced hepatic dysfunction may inhibit ability to metabolize drugs.
- Disulfiram-like reaction in the presence of certain drugs.
- Additive central nervous system depression with other central nervous system depressants.

Clinically Documented Interactions

- Acitretin, Central nervous system depressants, Disulfiram

Drug or drug Group

- Allopurinol

Properties Promoting Drug Interaction

- Inhibits hepatic drug-metabolizing enzymes.
- Febuxostat (another drug used in gout) will also inhibit the metabolism of azathioprine and mercaptopurine.

Clinically Documented Interactions

- Azathioprine, and Mercaptopurine.

Drug or drug Group

- Antacids

Properties Promoting Drug Interaction

- Antacids may adsorb drugs in gastrointestinal tract, thus reducing absorption.
- Antacids tend to speed gastric emptying, thus delivering drugs to absorbing sites in the intestine more quickly.
- Some antacids (eg, magnesium hydroxide with aluminum hydroxide) alkalinize the urine somewhat, thus altering excretion of drugs
- sensitive to urinary pH.

Clinically Documented Interactions

- Atazanavir, Dasatinib, Indinavir, Iron, Itraconazole, Ketoconazole, Quinolones, Rosuvastatin, Salicylatesm, and Tetracyclines

Drug or
drug Group

- Anticoagulants, oral

Properties
Promoting
Drug
Interaction

- Susceptible to inhibition of CYP2C9 (warfarin), CYP3A4 (apixaban, rivaroxaban), and P-glycoprotein (apixaban, dabigatran, rivaroxaban).
- Warfarin highly bound to plasma proteins.
- Anticoagulation response altered by drugs that affect clotting factor synthesis or catabolism.

Clinically
Documented
Interactions

- Drugs that may increase anticoagulant effect: Amiodarone, Anabolic steroids, Cimetidine, Clofibrate, Dextrothyroxine, Disulfiram, Fluconazole, Fluoxetine, Ketoconazole, Metronidazole, NSAIDs, Ritonavir, Salicylates, Thyroid hormones, Trimethoprim-sulfamethoxazole, and Verapamil.
- Drugs that may decrease anticoagulant effect: Aminoglutethimide, Barbiturates, Bosentan, Carbamazepine, Cholestyramine, Glutethimide, Primidone, Rifabutin, Rifampin, Hypoglycemics, oral, and Phenytoin.

Drug or
drug Group

- Antidepressants, tricyclic and heterocyclic

Properties
Promoting Drug
Interaction

- Inhibition of amine uptake into postganglionic adrenergic neuron. Antimuscarinic effects may be additive with other antimuscarinic drugs. Metabolism inducible. Susceptible to inhibition of metabolism via CYP2D6, CYP3A4, and other CYP450 enzymes.

Clinically
Documented
Interactions

- Amiodarone, Barbiturates, Cimetidine, Clonidine, Guanadrel, Guanethidine, Haloperidol, Rifampin, SSRIs, Sympathomimetics, and Terbinafine.

Drug or
drug Group

- Azole antifungals

Properties
Promoting
Drug
Interaction

- Inhibition of CYP3A4 (itraconazole = ketoconazole > posaconazole > voriconazole > fluconazole).
- Inhibition of CYP2C9 (fluconazole, voriconazole).
- Inhibition of P-glycoprotein (itraconazole, ketoconazole, posaconazole).
- Susceptible to enzyme inducers (itraconazole, ketoconazole, voriconazole).
- Gastrointestinal absorption pH-dependent (itraconazole, ketoconazole, posaconazole).

Clinically
Documented
Interactions

- Antivirals, Barbiturates, Benzodiazepines, Calcium channel blockers, Carbamazepine, Colchicine, Cyclosporine, Ergot alkaloids, HMG-CoA reductase inhibitors, Opioid analgesics, Quinidine, Phenytoin, Phosphodiesterase inhibitors, Proton pump inhibitors (PPIs), Rifabutin, Rifampin, Sirolimus, and Tacrolimus.

Drug or drug Group

- Barbiturates

Properties Promoting Drug Interaction

- Induction of hepatic microsomal drug metabolizing enzymes and P-glycoprotein.
- Additive central nervous system depression with other central nervous system depressants.

Clinically Documented Interactions

- Beta-adrenoceptor blockers, Calcium channel blockers, Central nervous system depressants, Corticosteroids, Delavirdine, Doxycycline, Estrogens, Phenothiazine, Quinidine, and Valproic acid.

Drug or drug Group

- Beta-adrenoceptor blockers

Properties Promoting Drug Interaction

- Beta-blockade (especially with nonselective agents such as propranolol) alters response to sympathomimetics with β -agonist activity (eg, epinephrine, albuterol).
- Beta blockers that undergo extensive first-pass metabolism may be affected by drugs capable of altering this process.
- Beta blockers may reduce hepatic blood flow.

Clinically Documented Interactions

- Drugs that may increase β -blocker effect: Amiodarone, Cimetidine, SSRIs, and Terbinafine.
- Drugs that may decrease β -blocker effect: NSAIDs.
- Effects of β blockers on other drugs: Insulin, Prazosin, and Sympathomimetics.

Drug or drug Group

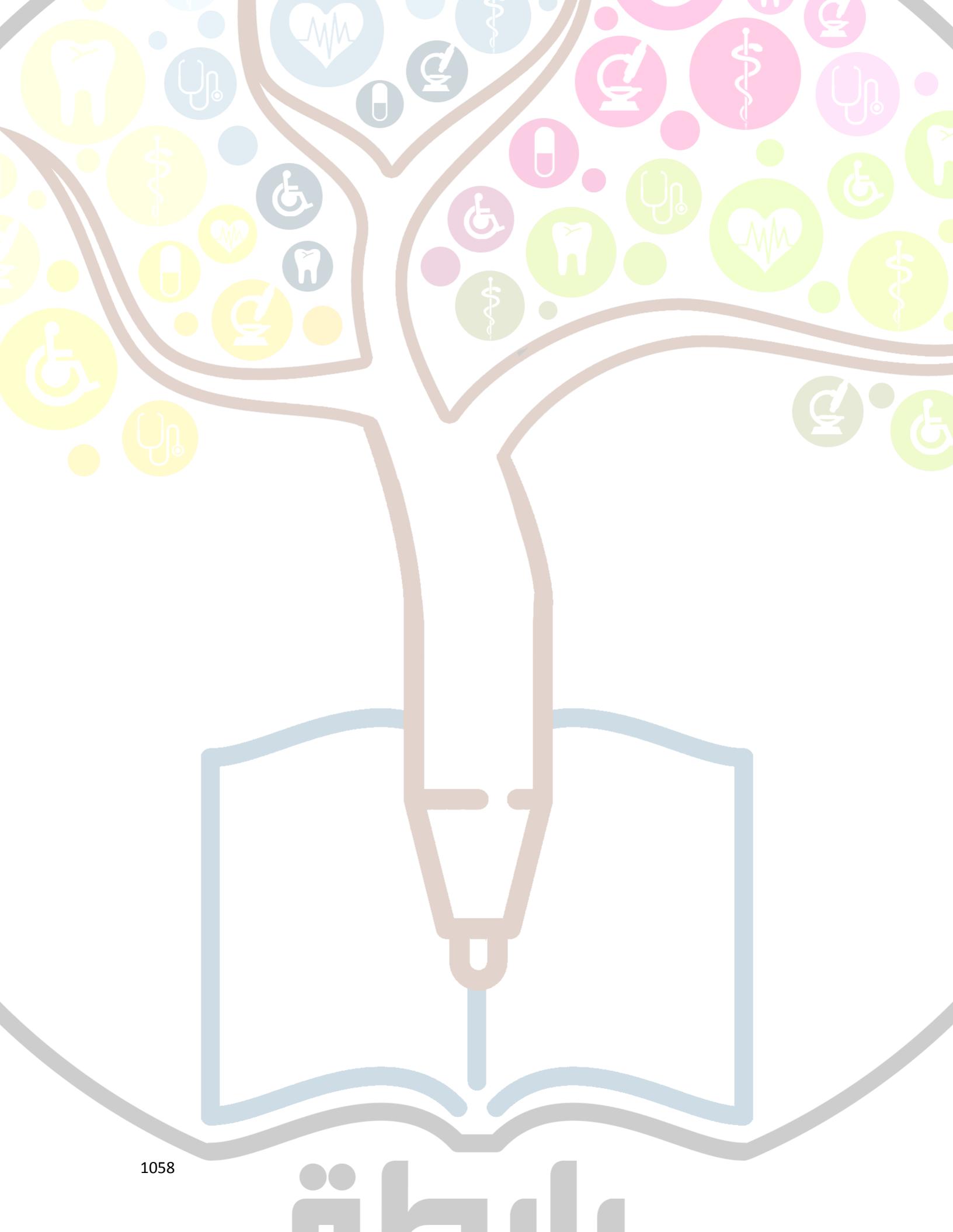
- Bile acid-binding resins

Properties Promoting Drug Interaction

- Resins may bind with orally administered drugs in gastrointestinal tract.
- Resins may bind in gastrointestinal tract with drugs that undergo enterohepatic circulation, even if the latter are given parenterally.

Clinically Documented Interactions

- Furosemide, Mycophenolate, Thiazide diuretics, and Thyroid hormones.



Drug or drug Group

- Calcium channel blockers

Properties Promoting Drug Interaction

- Verapamil, diltiazem, and perhaps nicardipine inhibit hepatic drug-metabolizing enzymes and P-glycoprotein. Metabolism (via CYP3A4) of diltiazem, felodipine, nicardipine, nifedipine, verapamil, and probably other calcium channel blockers subject to induction and inhibition.

Clinically Documented Interactions

- Carbamazepine, Clarithromycin, Colchicine, Conivaptan, Cyclosporine, Erythromycin, Phenytoin, Rifampin, Sirolimus, and Tacrolimus.

Drug or drug Group

- Carbamazepine

Properties Promoting Drug Interaction

- Induction of hepatic microsomal drug metabolizing enzymes and P-glycoprotein.
- Susceptible to inhibition of metabolism, primarily by CYP3A4.

Clinically Documented Interactions

- Cimetidine, Clarithromycin, Corticosteroids, Cyclosporine, Danazol, Doxycycline, Estrogens, Haloperidol, Isoniazid, Propoxyphene, Rifampin, Sirolimus, St. John's wort, and Tacrolimus.

Drug or drug Group

- Chloramphenicol

Properties Promoting Drug Interaction

- Inhibits hepatic drug-metabolizing enzymes.

Clinically Documented Interactions

- Phenytoin and Sulfonylurea hypoglycemics.

Drug or
drug Group

- Cimetidine

Properties
Promoting
Drug
Interaction

- Inhibits hepatic microsomal drug-metabolizing enzymes. (Ranitidine, famotidine, and nizatidine do not.) May inhibit the renal tubular secretion of weak bases.

Clinically
Documented
Interactions

- Benzodiazepines, Lidocaine, Procainamide, Quinidine, and Theophylline.

Drug or
drug Group

- Cisapride

Properties
Promoting
Drug
Interaction

- Susceptible to inhibition of metabolism by CYP3A4 inhibitors.
- High cisapride serum concentrations can result in ventricular arrhythmias.

Clinically
Documented
Interactions

- Clarithromycin, and Erythromycin.

Drug or
drug Group

- Colchicine

Properties
Promoting
Drug
Interaction

- Susceptible to inhibition of CYP3A4 metabolism and P-glycoprotein transport.

Clinically
Documented
Interactions

- Amprenavir, Boceprevir, Carbamazepine, Clarithromycin, Conivaptan, Cyclosporine, Diltiazem, Erythromycin, Fluconazole, Imatinib, Posaconazole, Rifampin, Ritonavir, and Verapamil.

• Cyclosporine

Drug or drug Group

- Metabolism inducible. Susceptible to inhibition of elimination by CYP3A4 and P-glycoprotein. (Tacrolimus and sirolimus appear to have similar interactions.)

Properties Promoting Drug Interaction

- Drugs that may increase cyclosporine effect: Amiodarone, Amprenavir, Clarithromycin, Indinavir, Nefazodone, Quinupristin, and Ritonavir.
- Drugs that may decrease cyclosporine effect: Barbiturates, Bosentan, Carbamazepine, Efavirenz, Phenytoin, and Rifampin:

Clinically Documented Interactions

• Digitalis glycosides

Drug or drug Group

- Digoxin susceptible to alteration of gastrointestinal absorption.
- Renal and nonrenal excretion of digoxin susceptible to inhibition.
- Digitalis toxicity may be increased by drug induced electrolyte imbalance (eg, hypokalemia).

Properties Promoting Drug Interaction

- Drugs that may increase digitalis effect: Amiodarone, Clarithromycin, Cyclosporine, Diltiazem, Potassium-depleting drugs, Propafenone, Quinidine, Ritonavir, and Verapamil.
- Drugs that may decrease digitalis effect: Kaolin-pectin.

Clinically Documented Interactions

• Disulfiram

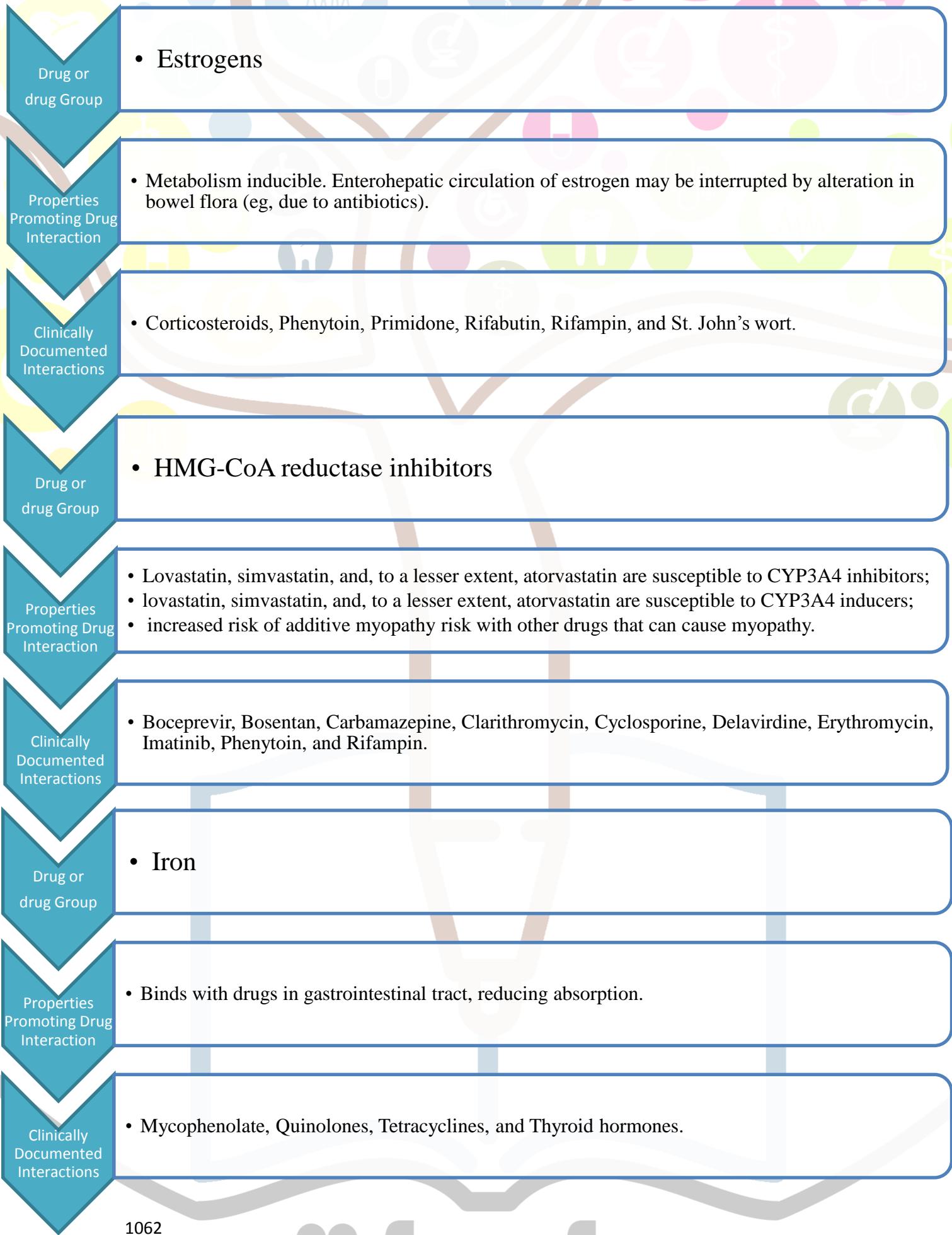
Drug or drug Group

- Inhibits CYP2C9. Inhibits aldehyde dehydrogenase.

Properties Promoting Drug Interaction

- Benzodiazepines, and Phenytoin.

Clinically Documented Interactions



- Drug or drug Group
- Levodopa

- Properties Promoting Drug Interaction
- Levodopa degraded in gut prior to reaching sites of absorption.
 - Agents that alter gastrointestinal motility may alter degree of intraluminal degradation.
 - Anti-parkinsonism effect of levodopa susceptible to inhibition by other drugs.

- Clinically Documented Interactions
- MAOIs, Phenothiazines, and Pyridoxine.

- Drug or drug Group
- Lithium

- Properties Promoting Drug Interaction
- Renal lithium excretion sensitive to changes in sodium balance. (Sodium depletion tends to cause lithium retention.)
 - Susceptible to drugs enhancing central nervous system lithium toxicity.

- Clinically Documented Interactions
- Diuretics (especially thiazides) and Theophylline.

- Drug or drug Group
- Macrolides

- Properties Promoting Drug Interaction
- The macrolides clarithromycin and erythromycin are known to inhibit CYP3A4 and P-glycoprotein.
 - Azithromycin does not appear to inhibit CYP3A4 but is a modest inhibitor of P-glycoprotein.

- Clinically Documented Interactions
- Benzodiazepines, Ergot Alkaloids, Phosphodiesterase Inhibitors, Pimozide, Quinidine, and Theophylline.

Drug or drug Group

- Monoamine oxidase inhibitors (MAOIs)

- Properties Promoting Drug Interaction
- Increased norepinephrine stored in adrenergic neuron. Displacement of these stores by other drugs may produce acute hypertensive response.
 - MAOIs have intrinsic hypoglycemic activity.

- Clinically Documented Interactions
- Anorexiants, Antidiabetic agents, Guanethidine, Phenylephrine, and SSRIs.,

Drug or drug Group

- Nonsteroidal anti-inflammatory drugs (NSAIDs)

- Properties Promoting Drug Interaction
- Prostaglandin inhibition may result in reduced renal sodium excretion, impaired resistance to hypertensive stimuli, and reduced renal lithium excretion.
 - Most NSAIDs inhibit platelet function; may increase likelihood of bleeding due to other drugs that impair hemostasis.

- Clinically Documented Interactions
- ACE inhibitors, Angiotensin II receptor blockers, Furosemide, and Thiazide diuretics.

Drug or drug Group

- Phenytoin

- Properties Promoting Drug Interaction
- Induces hepatic microsomal drug metabolism.
 - Susceptible to inhibition of metabolism by CYP2C9 and, to a lesser extent, CYP2C19.

- Clinically Documented Interactions
- Drugs whose metabolism is stimulated by phenytoin: Corticosteroids, Doxycycline, Methadone, and Quinidine.
 - Drugs that inhibit phenytoin metabolism: Amiodarone, Chloramphenicol, Felbamate, Metronidazole, and Sulfamethoxazole.
 - Drugs that enhance phenytoin metabolism: Bosentan, Carbamazepine, Rifampin, and St. John's wort.

• Pimozide

Drug or drug Group

- Properties Promoting Drug Interaction
- Susceptible to CYP3A4 inhibitors; may exhibit additive effects with other agents that prolong QTc interval.

Clinically Documented Interactions

- Nefazodone.

Drug or drug Group

- Properties Promoting Drug Interaction
- Potassium-sparing diuretics (amiloride, eplerenone, spironolactone, triamterene)

Clinically Documented Interactions

- Additive effects with other agents increasing serum potassium concentration.
- May alter renal excretion of substances other than potassium (eg, digoxin, hydrogen ions).

Drug or drug Group

- Properties Promoting Drug Interaction
- Potassium-sparing diuretics and Potassium supplements.

Clinically Documented Interactions

- Probenecid

Drug or drug Group

- Properties Promoting Drug Interaction
- Interference with renal excretion of drugs that undergo active tubular secretion, especially weak acids.
 - Inhibition of glucuronide conjugation of other drugs.

Clinically Documented Interactions

- Clofibrate, Methotrexate, Pralatrexate, Penicillin, and Salicylates.

- Quinidine

- Properties Promoting Drug Interaction
- Substrate of CYP3A4. Inhibits CYP2D6.
 - Renal excretion susceptible to changes in urine pH.
 - Additive effects with other agents that prolong the QTc interval.

- Clinically Documented Interactions
- Acetazolamide and Rifampin.

- Quinolone antibiotics

- Properties Promoting Drug Interaction
- Susceptible to inhibition of gastrointestinal absorption. Some quinolones inhibit CYP1A2.

- Clinically Documented Interactions
- Caffeine, Sucralfate, and Theophylline.

- Rifampin

- Properties Promoting Drug Interaction
- Inducer (strong) of hepatic microsomal drug-metabolizing enzymes and P-glycoprotein.

- Clinically Documented Interactions
- Corticosteroids, Sulfonylurea hypoglycemics, and Theophylline.

- Salicylates

Drug or drug Group

- Interference with renal excretion of drugs that undergo active tubular secretion.
- Salicylate renal excretion dependent on urinary pH when large doses of salicylate used.
- Aspirin (but not other salicylates) interferes with platelet function.
- Large doses of salicylates have intrinsic hypoglycemic activity.

Properties Promoting Drug Interaction

Clinically Documented Interactions

- Corticosteroids, Methotrexate, and Sulfapyrazone.

Drug or drug Group

- Selective serotonin reuptake inhibitors (SSRIs)

Properties Promoting Drug Interaction

- SSRIs can lead to excessive serotonin response when administered with other serotonergic drugs (eg, MAOIs).
- Some SSRIs inhibit various cytochrome P450s including CYP2D6, CYP1A2, CYP3A4, and CYP2C19.

Clinically Documented Interactions

- Theophylline.

Drug or drug Group

- Theophylline.

Properties Promoting Drug Interaction

- Susceptible to inhibition of hepatic metabolism by CYP1A2. Metabolism inducible.

Clinically Documented Interactions

- Smoking.

Pharmacokinetic Mechanisms

The **gastrointestinal absorption** of drugs may be affected by concurrent use of other agents that:

- (1) have a large surface area upon which the drug can be adsorbed,
- (2) bind or chelate,
- (3) alter gastric pH,
- (4) alter gastrointestinal motility,
- or (5) affect transport proteins such as P-glycoprotein and organic anion transporters.

The mechanisms by which drug interactions alter drug distribution include

- (1) competition for plasma protein binding,
- (2) displacement from tissue binding sites, and
- (3) alterations in local tissue barriers,

The **metabolism** of drugs can be stimulated or inhibited by concurrent therapy. Drug metabolism primarily occurs in the liver and the wall of the small intestine, but other sites include plasma, lung, and kidney.

- Induction (stimulation) of cytochrome P450 isozymes in the liver and small intestine can be caused by drugs such as barbiturates, carbamazepine, nevirapine, phenytoin, primidone, rifampin, rifabutin, and St. John's wort. Enzyme inducers can also increase the activity of phase II metabolism such as glucuronidation.
- Drugs that may inhibit the cytochrome P450 metabolism of other drugs include amiodarone, androgens, atazanavir, chloramphenicol, cimetidine, ciprofloxacin, clarithromycin, cyclosporine, diltiazem, diphenhydramine, erythromycin, fluconazole, fluoxetine, furanocoumarins

- A reduction in only the absorption rate of a drug is seldom clinically important,
- Whereas a reduction in the extent of absorption is clinically important if it results in subtherapeutic serum concentrations.

The clinical importance of protein binding displacement has been overemphasized; current evidence suggests that such interactions are unlikely to result in adverse effects. Displacement from tissue binding sites would tend to transiently increase the blood concentration of the displaced drug.

- Enzyme induction does not take place quickly; maximal effects usually occur after 7–10 days and require an equal or longer time to dissipate after the enzyme inducer is stopped.
Rifampin, however, may produce enzyme induction after only a few doses.
- Inhibition of metabolism generally takes place more quickly than enzyme induction and may begin as soon as sufficient tissue concentration of the inhibitor is achieved. However, if the half-life of the affected (object) drug is long, it may take a week or more (three to four half-lives) to reach a new steady-state serum concentration.

(substances in grapefruit juice), isoniazid, itraconazole, ketoconazole, metronidazole, mexiletine, miconazole, omeprazole, paroxetine, quinidine, and verapamil,

The renal excretion of active drug can also be affected by concurrent drug therapy.

The renal excretion of certain drugs that are weak acids or weak bases may be influenced by other drugs that affect urinary pH. For some drugs, active secretion into the renal tubules is an important elimination pathway.

P-glycoprotein, organic anion transporters, and organic cation transporters are involved in tubular secretion of some drugs. Inhibition of these transporters inhibit renal elimination with attendant increase in serum concentrations.

Pharmacodynamics Mechanisms:

When drugs with similar pharmacologic effects are administered concurrently, an additive or synergistic response is usually seen.

The two drugs may or may not act on the same receptor to produce such effects. In theory,

- Drugs acting on the same receptor or process are usually additive, eg, benzodiazepines plus barbiturates. Drugs acting on different receptors or sequential processes may be synergistic, eg, nitrates plus sildenafil or sulfonamides plus trimethoprim.
- Conversely, drugs with opposing pharmacologic effects may reduce the response to one or both drugs.

Combined Toxicity:

The combined use of two or more drugs, each of which has toxic effects on the same organ, can greatly increase the likelihood of organ damage. For example, concurrent administration of two nephrotoxic drugs can produce kidney damage, even though the dose of either drug alone may have been insufficient to produce toxicity.

Furthermore, some drugs can enhance the organ toxicity of another drug, even though the enhancing drug has no intrinsic toxic effect on that organ.

