

Pharmacology

M302

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HELLO
· A · N · D ·
Welcome

Main topics ►

- Basic principles of Pharmacology ►
- Effect of drug therapy on the nervous system ►
- Skeletal muscle relaxant ►
- Drug therapy and treatment of pain and inflammation ►
- Pharmacotherapy and rehabilitation ►
- Drug therapy and cardiovascular disorder ►
- Drug therapy and Respiratory disorder ►
- Drug therapy and bone & joint disorder ►

1- Basic principles of Pharmacology ►

- ▶ -Definition
- ▶ -Importance of Pharmacology for physical therapy students.
- ▶ -Pharmacotherapy in health and disease
- ▶ -Sources of the drug
- ▶ -Routes of drug administration
- ▶ - Pharmacokinetics
- ▶ - Pharmacodynamics
- ▶ - Dose-response relationships
- ▶ - Adverse drug reactions
- ▶ - Drug interactions
- ▶ -Drug safety

Pharmacology is the science that deals with drugs and the scientific principles of drug action on living organisms.

Drugs: any substances that can be used in the diagnosis, prevention and treatment of disease.

A **medicine** is a chemical preparation, which contains one or more drugs, administered with the intention of producing a therapeutic effect.

-**Physical therapy students study pharmacology** to understand how medications can affect a patient's physical function and rehabilitation process, which is crucial for patient safety, effective treatment planning, and interprofessional collaboration with other healthcare providers. By knowing common drugs and their side effects, PTs can monitor for adverse drug reactions, adjust therapy plans to maximize benefits and minimize risks, educate patients on medication adherence, and communicate effectively with doctors and pharmacists to ensure comprehensive patient care.

Key Reasons for Studying Pharmacology

Patient Safety and Efficacy:

Physical therapists need to know the medications their patients are taking to understand how drugs might impact their physical functioning, pain levels, cognition, and energy, thereby reducing the risk of medication-related harm and enhancing treatment effectiveness.

Treatment Planning:

Understanding pharmacology allows PTs to modify their therapy plans to account for the effects of medications. For instance, if a patient is on a beta-blocker, a physical therapist cannot use heart rate as a reliable indicator of exercise intensity.

Recognizing Side Effects:

Therapists can help patients recognize potential side effects that may interfere with their rehabilitation, such as increased fatigue or decreased motivation.

- **Medication Adherence and Education:**
 - ▶ PTs can educate patients about the importance of taking their prescribed medications correctly, which is vital for achieving therapeutic benefits and successful rehabilitation outcomes.
- **Interprofessional Communication:**
 - ▶ Knowledge of pharmacology helps physical therapists to engage in collaborative discussions with physicians, nurses, and pharmacists, contributing to more integrated and comprehensive patient care.



- **Sources of drugs**

- 1-Natural ►**

- Plant as **Digoxin** from *digitalis purpurea*.

- microorganism as **penicillin** from fungus ►

2-Synthetic ►

-Chemically: Sulphonamide. ►

-Genetically engineering (rDNA technology): Human insulin. ►

○ **Classes of drugs**

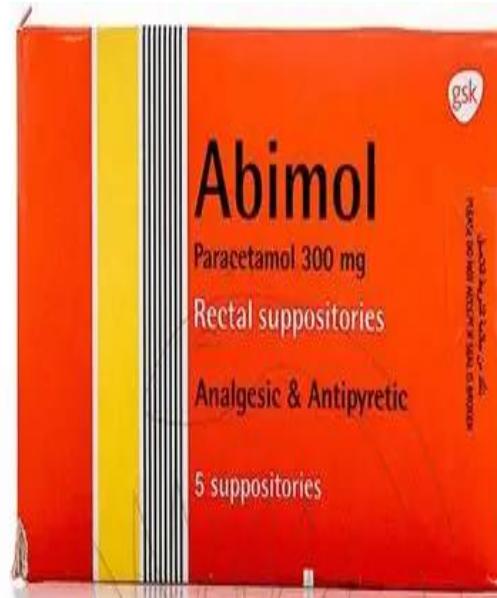
1-Prescription only medication (POM): only for prescription. ►

2-Over the counter (OTC) drugs: used by the public without
prescription



► Names (Nomenclature) of drugs:

1. Chemical name
2. Non-proprietary = Generic name (may be referred to as scientific name).
3. Proprietary = Commercial name (may be referred to as trade name).



- **Route of drug administration**

1-Enteral ►

Enteral administration (administering a drug by mouth) is the safest and most common, convenient, and economical method of drug administration.

A. Oral: Oral administration provides many **advantages**. ►

They are easily self-administered, and toxicities and/or overdose of oral drugs may be overcome with antidotes, such as activated charcoal.

However, the pathways involved many **disadvantages such as:** ►

-Not suitable for patients suffering from vomiting and diarrhea. ►

-Not suitable in emergency. ►

-First pass effect, (inactivation or elimination of part or whole of the drug before reaching the systemic circulation). ►

- **To overcome hepatic first pass effect**

If partial→ increase the dose of the drug. ►

If complete→use another routes such as IV and sublingual. ►

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

a. **Enteric-coated preparations:** An enteric coating is a chemical envelope that protects the drug from stomach acid, delivering it instead to the less acidic intestine, where the coating dissolves and releases the drug. Enteric coating is useful for certain drugs (for example, omeprazole) that are acid unstable.

Drugs that are irritating to the stomach, such as aspirin, can be formulated with an enteric coating that only dissolves in the small intestine, thereby protecting the stomach.

b. Extended-release preparations: Extended-release medications have special coatings or ingredients that control the drug release, thereby allowing for slower absorption and a prolonged duration of action.

ER formulations can be dosed less frequently and may improve patient compliance.

Additionally, ER formulations may maintain concentrations within the therapeutic range over a longer period of time, as opposed to immediate-release dosage forms.

ER formulations are advantageous for drugs with short half-lives.

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

B. Sublingual/buccal: Placement under the tongue allows ►

a drug to diffuse into the capillary network and enter the

systemic circulation directly. Sublingual administration has

several advantages, including ease of administration, rapid

absorption, and avoidance of first pass metabolism.

The buccal route (between the cheek and gum) is similar ►

to the sublingual route.



2-Parenteral

A-Intravenous injection (I.V) ►

- Advantage**

- 100% bioavailability (fraction of the drug reach the systemic circulation unchanged).** ►

- No first pass effect.** ►

- Suitable in emergency and for irritant drug.** ►

- Suitable for acid labile drugs.** ►

- Suitable for patient suffer from coma and vomiting.** ►

- Disadvantage** ►

- Must be sterile (pyrogenic free).** ►

- Not suitable for oily and suspended drugs.** ►

- Spreading of infection.** ►

- Required professional person** ►

B-Intramuscular injection (I.M) ▶

-Suitable for solution, suspension and oily drugs.

-Better absorption than S.C but less than I.V.

C-Subcutaneous (S.C) ▶

Absorption rate is slower than IV and IM.

D-Intradermal injection (I.D) ▶

Sensitive tests ▶



E-Other injection ►

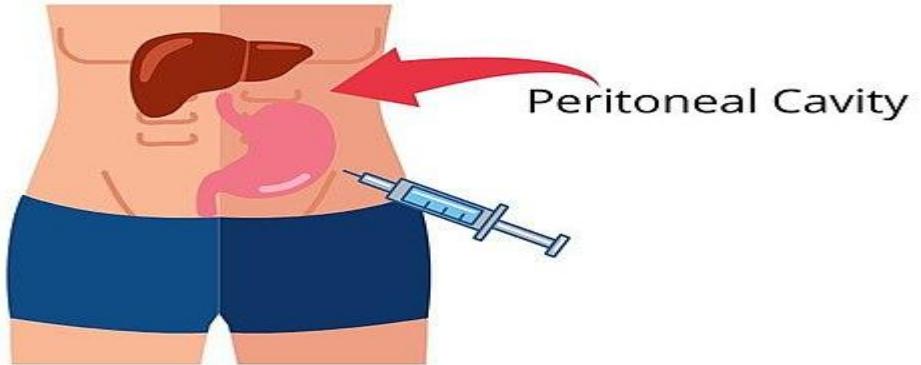
Intra-cardiac (injections that are given directly into the heart muscles or ventricles. They can be used in emergencies, although they are rarely used in modern practice), **Intra-peritoneal** (widely used to administer chemotherapy drugs to treat some cancers, particularly ovarian cancer), **Intrathecal** (is a route of administration for drugs via an injection into the spinal canal, or into the subarachnoid spaceso that it reaches the cerebrospinal fluid (CSF). It is useful in several applications, such as for spinal anesthesia, chemotherapy) .

4-Inhalation ►

Inhalation routes, both oral and nasal, provide rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium. Drug effects are almost as rapid as those with IV bolus. Drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol are administered via inhalation.

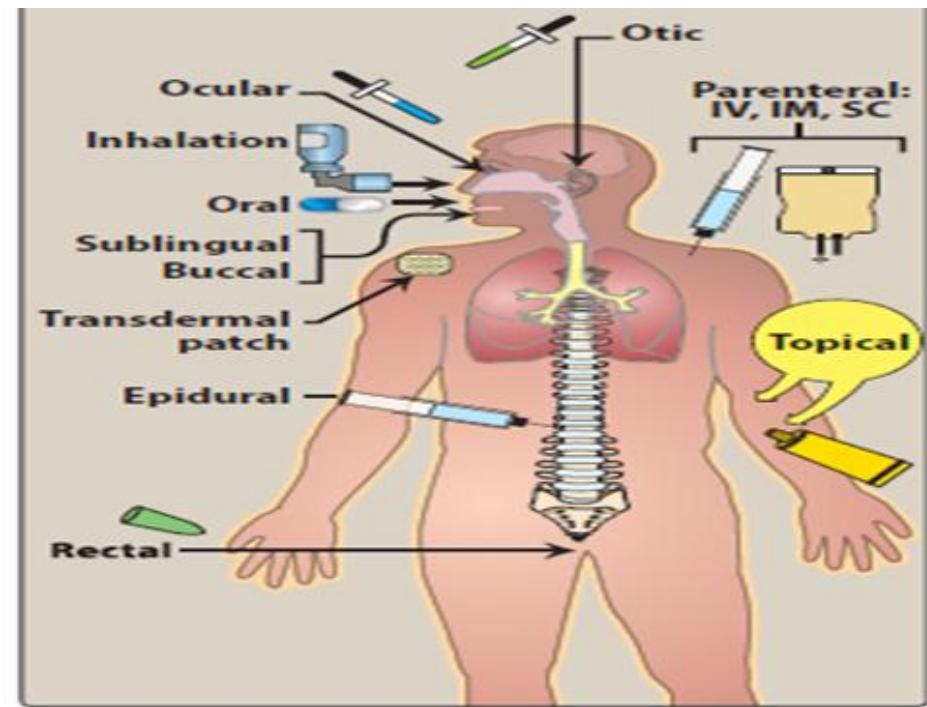
This route is effective and convenient for patients with respiratory disorders (such as asthma or chronic obstructive pulmonary disease), because the drug is delivered directly to the site of action, thereby minimizing systemic side effects.

Examples of drugs administered via inhalation ➤ include bronchodilators, such as salbutamol, and corticosteroids, such as fluticasone.



5-Topical ➤

is used when a local effect of the drug is desired. ➤ For example, **clotrimazole** is a cream applied directly to the skin for the treatment of **fungal infections**.



Pharmacology

Pharmacokinetics
Action of the body on
the drug

Pharmacodynamics
Action of the drug on
the body

Pharmacotherapeutics
Therapeutic uses

- ▶ **Pharmacotherapy** is the use of drugs to treat, cure, or prevent diseases and relieve symptoms.
- ▶ In health, it can involve prophylaxis to prevent future illnesses, such as using statins to prevent cardiovascular disease.
- ▶ In disease, pharmacotherapy treats conditions ranging from bacterial infections with antibiotics to depression with antidepressants, aiming to manage symptoms, address the root cause, and improve overall health outcomes through effective and safe use of medications

► **Pharmacotherapy in Health (Prevention)**

- **Prophylaxis:**

- In healthy individuals, pharmacotherapy can be used to prevent diseases from developing.

- **Examples:**

- Taking medication to prevent heart attacks or strokes (e.g., blood thinners).
 - Using antibiotics to prevent bacterial infections after exposure to a pathogen.

► **Pharmacotherapy in Disease (Treatment)**

- **Symptomatic Relief:**

- Drugs can alleviate or manage the symptoms of a disease.

- **Examples:**

- Pain relievers (e.g., [acetaminophen](#)) for various ailments.
 - [Antihistamines](#) to relieve allergy symptoms.
 -

- **Examples of Diseases Treated:**

- **Infections:** [Antivirals](#) for viral infections or [antibiotics](#) for bacterial ones.
 - **Mental Health:** [Antidepressants](#) for depression and other mood disorders.
 - **Chronic Conditions:** Management of diseases like diabetes, cardiovascular disease,

Pharmacokinetic

Effect of the body on the drug.

Consist of four processes (**ADME**).

A-Absorption

Transfer of the drug from the site of administration to the blood.

- Mechanism of absorption

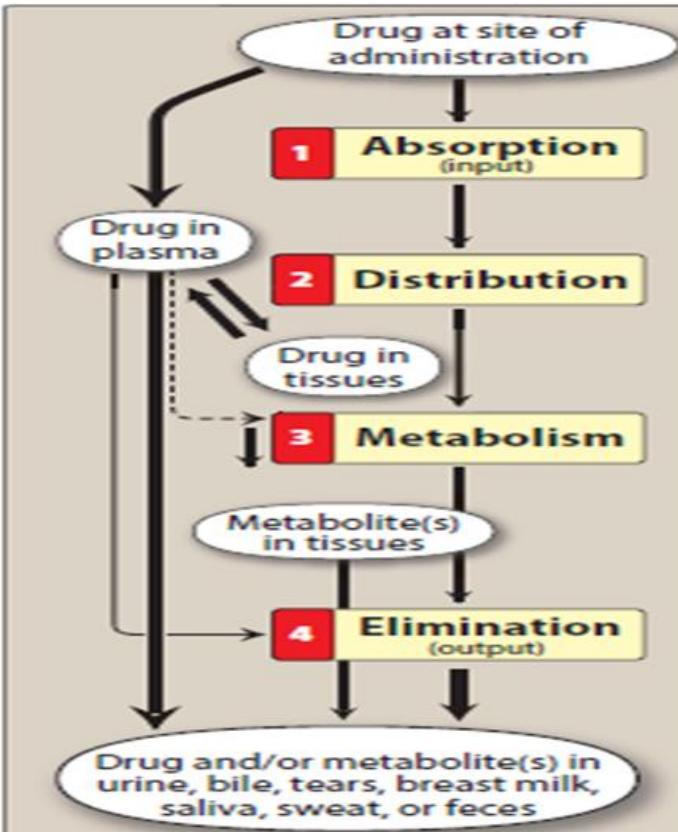
1-Passive transport

A-Simple diffusion

The drug moves from a region of high concentration to one of lower concentration.

No need for energy and carrier.

The drug must be high lipid solubility and small molecular weight.



 **Most drugs are either weak acids or weak bases**

Weak acid drugs → less ionized in acidic medium → increase absorption ►

Weak base drugs → less ionized in basic medium → increase absorption. ►

Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane lipid bilayers.

B- Facilitated diffusion ►

Facilitate the passage of large molecules as glucose. ►

No need for energy. ►

Need carrier protein. ►

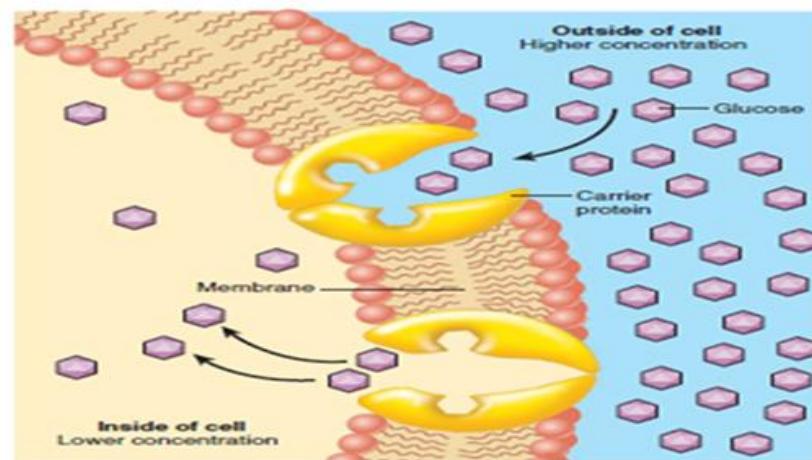
These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells and moving them from an area of high concentration to an area of low concentration.

2. Active transport ►

Movement of drugs against a concentration gradient, from a region of low drug concentration to one of higher drug concentration.

Need carrier and energy. ►

Energy-dependent active transport is driven by the hydrolysis of adenosine triphosphate. ►



3. Endocytosis and exocytosis ►

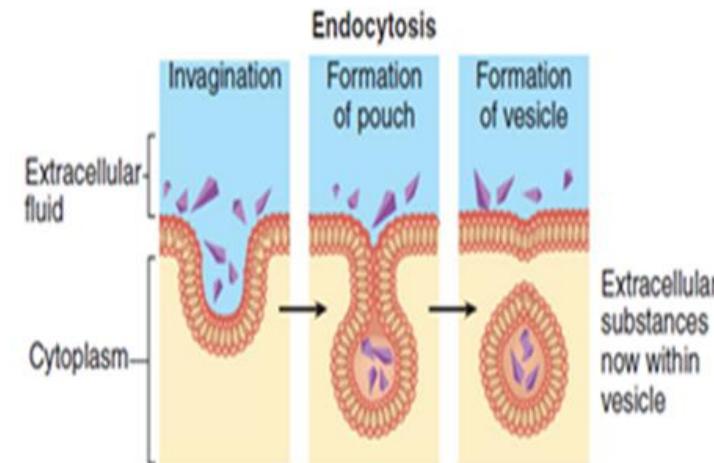
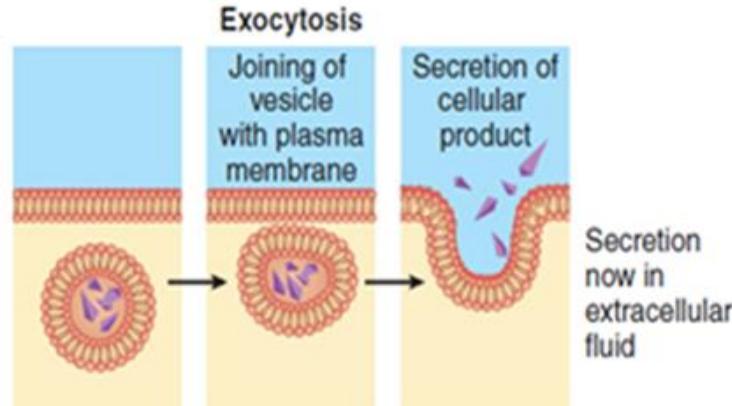
This type of absorption is used to transport drugs of exceptionally large size across the cell membrane.

Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug filled vesicle.

Exocytosis is the reverse of endocytosis. ►

Vitamin B12 is transported across the gut wall by endocytosis, ►

whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular vesicles in the nerve terminal and released by exocytosis.



Factors affecting absorption

1-Patient related factors ➤

A-Route of administration IV > IM > SC > Oral . ➤

Intravenous injection (I.V.): 100% of the drug reaches the systemic circulation almost immediately. ➤

Intramuscular injection (I.M.): most of the drug is rapidly absorbed due to the high vascularity of skeletal muscles.

Subcutaneous injection (S.C.): absorption is less than after I.M. injection because the S.C. tissue is much less vascular than the skeletal muscles. ➤

Inhalation: lipid soluble drugs as inhalation general anesthesia are rapidly and almost completely absorbed because the alveoli have a very wide surface area and very rich blood supply.

Sublingual: drugs given as sublingual pellets –as nitroglycerin in treatment of acute anginal attacks-are better and more rapidly absorbed than orally administered drugs Because they reach the systemic circulation directly and avoid passage through GIT and the liver.

B-Absorbing surface area. ►

Increase the surface area→ increase absorption ►

small intestine (about 1000 times the surface area of the stomach due to the presence of microvilli) ►

C-Blood flow to the absorption site: The intestines receive much more blood flow than the stomach, so absorption from the intestine is favored over the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thereby minimizing absorption.]

D-Expression of P-glycoprotein: P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes.

It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. “pumps” drugs out of the cells. Thus, in areas of high expression, P-glycoprotein reduces drug absorption.

E-Gastrointestinal motility, may be altered by disorders as migraine or diabetic neuropathy cause gastric stasis and slow drug absorption.



2-Drug related factors

- a- Lipid solubility: high lipid solubility → high absorption.
- b-Ionization: Non ionized drug → high absorption.
- c-Valency: ferrous iron (Fe^{2+} absorbed more than ferric iron Fe^{3+}).
- d-Nature: inorganic (small molecule) > organic (large molecule).
- e-Pharmaceutical preparation: solution > tablets.
- f-PH of the drug: Most of the drugs are weak acids or weak base.
 - Acidic drugs are largely unionized in the stomach and absorbed faster, while basic drugs are absorbed faster in the intestine.
- g-some drugs reduce motility (muscarinic receptor blockers (**Atropine**) or increase it (**metoclopramide**)).
- h-Physicochemical factors.
 - tetracycline binds strongly to Ca^{2+} , and calcium-rich foods (milk) prevent its absorption.





If you have any question: Don't hesitate to contact me

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Bioavailability

it is the fraction (proportion or percentage) of the chemically unchanged drug reaching the systemic circulation following administration by any route.□

For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%.

Determining bioavailability is important for calculating **drug dosages for non-intravenous routes of administration.**

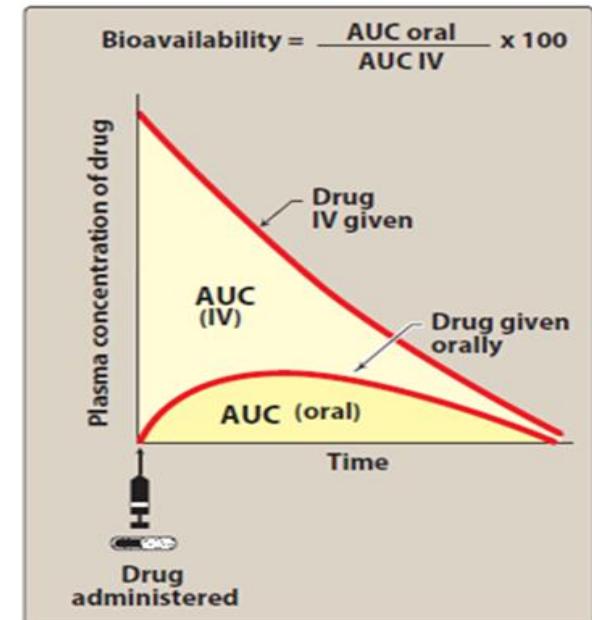
1. Determination of bioavailability: Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with levels achieved by IV administration.

After IV administration, 100% of the drug rapidly enters the circulation.

- When the drug is given orally, only part of the administered dose appears in the plasma.

By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured.

- The total AUC reflects the extent of absorption of the drug.
- Bioavailability of a drug given orally is the ratio of the AUC following oral administration to the AUC following IV administration (assuming IV and oral doses are equivalent).



2. Binding of drugs to plasma proteins •

Binding to plasma proteins •

Increase in binding of drug to plasma proteins → decrease distribution of the drug. •

Albumin is the major drug-binding protein and may act as a drug reservoir (as the concentration of free drug decreases due to elimination, the bound drug dissociates from the protein).

This maintains the free drug concentration as a constant fraction of the total drug in the plasma.

<i>Free Form</i>	<i>Bound Form</i>
<ul style="list-style-type: none">• Diffusible.• Active.• Liable to liver metabolism.• Liable to renal excretion (mostly by glomerular filtration).	<ul style="list-style-type: none">• Non-diffusible (confined to plasma).• Inactive.• Not liable to liver metabolism.• Not liable to renal excretion.• Acts as a "reservoir".

3-Lipophilicity

The chemical nature of a drug strongly influences its ability to cross cell membranes.

Lipophilic drugs readily move across most biologic membranes.

4-Volume of distribution

The apparent volume of fluid into which an administered drug is dispersed.

V_d (volume of distribution) = Q (total amount of drug in the body) / C_p (Plasma concentration of the drug).

If the drug has high volume of distribution → the drug has low affinity to bind to plasma protein.

If the drug has low volume of distribution → the drug has high affinity to bind to plasma protein

C-Metabolism

It is the conversion of the drug from nonpolar to polar form to facilitate excretion.

The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II.

1. Phase I

Phase I reactions convert lipophilic drugs into more polar molecules by introducing or unmasking a polar functional group, such as –OH or –NH₂.

Phase I reactions usually involve reduction, oxidation, or hydrolysis.

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

They are catalyzed by the cytochrome P450 system (also called microsomal mixed-function oxidases).

The P450 system is important for the metabolism of many endogenous compounds (such as steroids, lipids) and for the biotransformation of exogenous substances (xenobiotics).

Cytochrome P450, designated as CYP, is a superfamily of heme-containing isozymes that are **located in most cells**, but primarily in the **liver and GI tract**.

The family name is indicated by the Arabic number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A. A second number indicates the specific isozyme, as in CYP3A4.

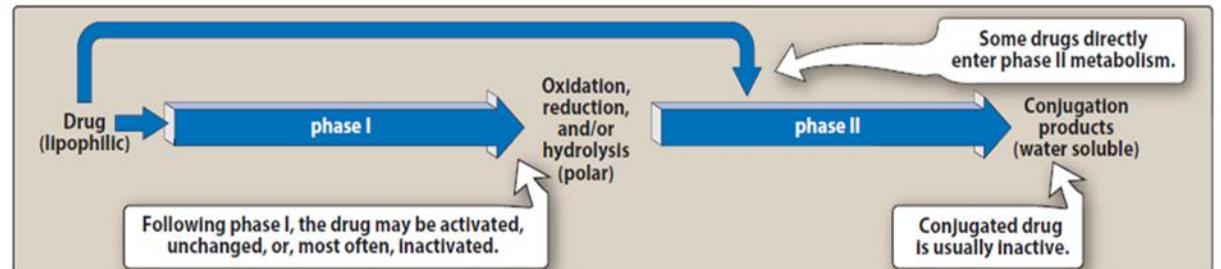
2. Phase II

This phase consists of conjugation reactions.

If the metabolite from phase I metabolism is sufficiently polar, it can be excreted by the kidneys.

However, many phase I metabolites are still too lipophilic to be excreted. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble compounds that are often therapeutically inactive.

The highly polar drug conjugates are then excreted by the kidney or in bile.



Results of metabolism

1-Active drug====→Inactive •

Acetylcholine ==→ Choline + acetic acid •

2-Inactive drug (prodrug)====→Active •

Imipramine ===→ Desipramine •

3-Active drug====→Active •

Phenacetin==→ Acetaminophen •

4-Non-Toxic drug====→Toxic •

Methyl alcohol==→ Formaldehyde •

Factors affecting metabolism

1-Age •

- Deficiency of liver microsomal enzymes especially in child → prolonged action of drug lead to increase toxicity, as chloramphenicol when used in babies cause **Grey baby syndrome** (a rare but serious, even fatal, side effect that occurs in newborn infants (especially premature babies) following the accumulation of the antibiotic chloramphenicol.)
- Common signs and symptoms include loss of appetite, vomiting, ashen gray color of the skin, hypotension (low blood pressure), cyanosis (blue discoloration of lips and skin), hypothermia, cardiovascular collapse, hypotonia (muscle stiffness), abdominal distension, irregular respiration.

2-Sex differences •

Metabolic differences between sexes have been noted, for a number of drugs. •

Female sex hormones are hepatic microsomal enzyme inhibitors whereas male sex hormones act as inducers. •

3-State of health •

Presence of disease alters in the normal metabolism. •

4-Inhibition of microsomal enzymes

**Certain drugs inhibit the activity of microsomal enzymes→ decrease metabolic rate→lead to
prolongation of the action of drugs→ increase the activity and may lead to toxicity.**

5-Induction of microsomal enzymes

**Certain drugs increase the activity of microsomal enzymes→ increase metabolic rate→
decrease the activity of the drug.**

Hepatic microsomal enzyme (HME) inducers: carbamazepine, phenobarbital and rifampicin.

Hepatic microsomal enzyme (HME) inhibitors: cimetidine, omeprazole, erythromycin and
ketoconazole.

E-Excretion

The process that involves excretion of drug outside the body.

❖ Routes of drug excretion

1-Renal

Most drugs leave the body in the urine.

Lipophilic substances are not eliminated efficiently by the kidney. Consequently, lipophilic drugs are metabolized to more polar products, which are excreted in urine

Drugs differ greatly in the rate at which they are excreted by the kidney, ranging from penicillin, which is cleared from the blood almost completely on a single transit through the kidney, to diazepam, which is cleared extremely slowly.

Elimination of drugs via the kidneys into urine involves the processes of **glomerular filtration**, **active tubular secretion**, and **passive tubular reabsorption**.

- 1. **Glomerular filtration:** for water soluble non bound drugs.
- 2. **Proximal (active) tubular secretion:** as penicillin.
- 3. **Distal (passive) tubular reabsorption:** for lipid soluble drugs

- **Reabsorption affected by PH:**

Acidification of urine (Vit C) → increase excretion of basic drugs as ephedrine.

Alkalization of urine (NaHCO₃) → increase excretion of acidic drugs as aspirin.

For example, a patient presenting with phenobarbital (weak acid) overdose can be given bicarbonate, which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

2-GIT •

Saliva as iodide and morphine, stomach as morphine. •

3-Skin •

Sweat glands as rifampicin. •

4-breast (milk) as nicotine& morphine •

5-Lung •

Gases as nitrous oxide and halothane. •

Elimination by these routes is quantitatively negligible compared with renal excretion, although excretion into milk can sometimes be important because of effects on the baby.

- Total body clearance

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

$$CL_{total} = CL_{hepatic} + CL_{Renal} + CL_{Pulmonary} + CL_{Others} •$$

- **Pharmacodynamics**

Pharmacodynamics describes the **actions** of a drug on the body (mechanism of action of drugs) and the influence of drug concentrations on the magnitude of the response.

The binding of drug molecules to cells •

A drug will not work unless it is bound to drug targets: •

- Receptors. •
 - Enzymes. •
 - Carrier molecules (transporters). •
 - Ion channels. •
- Most drugs exert their effects, both beneficial and harmful, by interacting with **receptors** (that is, any biological molecule to which a drug binds and produces a response) present on the **cell surface or within the cell**.

The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process • called signal transduction.

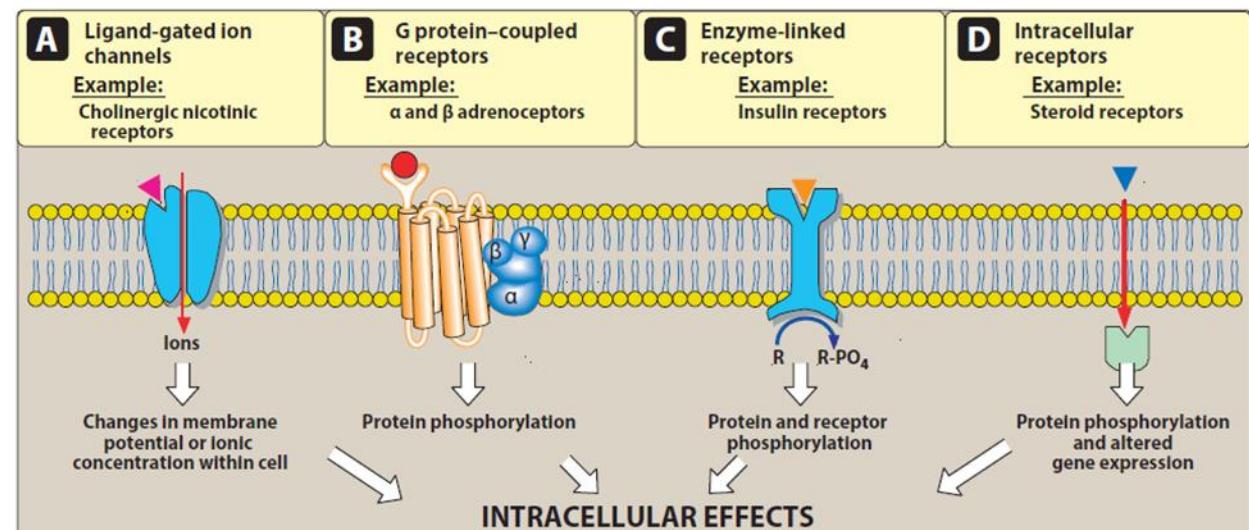
D+R =DR complex •

D → Drug , R → Receptor. •

DR → Drug-Receptor complex •

-Biological effect increase when the drug receptor complex increases. •

-Drug or any substance (activate or inactivate receptor) called ligand. •



- Classification of receptors

- 1-Ligand-gated ion channels.

- The extracellular portion of ligand-gated ion channels usually contains the ligand binding site. This site regulates the shape of the pore through which ions can flow across cell membranes. The channel is usually closed until the receptor is activated by an agonist, which opens the channel briefly for a few milliseconds.

- For example, cholinergic Nicotinic receptors.

- 2-G-Protein-coupled receptors

- G-Protein → Protein located in the cytoplasm between receptor and cell.

- Main types:

-**G_s** (stimulatory) → activate adenylate cyclase → increase cyclic adenosine monophosphate •

(cAMP) → open Ca⁺⁺ channels and increase Ca⁺⁺ influx from sarcoplasmic reticulum (SR).

-**G_i** (inhibitory) → inactivate adenylate cyclase → decrease cyclic adenosine monophosphate •

(cAMP) → decrease Ca⁺⁺ influx.

-**G_q** (stimulatory) → increase phospholipase-C (PLC) → PLC break phosphatidylinositol •

biphosphate (PIP2) into inositol triphosphate (IP3) and diacylglycerol (DAG) → IP3 increase Ca⁺⁺ influx.

3-Enzyme linked receptors •

When activated, these receptors undergo conformational changes resulting in increased cytosolic enzyme activity, depending on their structure and function. The most common enzyme linked receptors possess tyrosine kinase activity as part of their structure.

For example, when the peptide hormone insulin binds to two of its receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself.

4. Intracellular receptors •

The receptor is entirely intracellular, and, therefore, the ligand must diffuse into the cell to interact with the receptor. In order to move across the target cell membrane, the ligand must have sufficient lipid solubility.

For example, steroid hormones exert their action on target cells via intracellular receptors. •

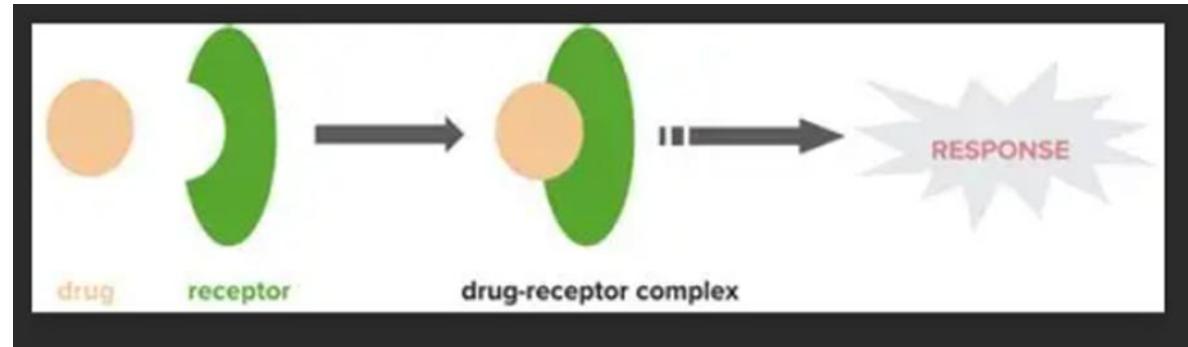
❖ Ligand-receptor interaction

Ligand is any substance combines with receptor. •

- **Types of ligands**

1-Ligand has affinity and efficacy to receptor: **Agonist**. •

2-Ligand has affinity and not have efficacy to receptor: **Antagonist**. •



Affinity is the tendency of a drug to combine with receptor •

Graded dose-response relations •

As the **concentration** of a drug increases, its **pharmacologic effect** also gradually increases until all the receptors are occupied (the maximum effect).

Plotting the magnitude of response against increasing doses of a drug produces a graded dose-response curve. •

- Two important properties of drugs, **potency** and **efficacy**, can be determined by graded dose-response curves

1-Potency •

Potency is a measure of the amount of drug necessary to produce an effect of a given magnitude. •

The concentration of drug producing 50% of the maximum effect (EC₅₀) is usually used to determine •
potency.

The EC₅₀ for Drugs A , B and C indicate that Drug A is more potent than Drug B and C, because a lesser •
amount of Drug A is needed when compared to Drug B and C to obtain 50-percent effect.

EC₅₀ = drug dose that shows 50% of maximal response.

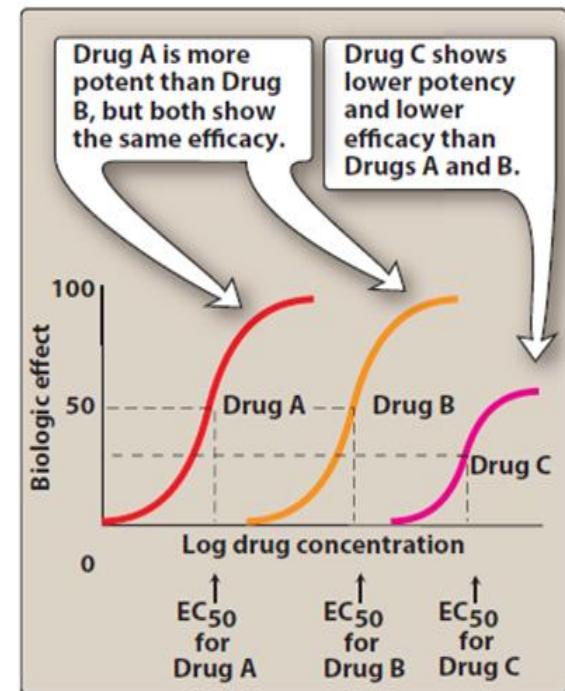


Fig: Typical dose-response curve for drugs showing differences in potency and efficacy.

2-Efficacy •

is the tendency of the drug-receptor complex to elicit a response. •

Maximal efficacy of a drug (E_{max}) assumes that all receptors are occupied by the drug, and no increase in response is observed • if a higher concentration of drug is obtained.

➤ Types of agonists

A. Full agonists •

If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it • is a full agonist.

Full agonists bind to a receptor, stabilizing the receptor in its active state and are said to have an intrinsic activity of one. •

For example, phenylephrine is a full agonist at α_1 -adrenoceptors, because it produces the same E_{max} as does the endogenous ligand, norepinephrine. •

B. Partial agonists •

have intrinsic activities greater than zero but less than one. •

Even if all the receptors are occupied, partial agonists cannot produce the same Emax •
as a full agonist.

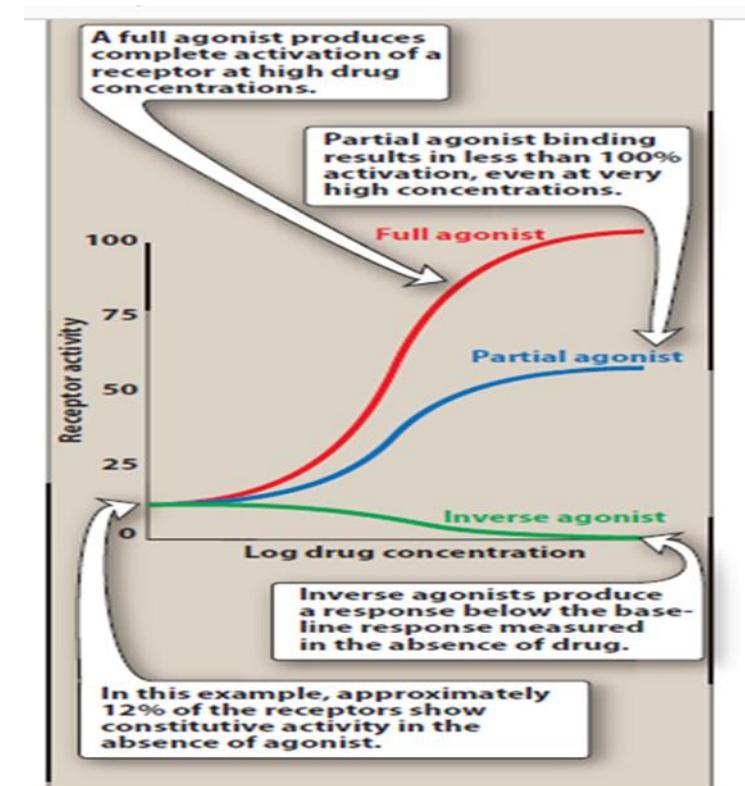
However, a partial agonist may have an affinity that is greater than, less than, or •
Equivalent to that of a full agonist.

2. Antagonists •

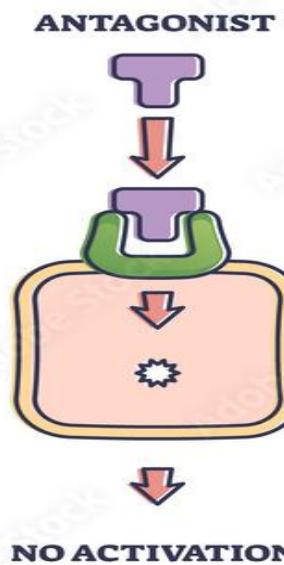
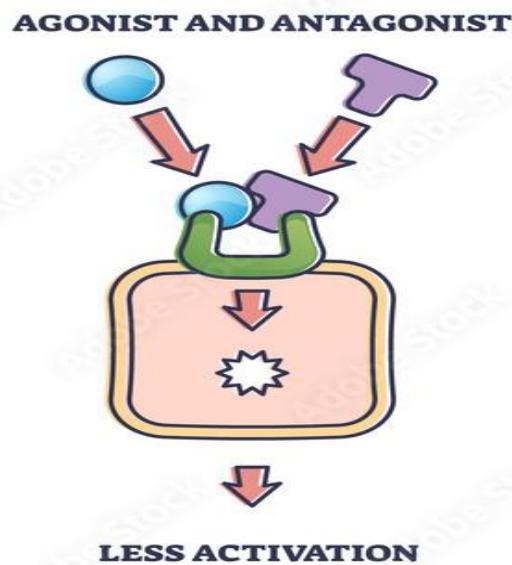
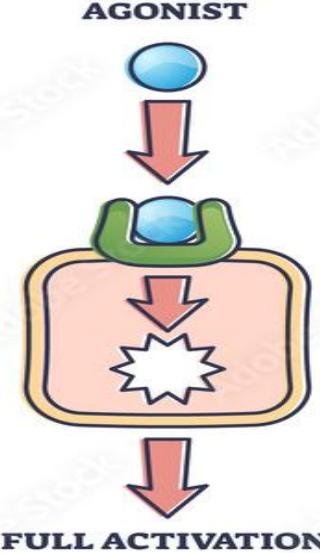
Antagonists bind to a receptor with high affinity but possess zero intrinsic activity. •

An antagonist has no effect in the absence of an agonist but can decrease the effect •
of an agonist when present.

Antagonism may occur either by blocking the drug's ability to bind to the receptor or •
by blocking its ability to activate the receptor. •



AGONISTS VS ANTAGONISTS



Types of Antagonist •

1. Competitive antagonists: •

If both the antagonist and the agonist bind to the same site on the receptor in a reversible manner, they are said to be “**competitive**.”

The competitive antagonist prevents an agonist from binding to its receptor and maintains the receptor in its inactive state.

For example, the antihypertensive drug **terazosin** competes with the endogenous ligand norepinephrine at α_1 -adrenoceptors. However, this inhibition can be overcome by increasing the concentration of agonist relative to antagonist.

•

2. Noncompetitive antagonists:

Irreversible antagonists bind covalently to the active site of the receptor, thereby reducing the number of receptors available to the agonist.

In contrast to competitive antagonists, the effect of irreversible antagonists cannot be overcome by adding more agonist.

Thus, noncompetitive antagonists are considered **irreversible antagonists.**

A fundamental difference between competitive and noncompetitive antagonists is that **competitive antagonists reduce agonist potency** and **noncompetitive antagonists reduce agonist efficacy (decrease Emax).**

3. Functional antagonism: An antagonist may act at a **completely separate receptor**, initiating effects that are functionally opposite those of the agonist.

•

A classic example is the functional antagonism by epinephrine to **histamine-induced bronchoconstriction**

Histamine binds to H1 histamine receptors on bronchial smooth muscle, causing **bronchoconstriction** of the bronchial tree.

Epinephrine is an agonist at β_2 -adrenoceptors on bronchial smooth muscle, which causes **bronchodilation**

•

✓ Regulation of receptors

1-Continuous stimulation of receptors with agonist → decrease number of receptors and sensitivity →

Down regulation. •

2-Continuous stimulation of receptors with antagonist → increase number of receptors and sensitivity →

Up regulation. •

•

Receptors and disease

Some diseases are linked to receptor malfunction:

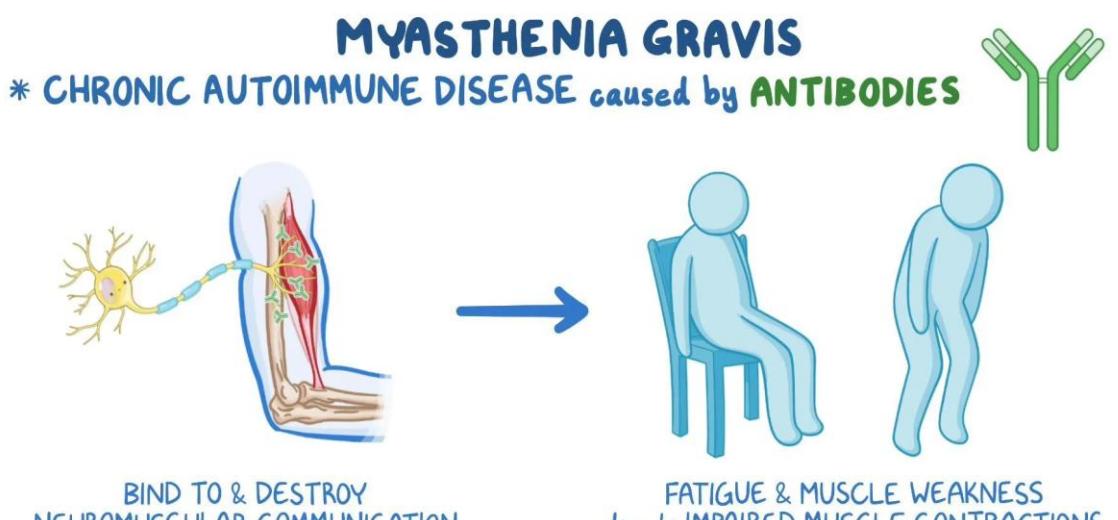
autoantibodies directed against receptor proteins Ex. **myasthenia gravis**

disease of the neuromuscular junction due to autoantibodies that inactivate nicotinic acetylcholine receptors

Myasthenia gravis

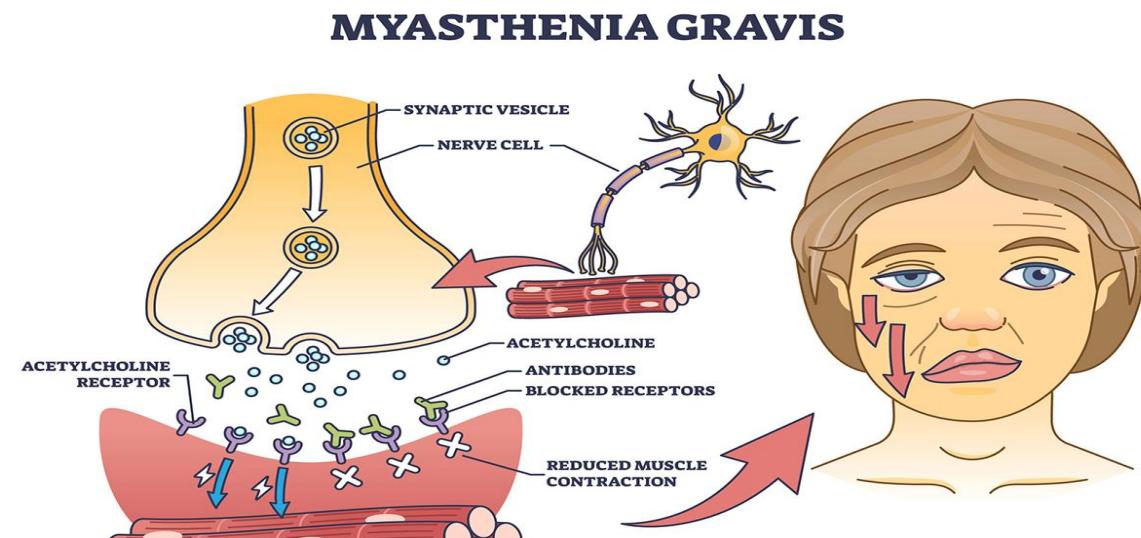
is a condition that happens when communication between nerves and muscles breaks down. This causes muscles to feel weak and get tired quickly. This condition may affect any of the muscles you control, called **voluntary muscles**. Certain muscle groups are more commonly affected than others.

These include muscles in the **face, throat, arms and legs**.



- The exact cause of myasthenia gravis is not known. Myasthenia gravis is an autoimmune condition. These conditions happen when the immune system creates antibodies that mistakenly work against or attack healthy cells or tissue.
- Nerves communicate with muscles by releasing chemicals called neurotransmitters that send signals between cells.
- In myasthenia gravis, the immune system mistakenly makes antibodies that stop the neurotransmitter acetylcholine from communicating with muscles.
- The antibodies destroy or block the path to muscle cells called receptor sites.
- With fewer receptor sites available, the muscles receive fewer nerve signals. This causes muscle weakness.

- Treatment
- Medicines
 - **Cholinesterase inhibitors.** Medicines such as pyridostigmine (Mestinon, Regonol) improve communication between nerves and muscles. These medicines aren't a cure but may improve muscle contraction and strength in some people.
 - Possible side effects include gastrointestinal upset, diarrhea, nausea, and too much saliva and sweat.
- **Corticosteroids.** Corticosteroids such as prednisone block the immune system, making it less able to produce antibodies. But use of corticosteroids over a long period of time can lead to serious side effects. These include bone thinning, weight gain, diabetes and a higher risk of some infections.



- **Immunosuppressants.**
- . These medicines could include **azathioprine, cyclosporine, methotrexate or tacrolimus.**
- These medicines, which can take months to work, might be used with corticosteroids.
- **Side effects of immunosuppressants, such as a higher risk of infection and liver or kidney damage, can be serious.**
- **Intravenous therapy**
- The following therapies are usually used for a short time to treat symptoms that suddenly get worse. They also may be used before other therapies or surgery.
- **Plasmapheresis.**
- This procedure uses a blood-filtering machine similar to that used for dialysis. The machine removes antibodies from the blood that block the transmission of signals from nerve endings to your muscles. However, the benefits from this procedure usually last only a few weeks. Having this done several times can make it hard to find veins for further treatments.
- Risks of plasmapheresis include a drop in blood pressure, bleeding, heart rhythm conditions and muscle cramps.
- Some people have an allergic reaction to the solutions used to replace the plasma.



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Pharmacology

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❖ Dose

The amount of drug given to the patient at a time •

● Types of doses

Therapeutic dose: the average dose that produce therapeutic effect. •

Maximum tolerated dose: the largest dose of a drug that can be taken safely. •

Initial dose: the dose used at start of treatment. •

Maintenance dose: the dose required to maintain a therapeutic effect. •

Lethal or fetal dose: the dose that produce death. •

•

❖ Therapeutic index and margin of safety

The therapeutic index (TI) of a drug is the ratio of the minimum dose of a drug that produces toxicity and the minimum dose that produces the therapeutic response is called therapeutic index (or safety margin).

TI = LD 50 / ED 50 •

LD50= drug dose that produce death in 50% of population. •

ED50= drug dose that produce therapeutic effect in 50% of population. •

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

It is a key factor in classifying a drug as easy or difficult to use

1. Warfarin (example of a drug with a small therapeutic index)

At higher doses of warfarin, anticoagulation resulting in hemorrhage occurs in a small percent of patients.

2. Penicillin (example of a drug with a large therapeutic index):

It is safe and common to give doses in excess of that which is minimally required to achieve a desired response without the risk of adverse side effects.



✓ Factors affecting the dosage and action of the drug

1-Age, weight and body surface area •

Adult dose (20-60 years of age) and weight about 70kg. •

Elderly required small dose (due to decrease renal excretion and decrease hepatic metabolism). •

Children requires small dose (due to immature kidney and liver and decrease plasma protein). •

2-Sex •

A-Female need smaller dose than male due to: •

-High fat content → increase fat in the body → slow rate of oxidation → decrease metabolism → increase drug effect.

B-Some drugs avoided in pregnancy, lactation and menstruation. •

Pregnancy causes physiological changes that can influence drug disposition in mother and fetus. •

--Maternal plasma albumin concentration is reduced, influencing drug protein binding. •

-Cardiac output is increased, so increases renal blood flow and increases renal elimination of drugs. •

C-Drugs that are transferred to the fetus are *slowly* eliminated, because •

-the activity of most drug-metabolizing enzymes in fetal liver is much less than in the adult, •

-the fetal kidney is not an efficient route of elimination because excreted drug enters the amniotic fluid, which is swallowed by the fetus. •

3-Routes of administration

IV > IM > SC > Oral.

4-Time of administration

Irritant drugs are better taken after meals e.g. Aspirin.

Central nervous system stimulant drugs should be not given at night as they may cause insomnia e.g. ephedrine.

5-Genetic abnormality

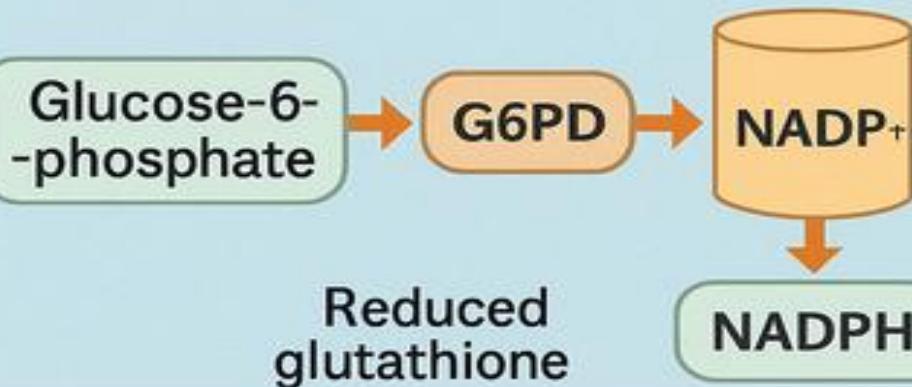
-Abnormal reaction due to genetic abnormality.

For example, **Primaquine and chloramphenicol drugs** may induce hemolytic anemia in patient with glucose-6-phosphate dehydrogenase (**G6PD**) deficiency.

-G6PD enzyme protects RBCs from damage, it is responsible for convert NADP into NADPH which make detoxification of the drug through glutathione system.

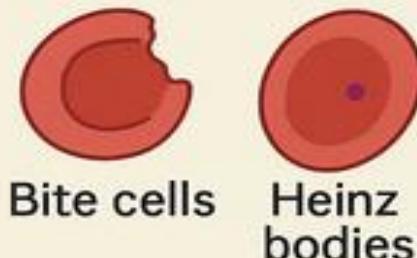
G6PD Deficiency

Pathway



Labs & Smear

- Hemoglobin
- ↑ LDH
- Haptoglobin
- Reticulocyte count



Triggers

- Infections (eg., pneumonia, hepatitis)
- Drugs (e.g., sulfa drugs, antimalarials)
- Fava beans

Treatment

- Avoid triggers
- Give supportive care
- Rarely, transfusions

Adverse drug reaction •

An “adverse reaction” may be defined as any reaction which is harmful , unintended and •
which occurs at normal doses.

They may be: •

a- Dose related adverse reactions. •

b- Non – dose related adverse reactions. •

•

✓ Dose related adverse reactions

These will occur in all patients if the drug is administered with therapeutic doses •

A-Excessive therapeutic effect •

When the drug produces a greater effect than is therapeutically necessary. •

Ex. when an anticoagulant prolongs the clotting time more than is required. •

B-Side effects •

These are unwanted effects of drugs due to the pharmacological properties of the drug.

Ex. **constipation** produced by **morphine** when used as an analgesic.

C-Secondary effects •

- Sometimes the wanted pharmacological actions of the drug indirectly cause an unwanted effect.
- infection of the gut caused by the overgrowth of resistant organisms when a patient is given an oral broad-spectrum antibiotic (*superinfection*).

✓ **Non-dose related adverse reactions**

A-Drug idiosyncrasy

Is a qualitatively abnormal, and usually harmful, drug effect that occurs in a small proportion of individuals.

Chloramphenicol causes aplastic anemia in 1 in 50000 patients due to genetic abnormalities.

B-Hypersensitivity (Drug allergy)

Antigen-Antibody reaction leads to release of histamine as in anaphylactic shock due to penicillin.

C-Tolerance

Failure of responsiveness to the usual dose.

Types: •

Congenital tolerance: Genetic factors are possibly involved. •

Acquired tolerance: as in tachyphylaxis as β_2 -agonist agonist (Salbutamol). •

D-Desensitization and Tachyphylaxis •

Often, the effect of a drug gradually diminishes when it is given continuously or repeatedly. •

The term refractoriness is used to indicate a loss of therapeutic efficacy. •

Desensitization = tachyphylaxis often develops in **few minutes** •

The term **tolerance** is used to describe gradual decrease in responsiveness (**days or weeks**). •

Drug resistance is a term used to describe the loss of effectiveness of antimicrobial or antitumor drugs •

E-Dependence •

- It usually occurs with CNS acting drugs. •
- It is a phenomena related to tolerance. •
- It involves a certain degree of tissue adaptation. •
- Withdrawal of the drug could produce unpleasant symptoms. •

- **Types of dependence**

Habituation	Addiction
Mild degree of drug dependence Psychic dependence When drug stopped→ some emotional distress for a relative short period. e.g. Smoking and Coffee.	Serious form of drug dependence Psychic and physical dependence When drug stopped→ withdrawal symptoms → reverse the normal pharmacological action e.g. Morphine and Heroin.

Drug-Drug interaction

A-Pharmacokinetic interaction

1-Absorption

-Gastric emptying rate

Atropine decrease absorption of paracetamol due to decrease gastric emptying rate.

-PH of the site of absorption

Weak acid drugs are more absorbed in the stomach and weak basic drugs are absorbed in the intestine.

-Presence of food and other drugs in the GIT

2-Distribution

Aspirin displace oral anticoagulants and oral hypoglycemic from their plasma binding sites → increase activity of anticoagulants and oral hypoglycemic drugs.

3-Metabolism

-Hepatic microsomal enzyme (HME) inducer e.g. Phenytoin → increase metabolism of other drugs

-HME inhibitors e.g. Cimetidine → decrease metabolism of other drugs.

4-Excretion •

-Probenecid → decrease excretion of penicillin. •

-PH change e.g. acidification of urine → increase excretion of weak base drugs. •

•

B-Pharmacodynamic interaction •

Drug interact with other drugs when both are present in the body. •

Increase in drug effect

Addition

Algebraic sum of the 2
drugs effect

$$1+1=2$$

Acetylcholine+histamine
in contraction of intestine.

Synergism

the combination effect more
than algebraic sum.

$$1+1=>2$$

Ethanol+barbiturate-->severe
CNS depression

Potentiation

drug which has no effect, by
itself, increases the effect of
another active drug $0+1=>1$

Barbiturate+Salicylate

Drug Safety •

All drugs have side effects, but the extent of their impact and severity varies from **mild** (such as mild itching or mild headache) to **severe** (such as severe rash, damage to vital organs, primarily the liver and kidneys, and possibly even death).

- Among the factors that may increase the severity of the side effects, **the type of medications and the type of patients using them** are the most important.
- Some drugs may not cause serious symptoms, such as certain types of **antibiotics**; other medications may cause serious symptoms, such as certain **cancer drugs, anti-diabetic medications, medications to control elevated blood lipids**.

- Nonetheless, serious adverse reactions can arise from widely used and well-known medications. For example, many people might believe that paracetamol, which is sold as Panadol, Fevadol, Tylenol and under other trade names, is very safe and would not cause serious side effects. However, this drug can induce dangerous side effects at high doses, particularly ones affecting the liver.
- What makes this worse is that the drug is found in many combinations used for cold and flu, and the patient might be unaware of this and take extra doses, leading to a direct liver injury.

- Specific patient populations and drug safety
- Pregnant and lactating women
- Each phase of pregnancy, which lasts nine months, is considered important and critical during the use of any medication.
- Pregnancy is divided into three major trimesters: the first trimester (the first three months), the second trimester (the second three months), and the third trimester (the last three months of pregnancy).
- .

- As mentioned earlier, all these trimesters are important periods; therefore, a pregnant woman must not take any medication without consulting a specialist (a physician or a pharmacist) about the safety of the medication as it may affect the formation of the fetus, as was the case with the use of **thalidomide**, as mentioned above.

- The danger of effects of drugs is not limited to taking drugs during pregnancy: deleterious effects on the fetus may be experienced even if a medication is taken within a short time period before pregnancy (perhaps several weeks)
 - For example, the drug **isotretinoin** (Roaccutane), used for the treatment of acne, is considered one of the most dangerous medications during pregnancy as it has teratogenic effects on the fetus; therefore, it is contraindicated during pregnancy. Thus, with the use of this drug, it is important to consult and advise women not to become pregnant even after cessation of drug use. This could occur by informing them of the matter and advising them to consider the possibility of using contraception.

Thalidomide tragedy was a medical disaster in the late 1950s and early 1960s when the drug thalidomide, used as a sedative and to treat morning sickness in pregnant women, caused severe birth defects in thousands of children worldwide. The drug was linked to limb malformations and other deformities (Phocomelia), leading to its withdrawal in 1961.



- **Contraindication**
- The disease in which the drug should be avoided, e.g. Aspirin is contraindicated in peptic ulcer.
- Also, during the period of lactation, mothers should consult professionals before use of any medication because some medications can be excreted in breast milk, which may have a negative impact on the infant. These warnings should not be applied only to chemically synthesized drugs, but should also be considered while using any herbal medicines or anything that is taken or used as a medicine.

- **Old people (geriatrics)**
- The geriatric group is considered to be **most vulnerable** to the effect of medications and so it is very important to consider their health status before prescribing any medication, for several reasons.

A- The physiological functions of many body organ decline with age, especially important organs such as the liver and kidneys.

B- Older people may also suffer from dementia or “impaired memory” and so forget to take their medications).

C-Older people can suffer from many chronic illnesses, such as high blood pressure, diabetes, and high blood cholesterol and lipids, possibly necessitating the chronic use of multiple medications, which may conflict with each other – what is known as **drug-drug interaction**.

- Depending on the type of interaction between drugs, it is possible that the drug level in the plasma would increase too much, leading to toxicity and severe adverse reactions. The opposite can be true as well – the drug may be in low plasma concentrations, exposing the patient to dangers and complications of the illness that was supposed to be controlled by that drug.

- In addition, older patients tend to try and use **herbal extracts**, for which there are not enough scientific data about components which may be dangerous or which could interact with their prescribed medications. This could worsen the conditions they suffer from, such as chronic, heart, liver and kidney diseases.
- Also, certain types of **food may interact with the prescribed medications**, with the same outcomes as those mentioned regarding drug–drug interactions, but with different mechanisms.
- Alcohol affects metabolism greatly and thus may lead to toxicity when taken with drugs prescribed in the normal dosage regimen.
- Last, the patient must understand and learn the proper method and use of medications to avoid misuse of the drug, which may lead to either side effects or lack of efficacy and benefit. One may use the previously mentioned methods of prevention for any patient, whether the elderly or the others.
- It is important to point out that the concepts of drug safety and the proper use of medications are not limited to a certain class of patient or medication users, but are applied to any person who uses a medication

- Children (pediatrics)
- The second category to consider, which is no less important than the category of pregnant women, is children. It is crucial to take extreme caution when using any medications for children as many medications are divided depending on age group – some medications are **contraindicated** in patients **less than 18 years or less than 12 years old**, and also some medications are contraindicated for use in children less than two years old.
- The reasons include mostly the **lack of scientific studies and clinical trials needed to evaluate the safety** of these medications in each age group separately.
- In addition, **children's vital organs are not mature**, and thus exposure to certain medications may lead to toxic side effects as the body is mostly unable to fully metabolize or excrete the drugs. This would lead to the presence of active compounds in the body for an extended period of time as well as an increase in their levels in the body, inducing toxic effects.
- This can usually be avoided by adjusting the dose but, as mentioned earlier, the lack of clinical studies to evaluate the pharmacokinetic profile of these drugs makes it difficult to adjust the dose; thus many drugs are not recommended for use in certain age groups.

- Furthermore, it is important to use medications in this age group in the exact dose prescribed or recommended, as deviation from that dose may lead to severe side effects if increased or would render the drug ineffective, imposing a danger on children as the disease is not being treated effectively.
- What also contributes to this problem is that a drug can be formulated in **different dosage forms**.
- For example, a medication can be formulated in the form of syrups, tablets, capsules, and suppositories. This may have an impact as each dosage form has a different pharmacokinetic profile, especially as regards their absorption rate – e.g., syrups have faster absorption than tablets or suppositories – and thus the dose should be taken as prescribed by the physician and reviewed by the pharmacist

- Aspirin, or “acetylsalicylic acid”, which is widely used as an analgesic and antipyretic, is one of the drugs that are safely used in adult groups but contraindicated in children, as it could lead to a severe adverse effect known as “Reye’s Syndrome”.
- Thus, a safer alternative to be given to children would be paracetamol and ibuprofen in the correct adjusted dose and based on weight as well.
- It is important to consider the **weight** of the child while prescribing medications and their **doses**, as the dosages of most drugs used for children are calculated based on the weight of the child.
- The **storage** of pediatric medications is important as well. Every dispensed drug is accompanied by instructions for proper storage, such as the suitable recommended temperature for that purpose. There are some important instructions that may be overlooked by parents, such as making sure the medications have not expired. Also families need to be very careful with medications in general and be aware that they must be kept out of reach of children to prevent accidental ingestion, which could be fatal in many situations.

- **Minimizing drug side effects**
- As previously stated, each drug has its side effects; however, it is possible to avoid these side effects by using the drug in the proper way, and by following the instructions included in the drug leaflet or provided by the pharmacist or the physician.
- Knowing the necessary information about a medicine is considered the **first step** in avoiding side effects.
- For example, when a patient knows that a drug should not be taken at a certain time or with another drug, he/she can avoid the incidence of inappropriate drug interactions and gain the full benefit from his/her medications.
- Similarly, when a patient knows that he/she should not take a particular drug with food or certain types of it, again his/her medications will be efficacious, with minimal adverse reactions.
- When a pregnant woman knows she must not take any medication before consulting the doctor or pharmacist, then she will avoid deleterious effects that may be induced by teratogenic medications and will continue with a safe pregnancy

- *Some questions and points considered during patient counseling that are usually raised by healthcare professionals include:*
- -Should the patient avoid taking a certain medication with other medications?
- -Should the patient avoid taking it with certain food or beverages?
- -What are the expected side effects of the drugs?
- -The medical team should encourage the patient to mention over-the-counter (OTC) medications bought directly from the pharmacy without a prescription, such as cough and cold medications including paracetamol or aspirin.
- -The medical team should encourage the patient to bring all his/her medications when he/she goes to see his/her physician.
- -The medical team should counsel the patient about all herbal medications that he/she uses, as well as vitamins and dietary supplements.
- -The patient should feel comfortable in asking the physician or the pharmacist how his/her drugs work to produce their medical effects.
- -Patients should be informed about the proper use of the medications; how many/much, how many times a day, and for how long.
- -Patients should be informed regarding the proper uses of injectable medications such as insulin injections.
- -The medical team should provide all information required by patients regarding the proper storage of medications, as there are many drugs that are affected by exposure to light or storage at inappropriate temperatures.
- - The patient should ask his/her physician or pharmacist about the active ingredients in OTC medications, as some may contain paracetamol and using multiple medications may lead to the ingestion of extra doses, resulting in liver damage.



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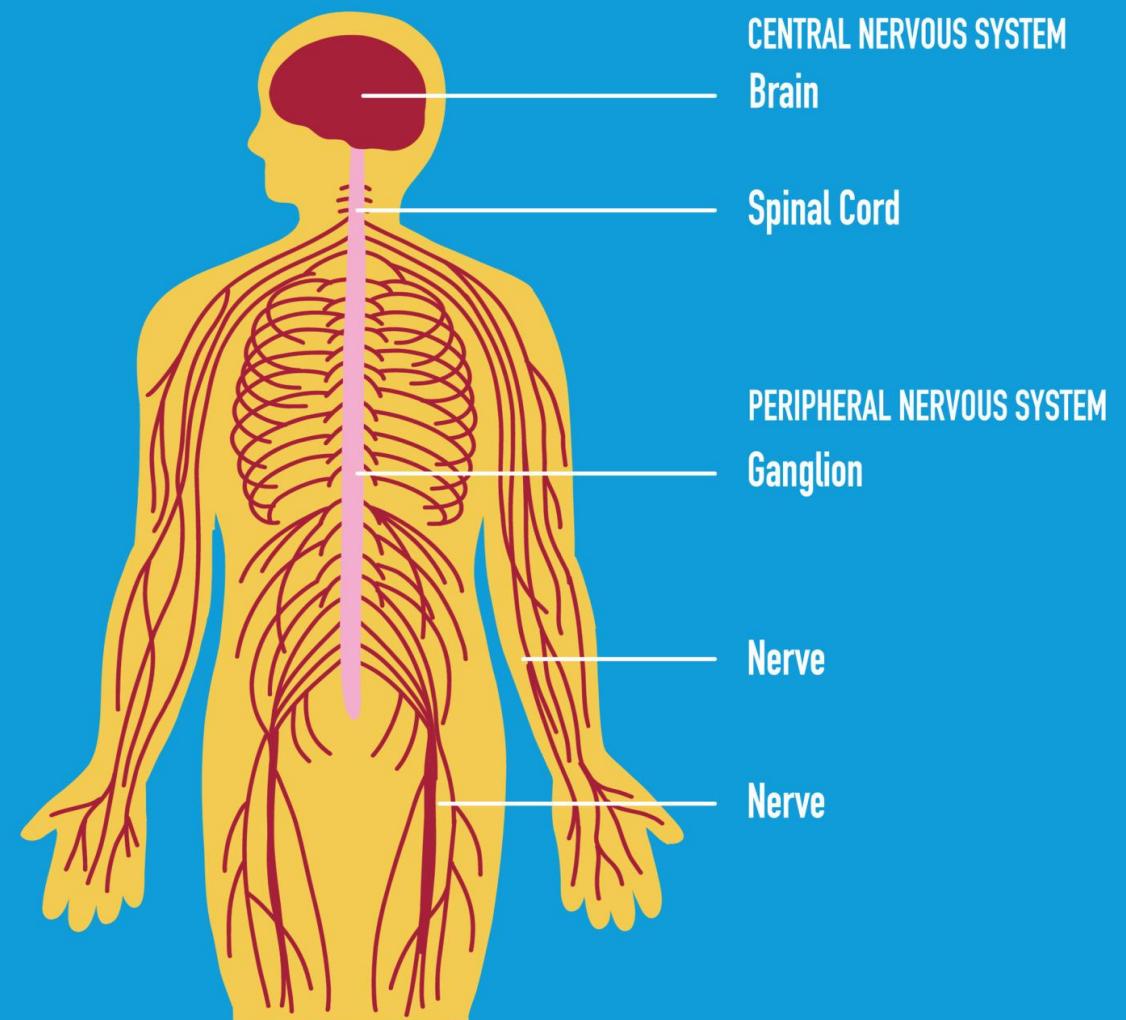
Pharmacology

M302

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NERVOUS SYSTEM



- **Chapter: Two**

- **Classification of The Nervous system**

- **The Autonomic nervous system**

- **Neurotransmitters**

- **Receptors**

- **The Parasympathetic system**

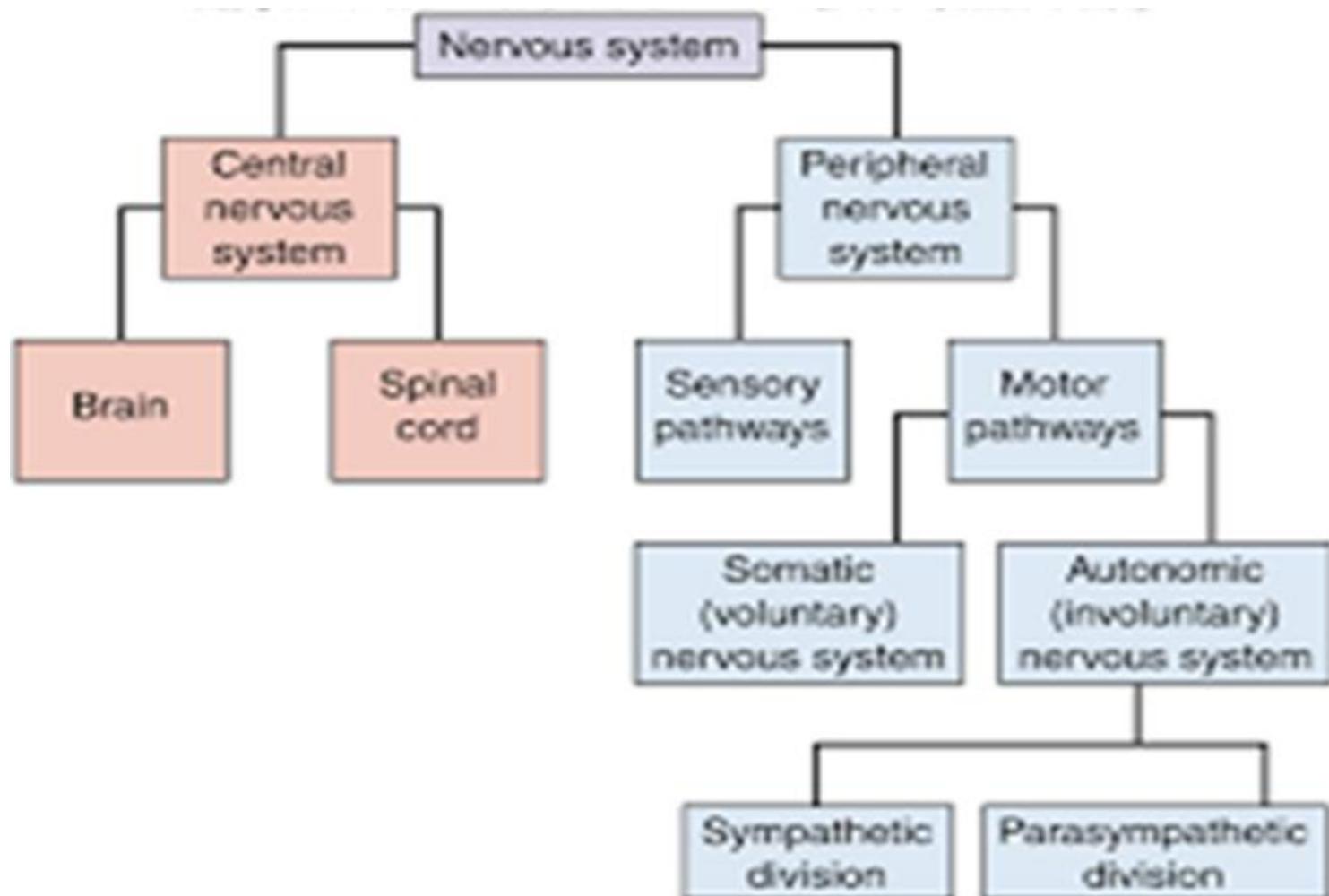
- **Parasympathomimetic**

- **Parasympatholytic**

- **The Sympathetic system**

- **Sympathomimetic**

- **Sympatholytic**



The Nervous system

Classification of the nervous system

1-Central nervous system

A-the brain.

B-Spinal cord.

2-Peripheral nervous system

It consist of nerves that emerge out from the brain and spinal cord.

Somatic nervous system: It is the part of the nervous system that controls the activities of voluntary reactions (skeletal muscle) in our body.

Autonomic nervous system: It is the part of the nervous system that controls the involuntary reactions (smooth muscle, cardiac muscle, endocrine and exocrine glands) in our body.

1-C.V.S (Heart & blood vessels)

2-Smooth muscles

- a. Eye
- b. Bronchi
- c. GIT
- d. Urinary Tract
- e. Sex organs

3-Glands

- a. Salivation
- b. Sweating

Classification of the autonomic nervous system

1-Sympathetic nervous system.

2-Parasympathetic nervous system.

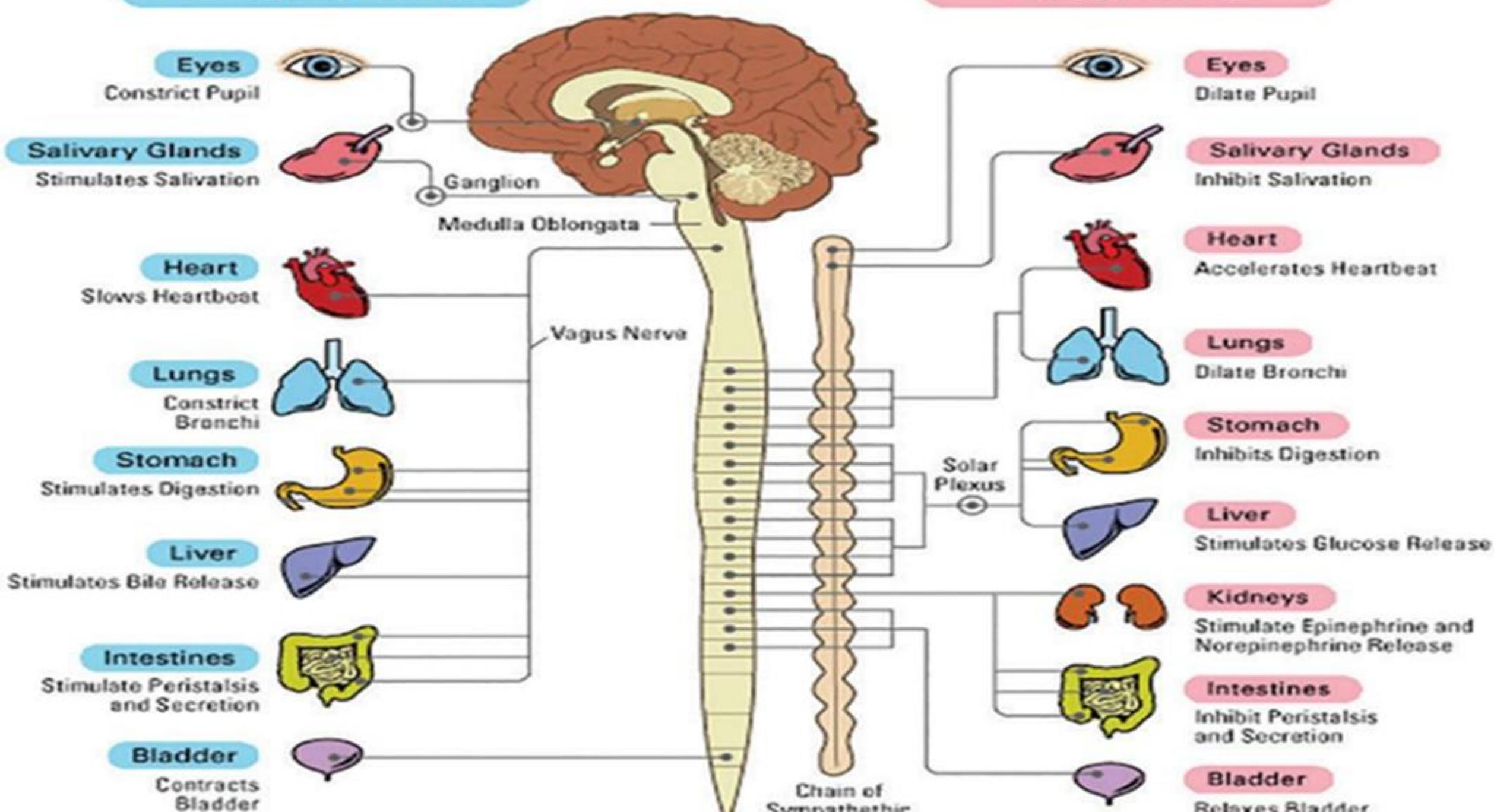
It is formed of 2 efferent neurons interrupted by a ganglion (preganglionic and postganglionic neuron).

Preganglionic neuron: originates from CNS and terminates on autonomic ganglia.

Postganglionic neuron: Originates from autonomic ganglia and terminates on the effector organ (muscle or gland).

Parasympathetic

Sympathetic



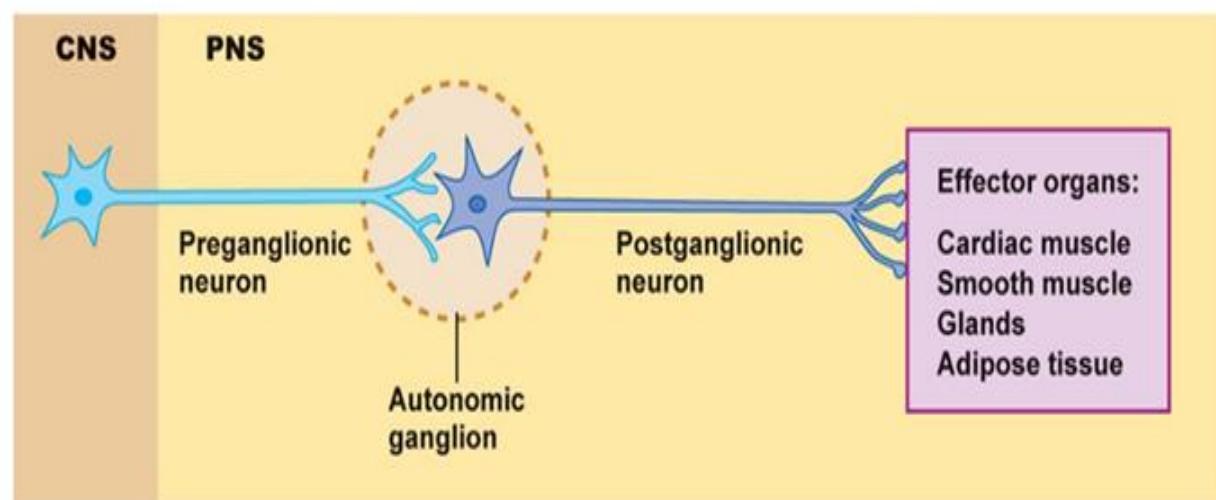
The autonomic ganglia

Collections of neural cells, outside CNS that act as a site of relay of autonomic nerves.

It is a site of relay: any autonomic nerve must relay in a ganglion before it supplies the target organ.

The neuron before it is named, **preganglionic** and the neuron after it is named, **postganglionic**.

The chemical neurotransmitter in the autonomic ganglia is **acetylcholine**.



Chemical transmission in the autonomic nervous system

The process by which nerve terminals stimulate an effector cell.

- Chemical neurotransmitters**

Chemical mediators, which are released at the nerve terminals to transmit the nerve impulse as acetylcholine, noradrenaline, adrenaline, dopamine and serotonin:-

1-Between pre and postganglionic fibers.

2-Between postganglionic fibers and effector tissues.

1-Acetylcholine

Site of release

a-All preganglionic neuron(sympathetic and parasympathetic).

b-All post ganglionic neuron of parasympathetic nervous system.

c-Postganglionic sympathetic fibers to blood vessels of skeletal muscle and sweat glands.

d-At the junction between motor nerves and skeletal muscle (neuromuscular junction).

Synthesis

Acetyl coenzyme A + choline by Choline acetyl transferase enzyme to give Acetylcholine.

Storage

Clear vesicles in synaptic knobs.

Release

Action potential then voltage gated Ca⁺⁺ channel opens that increase Ca⁺⁺ influx, and Ach are released by exocytosis.

Destruction of acetylcholine

After combining with its receptors (lock and key theory) and performing its action. Acetylcholine is rapidly destroyed by acetyl choline esterase enzyme into choline and acetate.

Two types of choline esterase exist:

1-True choline esterase present at the site of release of Ach.

2-Pseudo choline esterase present in the plasma.

- Receptors of acetylcholine (Cholinergic receptors)

1-Muscarinic receptors.

- They are present in all postganglionic parasympathetic and postganglionic sympathetic nerve fibers to blood vessels of skeletal muscle and sweat glands.
- They are stimulated by pilocarpine, and muscarine and blocked by atropine.

2-Nicotinic receptors

- They are present in all preganglionic parasympathetic and sympathetic (autonomic ganglia) and neuromuscular junction.
- They are stimulated by small dose of nicotine, and blocked by nicotine in large dose, and hexamethonium.

2-Noradrenaline

Site of release

1-All sympathetic postganglionic nerve fibers except, those to sweat glands and blood vessels of skeletal muscle.

2-Together with adrenaline, both are released as hormones from the adrenal medulla.

Synthesis

Phenylalanine convert to Tyrosine by hydroxylase.

Tyrosine convert to DOPA by hydroxylase.

DOPA convert to Dopamine by **decarboxylase**.

Dopamine convert to Noradrenaline by hydroxylase.

Noradrenaline convert to Adrenaline by **N-methyl transferase**.

Storage

Granulated vesicles in synaptic knobs.

Release

As acetylcholine.

Inactivation

1-Active reuptake into the vesicles of the nerve endings (50-80%).

2-Destruction by enzymes:-

a-Monoamine oxidase enzyme(MAO).

b-Catechol-O-methyl-transferase (COMT).

Adrenergic receptors

1-Alpha receptors (α_1 , α_2)

Stimulation of α_1 and α_2 produce excitatory effects except on the gastrointestinal system.

2- beta receptors (β_1 , β_2 , β_3)

β_1 : heart

β_2 : bronchi

β_3 : adipose tissue

Stimulation of beta receptors produce mainly inhibitory except heart, hormone and metabolism

	Adrenaline	Noradrenaline
Suprarenal medulla	80%	20%
Chemical transmitter	Only in CNS	CNS+PNS
strength	Stronger 5-10 times due to it's methyl group	
Action on α and β receptors	α and β equally	Stimulate α more than β

Parasympathomimetic (Cholinomimetics)

- **Definition:** drugs which stimulate muscarinic and nicotinic receptors.
- **Mode of action & classification:**

Directly acting cholinomimetics

I) Directly acting: stimulate muscarinic receptors directly

Choline esters	Cholinomimetic alkaloids
1. Acetylcholine (muscarinic and nicotinic)	1. Pilocarpine (only muscarinic)
2. Methacholine (only muscarinic)	2. Muscarine
3. Carbachol (muscarinic and nicotinic)	
4. Bethanechol (only muscarinic)	

II) Indirectly acting: "Anticholine esterase"

They inhibit choline esterase enzymes -- Ch.E. enzymes (true, pseudo) leading to accumulation of endogenous Ach.

a. <u>Reversible:</u> 1. Physostigmine 2. Neostigmine 3. Neostigmine substitutes	b. <u>Irreversible: organophosphorus compounds</u> 1. Di isopropyl fluorophosphate (DFP) 2. Echothiophate – can't pass BBB 3. Metriphonate 4. War gases: Sarin – Soman – Tabun
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- **Actions of Parasympathomimetic**

1. **Eye:**

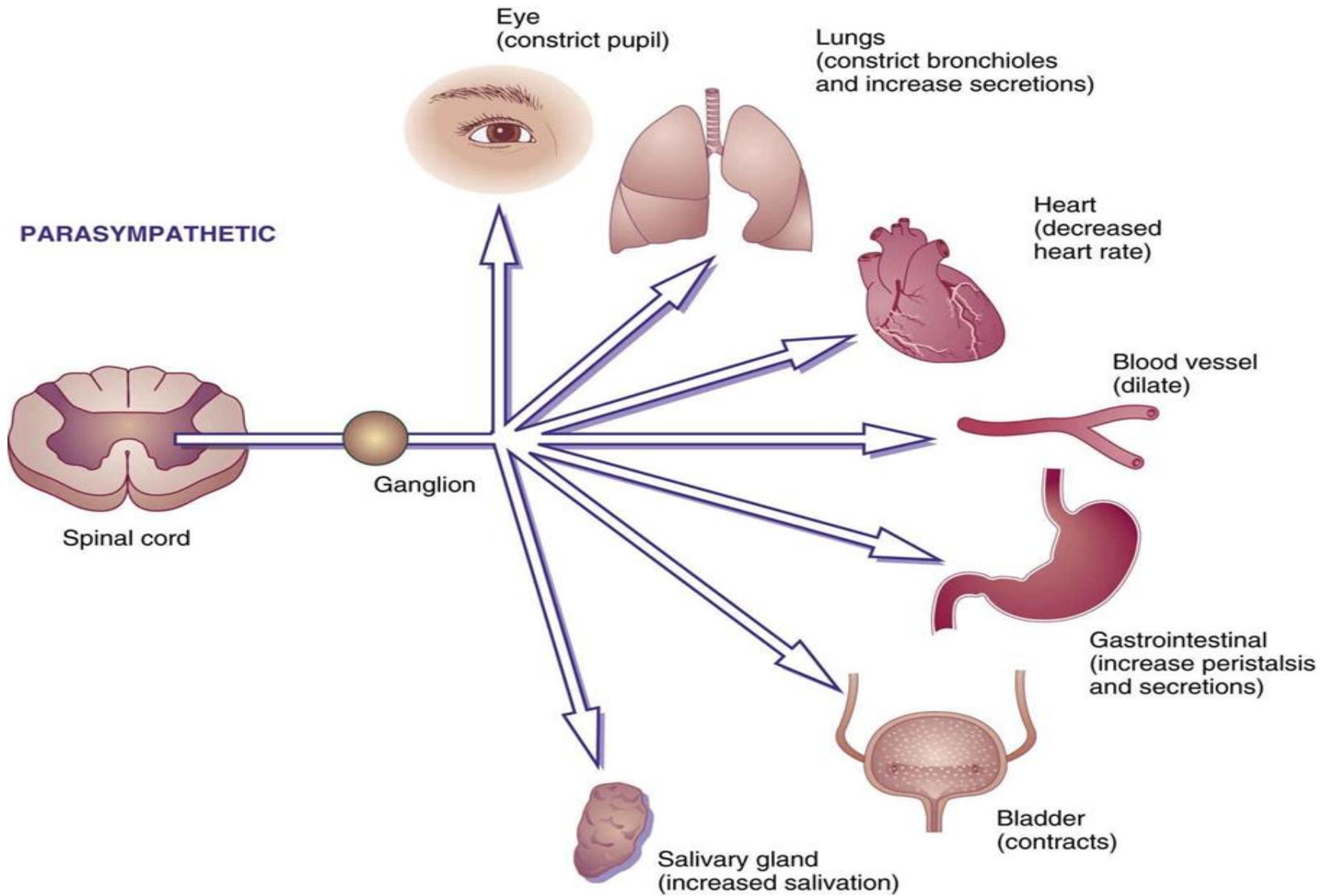
1. **Miosis: Contraction of constrictor pupillae muscle**
2. **Accommodation to near vision: Contraction of ciliary muscle**
3. **Decrease intraocular pressure: Increase aqueous drainage**

2. **CVS:**

- **Heart:**

1. **Decrease contractility**
2. **Negative chronotropic = Bradycardia = Decrease heart rate**
3. **Decrease atrio - ventricular (AV) conduction**

- **Blood vessels: Vasodilatation** **Blood pressure: Hypotension**



3- Bronchi: Bronchospasm, Increased bronchial secretions

4- GIT: Stimulation of gut motility and relaxation of sphincter- Increased gastric and salivary secretions - Nausea, Vomiting, Diarrhea and GI cramps

5-Urinary tract: Contract bladder and relax sphincter, so promotes urination

6-Secretions: Increased secretions of bronchial, salivary, gastric and lacrimal glands.

7-Neuromuscular junction (NMJ): Nicotinic Actions: Muscle twitches

8-Autonomic ganglia and Adrenal medulla: Nicotinic Actions: Increased secretions of catecholamines (noradrenaline and adrenaline)

- **Uses of Parasympathomimetics**

1. Treatment of dry mouth (Xerostomia) (Pilocarpine, Cevimeline)

2. **Eye:**

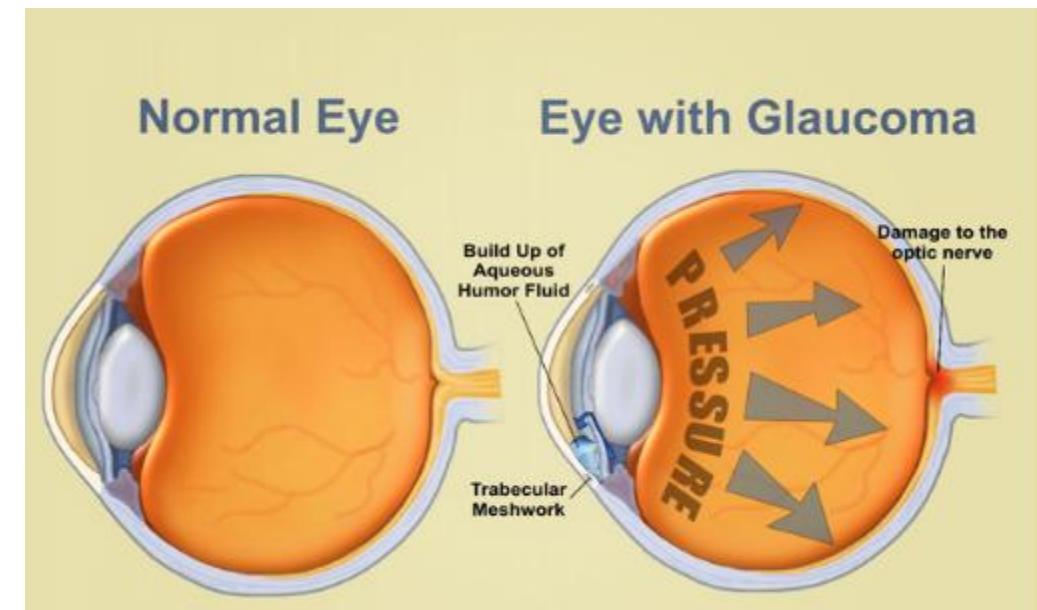
a. Used in glaucoma (Pilocarpine, Physostigmine)

b. Counteract action of mydriatics

3. Post operative paralytic ileus (Bethanechol, Neostigmine)

4. Urine retention (Postoperative and after spinal cord injury or disease)

(Bethanechol, Neostigmine)



5-Musculoskeletal:

- a. Treatment of myasthenia gravis (Neostigmine - Pyridostigmine)
- b. Reverse the paralysis caused by competitive neuromuscular blockers following surgery (Neostigmine - Edrophonium)
- c. Treatment of curare toxicity (Neostigmine)

6-Used in treatment of atropine poisoning (Physostigmine - Neostigmine).

7-Used in treatment of Alzheimer's disease (Anticholinesterases: Donepezil).

Side Effects and Contraindications of Parasympathomimetic

<u>Side Effects</u>	<u>Contraindications/cautions</u>
Nausea, vomiting and diarrhea Excessive salivation and sweating	1. Gastroduodenal ulcers
Urinary urgency	1. Urinary incontinence Mechanical urinary obstruction
Bronchoconstriction	Bronchial asthma
	Coronary insufficiency Hypotension Bradycardia
	Hyperthyroidism--Precipitates atrial fibrillation Never IV or IM --Severe bradycardia-- Antidote = Atropine

Indirect Acting Reversible Parasympathomimetic

They inhibit choline esterase enzymes -- Ch.E. enzymes (**true, pseudo**) leading to accumulation of endogenous Ach.

	Physostigmine	Neostigmine
Absorption	Complete absorption	Partial absorption from GIT
Distribution	Pass BBB	Cannot Pass BBB
Metabolism	Metabolized by cholinesterase enzyme	
Pharmacodynamics	Anticholinesterase ► Increased acetylcholine Muscarinic actions: Mainly on the eye Nicotinic actions: Muscle twitches	Muscarinic actions: Mainly on GIT and urinary tract
	-No direct action on skeletal muscles CNS stimulation: Convulsions in high dose	-Powerful muscle stimulation Nicotinic action Direct action on skeletal muscles



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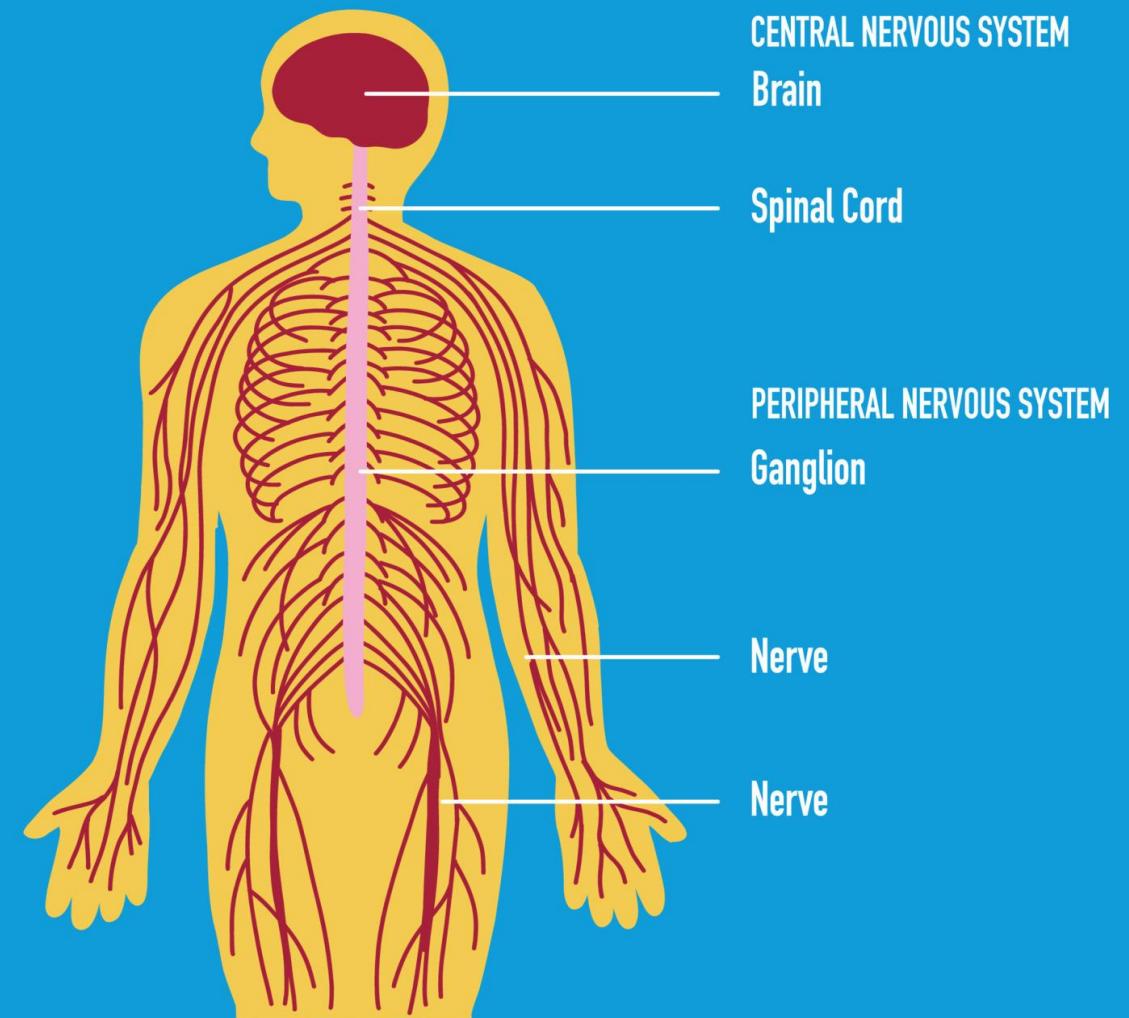
Pharmacology

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NERVOUS SYSTEM



Directly acting cholinomimetics

I) Directly acting: stimulate muscarinic receptors directly

Choline esters	Cholinomimetic alkaloids
1. Acetylcholine (muscarinic and nicotinic)	1. Pilocarpine (only muscarinic)
2. Methacholine (only muscarinic)	2. Muscarine
3. Carbachol (muscarinic and nicotinic)	
4. Bethanechol (only muscarinic)	

II) Indirectly acting: "Anticholine esterase"

They inhibit choline esterase enzymes -- Ch.E. enzymes (true, pseudo) leading to accumulation of endogenous Ach.

a. <u>Reversible:</u>	b. <u>Irreversible: organophosphorus compounds</u>
<ul style="list-style-type: none">1. Physostigmine2. Neostigmine3. Neostigmine substitutes	<ul style="list-style-type: none">1. Di isopropyl fluorophosphate (DFP)2. Echothiophate – can't pass BBB3. Metrifonate4. War gases: Sarin – Soman – Tabun5. Parathion – Malathion

	Physostigmine	Neostigmine
Absorption	Complete absorption	Partial absorption from GIT
Distribution	Pass BBB (blood brain barrier)	Cannot Pass BBB
Metabolism	Metabolized by cholinesterase enzyme	
Pharmacodynamics	<p>Anticholinesterase ► Increased acetylcholine</p> <p>Muscarinic actions: Mainly on the eye (eye drops: strong miotic action)</p> <p>Nicotinic actions: Muscle twitches</p>	
	<p>Muscarinic actions: Mainly on GIT and urinary tract (urine retention, paralytic ileus,)</p> <p>-No direct action on skeletal muscles</p> <p>CNS stimulation: Convulsions in high dose</p>	<p>-Powerful muscle stimulation</p> <ul style="list-style-type: none"> ➤ Direct action on skeletal muscles (myasthenia gravis)

- **Members of Neostigmine Substitutes:**

1. **Edrophonium:** Selective on skeletal muscles, short duration of action (5 min).
2. **Pyridostgmine:** Selective on skeletal muscles, longer duration of action (myasthenia gravis).
3. **Donepezil:** Selective for Alzheimer disease.

B -Irreversible Indirect Acting Parasympathomimetic (Anticholinesterases)

- Non-competitive irreversible inhibitors of cholinesterase enzyme.
- inhibition of cholinesterase enzyme -- accumulation of endogenous acetylcholine--
Muscarinic + Nicotinic actions
- Highly lipid soluble--can be absorbed from any site as intact skin -- Distribute to all tissues --can pass BBB Except Echothiopate-- CNS actions --Action ends by resynthesis of new enzymes ► Long duration of action (3 w.- 3 m)

- **Organophosphorus Poisoning**

***Causes:**

1. Inhalation of sprays or dust of insecticides
2. Skin contamination 3. Food contamination
4. War gases 5. Suicide attempts

***Mechanism of toxicity:**

Irreversible inhibition of acetylcholinesterase due to phosphorylation of the active site of the enzyme.



Dr. AM Fouad MD, PhD
Autonomic Pharmacology - Lecture 12: Indirect acting parasympathomimetics



Dr. AM Fouad MD, PhD



- This leads to accumulation of acetylcholine and subsequent over-activation of cholinergic receptors at the neuromuscular junctions and in the autonomic and central nervous systems
 - **Symptoms:**

1. Muscarinic symptoms

1. Miosis (Pinpoint pupil)
2. Salivation
3. Sweating
4. Lacrimation
5. Nausea and vomiting
6. Colic and diarrhea
7. Bronchospasm and increased bronchial secretions
8. Bradycardia and arrhythmia
9. Hypotension

2- Nicotinic symptoms

1. Muscle twitches and fasciculations
2. Weakness and paralysis of diaphragm and respiratory muscles

3- CNS symptoms

1. Headache 2. Dizziness 3. Restlessness

4-Confusion 5. Convulsions 6. Coma

7. Depression of respiratory centre

4- Intermediate syndrome

- Subacute (1-4 days) muscle weakness due to cholinesterase inhibition

5-Delayed polyneuropathy

1. Uncommon
2. Severe intoxication
3. Intermittent and chronic (1-2 weeks) contact with pesticides “Occupational exposure”
4. Weakness of arms and legs

***Cause of death:**

- 1. Respiratory failure 2. Hypotension

Prophylaxis	<ol style="list-style-type: none"> 1. Use gloves 2. Spray with the direction of wind 3. Proper washing of vegetables and fruits
Positioning	<p><u>Comatosed or vomiting</u></p> <ol style="list-style-type: none"> 1. Lateral 2. Head down 3. Neck extension <p>To reduce aspiration of secretions</p>
Care of respiration	<ol style="list-style-type: none"> 1. Airway 2. Breathing 3. Circulation
Decontamination	<ol style="list-style-type: none"> 1. Removal of all clothing 2. Washing skin with soap and water to prevent further absorption
Stomach wash	<p>If ingested insecticides</p> <ol style="list-style-type: none"> 1-Activated charcoal 2-Adsorption of toxin and reduce absorption
Atropine	<ol style="list-style-type: none"> 1. Large initial IV or IM dose (1 - 2 mg/ 5 -15 minutes) 2. Maintenance IV infusion 3. <u>Initial dose until target end points</u> <p>a- Dilated pupils b- Heart rate > 80 / min.</p>

Atropine

c-Systolic blood pressure > 80 mmHg

d-Clear chest with absence of wheezes

No effect on skeletal muscles

Cholinesterase regenerators (Oximes)

-Pralidoxime (PAM)

**-Di-acetyl- monoxime
(DAM)**

- 1. Reactivation of acetylcholinesterases**
- 2. Restoration of skeletal muscle strength**
- 3. Improving diaphragmatic weakness**
- 4. Protect enzyme from further inhibition**
- 5. Not used in poisoning with reversible anticholinesterases**

Anticonvulsants

1. Diazepam

2. Barbiturates

- PARASYMPATHOLYTICS

- Atropine

- Natural Belladonna alkaloid (also present in Datura).



- **Pharmacokinetics:**

- Absorption: from all sites except intact skin.
- Distribution : Passes BBB
- Metabolism: in liver
- Excretion: in urine (1/3 is excreted as such). Acidification ↑its excretion.

- **Pharmacodynamics:**

- **A- Parasympatholytic Action:**

- Atropine blocks the muscarinic by competition with A.Ch.
- It does not affect its release. (Inhibits Guanylate Cyclase enzyme, decrease cGMP).

I. **C.V.S:**

Heart: tachycardia due to blockage of the vagal tone to S.A. node..

Blood vessels:

- Therapeutic dose: No effect (most BV lack PS innervation).
- Large dose esp. in children == atropine flush (may be due to histamine release)

Blood Pressure:

- No significant action.
- Reverses hypotension of A.Ch, carbachol, Neostigmine (N & M).
- Abolishes hypotension of Methacholine, Bethanecol, Pilocarpine (M only)

II-S.M.F:

- 1. Eye:** increase IOP by local or systemic administration – duration of action of atropine on eye 7-10 days
- 2. Respiration:**
 - Bronchodilatation.
 - Reduce secretions (thick – viscid, difficult to expel).
- 3. GIT:**
 - Relax wall (antispasmodic) and constrict sphincters.
 - Reduce secretions (Antisecretory) --constipation.
- 4. Urinary:**
 - Relax wall and constrict sphincters of bladder (urine retention).
 - Relax ureter.



|

III-Secretions: Reduce all secretions (except milk, bile, urine)

↓ Salivary secretion (dry mouth) - ↓ Lacrimation - ↓ bronchial – ↓ gastric secretion.

↓ Sweat (atropine fever)

B- Local Anesthetic Action: mild

C- CNS: Both stimulant & depressant actions but mainly stimulants

Uses

- A- Parasympatholytic (general):

1-Preanesthetic medication.

- a. Counteract excess vagal tone during operation.
- b. ↓ Salivary s. (prevent bronchopneumonia) and ↓bronchial s. (prevent lung collapse).

2-Vagotonia (↑vagal tone): vasovagal attack, carotid sinus syndrome due to excess vagal tone.

3-Treatment of Physostigmine and organophosphorus compounds toxicity.

B-Parasympatholytic (Systems):

1.CVS: heart block (digitalis, infarction)

2.Eye: Fundus examination (derivatives are better).

- Iritis to prevent adhesions – cut recent adhesion alternatively with miotics.

3.Respiration: bronchial asthma – not preferred -- viscous secretion difficult to expel
(Ipratropium & tiotropium by inhalation are better)

4.GIT: intestinal colic, antiemetic, antidiarrheal, peptic ulcer.

5.Urinary: - Renal colic

- Nocturnal enuresis (Emepronium is a better derivative)

6.Secretion: hyperhidrosis (excess sweating)

7.CNS: Antiparkinsonian

Toxicity “Adverse Effects” = Datura Toxicity

A- Exaggerated Parasympatholytic effects

1. **CVS**: tachycardia.
2. **Eye**: mydriasis, blurred vision with ↑IOP (may precipitate glaucoma).
3. **GIT**: constipation.
4. **Urinary**: urine retention especially in prostatic patient.
5. **Secretion**: dry mouth and dry skin (atropine fever, atropine flush).

B- CNS: excitation, hallucination, convulsions followed by coma and depression of R.C. (cause of death)

- **Treatment of Atropine Toxicity:**

1. **Gastric lavage with tannic acid.**
2. **O₂ and artificial respiration.**
3. **Cold fomentation → ice bags.**
4. **Sedatives as diazepam**
5. **Physostigmine 0.5-1 mg SC / 3 hours (specific antidote),but used with caution.**

- **Contraindications:**

1. **Heart:** angina, arrhythmia.
2. **Eye:** glaucoma.
3. **GIT:** constipation, paralytic ileus.
4. **Urinary:** senile enlargement of prostate.
5. **Secretion:** fevers.

Antimuscarinic Drug	Main Indication
Ipratropium	Bronchial asthma
Pirenzepine	Peptic ulcer
Lomotil (atropine- diphenoxylate comb)	Diarrhea
Buscopan (hyoscine bromide)	Renal and intestinal colic
Oxybutinin	Acute cystitis
Tolterodine	Urine incontinence
Homatropin, Eucatropine	Eye fundus examination
Hyoscine	Motion sickness
Benztropine	Parkinson's disease

- **Skeletal Muscle Relaxants**

Classification

II-Paralytic drugs:

1- Neuromuscular blockers:

- A- Competitive
- B- Depolarizing

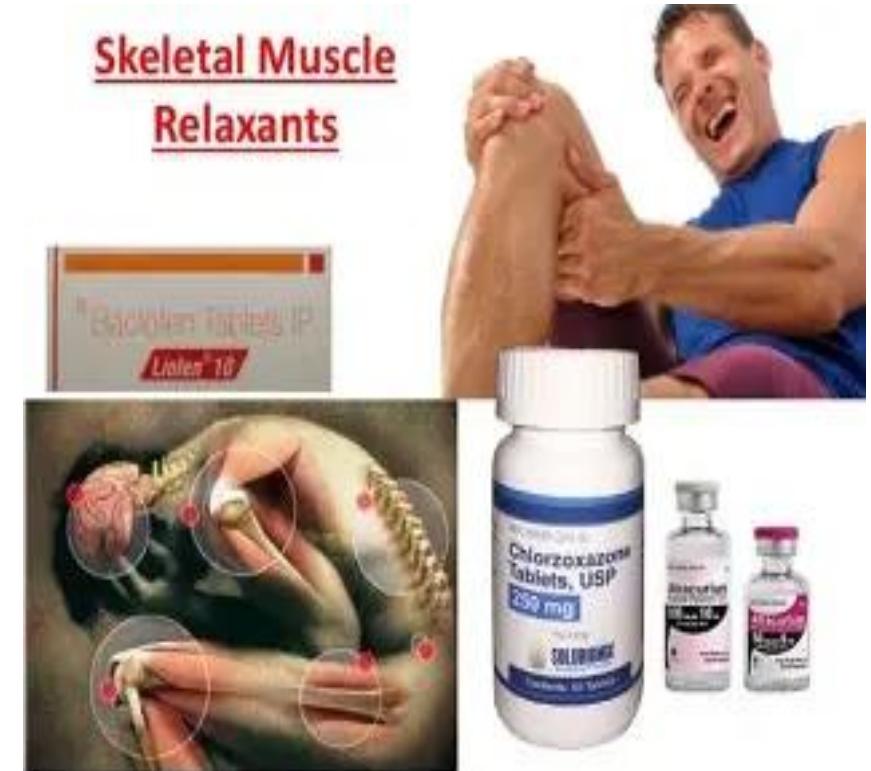
2- Botulinum toxin

II- Spasmolytic drugs:

1. Antispasmodic drugs:

1. Carisoprodol
2. Chlorzoxazone
3. Cyclobenzaprine
4. Orphenadrine
5. Methocarbamol
6. Idrocilamide (Topical)

Skeletal Muscle Relaxants



2-Antispasticity drugs:

A- Central:

1. Baclofen
2. Tizanidine
3. Diazepam
4. Gabapentin - Pregabalin
5. Pro gabide

B- Peripheral: Dantrolene

III-Experimental agents:

1. Inhibition of Acetylcholine synthesis:

- A- Hemicholinium
- B- Triethylcholine

2. Inhibition of Acetylcholine release:

- A- Excess Mg
- B- Lack of Ca

3. Inhibition of Acetylcholine storage → Vesamicol

Neuromuscular Blocking Drugs

(Parasympatholytics)

Classification

I. Competitive NMBs:

- 1. Tubocurarine (Curare)**
- 2. Atracurium**
- 3. Cisatracurium**
- 4. Pancuronium**
- 5. Rocuronium**

II. Depolarizing NMB → Succinylcholine

- Basic Pharmacology

- I. **Kinetics:**

- **Absorption:** Inactive orally so they must be administered parenterally
 - **Distribution:** Poorly lipid-soluble which limits entry into the CNS

-

- I. **Therapeutic Uses:**

- 1. **Surgical relaxation:** esp. intraabdominal & intrathoracic procedures.
 - 2. **Tracheal intubation:** by relaxing the pharyngeal & laryngeal muscles.
 - 3. **Control of ventilation:** for critically ill patients and in the ICU
 - 4. **Treatment of convulsions:** severe tetany or status epilepticus

-

- **1-Competitive NMBs**

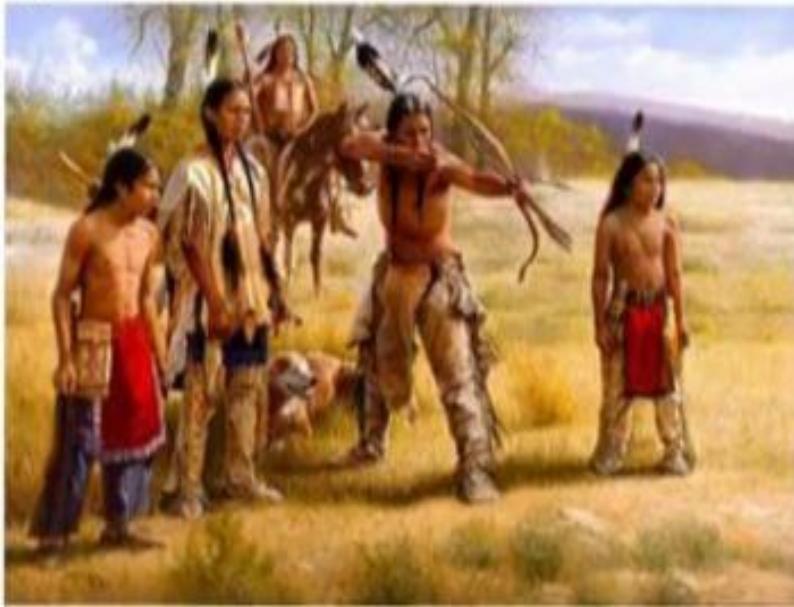
- **Mechanism of action:**

- Competitive neuromuscular blocking drugs compete with acetylcholine (ACh) at the nicotinic receptor on the post-synaptic membrane of the motor endplate.
- They block the action of ACh and prevent depolarization --paralysis
- Larger muscles e.g. abdominal, trunk, and diaphragm are more resistant to neuromuscular blockade than smaller muscles e.g. facial, foot and hand.
- The diaphragm is usually the last muscle to be paralyzed.
- Recovery of muscles usually occurs in reverse order.

Skeletal Muscle Relaxants

➤ History:-

- During the 16th century, European explorers found the Native American in Amazon Basin of South America were using Curare, an arrow poison that produced skeletal muscle paralysis, to kill animals.
- This poison, known today as Curare. Its active ingredient, Tubocurarine, (neuromuscular blocker).
- Tubocurarine block nicotinic acetylcholine receptors, at the neuromuscular junction.
- By 1943, neuromuscular blockers became used as muscle relaxants in the anesthesia and surgery.



Drug	Elimination	Duration (minutes)	Cardiac M ₂ receptors	Histamine release	Notes
1- Tubocurarine	Kidney	> 50	None	Moderate	Prototype
2- Atracurium	Spontaneous 'Hofmann elimination'	20 - 35	None	Slight	
3- Cisatracurium	Mostly spontaneous	25–45	None	None	
4- Pancuronium	Kidney	>35	Moderate Block	None	
5- Rocuronium	Liver (80%) and kidney	20–35	Slight Block	None	1- Least potent 2- Fastest onset 3- Shortest action

Reversal of Competitive NM Blockade

1- Neostigmine, Pyridostigmine & Edrophonium:

- Mechanism: AchE inhibition →Ach accumulation →displace the blocker

- **Drug Drug Interactions:**

1. **Potentiation:**

1. **General anesthetics:**

2. **Local anesthetics**

3. **Quinidine**

4. **Aminoglycosides**

2. **Antagonism → Cholinesterase inhibitors: e.g. neostigmine and pyridostigmine**

2- Depolarizing NMB = Succinylcholine

Mechanism of action:

1. Phase I:

- **Succinylcholine binds to activates Nm receptors →muscle contraction**
- **Succinylcholine slowly dissociates from the nicotinic receptors persistent depolarization →paralysis**
- **Effect of neostigmine →worsening**

2. Phase II:

- **Prolonged exposure to succinylcholine →receptor desensitization**
- **Effect of neostigmine →recovery**
-

- **Duration of action** → less than 10 minutes due to rapid hydrolysis by plasma pseudocholinesterase enzyme

•

- **Adverse effects:**

1. **Cardiovascular effects:**

- Transient bradycardia may occur due to M₂ stimulation

2. **Prolonged apnea:**

- Cause: congenital or acquired deficiency of pseudocholinesterase enzyme

- Treatment:

- Phase I → Fresh frozen plasma, Phase II → Neostigmine preceded by atropine

3. **Malignant hyperthermia**

4. **Hyperkalemia**

5. **Increased IOP**

6. **Increased intragastric pressure**

- 7- **Muscle pain**



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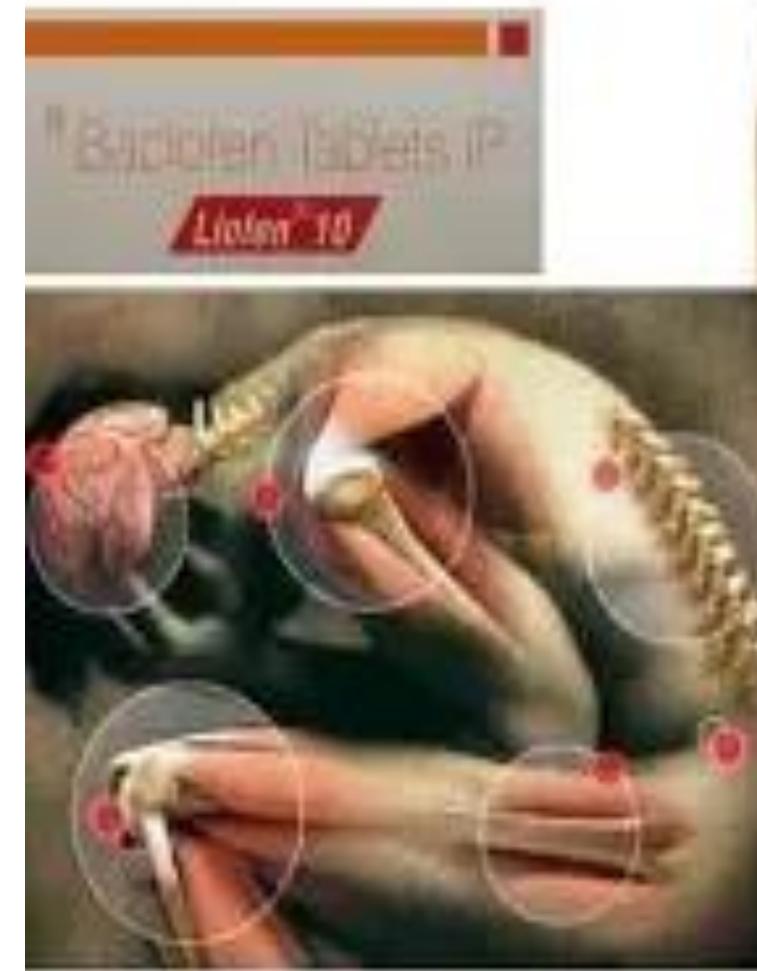
Pharmacology

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Skeletal Muscle Relaxants



- **Antispasmodic drugs**

- These drugs are used mostly for muscle spasm and muscle hyperactivity, which occurs as a secondary phenomenon in association with musculoskeletal pain.

1. **Carisoprodol:**

- CNS depression→ Sedation, alteration pain perception.
- A prodrug of meprobamate (anxiolytic agent → abuse, dependence)
- Carisoprodol is a centrally acting skeletal muscle relaxant and it is thought to block interneuronal activity by activating GABA-A receptors in the descending reticular formation and spinal cord.
- Carisoprodol is FDA approved for relief of muscle spasm associated with acute musculoskeletal conditions.

- The common side effects of carisoprodol are drowsiness, and it can cause **psychological and physical dependence**.
- Used with caution in renal and hepatic patients.



2- Cyclobenzaprine:

- Cyclobenzaprine is an antagonist at one or more of the serotonin 5-HT₂ receptor subtypes and thus it reduces muscle tone via its antagonism of 5- HT_{2C} receptors.

-Its site of action is thought to be in the brainstem level of the central nervous system rather than the spinal cord level.

- Cyclobenzaprine's chemical structure, dosing, and side-effect profile are very similar to other tricyclic antidepressants (TCAs), even though it is not classified as such.**
- Like the TCAs it has a strong anticholinergic effects and long elimination half-life (12–24 hours).**
- Cyclobenzaprine is FDA approved for relief of muscle spasm associated with acute, painful musculoskeletal conditions.**

3. Methocarbamol:

- Methocarbamol acts centrally.
- Although the exact mechanism of action is not fully understood, it is thought to be due to methocarbamol's sedative properties (General CNS depression).
- Used as adjunctive to rest and physical therapy in the management and treatment of acute musculoskeletal pain.
- **Side effects:** Dizziness, drowsiness, Lightheadedness.
- **Formulation:** Oral and Parenteral.
- **Black, brown or green urine are possible.**



4. Orphenadrine:

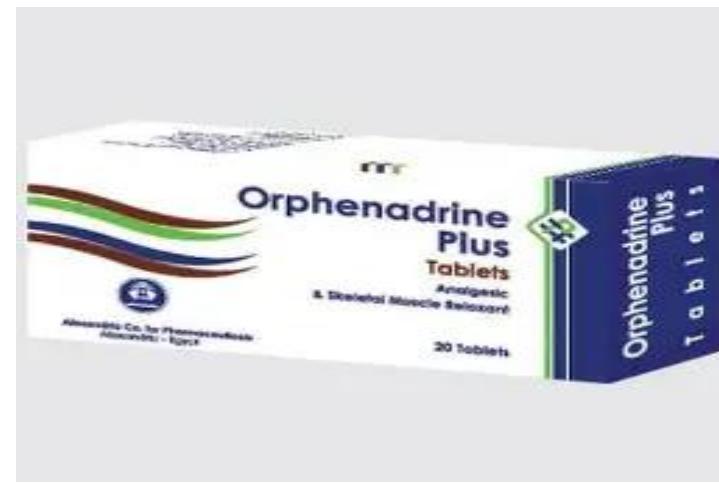
It has muscle-relaxant and analgesic properties.

- **Mechanism of action:**

Unknown but may be due to anticholinergic activity in the brain stem

- **Uses:**

1. **Acute musculoskeletal conditions as adjunctive to rest and physical therapy.**
 2. **Parkinsonism**
-
- **The main side effects are anticholinergic in nature (drowsiness, urinary retention, dry mouth, constipation)**



5. Chlorzoxazone:

- Although its exact mechanism of action is unknown, chlorzoxazone appears to act at the spinal cord and subcortical levels of the brain to inhibit multisynaptic reflex arcs involved in producing and maintaining muscle spasms. Used in combination with analgesic as ibuprofen.
- The main side effects of chlorzoxazone are dizziness, drowsiness and rare cases of **hepatotoxicity**.

6. Idrocilamide:

- Used as a topical cream to treat lumbago and other kinds of muscular pain.
- It acts intracellularly by decreasing sarcoplasmic reticulum calcium release

- **Antispasticity drugs**

1. **Baclofen**

- **Mechanism of action:**
- Baclofen is GABA-B agonist.



- **Actions:**
- 1. **Antispasticity effect:**

- Presynaptic: Inhibit release of glutamate by the upper motor neuron nerve terminal ($\downarrow\downarrow$ Ca)
- Postsynaptic: inhibits spinal lower motor neuron (open K channels).
- Used in muscle spasticity in spinal cord injury, cerebral palsy, multiple sclerosis



2. Analgesic effect:

- Reduces pain in patients with spasticity, by inhibiting the release of substance P (neurokinin-1) in the spinal cord.

3. Convulsant effect: increases seizure activity in epileptic patients

- **Adverse effects:**
- The main side effects include drowsiness, confusion, dizziness, and weakness.
- There is a risk of seizures and hallucinations if this medication is **withdrawn abruptly**, so it should always be tapered off slowly.
- Used with caution in impaired renal function.

2. Tizanidine

- **Mechanism of action:**
 - Chemically related to clonidine, tizanidine is an α -2 agonist.
-
- **Actions:**
 - Antispasticity effect → acts presynaptic → stimulate presynaptic α_2 receptors to decrease glutamate release from corticospinal and sensory nerve terminals.
 - **Adverse effects:**
1. Drowsiness
 2. Hypotension
 3. Dry mouth
 4. Hepatotoxicity (monitor liver function tests)
 5. Abrupt discontinuation → rebound hypertension.



- **Botulinum toxin (Botox)**
- **Mechanism of action:** (Peripheral action)
- Block nerve function by inhibition Ach release from neuromuscular junction this cause skeletal muscle paralysis for 3 – 6 months.

Route of administration: injected locally into the muscle

Therapeutic Uses:

1. Spasticity, Dystonia
2. Blepharospasm and strabismus
3. Overactive bladder
4. Prevent development of wrinkles by paralyzing muscles of the face

3. Diazepam



- **Mechanism of action:**
- Benzodiazepines facilitate the action of GABA in the spinal cord.
- **Spasmolytic effect:**
- Postsynaptic: inhibits spinal lower motor neuron.
- They produce sedation at the doses required to reduce muscle tone.
- Effective for short term use in muscle spasticity and muscle spasm.

4. Gabapentin – Pregabalin

- **Gabapentin** is antiepileptic drug that has shown considerable promise as a spasmolytic agent in several studies involving patients with multiple sclerosis.
- **Pregabalin** is a newer analog of gabapentin that may also prove useful in relieving painful disorders that involve a muscle spasm component.

- Direct acting skeletal muscle relaxant

6. Dantrolene

- **Mechanism of action:**
- Dantrolene interferes with the release of calcium through this sarcoplasmic reticulum calcium channel by binding to the ryanodine receptor (RyR1) and blocking the opening of the channel.
- Dantrolene reduces skeletal muscle strength by interfering with excitation contraction coupling in the muscle fibers.

- **Therapeutic Uses:**

1. **Chronic muscle Spasticity:** oral
2. **Malignant hyperthermia:** IV



- **Adverse effects:**

1. **Generalized muscle weakness**
2. **Sedation**
3. **Hepatitis**

Dantrolene Sodium for Injection, USP

Sterile Lyophilized Powder



Dantrolene Sodium for Injection, USP is now available from Hikma Canada Limited.

No.	Description	Strength	Units Per Pack	DIN	Pack Bar Code	Unit of Use Bar Code
0041AL01	Clear Glass Vial	20 mg per vial	6	02529998	837641001376	(01)00837641011375

SKELETAL MUSCLE RELAXANT
FOR INTRAVENOUS USE ONLY
PRESERVATIVE FREE
THE VIAL STOPPERS ARE NOT MADE WITH
NATURAL RUBBER LATEX

Each vial contains: 20 mg dantrolene sodium, 3000 mg mannitol, and sodium hydroxide (to adjust pH)



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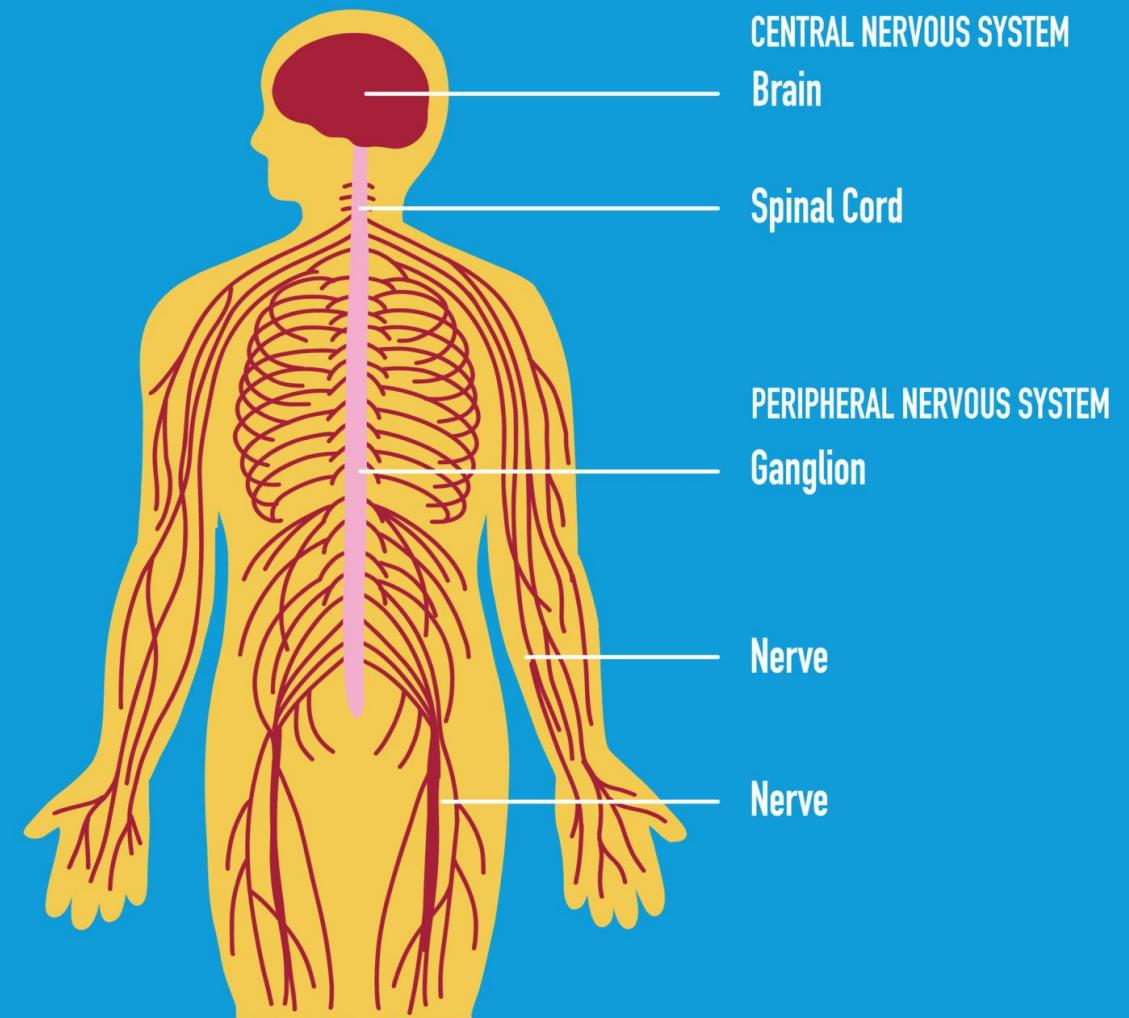
Pharmacology

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NERVOUS SYSTEM



Sympathomimetics

Catecholamines and Non-catecholamines

Catecholamines → Contain a Catechol nucleus

Natural	Synthetic
Adrenaline	Isoprenaline
Noradrenaline	Dobutamine
Dopamine	

Non-Catecholamines

CNS Stimulants:

- Ephedrine, Amphetamine, Metamphetamine

• Adrenaline=Epinephrine

- Source →Natural: synthesized and secreted by the adrenal medulla.
- Chemistry: - Adrenaline is a catecholamine.
- Storage:

- Adrenaline is light sensitive and easily oxidized in air to adrenochrome (pink and toxic) →stored in dark ampoules or transparent ampoules where air is replaced by nitrogen).

- Pharmacokinetics

1- Absorption

- Not absorbed orally:

1. Rapidly metabolized in intestinal cells and liver MAO & COMT enzymes → VMA (inactive metabolite).
2. VC of GIT mucosa → limit absorption

2- Distribution

- Catecholamines are water soluble → don't pass the BBB easily.

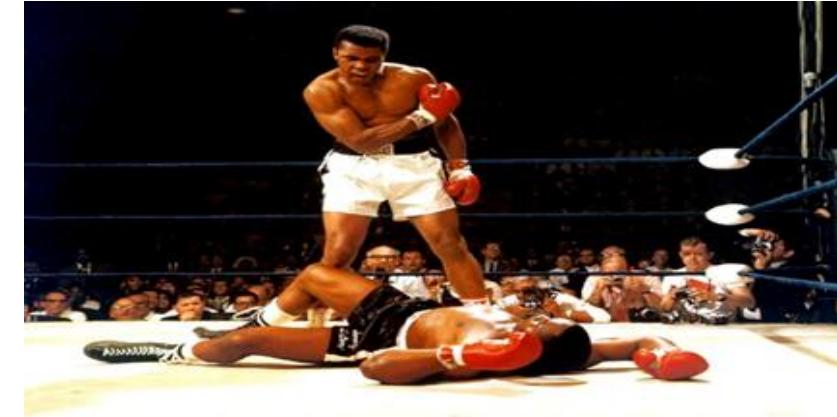
3- Elimination

1. Liver metabolism: major fate (80%) → VMA
2. Reuptake: 18% → Tissues & Neurons
3. Renal excretion: minor fate 2% excreted unchanged in urine + VMA

Pharmacodynamic

1-The head and neck

- a-Dilatation of the pupil by contraction of the dilator pupillary muscle (Mydriasis).**
- b-Exophthalmos (Protrusion of the eye ball).**
- c- Vasoconstriction of the blood vessels of salivary glands and little viscous and concentrated secretion.**
- d-The cerebral blood flow is increased and the mental alertness is increased.**
- e-Vasoconstriction of skin blood vessels.**
- f-Sweating.**



2-Chest

a-Heart

- Increase heart rate
- Increase force of contraction.
- Increase oxygen consumption by the heart.
- Vasodilation of coronary blood vessels.

b-Lung

- Vasoconstriction of the blood vessels of the lung.
- Relaxation of the bronchial smooth muscle causing bronchial dilation.

3-Abdominal viscera

- Glycogenolysis in the liver → increase blood glucose level.
- Lipolysis → increase free fatty acid liberation.
- Decreased secretion and motility of stomach and intestine.

- Vasoconstriction of abdominal blood vessels.
- Secretion of adrenaline and noradrenaline from adrenal medulla.
- Squeezing of splenic capsule → pouring of stored blood into the circulation.

4-Pelvis

a-Retention of urine by:

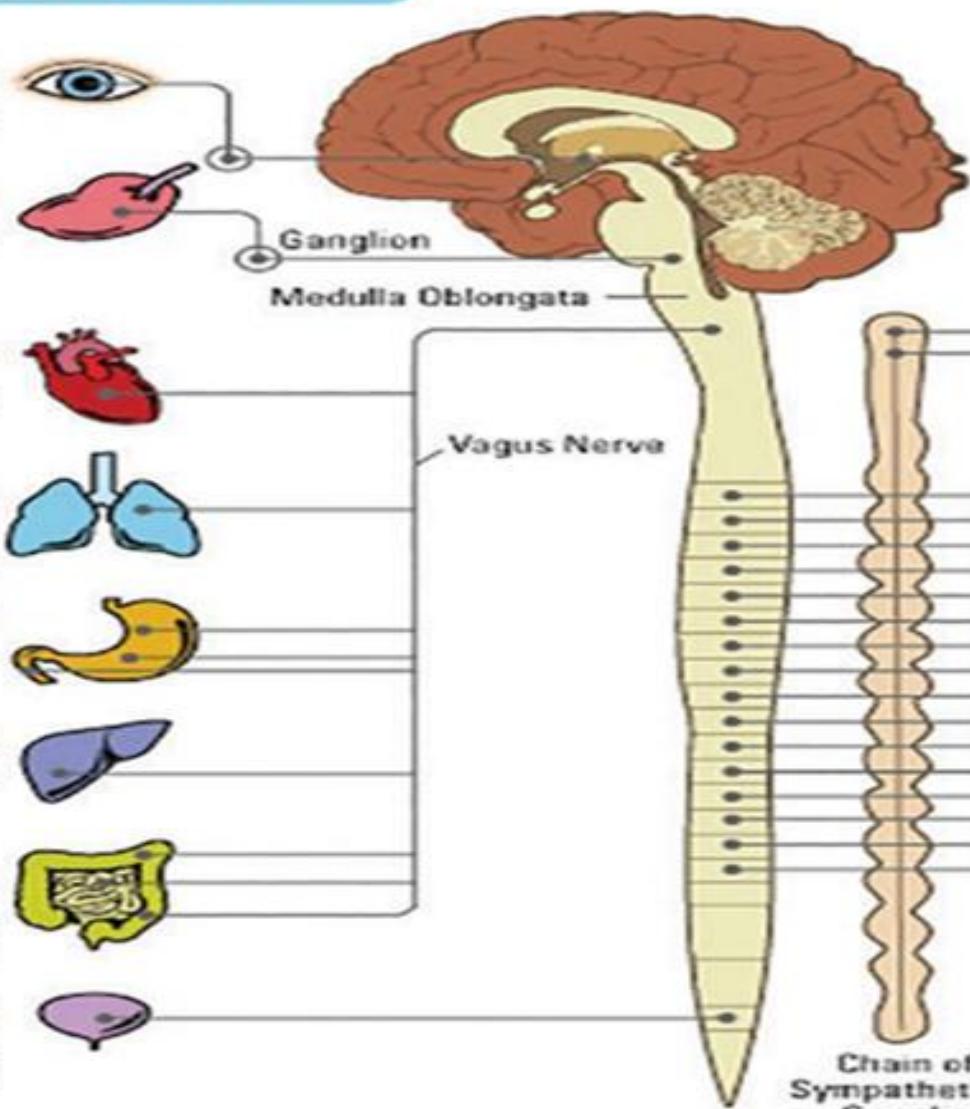
- Relaxation of wall of urinary bladder.
- Contraction of internal urethral sphincter.

b-Retention of stool by:

- Relaxation of wall of anal canal.
 - Contraction of internal anal sphincter.
- c-Vasoconstriction of blood vessels of external genitalia.

Parasympathetic

- Eyes Constrict Pupil
- Salivary Glands Stimulates Salivation
- Heart Slows Heartbeat
- Lungs Constrict Bronchi
- Stomach Stimulates Digestion
- Liver Stimulates Bile Release
- Intestines Stimulate Peristalsis and Secretion
- Bladder Contracts Bladder



Sympathetic

- Eyes Dilate Pupil
- Salivary Glands Inhibit Salivation
- Heart Accelerates Heartbeat
- Lungs Dilate Bronchi
- Stomach Inhibits Digestion
- Liver Stimulates Glucose Release
- Kidneys Stimulate Epinephrine and Norepinephrine Release
- Intestines Inhibit Peristalsis and Secretion
- Bladder Relaxes Bladder

Schema Explaining How Parasympathetic and Sympathetic Nervous Systems Regulate Functioning Organs

Therapeutic uses

- **A- Local uses:**

1. Prolongation of action of local anesthetics: given with them S.C. to delay absorption.
2. Hemostatic in epistaxis as nasal pack.
3. Decongestion of mucous membrane of the nose & the eyes
4. Acute bronchial asthma inhalation

B-Systemic uses:

1. Suppression of Allergy

Adrenaline is a physiological antagonist of histamine (acting on 2 different receptor sites).

Histamine (bronchoconstriction, decrease BP).

Adrenaline (bronchodilator, increase BP).

2. CVS: Cardiac resuscitation given intracardiac in cardiac arrest.

3. Respiratory system: Bronchial asthma (S.C.).



Side Effects	Contraindications
<p>Alpha</p> <ol style="list-style-type: none"> 1. Hypertension & cerebral hemorrhage. 2. If given with local anesthesia in fingers or toes → gangrene. 	<ol style="list-style-type: none"> 1. Hypertension. 2. with local anesthesia in fingers or toes .
<p>Beta</p> <p>3- Tachycardia, palpitation, arrhythmia.</p>	<p>3- Heart ischemia, arrhythmia</p> <p>4- Hyperthyroidism</p>

- **Noradrenaline (NA)**

- **Norepinephrine (α + Weak β_1)**

- Natural sympathomimetic catecholamine.
- Chemical transmitter at post-ganglionic sympathetic NE.
- Oxidized to adrenochrome on exposure to light.

- **Pharmacokinetics (ADME):-**

Absorption: oral ineffective- Not given SC or IM because of its strong vasoconstrictor action → Necrosis. So, it is given only by IV infusion.

- **Pharmacodynamics:**

- 1. Sympathomimetic: α + weak β_1 acts directly, rapid onset, short duration

The effect on beta₁ is masked by the reflex vagal stimulation.

Blood vessels: Vasoconstriction of skin blood vessels.

BP: increase both systolic & diastolic (increase PR).

- **Therapeutic uses**

Acute hypotensive state: during spinal anaesthesia, shock.

IV infusion 1/1000 diluted in saline or glucose.

BP + ECG monitor are frequently done.

Don't stop infusion suddenly to avoid sudden ↓ of BP

Side Effects	Contraindications
<p>a: 1- Hypertension & cerebral hemorrhage.</p> <p>2- If given with local anesthesia in fingers or toes → gangrene.</p>	<ol style="list-style-type: none">1. Hypertension.2. with local anesthesia in fingers, toes .

• DOPAMINE

(Dopaminergic + β -1 + α)

Sympathomimetic Catecholamine.

IV infusion rate	Receptors	Effect
Low (2-3 μ /kg/min)	* D1 (in renal, coronary, cerebral & mesenteric BV)	-VD → decrease PR -increase Renal blood flow & urine output
Moderate (5-8 μ /kg/min)	β 1	+ve inotropic >+ve chronotropic (increase CO and systolic BP)
High (10-12 μ /kg/min)	Alpha	Generalized VC

- NB. **IV infusion, slowly**
- ECG monitoring
- stop gradually
- **Therapeutic uses:**
- **Shock:** Cardiogenic, hemorrhagic, hypovolemic.
- **Heart Failure:** especially if with hypotension

DOBUTAMINE

- **(Selective B1 + Weak α)**
- Synthetic sympathomimetic catecholamine related to isoprenaline.
 - **Pharmacodynamics:**
 - Selective β-1 stimulant (+ weak α).
 - ↑force of contraction without ↑HR (more +ve inotropic than chronotropic effect).

- **Pharmacotherapeutics:**

- **Preparations & dose:**

- **IV infusion, 2.5-15 µ/kg/min. (same precautions as dopamine).**

- **Take care:**

- **ECG monitoring.**

- **Stop gradually.**

- **Measure BP & urine output.**

- **Give fluid before dopamine.**

- **Therapeutic uses:**

- **Shock: Cardiogenic (due to myocardial infarction).**

- **Heart Failure: especially if accompanied with hypotension.**

Isoproterenol (Isoprenaline)

- **Source** → Synthetic catecholamine
- **Mechanism of action:** Isoproterenol stimulates β_1 & β_2

- **Therapeutic uses:-**
- Heart Block: not commonly use and not of first choice
- Bronchial asthma: also, not commonly use and not of first choice
- Rarely used due to its nonselectivity.

Other Sympathomimetics

Alpha - Agonists			
α1- Agonists		α2- Agonists	
1- Vasopressors	2- Nasal Decongestants	3- Anti-HT	4- Muscle relaxants
1- Noradrenaline Phenylephrine Ephedrine	1- Oral: Phenylpropanolamine 2- Local (nasal drops) - Phenylpropanolamine - Naphazoline - Tetrahydrozoline - Xylometazoline	Clonidine = α2B	Tizanidine = α2A
Uses: - Acute hypotension	Uses: 1- Rhinitis 2- Cold 3- Sinusitis	Uses: - Hypertension	Uses: - Skeletal muscle spasm.
Beta - Agonists			
β1- Agonists	β2- Agonists		
1- Cardiac Stimulants		2- Vasodilators	3- Bronchodilators
1- Non-selective: - Adrenaline - Isoprenaline 2- Selective β1: - Dobutamine - Dopamine	Salbutamol	Salbutamol	4- Uterine relaxants
			Ritodrine



THANK
YOU

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- **SYMPATHETIC DEPRESSANTS (Sympatholytic)**

- **Adrenergic receptor blockers:**
- A- Alpha adrenergic blockers → e.g. phentolamine.
- B- Beta adrenergic blockers → e.g. propranolol.
- C- Alpha & Beta adrenergic blockers → e.g. labetalol.
- **Drugs acting centrally stimulating presynaptic-alpha2 receptor (alpha2 agonists):**
- Inhibit noradrenaline release.
- Clonidine, guanfacine and α-methyldopa.

- **ALPHA-BLOCKERS**

- Most α - Blockers block alpha-receptors mostly in blood vessels so produce vasodilatation
- The ones most commonly used are Selective α 1-blockers: prazosin, doxazosin (long duration of action).
- Tamsulosin (selective α 1A blocker) is more effective.

THERAPEUTIC USES OF ALPHA-BLOCKERS

Selective α blocker: in primary hypertension.

Peripheral vascular diseases.

Reverse VC: caused by leakage of NA. during IV infusion

Benign prostatic hyperplasia (BPH): antagonize smooth muscle contraction in enlarged prostate by selective α-blocker as **prazosin, doxazosin**

Common side effect: first dose syncopal syndrome.

- Beta Blockers

- Classification of beta blockers:

Non selective blocker $\beta_1 \& \beta_2$	Selective blocker $\beta_1 > \beta_2$	Selective blocker β_2	Block β & α_1
1. Propranolol	1. Metoprolol	Butoxamine	- Labetalol
2. Nadolol	2. Atenolol	(not used)	- Carvedilol
3. Oxprenolol	3. Acebutolol	only for academic	- Medroxalol
4. Pindolol	4. Bisoprolol	interests	- Bucindolol
5. Sotalol	5. Nebivolol		
6. BB on eye: Timolol, betaxolol, levobunolol, carteolol	6. Esmolol		

- Uses of Beta-Blocker

- I-C.N.S:

1. Antianxiety (antagonize somatic manifestation of anxiety).
2. Reduce tremors. Beta blockers can be used for tremors due to Parkinsonism or sympathetic overactivity.
3. Migraine prophylaxis

-

- II. Eye:

- Open angle glaucoma:

- Timolol eye drops - decrease IOP (decrease aqueous humor without affecting pupil size)

III-C.V.S:

Heart:

1. Angina pectoris prophylaxis(stable or atherosclerosis) (in between attacks):

- Reduce work of the heart and O₂ consumption.
- Reduce exercise. • Reduce BP. • Reduce anxiety.
- BB are used in angina due to coronary atherosclerosis & not in vasospastic

2. Acute phase of myocardial infarction - to:

- Reduce complications especially arrhythmia by antiarrhythmic action +
Blockade of adrenaline induced hypokalemia.

3. Arrhythmia: atrial and ventricular secondary to sympathomimetics, thyrotoxicosis, digitalis

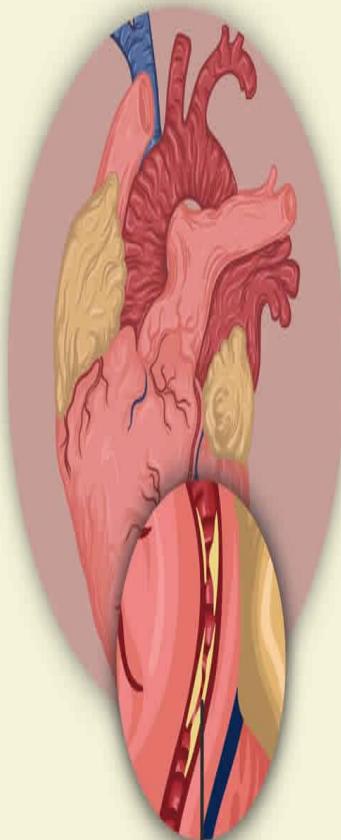
4. Blood Pressure:

III-Essential hypertension (mild, moderate).

V-Pheochromocytoma (together with alpha-blocker).

- II- Selective β_1 . Blockers
- They have some clinical advantages:
- 1- Less liable to produce Raynaud's phenomenon.
- 2- Less " " " bronchospasm.
- 3- Less " " " hypoglycemia.
- 4- Less " " " lipoprotein changes.
- 5- Less " " " K changes.
- However, it should be noted that cardioselectivity (beta 1 selectivity is not absolute & is lost with high doses).
- Side effects and Contraindications of Beta Blockers
- The next page

System	Side effects	Contraindications
I- C.N.S.	-Sedation, depression, night mares, impotence (only in lipophilic B.B. crossing BBB).	- Severe depression (use hydrophilic B.B.).
II- C.V.S. 1-Heart	- Heart failure in cases of inadequate myocardial function as myocardial infarction - Heart block (atropine is antidote).	-Variant (Prinzmetal) angina - Congestive H.F. - Heart block & severe bradycardia - Not used with verapamil or diltiazem: decrease contraction & conduction > H.F. & Block
2- B.V.	-Cold extremities. Raynaud's phenomenon, numbness, tingling.	- Raynaud's phenomenon & Other peripheral vascular diseases.
3- B.P. III-Respiration	Hypotension -Precipitate acute attack of Bronchial asthma in asthmatics.	Hypotension -Bronchial asthma.
IV-Metabolism	-Hypoglycemia (severe in pt. receiving insulin or oral hypoglycemic) [coma can occur without warning] -Atherosclerosis (\downarrow HDL) -Hyperkalemia especially in uremic patients	- Hypoglycemia in insulin or oral hypoglycemic treatment.
V- Others	- Sudden discontinuation (withdrawal syndrome)-> sympathetic overactivity and precipitation of anginal attack.	



Blocked

Coronary Artery



Tightness or
pain in chest

Raynaud's Phenomenon



White due
to lack of
blood flow



Blue due to
lack of oxygen



Red when
blood flow
returns

Pharmacology

M302

Presented by
Arwa A. Hassan

Lecturer of Pharmacology & BCPS



• Aspirin

-Prototype of NSAIDs

- Chemical name: Acetylsalicylic acid



1. Pharmacokinetics:

- -Weak acid
- -Absorbed from stomach and upper small intestine
- -Hydrolyzed to pharmacologically active 'salicylate'
- -Salicylate is highly bound to plasma proteins → **Drug interactions**
- Renal excretion → Conjugates of salicylate
- Increased renal excretion by alkalinization of urine



2. Pharmacodynamics "mechanism of action"

-Irreversible inhibition ‘acetylation’ of cyclo-oxygenase ‘COX-1 and COX-2’

Inhibits prostaglandins (PGs) synthesis

- Cyclooxygenase-1 (COX-1) is responsible for the physiologic production of prostanoids, whereas cyclooxygenase-2 (COX-2) causes the elevated production of prostanoids that occurs in sites of chronic disease and inflammation.

COX-1 is a constitutive enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive and kidney functions.

- COX-2 (Pathological) is constitutively expressed in tissues such as the brain, kidney, and bone. Its expression at other sites is increased during states of chronic inflammation.

- Pharmacological Actions"

- I. Analgesic

1. **Mild –to-moderate musculoskeletal pain**
2. **Modest analgesia**
3. **If pain is due to inflammation -- Anti-inflammatory effect of aspirin contributes to pain relief**
4. **No sedation**
5. **No tolerance**
6. **No physical dependence**

II- Anti-inflammatory

- 1. Inhibits PGs mediated responses**
- 2. Relieves signs and symptoms**
- 3. No effect on disease pathology**
- 4. Effective in rheumatoid arthritis**
- 5. Full antiarthritic doses may be as high as 4-10 g/day**

III- Antipyretic

1. Reduces synthesis of prostaglandins (mediators of fever) in the brain.
 2. Increases peripheral heat loss via skin > Vasodilatation of peripheral blood vessels → Diaphoresis.
 3. Affect response of hypothalamus to interleukins.
 4. Does not reduce heat production
-

IV- Effects on Blood Clotting

1. Irreversible Inhibition of platelet aggregation
2. Other NSAIDs → Reversible effect on clotting.

V- Effects on Respiration

1. High doses → Respiratory stimulation
2. In asthmatics → precipitates acute attack of asthma

VI- Effects on GIT

1. Due to reduced PGE2 and PGI2
2. Mucosal damage
3. All doses -- Microbleeding > Detected as occult blood in stool
4. Ulcerogenic ‘Gastric ulcers’ → Long term, high doses
5. Increased risk of GI bleeding → Antiplatelet effects

VII- Effects on Uric Acid

1. Daily doses < 1-2 g/day ► Reduces uric acid secretion
2. High doses > 2g/day ► Improves gout; but not well tolerated

VIII- Effect on the kidney

- Decrease renal blood flow

- **Therapeutic Uses:**

1. **Fever**
2. **Headache**
3. **Myalgia**
4. **Neuralgia**
5. **Dysmenorrhea**
6. **Osteoarthritis**
7. **Rheumatic fever**
8. **Rheumatoid disease**
9. **Antithrombotic**
10. **-Terminate use one week before surgery-**

- **Methylsalicylate**
- **Topical counterirritant**

- **Salicylic acid**

Topical keratolytic -- Wart

- **Corn**
- **Callus**

- **Side Effects & Toxicity**

- I. **Allergic Reactions**

- 1. Increased risk in asthmatics
 - 2. Treatment → Epinephrine
 - 3. Contraindicated in asthmatics
 - 4. Hemolysis in patients with G-6-PD deficiency '*Idiosyncracy*'

II- Reye Syndrome ‘Hepatotoxicity and Encephalopathy’

1. Rare, BUT fatal
2. Resulting from viral infection ‘*Influenza*’
3. Avoid giving aspirin to children with viral illness
4. Give acetaminophen ‘*Paracetamol*’

III- Salicylism ‘Low grade aspirin toxicity’

1. Tinnitus “Ototoxicity”
2. Hyperpyrexia
3. Dizziness, drowsiness and confusion
4. GIT upset {*Nausea and vomiting*}
5. Increased respiratory rate ‘*Tachypnea*’

Salicylate Poisoning

- 1. Fatal medical emergency**
- 2. Average lethal doses, taken at once: -**
 - a. Adults: 10 -30 g**
 - b. Children: 5- 8 g**
- 3. Cause of death → Respiratory arrest during febrile convulsions**
- 4. Treatment of poisoning → No antidote**

a- Symptomatic treatment

b-Gastric lavage

c-Alkalization of urine

d-Vit K I.M or slowly I.V.

Aspirin and Pregnancy

- 1. First trimester > Low teratogenic risk**
- 2. At birth > Increased bleeding risk -- Due to antiplatelet effect**
- 3. Delayed labor -- Due to reduced PG synthesis**
- 4. Avoid NSAIDs → Especially during 1st and 3rd trimesters**

Drug Interactions:

- I. Aspirin displaces other drugs from their plasma protein binding sites ► Increased effect of other drugs**
 - 1. Oral hypoglycemics → Increased incidence of hypoglycemia**
 - 2. Warfarin → Increased risk of bleeding**
- II. Aspirin antiplatelet effect ► Increased bleeding risk with warfarin.**
- III. Aspirin ulcer risk► Increased with use of alcohol.**
- IV. Interfere with hypertensive effect of β -blocker**
- V. Antacids with Aspirin→ Complex excreted in urine.**

- **Contraindications:**

1. Peptic ulcer
 2. Bronchial asthma
 3. Gout
 4. Bleeding tendencies
 5. Children with viral infections
 6. 3rd trimester of pregnancy
 7. Severe liver damage
 8. Vitamin K deficiency
 9. Hemophilia (thrombocytopenia)
 10. Severe renal impairment
- **Caution:** patients taking anticoagulant

The word "THANK YOU" is spelled out in large, stylized letters made of various colorful beads and small objects. The letters are arranged horizontally. The 'T' and 'H' are filled with pink, red, and orange beads. The 'A' and 'N' are filled with a mix of pink, red, and blue beads. The 'K' and 'Y' are filled with pink and red beads. The 'U' is filled with blue and white beads. The letters have a three-dimensional, textured appearance.

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Pharmacology

M302

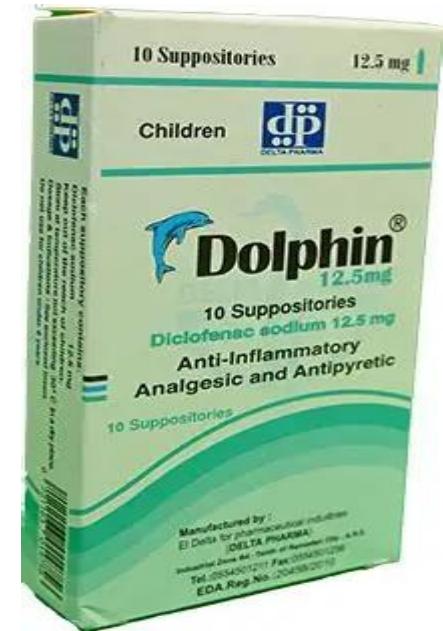
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- **Other Non steroidal anti-inflammatory drugs (NSAIDs)**

1. Ibuprofen
2. Naproxen
3. Ketoprofen
4. Indomethacin
5. Diclofenac
6. Piroxicam
7. Meloxicam
8. Tolmetin
9. Ketorolac
10. Celecoxib



- **Ibuprofen, Naproxen, Ketoprofen**

1. No antiplatelet effect
2. Fewer drug interactions
3. Same contraindications **EXCEPT** Reye syndrome and hyperuricemia / gout
4. Long term use > Increased liver enzymes

- **Indomethacin**

1. Most potent inhibitor of cyclo-oxygenase
2. Greater GIT distress
3. Neurotoxicity

- **Diclofenac**

1. Rapid onset, Short duration
2. More nephrotoxic



- **Piroxicam** Long duration (once daily) **Meloxicam**

1. Analog of piroxicam
2. Preferential inhibition of COX-2

- **Phenylbutazone**

- Many severe adverse effects

- ▶ Avoid

- **Dipyrone**

- Avoid -- Bone marrow depression

- → Agranulocytosis (decrease in white blood cells count),

- Anaphylaxis, Asthma.



- **Ketorolac**

1. Analgesic effect comparable to usual doses used for morphine and meperidine
2. Little anti-inflammatory action
3. Ulcerogenic
4. No respiratory center depression
5. No addiction



Comparison between Cox-1 and COX-2 Inhibitors

COX-1 Inhibitors

COX-2 Inhibitors

Involved in most side effects of NSAIDs especially:

- a. **Gastric ulcer**
- b. **Bronchospasm**

Responsible for desired actions of NSAIDs:

- a. **Antipyretic**
- b. **Analgesic.**
- c. **Anti-inflammatory:**

- **COX-2 Inhibitors**

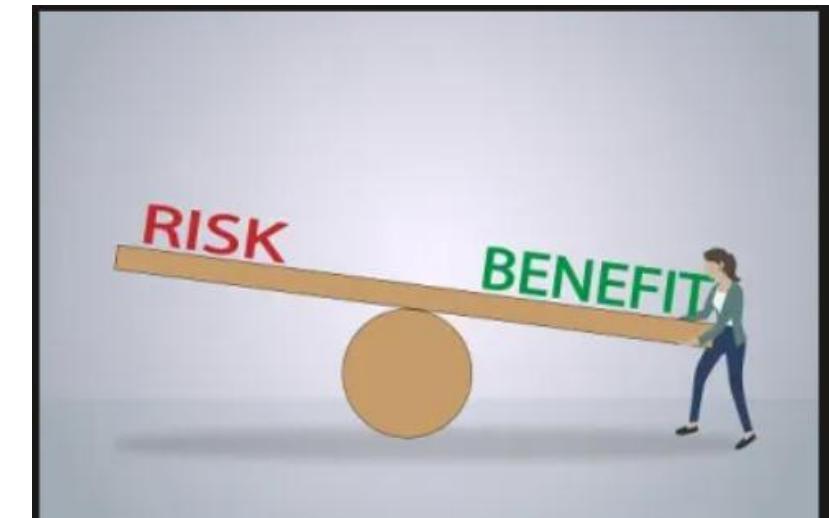
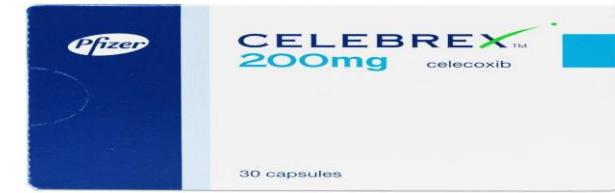
1. Lower incidence of gastric ulcers
2. Safer for asthmatics
3. Safer for those taking warfarin
4. Increased risk of myocardial infarction and stroke

- **Celecoxib**

1. Prototype
2. Contraindicated in patients allergic to sulfonamides

- **Rofecoxib**

- Withdrawn from market > Due to increased risk of myocardial infarction



- By selectively inhibiting the COX-2 isoform, COX-2- selective NSAIDs reduce GI events but may **increase the risk of cardiovascular events** in certain patients.
- One theory is that **COX-2** is responsible for the production of **prostacyclin**, a vasodilatory and antiplatelet prostaglandin. In contrast, **COX-1** controls the production of **thromboxane A2**, a vasoconstrictor and platelet aggregator.
- Selective inhibition of COX-2 results in decreased prostacyclin levels relative to thromboxane A2 levels.
- An **imbalance** in the **thromboxane A2: prostacyclin ratio** ensues, which creates an environment that favors **thrombosis**. COX-2 inhibitors should be reserved for patients at **high risk for GI complications** and **low risk for cardiovascular events**. COX-2 inhibitors should be used with caution in patients with **heart failure or hypertension**.

- Acetaminophen ‘Paracetamol’:

- Effects:

1. Analgesic
2. Antipyretic
3. NOT anti-inflammatory “NOT NSAID”

- Similarities to aspirin:

- Equipotent to aspirin as analgesic and antipyretic

- Differences to aspirin

1. No anti-inflammatory effect
2. No effect on uric acid
3. No antiplatelet effect
4. No adverse GI effects
5. Not contraindicated in asthma
6. No Reye concerns
7. No drug – drug interactions



- **Toxicity**

1. Lethal dose:

- a. **Adults > 7 g**
- b. **Children 150 – 200 mg/kg**

2. Liver failure

3. Increased incidence of liver damage

(as little as 4 g/day):

- a. Fasting b. Alcohol

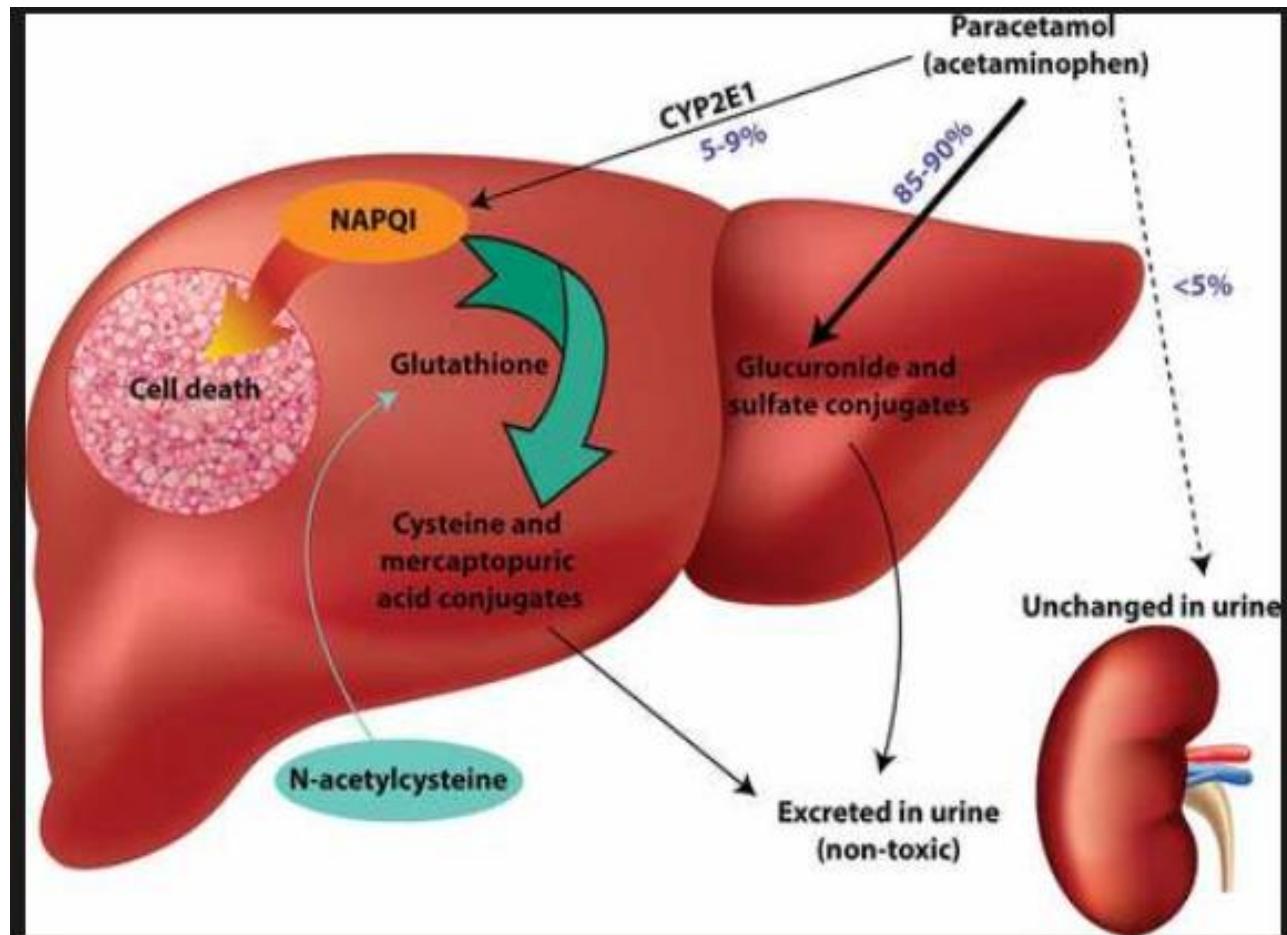
1. **Antidote “N-acetylcysteine”:**

- a. Lifesaving ▶ Give as soon as possible
- b. Not well tolerated -- Bad odor and taste

- **Alcohol**

1. No potentiation of gastric irritation

2. Ethanol increases hepatotoxicity



- **Narcotic (Opioid) Analgesics**
- CNS depressants, potent analgesics for all types of pain, without loss of consciousness and prolonged use leads to addiction
- **Classification**
- **Opioid Agonists**
 - i. Natural Phenanthrene Alkaloids of Opium
 - i. Morphine ii. Codeine
 - ii. Semisynthetic Morphine (Phenanthrene) Derivatives
 - i. Heroin {Diacetylmorphine}
 - ii. Dihydromorphinone iii. Dihydrocodeinone
 - iii. Synthetic (Non-Phenanthrenes) Morphine Substitutes
 - i. Meperidine ii. Fentanyl iii. Fentanyl Derivatives
 - i. Methadone v. Tramadol

- **Natural Opium Alkaloids**
- **Phenanthrene Opium Alkaloids**
- **Narcotic, analgesic, addictive and spasmogenic on smooth muscles, Morphine “Main constituent”, 10% of opium, Codeine 1% of opium**

• **Morphine**

- **Pharmacokinetics**
- **Absorption**
 - i. **Orally → Low oral bioavailability {25 – 30%}**
 - ii. **Better absorbed after SC and IM injections**
 - iii. **Shock → Slow diluted IV injection**



Distribution

- i. All over the body
- ii. Passes blood brain barrier (BBB)
- iii. Passes placental barrier
- iv. Pregnancy → Addiction of fetus
- v. Labor → Neonatal asphyxia

► **Treat by naloxone:**

IM to mother before labor

- **Metabolism**

- i. **Extensive (70-75%) hepatic first pass metabolism**
- ii. **Conjugated with glucuronic acid by hepatic microsomal enzymes ►**

- ***Deficient in extremities of age → Supersensitivity***

- → **Active morphine-6-glucuronide {10%}**

- **More active than morphine**

- → **Inactive morphine-3-glucuronide {90%}**

- **Excretion**

- i. **Saliva →**

- ii. **Stomach → Stomach wash in all cases of poisoning**

- iii. **Bile → Enterohepatic circulation**

- iv. **Urine → Major route of excretion**

- v. **t_{1/2} → 2 – 3 hours**

- **Duration of Action → 6 – 8 hours**

- **Pharmacodynamics**
- **Mechanism of Action**
- **A-Direct** → Stimulation of opiate receptors in CNS {brain & spinal cord} and periphery {gut and adrenal medulla} Leading to:
 - Inhibits release of substance P and modulate release of several neurotransmitters
(↓release of norepinephrine in CNS lead to sedation)
 - **B. Indirect** → Release of natural endogenous opioid peptides
 - {endorphins, enkephalins and dynorphins} “pleasure substances that increase during stress
 - **Types of opiate receptors**
 - i. Mu (μ): Supraspinal analgesia, euphoria, RC inhibition, miosis and constipation
 - ii. Kappa (κ): Spinal analgesia, miosis, less sedation and less RC inhibition

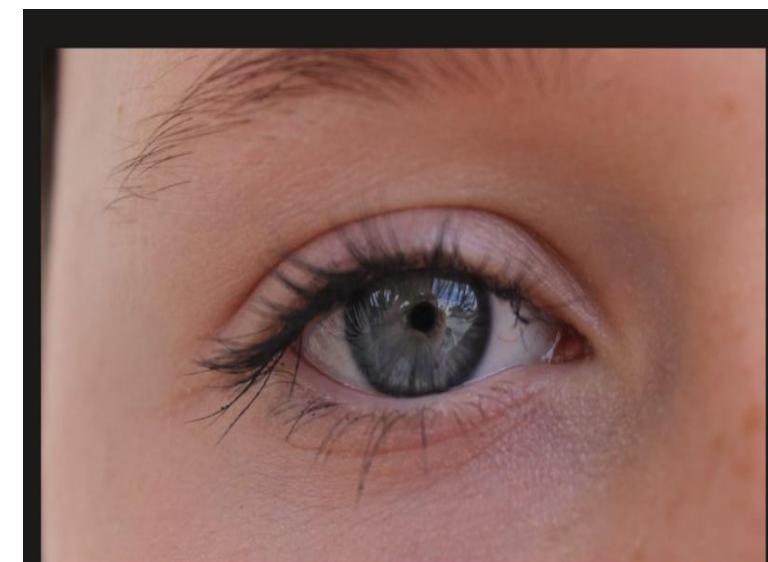
- **CNS** → Mixed stimulation and depression

1. **Stimulation:**

- i. Euphoria
- ii. **Occulomotor nerve** ► Miosis “Pin point pupil”
- iii. **Vagal center “Cardiac Inhibitory Center”** ► Bradycardia
- iv. **Chemoreceptor trigger zone (CTZ)** “Small dose” ►

Nausea and vomiting

- i. **Antidiuretic hormone (ADH)** ► Edema + Oliguria



2-Depression

- i. Analgesia ► All types of pain, WITHOUT affecting other sensations; **EXCEPT** itching → Due to histamine release
- ii. Narcosis
- iii. Respiratory Center ► Hypoventilation and Hypoxia
- iv. Cough center ► Antitussive
- v. VMC ► Hypotension

- **CVS**
 - → **Small therapeutic dose** ► No effect
 - → **Large dose, especially IV** ► Hypotension
 - Inhibit Vasomotor center (VMC)+ Stimulate vagal center
 - Direct Venodilator
 - Histamine release ► Vasodilatation
 - **Respiratory system**
 1. Decreases sensitivity of Respiratory Center (RC) to CO₂
 2. Depresses cough center ► Central antitussive
 3. Histamine release
 - Large dose → Bronchospasm
 4. Induces bronchospasm

- **GIT**

1. **Spasmogenic** ► Increases tone of muscles and spasm of sphincters
Decreases propulsive peristalsis and inhibits defecation reflex→
Constipation.
2. **Decreases gastric, biliary, and pancreatic secretions.**

Biliary tract

- **Spasmogenic** ► Spasm of wall of gall bladder and sphincter of Oddi
→ **Increase intrabiliary pressure**
 - **Avoid after cholecystectomy and add atropine in intestinal colic**

- Urinary tract → Spasmogenic ► Spasm of ureter → Add atropine in renal colic + Spasm of sphincters → Urine retention especially in old people with enlarged prostate.

Oliguria → Increased ADH

- Uterus → interfere with uterine contraction and, also passes placental barrier ► Neonatal asphyxia
- Skin → Sweating and Histamine release ► Itching and wheal formation.
- Metabolism
→ Decreases basal metabolic rate

- Dosing and Route of Administration
- SC {10 mg}; IM {10 mg}; IV {5 mg}; Oral {30 mg}

- Therapeutic Uses

- I. Pain ► Analgesic in severe visceral pain
 1. Cardiac pain {Myocardial infarction}
 2. Cancer pain {Especially terminal stages}
 3. Colic {Add atropine in intestinal and renal colic}
 4. Bone fractures {**Except** skull as morphine is contraindicated in head injury}
 5. Postoperative {**Except** biliary and eye operations}

2-Pulmonary edema due to acute left ventricular failure

- 1. Venodilator: Decreases venous return ► Decreases end diastolic volume
→ Decreases preload ► Decreases pulmonary congestion**
- 2. Sedation: Depress sympathetic ► Arteriodilator → Decreased total peripheral resistance ► Decreased afterload**
- 3. Slow respiration**

3-Adjunctive to Preanesthetic medication in major surgery

To provide analgesia, sedation.

- **Adverse Effects**

1. Interfere with proper diagnosis of head injury and acute abdomen
2. Inhibition of respiration
3. Pinpoint pupil
4. Nausea and vomiting
5. Bronchospasm
6. Constipation
7. Urine retention
8. Neonatal asphyxia
9. Itching
10. Dependence
- 11-Hypotension
- 12- bradycardia

- **Contraindications**
 - i. **Head injury**
 - ii. **Miosis → Interfere with proper diagnosis**
 - iii. **RC Inhibition → Increase CO₂ ► Cerebral vasodilatation → Increases synthesis of CSF → Increases intracranial tension ► More RC inhibition**
 - iv. **Epilepsy**
 - v. **Respiratory diseases {Asthma – COPD}**
 - vi. **Acute undiagnosed abdominal pain**
 - **Morphine ► Analgesia → Interfere with proper diagnosis**
 - i. **Pregnancy and Lactation**
 - **Addict fetus ► Withdrawal symptoms after labor**

- i. Labor → Neonatal asphyxia
- ii. Advanced liver disease → Deficient metabolism
- iii. Extremities of age → Deficient metabolism
- iv. Myxedema
 - Decrease metabolism ► More CNS inhibition + Decrease basal metabolic rate → Myxedema coma {Hypotension, bradycardia, hypothermia, hypoventilation}

V. Biliary colic

Vi. Allergy to morphine

Vii. History of addiction to morphine or other opiates Poisoning

i. Poisoning

- **Acute Morphine Poisoning**
- **Manifestations**
 - 1- Pin point pupil 2- Hypothermia
 - 3- Hypotension 4- Hypoventilation
 - 5- Coma
- **Cause of Death**
- **Respiratory failure**
- **Treatment:**
 1. Artificial respiration
 2. No pure oxygen → Apnea
 3. Stomach wash ► Even with parenteral poisoning
 4. Potassium permanganate + Charcoal + Magnesium sulfate
 5. Specific morphine antagonist: Naloxone 0.4-2 mg IV or Naltrexone

The word "THANK YOU" is spelled out in large, stylized letters made of various colorful beads and small objects. The letters are arranged horizontally. The 'T' and 'H' are filled with pink, red, and orange beads. The 'A' and 'N' are filled with a mix of pink, red, and blue beads. The 'K' and 'Y' are filled with pink and red beads. The 'U' is filled with blue and white beads. The letters have a three-dimensional, textured appearance.

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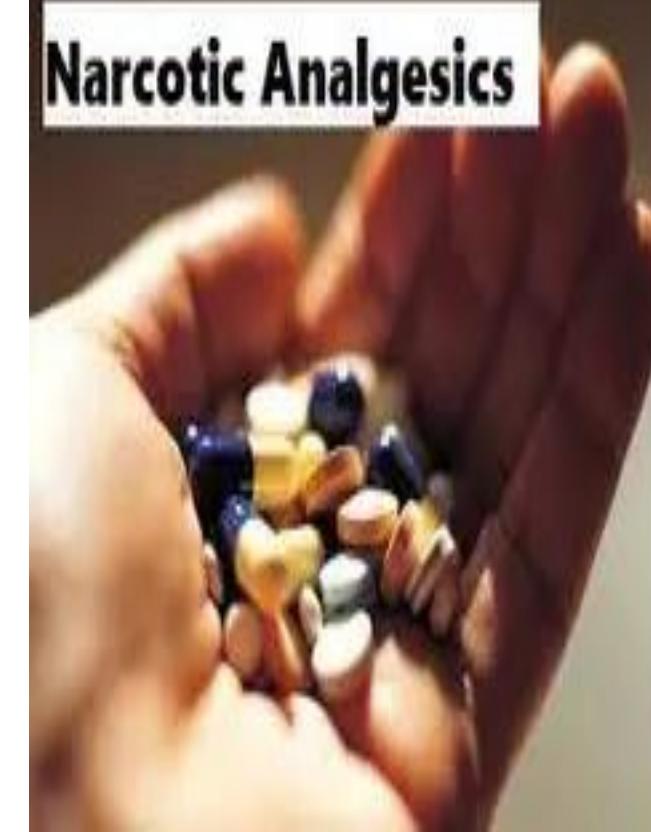
Pharmacology

M302

Presented by
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Narcotic Analgesics



Addiction = Chronic Poisoning

Physical dependence: Caused by decreased endogenous endorphins and enkephalins

Sudden stop of morphine {symptoms begin 8-10 hours after last dose} or use of morphine antagonist precipitates withdrawal syndrome

Symptoms of Addiction:

- 1- Pin point pupil 2- Constipation
- 3- Psychosis {Drug seeking habit} 4- Moral deterioration



Manifestations of Withdrawal {Abstinence} Syndrome:

- | | | |
|--|------------------------|---------------|
| 1- Anxiety | 8. Severe pain “Aches” | 9. Fever |
| 5-Lacrimation | 11. Hyperventilation | |
| 3- Rhinorrhea | | |
| 4-Reversal of all actions
of morphine | | |
| | | |
| 7. Excitation | | |
| 10. Mydriasis | | |
| Hypertension | | |
| 13. Tachycardia | 14. Diarrhea | 15. Urination |
| 16. Salivation | 17. Sweating | 18. Tremors |
| 19. Convulsions | | 20. Coma |

- Management of Morphine Addiction
- Hospitalization and Psychotherapy
- Gradual withdrawal of morphine → Till the stabilizing dose
- Gradual substitution with methadone
 - As morphine with less withdrawal manifestations
- Gradual withdrawal of methadone
- Clonidine → Control many withdrawal symptoms {Inhibits sympathetic hyperactivity during withdrawal}
- Add benzodiazepine as sedative, hypnotic.

- **Other Opioid Agonists**

- I. **Codeine {Methylmorphine}**

1. Phenanthrene opium alkaloid

2. 1% of opium

Pharmacokinetics

Bioavailability 60%, more lipid soluble

Pharmacodynamics

- As morphine **BUT:**

- | | |
|--------------------------|--|
| i. Less potent analgesic | ii. Less addictive |
| iii. Less RC depression | iv. Produces excitation in large doses |

Therapeutic Uses

A-Analgesic

b-Antitussive in cough therapy

Contraindicated in **children**

2-Semisynthetic Morphine

a-Heroin

Removed from the market, clinically not used because its highly addictive.

3-Synthetic opioid analgesic

a-Meperidine

Opioid agonist, has the same action of morphine **except some differences:-**

1-Higher bioavailability (50%).

2-Less potent analgesic.

3-Has antimuscarinic effect (Atropine like action → spasmolytic, No vagal stimulation).

4-Used in situations where morphine is **contraindicated** such as:-

A-Biliary colic.

B-During labor (shorter duration of action).

C-Safer than morphine in Myocardial infarction.

- **B-Fentanyl**
- More potent as analgesic than morphine.
- Used as patches.
- Safe in patient with renal impairment.



• **C-Methadone**

- Equipotent as morphine, but less addictive.
- **Main use:-**
- Morphine addiction treatment, chronic morphine toxicity.
- Substitute morphine with methadone : then remove gradually and add benzodiazepine(diazepam: sedative, hypnotic).



- **D-Tramadol**
- As morphine but, it decrease reuptake of norepinephrine and serotonin, ↑ their level in the brain tissue→ neuropsychiatric effects.
- Used as analgesic postoperative in orthopedic surgery .
- Increase seizure risk in predisposed patients or with history of epilepsy.
- **E-Loperamide, Diphenoxylate**
- Opioid agonist, peripheral only, not pass BBB.
- Used in the treatment of diarrhea.
- Mixed with atropine to prevent dependence.

- **Mixed agonist/antagonist.**
- **Nalbuphine, Nalorphine, Butorphanol, Pentazocine**
- **Used as analgesic in severe pain as an alternative to morphine with less euphoria, respiratory depression.**
- **Not used in addict patient and in myocardial infarction.**
- **Opioid antagonist**
- **Naloxone: injection, short duration (one hour)**
- **Used in acute morphine poisoning.**
- **Naltrexone: Oral, long duration of action.**



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