Pharma Guide

Essentials of Basic and Clinical Pharmacology

Prepared by

Dhshan Hassan Dhshan

Student on

Faculty of Pharmacy Al-azhar University

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For contact

www.facebook.com/dr.dhshan dr.dhshan@yahoo.com

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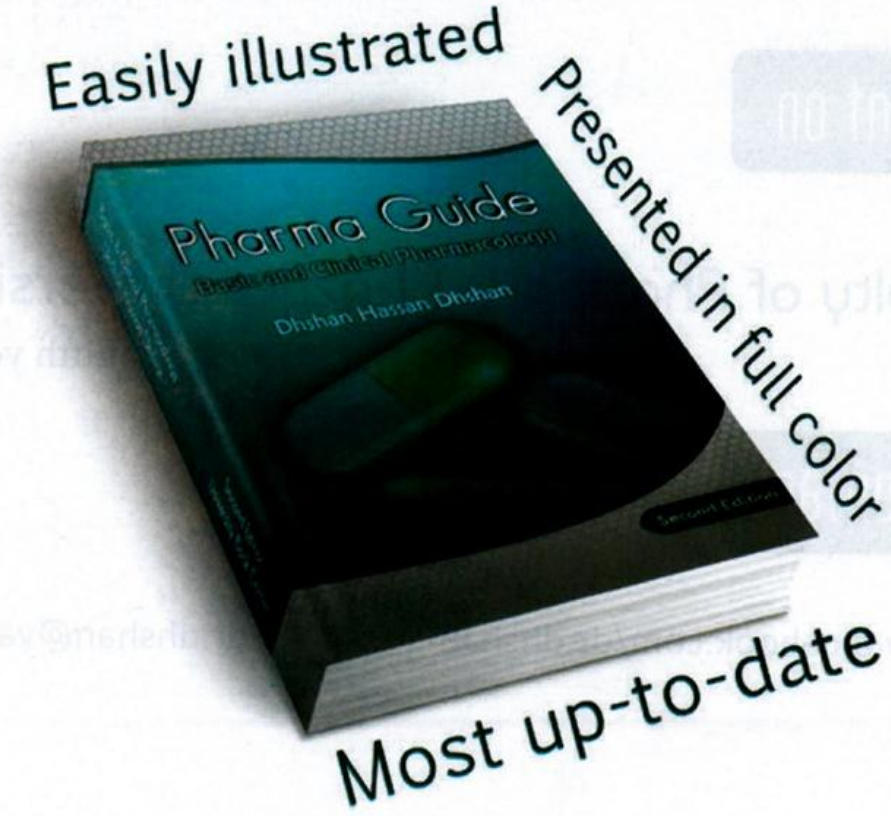


Introduction

(GENERAL PHARMACOLOGY)

What is Pharmacology?

What is Pharmacology?

- It is the science that deals with the study of chemical substance (drugs).
- **The study of drug:**
  - What they are? - How they work? - What they do?

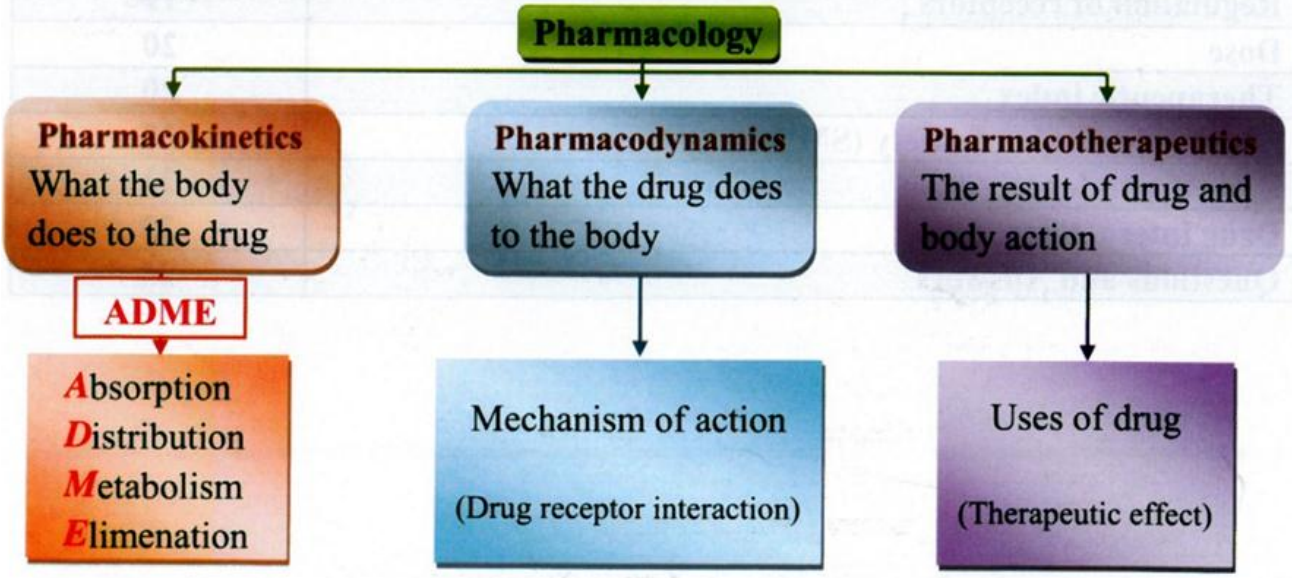
What is Toxicology?

- It is a branch of pharmacology which deals with the undesirable effects of chemicals and drugs on living system.

Drugs (Therapeutic agent):-

- **Definition (Def.):** Any substance other than food can be used in prevention, diagnosis, or treatment of diseases.
- **Sources of drugs:**
  1) **Natural**
     - Plant e.g. Pilocarpine.
     - Animal e.g. Heparin.
     - Microorganisms e.g. Antibiotics.
     - Minerals e.g. Ferrous sulfate.
  2) **Synthetic**
     - Chemically e.g. Sulphonamides.
     - Genetic engineering (rDNA technology) e.g. Human insulin.
- **Names of drugs:**
  1) **Chemical name** e.g. Acetylsalicylic acid
  2) **Generic name** e.g. Aspirin
  3) **Trade name** e.g. Rivo

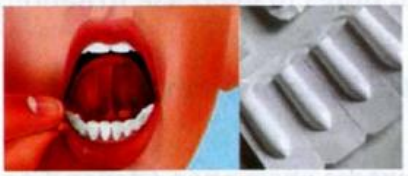
- **Classes of drugs:**
  1) **Prescription only medication (POM):** Only for prescription.
  2) **Over the counter (OTC) drugs:** Used by the public without a prescription.



Routes of administration

Oral | Parenteral | Mucosal | Inhalation | Topical





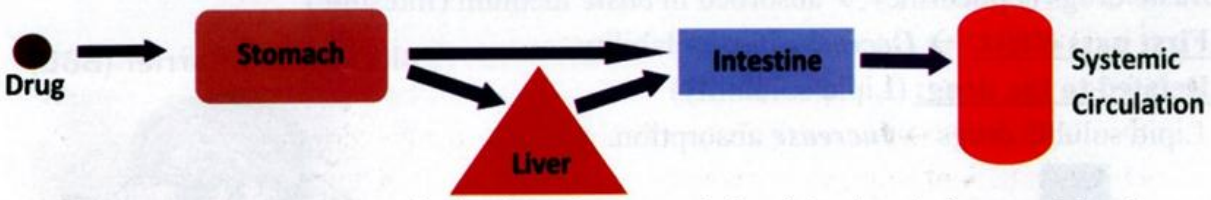

1: Oral route:-

- **Advantage:**

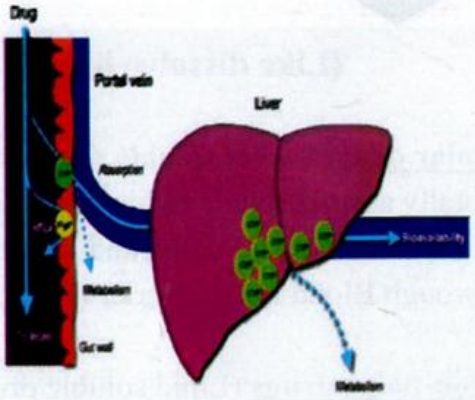
1: Most common 2: More safe 3: Non irritant
4: Easy of administration 5: Economic 6: Palatable

- **Disadvantage:**

1: Not suitable for patient suffering from vomiting and diarrhea.
2: Not suitable in emergency and very irritant drugs.
3: Affected by PH.
4: **First pass effect** (Pre-systemic metabolism): (***Decrease*** bioavailability of drug)



- **Def.** → Inactivation or elimination of part or whole of the drug before reaching the systemic circulation.
- **Sites:**
  1) **Gut first pass effect**:
     - Gastric acidity → Benzyl penicillin
     - Digestive enzyme → Insulin
     - Mucosal enzyme → Tyramine
  2) **Hepatic First pass effect:**
     - Complete →Nitroglycerine
     - Partial → Propranolol
     - Minimal → Atenolol



- **To overcome hepatic first pass effect:**
  - If partial → increase dose of drugs
  - If complete → use other rout → Sublingual Nitroglycerine

➢ Factors affecting oral absorption:-

1: Presence of food and other drugs in the GIT:

- Amino acids ***compete*** for the same carrier of L-dopa.
- Ca^{2+} from milk ***decrease*** absorption of tetracycline.
- Tannic acid from tea and tetracycline ***decrease*** absorption of iron.
- Food dilutes drugs and ***decrease*** absorption.
- Food is useful in irritant drugs to ***decrease*** irritation.

2: State of health of GIT:

- Presence of disease in GIT ***decreases*** absorption.

3: Gastric emptying rate:

- May be ***increase*** or ***decrease*** absorption (***depend on drugs***):
  For Example → In ***high*** emptying rate
  - ***Increase*** absorption of Paracetamol (***Rapid*** rate of dissolution and disintegration)
  - ***Decrease*** absorption of Digoxin (***Slow*** rate of dissolution and disintegration)
- N.B →Atropine ***decreases*** motility of GIT → ***decrease*** emptying rate.

4: Motility of GIT:

- ***Increase*** Motility (Diarrhea) → ***decrease*** absorption.
- ***Decrease*** Motility (Constipation) → ***Increase*** absorption.

5: PH of GIT:

- ***Acidic*** drugs (Aspirin) → absorbed in ***acidic*** medium (Stomach).
- ***Basic*** drugs (Ephedrine) → absorbed in ***basic*** medium (Intestine).

6: First pass effect: → ***Decrease*** bioavailability.

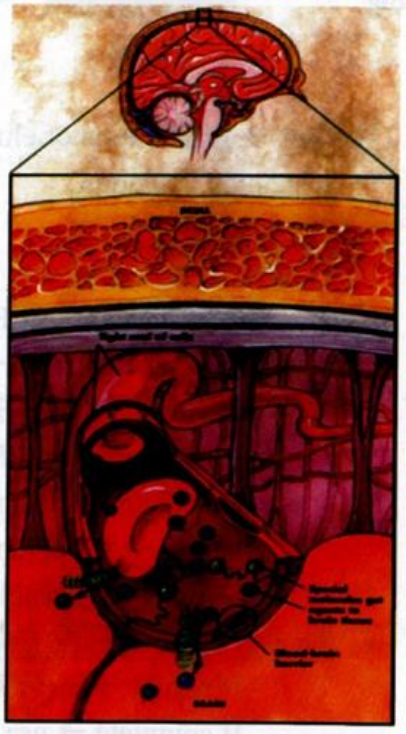
7: Related to the drug: (Lipid solubility)

- Lipid soluble drugs → ***Increase*** absorption.

(Like dissolve like)

- **Polar drugs** (water soluble drug) not totally absorbed (due to high amount of lipid content in the cells) and not pass through Blood Brain Barrier (BBB).
- **Non-polar drugs** (Lipid soluble drugs) highly absorbed and Pass BBB.

Blood-Brain Barrier (BBB)

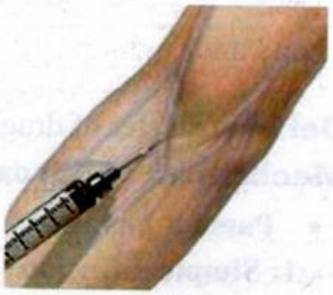


2: Parenteral route (injection):-

➢ A: Intravenous (IV) injection:

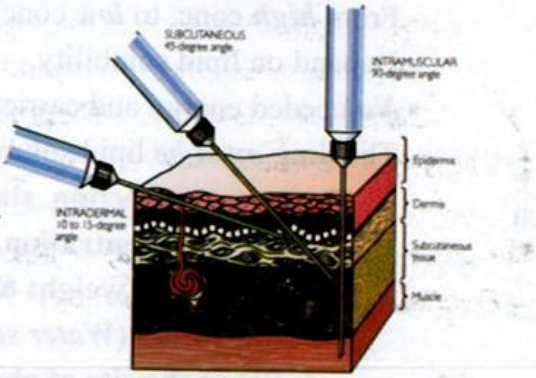
- **Advantage:**

1: 100% bioavailability (the amount of drug reached to blood).
2: No first pass effect.
3: Suitable for irritant drug.
4: Suitable in emergency.
5: Suitable for acid labile drugs.



- **Disadvantage:**

1: low safety (Allergy → Anaphylactic shock).
2: Must be sterile (Pyrogenic reaction).
3: Spreading of infection (Viral hepatitis).
4: Required professional person.
5: Not suitable for oily and suspended drugs.



➢ B: Intramuscular (IM) injection:-

- Suitable for solution, suspension and oily drugs.
- Better absorption than SC but less than IV.

➢ C: Subcutaneous (SC) injection:-

- Absorption rate is slower than IV and IM.
- It is suitable for drugs that are non-irritant in aqueous solution or fine suspension.

➢ D: Intradermal (ID) Injection:-

- Sensitive tests.

➢ E: Other injection:-

- E.g. - Intra-cardiac - Intra-bone marrow - Intrathecal (CSF) - Intra-peritoneal

3: Mucosal route:-

Buccal or Sublingual	Ocular	Vaginal	Nasal	Rectal
Systemic delivery of drugs	Local delivery of drugs	Systemic or local delivery of drugs		

4: Inhalation:-

- Systemic delivery of drugs.
- Highly blood supply and wide surface area.
- Highly absorbed (high bioavailability).
- Many drugs make lung irritants.

4: Topical:-

- Usually local effect but high lipid soluble drugs can be absorbed.
- Transdermal drug delivery system (TDDS) enhance skin absorption e.g. Skin patches of nicotine.

IV > IM > SC > Oral > Skin

Pharmacokinetics

- **Def.** → Effect of the body on the drug.
- **Consist of 4 process (ADME):-**

1) Absorption

- **Def.** → Transfer of drug from the site of administration to the systemic circulation.
- **Mechanism of Absorption:-**
  - **Passive Transfer:-**

1: Simple diffusion (Lipid diffusion):

- From ***high*** conc. to ***low*** conc. (***Along*** concentration gradient).
- Depend on lipid solubility.
- ***No*** needed energy and carrier.
- The drug ***must be*** lipid soluble and small in molecular weight.

❖ **Factors affecting simple diffusion:-**

1: **Dose concentration** (***Increase*** dose concentration →***Increase*** absorption).
2: **Molecular weight & size** (***Increase*** Mwt. → ***Decrease*** absorption).
3: **Ionization** (***Water soluble*** drug (Ionized) → ***Decrease*** absorption).
4: **PH at the site of absorption.**

- **Most of drugs are weak acids or weak bases**

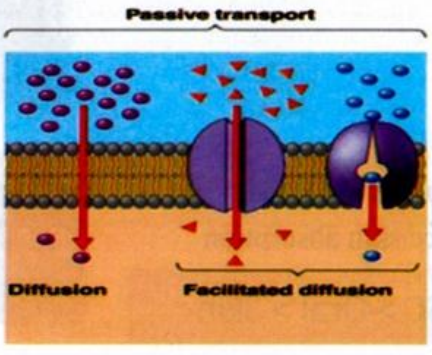
Weak acid drugs → less ionized in *acidic* medium → *decrease* ionization → *Increase* Absorption
Weak base drugs → less ionized in *basic* medium → *decrease* ionization → *Increase* Absorption

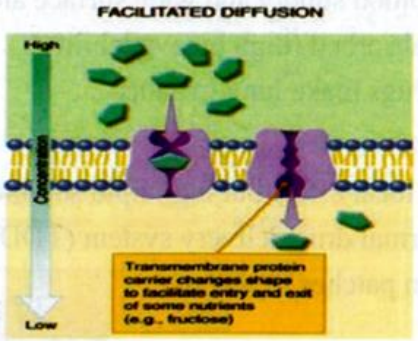
2: Filtration (Osmosis): ***No*** carrier and energy.

- **Special Transfer:-**

1: Facilitate Diffusion:

- From ***high*** concentration to ***low*** concentration (***Along*** concentration gradient).
- ***Need carrier*** and ***not need*** energy → e.g. Glucose (If the conc. gradient is favourable) and fructose.



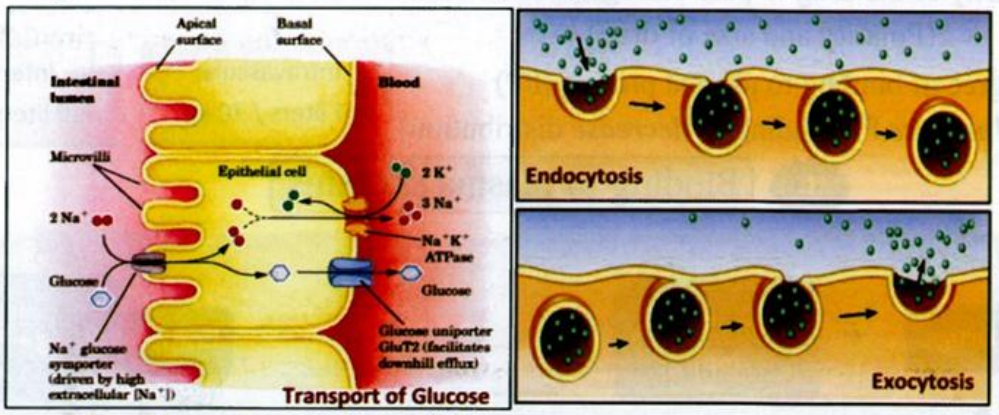


2: Active transport:

- From ***low*** concentration to ***high*** concentration (***Against*** concentration gradient)
- ***Need carrier*** and ***need energy*** → e.g. Glucose (Na^+/K^+ pump).

3: Pinocytosis or Endocytosis:

- Drugs of exceptionally large size.
- Engulfment of a drug molecule by the cell membrane.
- E.g. → (Vit.B12 + intrinsic factor) complex.



➢ Factors affecting absorption of drugs:-

1: Patient-Related factors:

- **Route of administration** → IV > IM > SC > Oral > Skin
- **Absorbing surface** →***Increase*** surface → ***Increase*** absorption.
- **Systemic circulation** →Shock and heart failure → ***decrease*** absorption.
- **Presence of other drugs** →Adrenaline SC→Vasoconstriction (VC)→↓absorption.
- **Specific factors** → E.g. intrinsic factor for Vit.B12.

2: Drug-Related factors:

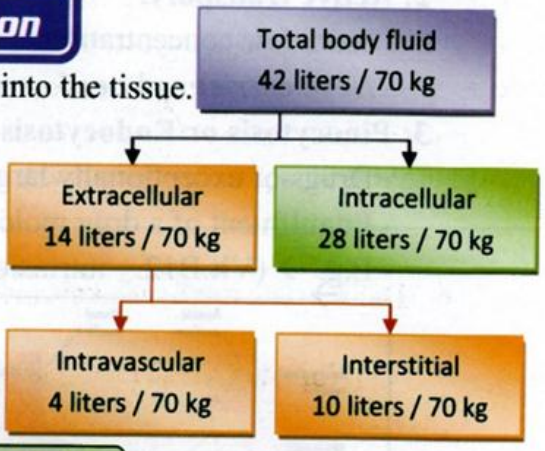
- **Lipid solubility** → High lipid solubility drug → High absorption.
- **Ionization** → Non-ionized drugs → High absorption.
- **Valency** → Ferrous iron (Fe^{2+}) absorbed ***more*** than ferric iron (Fe^{3+}).
- **Nature** → Inorganic (Small molecules) > Organic (Big molecules).
- **Pharmaceutical preparation** → Solution > Suspension > Tablet
- **PH of the drug**
  - Most of drugs are weak acid or weak base, the ionization of drugs may markedly reduce their ability to permeate membrane.
  - The degree of ionization drugs are determined by the surrounding pH on their pK_a.
  - Acidic drug are largely unionized in stomach and absorbed faster, while basic drug are absorbed faster in intestine.

Henderson-Hasselbalch equation (Determination degree of ionization)

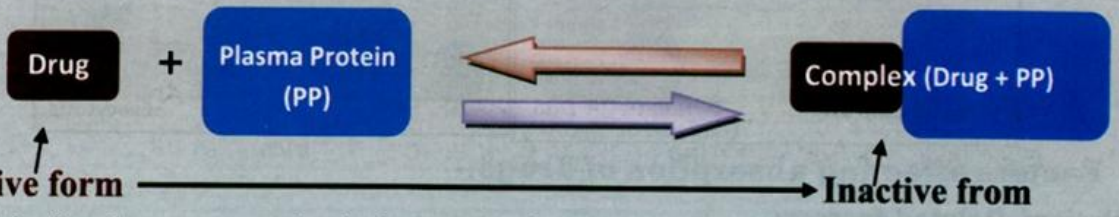
- For weak acid drugs: pK_a = log Unionized form / Ionized form
- For weak base: pK_a = log ionized form / unionized form

2) Distribution

- **Def.** → The transfer of drug from the blood stream into the tissue.
- **Depend on :-**
  - ***Increase*** blood flow → ***Increase*** distribution (Lung > Liver > Brain)
  - Ability of the drug to pass biological membrane (Polarity and size of drug)
  - Degree of binding to plasma protein (PP) (***Increase*** PP binding → ***decrease*** distribution)



1 Binding to plasma proteins



- When the free drug concentration is decreased → the binding drug converted to free drug → to give the same action.

- Amount of free drug can be increase by:-

1: Displacement by other drugs → Replacement of one drug by another.

→E.g. Aspirin and Warfarin (Anticoagulant) →Aspirin displaces warfarin due to high affinity to PP → increase free active Warfarin → Increase toxicity of warfarin.

- Drugs with high affinity for PP are Aspirin, Sulfonamides and Chloramphenicol can replace the other drugs e.g. Warfarin.

2: Decrease in albumin or plasma protein → Liver disease.

2 Patterns of distribution

1: Intravascular (Single compartment):

- Drug (High Mwt) is retained in the blood compartment.
- E.g. Drug pound to plasma proteins and polysaccharides (Heparin and Dextran)

2: Extracellular (Two compartment) = Intravascular + Interstitial:

- Drug (Small Mwt) ***can*** filtrate but ***can not*** pass through cell membrane (Lipid membrane).
- E.g. Quaternary ammonium compound (Neostigmine) and Mannitol (Osmotic diuretic).

3: All over the body (Multi-compartment) = Intra + Extracellular:

- Drug (small Mwt) ***can*** filtrate but ***can*** pass through cell membrane (Lipid membrane).
- Tertiary amines (Physostigmine), Alcohol and aspirin.

4: Tissue reservoirs:

Hair	Liver	Thyroid	Heart	Fate	Bone
Arsenic	Vitamin B_{12}	Iodine	Digitalis	Thiopentone	Ca^{2+}

5: Blood brain barrier (BBB): → Lipid cellular barrier → only lipid soluble (Non-ionized).
- Inflammation (Meningitis) → Increase permeability of BBB.

6: Placenta barriers: → Lipid cellular barrier
- If the drug pass placenta during pregnancy → Teratogenicity e.g. Tetracyclines.
- If the drug pass placenta during labor → Neonatal asphyxia e.g. Morphine and barbiturates.

3 Volume of distribution

- Def. → The **apparent volume** of fluid into which an administrated drug is dispersed.

$$V_d \text{ (Volume of distribution)} = \frac{\mathbf{Q} \text{ (Total amount of drug in the body)}}{\mathbf{C_p} \text{ (Plasma concentration of the drug)}}$$

- Useful to determine the total amount of drug in the body ($Q = C_p \times V_d$).
- Can be used to calculate ***the amount of drug needed to achieve a desired C_p*** →
  - (V_d)(target concentration = C_1) = amount of drug initially in the body.
  - (V_d)(higher conc. = C_2) = amount of drug in the body needed to achieve a desired C_p.

The additional dosage needed = $V_d (C_2 - C_1)$

- If the drug has ***high*** V_d → the drug has ***low*** affinity to binding to PP.
- If the drug has ***low*** V_d → the drug has ***high*** affinity to binding to PP.

3) Metabolism

➢ **Def.**→ Metabolism or biotransformation usually conversion of drug from non-polar → polar → more polar → to facilitate excretion.

➢ **Sites of Metabolism:-**

Hepatic microsomal biotransformation

- In hepatic smooth endoplasmic reticulum.
- Oxidation (cytochrome P450), reduction, hydrolysis and glucuronidation only.
- ***Can*** be induced and inhibited.
- Activity is ***unstable***.

Non-hepatic microsomal biotransformation

- In lung, kidney, skin and plasma.
- Oxidation, reduction, hydrolysis, all conjugation except glucuronidation.
- ***Can't*** be induced and inhibited.
- Activity is ***stable***.

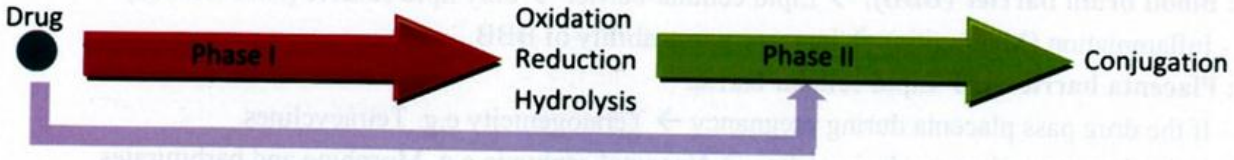
➢ **Classification :-**

Phase I

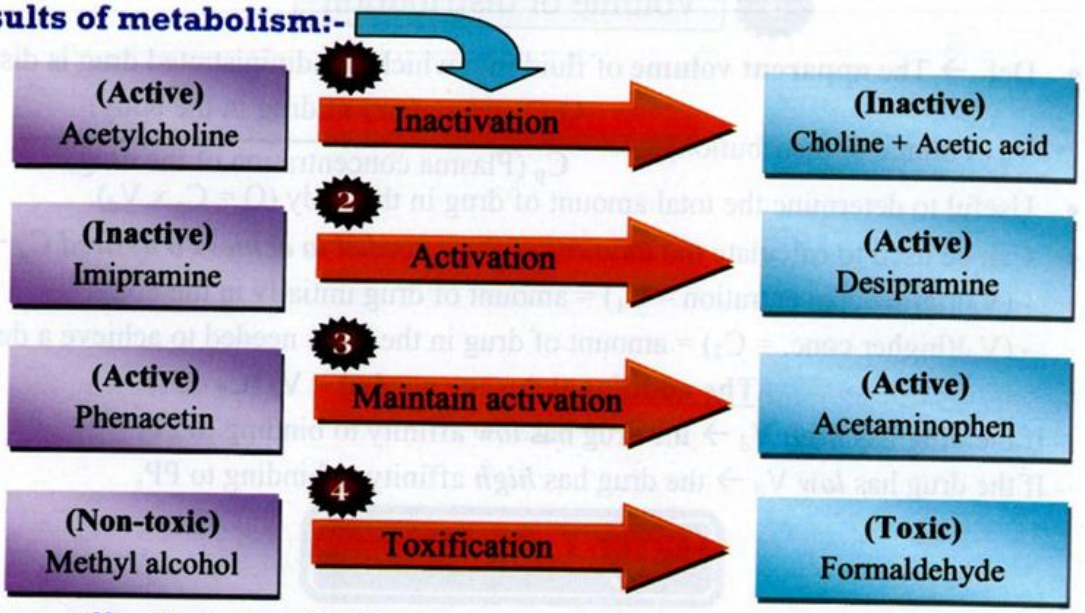
1: Oxidation e.g. Phenacetin → Acetaminophen
2: Reduction e.g. Chloral hydrate →Tri-chloro ethanol
3: Hydrolysis e.g. Acetylcholine → Choline + Acetic acid

Phase II (Conjugation)

Conjugation with →
1: Acetic acid (Acetylation) e.g. Isoniazid
2: Methylation e.g. Nor-adrenaline
3: Sulfate → Phenols
4: Glycine →Aspirin
5: Glucuronic acid → Chloramphenicol



➢ Results of metabolism:-



➢ Factors affecting metabolism:-

- **Age:** Deficiency of liver microsomal enzyme specially in child → prolonged action of drug increase toxicity e.g. Chloramphenicol (Grey baby syndrome).
- **Sex differences :** Metabolism rate of certain drugs faster in male than female e.g. Diazepam.
- **Genetic factor:** Absence of specific gene responsible for synthesis of special enzyme essential for normal metabolism.
- **State of health:** Presence of disease → alters in the normal metabolism.
- **Inhibition of microsomal enzymes:** Certain drugs inhibits the activity of microsomal enzyme → decrease metabolism rate → leading to prolongation the action of other drugs → increase activity and may leading to toxicity.
- **Induction of microsomal enzymes:** Certain drugs increase the activity of microsomal enzyme → leading to increase metabolism rate → decrease activity of drug other drugs.

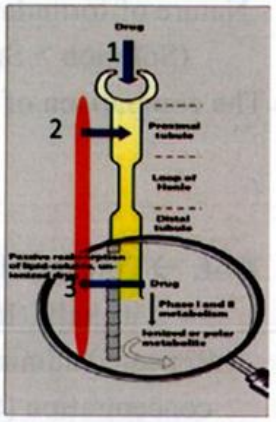
Hepatic microsomal enzyme (HME) inducers	Carbamazepine, Phenobarbital and Rifampicin.
Hepatic microsomal enzyme (HME) inhibitors	Cimetidine, Chloramphenicol, Omeprazole, Erythromycin and Ketoconazole

4) Excretion

- **Def.** → The process which involve excretion of drug outside of the body.
- **Routes of drug excretion:**

Renal	GIT	Skin	Lung
	Saliva (Iodide & Morphine) ***Stomach*** (Morphine) ***Bile*** - ***Feces***	***Sweat gland*** Rifampicin ***Breast (milk)*** Nicotine & Morphine	Gases e.g. Nitrous oxide (N_2O) and Halothane

1: Glomerular filtration: For water soluble non bound drugs.
2: Proximal (Active) tubular secretion: e.g. Penicillin.
3: Distal (Passive) tubular reabsorption: For lipid soluble drugs.
- ***Reabsorption may affected by pH :-***
  - *Acidification* of urine (Vit. C) → *Increase* excretion of *basic drugs* e.g. Ephedrine.
  - *Alkalization* of urine ($NaHCo_3$) → *Increase* excretion of *acidic drugs* e.g. Aspirin.



Method used to prolong duration of action of drugs

1 Decrease Absorption

1) Add Vasoconstrictor (Adrenaline + local anesthesia)
2) Use sparingly soluble complex (Protamine zinc insulin)
3) Use of drug in oil (Vasopressin in oil)
4) Use of slow release (SR) tablets
5) Use SC pellet implantation (DOCA in Addison's disease and contraception)

2 Decrease Metabolism

Use HME inhibitors e.g. Omeprazole & Erythromycin

3 Decrease Excretion

Probenecid with Penicillin

4 Increase protein binding

Add methoxy group to sulfonamide

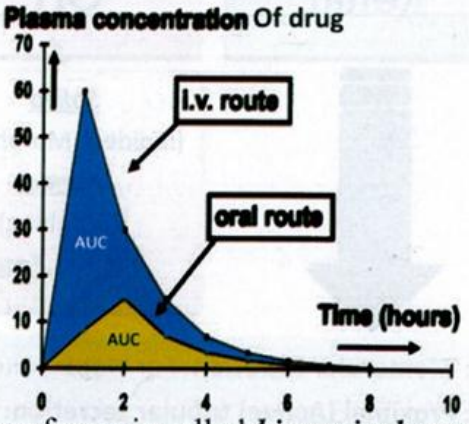
Pharmacokinetic parameters

1) Bioavailability (BA)

➢ **Def.** → The amount of administration drug reached to systemic circulation.

Oral bioavailability (F) = AUC_{oral}/AUC_{iv} X 100

AUC = Area under curve



➢ **Factors affecting bioavailability:-**

- First pass effect → ***Decrease*** bioavailability.
- Physicochemical properties of the drug.
  (Polarity – solubility – Particle size)
- Nature of formulation.
  (Solution > Suspension > Tablet)

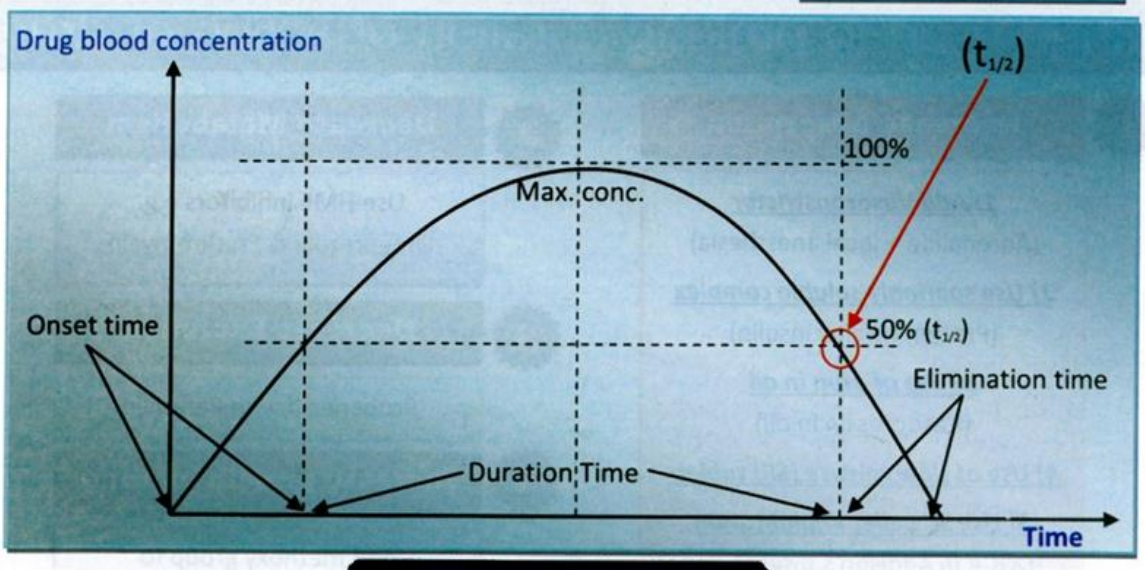
N.B: The comparison of the bioavailability of two dosage forms is called ***bioequivalence***.

2) Plasma half-life ($t_{1/2}$)

➢ **Def.** →Time needed by the body to decrease a plasma concentration of drug to its half. (It depend on clearance and Vd)

- Repeated administration of a drug at regular IV will reach plateau plasma concentration (Steady state concentration (C_{ss})) within 4-5 $t_{1/2}$
- The drug reach 90% of its final C_{ss} level = 3.3 X $t_{1/2}$

C_{ss} α Infusion rate

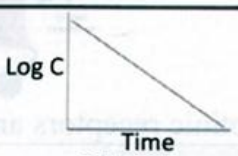
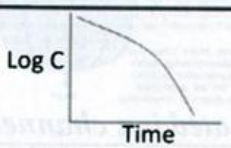


3) Clearance (Cl)

➢ **Def.** → It is volume of plasma cleared from the drug per unit time (ml/min).

$$Cl_{total} = Cl_{Hepatic} + Cl_{Renal} + Cl_{Pulmonary} + Cl_{others}$$

4) First order & Zero order kinetics

	First order (*Linear*) Kinetics	Zero order (*Saturation*) Kinetics
Def.	Elimination of the drug is directly proportional to its plasma concentration.	Elimination of the drug which is independent of time or concentration.
curve	 Linear	 Non-Linear
$T_{1/2}$	Constant	Increase with concentration
AUC	AUC α Concentration	AUC Not α Concentration
Change in dose	Dos not cause toxicity	Can cause toxicity
Example	Most drugs	Few drugs e.g. Alcohol
N.B: few drugs e.g. aspirin and phenytoin the type of elimination is dose related → At ***low*** concentration → first order → At ***high*** concentration → Zero order		

Pharmacodynamics

➢ **Def.** → What the ***drug*** does to the ***body*** (Mechanism of action of drugs)

Drug-Receptor interactions

$$D + R = DR$$

- D → Drug
- R → Receptor
- DR → Drug-Receptor complex.
- Biological effect ***increase*** when the drug receptor complex ***increases***.

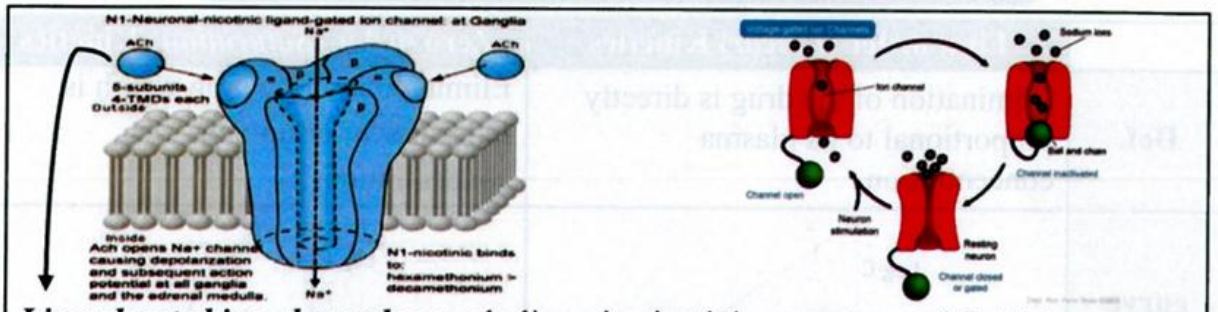
➢ **What is a Receptor?**

- Any biological molecule to which a drug binds and produces response.
- Drug or any substance activate or inactivate receptor called → **Ligand**.

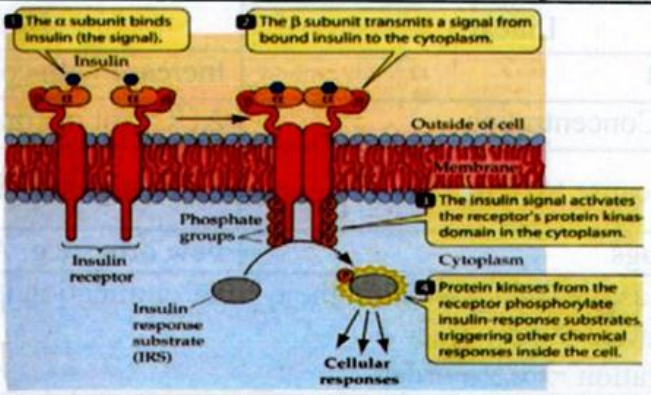
➢ **Major classes of receptors:-**

1. Ligand-gated and voltage-gated ion channels
2. G-protein-coupled receptors
3. Enzyme linked (Tyrosine kinase-linked) receptors
4. Intracellular receptors (e.g. Steroid receptors)

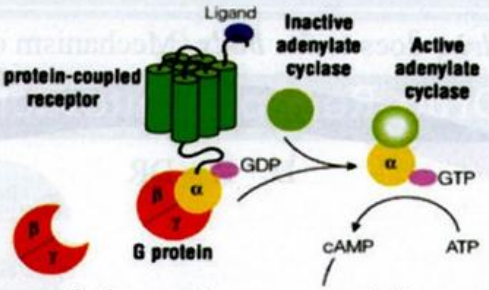
Classes of receptors



Ligand-gated ion channels e.g. cholinergic nicotinic receptors and GABA receptors



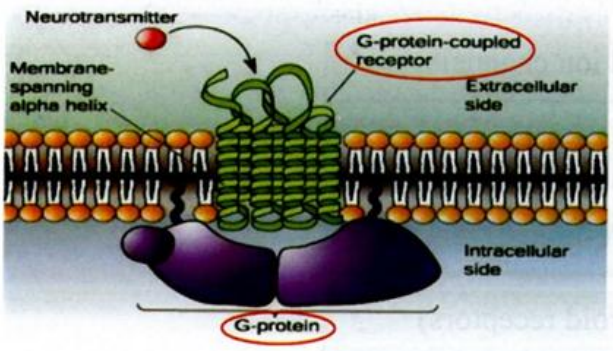
Tyrosine kinase-linked receptor e.g. insulin receptors

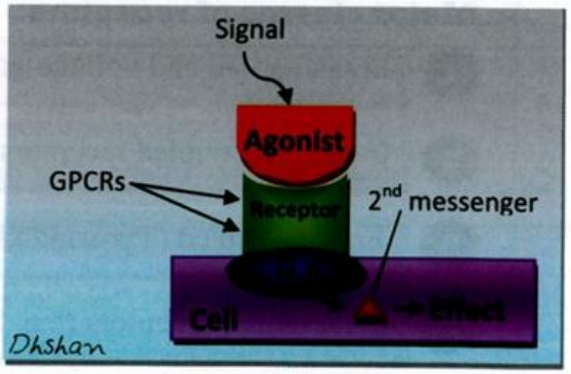


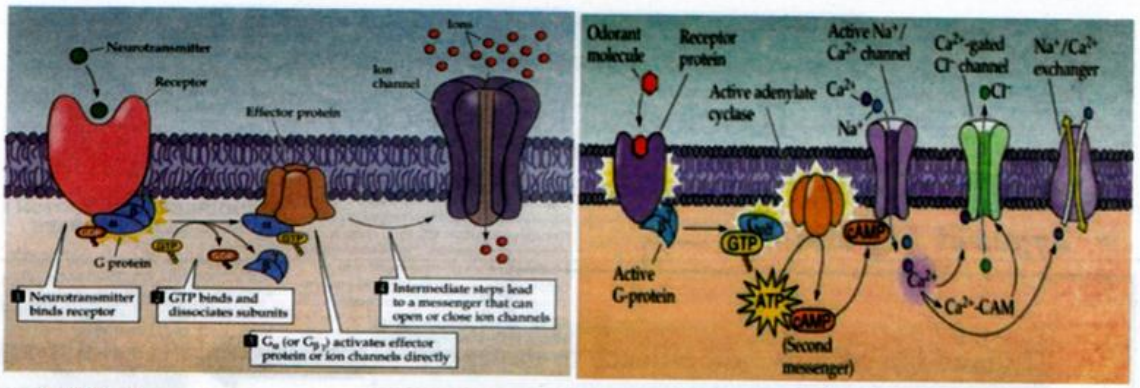
G-protein-coupled receptor e.g. α and β receptors

G-protein-coupled receptors (GPCRs)

- **G-protein and second messengers:-**
  - **G-protein** → Protein located in the cytoplasm between receptor and cell.

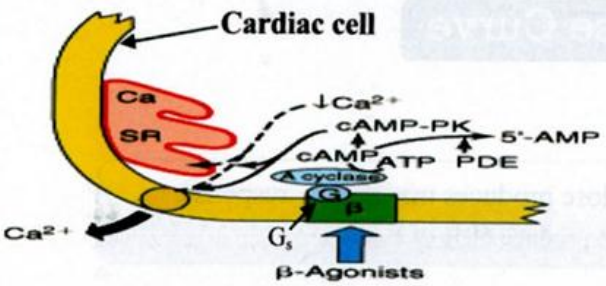






- **Main types:**
  - **G_s (Stimulatory)** → ***Activate*** adenylate cyclase → ***Increase*** cyclic adenosine monophosphate (cAMP) (secondary messenger) → Open Ca^{2+} channels and ***Increase*** Ca^{2+} influx from sarcoplasmic reticulum (SR).
  - **G_i (Inhibitory)** → ***Inactivate*** adenylate cyclase → ***Decrease*** cAMP → ***Decrease*** Ca^{2+} influx.
  - **G_q (Stimulatory)** → Increase phospholipase-C (PLC)→ PLC break phosphatidylinositol bisphosphate (PIP_2) into Inositol triphosphate (IP_3) and Diacylglycerol (DAG) → IP_3 ***increase*** Ca^{2+} influx.

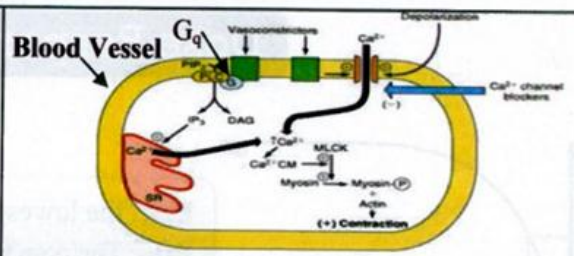
GPCRs in blood vessels and cardiac cell



β-agonist in cardiac muscle

Mechanism of G_s in cardiac cell:

Agonist binding to receptor → Stimulate receptor → stimulate G_s → Activate adenylate cyclase → ***Increase*** cAMP →***Increase*** Ca^{2+} from SR → ***Increase*** Ca^{2+} in the Cardiac Muscle → Activates myosin light chain kinase → Phosphorylates myosin→Interacts with actin →**Cardiac muscle contraction.**

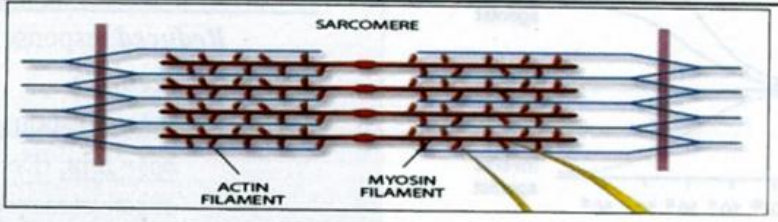


Vasoconstrictors Drugs

Mechanism of G_q in Blood vessel cell:

Agonist binding to receptor→ Stimulate receptor → stimulate G_q → increase PLC → PIP_2 → IP_3 + DAG

- ***Increase*** IP_3 →***Increases*** intracellular Ca^{2+}→Activates myosin light chain kinase →Phosphorylates myosin, interacts with actin → Contraction → **Vasoconstriction** (VC).



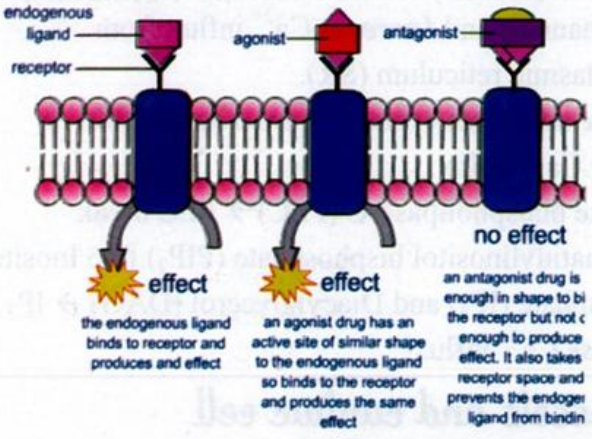
Ligand-receptor interaction

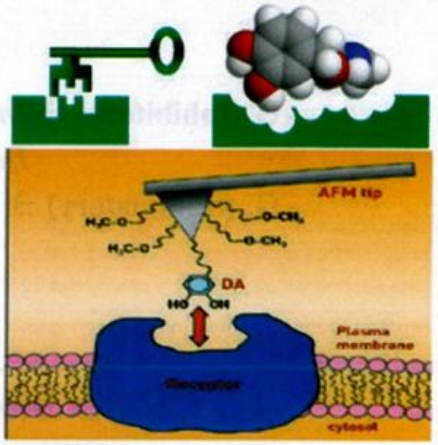
(Lock and key theory)

- **What is a Ligand?** Any substance combines with receptor.
- **Types of Ligand:-**

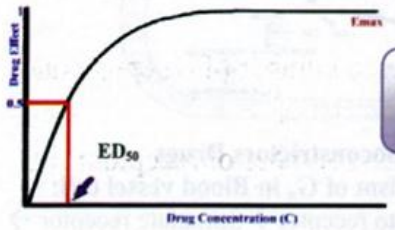
Ligand has affinity and efficacy to Receptor → **Agonist**

Ligand has affinity and not have efficacy to Receptor → **Antagonist**



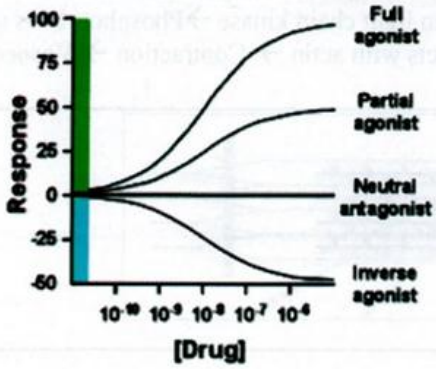


Dose Response Curve



E_{max}: the lowest dose produces maximum response.
ED_{50}: The dose that produce 50% of E_{max}.

Types of Agonists



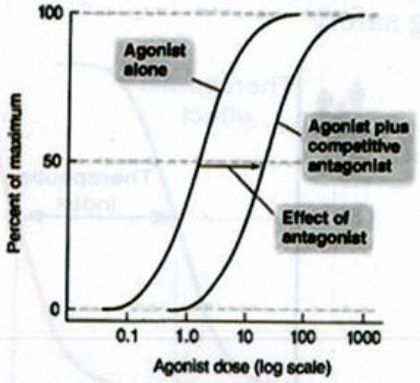
1: full agonist :
Maximum response efficacy

2: Partial (Dualist) agonist :
Reduced response or efficacy

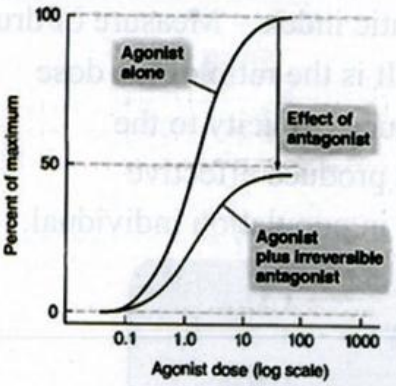
3: Inverse agonist :
Produce a response ***below the base line.*** (Decrease number of activated receptor)

Types of Antagonist (Blocker)

Competitive	Non competitive	
- Competed with the agonist on receptor and ***displaced*** by increase the dose of agonist.	- Act on the different site on the receptor and not ***displaced*** by increase the dose of agonist.	
- ***Parallel*** shift to the right in the curve.	- ***Non-Parallel*** shift to the right in the curve.	
- ***Decrease*** potency → ***Increase*** ED_{50}.	- ***Same*** potency → ***Same*** ED_{50}.	
- ***Same*** efficacy → ***Same*** E_{max}	- ***Decrease*** efficacy → ***Decrease*** E_{max}	
- E.g. Atropine	**Reversible**	**Irreversible**
	- Bind ***reversibly***	- Bind ***irreversibly***
	- ***Short*** acting	- ***Long*** acting
	- E.g. Succinylcholine	- E.g. Phenoxybenzamine



Competitive



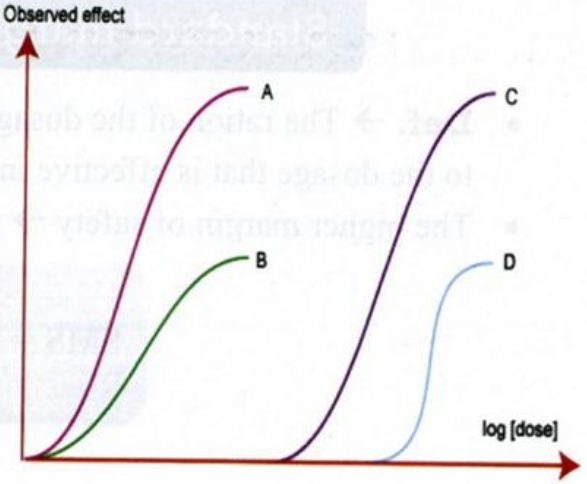
Non-competitive

Regulation of receptors

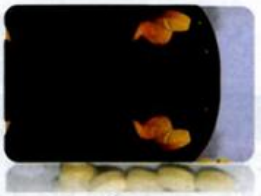
- Continuous stimulation of receptors with agonists → Decrease number of receptors and decrease sensitivity → ***Down regulation.***
- Continuous blocking of receptors with antagonists → Increase number of receptors and Increase sensitivity → ***Up regulation.***

Quiz: About the pharmacology of drug effect in the above figure, which of the following is incorrect?

A) B has higher potency than C
B) B has lower efficacy than C
C) When a competitive antagonist is added to drug A, its effect becomes like C.
D) When a non-competitive antagonist is added to drug A, its effect becomes like D.



Dose

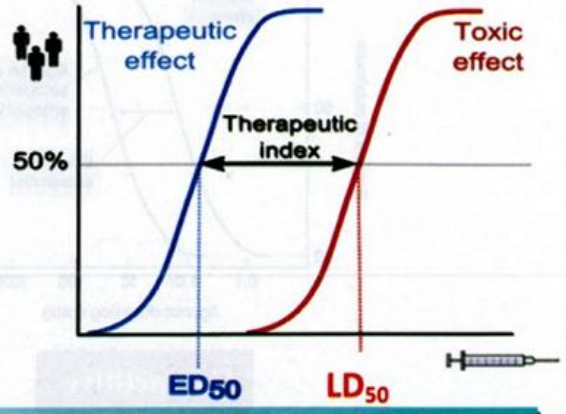


- **Def.** → The amount of drug given to the patient at a time.
- **Types of dose :-**
  - **Therapeutic dose:** The average dose that produce therapeutic effect.
  - **Maximum tolerated dose:** The largest dose of a drug that can be taken safely.
  - **Initial dose:** The dose used at start of treatment.
  - **Maintenance dose:** The dose required to maintain the therapeutic effect.
  - **Lethal dose or Fetal dose:** The dose that produce death.

Therapeutic Index (TI)

- Therapeutic index = Measure of drug safety
- **Def.** → It is the ratio of the dose that produces toxicity to the dose that produce effective response in population individual.

$$TI = \frac{LD_{50}}{ED_{50}}$$



TI = Therapeutic index.
LD_{50} = Drug dose that produces death in 50% of population.
ED_{50} = Drug dose that produces therapeutic effect in 50% of population.

N.B: ***Quantal dose response curve*** gives information about differences in the sensitivity of individuals to increasing doses of drugs.

Standard margin of safety (SMS)

- **Def.** → The ration of the dosage required to kill 1% of population compared to the dosage that is effective in 99% of population.
- The higher margin of safety → the better and safer.

$$SMS = \frac{LD_1}{ED_{99}}$$

➢ Factors affecting the dosage and action of drug :-

1: Age, weight and body surface area:

- Adult dose (20 - 60 years of age) and weight about 70 kg.
- Elderly required ***small dose*** (due to ***decrease*** renal excretion and ***decrease*** hepatic metabolism).
- Children required ***small*** dose (due to ***immature*** kidney and liver and ***decrease*** plasma protein).
- ***Calculation*** of child dose from adult dose.
  - ❖ **Young's formula :**

$$\text{Child dose} = \frac{\text{Adult dose X age in years}}{(\text{Age} + 12)}$$

  - ❖ **Dilling's formula :**

$$\text{Child dose} = \frac{\text{Adult dose X age in years}}{20}$$

  - ❖ **Clark's formula :**

$$\text{Infant dose} = \frac{\text{Adult dose X Wt. in pounds}}{150}$$

2: Sex:

- Female need ***smaller*** dose than male due to →
  - ❖ ***High fat*** content → ***increase*** fate in the body → ***slow rate*** of oxidation → ***decrease*** metabolism → ***increase*** drug effect.
  - ❖ Effect of sex hormone (estrogen) on liver Microsomal enzyme (LME).
  - ❖ Some drug avoided during pregnancy, lactation and menstruation.

3: Routes of administration:

- IV > IM > SC > Oral

4: Time of administration:

- Irritant drugs are better taken after meals e.g. Aspirin.
- CNS (Central Nervous System) stimulant drugs should be not given at night they may cause insomnia e.g. Ephedrine.

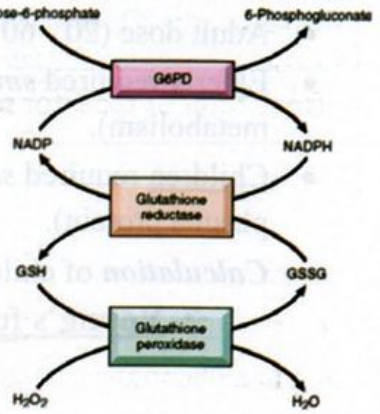
Symptoms of Insomnia

- Difficulty falling asleep
- Interrupted sleep
- Waking up early
- Light sleep
- Poor quality of sleep - not refreshed after sleeping

5: Genetic abnormality (Drug Idiosyncrasy)

- **Idiosyncrasy** (Pharmacogenetics) → Abnormal reaction due to genetic deficiency.

Example →



(Toxic)

- Primaquine, Sulfa and chloramphenicol are drugs may induce **hemolytic anemia** (Hemolysis of RBCs) in Patient with Glucose-6-phosphate dehydrogenase (G-6-PD) enzyme deficiency.
- G-6-PD enzyme protects RBCs from damage.
- G-6-PD enzyme responsible for convert NADP into NADPH which make detoxification of the drugs through glutathione system.

6: Hypersusceptibility (Supersensitivity) (Drug intolerance)	**7: Hypersensitivity (Drug allergy)**
- The greater response to Adrenaline in thyrotoxic patient. - Drug intolerance is commonly observed in infant → because metabolism and excretion not fully developed.	- Antibody-antigen interaction → increase release of histamine. **→ Symptoms** ***1 : skin reaction*** (Skin rash, itching and oedema) ***2: Fever*** ***3: Asthmatic attack*** (Difficult breathing) ***4: Anaphylactic shock*** e.g. Penicillin.

8: Tolerance

- **Def.** → Failure of responsiveness to the usual dose.
- **Types of tolerance:**
  - ✓ **Congenital Tolerance**

    - ❖ ***Racial*** → Ephedrine is not mydriatic in Negroes.

    - ❖ ***Species*** → Rabbits is tolerated large amount of belladonna due to ***atropine esterase enzyme*** in rabbit liver and plasma which rapidly detoxification of atropine.
    - ❖ ***Individual*** → Genetic factors are possibly involved.
  - ✓ **Acquired Tolerance**
    - ***Increase the dose to obtain the original effect***
      - ❖ ***Cross Tolerance*** → Between Nicotine and Lobeline (***similar***).
      - ❖ ***Tachyphylaxis*** (Acute) → e.g. Ephedrine → ***Increase*** blood Pressure then ***decrease*** (Gradually).
      - ❖ ***Bacterial resistance to antibiotics***.

Mechanism of acquired tolerance (Drug Desensitization)

Receptor Medicated	Non-Receptor Medicated
(Down-regulation of receptor) - Loss of receptor function. - Reduction of receptor number.	- Physiological adaptation - Reduction of receptor-coupled signalling component. - Reduction of drug concentration. - Change in kinetics of drugs.

Drug dependence

- It usually occurs after administration of CNS acting drugs.
- Is a phenomena related to tolerance.
- It involves a certain degree of tissue adaptation.
- Withdrawal of the drug could produce certain unpleasant symptoms.
- **Types of dependence:-**

Habituation	Addiction
- Mild degree of drug dependence. - ***Psychic*** dependence. - When drug stopped → develop some emotional distress for a relative short period. - E.g. Smoking and Coffee.	- More 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 Interactions

After administration of drugs

A Pharmacokinetic Interactions

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 more absorbed in the stomach and weak base drugs more absorbed in intestine.
- ***Presence of food and other drug 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

- ***HME inducers*** e.g. Phenytoin → ***increase*** metabolism of other drugs.
- ***HME inhibitors*** e.g. Cimetidine→ ***decrease*** metabolism f other drugs

4) Excretion

- Probenecid →***decrease*** excretion of penicillin.
- pH change e.g. acidification of urine → ***Increase*** excretion of weak base

B Pharmacodynamic Interactions

Def. → Drug interact with another drug when presence of both in the body.

➢ **May be →**

Increase in Drug effect

Addition (Summation)
- ***Algebraic sum*** of the 2 drugs effect.
- 1 + 1 = 2
- E.g. Acetylcholine + histamine in contraction of intestine

Synergism
- The combination effect ***more than*** algebraic sum.
- 1 + 1 => 2
- E.g. Ethanol and Barbiturates → Sever ↓CNS

Potentiation
- ***Inactive*** drug which ***increase*** activity of ***active*** drug.
- 0 + 1 => 1
- E.g. Physostigmine + Acetylcholine

Decrease in Drug effect

Antagonism

Chemical antagonism
- Chemical interaction between 2 drugs → ***decrease*** absorption.
- E.g. Heparin + Protamine sulfate

Physiological (Functional) antagonism
- 2 drugs act on 2 ***different receptors → Different mechanism of action → Different effect.***
- E.g. Adrenaline and Histamine

Bronchi → Adrenaline → β_2 → Bronchodilatation

Bronchi → Histamine → H_1 → Bronchoconstriction

Pharmacological antagonism
- 2 drugs act on the same receptor but one of them is agonist and the other is antagonist.

Non-competitive
Organophosphate with Acetylcholine

Competitive
Atropine with Acetylcholine

Questions

➢ Coose the best answer

1: Which route of administration is most likely to subject a drug to a first pass effect?

a. Intravenous b. Inhalational c. Oral d. Sublingual (SL) e. Intramuscular

2: Two drugs may act on the same tissue or organ through independent receptors, resulting in effects in opposite directions. This is known as

a. Physiologic antagonism b. Chemical antagonism c. Competitive antagonism

d. Irreversible antagonism e. Dispositional antagonism

3: Which of the following is classified as belonging to the tyrosine kinase family of receptors?

a. GABAA receptor b. β-adrenergic receptor c. Insulin receptor

d. Nicotinic II receptor e. Hydrocortisone receptor

4: Drug products have many types of names. Of the following types of names that are applied to drugs, the one that is the official name and refers only to that drug and not to a particular product is the

a. Generic name b. Trade name c. Brand name

d. Chemical name e. Proprietary name

5: Identical doses of a capsule preparation (X) and a tablet preparation (Y) of the same drug were compared on a blood concentration-time plot with respect to peak concentration, time to peak concentration, and AUC after oral administration as shown in the figure below. This comparison was made to determine which of the following?

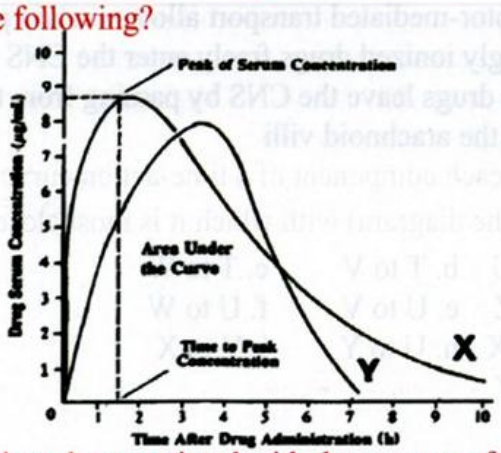
a. Potency

b. Extent of plasma protein binding

c. Bioequivalence

d. Therapeutic effectiveness

e. None of the above



6: Of the following characteristics, which is unlikely to be associated with the process of facilitated diffusion of drugs?

a. The transport mechanism becomes saturated at high drug concentrations

b. The process is selective for certain ionic or structural configurations of the drug

c. If two compounds are transported by the same mechanism, one will competitively inhibit the transport of the other

d. The drug crosses the membrane against a concentration gradient and the process requires cellular energy

e. The transport process can be inhibited noncompetitively by substances that interfere with cellular metabolism

7: In comparing the following possible routes, which is associated with the excretion of quantitatively small amounts of drugs or their metabolic derivatives?

a. Biliary tract **b. Kidneys** **c. Lungs**
d. Feces e. Milk

8: Of the following, which is a phase II biotransformation reaction?

a. Sulfoxide formation b. Nitro reduction c. Ester hydrolysis
d. Sulfate conjugation e. Deamination

9: Which of the following is unlikely to be associated with oral drug administration of an enteric-coated dosage form?

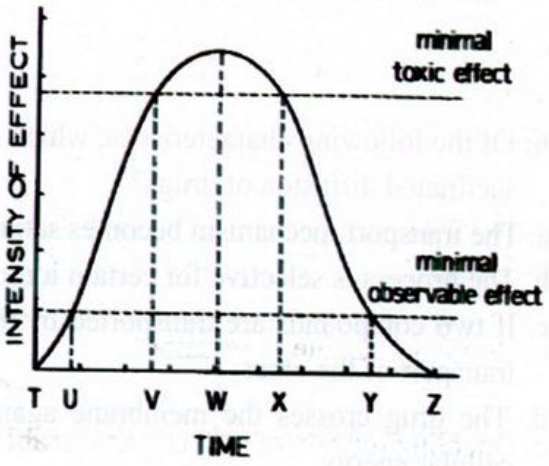
a. Irritation to the gastric mucosa with nausea and vomiting
b. Destruction of the drug by gastric acid or digestive enzymes
c. Unpleasant taste of the drug
d. Formation of non-absorbable drug-food complexes
e. Variability in absorption caused by fluctuations in gastric emptying time

10: Of the following, which is unlikely to be associated with drug distribution into and out of the central nervous system (CNS)?

a. The blood-brain barrier, which involves drug movement through glial cell membranes as well as capillary membranes, is the main hindrance to drug distribution to the CNS
b. Most drugs enter the CNS by simple diffusion at rates that are proportional to the lipid solubility of the non-ionized form of the drug
c. Receptor-mediated transport allows certain peptides to gain access to the brain
d. Strongly ionized drugs freely enter the CNS through carrier-mediated transport systems
e. Some drugs leave the CNS by passing from the cerebrospinal fluid into the dural blood sinuses through the arachnoid villi

11: For each component of a time-action curve listed below, choose the lettered interval (shown on the diagram) with which it is most closely associated:

a. T to U b. T to V c. T to W
d. T to Z e. U to V f. U to W
g. U to X h. U to Y i. V to X
j. X to Y



I: Time to peak effect

a	b	c	d	e	f	g	h	i	j

II: Time to onset of action

a	b	c	d	e	f	g	h	i	j

III: Duration of action

a	b	c	d	e	f	g	h	i	j

12: For each description below, select the transmembranal transport mechanism it best defines:

a. Filtration b. Simple diffusion c. Facilitated diffusion
d. Active transport e. Endocytosis

I: Lipid-soluble drugs cross the membrane at a rate proportional to the concentration gradient across the membrane and the lipid:water partition coefficient of the drug	a	b	c
	d	e	
II: Bulk flow of water through membrane pores, resulting from osmotic differences across the membrane, transports drug molecules that fit through the membrane pores	a	b	c
	d	e	
III: After binding to a proteinaceous membrane carrier, drugs are carried across the membrane (with the expenditure of cellular energy), where they are released	a	b	c
	d	e	

13: For each description of a drug response below, choose the term with which it is most likely to be associated:

a. Supersensitivity b. Tachyphylaxis c. Tolerance
d. Hyposensitivity e. Anaphylaxis

I: Immunologically mediated reaction to drug observed soon after administration

a	b	c	d	e

II: A rapid reduction in the effect of a given dose of a drug after only one or two doses

a	b	c	d	e

III: Hyperreactivity to a drug seen as a result of denervation

a	b	c	d	e

14: A drug, given as a 100 mg single dose results in a peak plasma concentration of 20µg/ml. the apparent volume of distribution is:

a. 0.5 L b. 1 L c. 2 L
d. 5 L e. 10 L

15: A drug with a half-life of 12 hours is administered by continues IV infusion. How long will it take for the drug to reach 90% of this final steady state level?

a. 18 hours b. 24 hours c. 30 hours
d. 40 hours e. 90 hours

16: Which of the following results in a doubling of the Steady state concentration Css of a drug?

a. Doubling the rate of infusion

b. Maintaining the rate of infusion but doubling the the loading dose.

c. Doubling the rate of infusion and doubling the concentration of the infused drug.

d. Tripling the rate of infusion.

e. Quadrupling the rate of infusion.

17: A heart failure patient shows digoxin toxicity. She received 125mcg as standard dose. Serum levels were reported to be 2 ng/ml (2mcg/L). Target therapeutic level is 0.8 ng/ml. What is additional dosage should she receive?

a. 25 mcg b. 50 mcg c. 75 mcg
d. 100 mcg e. 125 mcg

18: Drug X produces maximum contraction of cardiac muscle in manner similar to epinephrine. Drug X is considered to be a

a. Agonist b. Partial agonist c. competitive antagonist
d. Irreversible antagonist e. inverse agonist

19: Which of the following statements is correct?

a. If 10mg of Drug A produces the same response as 100 mg of drug B, drug A is more efficacious than drug B.

b. The greater the efficacy, the greater the potency of a drug.

c. In selecting a drug, potency is usually more important than efficacy.

d. A competitive antagonist increase the ED_{50}.

e. Variation in response to a drug among different individuals is most likely to occur with a drug showing a large therapeutic index.

20: Variation in the sensitivity of a population of individuals to increasing doses of a drug is best determination by which of the following?

a. Efficacy b. Potency c. Therapeutic index
d. Grade dose-response curve e. Quantal dose-response curve

Answers

1	2	3	4	5	6	7	8	9	10
c	a	c	a	c	d	e	d	e	d

11	12	13	14	15	16	17	18	19	20
I: c II: a III: h	I: b II: a III: d	I: e II: b III: a	d	d	a	b	a	d	e

Questions and answers from (References):

Basic and Clinical Pharmacology 12th edition, Katzung-Lange

Pharmacology 12th edition PreTest Self-Assessment and Review

Pharmacology 5th edition Lippincott Williams & Wilkins

ANS

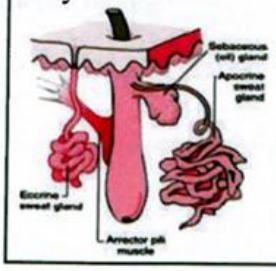
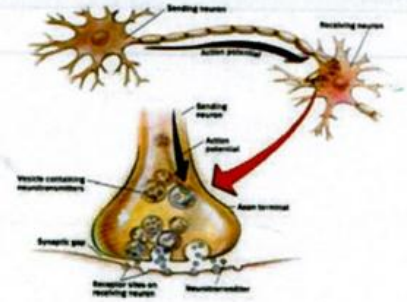
(AUTONOMIC NERVOUS SYSTEM)

Nervous system

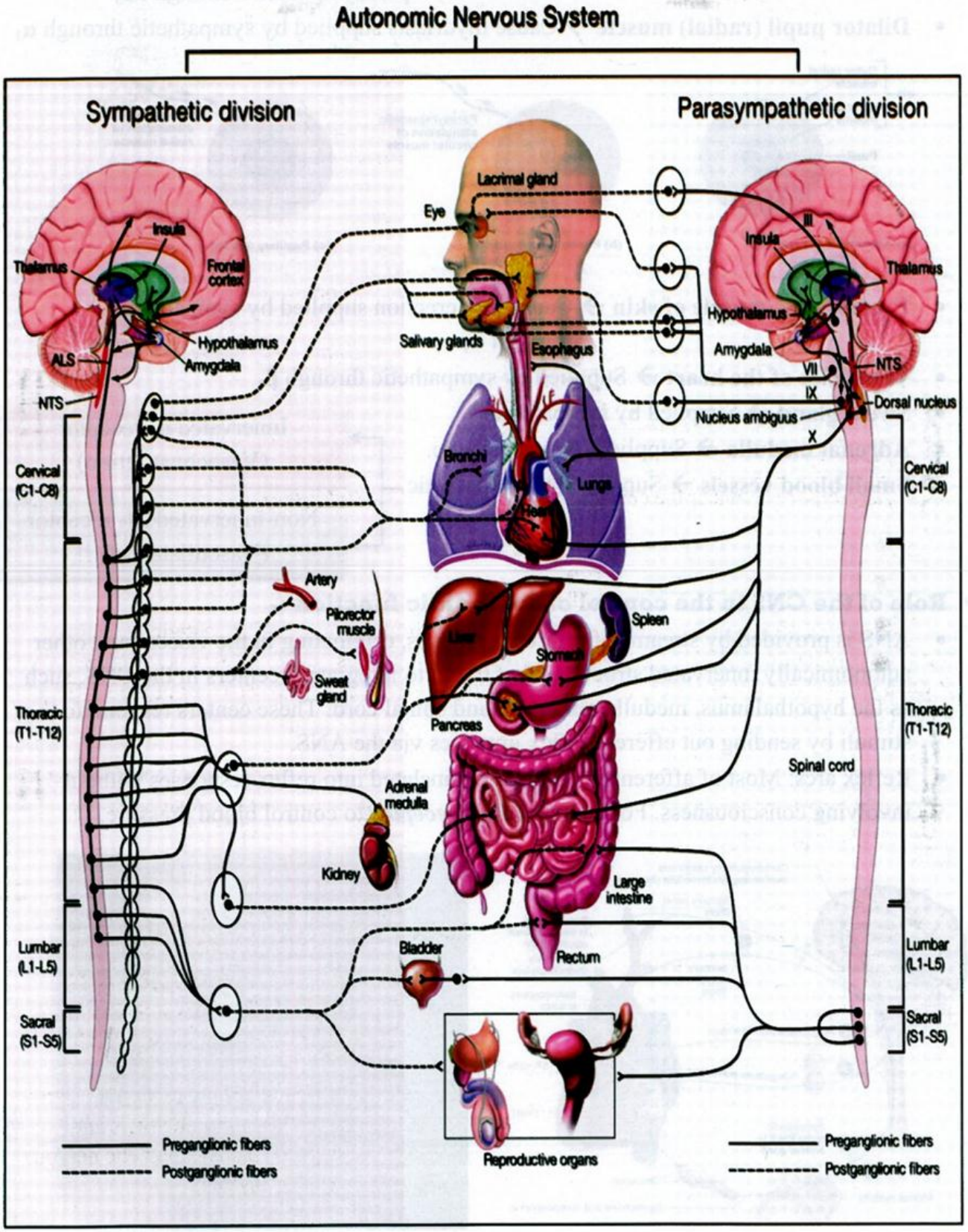
- **(CNS) Central Nervous System**
  - Brain
  - Spinal cord
- **(PNS) Peripheral Nervous System**
  - **Afferent Division**
    - Important in the reflex regulation of the system
  - **Efferent Division**
    - **Autonomic Nervous System**
      - Supply cardiac muscle, smooth muscle and exocrine gland.
      - ***Relay*** in autonomic ganglia which consist of ***preganglionic*** & ***postganglionic*** fibers.

      - ***Involuntary*** → under the control of CNS.
    - **Somatic Nervous System**
      - Supply skeletal muscle.
      - ***Don't relay*** in ganglia.

      - ***Voluntary***.

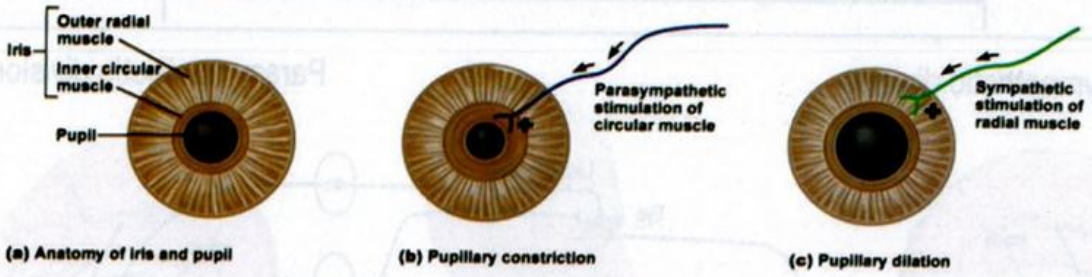
1) Sympathetic	2) Parasympathetic	3) Enteric neurons
(Thoraco-lumbar outflow) → Arise from thoracic and Lumbar regions (L_1 to L_2) of the spinal cord.	**(Cranio-sacral outflow)** → Arise from cranial nerves 3rd(Oculomotor) 7th(Facial) 9th(Glossopharyngeal) 10th(Vagus) and from 2nd,3rd and 4th sacral segments.	- The enteric nervous system is the ***third division*** of the ANS. - It is a collection of nerve fibers that innervate GIT. - This system functions independently of the CNS and control the motility, exocrine and endocrine secretions. - It is modulated by both the sympathetic and parasympathetic nervous system.
- Consist of ***short*** preganglionic fibers and ***long*** postganglionic fibers.	- Consist of ***long*** preganglionic fibers and ***short*** postganglionic fibers.	
Chemical transmitters - Adrenaline and Nor-adrenaline → **Except at**- Thermoregulatory sweat gland and adrenal medulla they release Ach  **Apocrine** (nonthermoregulatory) → Sympathetic. **Eccrine** (Thermoregulatory) → Parasympathetic	**Chemical transmitters** - Ach (Acetylcholine) 	

- **Most organs are supplied with dual innervations of sympathetic and parasympathetic which produce opposite effect.**



➢ Some organs are Supplied with one division of ANS :-

- **Constrictor pupil (circular) muscle (CPM)→** Cause miosis supplied by parasympathetic through M_3
- **Dilator pupil (radial) muscle →** Cause mydriasis supplied by sympathetic through α_1



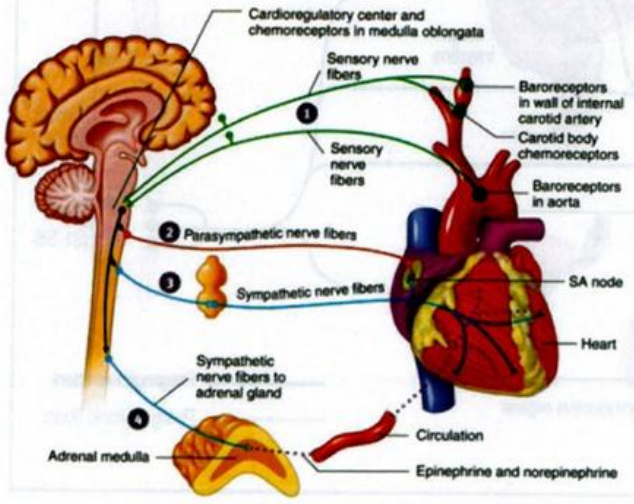
- **Erector pale muscle of skin →** Cause hair erection supplied by sympathetic through α_1
- **Ventricles of the heart →** Supplied by sympathetic through β_1
- **Sweat gland →** Supplied by sympathetic.
- **Adrenal medulla →** Supplied by sympathetic.
- **Small blood vessels →** Supplied by sympathetic.

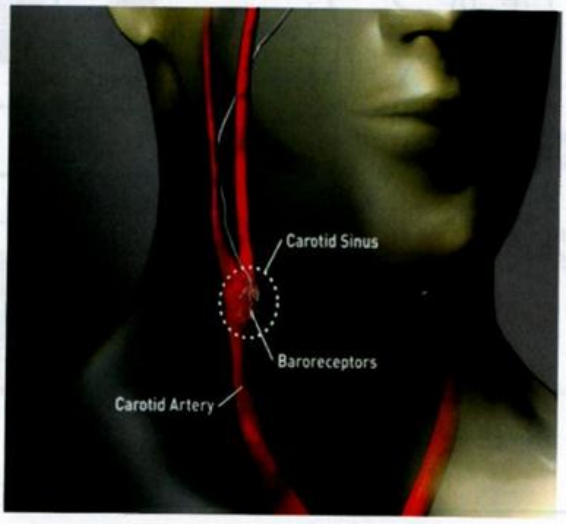
Innervated α_1 receptor (Vasoconstriction)

Non-innervated M_3 receptor (Vasodilatation)!!!

➢ Role of the CNS in the control of autonomic function :-

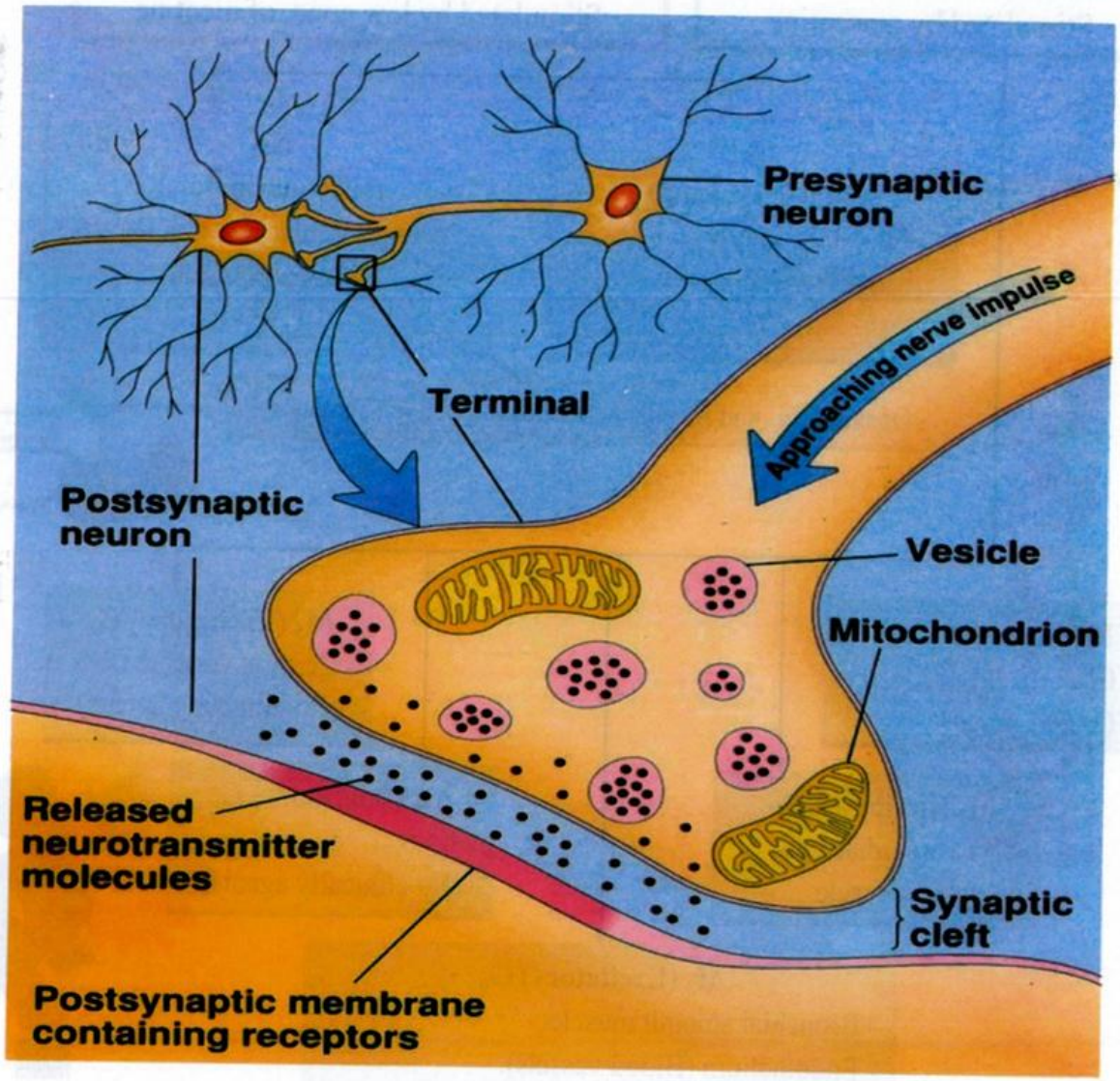
- ANS is provided by streams of afferent impulses, originating in the viscera and other autonomically innervated structures that travel to integrating centers in the CNS, such as the hypothalamus, medulla oblongata and spinal cord. These centers respond to the stimuli by sending out efferent reflex impulses via the ANS.
- Reflex arcs: Most of afferent impulses are translated into reflex responses without involving consciousness. For example ***Baroreceptor*** to control blood pressure.





Chemical Transmitters

- **Def.** → Chemical Substances released from stimulated nerve ending responsible for transmits of nerve impulse from one nerve fiber to other.
- **Location :-**
  - Chemical transmitter for parasympathetic is ACh.
  - Chemical transmitter for sympathetic is mainly adrenaline (Epinephrine) and nor-adrenaline (Nor-epinephrine)
  - Other transmitters e.g. Non-adrenergic Non-cholinergic (NANC) they act as co-transmitter → Small proportion of nerves e.g. Corpus cavernosum penis which release → Co-transmitter nitric oxide (NO) → Increase cGMP→ VD → Erection.



Synapse

See pages 16 & 17

Autonomic receptors

Parasympathetic (Cholinergic receptors)

Sympathetic (Adrenergic receptors)

Next page

Peripheral Cholinergic **(Muscarinic receptors)**

Central Cholinergic **(Nicotinic receptors)**

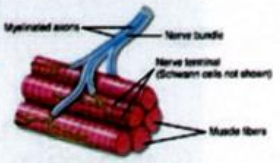
Stimulated by muscarine

Stimulated by low conc. of nicotine

N_N
(Nicotinic neural)
- Autonomic ganglia
- Adrenal medulla
- CNS

N_M
(Nicotinic muscle)
- Neuromuscular junction (NMJ).
(Skeletal muscle)

Opening Na^+ and K^+ channels (ligand-gated ion channels)



M_1 (Excitatory) G_q
- CNS (Brain)
- Gastric mucosa

M_5 (Excitatory) G_q
- Cerebral vessel & CNS
(No clinically agents)

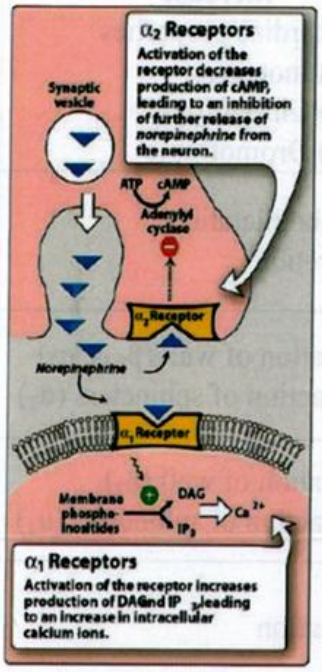
M_2 (Inhibitory) G_i
- Heart (cardiac cell)
- Smooth muscle

M_4 (Inhibitory) G_i
- CNS
(No clinically agents)

M_3 (Excitatory) G_q
- Bronchial smooth muscle.
- Endothelium (Blood vessels).
- Exocrine gland, Urinary bladder and Eye.

Sympathetic (Adrenergic receptors)

α (Alpha adrenergic receptor)



α subdivision

- α_{1A}, α_{1B}, α_{1C} & α_{1D}
- α_{2A}, α_{2B} & α_{2C}

For example → Tamsulosin is selective α_{1A} antagonist.

α_1 (Excitatory Action) G_q

- ***Postsynaptic*** on effector organ e.g. **Eye and Vascular smooth muscle.**

Action

VC

Mydriasis

α_2 (Inhibitory Action) G_i

- ***Presynaptic*** nerve ending
- β cell of pancreas

Action

CNS

Symp. activity

Renin and insulin

Nor-Adrenaline

(Feedback inhibition)

β (Beta adrenergic receptor)

β_1 (Excitatory) G_s

- Presynaptic nerve
- Postsynaptic effectors cells especially → **Heart**

Action

Renin

Heart contraction

lipolysis

β_2 (Inhibitory Action) G_s

- Presynaptic nerve.
- Postsynaptic effectors cells especially → **Bronchi, GIT and Skeletal muscle.**

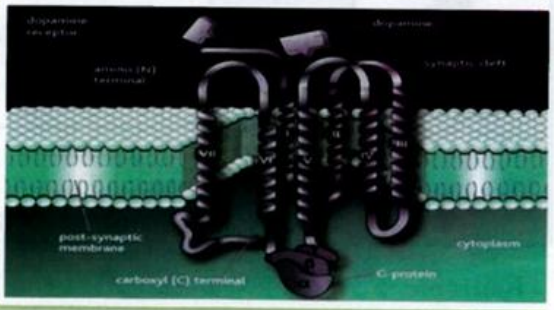
Action

Bronchodilatation, Relax smooth muscle (Uterine) and skeletal muscle twitches (VD)

β_3 (Excitatory Action) G_s

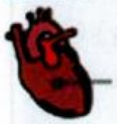
- Increase lipolysis (increase FFA)

Dopamine receptors	
D_1 and D_5 → Brain; effector tissues, especially smooth muscle of the renal blood vessels.	G_s
D_2 → Brain; effector tissues, especially smooth muscle; presynaptic nerve.	G_i
D_3 → Brain	G_i
D_4 → Brain, Cardiovascular system	G_i

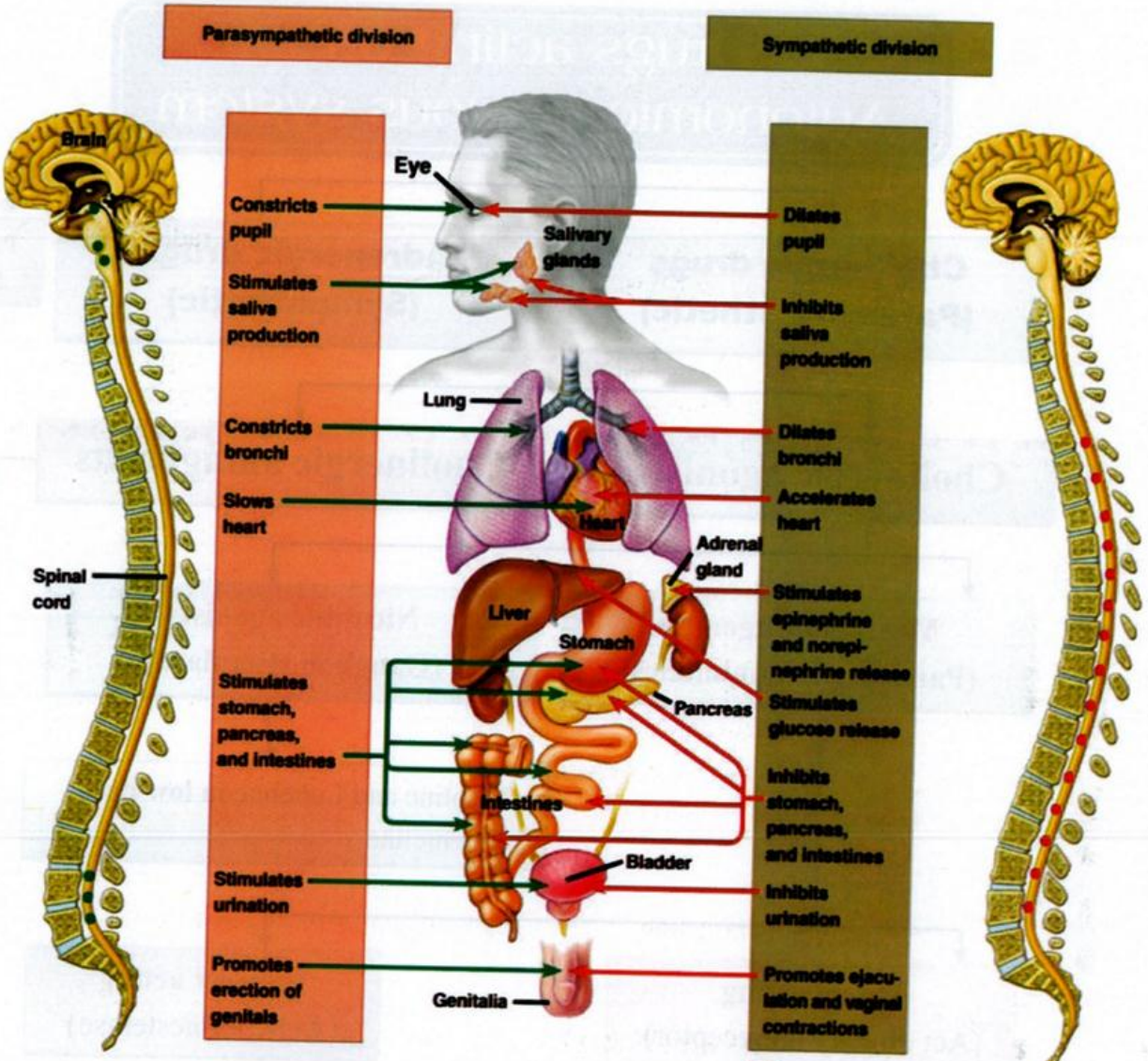


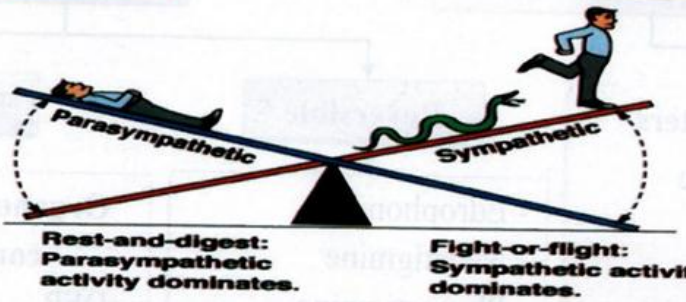
N.B: → β_2 → Gs → Increase cAMP in Smooth muscle → Relaxation of muscle (Inhibitory Action)
→ β_1 → Gs → Increase cAMP in Cardiac muscle → Contraction of muscle (Excitatory Action)

Effect of stimulation of Sympathetic and parasympathetic

Organ	Receptor	Parasympathetic	Receptor	Sympathetic
Eye 	M_3	Contraction circular muscle → Miosis	α_1	Contraction radial muscle → Mydriasis
Heart 	M_2	**Decrease** cardiac properties (-ve) Inotropic (-ve) Chronotropic (-ve) Dromotropic	β_1	**Increase** cardiac properties (+ve) Inotropic (+ve) Chronotropic (+ve) Dromotropic
Bronchi 	M_3	- Bronchoconstriction - ↑ Secretion	β_2	- Bronchodilatation - ↓ Secretion
GIT 	M_3	- Contraction of wall - Relaxation of sphincters	α & β	- Relaxation of wall (β_2 & α_2) - Contraction of sphincters (α_1)
UB 	M_3	- Contraction of wall. - Relaxation of sphincters.	α & β	- Relaxation of wall (β_2) - Contraction of sphincters (α_1)
Uterus 	M_3	- Contraction	β_2	- Relaxation
Salivation 	M	- Increase (Watery)	α_1	- Decrease
BV 	M_3	- Vasodilatation (VD) → due to release of NO	α & β	- Vasoconstriction (VC)→ α_1 - Vasodilatation (VD) on Skeletal muscle → β_2
Sex organ 	M_3	- Erection	α_1	- Ejaculation
Insulin release	M	- Increase	α & β	- Increase → β_2 - Decrease → α_2 (Main effect)
Metabolism	- Increase lipolysis → β_3 - Decrease lipolysis → α_2 - Increase Renin release → β_1			- Gluconeogenesis →β_2 & α - Glycogenolysis →β_2 & α - Decrease Renin release → α_2

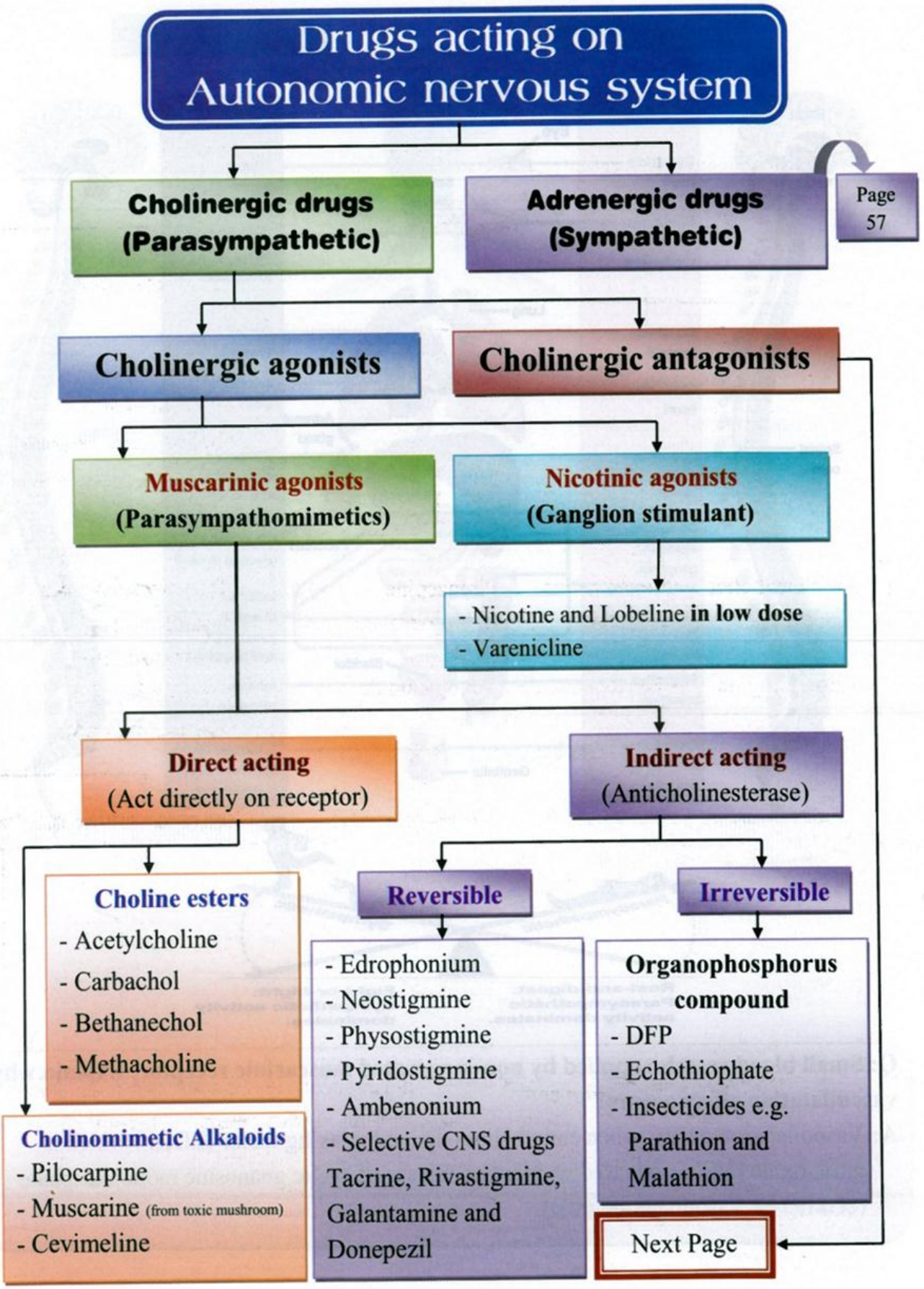
- **Inotropic** → Force of contraction.
- **Chronotropic** → Heart rate.
- **Dromotropic** → Conduction of the electrical impulses in the heart
- **Bradycardia** → Heart slowness
- **Tachycardia** → Accelerated of the heart

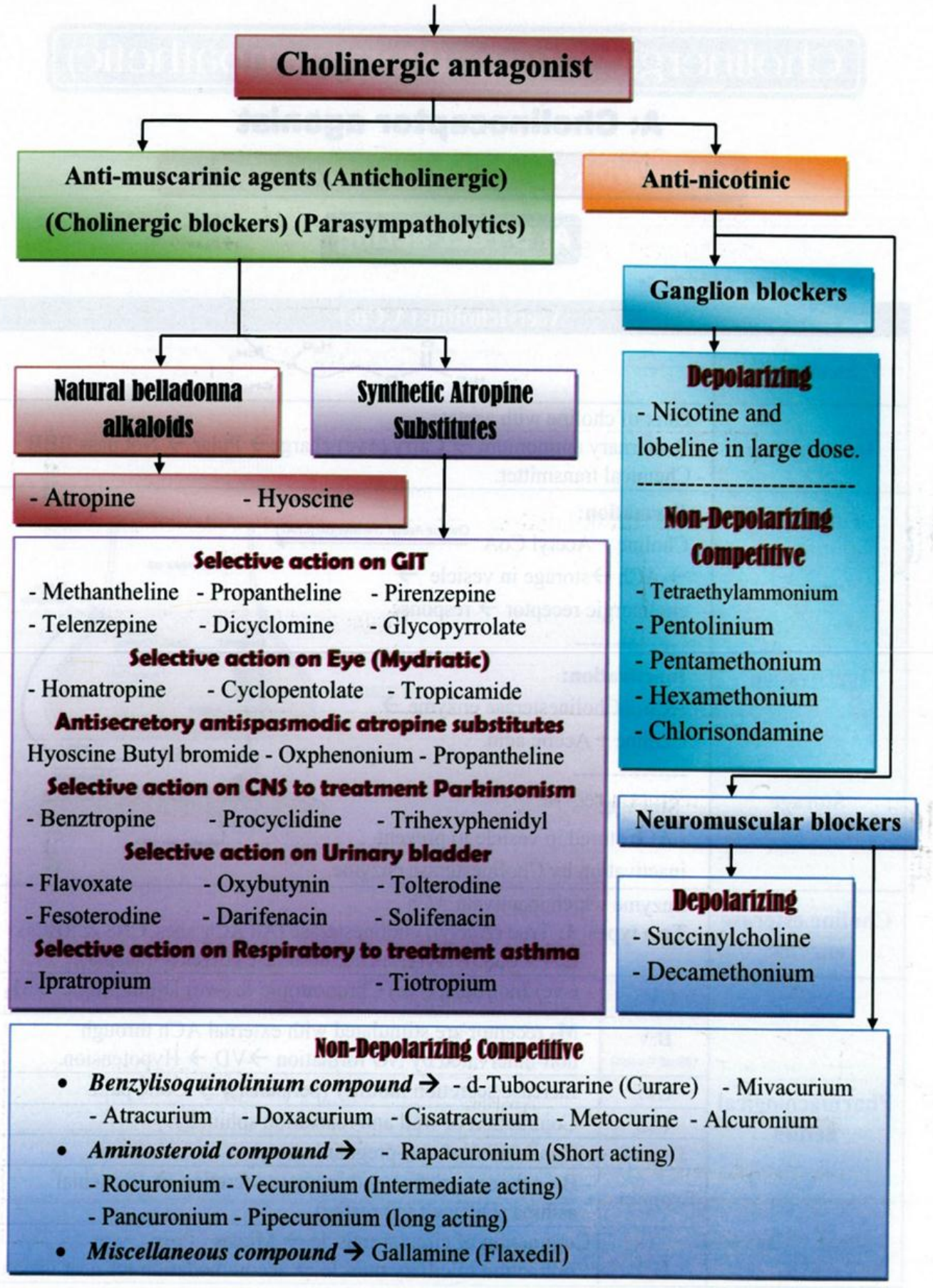




Q: Small blood vessels supplied by non-innervated muscarinic receptor, Explain why vasodilatation effect occurs?

A: Vasodilatation occurs when endothelium derived relaxing factor (EDRF) which is nitric oxide (NO) is released → increase release of cyclic guanosine monophosphate (cGMP) → Vasodilatation (VD).


Drugs acting on Autonomic nervous system
Cholinergic drugs (Parasympathetic)
Adrenergic drugs (Sympathetic)
Page 57
Cholinergic agonists
Cholinergic antagonists
Muscarinic agonists (Parasympathomimetics)
Nicotinic agonists (Ganglion stimulant)
- Nicotine and Lobeline in low dose
- Varenicline
Direct acting (Act directly on receptor)
Indirect acting (Anticholinesterase)
Choline esters
- Acetylcholine
- Carbachol
- Bethanechol
- Methacholine
Reversible
Irreversible
Cholinomimetic Alkaloids
- Pilocarpine
- Muscarine (from toxic mushroom)
- Cevimeline
- Edrophonium
- Neostigmine
- Physostigmine
- Pyridostigmine
- Ambenonium
- Selective CNS drugs Tacrine, Rivastigmine, Galantamine and Donepezil
Organophosphorus compound
- DFP
- Echothiophate
- Insecticides e.g. Parathion and Malathion
Next Page


Cholinergic antagonist
Anti-muscarinic agents (Anticholinergic)
(Cholinergic blockers) (Parasympatholytics)
Anti-nicotinic
Ganglion blockers
Natural belladonna alkaloids
Synthetic Atropine Substitutes
- Atropine - Hyoscine
Depolarizing
- Nicotine and lobeline in large dose.
Non-Depolarizing Competitive
- Tetraethylammonium
- Pentolinium
- Pentamethonium
- Hexamethonium
- Chlorisondamine
Selective action on GIT
- Methantheline - Propantheline - Pirenzepine
- Telenzepine - Dicyclomine - Glycopyrrolate
Selective action on Eye (Mydriatic)
- Homatropine - Cyclopentolate - Tropicamide
Antisecretory antispasmodic atropine substitutes
Hyoscine Butyl bromide - Oxphenonium - Propantheline
Selective action on CNS to treatment Parkinsonism
- Benztropine - Procyclidine - Trihexyphenidyl
Selective action on Urinary bladder
- Flavoxate - Oxybutynin - Tolterodine
- Fesoterodine - Darifenacin - Solifenacin
Selective action on Respiratory to treatment asthma
- Ipratropium - Tiotropium
Neuromuscular blockers
Depolarizing
- Succinylcholine
- Decamethonium
Non-Depolarizing Competitive
• Benzylisoquinolinium compound → - d-Tubocurarine (Curare) - Mivacurium
- Atracurium - Doxacurium - Cisatracurium - Metocurine - Alcuronium
• Aminosteroid compound → - Rapacuronium (Short acting)
- Rocuronium - Vecuronium (Intermediate acting)
- Pancuronium - Pipecuronium (long acting)
• Miscellaneous compound → Gallamine (Flaxedil)

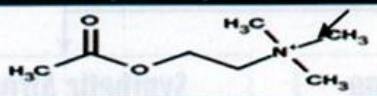
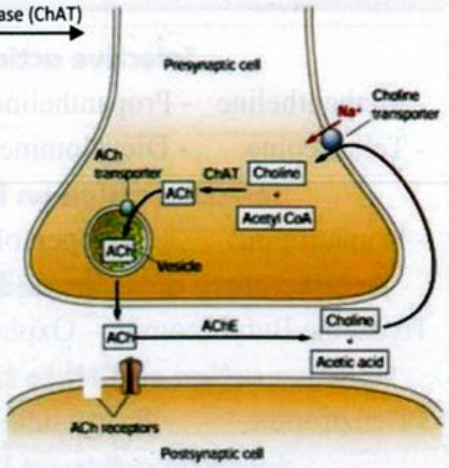
Cholinergic drugs (Parasympathetic)

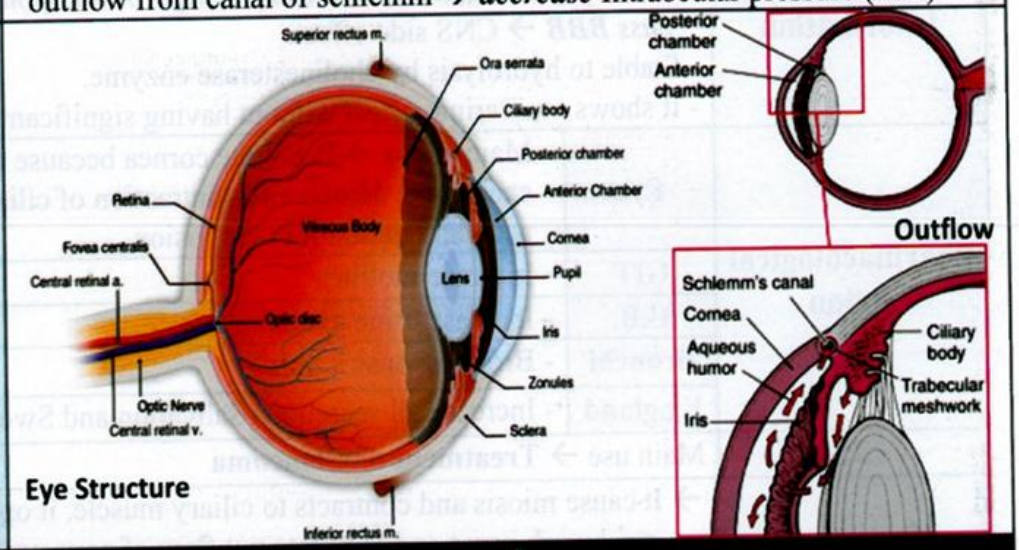
A: Cholinoceptor agonist

1: Muscarinic agonists (*Parasympathomimetics*)

A: Direct-acting

❖ **Choline esters :-**

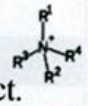
Acetylcholine (A.Ch.)		
Structure		
Information	- Ester of choline with acetate. - Quaternary ammonium → Carry (+ve) charge→ Polar → Not pass BBB - Chemical transmitter.	
Formation --- **Inactivation** --- **Storage**	**Formation:** Choline + Acetyl CoA $\xrightarrow{\text{Choline Acetyl Transferase (ChAT)}}$ → ACh →storage in vesicle → cholinergic receptor → response. --- **Inactivation:** ACh + Cholinesterase enzyme → Choline + Acetic acid. --- **Storage:** - ACh stored in vesicle to prevent inactivation by Cholinesterase enzyme.	
Choline esterase enzyme	- Enzyme which inactivate ACh - **Two types** **1:** True (Acetyl) cholinesterase (All ACh sites, CNS & RBCs). **2:** Pseudo (Butyryle) cholinesterase (Liver & Plasma).	
Pharmacological action	**CVS**	- (-ve) Inotropic, (-ve) Chronotropic & (-ve) Dromotropic →**M_2**
	B.V (Blood Vessels)	- **M_3** receptor are stimulated with external ACh through non-innervated by NO formation →VD → Hypotension.
	GIT	- Increase secretion motility (peristalsis) → Colic pain.
	U.B	- Contraction of wall and relaxation sphincter.
	Uterus	- Contraction of non-pregnant uterus.
	Bronchi	- Bronchoconstriction and Increase secretion → Bronchial asthma (Difficult to breathe).
	Eye	Contraction of circular muscle → Miosis Contraction of ciliary muscle → accommodation for near vision

	Exocrine gland	- Increase secretion → e.g. lacrimation, salivation and bronchial recreation.
	Nicotinic Receptor	- N_N → Stimulation of ganglia and adrenal medulla to release adrenaline and nor-adrenaline. - N_M → Stimulation of motor endplate (MEP) → Skeletal twitches.
Uses	➢ **No clinical uses → due to:-** - Multiplicity of action (***Non-selective***) act on all ACh receptors. - Short duration due to rapid inactivation by cholinesterase enzyme.	
Generic name ← **Carbachol** (Isopto® Carbachol) → Trade name		
Information	- Ester of choline with carbamic acid. - Totally resistant to two types of cholinesterase enzyme.	
Disadvantage	- Longer half-life and act on nicotinic and muscarinic (***Non-Selective***).	
Uses	- Used rarely except in eye drops to treat Glaucoma → ***Miosis*** and ***increase*** outflow from canal of schlemm → ***decrease*** Intraocular pressure (IOP).	
Eye Structure	 Eye Structure	
Bethanechol (Urotone®)		
Information	- Ester of β-methyl choline with carbamic acid. - Totally resistant to two types of cholinesterase enzyme. - ***Selective muscarinic*** receptor.	
Pharmacological action	➢ **Major action on GIT and Urinary bladder** • In GIT → Increase motility • In U.B → Contraction wall and relaxation sphincter	
Uses	➢ **Clinical uses** • Postoperative non-obstructive GIT disorder to prevent constipation. • Postoperative non-obstructive urinary tension • Gastro-paresis	

Methacholine (Provocholine®)	
Information	- Ester of beta-methyl choline with acetic acid. - Hydrolysed only by true-cholinesterase enzyme. - Act only on muscarinic receptor. - More selective on CVS. - Powder for inhalation not for injection.
Uses	- Provocative test diagnose bronchial asthma → ↑ asthma when inhaled. - Treatment of Peripheral vascular disease (PVD) & Paroxysmal tachycardia.

➢ **N.B:**

- All choline esters are quaternary ammonium compounds.
- i.e. → Carry charge → Polar → Non-lipid solubility → Don't pass BBB → No CNS effect.

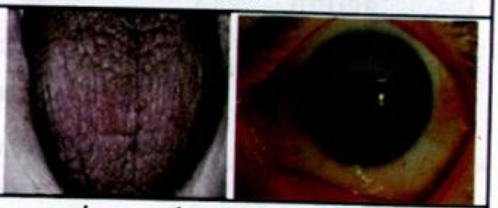


❖ Cholinomimetic Alkaloids :-

Pilocarpine (Isopto® carpine)		
Information	- Alkaloid of plant origin (***Pilocarpus leaflet***) - Tertiary amine alkaloid Not carry charge → non-polar → lipid soluble → ***pass BBB*** → CNS side effect. - Stable to hydrolysis by cholinesterase enzyme. - It shows muscarinic effect without having significant nicotinic effect.	
Pharmacological action	**Eye**	- Main effect → Penetrate cornea because it is non-polar → causing → ***Miosis*** and contraction of ciliary muscle → accommodation for near vision.
	GIT	- Increase motility
	U.B.	- Increase urine excretion
	Bronchi	- Bronchoconstriction
	Ex.gland	- Increase all secretion (Salivation and Sweating)
Uses	Main use → **Treatment of Glaucoma**	
Mechanism	→ It cause miosis and contracts to ciliary muscle, it opens the trabecular meshwork pores and facilitate out flow of aqueous humor into the canal of schlemm → Decrease IOP (Intraocular pressure).	
Side effects	- CNS side effect → CNS disturbance - Sweating and Salivation	

Q: Pilocarpine drug of choice for glaucoma?

Cevimeline (Evoxac®)	
Information	- The same action of pilocarpine except has low side effect.
Uses	- Treatment of ***Sjogren's syndrome*** (Dry mouth (xerostomia) and dry eye) by Increasing salivation and lacrimation
Side effects	- Nausea, vomiting, diarrhea, excessive sweating, rash and headache (10% of the patients).



B: Indirect-acting (Anticholinesterase)

➢ **N.B:**

- Don't act on receptor but act on cholinesterase enzyme → inhibit it → ↑ ACh.

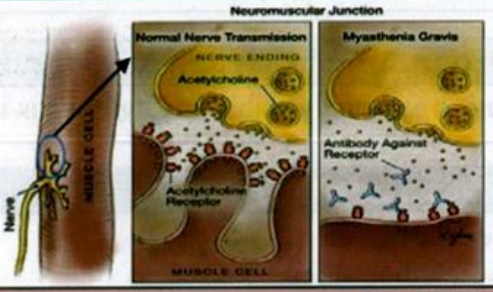
Reversible Anticholinesterase (ACE inhibitors)

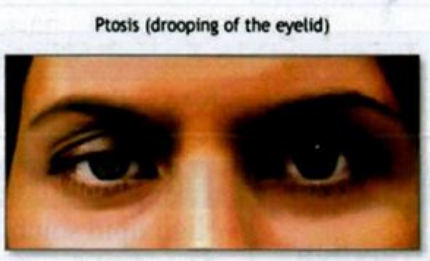
Bind reversibly with cholinesterase enzyme by ***hydrogen bond*** (Short acting) and ***weak covalent bond*** (Medium acting) → inactivate cholinesterase enzyme due to conformational change.

Short-acting drugs

Edrophonium (Enlon®)

Information	- Short duration 5-15 minutes due to rapid renal elimination (Unchanged in urine), More specific on skeletal muscle.
Uses	**1:** Diagnosis of myasthenia gravis → Increase muscle strength after administration (IV) of edrophonium (Indication to myasthenia gravis). **2:** For differentiating cholinergic crisis (↑ACh) and mysthenic crisis (↓ACh) **3:** Initiate treatment of curare poisoning.
Myasthenia gravis	Is an autoimmune disease in which antibodies break nicotinic receptor at MEP so fewer receptor are available for interaction with ACh → causing muscle weakness and relapse of eyelid.





Medium-duration drugs

Neostigmine (Prostigmin®)	Physostigmine (Antilirium®)
- Synthetic Quaternary ammonium compound.	- Naturally Tertiary amine alkaloid.
- ***Polar*** → Not Lipid soluble - ***Not Pass*** BBB → No CNS effect - Duration of action → 30 minutes to 2 hours.	- ***Non polar*** → Lipid soluble - ***Pass*** BBB → CNS effect - Duration of action → 2 hours to 4 hours.
- More specific on GIT and UB.	- More specific on Eye and CNS.
➢ **Uses** - Treatment of myasthenia gravis. - Stimulate the bladder and GIT in paralytic ileus and atony of urinary bladder after surgery. - Curare Poisoning (Antidote for Curare)	➢ **Uses** - Treatment of glaucoma → ***Decrease*** IOP - Increase GIT and bladder motility. - Antidote for atropine to reverse the central and peripheral side effect of atropine e.g. dry mouth, blurred vision, Flushing …
➢ **Adverse effects** - Flushing, salivation, hypotension, nausea, abdominal pain and diarrhea.	➢ **Adverse effects** - Convulsion and bradycardia. - Paralysis of skeletal muscle due to accumulation of ACh at the skeletal neuromuscular junction as a result of inhibition of cholinesterase enzyme.

Pyridostigmine (Mestinon®)	
Information	- Quaternary ammonium salt → Polar (Not cross BBB). - Duration of action are intermediate 3-6 hours and 4 to 8 hours) - Longer than neostigmine.
Uses	- ***Chronic management*** (Long term therapy) of myasthenia gravis.
Adverse effect	- Similar to Neostigmine.
Ambenonium (Mytelase®)	
Information	- Synthetic quaternary compound.
Uses	- Long term therapy of myasthenia gravis.
Demecarium (Humorsol Ocumeter®)	
Uses	- Eye drops for treatment glaucoma.
Anticholinesterase with selective CNS effect	
Tacrine, Donepezil (Alzepizil®), **Rivastigmine** (Exelon®), **Galantamine** (Reminyl®)	
Information	- Tacrine was the first to become available, but it has been replaced by others because of its hepatotoxicity.
Uses	- Treatment of Alzheimer disease (Deficiency of cholinergic neurons).
Adverse effect	- GI distress.

Irreversible Anticholinesterase (Organophosphorus compound)	
- Bond between phosphate and cholinesterase enzyme is extremely stable and hydrolysis in water at a very low rate.	
Di-isopropyl fluoro-phosphate (DFP)	
Information	- High lipid solubility → So used locally. - Absorbed from all membrane including skins.
Uses	- Chronic treatment of open angle glaucoma.
Echothiophate (Phospholine®)	
Information	- High long duration 1 weeks.
Uses	- Treatment of glaucoma.
Insecticides	
Malathion (Ovide®)	**Parathion** (Folidon®)
Less Toxic → due to rapidly metabolized into inactive product in birds mammals.	**Toxic** in human → due to not detoxified.

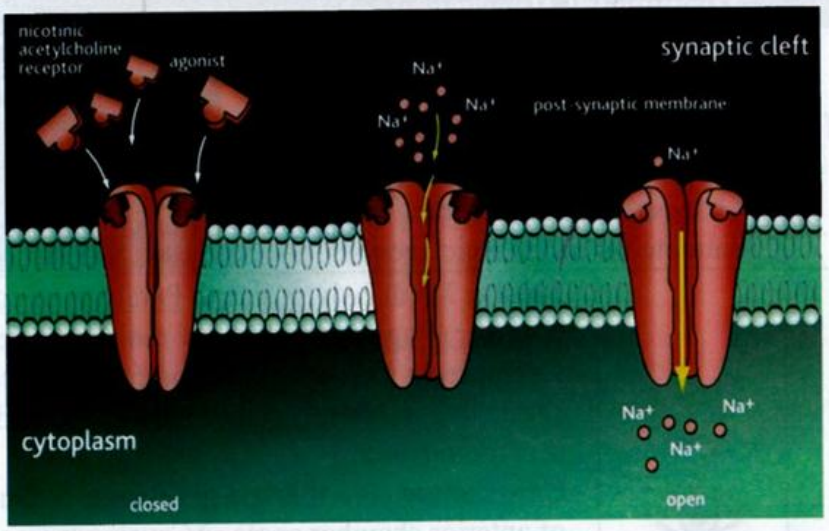
➢ **Treatment of toxicity acetylcholinesterase inhibitors:-**

- **Reactivation of acetylcholinesterase (AChE) :-**
  - **Pralidoxime** (Protopam®) can reactivate inhibited AChE (Not pass BBB).
  - **Pralidoxime** (Protopam®) removing the organophosphate from cholinesterase.
- **Other treatment** :-
  - **Atropine** (Atropine sulphate®) → Blocking Muscarinic (Prevent peripherally and centrally muscarinic side effect due to pass BBB).
  - **Diazepam** (Valium®) or other anticonvulsant agents (In case of Physostigmine).

2: Nicotinic agonist (*Ganglion stimulant*)

➢ **Nicotinic receptors :-**

- N_N → Adrenal medulla, CNS, Autonomic ganglia (Symp. and parasympathetic).
- N_M → Neuromuscular junction (NMJ).



Nicotine & Lobeline	
Information	- **NOT USED CLINICALLY** - In small dose → large dose act as blocker effect. - Stimulate nicotinic receptor on both sympathetic and parasympathetic ganglia.
Pharmacological action	- ***Sympathetic stimulation*** → increase adrenaline and nor-adrenaline release → increase cardiac force → increase cardiac output (CO)→ VC →Increase blood pressure (BP) - ***Parasympathetic stimulation***→ increase motility and all secretion.
Varenicline (Chantix®)	
Information	- Orally active - Long duration → 24 h. - Used to quit smoking - Acting as a partial agonist of the nicotinic receptor, and partially stimulates, the receptor without producing a full effect like nicotine.
Adverse effects	- Nausea and vomiting - Headache - Constipation - Sleep disturbance

B: Cholinoceptor antagonist (Parasympatholytics)

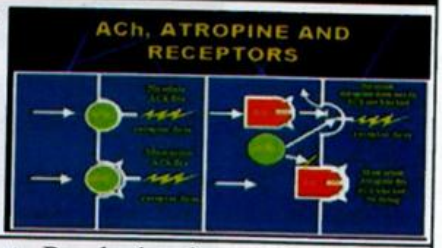
1: Antimuscarinic agents - Anticholinergic - Cholinergic blockers

A: Natural belladonna alkaloids

Atropine (dl-Hyoscyamine) (Isopto® Atropine)

Mechanism of action

- Has high affinity to muscarinic receptor.
- It's competitive antagonist of ACh → prevent ACh from binding.
- It's pass BBB → CNS effects.
- It has peripheral and central effect.
- Antidote for cholinergic agonists.



Pharmacological action

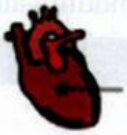
Eye

- **Passive Mydriasis** → due to Paralysis of constrictor (circular) Pupil muscle (allow radial muscle to contract)
- **Cycloplegia** (weakening of contraction of ciliary muscle) →due to Paralysis of ciliary muscle and loss of accommodation.
- **Cause acute closed angle glaucoma** → Due to narrowing of anterior chamber angle →Causing increase IOP.
- **Decrease lacrimation** → Dry or sandy eye.

Types of Glaucoma

- Closed angle (Acute) Glaucoma (Treatment by surgical)
- Open angle (Chronic) Glaucoma (Treatment by Medical)

CVS

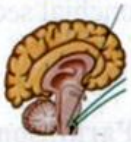
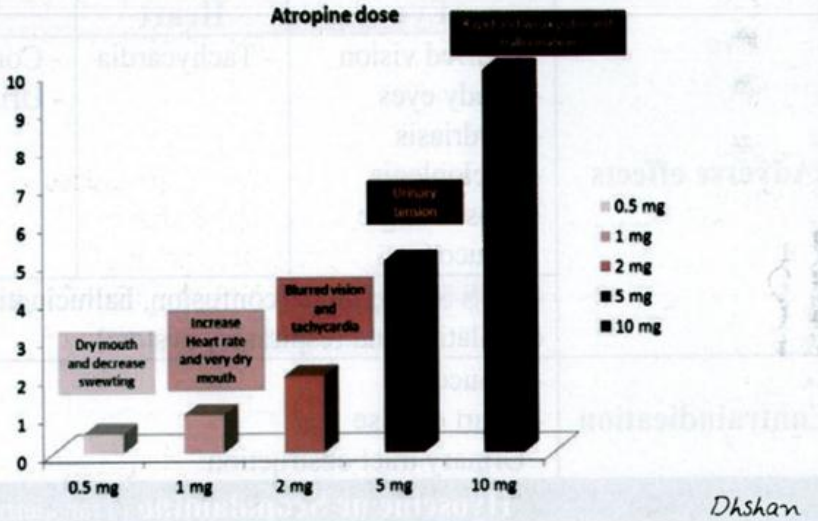
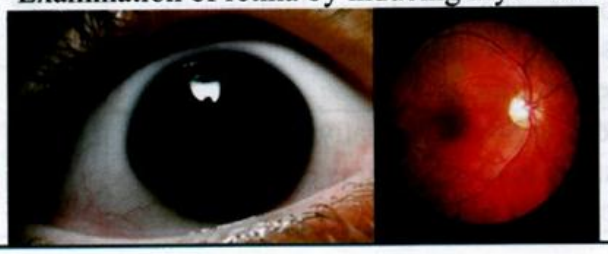


Therapeutic dose	High dose
A) Bradycardia (decrease heart rate)→ due to 1: Central activation of vagal afferent outflow. 2: Blocking of M_1 receptor on the inhibitory presynaptic neurone → increase ACh → M_2. **B) No effect on blood vessels**	**A) Tachycardia** (increase HR) → due to blocking the cardiac receptor on sinoatrial node (SA-node) **B) No effect on blood pressure.** **C) Vasodilatation** especially in children → Atropine flush.

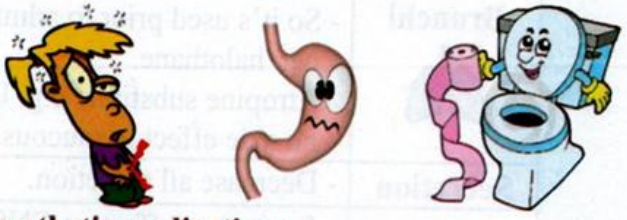
GIT

Antispasmodic effect

- Inhibit GIT motility → decrease tone → relaxation of wall
- Gastric HCl production is not significance → It's not effective in peptic ulcer **but** some derivatives are used for this effect e.g. **Pirenzepine** and **Telonzipine** → Which are selective M_1 antagonist → decrease acid secretion with less adverse effect than atropine.

	UB 	- Cause relaxation to wall and contraction to sphincter. - Contraindication in urinary tension specially urinary tension which associated with prostatic hyperplasia.
	Bronchi 	- Slight bronchodilator and decrease bronchial secretion. - So it's used prior to administration of inhaled anaesthesia e.g. halothane. - Atropine substitute e.g. Ipratropium is used it have little or no side effect in mucous secretion.
	Secretion	- Decrease all secretion.
	CNS 	- Excitatory effect on CNS due to stimulation of cerebral cortex. - Anti-tremors effect in Parkinsonism → Increase ACh increase tremors → Atropine pass BBB and decrease ACh action.
	Atropine poisoning	- Administration Physostigmine → Prevent peripheral and central atropine side effects → due to pass BBB
Pharmacokinetics (ADME)	- ***A***bsorbed from all sites. - ***D***istributed all over the body (Pass BBB) - ***M***etabolized mainly in liver - ***E***limination in urine (Acidification of urine → Increase excretion)	
Atropine Dose		
Uses	➢ **Ophthalmology (Eye) :-** - Measurement of refractive power. - Examination of retina by inducing mydriasis.  	

➢ **GIT :-**
- Antispasmodic agent.
- Antidiarrheal agent → Combination with weak opioid e.g. **Diphenoxylate**.



➢ **Pre-anesthetic medication :-**
- Anti-secretary (Decrease salivary and bronchial secretion).
- Protect heart from arrhythmia.
- Inhibition of vomiting center.

➢ **Adjuvant to L-Dopa therapy for Parkinson disease :-**

➢ **Prophylaxis of motion sickness :-**
- But Hyoscine is preferred.

➢ **Myocardial infarction**
- For treatment sinus node bradycardia.

➢ **Antidote for parasympathomimetic poisoning :-**
- E.g. Organophosphorus

Adverse effects

Eye	Heart	GIT	Skin & mouth
- Blurred vision - Sandy eyes - Mydriasis - Cycloplegia - Closed angle glaucoma	- Tachycardia	- Constipation - Urinary tension	- Dry mouth - Dry and red skin (Atropine Flush)

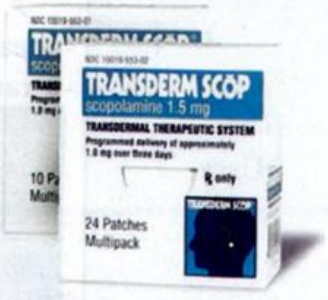
- **CNS Side effects** (confusion, hallucination, depression & collapse of circulation and respiratory system)

Contraindication
- Glaucoma
- Heart disease
- Urinary tract obstruction

Hyoscine or Scopolamine (Transderm scop®)

Information

➢ ***It differs from atropine in the following***
- It is more potent in mydriasis, cycloplegia and decrease secretion.
- It is less potent in heart and bronchial muscle.
- It produces amnesia and drowsiness.
- It has longer duration.



Uses
- Pre-anesthetic to produce sedative and amnesia
- **Prophylaxis in *motion sickness*** due to anti-emetic effect.

B: Synthetic and Semi-synthetic Atropine Substitutes

Drugs with selective actions on GIT (Antispasmodic and Anti-secretory)

Hyoscine Butyl-bromide (Buscopan®)

- ***Most popular***.
- Antispasmodic.
- Used IV, IM, Orally and rectally.

Pirenzepine (Gastrozepin®)

- Has selective for M_1 receptor → ↓ HCl.
- Cause tachycardia due to blocking of M_2.
- Used in peptic ulcer & longer duration.

Telenzepine

- Has selective for M_1 receptor → ↓ HCl.
- More potent than Pirenzepine.

Oxyphenonium (Spasmodin®)

Tiemonium methyl bromide (Visceralgine®)

Propantheline (Pro-Banthine®)

- Antispasmodic.

Dicyclomine (Spasmorest®)

- Antispasmodic.
- Weaker than Hyoscine Butyl-bromide.

Glycopyrrolate (Robinul®)

- Suppress salivary and bronchiolar secretions during surgical anesthesia (less tachycardia).

Drugs used in ophthalmology

Homatropine (Isopto® Homatropine)	Cyclopentolate (Cyclopentolate®)	Tropicamide (Mydriacyl®)

Drugs used in treatment of parkinsonism

Benztropine (Cogintol®)

Biperiden (Akineton®)

Treatment of Parkinson's Disease.

Orphenadrine (Norflex®)

-Relief pain due to spasm of skeletal muscle &Treatment of some aspects of Parkinson's Disease.

Drugs with selective actions on urinary bladder

Emepronium (Cetiprin®)

- Used in urinary incontinence.
- It causes ulceration of oesophagus.

Darifenacin (Enablex®)

- Used in urinary incontinence.

Solifenacin (Sofenacin®)

- Greater selective M_3.
- Drug interaction → With LME inhibitors → Prolong the QT interval

Oxybutynin (Uripan®)

- Reliving bladder spasm after urologic surgery.
- Used in urinary incontinence.

Fesoterodine (Toviaz®)

- Treat overactive bladder syndrome (OAB)

Tolterodine (Detrusitol®)

- Overactive bladder syndrome (OAB)

Propiverine (Mictonorm®)

Flavoxate (Genurin S.F®)

Drugs used selectively in respiratory disorder

Ipratropium (Atrovent®)

- More potent bronchodilator than atropine used as inhalation.
- Used in ttt of bronchial asthma and chronic obstructive pulmonary disease (COPD).
- ***No effect*** in mucous secretion.

Tiotropium (Spiriva®)

- The same action of Ipratropium but longer duration.

2: Antinicotinic agents

A: Ganglion Blockers (G.B)

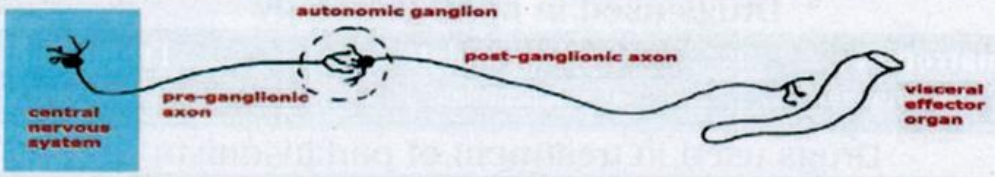
- They are drugs which block nicotinic receptors of both sympathetic and parasympathetic autonomic ganglia
- Classification according to mechanism of action.

Depolarizing G.B

- They are stimulatory in small dose and blocker in high dose.
- Stimulation → prolonged stimulation → Paralysis of ganglia.

Non-depolarizing G.B (Competitive)

- Inhibition of postganglionic action of ACh.



Depolarizing G.B			
Nicotine (in high dose)		**Lobeline** (in high dose)	
- NOT USED CLINICALLY			
Non-depolarizing G.B (Competitive)			
Pharmacological action	**Arterioles**	Sympathetic	VD → Hypotension
	Veins	Sympathetic	VD → Hypotension
	Heart	Parasympathetic	Increase heart rate (HR)
	Iris	Parasympathetic	Mydriasis
	Ciliary muscle	Parasympathetic	Cycloplegia
	GIT	Parasympathetic	Decrease motility →Constipation
	Urinary bladder	Parasympathetic	Relaxation of wall & contraction of sphincter.
	Sweat gland	Sympathetic	Decrease sweating.
	Salivary gland	Parasympathetic	Decrease salivation (Xerostomia).
	Erection	Parasympathetic	Impotency (Decrease erection)
	Ejaculation	Sympathetic	Failure of ejaculation
	CNS	Sedation and Tremors.	
Tetraethyl ammonium (TEA)		**Hexamethonium**	**Pentamethonium**
- QAC (Quaternary ammonium Compound). - Don't pass BBB.			
Pempidine		Tertiary amine (Non polar) → Pass BBB.	

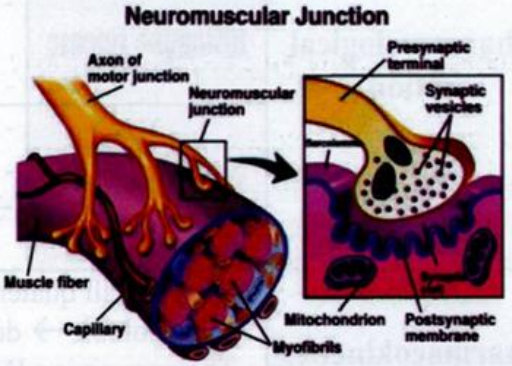
Trimethaphan (Arfonad®)	Mecamylamine (Inversine®)
- Mono sulfonium (S^+) - Don't pass BBB	- Secondary amine - Pass BBB
- Ultra short acting	- Longer action
- Not given orally (IV)	- Given orally
- Treatment of emergency hypertension	- Moderately hypertension
- Histamine release → Flushing & dizziness	- Not histamine release

B: Neuromuscular Blockers (NMB)

- Act on neuromuscular junction by blocking cholinergic receptor → to relax muscle.
- Their main clinical use is during surgical → Causing muscle relaxant of patient.
- Classification according to mechanism of action

Depolarizing NMB (Non-Competitive)

Non-depolarizing NMB (Competitive)



Non-depolarizing NMB (Competitive)

Benzyl-isoquinolinium compound

Tubocurarine or Curare
- The first drug that was found

Atracurium (Tracrium®)
- It can used in case of liver and kidney dysfunction.
- Slight histamine release
- Metabolized to laudanosine → which cause seizures.

Cisatracurium (Nimbex®)
- Isomer of atracurim.
- But have fewer side effects.
- Short duration.
- Hydrolysis by plasma.

Mivacurium (Pavulon®)
- Has more rapid recovery.
- Hydrolysis by plasma.

Metocurine (Metubine®)

Stronger than curare (4 times).

Amino-steroid compound

Short acting

Rapacuronium (Raplon®)
- Used in short surgical operation and metabolized in liver

→ **Side effects**
- Hypotension.
- Tachycardia.
- Fatal bronchospasm.

Intermediate acting

Rocuronium (Esmeron®)
- May cause allergic reaction

Vecuronium (Norcuron®)
- Metabolized in liver 35%.
- Biliary (50%) and renal excretion (15%).
- No histamine release

Miscellaneous

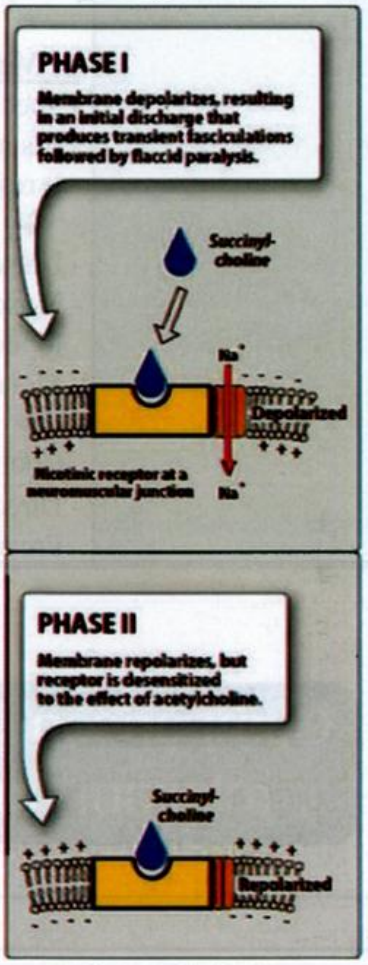
Gallamine (Flaxedil®)
- Tachycardia and increase blood pressure due to
1: Vagolytic action.
2: Tyramine like effect → Sympathomimetic.
3: Ganglion activity (No histamine release).

Long acting

Pancuronium (Pavulon®)
- **Tachycardia due to**
1: Atropine like action
2: Release of noradrenaline
3: Blocking the uptake of Noradrenaline.

Pipecuronium (Arduan®)
- Long acting

<table>
<tr><th colspan="3">Mechanism of action</th></tr>
<tr><td colspan="3"><u>- At low dose</u> → the combine with the nicotinic receptor preventing it from binding with ACh → inhibition of muscle contraction. Their action can be overcome by increase conc. of ACh.
<u>- At high dose</u> → they block the ion channels of the end plate →leading to further weakening of neuromuscular transmission and reduce the ability of anticholinesterase to reverse the action of non-depolarizing NMB relaxing effect.</td></tr>
<tr><td rowspan="3">Pharmacological action</td><td>Skeletal Muscle relaxation (paralysis)</td><td>- Relaxation of muscles not equal the first muscles to be relaxed are extrinsic eye muscle, then face, limps, neck, pharynx, intercostal and lastly the diaphragm.</td></tr>
<tr><td>Histamine release</td><td>- Some of them cause histamine release → hypotension, flushing and bronchospasm
- Tubocurarine - Mivacurium - Atracurium</td></tr>
<tr><td>Blood Vessels</td><td>- Produce all decrease in Blood Pressure (BP)
- Pancuronium - Atracurium - Mivacurium
→ Have CVS effect due to histamine release and ganglion blocker in large dose.</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="2">- They are all quaternary ammonium compound → Polar → ionized → not lipid soluble → don't pass BBB.
- They are giving IM or IV.
- Many of them are not metabolized in liver but redistribution occurs.</td></tr>
<tr><td>Uses</td><td colspan="2">- Adjuvant during surgical anaesthesia to provide skeletal muscle.
- Short surgical procedure (e.g. tracheal intubation).
- Electro-convulsion therapy (ECT) to control muscle contraction.</td></tr>
<tr><td rowspan="2">Adverse effect</td><td>CVS effects</td><td>- Hypotension due to histamine release and ganglionic blocker.
- Increase heart rate → due to vagolytic action, Atropine like action, release of Noradrenaline and blocking the uptake of Noradrenaline.</td></tr>
<tr><td>Respiratory system</td><td>- Bronchospasm with histamine release.</td></tr>
<tr><td>Contraindication</td><td colspan="2">- Asthmatic patient and anaphylactic reaction due to histamine release.</td></tr>
<tr><td>Drug interactions</td><td colspan="2">➢ <u>Antiacetylcholinsterase:</u>
→ Due to increase ACh→ reverse the action of non-depolarizing NMB.
➢ <u>Inhalation anesthesia (e.g. Halothane):</u>
→ They enhance non-depolarizing NMB effect i.e have additive effect with non-depolarizing NMB if used together the dose of both must be reduced.
➢ <u>Amino glycoside antibiotic (e.g. Gentamycin):</u>
→ Synergistic effect → Due to inhibit release of ACh from cholinergic nerve by competing with Ca^{2+}.
➢ <u>Ca^{2+} channels blockers:</u>
→ Synergistic effect → Due to decrease Ca^{2+} → decrease contraction → Increase effect of non-depolarizing NMB.</td></tr>
</table>

<table>
<tr><th colspan="3">Depolarizing NMB (Non-Competitive)</th></tr>
<tr><th>Succinylcholine (Succinylcholine®)</th><th colspan="2">Decamethonium (Syncurine®)</th></tr>
<tr><td>Pharmacokinetics</td><td colspan="2">Short duration due to
1: Rapid hydrolysis by plasma pseudo-Ch.E
2: Genetic variant in which the enzyme is decreased or absence
3: Redistribution
- Given by IV infusion because in any other rout it will degraded.</td></tr>
<tr><td>Mechanism of action</td><td>- They cause initial stimulation
→ Followed with prolonged inhibition.
➢ <u>Phase I</u>
- Open Na^+ channels associated with nicotinic receptor → depolarization
→ Increase muscle contraction.
➢ <u>Phase II</u>
- During continuous depolarization
→ Receptor desensitization
→ Resist depolarization and Don't response to ACh → Paralysis.</td><td rowspan="3"> 
</td></tr>
<tr><td>Pharmacological action</td><td>- Produces muscle fasciculation followed by paralysis.
- Don't produce ganglion blockers except in high dose.
- Has weak histamine release.</td></tr>
<tr><td>Uses</td><td>- Short surgical procedure (e.g. tracheal intubation).
- Electro-convulsion therapy (ECT) to control muscle contraction.</td></tr>
<tr><td>Adverse effects</td><td colspan="2"><u>1: Prolonged Apnea:-</u>
- When given to patient with genetic deficient in pseudocholinesterase → Paralysis of diaphragm.
<u>2: Bradycardia and increase bronchial secretion:-</u>
- If given as Pre-anaesthetic medication without atropine → Bradycardia and increase bronchial secretion due to →
- Have direct myocardial depressant effect on the heart
- Stimulates ganglia.
- Muscarinic stimulation.
<u>3: Post-operative muscle pain:-</u>
- Due to initial fasciculation.</td></tr>
</table>

4: Increase IOP :-

- Due to contraction of extra-ocular muscle → applying pressure to the eye ball.

5: Hyperkalmia:-

- Due to slight increase K^+ concentration in plasma.
- It causes serious arrhythmia and cardiac arrest.
- **Treatment →** IV infusion of regular insulin which decrease K^+ concentration in plasma (Insulin enhance entry of K^+ and prevent it is efflux from the tissues).

6: Malignant Hyperthermia:-

- Specially when halothane (Inhalation anaesthesia).
- It's rare but often fatal complication in genetically in susceptible patient.
- It results from rabid increase in muscle metabolism.

➢ **Characterized by →**

- Unexplained tachycardia.
- Muscle rigidity → increase muscle contraction and intensive pain→ due to increase of Ca^{2+} from sarcoplasmic reticulum.
- Metabolic acidosis.

➢ **Treatment →**

- Cooling patient.
- Direct skeletal muscle relaxant e.g. **Dantrolene** (DantRelax®) → Prevent release of Ca^{2+} from sarcoplasmic reticulum.

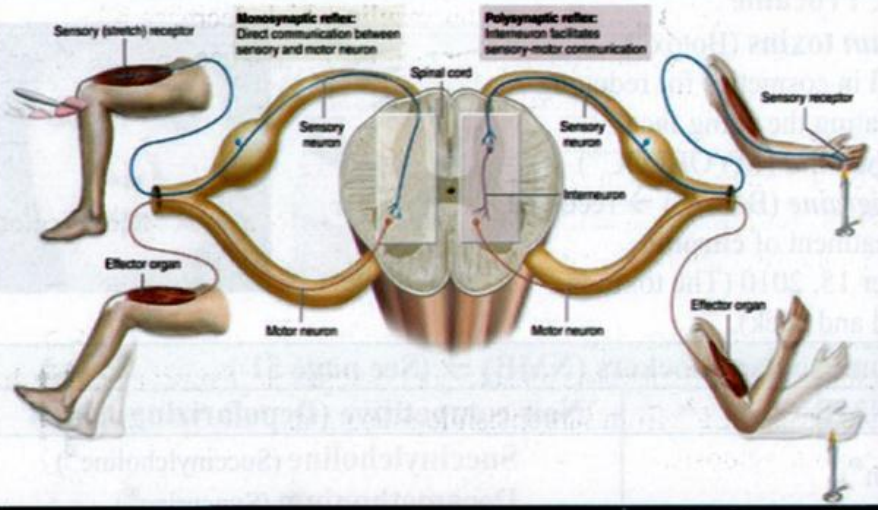
Comparison between non-depolarizing muscle relaxant and depolarizing muscle relaxant

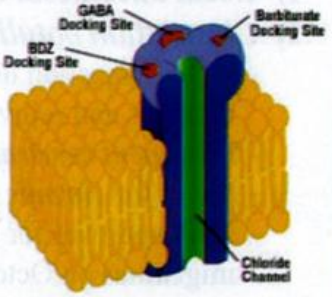
	Rocuronium	Saccinylcholine	
		Phase I	Phase II
Administration of Tubocurarine	Additive	Antagonistic	Augmented
Administration of Succinylcholine	Antagonistic	Additive	Augmented
Effect of Neostigmine	Antagonistic	Augmented	Antagonistic
Initial excitatory effect on Skeletal muscle	None	Fasciculation	None
Response to tetanic stimulus	Fade	No fade	Fade
Post-tetanic facilitation	Yes	No	Yes
Rate of recovery	30-60 min	4-8 min	> 20 min

Skeletal Muscle Relaxant

A) Central Muscle Relaxants

- They inhibit spinal and supra-spinal polysynaptic pathways → Decrease skeletal muscle tone without affecting voluntary activity → so it is used to relief pain of skeletal muscle.





Gamma amino butyric acid (GABA) Is Inhibitory Neurotransmitter in the brain By Opening Cl^- Channels

1) Barbiturates e.g. Phenobarbitone | 2) Benzodiazepines e.g. Diazepam

- Binding to the GABA receptor → increasing the affinity for GABA → Opening Cl^- Channels.
- Inhibit both polysynaptic and monosynaptic reflexes.

3) Baclofen (Lioresal®)

- Synthetic GABA derivative act on $GABA_B$ receptor.
- Inhibit both polysynaptic and monosynaptic reflexes.

4) Tizanidine (Sirdalud®)

- Central α_2 agonist → Muscle relaxant.

5) Mephenesin (Decontractyl®)

- Inhibit polysynaptic reflexes only.
- Used in painful muscle spasm and Strychnine poisoning.

6) Methocarbamol (Ibuflex®)

- Similar to Mephenesin but stronger and longer.

7) Carisoprodol (Myorelax®)

- Similar to Mephenesin but Inhibit both polysynaptic and monosynaptic reflexes.

8) Orphenadrine (Norflex®)

- Anti-muscarinic used in painful muscle spasm.

9) Chlorzoxazone (Myofen®)

- Acts on the spinal cord by depressing reflexes.
- Used as combination with NSAIDs e.g. Paracetamol.

10) Cyclobenzaprine (Multi-Relax®)

- Structurally related to the tricyclic antidepressants.
- Inhibit both polysynaptic and monosynaptic reflexes.

B) Peripheral Muscle Relaxants

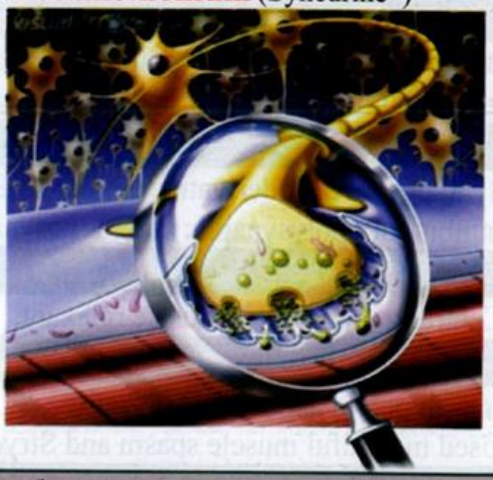
I) Drugs that decrease synthesis of Ach

1) **Hemicholinium** → Decrease Neuronal Uptake of Choline.
2) **Triethylcholine** → Decrease utilization of choline by choline-acetyl transferase.

II) Drugs that decrease release of Ach

1) **Local anesthesia** e.g. **Procaine**
2) ***Clostridium botulinum* toxins** (Botox®)
   - Botox® injection used in cosmetics for reducing wrinkles and rejuvenating the aging face.
   - ***Treatment cervical dystonia*** (MYOBLOC®)
   - ***Botox for chronic migraine*** (Botox®) → received FDA approval for treatment of **chronic migraines** on October 15, 2010 (The toxin is injected into the head and neck).

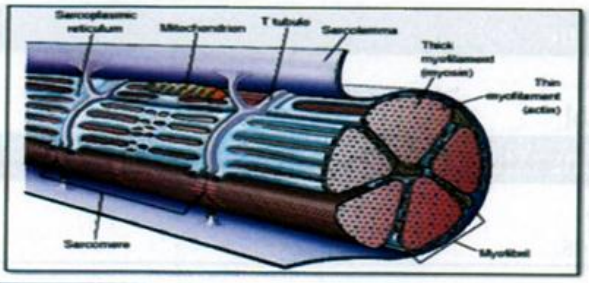
III) Neuromuscular Blockers (NMB) → (See page 51)

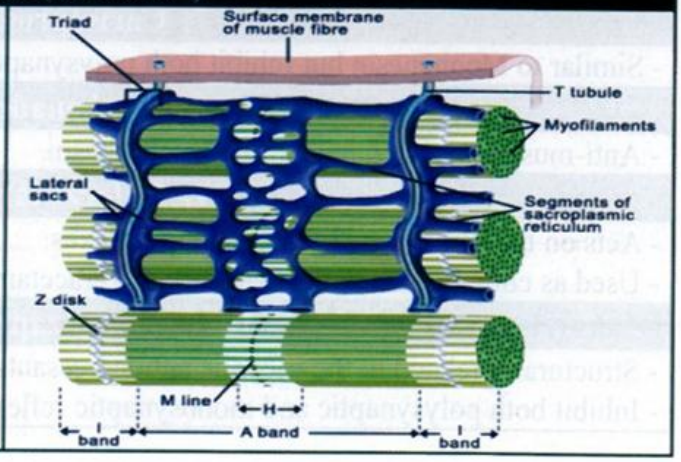
Competitive NMB	Non-competitive (Depolarizing) NMB
- **Atracurium** (Tracrium®) - **Cisatracurium** (Nimbex®) - **Mivacurium** (Pavulon®) - **Metocurine** (Metubine®) - **Rapacuronium** (Raplon®) - **Rocuronium** (Esmeron®) - **Vecuronium** (Norcuron®) - **Pipecuronium** (Arduan®) - **Pancuronium** (Pavulon®) - **Gallamine** (Flaxedil®)	- **Succinylcholine** (Succinylcholine®) - **Decamethonium** (Syncurine®) 

C) Direct Muscle Relaxant

Dantrolene (DantRelax®)

- The only one that affect direct excitability of Skeletal muscle.
- Decrease release of Ca^{2+} from sarcoplasmic reticulum.



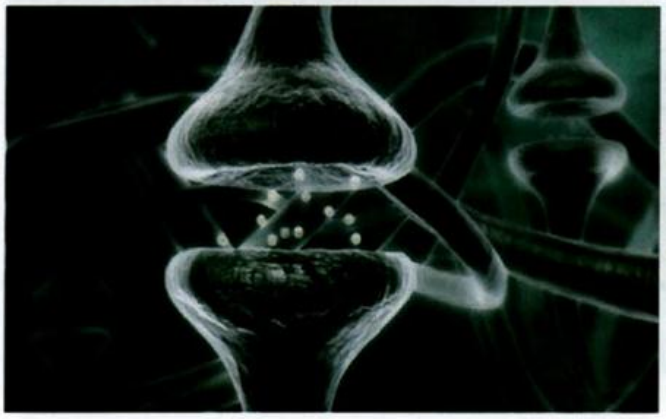


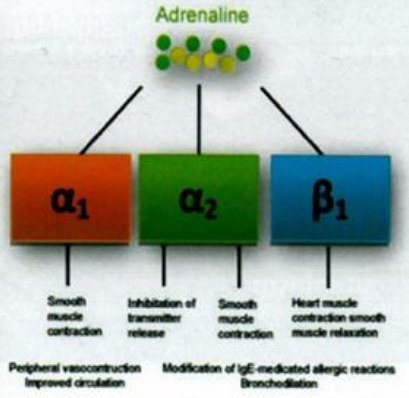
Drugs acting on Autonomic nervous system

- **Parasympathetic (Cholinergic receptor)**
- **Sympathetic (Adrenergic receptor)**
  - **Adrenergic agonists**
    - **Direct-acting**
      - **Non-Selective**
        - Adrenaline
        - Nor-adrenaline
        - Iso-proterenol
        - Dopamine
      - **Selective**

α_1	Phenylephrine - Methoxamine -Midodrine - Metaraminol Naphazoline - Tetrahydrozoline – Oxymetazoline - Xylometazoline
α_2	Clonidine - α-Methyldopa - Others
β_1	Dobutamine
β_2	Metaproterenol - Albuterol - Terbutaline - Salmeterol Formoterol - Ritodrine
D_1	Fenoldopam

    - **Mixed-acting**
      - Ephedrine
      - Pseudoephedrine
    - **Indirect-acting**
      - **Releasing agent**
        - Amphetamine
        - Tyramine
      - **Uptake inhibitor**
        - Cocaine
      - **MAO / COMT Inhibitors**
        - Pargyline
        - Entacapone
  - **Adrenergic antagonists** → Next Page





Adrenergic antagonists (Blockers)

α-Blockers

Non-selective
- Tolazoline
- Phentolamine
- Phenoxybenzamine

Selective α_1
- Prazosin
- Doxazosine
- Terazosin
- Tamsulosin
- Alfuzosin
- Indoramin

Selective α_2
- Yohimbine

β-Blockers

Non-selective
- Propranolol
- Nadolol
- Timolol

Selective β_1
- Acebutolol
- Atenolol
- Metoprolol
- Esmolol
- Betaxolol
- Celiprolol
- Nebivolol
- Bisoprolol

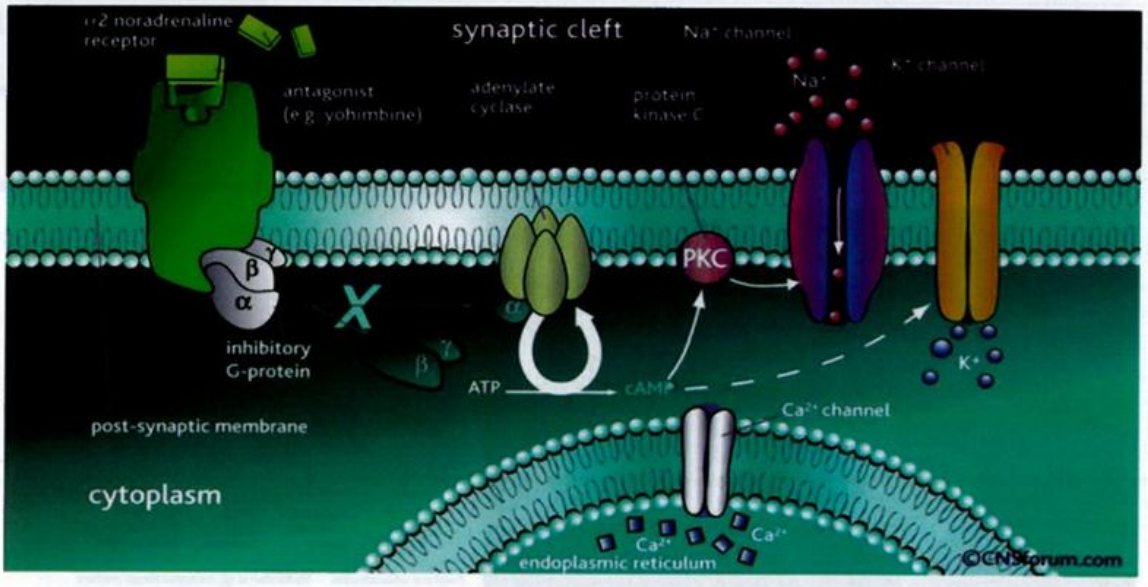
Drugs affecting Neurotransmitter Uptake or release

Drugs interfere with neurotransmitter
- Guanethidine
- Bethanidine
- Debrisoquine
- Bretylium

Drugs deplete NE store
- Reserpine

Mixed antagonist

- Labetalol
- Carvedalol



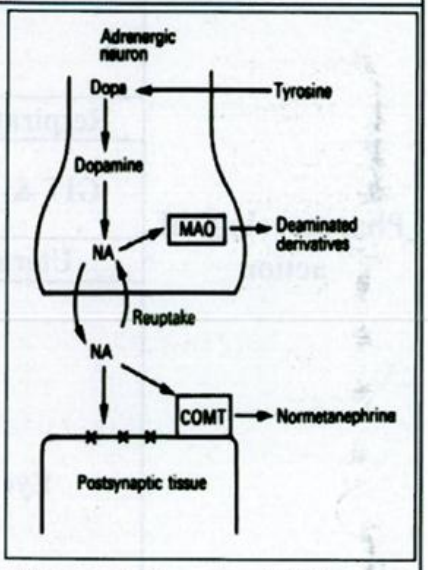
Adrnergic receptor (Sympathetic)

A: Adrenergic agonist

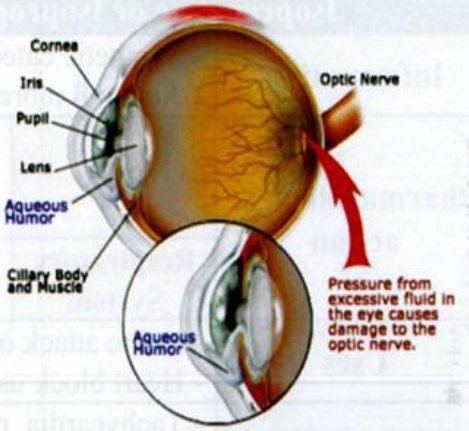
Direct-acting

A: Non-Selective

Adrenaline or Epinephrine (Epinephrine®)	
Information	- Natural catecholamine - Secreted by adrenal medulla 80% and Nor-adrenaline 20%. - L-isomer is 20 times more potent than D-isomer.
Biosynthesis	- **Tyrosine** -- *Hydroxylation*→ **Dopa** -- *decarboxylation*→ **Dopamine** -- *Hydroxylation* →**Nor-adrenaline** -- *Methylation* →**Adrenaline**
Uptakes of adrenaline	• **Uptake I (Neuronal):** - Adrenaline $\xrightarrow[\text{Mono-Amine Oxidase}]{\text{MAO}}$ VMA (Vanillyl-Mandelic Acid) - **N.B** →VMA Excreted in urine 4-8mg normal in day → increase in urine Pheochromocytoma (tumour in adrenal glands) - ***Uptake I inhibited by*** Cocaine, Amphetamine, Tricyclic antidepressants. • **Uptake II (Extra-neuronal)** - Epinephrine $\xrightarrow[\text{Catechol-O-methyl transferase}]{\text{COMT}}$ Metanephrine → VMA - ***Uptake II inhibited by*** Cortisone. • **Uptake III (Vesicle uptake)** - ***Uptake III inhibited by*** Reserpine.
Pharmacokinetics	- Adrenaline is ineffective orally due to rapid degradation by digestive juice and rapid metabolism by liver - **Routes of administration:-** - SC → VC → Slow absorption → Long duration and less toxicity. - IM → VD → Rapid absorption → Short duration and high toxicity. - IV → Sever hypertension and arrhythmia (Very dangerous) - Inhalation in bronchial asthma. - It can be given intra-cardiac for resuscitation - It may be used as eye drops in Glaucoma.



Pharmacological action	**Local effect**	- **Nose** → α_1 →VC → used in epistaxis and congestion. - **Skin** → Used with local anaesthesia e.g. Lidocaine → cause VC → decrease absorption → Prolonged the action → decrease toxicity. 
	CVS	**Heart** → β_1 - (+ve) → Inotropic, Chronotropic and Dromotropic **Blood vessels of skin and mucous membrane** → α_1 → VC → Increase peripheral resistance (PR)→ Increase blood pressure (BP) **BV(Blood vessels) of skeletal muscle** → β_2 → VD → Decrease PR → Decrease BP. **Coronary artery** →VD due to accumulation of metabolite e.g. Adenosine
	Respiratory	β_2 → Bronchodilatation (BD) → ttt of bronchial asthma.
	GIT & UB	→ β_2 → Relaxation of wall. → α_1 → Contraction of sphincter.
	Uterus	→ β_2 relaxation of uterus.
	Eye	→ α_1 →Mydriasis → but not used locally it will be broken down by tears alkalinity. - **Q: Dipivefrin** (Propine®) **used in treatment of glaucoma than adrenaline?** **A:** Dipivefrin is an epinephrine pro-drug that is converted to epinephrine by esterase enzyme in the cornea, it better than epinephrine however it is the same side effect and more easily passes from cornea because the adrenaline is more polar not pass to cornea and less irritant.
	Skin and salivation	- Hair erection. - Salivary gland → Viscous secretion.
	Metabolic effect	**Hyperglycaemic effect** - β_2 → VD → Increase Glycogenolysis →conversion of glycogen to glucose. - α_2 → Decrease Insulin secretion. - β_3 → Increase Lipolysis (increase free fatty acid).
	Adrenocortical effect	- Stimulation secretion of Cortisol

<table>
<tr><td rowspan="2">Pharmacological action</td><td>Anti-allergic effect</td><td>- It's physiological antagonist of histamine
Q: Adrenaline used as anaphylactic shock?
A: Adrenaline is physiological antagonist of histamine means it is
- VC→ α_1
- Bronchodilatation → β_2
- Stimulate secretion Cortisol.</td></tr>
<tr><td>Skeletal muscle effect</td><td>- Initial hyperkalaemia (↑ K^+) → α_1
- Then hypokalaemia → β_2 due to ↑ K^+ uptake
- Increase neurotransmitter in MEP due to increase Ca^{2+} influx then cause tremors due to increase ACh.</td></tr>
<tr><td>Clinical uses</td><td colspan="2">1: Acute bronchial asthma→ β_2
2: Acute insulin induced hypoglycaemia → α_2
3: Anaphylactic shock.
4: Added to local anaesthetics to Prolonged release.
5: In epistaxis (Haemostatic).
6: It's prodrug Dipivefrin used in treatment of open glaucon it case VC → Decrease formulation of aqueous humor.
7: Cardiac arrest.
 
</td></tr>
<tr><td>Side effects</td><td colspan="2">1: Cardiac arrhythmia → Tachycardia.
3: Sharp hypertension → leading to cerebral haemorrhage.
2: May cause gangrene of fingers → due to VC (induced when used with local anaesthesia)
4: CNS side effect e.g. tremors
  </td></tr>
<tr><td>Dosage</td><td colspan="2">→ Adult Dose for Cardiac arrest:-
- IV: 0.5 to 1 mg (5 to 10 mL of 1:10,000) once.
→ Adult Dose for Allergic Reaction:-
- IV: 0.1 to 0.25 mg (1 to 2.5 mL of a 1:10,000 solution) once slowly and cautiously over 5 to 10 minutes.
→ Adult Dose for Acute Asthma:-
- SC: 0.1 to 0.5 mg (0.1 to 0.5 mL of 1:1000 solution). May be repeated every 20 minutes to once every 4 hours as needed.
- Inhalation: Inhalation aerosol: 160 to 220 mcg (1 inhalation) once. an additional inhalation may be used after at least one minute.
→ Adult Dose for Dipivefrin (Propine®) eye drops:-
- 0.1%, is one drop in the eye(s) every 12 hours</td></tr>
<tr><td>Contraindication</td><td colspan="2">- Hypertension and Coronary heart disease and angina pain.
- Hyperthyroidism due to increase sensitivity to adrenaline.
- With local anaesthetic special around finger.</td></tr>
</table>

Noradrenaline (NA) or Norepinephrine (NE) (Levophed®)		
Information	- Naturally catecholamine (Secreted by adrenal medulla 20%). - Act on **α** receptors ***more than*** **β** receptors. - L-isomer is more potent than D-isomer.	
Pharmacological action	**CVS**	→ **BV** → It causes VC → α_1 → ↑PR → ↑BP. → **Heart** → Increase BP → cause reflex bradycardia.
	Respiratory	- It has no effect on bronchi.
	Uterus	- It cause contraction of uterus α_1.
Uses	- In case of acute hypotension.	
Side effects	- Hypertension which may cause cerebral haemorrhage. - Reflex bradycardia (reflex vagal stimulation).	
Isoprenaline or Isopropyl noradrenaline or Isoproterenol (Isuprel®)		
Information	- Synthetic catecholamine. - Act on **β** more than **α**.	
Pharmacological action	**CVS**	→ **Heart** → increase force of contraction, cardiac output (CO) and hear rate (HR) → β_1 → **BP** → it cause VD of blood vessels → β_2
	Respiratory System	- Bronchodilatation → β_2
Uses	- Acute attack of bronchial asthma used as inhaler or sublingual. - Heart block used as injection and sublingual.	
Adverse effects	- Tachycardia, palpitation and angina pain. - Flushing of skin and headache.	
Dopamine (DA) (Intropin®)		
Information	- Naturally catecholamine. - It's present CNS and peripherally (Not Pass BBB).	
Effect of Dosage	- In ***small*** dose → Act on D_1 receptor. - In ***moderate*** dose → Act on D_1 and β_1 receptors. - In ***high*** dose → Act on α_1 receptor.	
Pharmacological action	**Heart**	- + Ve inotropic and + Ve chronotropic → β_1 - At high dose → α_1 →VC → increase BP
	Renal action	- VD → Increase renal blood flow.
Uses	- Chronic Congestive Heart Failure (CHF) - Cardiogenic shock to increase renal blood flow. • Renal VD (D_1) → Increase Urine output. • + Ve inotropic effect (β_1) → Increase CO.	
Side effect	- Tachycardia, hypertension, nausea and vomiting.	
Q: We should control the dose of dopamine to the patient have cardiogenic shock? A: Due to it must be in moderate dose to increase renal blood flow (D_1) and increase CO (β_1) → but in high dose act on α_1 → VC → increase BP and decrease renal function.		
Dopexamine (Dopacard®)	- Stimulate D_1 and β_1 receptors. - Not dose dependant.	

Selective adrenoceptor agonists

❖ Selective β_1-adrenoceptor agonists:-

Dobutamine (Dobutrex®)	
Information	- Synthetic Catecholamine - IV infusion
Pharmacological action	- (+ve) Inotropic - (+ve) Chronotropic
Uses	- Heart block. - CHF (Congestive heart failure). - Cardiogenic shock → Increase blood in vital organ by increasing CO.
Adverse effect	- Tachycardia and angina. - Nausea and vomiting - Headache
Q: Doputamine is More selective in CHF than Dopamine? → Due to **1:** Selectivity to β_1 receptors not acts on D_1 receptors. **2:** Not increase in renal blood flow and it has greater inotropic effect than dopamine. **3:** In high dose not act on α_1 receptors.	
Prenalterol (Hyprenan®)	Like Dobutamine but non-catecholamine and effective orally.

❖ Selective D_1-adrenoceptor agonists:-

Fenoldopam (Corlopam®)	
Action	- It causes peripheral VD of renal blood vessels.
Uses	- IV infusion in severe (emergency) hypertension (Short duration 5 min.)
Adverse effects	- Headache, dizziness, flushing and tachycardia.

❖ Selective α_1-adrenoceptor agonists:-

- α_1 agonists used as vasopressors (treatment of hypotension), nasal decongestants and eye exams (Mydriasis)

Phenylephrine (Isopto® frin)	
Pharmacological action	- Potent VC →Increase PR → Increase BP - It has no effect on the heart but may cause reflex bradycardia. - No CNS effect.
Uses	- Hypotension - Paroxysmal atrial tachycardia. - Nasal decongestion. - Mydriatic (eye drops). - Used in combination with local anaesthesia to prolong the time of action.
Adverse effect	- Hypertensive headache. - Vomiting - Cardiac irregular.

Methoxamine (Vasoxine®)	
Uses	- Acute hypotension and Paroxysmal atrial tachycardia.
Midodrine (Gutron®)	
Information	- Is prodrug that is hydrolysed enzymatically to → **Desglymidodrine**
Uses	- Give orally to treatment hypotension.
Metaraminol (Aramine®)	
Information	- It is mixed acting→ Act on receptor and stimulates release of NE. - Give as single injection.
Uses	- Used in priapism (potentially painful in which the erect penis → does not return to its flaccid state) - Hypotension

Naphazoline (Naphcon-A®)	Tetrahydrozoline (Visine®)	Xylometazoline (Otrivin®)	Oxymetazoline (Afrin®)
Action	Vasoconstriction of nasal mucosa → Reduced congestion.		
Uses	Nasal decongestion and Red eye (allergic eye)		

Q: Why Oxymetazoline in high dose causes Hypotension?
A: Because it →
- Partial agonist presynaptic α_2 →decrease NE release.
- Partial agonist α_{2A} →↓cAMP →↓ Ca^{2+} influx →↑ K^+ → Hyperpolarization → Hypotension.

❖ Selective α_2-adrenoceptor agonists:-

Clonidine (Catapress®)

Mechanism of action

1) Stimulate presynaptic α_2 receptors → This binding decreases presynaptic Ca^{2+} levels, and inhibits the release of NE → lowering blood pressure.

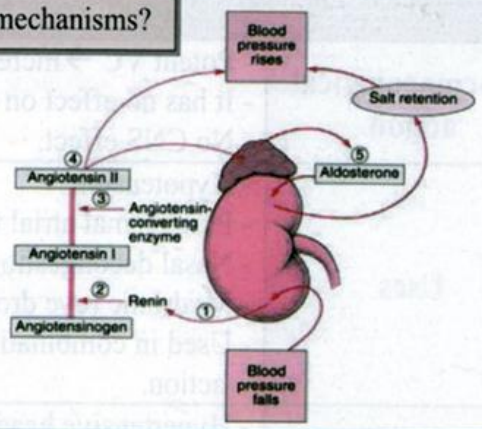
2) Stimulate central α_2 receptors → decrease sympathetic out flow → decreases NE and renin → decrease CO and resistance → lowering blood pressure.

3) Stimulate I_1 (Imidazoline) receptor → sympatho-inhibitory action →lower blood pressure.

Clonidine decrease BP by 3 mechanisms?

Renin angiotensin system

Renin
Angiotensin I ← Angiotensinogen
↓ ACE (Angiotensin Converting Enzyme)
Angiotensin II
↓
Highly VC → Increase BP



Q: Why Clonidine used with furosemide?
Clonidine cause Na^+ and water retention so used with furosemide (Diuretic drug) → Decrease Na^+ and water retention → increase renal out flow.

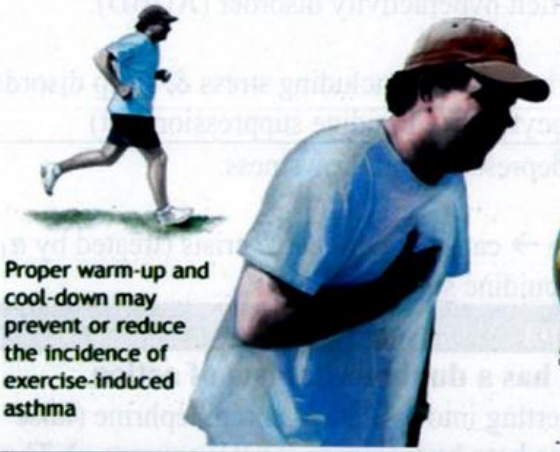
Uses	- Antihypertensive. - Treatment of withdrawal syndrome in opiates and alcoholics due do → decrease sympathetic out flow. - Treatment of attention deficit hyperactivity disorder (ADHD). - Can be used for migraine. - Can be used for psychiatric disorders including stress & sleep disorders. - Diagnosis of Pheochromocytoma (Clonidine suppression test)
Adverse effects	- **CNS effect** → sedation, depression and drowsiness. - **Constipation**. - **Sudden Stop** of clonidine → cause hypertensive crisis (treated by α_1 and β blocker). (Must Stop clonidine **slowly**)
α-Methyldopa (Aldomet®)	
Mechanism of action	**Methyldopa has a dual mechanism of action** **1)** It passes BBB and converting into α-Methyl-norepinephrine (false transmitter) by dopamine beta-hydroxylase (DBH) enzyme → The false transmitter is central α_2-agonist → decrease sympathetic out flow → decreases NE → decrease BP. **2)** It is a competitive inhibitor of dopa decarboxylase enzyme → which converts L-dopa into dopamine. (Dopamine is a precursor for norepinephrine and subsequently epinephrine).
Uses	- Hypertension in **pregnancy**.
Adverse effects	→ **Sympathetic blocked:** - Postural hypotension, failure of ejaculation and nasal congestion. → **CNS manifestation:** - Sedation, drowsiness, depression and Parkinsonian symptoms. → **Increase prolactin hormone:** - Due to inhibition of dopaminergic mechanism → Causing Gynecomastia (breast enlargement in male) and galactorrhea (spontaneous flow of milk from the breast). → **Allergy** → Bone marrow depression and hepatotoxicity.

Other drugs having colnidine like effect	
Guanabenz (Wytensin®)	Most common side effects during guanabenz therapy are dizziness, drowsiness, dry mouth, headache and weakness.
Apraclonidine (Iopidine®)	Used in glaucoma therapy. It is α_2 adrenergic agonist and weak α_1 adrenergic receptor agonist.
Guanfacine (Intuniv®)	Decrease blood pressure by activating central α_{2A} → reduced sympathetic outflow.
Lofexidine (Detoxydine®)	Short-acting anti-hypertensive, but ***more commonly used*** to alleviate physical symptoms of heroin and opiate withdrawal.
Brimonidine (Alphagan®)	Used in treatment of glaucoma (decrease synthesis of aqueous humor)

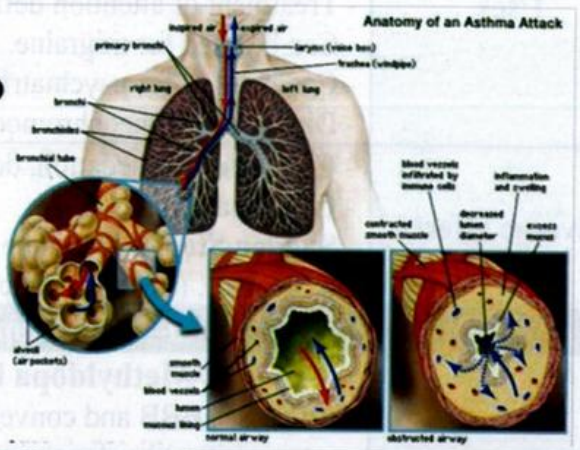
Drugs act only on imidazoline receptors (Agonists)	
Rilmenidine (Hyperium®)	**Moxonidine** (Cynt®)
- Treatment of hypertension.	

❖ Selective β_2-adrenoceptor agonists:-

- **Short acting β_2 agonists used in treatment of Bronchial asthma :-**



Proper warm-up and cool-down may prevent or reduce the incidence of exercise-induced asthma



Metaproterenol or Orciprenaline (Alupent®)	
Information	- Resistant to methylation by COMT. - Related to isoprenaline. - Effective Orally or inhalation.
Mechanism of action	- Stimulate β_2 receptor on bronchial smooth muscle and uterus muscle → Cause bronchodilatation and little relaxing effect on uterus. - Slight effect on β_1 → little effect on the Heart. - May be act as mast cell stabilizer (decrease release of histamine).

Albuterol or Salbutamol (Ventolin®)	Terbutaline (Bricanyl®)
- **Orally**: 2-4 mg orally 3-4 times daily. - **Inhalation aerosol**: 1-2 puffs (inhalations) every 4-6 hours as needed.	- **Orally:** 5 mg orally 3-4 times daily. - **Inhalation aerosol:** 2 Puffs separated by 60 seconds every 4 to 6 hours. - Currently used to delay preterm labor.

- **Long acting β_2 agonists used in treatment of Bronchial asthma :-**

Salmeterol (Metrovent®)	Formoterol (Foradil®)
- 1 inhalation (50 mcg) twice daily.	

Selective β_2 receptor agonist in Uterus

Ritodrine (Yutopar®)	
Information	- Short acting (IV or Orally). - Ritodrine is used to stop premature labor. - Ritodrine is no longer available in the United States.

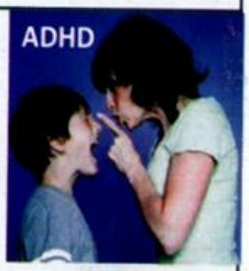
Q: Ritodrine is beneficial in Premature labor?

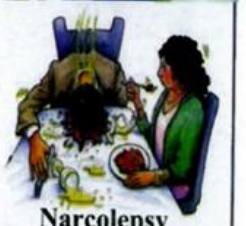
A: Due to Tocolytic effect → Selective β_2 receptor in uterus → relaxation uterus muscle → stop premature labor.

Indirect-acting

❖ **They Cause NE release from Sympathetic neurons.**

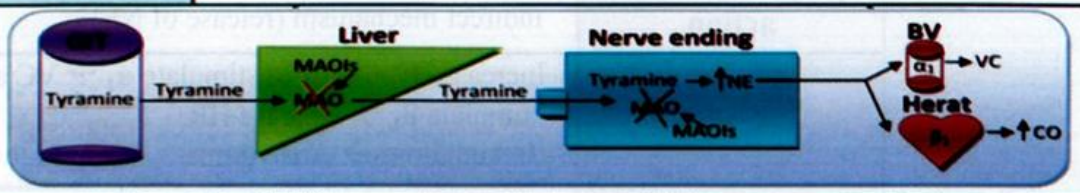
Amphetamine (Adderall XR®)		
Pharmacokinetics	- It is easily absorbed from mucous membranes, GIT and passes BBB. - l-isomer is slight more potent than d-isomer. - Rout of administration → Orally.	
Mechanism of action	- Increase release of nor-adrenaline and dopamine and prevent reuptake. - Powerful CNS stimulant.	
Pharmacological action	**Sympathomimetic action**	- It stimulate both **α** and **β** receptor through an indirect mechanism (release of NE).
	CVS	- Increase BP → due to stimulate α_1 → VC and stimulate β_1 → increase HR. - In high dose → Arrhythmia.
	CNS	- Due to increases central dopamine and NE → causing wakefulness and euphoria. - Stimulate cerebrospinal axis, cortex, brain stem and medulla → increase alertness and decrease fatigue. - Stimulation RC (Respiratory centre) and VMC (Vasomotor centre) - Analgesic effect. - Anorexigenic effect. - In high dose cause convulsion and Schizophrenia
	Smooth muscle	- Has insignificant effect on bronchi.
Uses	- Treatment of narcolepsy (Hypersomnia) and Obesity. - Attention Deficient Hyperactivity Disorder (ADHD). - Depression. - Parkinsonism → To elevate mood of patient.	
Side effects	- Psychotic effect (insomnia, anxiety, confusion & hallucination). - Hypertension. - Psychological, dependence and addiction (after prolonged use).	
Contraindication	- Schizophrenia. - Hypertension. - Coronary artery disease.	




Narcolepsy

Amphetamine Derivatives	
Methamphetamine	- As amphetamine but more CNS and Less CVS.
Methylphenidate (Ritalin®)	- As amphetamine but without Anorexigenic effect and less adverse effects.

Modafinil (Provigil®)	
Information	- It is a new amphetamine substitute.
Mechanism of action	- Increase concentration of NE, dopamine, serotonin and glutamine while decreasing GABA level.
Uses	- Improve wakefulness in narcolepsy.
Tyramine	
Information	- Indirect sympathomimetic present in fermented foods e.g. ripe cheese
Mechanism of action	- It is metabolized by MAO in liver → administration of MAO inhibitors increase Tyramine → increase release of catecholamine → Hypertensive crisis (treated by α_1 and β blocker).



Mixed-acting

Ephedrine (Ephedrine sulfate®)		Pseudoephedrine (Sudophine®)
Information	- It is a stereoisomer of ephedrine. - Act on receptor and stimulate release of NE.	
Pharmacokinetics	- Absorbed orally and resist MAO and COMT → long duration. - Ephedrine has CNS side effect but pseudoephedrine has ↓effect.	
Pharmacological action	**CVS**: - Ephedrine stimulate α_1 and release NE→ VC → increase BP - Ephedrine stimulate β_1 and release NE →↑ CO →↑ BP	
	CNS: - Ephedrine produce mild stimulation of the CNS causing insomnia.	
	Smooth and Skeletal muscle: - Ephedrine produce bronchodilator but less potent than epinephrine. - Ephedrine enhances contractility of skeletal muscle and improves motor function in myasthenia gravis.	
	Local: - Decongestant eye and nose. - Active mydriasis.	
Uses	**Ephedrine**: - Prophylactic agent in bronchial asthma. - Nasal decongestion due to local VC in nasal BV. - Treatment of Myasthenia gravis adjuvant with Neostigmine. - Mydriatic	**Pseudoephedrine**: - Nasal decongestion due to local VC in nasal BV **Q: Pseudoephedrine is better than ephedrine in nasal decongestion?** **A:** because ephedrine have CNS side effect (insomnia) and CVS side effect (hypertension).
Adverse effects of ephedrine	Hypertension and insomnia.	

B: Adrenergic antagonist

Adrenoceptor antagonist

1: α adrenoceptor antagonist (α adrenergic blocking)

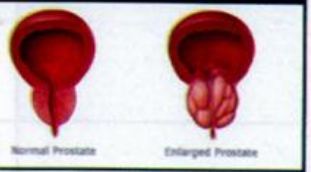
A: Non-selective α-adrenoceptor antagonist

Imidazoline derivatives	
Tolazoline (Priscoline®)	Phentolamine (Regitine®)
- They are ***reversible*** competitive antagonists with ***short acting***.	
Haloalkylamines	
Phenoxybenzamine (Dibenzyline®)	
- ***Irreversible*** non-competitive antagonists with ***long acting*** due to presence of N-chloro-ethyl group that enables the drug to bind covalently to the receptor.	
Information	- **Tolazoline** is less potent than **phentolamine**. - **Phentolamine** inhibits response to serotonin and may be agonist at muscarinic and histaminic receptor. - **Phenoxybenzamine** inhibits the reuptake of NE and block serotonin and histaminic and cholinergic receptors.
Pharmacological action	- **VD** due to α_1 receptor blocking → decrease peripheral resistance. - Cardiac stimulation (increase CO and HR) due to **reflex effect**. - **Tolazoline** and **phentolamine** stimulate GI smooth muscle and increase gastric secretion.
Routes of administration	- **Tolazoline** and **phentolamine** → parenterally - **Phenoxybenzamine** → orally
Uses	**1:** Hypertension in patients with pheochromocytoma (adrenal medullary tumor) **2:** Raynaud's phenomenon (peripheral vascular disease) **3:** Impotence (male erectile dysfunction)→ **VD** →Increase erection. **4:** Urinary retention associated with benign prostatic hyperplasia (BPH) due to relaxation of smooth muscle of prostate by blocking α receptor → improvement urine flow.
Adverse effects	**1:** Postural hypotension. **2:** Failure of ejaculation due to blocking α receptor in smooth muscle in vas deferens and ejaculatory ducts. **3:** Reflex tachycardia. **4:** Nasal congestion. **5:** Antihistaminic and anti-muscarinic side effects.
Q: Disadvantage of using non-selective α adrenoceptor blockers in male erectile dysfunction? A→fibrotic reaction, orthostatic hypertension & priapism (harmful pain in the erect penis)	

B: Selective α_1-adrenoceptor antagonist

Prazosin (Minipress®)	
Pharmacological action	- α_1 receptor present in vascular smooth muscle and coupled with Gq protein → Excitatory effect (release of Ca^{2+}) → Causing VC → α_1 receptor is blocked causing → **VD** - **VD** → decrease peripheral resistance → decrease BP. - **VD** in both artery and vein → decreases afterload and preload.
Route of Adm.	- Orally
Uses	**1:** Primary hypertension. **2:** CHF (Congestive Heart Failure) due to decreases preload and afterload. **3:** Urinary retention associated with BPH.
Adverse effects	**1: Initial Syncopal Attack** (First dose phenomenon) → ***Severe postural hypotension*** → to overcome that the first dose must be minimized and giving at bed time. **2:** Nasal congestion. **3:** May cause headache, dizziness, drowsiness and nausea. **4:** Long use in male → Failure of ejaculation. **5:** Na^+ and water retention used with diuretic drugs.
Q: Advantage of selective α_1 receptor antagonist over non-selective? **A: 1:** Less tachycardia due to don't release NE release from sympathetic nerve. **2:** Male sexual function is not severely affected.	

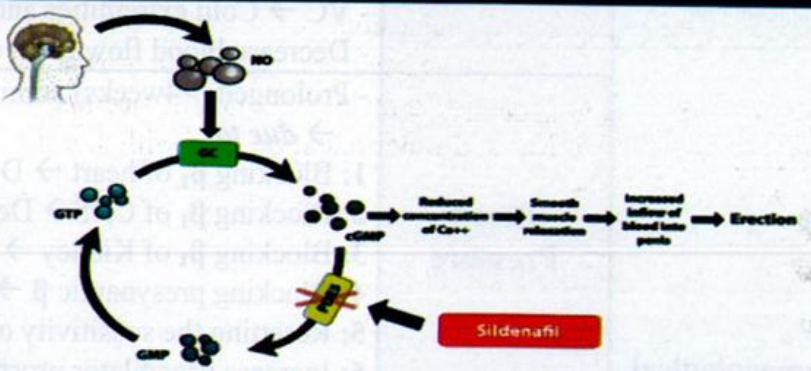
C: Selective α_1-adrenoceptor antagonist used in BPH

Alfuzosin (Xatral®)	Doxazosin (Cardura®)	Terazosin (Itrin®)
Uses	- Used in **Benign prostatic hyperplasia (BPH)** by Blocking α_1 receptors found in smooth muscle of prostate → Inhibit contraction of smooth muscle → Facilitate urine output from urinary bladder.	
Tamsulosin (Tamsulin®)		
Mechanism of action	- Tamsulosin has higher affinity for **α_{1A} receptor** found on smooth muscle of the prostate → Inhibiting prostate smooth muscle contraction.	
Dose	- Once daily.	
Uses	- Benign prostatic hyperplasia (BPH).	
Adverse effect	- Abnormal ejaculation.	
Other drugs used in BPH (Not act on α_1 receptors)		
Finasteride (Proscar®)		
Action	- It inhibit 5α-reductase enzyme which metabolises testosterone into the more potent androgen dihydrotestosterone this lead to reduction in prostate size with improve in urinary flow.	

D: Selective α_2-adrenoceptor antagonist

Yohimbine (Yohimbex®)	
Action	- Blockade of pre-synaptic α_2 adrenoceptors leads to increased release of neurotransmitters in the CNS and in the corpora cavernosa penis such as nitric oxide, noradrenaline, and dopamine
Uses	- Improvement of male sexual function. - Autonomic insufficiency → increase release of NE.
Adverse effects	- Tachycardia and hypertension. - Low therapeutic index
Dose	- A typical dose for sexual dysfunction would be 15-30mg, whereas 100mg would be considered dangerous.

Other drugs used in erectile dysfunction in male (Not act on α_2 receptors)

Sildenafil (Viagra®)	
Mechanism of action	 - Erection of penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. - NO → Activation of guanylate cyclase (GC) → Increase cyclic guanosine monophosphate (cGMP) → Decrease Ca^{2+} influx → Relaxation smooth muscle → VD → Erection. - Sildenafil is selective inhibitors of phosphodiesterase (PDE) which is responsible for degradation of cGMP into GMP → accumulation of cGMP → Erection. - Sildenafil has no effect in absence of sexual stimulation.
Dose	- 50mg ½ an hour before sexual intercourse.
Adverse effects (high dose)	- Headache, flushing, dyspepsia, nasal congestion and impaired vision, including photophobia and blurred vision.

Tadalafil (Cialis®)	Vardenafil (Levitra®)
Action	- Is a phosphodiesterase type-5 (PDE5) inhibitors. - Longer duration than Sildenafil. - Should not be taken more than once in 24 hours.

2: β adrenoceptor antagonist (β adrenergic blocking)

A: Non-selective β-adrenoceptor antagonist

Propranolol (Inderal®)		
Pharmacokinetics	- It has low bioavailability when given orally due to first pass effect.	
Pharmacological action	**Heart**	- (-ve) Inotropic & (-ve) Chronotropic (HR). - (-ve) Dromotropic (Slowed AV conduction). - Decrease cardiac work and O_2 consuming → useful in angina.
	Blood Vessels	- Blocking β_2 on the skeletal muscle → Block VD. - VC due to unopposed α receptor (blocking β receptor → All adrenaline and noradrenaline act on α receptor cause VC). - VC → Cold extremities and intermittent claudication. - Decrease blood flow to all organs except the brain.
	Blood Pressure	- Prolonged (>4weeks) administration → Hypotension → ***due to*** **1:** Blocking β_1 of heart → Decrease CO. **2:** Blocking β_1 of CNS→ Decrease sympathetic outflow. **3:** Blocking β_1 of Kidney → Decrease rennin release. **4:** Blocking presynaptic β → Decrease NE release. **5:** Resetting the sensitivity of broreceptor. **6:** Increase vasodilator prostaglandins (PGI_2).
	Respiratory System	- Blockade of β_2 receptors → Bronchoconstriction this is harmful in patients suffering from bronchial asthma.
	Eye	- Decrease aqueous humor formation → Increase IOP. - ***Not effect*** on pupil size or ciliary muscle or accommodation.
	Metabolic effect	**1:** Block β_2 in Liver → Decrease Glycogenolysis. **2:** Block β_2 in Pancreas → Decrease insulin release. **3:** Block β_2 in skeletal muscle → Hyperkalaemia. **4:** Block β_1 and β_3 → decrease Lipolysis. **5:** Increase triglycerides and decrease HDL.
	Q: Propranolol should be used with caution in insulin-dependent diabetics? **A:** It impairs recovery from hypoglycemia since catecholamine may be the major factors in stimulating glucose release from liver in response to hypoglycaemia (i.e. it masks the symptoms of hypoglycemia except sweating).	

	Plasma lipoproteins	- **Chronic use** → increase LDL (low density lipoprotein) (Bad cholesterol) and decrease HDL (high density lipoprotein) (good cholesterol) → Coronary artery disease.
	Na^+ retention	- Increase Na^+ retention → increase water in blood → increase blood volume → To avoid that → administration of diuretic to prevent Na^+ retention.
		Q: Drug interaction between Furosemide (Diuretic) and Propranolol?
Uses	**1:** Hypertension. **2:** Ischemic heart disease (Angina) → Decrease cardiac work and O_2 consuming. **3:** Cardiac arrhythmia → block A-V conduction. **4:** Hyperthyroidism (Thyrotoxicosis). → Thyrotoxicosis (increase secretion of thyroid hormone). → Types of thyroid hormone. - **T_4** → thyroxine-4 - **T_3** → thyroxine-3 → is more potent. → Propranolol inhibits the peripheral conversion of T_4 into T_3. **5:** Anxiety states to control sympathetic symptoms. **6:** Symptomatic treatment of alcohol and opiate withdrawal. **7:** Migraine prophylaxis due to VC effect to blood vessels in brain.	
Adverse effects	**1:** Bronchoconstriction. **2:** Hypotension. **3:** Bradycardia and heart block. **4:** Heart failure and physical fatigue due to decrease cardiac output. **5:** Increase incidence of hypoglycaemic episodes in type I diabetics. **6:** Cold extremities (symptoms of peripheral vascular disease) due to all adrenaline and nor-adrenaline act only in **α** receptors especially **α_1** →VC **7:** CNS effect → cross BBB → sleep disturbance. **8:** Increase plasma conc. of LDL → Atherosclerosis → Angina **9: Sudden Stop** β-blockers → Up-regulation of adrenoceptors → cardiac arrhythmia and hypertension (May cause sudden death).	
Contraindication	**1:** Bronchial asthma. **2:** Hypotension. **3:** Heart Failure (Avoid large dose) **4:** Partial heart blocker.	

Nadolol (Corgard®)	**Timolol** (Timogel®)
- More potent than Propranolol - Less central effect due to fewer lipids soluble. - Longer duration of action.	- More potent than Propranolol. - Used in treatment of **Chronic open-angle glaucoma**.
Sotalol (Betacor®)	- Antiarrhythmic and Antihypertensive.

B: Selective β_1-adrenoceptor antagonist

Metoprolol (Betaloc®)	**Atenolol** (Atelol®)
- Absorbed in GI. - Low bioavailability due to first-pass. - Used once daily due to extend release. - Used as Antihypertensive and anti-anginal.	- Water soluble drug → Not pass BBB - Accumulation in renal tubules→ Renal failure - More effective in combination with diuretic. - Used as Antihypertensive and anti-anginal.
Esmolol (Brevibloc®)	**Nebivolol** (Nebilet®)
- Ultra-short acting (IV) about 10 min →due to rabid metabolized. - **Uses (Antiarrhythmic drug):-** 1: Controlling supraventricular arrhythmia. 2: Arrhythmia associated with thyrotoxicosis. - **Adverse effects:-** 1: Bradycardia 2: Heart failure	- ***Stimulate releasing of Nitric oxide*** (endothelium-derived relaxing factor) (EDRF) → NO → **VD** - **Uses:-** - Used as Antihypertensive and anti-anginal. - **Adverse effects:-** → Bradycardia, fatigue, vivid dreams and cold hands.
Betaxolol (Betoptic®)	**Bisoprolol** (Concor®)
- Long acting agent. - Used in glaucoma.	- Used as Antihypertensive and anti-anginal.

Q: Advantage of using selective β_1-adrenoceptor antagonist in treatment of hypertension than non-selective?

A: They can be used in hypertension patient with:
1: Impaired pulmonary function.
2: Peripheral vascular disease.
3: Diabetic patient receiving insulin or oral hypoglycemic agents.

C: β-adrenoceptor antagonist with a partial agonist activity

Pindolol (Visken®)	**Penbutolol** (Levatol®)	**Acebutolol** (Sectral®)
- They are not pure blockers. - They are weakly stimulate both β_1 and β_2 receptors. - They have intrinsic sympathomimetic activity (ISA).		
Advantage:- - They minimize the disturbance of lipid and carbohydrate metabolism → used in diabetic's patient. - They are effective in hypertensive patient with moderate bradycardia		
Celiprolol (Celectol®)		
- It is a β_1 selective antagonist with modest capacity to activate β_2 receptors. - It may have less bronchoconstriction effect in asthma.		

3: Mixed adrenoceptor antagonist

Labetalol (Labipress®)	
Information	- It is block **β** receptors and **α_1** receptors.
Uses	➢ **In hypertension of →** **1: Pheochromocytoma** **2:** Hypertensive emergencies → rapidly decrease BP. **3:** Treatment of pregnancy induced hypertension.
Adverse effect	- Postural hypotension and dizziness.

Carvedilol (Carlol V®)

- Antioxidant.
- It is **useful in CHF** due to → its ability to attenuate free radical-induced lipid peroxidation and decrease vascular wall thickening.

Drug interaction with β-adrinoceptor antagonist

Pharmacokinetics drug interaction	
Enzyme Inhibitors → e.g. **- Cimetidine**	→ Inhibition hepatic metabolism of drugs → increase plasma concentration of β blockers → increase activity of β blockers may be lead to toxicity.
Enzyme Inducers → e.g. **- Barbiturates**	→ Increase hepatic metabolism of drugs → decrease plasma concentration of β blockers → decrease activity of β blockers may be lead to loss of activity.
Other effects	→ **β** Blockers decrease CO → decrease hepatic blood flow → decrease metabolism of other drugs e.g. lignocaine and chlorpromazine.
Pharmacodynamic drug interaction	
Sympathomimetics drugs having α & β agonist action	→ Adrenaline release → act only in **α** receptors due to **β** receptors are blocked → VC effect.
Verapamil (Ca^{2+} channel blockers)	→ Verapamil → have stronger (-ve) inotropic and (-ve) Chronotropic → when given with β-blockers → **additive effect** Cause → Cardiodepression (bradycardia, heart block, heart failure and postural hypotension).
NSAIDs → e.g. **- Indomethacin**	→ NSAIDs inhibit formulation of prostaglandin → decrease renal VD → decrease renal blood flow → water and salt retention → decrease antihypertensive effect of β-blockers.
Insulin and sulfonylureas	→ Non-selective β blockers potentiate the hypoglycemic effect of insulin and sulfonylurea.

Adrenergic neuron blockers

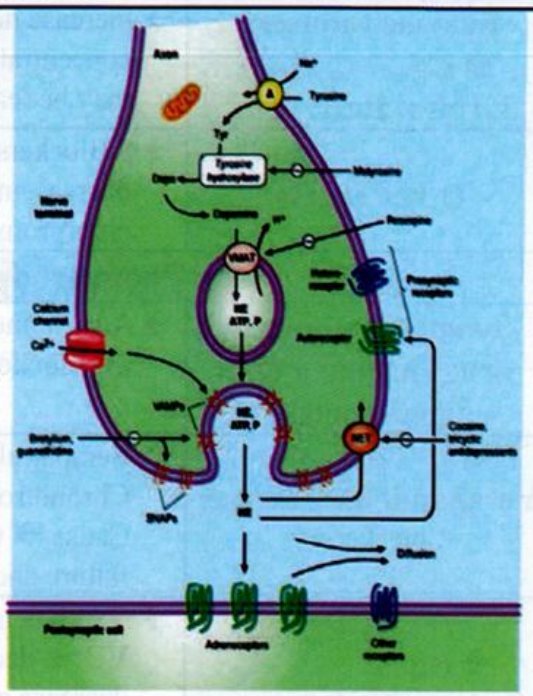
Drugs that interfere with neurotransmitter (NE) release

Guanethidine (Ismelin®)	
- Act by blocking the release of stored NE → gradual decrease BP and HR.	
Uses	- Rapid control of blood pressure in a hypertensive emergency.
Adverse effects	- Postural hypotension. - Failure of ejaculation. - Nasal congestion.

Guanethidine similar drugs		
Bethanidine	Debrisoquine	Bretylium (Bretylol®)
- Similar to Guanethidine	- Similar to Guanethidine	- Used as Antiarrhythmic

Drugs that deplete NE store

Reserpine (Hypoten®)	
Information	- It is a rauwolfia alkaloid. - It has slow onset and longer duration.
Mechanism of action	- Inhibition of the uptake of NE into vesicle → NE not stored→Increase intra-neuronal degradation of NE by MAO. - This action occurs both centrally and peripherally.
Uses	- Treatment of mild hypertensive.
Adverse effect	- Sedation → due to depletion of stores of catecholamines and serotonin in brain. - Parkinsonism due to depletion of dopamine from basal ganglia. - Diarrhea and hyperacidity. - Bradycardia and nasal congestion.



N.B:
- Cocaine and Tricyclic antidepressant inhibits uptake of NE → Increase concentration of NE in synapes → Sympathatic stimulation.

Questions

➢ Coose the best answer

21: Of the many types of adrenergic receptors found throughout the body, which is most likely responsible for the cardiac stimulation that is observed following an intravenous injection of epinephrine?

a. α_1-adrenergic receptors b. α_2-adrenergic receptors c. β_1-adrenergic receptors
d. β_2-adrenergic receptors e. β_3-adrenergic receptors

22: The enzyme that is inhibited by echothiophate iodide is

a. Tyrosine hydroxylase b. Acetylcholinesterase (AChE)
c. Catechol-O-methyltransferase (COMT) d. Monoamine oxidase (MAO)
e. Carbonic anhydrase

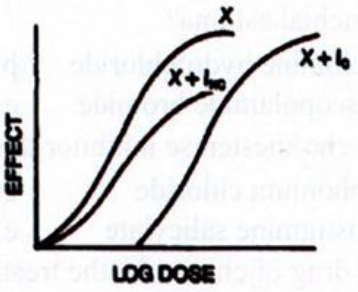
23: Applied to the skin in a transdermal patch (transdermal therapeutic delivery system), this drug is used to prevent or reduce the occurrence of nausea and vomiting that are associated with motion sickness.

a. Diphenhydramine b. Chlorpromazine c. Ondansetron
d. Dimenhydrinate e. Scopolamine

24: The non-selective β-adrenergic blocking agent that is also a competitive antagonist at α_1-adrenoceptors is

a. Timolol b. Nadolol c. Pindolol
d. Acebutolol e. Labetalol

25: The contractile effect of various doses of norepinephrine (NE) (X) alone on vascular smooth muscle is represented in the figure.



When combined with an antagonist (I_C or I_{NC}), a shift in the dose response curve occurs. The curve labeled $X + I_{NC}$ would most likely occur when vascular smooth muscle is treated with NE in the presence of

a. Terazosin b. Phentolamine c. Labetalol
d. Phenoxybenzamine e. Prazosin

26: The reversible cholinesterase inhibitor indicated in the treatment of Alzheimer's disease is

a. Tacrine b. Edrophonium c. Neostigmine
d. Pyridostigmine e. Ambenonium

27: Hypotension, bradycardia, respiratory depression, and muscle weakness, all unresponsive to atropine and neostigmine, would most likely be due to

a. Diazoxide b. Isofluorphate c. Tubocurarine
d. Nicotine e. Pilocarpine

28: Ritodrine hydrochloride is used in the treatment of

a. Parkinson's disease b. Bronchial asthma c. Depression
d. Hypertension e. Premature labor

29: The skeletal muscle relaxant that acts directly on the contractile mechanism of the muscle fibers is

a. Gallamine b. Baclofen c. Pancuronium
d. Cyclobenzaprine e. Dantrolene

30: A predictably dangerous side effect of nadolol that constitutes a contraindication to its clinical use in susceptible patients is the induction of

a. Hypertension b. Cardiac arrhythmia c. Asthmatic attacks
d. Respiratory depression e. Hypersensitivity

31: All of the following drugs are used topically in the treatment of chronic open-angle glaucoma. Which of these agents reduces intraocular pressure by decreasing the formation of the aqueous humor?

a. Timolol b. Echothiophate c. Pilocarpine
d. Isofluorphate e. Physostigmine

32: Pralidoxime chloride is a drug that

a. Reduces the vesicular stores of catecholamines in adrenergic and dopaminergic neurons
b. Blocks the active transport of choline into cholinergic neurons
c. Reactivates cholinesterases that have been inhibited by organophosphate cholinesterase inhibitors
d. Stimulates the activity of phospholipase C with increased formation of inositol triphosphate
e. Inhibits the reuptake of biogenic amines into nerve terminals

33: Which of the following anti-muscarinic drugs is used by inhalation in the treatment of bronchial asthma?

a. Dicyclomine hydrochloride b. Cyclopentolate hydrochloride c. Ipratropium bromide
d. Methscopolamine bromide e. Trihexyphenidyl hydrochloride

34: The cholinesterase inhibitor that is used in the diagnosis of myasthenia gravis is

a. Edrophonium chloride b. Ambenonium chloride c. Malathion
d. Physostigmine salicylate e. Pyridostigmine bromide

35: The drug of choice for the treatment of anaphylactic shock is

a. Epinephrine b. Nor-epinephrine c. Isoproterenol
d. Diphenhydramine e. Atropine

36: A 58-year-old male with angina is treated with atenolol. Select the mechanism of action of atenolol.

a. α-adrenergic agonist b. α-adrenergic antagonist c. β-adrenergic agonist
d. β-adrenergic antagonist e. Mixed α and β agonist f. Mixed α and β antagonist

37: A 35-year-old male with a pheochromocytoma is treated with labetalol. Select the mechanism of action of labetalol.

a. α-adrenergic agonist b. α-adrenergic antagonist c. β-adrenergic agonist
d. β-adrenergic antagonist e. Mixed α and β agonist f. Mixed α and β antagonist

ANS

38: A 16-year-old male treated for bronchial asthma develops skeletalmuscle tremors. Which of the following agents may be responsible for this finding?

a. Ipratropium b. Zileuton c. Beclomethasone
d. Cromolyn e. Salmeterol

39: Which of the following agents should a patient take for a stuffy, runny nose?

a. Oxymetazoline b. Albuterol c. Clonidine
d. Terbutaline e. Metoprolol

40: A 10-year-old male displays hyperactivity and is unable to focus on his schoolwork because of an inability to focus on the activity. Which of the following might prove effective in this patient?

a. Methylphenidate b. Terbutaline c. Dobutamine
d. Pancuronium e. Prazosin f. Scopalamine

41: Which of the following agents might mask the hypoglycemia in treated diabetics?

a. An α-adrenergic agonist b. An α-adrenergic antagonist c. A β-adrenergic agonist
d. A β-adrenergic antagonist e. A cholinergic agonist f. A cholinergic antagonist

42: For each patient, which drug was given?

a. Diazepam b. Doxazosin c. Scopolamine d. Cyclobenzaprine e. Propantheline
f. Atracurium g. Atenolol h. Baclofen i. Timolol j. Phentolamine

I: A 65-year-old male complains of losing his vision. Retinal examination reveals optic nerve cupping. Peripheral vision loss is observed on visual field tests, and his intraocular pressure is increased. Following treatment with a drug, he has improved visual acuity and decreased intraocular pressure.

a	b	c	d	e	f	g	h	i	j

II. A 30-year-old female is being prepared for anesthesia before exploratory surgery for a mass in her neck. In addition to using an inhalation anesthetic, a drug is given that causes complete paralysis of the skeletal muscles.

a	b	c	d	e	f	g	h	i	j

43: Match the descriptions of use with the appropriate drug.

a. Pilocarpine	1: Used in pheochromocytoma
b. Methylphenidate	2: Used in glaucoma
c. Propranolol	3: Used in Thyrotoxicosis
d. Ritodrine	4: Used in ADHD (attention-deficit hyperactivity disorder)
e. Labetalol	5: Used in premature labor

44: Short acting amino-steroid used as non-depolarizing neuromuscular blocker is

a. Atracurium b. Gallamine c. Rocuronium
d. Rapacuronium

45: New drug used to quit smoking by stimulation of nicotinic receptor is

a. Salmeterol b. Varenicline c. Cevimeline
d. Carbachol e. Echothiophate

46: Drug used treatment of Sjogren's syndrome

a. Salmeterol b. Varenicline c. Cevimeline
d. Carbachol e. Echothiophate

47: A 75-year-old man who was a smoker is diagnosed with chronic obstructive pulmonary disease and suffers from occasional bronchospasm. Which of the following would be effective in treating him?

a. Ipratropium aerosol b. Scopolamine patches c. Mecamylamine
d. Oxygen

48: The prolonged apnea sometimes seen in patients who have undergone an operation in which succinylcholine was employed as a muscle relaxant has been shown to be due to:

a. Urinary atony.
b. Depressed levels of plasma cholinesterase.
c. A mutation in acetylcholinesterase.
d. A mutation in the nicotinic receptor at the neuromuscular junction.

49: A 50-year-old male farm worker is brought to the emergency room. He was found confused in the orchardand since then has lost consciousness. His heart rate is 45, and his blood pressure is 80/40 mm Hg. He is sweating and salivating profusely. Which of the following treatments is indicated?

a. Physostigmine. b. Norepinephrine. c. Trimethaphan.
d. Atropine. e. Edrophonium.

50: Drug used in BPH and selective antagonist on α_{1A} receptor on the smooth muscle of prostate

a. Alfuzosin b. Doxazosin c. Terazosin
d. Tamsulosin e. Finasteride

Answers

21	22	23	24	25	26	27	28	29	30
c	b	e	e	d	a	d	e	e	c

31	32	33	34	35	36	37	38	39	40
a	c	c	a	a	d	f	e	a	a

41	42		43		44	45	46	47	48	49	50
d	I	II	a	2	d	b	c	a	c	d	d
	i	f	b	4							
			c	3							
			d	5							
			e	1							

Questions and answers from (References):

Basic and Clinical Pharmacology 12th edition, Katzung-Lange
Pharmacology 5th edition Lippincott Williams & Wilkins
Pharmacology 12th edition PreTest Self-Assessment and Review

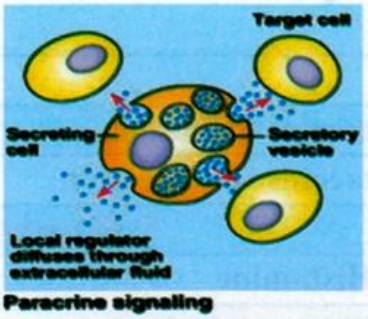
Autacoids

(ACTIVE SUBSTANCES IN THE BODY)

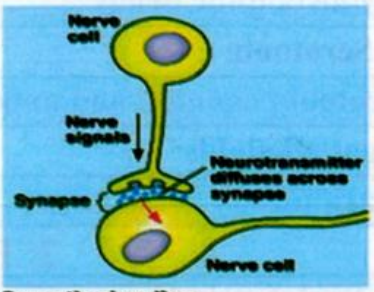
Autacoids

➢ Autacoids (local hormones) :-

- The word autacoids come from the Greek "Autos" (self) and "Acos" (relief, i.e. drug).
- Autacoids can be defined as **active substance in the body**.
- These effects can sometimes be undesirable and cause death. To prevent these **autacoids antagonists** are used.



Paracrine signaling

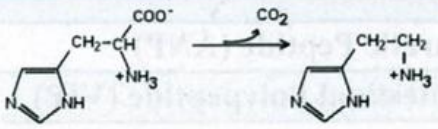


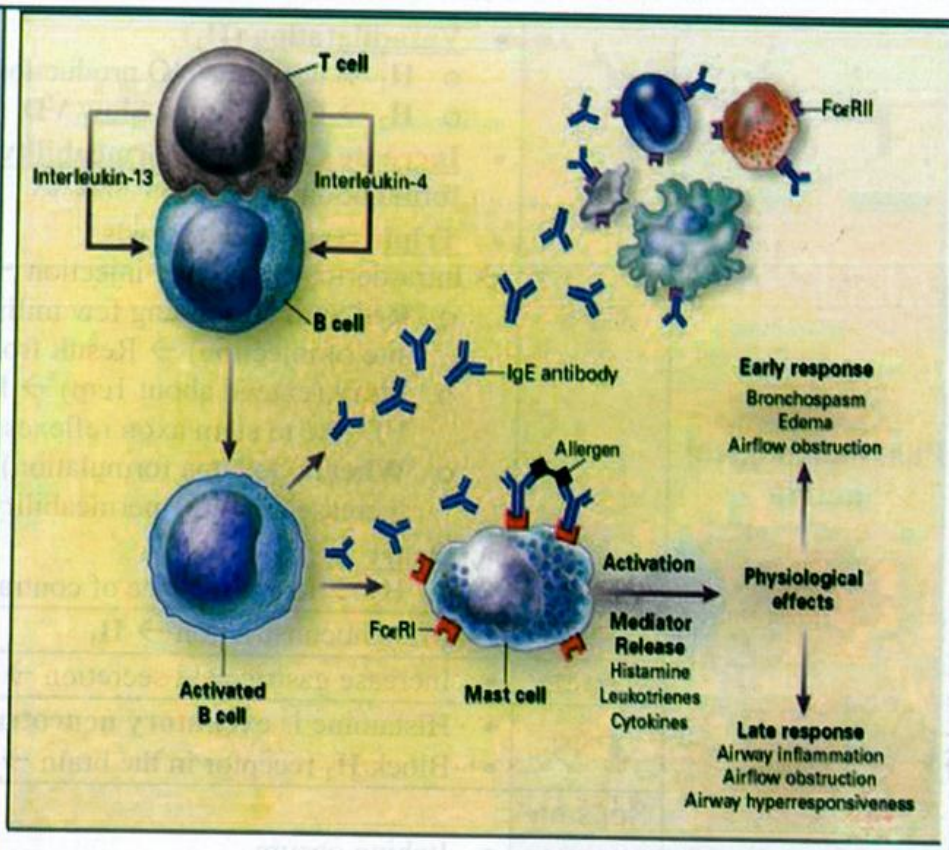
Synaptic signaling

➢ Classification :-

- **Decarboxylated amino acids**
  - Histamine
  - Serotonin
- **Polypeptides**
  - Angiotensin
  - Kinins
  - Vasopressin
  - Atrial Natriuretic Peptide (ANP)
  - Vasoactive Intestinal Polypeptide (VIP)
  - Substance P
- **Eicosanoids**
  - Prostaglandins
  - Leukotrienes

➢ Decarboxylated amino acids :-

Histamine	
Biosynthesis	 *Histidine* *Histamine*
Storage	• **Tissues** - It is found in most tissues but is present in high conc. in the lungs, skin and GIT. • **Cells** - It is found largely in mast cells and basophils. • **Neurons** - Histaminergic neurons in the brain.
Release	**1: Hypersensitivity reaction** (Type I) (immediate hypersensitivity)→ result of antigen/antibody reaction → Antigen (Allergen) react with antibody (IgE) on the mast cell → these reaction increase release Histamine.



2: Chemical histamine releasers e.g. Morphine and Curare.

Mechanism of action

- Histamine binding by histamine receptor (H_1-H_2-H_3-H_4) → Biological action.

Histamine receptors

Type		Location	Function
H_1	G_q	- Smooth muscle - Endothelium - Brain (CNS)	-Vasodilatation. - Spasmogenic on smooth muscle e.g. Bronchi, GIT & uterus. - Skin → Itching, pain and triple response.
H_2	G_s	- Gastric Mucosa - Cardiac muscle - Brain (CNS)	- Cardiac stimulation (+ve Inotropic and chronotropic) - Increase Gastric HCl secretion.
H_3	G_i	- Presynaptic neurons. - Brain (CNS)	- Decreased neurotransmitter release: Histamine, Acetylcholine, Nor-epinephrine, Serotonin.
H_4	G_i	- Neutrophils - Eosinophils	- Plays a role in chemotaxis.

Pharmacological action	**CVS**	• **Vasodilatation (H_1)** o H_1 → Rapid → NO production → VD o H_2 → Cause Some Slow VD • **Increase Capillary permeability** → Edema formulation → H_1 • **Triple response of Lewis** → Intra-dermal histamine injection → cause o **Red spot** (extending few millimeters around the site of injection) → Result from direct VD (NO). o **Flare** (extend about 1cm) → Result from Indirect VD due to stem axon reflexes. o **Wheal** (Oedema formulation) → Result from increase capillary permeability. • **Heart** o H_2 → Increase force of contraction and HR
	SM	• Bronchoconstriction → H_1
	HCl	• Increase gastric acid secretion → H_2
	CNS	• Histamine is **excitatory neurotransmitter** in the brain. • Block H_1 receptor in the brain → Sedation.
	Sensory nerve ending	• Itching occurs.

Histamine antagonist

1) Physiological antagonist of histamine (Adrenaline) :-

- Adrenaline it is a physiological antagonist of histamine.
- Adrenaline having apposite to those histamine on H_1 receptor due to cause
  - Bronchodilatation → β_2 and cause vasoconstriction → α_1.

2) Inhibitors of histamine release :-

A) Mast cell stabilizers e.g. Cromolyn - Cromoglycate - Nedocromil - Ketotifen
→ They decrease Ag/Ab reaction → Decrease histamine release from mast cell
→ used as prophylactics in bronchial asthma.

B) β_2-adrenoceptor agonists e.g. Salbutamol

C) Methyl-Xanthines (PDE inhibitors) e.g. Theophylline

3) Corticosteroids e.g. Cortisone

4) Histaminase enzyme (Di-amine Oxidase)

➔ Responsible for metabolizing increased levels of histamine.

5) Histamine receptors blockers

A: H_1 receptor blockers

B: H_2 receptor blockers

C: H_3 receptor blockers

D: H_4 receptor blockers

A: H_1-receptor antagonist

First generation

Pass BBB (Potent Sedation) and Short duration

→ due to pass BBB → these drugs have many actions in addition of H_1-blockers e.g. Anti-cholinergic, Anti-emetic, Anti-serotonin and local anesthetic effect.

Chemical class	Drugs	Common uses
Ethanolamines	Diphenhydramine (Dramenex®)	- **Motion sickness** - Parkinson's disease
	Carbinoxamine (Palgic®)	- **Hay fever** - Cough preparations
	Clemastine (Tavegyl®)	- **Allergic reactions**
	Dimenhydrinate (Dramamine®)	- **Motion sickness**
	Doxylamine (Donormyl®)	- **Insomnia**
Ethylenediamines	Pyrilamine or Mepyramine	- Common cold preparations
	Tripelennamine (Pyribenzamine®)	- Psychoactive drug
	Antazoline (Calazole®)	- Skin calming preparations
Alkylamines	Chlorpheniramine (Anallerge®)	- **Allergic reactions**
	Triprolidine (Actifed®)	- Common cold preparations
	Pheniramine (Avil®)	- **Allergic reactions**
	Dimetindene (Fenistil®)	- **Allergic reactions**
Piperazines	Hydroxyzine (Atarax®)	- **Schizophrenia**
	Cyclizine (Emetrex®)	- Combined with vit. B6 → as **antiemetic** (Emetrex®)
	Meclizine (Navidoxine®)	- Combined with vit. B6 → as **antiemetic** in pregnancy (Navidoxine®)
Phenothiazines	Promethazine (Phenergan®)	- Motion sickness - Allergic reactions
	Mequitazine (Primalan®)	- Allergic reactions
Piperidines	Cyproheptadine (Triactin®)	- Anti-serotonin agent also has appetite stimulants effect.
	Phenindamine (Nolahist®)	- Allergic reactions

Second generation		
↓Pass BBB (↓Sedation) and Long duration (24 hours)		
- These drugs have **no** Anti-cholinergic, **no** Anti-emetic and **no** Anti-serotonin.		
Systemic	Acrivastine (Semprex®)	Cetirizine (Zyrtec®)
	Ebastine (Kestine®)	Loratadine (Claritine®)
	Mizolastine (Zolim®)	
Local	Azelastine (Zalastin®)	Levocabastine (Livostin®)
Third generation		
Derivatives of second-generation drugs intended to have increased efficacy with fewer adverse drug reactions (No Sedation & Long duration)		
Systemic	Levocetirizine (Allear®)	Desloratadine (Aerius®)
	Fexofenadine (Allerfen®)	

Q: Drug interaction between Terfenadine and Erythromycin?

A: Terfenadine (Pro-drug) is metabolized to **Fexofenadine (Active drug)**, Erythromycin (LMEIs) inhibit this metabolism → Increase concentration of Terfenadine in the blood → **Block K^+ channels** in the heart which responsible for repolarization of the action potential → Arrhythmia.

➢ Pharmacological action of first generation :-

Sedation	→ Pass BBB → and block H_1-receptor in the brain prevent excitatory effect of histamine in the brain → Sedation.
Antinausea and antiemetic actions	→ Due to suppress chemoreceptor trigger zone (CTZ)
Antiparkinsonian effect	→ Due to muscarinic blocker effect
Anticholinoceptor action	→ Atropine like effect
α-Adrenoceptor blocker action	→ E.g. **Promethazine**
Serotonin blocking action	→ e.g. **Cyproheptadine**
Local anesthetic effect	→ Due to block Na^+ channels

➢ Clinical uses :-

- **Allergic reactions:**
  - In allergic rhinitis and urticaria (hay fever).
  - Atopic dermatitis first generation is beneficial due to sedative effect.
  - Not beneficial in bronchial asthma and angioedema due to in asthma and angioedema → increase release of histamine and other mediator antihistaminic drugs block only histamine action.
- **Motion sickness:**
  - H_1-blocker is the most effective in motion sickness e.g. **Diphenhydramine, Promethazine** and **Dimenhydrinate**.

- **Somnifacient (Hypnotic):**
  - First generation antihistaminic used in treatment of insomnia e.g. **Doxylamine** → Strong sedative.

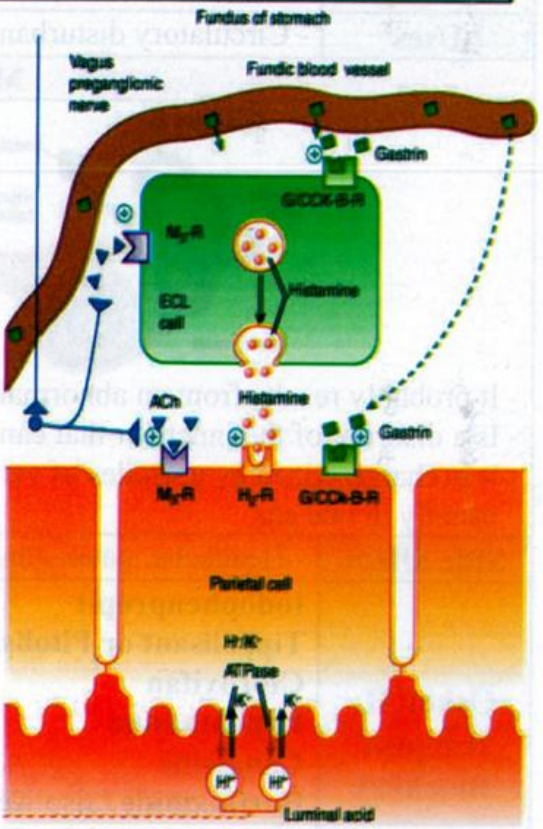
➢ Drug interactions :-

- With anxiolytic and hypnotic drugs e.g. **benzodiazepines** (BDZs) → increase effect (Additive effect).
- With **MAO inhibitors** → increase anticholinergic effects.
- First generation H_1-receptor blockers with cholinesterase inhibitors in treatment of Alzheimer's disease e.g. **Rivastigmine** → Decrease effect.

B: H_2-receptor antagonist	
Drug	**Relative Potency**
Cimetidine (Not used)	**1**
Ranitidine (Zantac®)	**4-10**
Nizatidine (Ulefree®)	**4-10**
Famotidine (Antodine®)	**20-50**

➢ Mechanism of action :-

1) H_2 receptor blocker → block the actions of histamine at all H_2 receptors.
2) Decrease histamine release from enterochromaffin-like (ECL) cell.
3) Reduce effect of other substances that promote acid secretion such as gastrin and acetylcholine.



➢ Clinical uses :-

- **Peptic ulcer disease (PUD)**
- **Gastroesophageal reflux disease (GERD)**
  - **But** proton pump inhibitors (PPIs) are more potent and preferentially used in the treatment of this disorder.
- **Non-ulcer dyspepsia**
- **Prevention of stress ulcer**

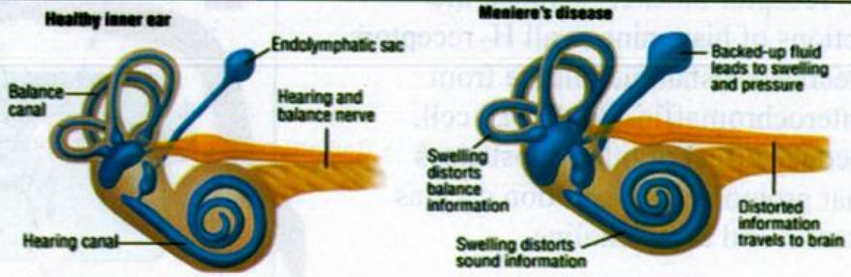
➢ Adverse effects :-

- **Adverse effect of Ranitidine, Nizatidine** and **Famotidine** Occurring in less than 3% of patient include diarrhea, headache and fatigue.

- **Adverse effect of Cimetidine :**
  - Cimetidine inhibits binding of dihydrotestosterone to androgen receptors (Anti-androgenic effect) and increase serum prolactin cause→
    - Gynecomastia in male (Increase prolactin).
    - Impotence in male (Anti-androgenic effect).
    - Galactorrhea in female (Increase prolactin).

➢ Drug interactions :-

- Cimetidine is LME inhibitor → Increase effect of other drug e.g. **warfarin**.
- All of H_2-blocker except **Famotidine** inhibit gastric first pass metabolism of **ethanol** (**Alcohol**) especially in women resulting in increased bioavailability of ethanol → increase blood ethanol level.

C: H_3-receptor antagonist	
Betahistine (Betaserc®)	
Mechanism of action	- Block H_3 receptor → dilates the blood vessels within the middle ear which can relieve pressure from excess fluid and act on the smooth muscle.
Uses	- Circulatory disturbance and Ménière's disease
Ménière's disease	
	
- It probably results from an abnormality in the way fluid of the inner ear is regulated. - Is a disorder of the inner ear that can affect hearing and balance to a varying degree. - It is characterized by episodes of vertigo and tinnitus and progressive hearing loss, usually in one ear.	
Side effect	- Headache, nausea and decreased appetite.
Other H_3 receptor Blockers	**Iodophenpropit** **Tiprolisant or Pitolisant** **Ciproxifan** **Impentamine** **Conessine** **Burimamide** (also weak **H_2** antagonist) **Clobenpropit** (also **H_4** antagonist) **Thioperamide** (also **H_4** antagonist)

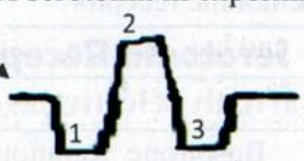
D: H_4-receptor antagonist
Clobenpropit and **Thioperamide**

Serotonin (5-Hydroxytryptamine) (5-HT)	
Information	- Serotonin is a monoamine neurotransmitter.
Biosynthesis	- From **L-Tryptophan** (amino acid) by decarboxylation reaction.
Storage	1) Approximately 90% of the human body's total serotonin is located in the enterochromaffin cells in the gut. 2) In blood serotonin is found in platelets. 3) Brain (CNS).
Inactivation	→ **Serotonin** is metabolized by MAO → Give intermediate product, **5-Hydroxyindoleacetaldehyde** → is further oxidized by aldehyde dehydrogenase to → **5-Hydroxyindoleacetic acid (5-HIAA)**. - **5-HIAA** → Normal 2-10 mg/day in urine. - ***Increase*** 5-HIAA in patient with carcinoid tumors of the enterochromaffin.
General Function	- Appetite, aggression, migraine, anxiety, cognition, learning, memory, mood, nausea, sleep, and thermoregulation.
Melatonin Hormone	- **Serotonin** is also a precursor of **melatonin** in the pineal gland. - Melatonin responsible for regulate **circadian** (Biological clock). - Production of melatonin is inhibited by light and increases in night. - Melatonin stimulates immune system and suppress cancer cell. - Melatonin used in sleep and mood disorders, cancer, reduced body weight and other uses. قال الله سبحانه وتعالى (اللَّهُ الَّذِي جَعَلَ لَكُمُ اللَّيْلَ لِتَسْكُنُوا فِيهِ وَالنَّهَارَ مُبْصِراً) غافر 61
Mechanism of action	- The action of serotonin is mediated through a large number of cell membrane receptor.

Serotonin Receptor Subtypes			
Subtype		**Partially selective agonists**	**Partially selective antagonists**
5-HT_{1A}	**G_i**	Buspirone, Repinotan	Robalzotan, Mefway (^{18}F)
5-HT_{1B}	**G_i**	Sumatriptan	Isamoltane
5-HT_{1D}	**G_i**	Sumatriptan, Eletriptan	
5-HT_{1E}	**G_i**		
5-HT_{1F}	**G_i**	Lasmiditan	
5-HT_{1P}	**G_o**	5-Hydroxyindalpine	Renzapride
5-HT_{2A}	**G_q**	α-Methyl-5-HT	Ketanesrin
5-HT_{2B}	**G_q**	α-Methyl-5-HT	
5-HT_{2C}	**G_q**	α-Methyl-5-HT	Mesulergine
5-HT_3	**Na^+/k^+**	2-Methyl-5-HT	Granisetron, Ondansetron, others
5-HT_4	**G_s**	Renzapride, Metoclopramide	
5-$HT_{5A,B}$	**G_i**		
5-HT_6	**G_s**		
5-HT_7	**G_s**		Clozapine

Table from Basic and Clinical Pharmacology, Katzung-Lange, 2012, p 282

➢ Pharmacological action :-

Nervous system	• **Brain:** - Responsible for mood, appetite, sleep, cognition, sensory perception, motor activity, temperature regulation, sexual behavior and hormone secretion. • **Nerve ending:** - Like histamine, serotonin is a potent stimulant of pain and itch sensory nerve ending. - **Serotonin** → activation of **5-HT$_3$** receptor on these afferent vagal nerve ending → Chemoreceptor reflex (**Bezold-jarisch reflex**) → bradycardia, hypotension and decrease CO. • **N.B:** - **5-HT$_3$** present in GIT and in the vomiting center. - **5-HT$_4$** Play important role in enteric nervous system function.
Respiratory system	- Small direct stimulant of bronchial smooth muscle → Bronchoconstriction → **5-HT$_{2A}$**
CVS	- Serotonin directly causes the contraction of vascular smooth muscle (VC) → **5-HT$_{2A}$** - Serotonin is a powerful VC except in skeletal muscle and the heart, where it dilates blood vessels. - Platelet aggregation by activation **5-HT$_{2A}$**. → **Triphasic blood pressure response of serotonin** • Injection of serotonin in experimental animal.  **1:** Decrease HR, CO and BP due to chemoreceptor response. **2:** Increase in BP due to VC. **3:** Decrease in BP due to VD in vessels supplying skeletal muscle.
GIT	- Powerful stimulant of GI smooth muscle → Increasing tone and facilitate peristalsis→ **5-HT$_2$** - Activation of **5-HT$_4$** receptor in the enteric nervous system → Increase ACh release.
Skeletal muscle	- **5-HT$_2$** receptors are present on skeletal muscle membranes.
Serotonin syndrome	- **Serotonin syndrome** → is a condition associated skeletal muscle contraction and precipitated when MAO Inhibitors Are given with serotonin agents especially selective serotonin reuptake inhibitors (SSRIs) - **Symptoms** → Hypertension, Agitation, mental confusion, Hyperthermia, diarrhea, tremors and muscle rigidity.

Serotonin Agonists in Clinical Use

Buspirone (Buspar®)

- Selective **5-HT$_{1A}$** agonist, which is an effective non-benzodiazepine anxiolytic.

Sumatriptan (Imigran®) | Zolmitriptan (No-Migrain Z®)

- Selective **5-HT$_{1D}$** and **5-HT$_{1B}$** agonists effective in the treatment of acute migraine → due to VC of intracranial blood vessels.

→ **Adverse effects:-**

- Coronary artery vasospasm (Not used in ischemic heart disease e.g. angina pectoris).

Tegaserod (Zelmac®)

- Partial agonist **5-HT$_4$** receptor of the enteric nervous system in the GIT → stimulates GI motility.
- Used in treatment **irritable bowel syndrome-constipation (IBS-C)**
- Removed from the market in 2007 due to FDA concerns about possible increased risks of heart attack or stroke.

Mosapride (Fluxopride®)

- Selective **5-HT$_4$** agonist → accelerates gastric emptying and is used for the treatment of acid reflux, irritable bowel syndrome-constipation and functional dyspepsia.

Serotonin Antagonists in Clinical Use

Phenoxybenzamine (Dibenzylene®)

- It is α-adrenoceptor blocker and has blocking action at **5-HT$_{2A}$** receptor.

→ **Uses** → Hypertension and **carcinoid tumor**.

Cyproheptadine (Phenergan®)

- It is **H$_1$** receptor blocker and has blocking action at **5-HT$_2$ (5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{2C}$)**.

→ **Uses** →Treat allergic reactions (specifically hay fever), serotonin syndrome, **stimulate the appetite** and Prophylaxis of migraine.

Pizotyline or Pizotifen (Mosegor®)

- It is block **5-HT$_{2A}$, 5-HT$_{2C}$** receptors and has blocking **H$_1$** receptor.

→ **Uses** → **Prophylaxis of migraine** and as an **appetite stimulant**.

→ **Adverse effects** → Sedation, weight gain and anti-muscarinic effect.

Ketanserin (Ketensin®)

- It is block **5-HT$_{2A}$, 5-HT$_{2C}$** and it has α-adrenoceptor and H$_1$ receptor blockers.

→ **Uses** → Hypertension and used as Radio-ligand.

Ondansetron (Zofran®) | Granisetron (Kytril®) | Tropisetron (Navoban®)

- It is block **5-HT$_3$**

→ **Uses** →Prevention of **nausea and vomiting** associated with surgery and cancer chemotherapy.

→**Side effects** → Headache and diarrhea.

Ergot alkaloids

Source	- Ergot alkaloids produced by ***Claviceps purpurea*** (Fungi) - This fungus synthesizes histamine, ACh, Tyramine and other biologically active products in addition to score or more of unique of ergot alkaloids.
Action	- These alkaloids affect on α-adrenoceptor, dopamine receptors and 5-HT receptors.
Classification	
Peptide alkaloids	**Ergotamine** (Metograine®)
	Bromocriptine (Parlodel®)
Amine alkaloids	**Ergometrine or Ergonovine** (Methergin®)
	Lysergic acid diethylamide (LSD) (Delysid®)
	Methysergide (Sansert®)

➢ Effect of ergot alkaloids at several receptors :-

Ergot Alkaloids	α-adrenergic receptor	Dopamine receptor	Serotonin receptor ($5HT_2$)	Uterine smooth muscle
Bromocriptine	-	+++	-	0
Ergonovine	++	- (PA)	+++	
Ergotamine	-- (PA)	0	+ (PA)	+++
LSD	0	+++	-- (++ in CNS)	+
Methysergide	+/0	+/0	--- (PA)	+/0

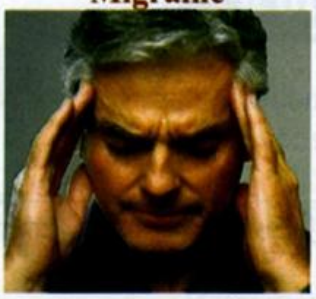
Agonist effects are indicated by +, antagonist by -, (PA) means partial agonist
(Table from Basic and Clinical Pharmacology, Katzung-Lange, 2012, p 288)

➢ Pharmacological action :-

CNS	- **LSD** → Hallucinogenic - **Suppression** of pituitary prolactin secretion → **D_2** agonist effect. - **Stimulation** of CTZ and CIC (Cardio-inhibitory center). - **Inhibition** of VMC (Vasomotor center) & RC (respiratory center)
Spasmogenic effect on smooth muscle	
Vascular smooth muscle	- **Strong VC** → due to partial agonist effect at **α_1** & **5-HT_2** effects. - Hydrogenated ergot alkaloid derivative e.g. **Dihydro-ergotoxine** that have reduced serotonin partial agonist effects and increased selective α-receptor blocking effect.
Uterine smooth muscle	→ **<u>In very small dose</u>** → Contraction and relaxation. → **<u>At higher dose</u>** → Powerful and prolonged contraction (Oxytocic effect). - **Ergometrine** is more selective → drug of choice in obstetric application.
Other SM	- Little effect on bronchi and urinary smooth muscle.
GIT	- May be induced nausea, vomiting and diarrhea. → Nausea and vomiting due to stimulation of CTZ.

Clinical Uses

Migraine



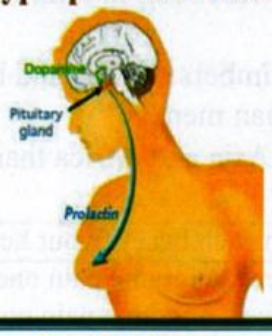
Ergotamine (Metograine®)

- **Acute attacks migraine** → due to **partial agonist** effect at **5-HT_{1D}** and α-adrenoceptor → **VC** (Combined with caffeine to facilitate absorption)

Methysergide (Sansert®)

- **Prophylaxis of migraine** → due to strong **5-HT_2 antagonist**.

Hyperprolactinemia



Bromocriptine (Parlodel®)

- Bromocriptine is a **potent agonist** at dopamine **D_2** receptors.

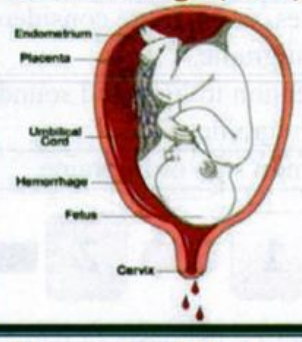
Cabergoline (Dostinex®)

- Similar to Bromocriptine but more potent.

Lysuride (Dopergin®)

- Lisuride is a dopamine and serotonin receptor partial agonist.

Postpartum haemorrhage (PPH)



Ergometrine or Ergonovine (Methergin®)

- It acts at α-adrenergic, dopaminergic, and serotonin receptors
- Prevent bleeding after childbirth by causing smooth muscle tissue in the blood vessel walls to narrow → reducing blood flow.
- It is usually combined with **Oxytocin** (Syntocinon®) as (Syntometrine®).

Diagnosis of Variant angina

Ergometrine or Ergonovine (Methergin®)

- Ergonovine induce spasm of the coronary arteries → It is **used to diagnose Variant (Prinzmetal's) angina.**

Adverse effects

GI disturbance (Diarrhea, nausea and vomiting).

In over dose → Prolonged vasospasm → Gangrene and require amputation.

Chronic therapy with methysergide → (Cardiac Murmur) (Abnormal heart sound).

CNS effects → Hallucination.





Migraine

➢ Migraine

- Is a chronic disorder characterized by moderate to seve headaches together with nausea. It is believed to be a neurovascular disorder.
- The word derives from the Greek (hemikrania), "pain on one side of the head".
- Migraines are related to a mix of environmental and genetic factors. About two-thirds of cases run in families, Fluctuating hormone levels may also play a role.
- Migraine affects approximately equal numbers of girls and boys before puberty, but about two to three times more women than men.
- Rates of migraines are slightly lower in Asia and Africa than in Western countries.

➢ Migraine signs :-

Throbbing or Pulsating Pain	- Feel the pain with each beat of your heart
One Sided Head Pain	- Most of patient feels migraine pain one-sided head pain. - Some of patient feels migraine pain on both sides, in their neck, or at the front or back of their head.
Nausea or Vomiting	- Nausea and vomiting are a very common signs of migraine.
Vision Disturbances or "Aura"	- Vision disturbances, or aura, are considered a common warning sign of classical migraine.
Sensitivity to Light and Sound	- Sensitivity or Aversion to light and sound is one of the most striking signs of migraine.
Dizziness	- Dizziness is common sign of migraine.

➢ Migraine stages (phases) :-

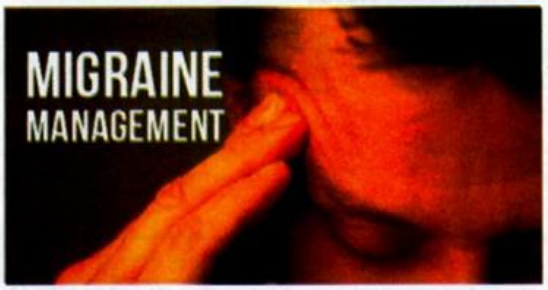
1) Prodrome	- May occur days before the onset of pain or aura → Including: altered mood, irritability, depression or euphoria, fatigue,
2) Aura	- Usually occur up to one hour to the headache - Characterized by Change in visual perception
3) Pain (Headache)	- Headache pain may be moderate or severe. (2hr. → 72 hr.)
4) Postdrome	- Symptoms can last several days after headache. - The patient may feel tired and have head pain, cognitive difficulties, gastrointestinal symptoms and mood changes.

➢ Pathophysiology (Causes) of migraine :-

- Genetics (about 70%)
- Cortical spreading depression (CSD) is a wave of electrophysiological hyperactivity followed by a wave of inhibition, usually in the visual cortex.)
- Vascular → When the constriction of blood vessels in the brain stops → VD and inflammation are occurs.
  - → N.B: Some Lifestyle factors e.g. stress, hunger, fatigue and Environmental factors responsible for migraine attack.

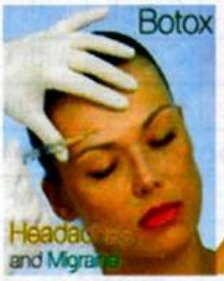
➢ Classification of Migraine:-

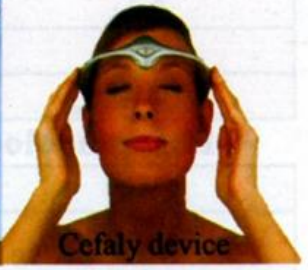
Migraine with Aura (MWA) (Classical Migraine)	- This type of migraine, formerly called **"classic migraine"**, accounts for around 15% of all migraine headaches. - An aura is a series of changes → visual, sensory, and cognitive changes that precede a migraine headache.
Migraine without Aura (MWOA) (Common Migraine)	- Almost 80% of migraine patients get migraines without aura (this particular type of migraine was previously known as **"common migraine"**. - This type of migraine typically lasts from 4 to 72 hours.
Uncommon Types of Migraine	- Hemiplegic Migraine, Basilar Migraine, Abdominal Migraine, Ophthalmoplegic Migraine and Status Migrainous.



➢ Management of migraine :-

- **Acute attack :-**
  - **Ergotamine**
  - **Analgesics** e.g. NSAIDs (**Paracetamol**) and **caffeine**
  - **Anti-emetics** e.g. **Metoclopramide**
  - **Sedative** e.g. **BDZs** e.g. **Diazepam**
- **Severe attack :-**
  - **Ergot alkaloids** → **Ergotamine** + **Caffeine** + **Paracetamol** + **Metoclopramide** = (Metograine®)
  - **Triptans e.g. Sumatriptan** (Imigran®) , **Zolmitriptan** (No-Migrain Z®) and **Almotriptan** (Triptagrain®)
  - **New treatments** → ***Clostridium botulinum* toxins** (Botox®) → **TENS technology e.g.** Cefaly device.
- **Prophylaxis :-**
  - **Anti-serotonin**
    - **Methysergide** (Sansert®)
    - **Cyproheptadine** (Phenergan®)
    - **Pizotifen** (Mosegor®)
  - **Antidepressant drugs e.g. Fluoxetine**
  - **Propranolol** (Inderal®) → Most common used
  - **Clonidine** (Catapress®)
- **Drug contraindicated in migraine headache:-**
  - **Reserpine**
  - **Oral contraceptives**

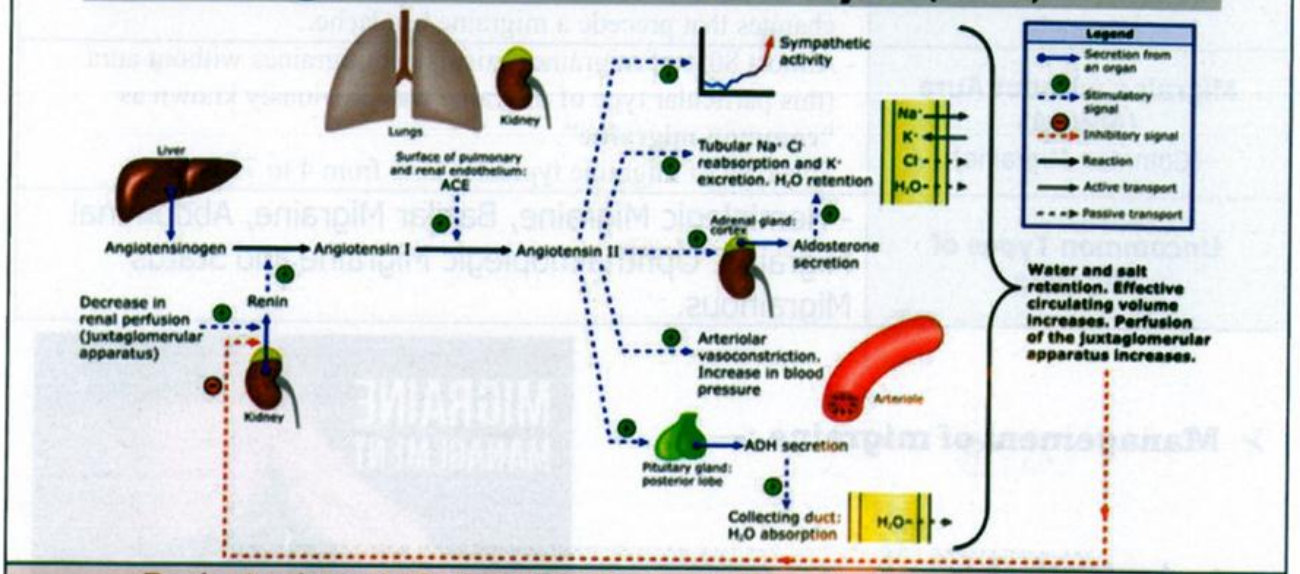




➢ Polypeptides :-

Angiotensin II

Renin-angiotensin-aldosterone system (RAAS)



Renin-Angiotensin System (Or) Renin-Angiotensin-Aldosterone System

- **Angiotensinogen** is synthesized in the liver and its production is increased by corticosteroid, estrogen, thyroid hormone.
- **Renin** secretion by kidney and convert angiotensinogen → to angiotensin I (ANG I).
- **Angiotensin converting enzyme (ACE)** converts angiotensin I → to angiotensin II.
- **Angiotensin II** acts by binding Angiotensin receptors and cause →

Angiotensin II

→ Potent direct **vasoconstrictors** (VC)
→ **Increase** secretion of **Aldosterone** & **Na^+ and water retention**
→ **Increase Sympathetic activity** (Increase release of NE)
→ **Increases** secretion of **ADH** and **ACTH** (Increase Drinking)
→ Also **Stimulate Glucocorticoid** synthesis

Angiotensin receptors	
AT_1	Coupled with G_q, Vasoconstriction and High affinity for Inhibitor
AT_2	Coupled with G_i, Vasodilatation and Low affinity for Inhibitor
AT_3 - AT_4	Unclear mechanism

➢ Pharmacological action :-

CVS	- Very potent VC (40 more times than noradrenaline).
Autonomic nerve	- Stimulate autonomic ganglia →↑ Sympathetic activity → Increase release of epinephrine and norepinephrine.
Adrenal cortex	- Stimulate aldosterone synthesis - High Concentration of ANG →↑ glucocorticoid synthesis.
Kidney	- Cause renal VC → Increase Na^+ reabsorption and inhibit renal release.
CNS	- Increase the secretion of ACTH and ADH (Vasopressin).
Cell Growth	- Mitogenic effect → hypertrophy and remodeling of heart & BV

➢ Inhibitors of the renin-angiotensin system :-

- **1: Drug that block renin secretion:**
  - **Clonidine**
  - **Propranolol** and other β Blockers

→ Inhibit secretion of renin

- **2: Angiotensin-converting enzyme (ACE) inhibitors:**

Captopril (Capoten®)	**Fosinopril** (Monopril®)	**Enalapril** (Renitec®)
Benazepril (Cibacen®)	**Lisinopril** (Zestril®)	**Perindopril** (Coversyl®)
Cilazapril (Zapritens®)	**Ramipril** (Tritace®)	**Imidapril** (Tanatril®)

Mechanism of action	- ACE inhibitors block the conversion of angiotensin I to angiotensin II. - ACE inhibitors also inhibit the degradation of other substances e.g. Bradykinin (Inflammatory mediator)
Adverse effects	- **Dry persistence cough** and **angioedema** due to increased levels of Bradykinin. - **Hyperkalemia** due to decrease aldosterone secretion. - **Renal impairment** - **Fetopathic potential** (Teratogenicity) → Decrease Organogenesis of lung and fetal abnormalities and may cause fetal death.
Drug interactions	**1:** K^+ sparing diuretics or K^+ supplements → Hyperkalemia. **2:** NSAIDs → due to decrease Prostaglandins (PGs) o Decrease renin secretion o Hyperkalemia o Blocking bradykinin → Decrease hypotensive effect **3:** Angiotensin receptor blockers (ARBs) **4:** Renin inhibitors e.g. **Aliskiren**
Contraindication	- Pregnancy, lactation, Chronic obstructive pulmonary disease (COPD) and Impaired renal function.

- **3: Angiotensin receptor blockers (ARBs) :**

Losartan (CozAAr®)	**Irbesartan** (Aprovel®)	**Valsartan** (Diovan®)
Candesartan (Atacand®)		**Eprosartan** (Teveten®)
Telmisartan (Micardis®)		**Olmesartan** (Erastapex®)

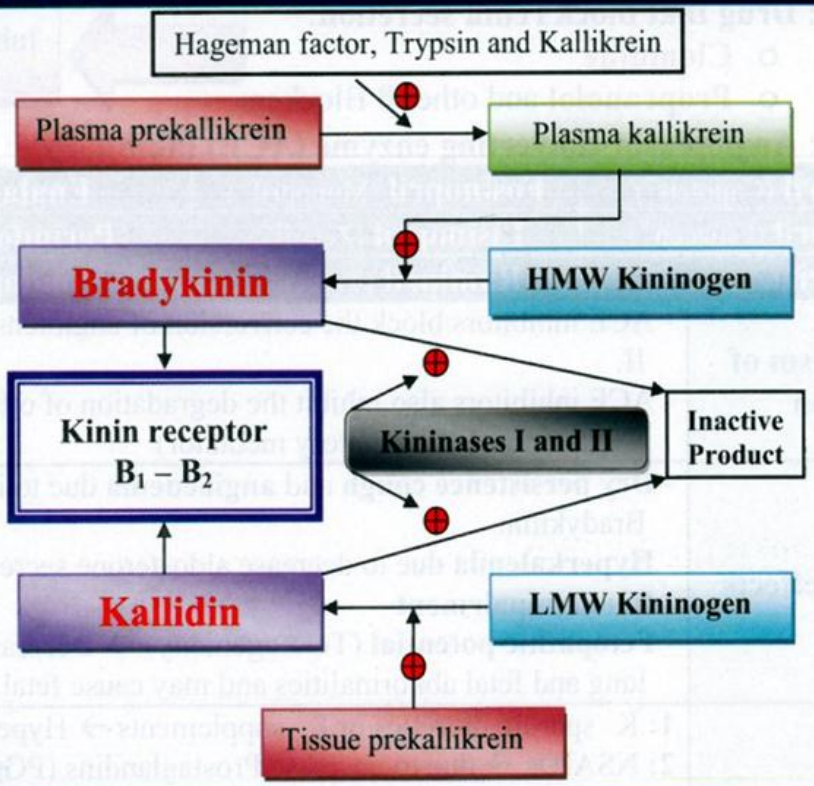
Mechanism	- These drugs block AT_1 receptor → Prevent effects of Ag II
Adverse effects	- No or less cough and angioedema.
Contraindication	- Pregnancy, lactation and COPD (Less than ACE inhibitors)

- **4: Renin inhibitors:**
  - **Aliskiren** (Tekturna®)
    - **Adverse effects** includes cough and angioedema, hyperkalemia and in high dose cause diarrhea.

Renin angiotensin system inhibitors → used in treatment of **hypertension**

Kinins (Bradykinin and Kallidin (lys-bradykinin))

Biosynthesis (Kinin-kallikrein system)



Inactivation	- Kinins are metabolized rapidly ($T_{1/2}$ < 15 second) by two plasma kininases I and II

Kinin Receptors

B_1	- Limited distribution. - Participate in the inflammatory response.
B_2 (B_{2A}, B_{2B})	- Widespread distribution. - Participates in bradykinin vasodilator role.

➢ Pharmacological action :-

CVS	- **Potent direct effect** on <u>arteriolar</u> VD due to NO formation. - Predominant effect on veins is contraction - Increase HR, contraction and CO due (Reflex, due to VD). - Increase capillary permeability → Oedema formation.
Role in inflammation	→ ***Four classic symptoms*** - Redness, local heat, swelling and pain.
Sensory nerve	- Potent pain inducer
Other effects	- Slow contraction of the muscle of GIT, bronchi and uterus. - Has a protective role in ischemic stroke-induced brain injury and CVS diseases, on other hand it is implicated in cancer and some CNS diseases.

➢ Drugs affecting the kinin-kallikrein system :-

- The synthesis of kinins can be stimulated with the ACE inhibitors.
- The synthesis of kinins can be inhibited with the kallikrein inhibitors.
- Kinins receptor antagonist.

Kallikrein inhibitors	
Aprotinin (Trasylol®)	
Mechanism of action	- Inhibits kallikrein. - Inhibits mediator of the inflammatory response, fibrinolysis and thrombin generation.
Uses	- Injection to reduce bleeding during complex surgery. - In operative settings where cardiopulmonary bypass can be rapidly initiated.
Adverse effect	- Fatal anaphylactic reaction.
Ecallantide (Kalbitor®)	
Mechanism	- Reversibly inhibiting the activity of plasma kallikrein.
Uses	- Treatment of hereditary angioedema (HAE).
Kinins receptor antagonists	
Icatibant (Firazyr®)	
Mechanism	- Blocking the binding of bradykinin to the bradykinin $\mathbf{B_2}$ receptor.
Uses	- Treatment of hereditary angioedema (HAE).

Vasopressin or Arginine vasopressin (AVP) or ADH

- Regulate the body retention of water (it is released when the body is dehydrated).
- Responsible for increasing water absorption in the collecting ducts of the kidney → reducing urine volume → Increase Blood Pressure.

Atrial Natriuretic Peptide (ANP)

- Polypeptide released from atrium → Increase Glomerular filtration rate (GFR) → Increase Na^+ excretion in urine.
- Decrease Renin and Aldosterone.

Vasoactive Intestinal Polypeptide (VIP)

- Polypeptide chemical transmitter in CNS and peripheral.
- Smooth muscle relaxation (GIT and Bronchi).
- Cause Vasodilatation.

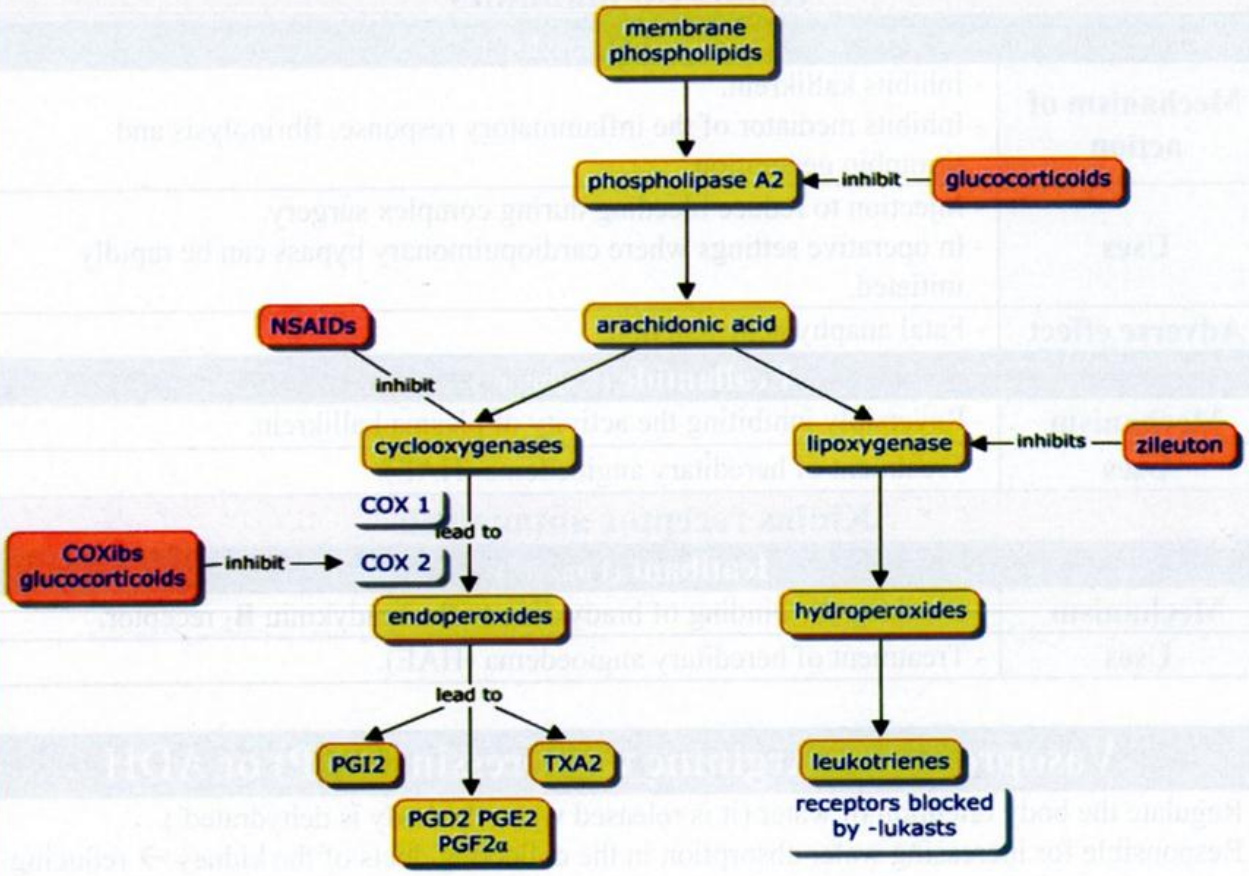
Substance-P (SP)

- Polypeptide Neurotransmitter metabolized by ACE.
- Increase Intestinal motility and bronchospasm.
- Responsible for **Pain transmitter**.
- Morphine, Endorphins and Enkephalins → Decrease release of Supstance-P.

➢ Eicosanoids :-

Prostaglandins (PG) & Leukotrienes (LT)

➢ Biosynthesis of Eicosanoids :-



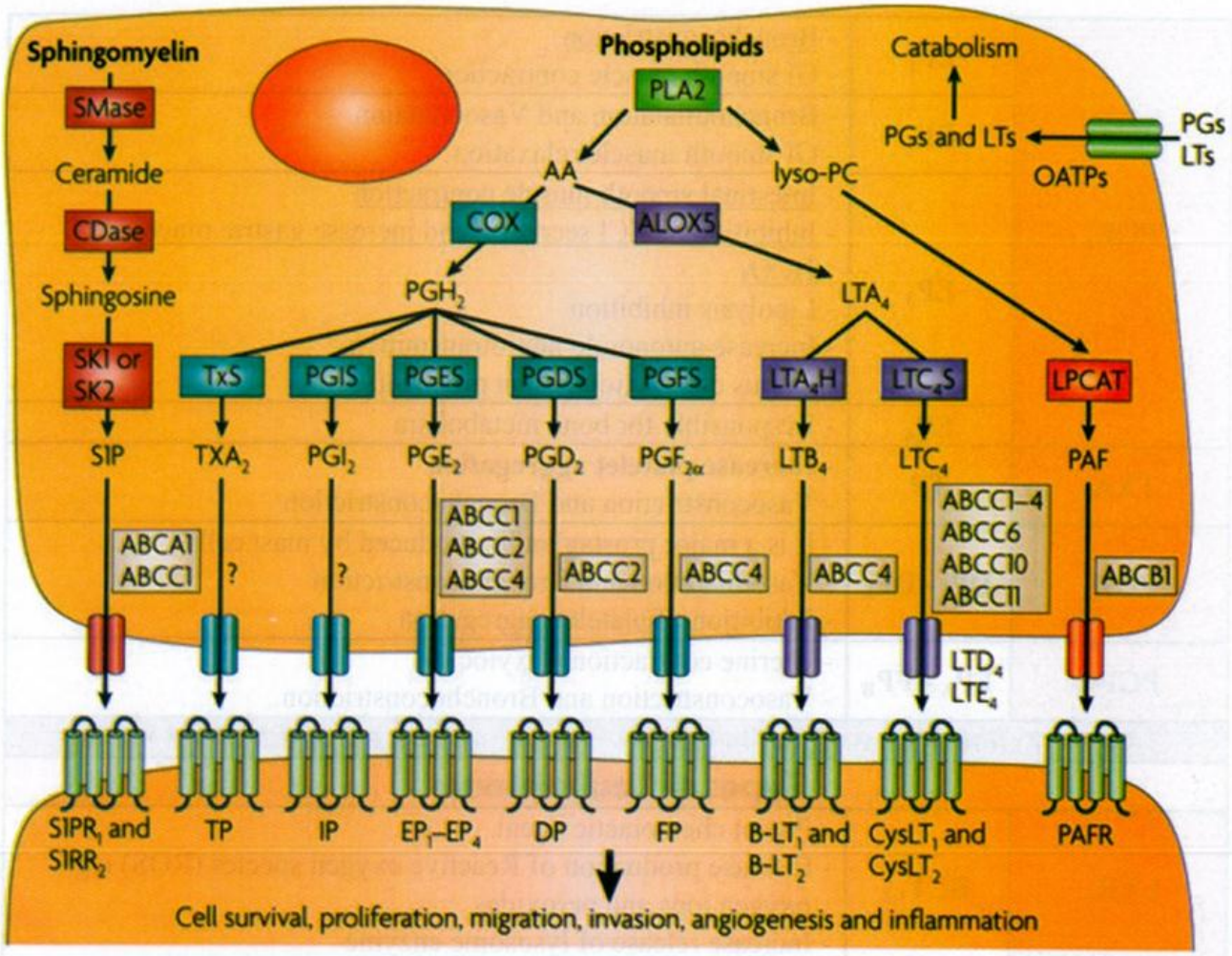
Types of Prostaglandins (Prostanoids)

Type	Receptor	Function
PGI_2 (Prostacyclin)	**IP**	- Vasodilation - Inhibit platelet aggregation - Bronchodilatation - Increase renin release
PGE_1		- Bronchodilatation - **Vasodilatation (Induce erection in penis)** - Inhibition of HCl secretion, increase gastric mucous and HCO_3^- - Increase renin secretion - Increase Na^+ and water excretion. - Decrease Platelet aggregation - Contraction of uterus and intestinal smooth muscle

PGE_2	EP_1	- Bronchoconstriction - GI smooth muscle contraction
	EP_2	- Bronchodilatation and Vasodilataion - GI smooth muscle relaxation
	EP_3	- Intestinal smooth muscle contraction - Inhibition of HCl secretion and increase gastric mucous & HCO_3^- - Lipolysis inhibition - Increase autonomic neurotransmitters - Uterus contraction (when pregnant)
	EP_4	- Responsible for bone metabolism
TXA_2	TP	- **Increase platelet aggregation** - Vasoconstriction and Bronchoconstriction
PGD_2	DP_1 - DP_2	- It is a major prostaglandin produced by mast cells - Vasodilatation and Bronchoconstriction - Inhibition of platelet aggregation
$PGF_{2\alpha}$	FP_A - FP_B	- Uterine contraction (Oxytocic) - Vasoconstriction and Bronchoconstriction
Action of Prostaglandin in CNS → Fever and Pain transmission		
Types of Leukotrienes		
LTB_4	$BLT_{1,2}$	- Potent chemotactic agent. - Increase production of Reactive oxygen species (ROS) e.g. oxygen ions and peroxides - Increase release of lysosome enzyme
LTC_4, LTD_4, LTE_4	$CysLT_{1,2}$	- **Potent** bronchoconstriction - Vasodilatation

➢ Prostaglandins analogue and its uses :-

PG	Analogue	Uses
PGE_2	**Dinoprostone** (Cervidil®)	- Abortion and facilitate labor
$PGF_{2\alpha}$	**Carboprost** (Hemabate®)	- Used in postpartum hemorrhage
	Latanoprost (Xalatan®)	- Glaucoma
	Bimatoprost (Lumigan®)	
	Travoprost (Travatan®)	
	Unoprostone (Rescula®)	
PGE_1	**Misoprostol** (Misotac®)	- NSAIDs associated Peptic ulcer. - Commonly used for labor induction
	Alprostadil (Prostavasin®)	- Impotence (Erectile dysfunction)
PGI_2	**Epoprostenol** (Flolan®)	- Pulmonary arterial hypertension



➢ Prostaglandins synthesis inhibitors :-

- Glucocorticoids
- NSAIDs (Inhibit COX enzyme) e.g. Aspirin and Indomethacin

➢ Leukotriene antagonist :-

- **Leukotriene Pathway inhibitors:**
  - **Zileuton** → inhibits 5-Lipoxygenase enzyme.
  - **Zafirlukast** (Ventair®) - **Montelukast** (Clear air®)
    → Leukotriene receptors (LTC_4 - LTD_4 - LTE_4) antagonist
    → used in treatment of **bronchial asthma**

➢ Thromboxane inhibitors :-

- **Aspirin** in small dose (75-150 mg) → Decrease synthesis of TXA_2.
- **Dazoxiben** → Inhibits thromboxane synthase → Decrease TXA_2.
  → Used as prophylactic against blood coagulation

➢ Inhibition of eicosanoid release :-

- **Cromolyn** (Nasalcrom®)
  → Mast cell stabilizer (Used in bronchial asthma)

Questions

➢ Coose the best answer

51: Sumatriptan succinate is effective for the treatment of acute migraine headaches by acting as

a. An antagonist at β_1- and β_2-adrenergic receptors
b. A selective antagonist at histamine (H_1) receptors
c. An inhibitor of prostacyclin synthase
d. An agonist at nicotinic receptors
e. A selective agonist at 5-hydroxytryptamine 1D ($5\text{-}HT_{1D}$) receptors

52: Currently, three subtypes of histamine receptors are proposed: H_1 and H_2 receptors are found in peripheral tissues and the central nervous system (CNS), and H_3 receptors are found in the CNS. The second messenger pathway that mediates H_1-receptor stimulation is

a. Increased formation of inositol trisphosphate
b. Elevation of intracellular cyclic adenosine monophosphate
c. Activation of tyrosine kinases
d. Inhibition of adenylate cyclase activity
e. Activation of sodium (Na^+) ion flow into the cell

53: Which of the following is an H_2-receptor antagonist?

a. Sumatriptan
b. Cyproheptadine
c. Ondansetron
d. Cimetidine
e. Fluoxetine

54: A 27-year-old male has sprained his ankle, which is swollen and painful, while skiing. X-ray examination is negative except for the appearance of swelling. A non-steroidal anti-inflammatory drug (NSAID) is administered. Which of the following would be decreased?

a. Histamine
b. Cortisol
c. Bradykinin
d. Prostacyclin
e. Uric acid

55: A 29-year-old female has a 10-year history of migraine headaches. She can usually sense onset. Which of the following agents is the drug of choice for countering acute onset of her headaches?

a. Ergotamine
b. Propranolol
c. Methysergide
d. Pseudoephedrine
e. Aspirin

56: A 40-year-old male with a diagnosis of moderate to severe asthma is placed on zileuton. What is the mechanism of action of zileuton?

a. Inhibition of cytokine production
b. Inhibition of leukotriene production
c. Inhibition of mediator release
d. Inhibition of muscarinic receptor action
e. Inhibition of calcium (Ca^{2+}) channel activity

57: A newborn infant is being prepared for surgical repair of a patent ductus arteriosus. Which of the following agents may be administered preoperatively?

a. Zafirleukast
b. Misoprostol
c. Timolol
d. Methysergide
e. Alprostadil [prostaglandin E_1 (PGE_1)]

58: Which of the following is an H_2 receptor antagonist with Anti-androgenic effects?

a. Betahistine
b. Cimetidine
c. Cetirizine
d. Ranitidine
e. Fexofenadine

59: Which of the following is a substances released from mast cell during anaphylactic reaction?

a. Histamine b. Leukotrienes c. Cytokines
d. Prostaglandins e. All of the above

60: Which of the following is an antihistaminic pro-drug when administrated with LME inhibitors cause arrhythmia?

a. Terfenadine b. Fexofenadine c. Levocetirizine
d. Azelastine e. Cetirizine

61: Which of the following is an antihistaminic drug used in Ménière's disease?

a. Meclizine b. Betahistine c. Clemastine
d. Hydroxyzine e. Doxylamine

62: Which of the following is a hormone produced from serotonin?

a. Vasopressin b. Testosterone c. Melatonin
d. Growth hormone e. Insulin

63: Which of the following is a drug selective 5-HT_{1A} agonist used in insomnia?

a. Ketanserin b. Tegaserod c. Pizotifen
d. Mosapride e. Buspirone

64: Which of the following is a drug used to prevent nausea and vomiting associated with surgery and cancer chemotherapy by blocking 5-HT_3 receptor?

a. Cyproheptadine b. Lysuride c. Ondansetron
d. Pizotyline e. Ergotamine

65: Which of the following is a drug used to decrease prolactin hormone from pituitary by stimulating D_2 receptor?

a. Ergometrine b. Bromocriptine c. Losartan
d. Clemastine e. Ergotamine

Answers

51	52	53	54	55	56	57	58	59	60
e	a	d	d	a	b	e	b	e	a

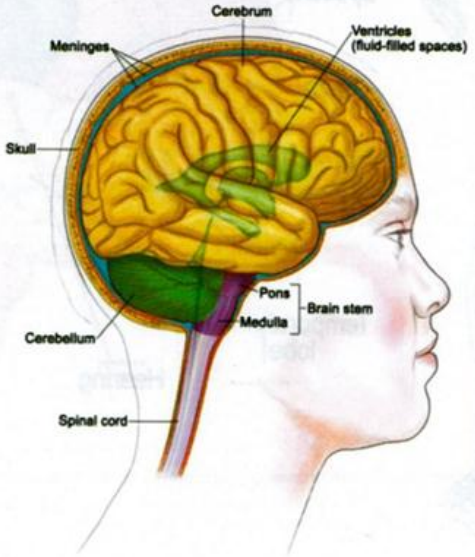
61	62	63	64	65
b	c	e	c	b

Questions and answers from (References):

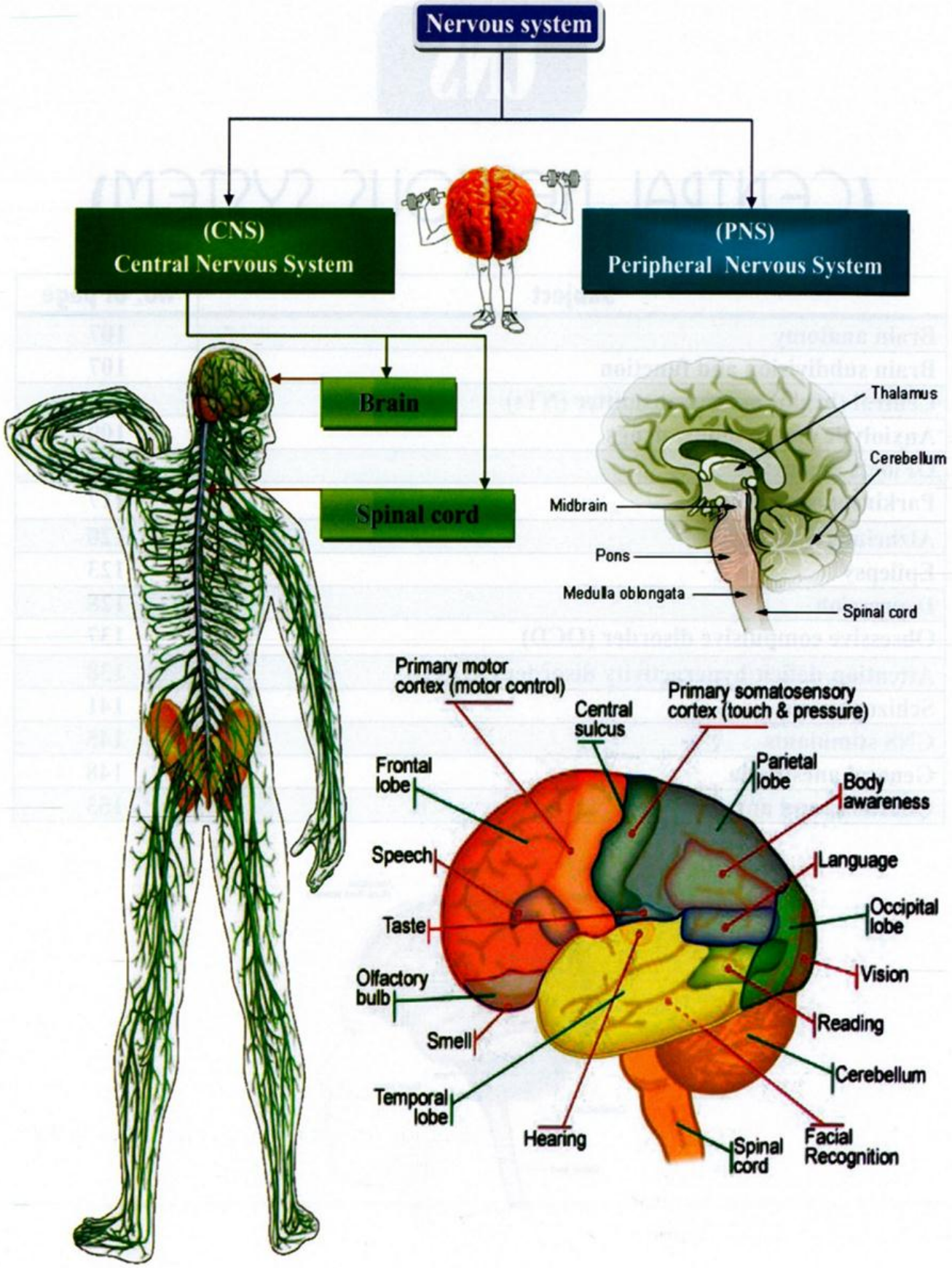
Basic and Clinical Pharmacology 12th edition, Katzung-Lange
Pharmacology 5th edition Lippincott Williams & Wilkins
Pharmacology 12th edition PreTest Self-Assessment and Review

CNS

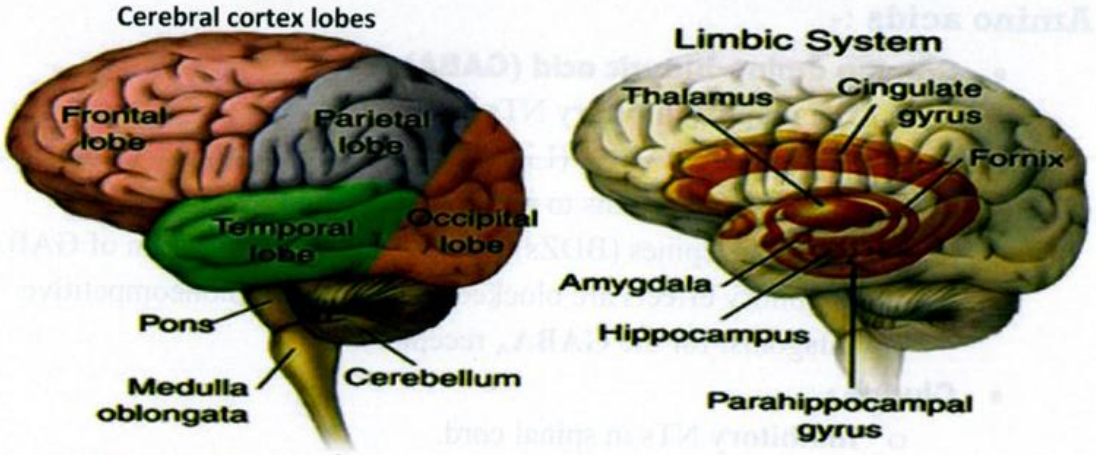
(CENTRAL NERVOUS SYSTEM)



CNS


Nervous system
(CNS)
Central Nervous System
(PNS)
Peripheral Nervous System
Brain
Spinal cord
Thalamus
Cerebellum
Midbrain
Pons
Medulla oblongata
Spinal cord
Primary motor cortex (motor control)
Central sulcus
Primary somatosensory cortex (touch & pressure)
Frontal lobe
Parietal lobe
Body awareness
Speech
Language
Taste
Occipital lobe
Olfactory bulb
Vision
Smell
Reading
Cerebellum
Temporal lobe
Hearing
Spinal cord
Facial Recognition

Anatomical subdivision of the brain



➢ **Forebrain :-**

- **Cerebral cortex :**
  - ***Function***: Thought, speech, perception and reasoning (Receives and processes sensory information).
- **Basal ganglia :**
  - ***Function***: Voluntary movement.
- **Limbic system :**
  - ***Function***: Behavior, Emotional reaction, Learning and memory.
- **Thalamus :**
  - ***Function***: Sensory processing (Pain sensation).
- **Hypothalamus :**
  - ***Function***: Regulation of body temperature, emotions, sleeping, hunger, thirst and sexual response

➢ **Midbrain :-**

- ***Function:*** Vision and hearing (due to presence of their centers in it).

➢ **Hindbrain :-**

- **Cerebellum :**
  - ***Function:*** Movement, balance and posture.
- **Pons :**
  - ***Function:*** Respiration (due to respiratory center) and Relays sensory information between the cerebrum down to the cerebellum and medulla oblongata.
- **Medulla oblongata :**
  - ***Function:*** Heart rate and blood pressure regulation (Autonomic function).

Central (brain) neurotransmitter (NTs)

➢ Amino acids :-

- **Gamma amino-butyric acid (GABA) :**
  - The **major inhibitory** NTs in the CNS.
  - Act on both $GABA_A$ (Ligand gated ion channel (Cl^- channel)) and $GABA_B$ (G-proteins to potassium channels) receptors.
  - Benzodiazepines (BDZs) act by enhancing the action of GABA.
  - Inhibitory effects are blocked by Picrotoxin (noncompetitive antagonist for the **$GABA_A$** receptor).
- **Glycine :**
  - **Inhibitory** NTs in spinal cord.
  - Act on Glycine receptor (GlyR) → opening Cl^- channels.
  - Strychnine selective glycine receptor blocker.
- **Aspartate and glutamate :**
  - Both are **excitatory** NTs in CNS.
  - They act on N-methyl-D-aspartate (NMDA) receptor.

➢ Acetylcholine :-

- It is excitatory NT in the basal ganglia (Act on M_1 receptor).
- Loss of cholinergic neurons in the bran results in Alzheimer's disease
- Its excitatory effects are blocked by Atropine.

➢ Monoamines :-

- **Dopamine :**
  - Generally exerts a slow inhibitory action on the CNS.
  - Dysfunction of the dopamine system is also implicated in Parkinson's disease and schizophrenia.
- **Norepinephrine (NE) :**
  - Mainly located in the locus coeruleus and the lateral tegmental field.
  - May be involved in regulation of mood and blood pressure.
- **5-Hydroxy tryptamine (5-HT) (Serotonin) :**
  - It has both excitatory ($5\text{-}HT_3$) and inhibitory ($5\text{-}HT_{1A}$) effects.
  - It is secreted by neurons in pons and mid brain.
  - It is responsible for regulation of mood, sleep, appetite and temperature.

➢ Peptides :-

- **Opioids :** → E.g. Endorphins, Enkephalins and Dynorphins.
- **Non-oipoids :** → E.g. Neurotensin, Neuropeptide and Substance-P.

In normal Situation There is a balance between the excitatory NTs and the inhibitory NTs.

Anxiolytic and hypnotic drugs

- **Anxiolytic:** is a drug that reduces anxiety (a sedative).
- **Hypnotic:** is a drug that induces sleep.

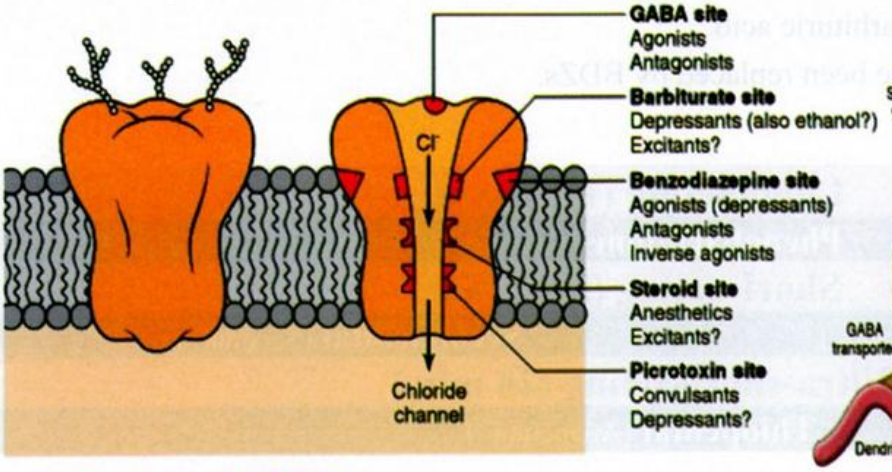
I: Benzodiazepines (BDZs)

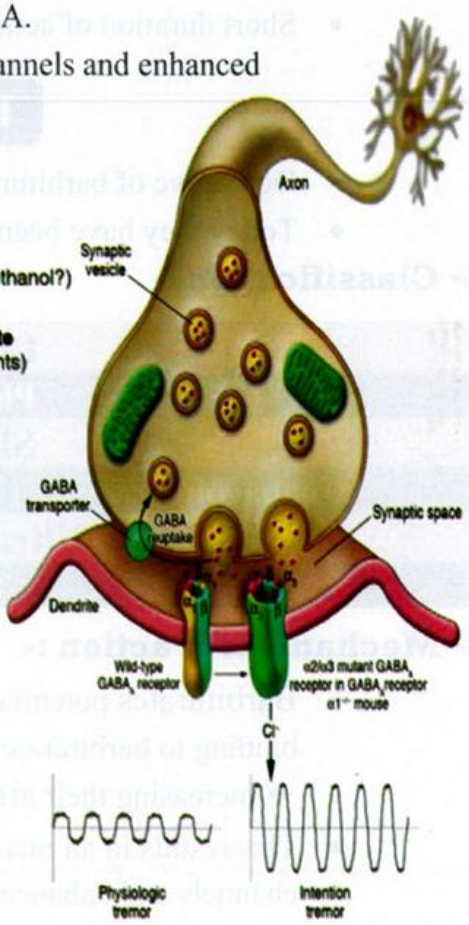
Classification and examples :-

Long-acting ($t_{1/2}$ > 24 hrs.)		
Diazepam (Valium®)	Clorazepate (Tranxene®)	Clonazepam (Rivotril®)
Intermediate-acting ($t_{1/2}$ = 12-24 hrs.)		
Bromazepam (Calmepam®)	Lorazepam (Ativan®)	Temazepam (Restoril®)
Short-acting ($t_{1/2}$ < 12 hrs.)		
Midazolam (Dormicum®)	Alprazolam (Xanax®)	Oxazepam (Comedormir®)

Mechanism of action :-

- BDZs potentiate the action of GABA by binding to BDZs site on $GABA_A$ receptors → increasing their affinity for GABA.
- This results in an increased opening of Cl^- channels and enhanced hyperpolarization → Sedative effect.





Actions of BDZs :-

- Minor tranquilizing action (Antianxiety).
- Sedative and hypnotic effect.
- Anticonvulsant and antiepileptic action.
- Anesthetic action.
- Slight effect on CVS and respiration.
- Slight muscle relaxant action.

➢ Clinical (Therapeutic) uses :-

- Anxiety disorder (long-acting drugs)
- Sleep disorder (short-acting drugs)
- Epilepsy (Seizures)
- Muscle spasm and rigidity
- Pre-anesthetic medication
- Alcohol withdrawal syndrome

➢ Adverse effect :-

- Drowsiness, confusion and ataxia.
- Chronic use of high doses produces tolerance and dependence.
- Respiratory depression and hypotension.

➢ BDZs antagonist :-

Flumazenil (Anexate®)

- It is a GABA receptor antagonist.
- It is given by IV administration only because of its high hepatic first-pass metabolism.
- Short duration of action used by repeated injection.

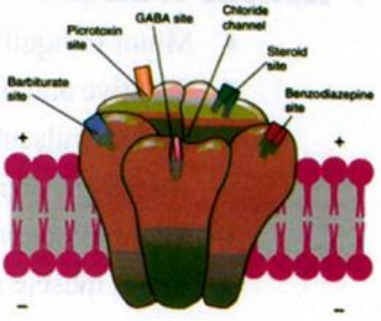
II: Barbiturates

- Derivative of barbituric acid.
- Today they have been replaced by BDZs.

➢ Classification :-

Long-acting (1-2 days)
Phenobarbitone (Sominal®)
Short-acting (3-8 hrs.)
Amobarbital (Amytal®) | **Secobarbital** (Seconal®)
Ultra-short-acting (20 min.)
Thiopental (Anapental®)

➢ Mechanism of action :-



- Barbiturates potentiate the action of GABA by binding to barbiturate site on $GABA_A$ receptors → increasing their affinity for GABA.
- This results in an increased opening of Cl^- channels and enhanced hyperpolarization → Sedative effect.

➢ Pharmacological action :-

CNS	- **Therapeutic dose** → Sedation - **Large dose** → Hypnosis, coma and death.
CVS	- **Therapeutic dose** → Minimal effect - **Large dose** → Hypotension due to depression in vasomotor center (VMC)
Respiration	- **Large dose** → Respiratory depression and death due to depression in respiratory center (RC)
Liver (Metabolism)	- Hepatic microsomal enzyme inducer → Increase metabolism of other drugs → decreases effect of other drug.

➢ Therapeutic Uses :-

- Hypnotic to treat insomnia
- Anesthesia → **Thiopental** (Anapental®) IV
- Anticonvulsant → **Phenobarbital** (Sominal®)

➢ Side effects :-

- Hypersensitivity reaction
- Cardiovascular and respiratory depression
- Tolerance and dependence (More than BDZs).

➢ Drug interaction :-

- Barbiturates induce the hepatic metabolism of many drugs as Warfarin, Tolbutamide and Corticosteroids → thus decrease therapeutic effect.

Why BDZs are preferred to barbiturates as sedative / hypnotic?

- High therapeutic index.
- More selective on CNS.
- Mild physical dependence and tolerance.
- Little cardiovascular and respiratory depression.
- Not significantly enzyme inducer.
- Available specific antidote → **Flumazenil** (**Anexate®**).

III: Other sedative, hypnotic drugs (Non BDZs Hypnotics)

Chloral hydrate (Chloral®)

- Hypnotic effects of chloral hydrate are believed to be due to its active metabolite trichloroethanol (The mechanism of action is not known).
- Induces sleep in about 30 min.
- **Adverse effects** → Rashes, gastric discomfort and severe renal, cardiac and hepatic failure.

Buspirone (Buspar®)

- It is a partial agonist on **5-HT$_{1A}$** receptors in the brain → Sedation.
- It has **no** muscle relaxant or antiepileptic effect.
- Used to treat generalized anxiety disorder (GAD).
- Common adverse effect → dizziness, drowsiness, nausea and headache.

Zolpidem (Stilnox®) | Zaleplon (Siesta®)

- Potentiates GABA, by binding to a subset of the BDZs receptor family BZ$_1$.
- Short acting (Zolpidem → $t_{1/2}$ = 2 hrs), (Zaleplon → $t_{1/2}$ = 1 hrs)
- Metabolized by CYP450.
- Not used with LME inhibitors e.g. Erythromycin → increase drug effect.

Eszopiclone (Sleepez®) | Zopiclone (Hypnor®)

- Potentiates GABA, by binding to a subset of the BDZs receptor family BZ$_1$.
- Effective for up to 6 months.

Ramelteon (Rozerem®)

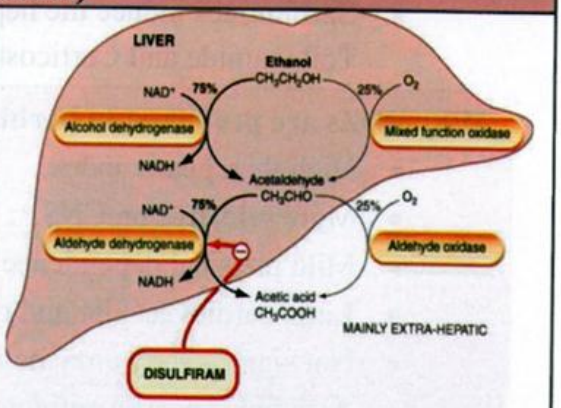
- Selective agent at the **MT$_1$** and **MT$_2$** subtype of melatonin receptors.
- Used for treatment of insomnia.
- **Not** produce dependence and withdrawal effects.

Antihistaminic (First generation) (See Page)

e.g → Doxylamine (Donormyl®)

Ethanol (Ethyl alcohol)

- Ethanol is a CNS depressant producing sedation and hypnosis with increasing dose.
- Ethanol metabolized to acetaldehyde by alcohol dehydrogenase and then to acetate (Acetic acid) by aldehyde dehydrogenase.



Toxicity of ethanol

A) Acute toxicity:-

E.g. Euphoria, Blurred vision, hypothermia, vomiting, Hypoglycemia, respiratory failure → Death.

B) Chronic toxicity (Alcoholism):-

E.g. Dependence and tolerance → Addiction, Devitalization of all organs especially liver (Liver cirrhosis), Hallucination and decrease Immunity.

Disulfiram (Antabuse®)

- Block the oxidation of acetaldehyde by inhibiting aldehyde dehydrogenase enzyme.
- Accumulation of acetaldehyde → Flushing, tachycardia, Nausea and hyperventilation

Analgesic drugs

Central analgesic
These are drugs which relieve pain by central action

Peripheral analgesic
Relieve pain by peripheral action → E.g.
Atropine in colic pain
Nitroglycerine in angina pain

Narcotic (opioid) analgesic
E.g. Morphine

Analgesic antipyretic
E.g. NSAIDs (Aspirin)

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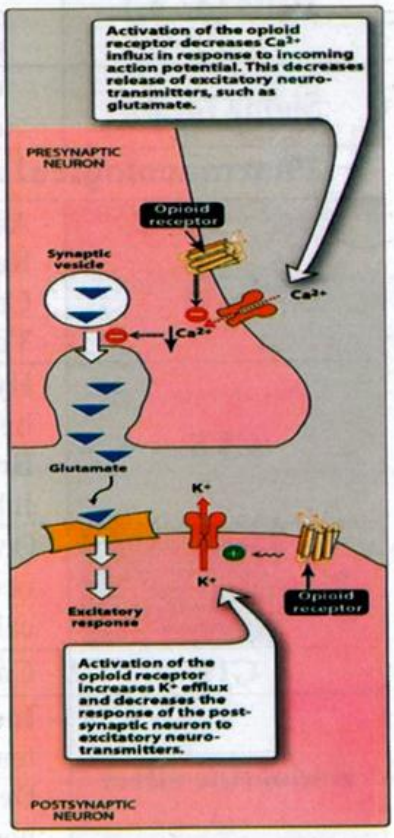
OPioids analgesic

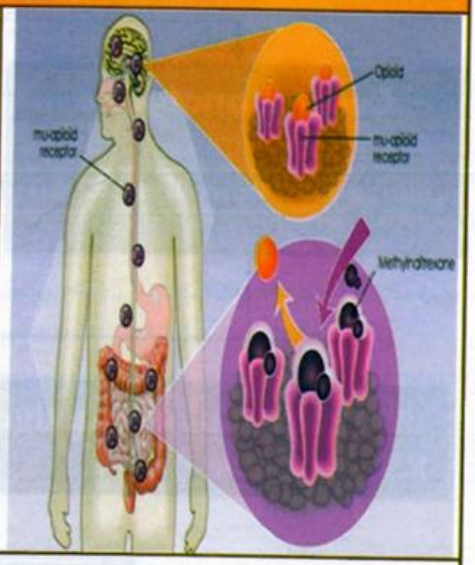
- **Def.:** These are natural or synthetic compounds that produce morphine-like effect.
- **Endogenous opioid peptides are** → Endorphins, Enkephalins and Dynorphins → which bind to opioid receptors.

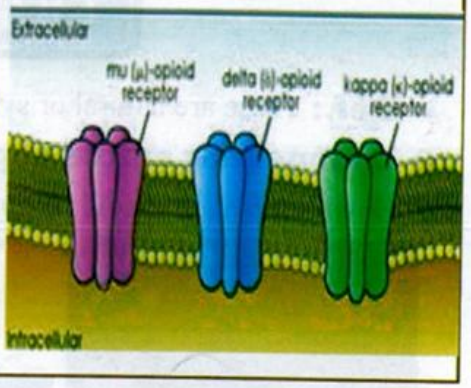


- **Mechanism of action :-**
  - Morphine stimulates specific opioid receptors in the CNS.
  - Stimulation of opioid receptors decreases release of substance-P which responsible for pain transmission in the spinal cord.
  - All opioid receptors are coupled to inhibitory G-protein that leads to potassium channels activation and calcium channels inhibitory this leads to hyperpolarization of nerve cell.
  - Inhibition of nerve cell leads to decrease release of excitatory neurotransmitters.

➢ Types of opioid receptors :-

Receptor	Function
Mu (μ_1, μ_2)	**μ_1:** o Supra spinal and spinal analgesia o Physical dependence **μ_2:** o Respiratory depression o Euphoria o Physical dependence o Miosis o Constipation **μ_3:** o Unknown
Kappa (κ_1, κ_2, κ_3)	o Supra spinal and spinal analgesia o Less respiratory depression and miosis o Dysphoria
Delta (δ_1, δ_2)	o Supra spinal and spinal analgesia o Constipation
Sigma (σ_1, σ_2)	o Dysphoria o Hallucination





➢ Pharmacological action :-

CNS	- **Analgesia, sedation** and **euphoria**. - **Respiratory depression** → depression of Respiratory Center (RC). - **Cough suppression** → Depression of Cough Center. - **Vomiting** → Stimulation of Chemoreceptor Trigger Zone (CTZ).
CVS	- **Hypotension** → due to inhibition of VasoMotor Center (VMC) and histamine release from mast cells. - **Bradycardia** → due to stimulation of vagal center (Cardiac Inhibitory Center-CIC)
Eye 	- Opioids stimulate μ and κ receptors at Edinger-Westphal nucleus of oculomotor nerve to constrict the pupil causing miosis which is called → **Pin-Point pupil (PPP)**.
GIT	- **Constipation** →due to decrease intestinal peristalsis → μ receptors.
Endocrine effect	- **Increase** release of antidiuretic hormone **(ADH)** causing urinary tension. - **Decrease** release of luteinizing hormone **(LH)**, follicle stimulating hormone **(FSH)** and Adrenocorticotrophic hormone **(ACTH)**.

➢ Therapeutic uses :-

- **Analgesic in severe pain** → e.g. Postoperative, cancer, fracture & myocardial infarction.
- **Used in pre-anesthetic medication.**
- **Treatment of acute pulmonary edema** as it → decreases anxiety & pulmonary pressure.
- **Relief of cough.**
- **Treatment of diarrhea.**

➢ Adverse effect :-

- Respiratory depression, constipation, vomiting, endocrine disturbance, urinary retention, hypotension, tolerance and physical dependence.

➢ Contraindication :-

- **Acute respiratory disease** (Bronchial asthma) as it cause depression of RC and increase histamine release.
- **Head injury** as it increase intracranial pressure (ICP).
- **Paralytic ileus** as it causes constipation due to decrease intestinal peristalsis.
- **Benign prostatic hyperplasia (BPH)** as it increases ADH causing urinary retention.
- **Adrenal insufficiency** as it decreases ACTH.
- **Pregnancy and labor**.

Strong agonists		
Morphine (MST®)	- Natural → from Opium alkaloids.	
Meperidine (Demerol®)	- Synthetic opioid structurally unrelated to morphine. - Has Atropine like effects.	
Fentanyl (Duragesic®)	- Derivative of Meperidine and strong (100) analgesic than Morphine	
Sufentanil (Sufenta®)	**Alfentanil** (Alfenta®)	**Remifentanil** (Ultiva®)
- Related to Fentanyl		
Methadone (Amidone®)	- Less euphoria and longer (1-2 days) duration of action. - Mechanism same as Morphine in addition, Block NMDA receptors.	
D-propoxyphene (Doloxene®)	- Derivative of Methadone (formulated with Aspirin or Acetaminophen)	
Heroin	- Produced by Di-acetylation of Morphine → Increase Potency.	
Oxymorphone (Opana®)	**Oxycodone** (Oxycontin®)	
- Semisynthetic derivative of morphine (sometimes formulated with Aspirin or Acetaminophen).		
Hydromorphone (Jurnista®)	**Hydrocodone**	
- Semisynthetic derivative of morphine and codeine.		

Mixed agonist-antagonists and partial agonists		
Pentazocine (Fortral®) **Nalbuphine** (Nubain®)	- Agonist on **κ** receptors & weak antagonist at **μ** receptors.	
Buprenorphine (Subutex®)	- Partial **μ** agonist	
Used in treatment of heroin addiction		
Miscellaneous		
Codeine (Codaphen®)	- Codeine (Methyl Morphine) → Natural from Opium alkaloids → It is a weak/moderate **μ** agonist - Used in treatment of dry cough (Good anti-tussive activity). - Used in mild and moderate pain (with or without Aspirin)	
Tramadol (Contramal®)	- It is a weak **μ** agonist. - Used to manage moderate pain. - Increase NE and serotonin → Due to inhibition of uptake.	
Tapentadol (Nucynta®)	- It is the first new drug of the centrally acting analgesic that binds the **μ**-opioid receptor (Used to manage moderate to severe pain).	
Dextromethorphan (Codiphan®)	- It has antitussive action. - Free of analgesic and addiction properties. - Less constipation compared to codeine.	
Diphenoxylate (Lomotil®)	- Opiate receptor agonists that stimulate **μ** receptors in GI to decrease the peristalsis and constrict the sphincters.	
Loperamide (Imodium®)	- They are used in treatment of diarrhea (combined with Atropine)	
Nefopam (Acupan®)	- Centrally-acting but **non-opioid analgesic drug**.	
Opiate withdrawal syndrome	**Stage I : Up to 8 hours**	Anxiety and drug carving
	Stage II : 8-24 hours	Anxiety, Insomnia, GI disturbance, Rhinorrhea, Mydriasis and diaphoresis
	Stage III : Up to 3 days	Tachycardia, Nausea, Vomiting, Hypertension, Diarrhea, Fever, Chills, Tremors, Seizures and muscle spasm.
Opioids antagonist		
- Opioids antagonist rapidly reverse the effect of agonists, Such as Morphine. - Used in treatment of opiate withdrawal syndrome.		
Naloxone (Narcan®)	- It is used to reverse respirator depression of morphine toxicity. - It is competent antagonist at all the opioid receptors. - It is short-acting (1-2 hours) so it is given by IV not used orally.	
Naltrexone (Anarcol®)	- Pure antagonist, more selective on **μ** receptors. - It is long-acting (10 hours), so it is well absorbed orally.	
Nalmefene (Revex®)	- Similar to **Naloxone** but longer in $t_{1/2}$.	
Other drugs used in opiate withdrawal syndrome		
Lofexidine (Detoxydine®)	- α_2-adrenergic receptor agonist, more commonly used to alleviate physical symptoms of heroin and opiate withdrawal.	
Saliva Test (Oral Four®) → Test for Cannabis, Opiate, Cocaine and methamphetamine.		

Neurodegenerative Diseases

➢ **Neurodegenerative diseases:**

- Progressive loss of structure or function of neurons, including death of neurons.
- Many neurodegenerative diseases including Parkinson's and Alzheimer's occur as a result of neurodegenerative processes.

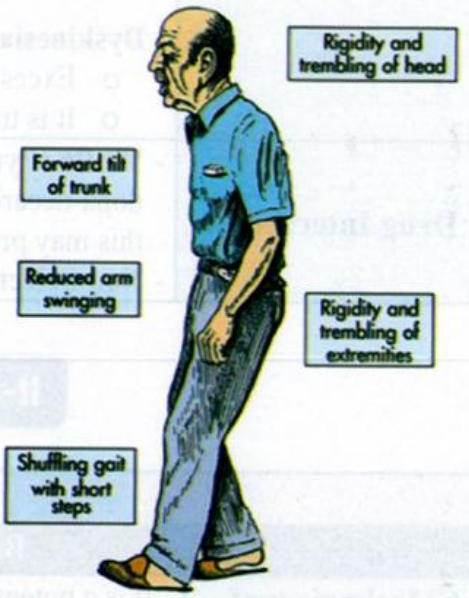
1 Parkinsonism

➢ **Parkinson's disease (PD):** is a neurological disorder of the basal ganglia.

➢ **Parkinsonism:** Term used for a motor syndrome whose main symptoms are tremor at rest stiffness, slowing of movement and postural instability.

➢ **Parkinsonism characterized by :-**

- Resting tremors.
- Bradykinesia (Slowness of movement).
- Postural instability.



➢ **It results from (Pathophysiology) :-**

- Loss of dopaminergic system (due to damage of dopaminergic neurons) and so relative excess of acetylcholine (ACh).

➢ **Etiology (Causes) :-**

- Idiopathic (Unknown cases)
- Corticobasal degeneration
- Wilson's disease
- Drugs e.g. Chlorpromazine and Reserpine
- Brain tumors
- Toxins (Carbon monoxide, Manganese and Methyl Phenyl Tetrahydro-Pyridine (MPTP)

Antiparkinsonian drugs

I- Levodopa (L-dopa)

Information	- Dopamine can't be given in the treatment of PD as it doesn't penetrate the BBB. - L-dopa is metabolized to dopamine by the dopa-decarboxylase enzyme. - More than 95% of L-dopa is metabolized outside the brain. - Less than 5% enters the brain. L-dopa is combined with **peripheral dopa-decarboxylase inhibitors** (**Carbidopa** and **Benserazide**) which not cross BBB → this increase brain level of dopamine and decrease peripheral side effects.
Preparations	**L-dopa** (200 - 250 mg) + **Carbidopa** (25 - 50 mg) = (Sinemet®) **L-dopa** (50 mg) + **Benserazide** (25 mg) = (Madopar®)

Adverse effects	- **Nausea** and **vomiting**: are caused by stimulation of chemoreceptor trigger zone (CTZ) → this can be reduced by using dopamine receptor antagonist on CTZ e.g. **Domperidone** (Motillium®). - **Agitation, confusion** and **hallucination:** o Due to stimulation of dopamine receptor. - **Fluctuation in response (On-Off phenomenon) :** o ***It means*** → On period of improved mobility with Off periods of akinesia. o ***This may results from :*** - Decrease sensitivity of dopaminergic receptors. - Fluctuation in plasma L-dopa concentration (Short half-life). → This can be corrected by giving drug holidays (3-21 days). - **Dyskinesia** : o Excessive and abnormal involuntary movement. o It is treatment by reduce the dose of L-dopa.
Drug Interaction	- **Vit.B6 (Pyridoxine)** → Enhances the activity of the dopa-decarboxylase and increase the peripheral metabolism of L-dopa this may prevent the therapeutic effect of L-dopa. - **Non-Selective MAO inhibitors** → Severe hypertension.

II- Dopamine agonists

A- Ergot alkaloids		
Bromocriptine (Parlodel®)		
Mechanism of action	- It is a potent D_2 agonist and partial agonist on D_1 receptor. - It inhibits the release of prolactin hormone from pituitary gland.	
Therapeutic uses	- **Parkinsonism** - **Hyperprolactinemia** - Suppress lactation. - Galactorrhea. - Amenorrhea.	
Lisuride (Dopergin®)		**Pergolide** (Permax®)
Mechanism	- They activate D_1 and D_2 receptor.	
B- Non-ergot alkaloids (derivatives)		
Examples	**Pramipexole** (Mirapex®)	- D_3 receptor agonist
	Ropinirole (Requip®)	
	Rotigotine (Neupro®)	
	Apomorphine (Apokyn®)	- Can't be used clinically because of its serious side effect.

III- Monoamine oxidase B (MAO-B) inhibitors

Selegiline (Jumex®)	Rasagiline (Rasanopark®)
Types of MAO	- **MAO-A** → Metabolizes NE, Serotonin and Dopamine. - **MAO-B** → Metabolize Dopamine selectively.
Mechanism	- These drugs inhibit **MAO-B** and used as adjunct therapy.
Information	- **Selegiline** is metabolized to amphetamine and methamphetamine which may induce sleep disturbances and hallucination. - **Rasagiline** is not metabolized to amphetamine like substances.

IV- Catechol-O-Methyl-Transferase (COMT) inhibitors

Tolcapone	Entacapone (Comtan®)
Mechanism of action	- They prevent the metabolism of L-dopa in peripheral tissues to 3-O-methyl-Dopa, this lead to increased central uptake of L-dopa.
Information	- **Tolcapone** has been associated with hepatic damage (hepatotoxicity) currently it is replaced with **Entacapone**.

V- Anticholinergic drugs

Benztropine (Cogentin®)	Biperiden (Akineton®)	Trihexiphenidyl (Parkinol®)
Mechanism of action	- They decrease excitably actions of cholinergic neurons by blocking the muscarinic receptors. They improve tremors of parkinsonism.	

VI- Other treatments

Amantadine (Symmetrel®)	
Information	- Antiviral agent used for in the treatment of influenza.
Mechanism	- It acts by →Increase release of and decrease uptake of dopamine.
Side effects	- Insomnia, Confusion, Hallucination, Hypotension and **Ankle edema**.

Deep brain stimulation (DBS)

- FDA approved DBS as a treatment for Parkinson's disease in 2002.
- Is a surgical treatment involving the implantation of a medical device which sends electrical impulses to specific parts of the brain. (See page 126)

❖ Optimization of L-dopa treatment :-

- Inhibition of dopa-decarboxylase in peripheral tissues by **Carbidopa** and **Benserazide.**
- Inhibition of dopamine degradation in the CNS by **Rasagiline.**
- Reduction of L-dopa break down in the peripheral tissues by **Entacapone.**
- Block of dopamine receptors in CTZ by **Domperidone**.

Levodopa
Carbidopa
Entacapone → (Stalevo®)

2 Alzheimer's Disease

➢ Definition :-

- Is a slowly progressive neurodegenerative disease of the brain that is characterized by impairment of memory and eventually by disturbances in reasoning, planning, language, and perception.
- Is a **dementia** associated with a progressive loss of cognitive function.

➢ Dementia → Dementia is a syndrome characterized by:

- Impairment in memory.
- Impairment in another area of thinking such as the ability to organize thoughts and reason, the ability to use language, or the ability to see accurately the visual world.

➢ Symptoms :-

- **The cardinal feature of Alzheimer's disease :-**
  - Progressive loss of memory and disordered cognitive function.
- **Symptoms normally progress in these stages:-**
  - **Stage 1 (Mild)**
    - Getting lost.
    - Difficulty managing money and paying bills.
    - Repetitive questions and conversations.
    - Taking longer than usual to finish routine daily tasks.
    - Losing things or misplacing them in odd places.
  - **Stage 2 (Moderate)**
    - Forget recent events and their personal history.
    - Become more disoriented & disconnected from reality.
    - Memories of the distant past may be confused with the present.
    - Reading and writing skills are also progressively lost.
  - **Stage 3 (Severe) (Advanced stage)**
    - lose the ability to feed themselves
    - Language is reduced to simple or single words, leading to complete loss of speech.
    - Death is usually associated with complications of immobility (e.g., pneumonia or pulmonary embolism).

➢ Pathophysiology :-

- The cause for most Alzheimer's cases is still essentially unknown.
- Several competing hypotheses exist trying to explain the cause of the disease

1) Cholinergic hypothesis

- The oldest hypothesis on which most currently available drug therapies are based.
- Acetylcholine needed to pass signals along from cell to cell.

A) Neurochemical changes in the brain occur:

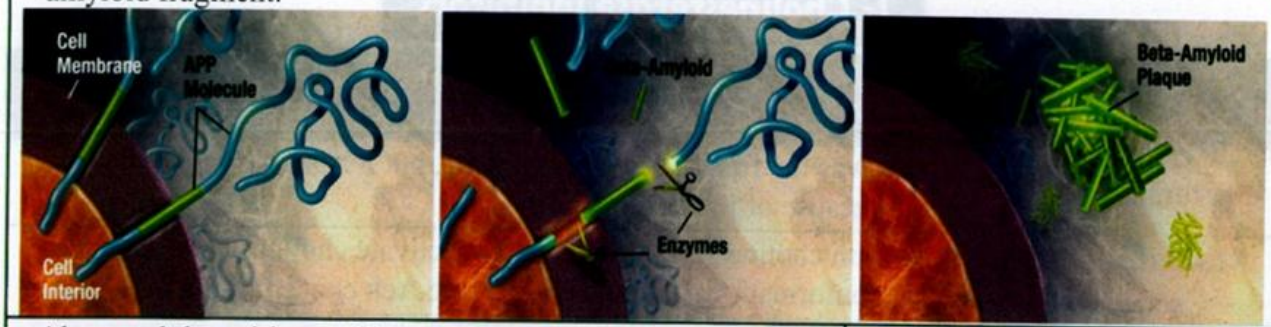
- Loss of cholinergic neurons or Loss of Ach

B) Cholinergic nerves are mainly affected:

- Increase ACh esterase (Responsible for degrade ACh)
- Decrease ACh transferase (Responsible for formation of ACh)

2) Amyloid hypothesis

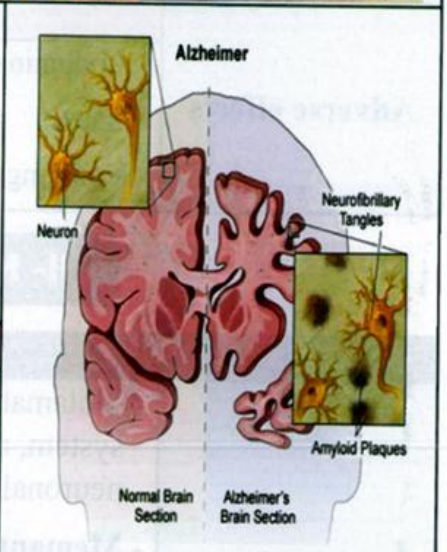
- Enzymes act on the APP (amyloid precursor protein) and cut it into fragments to form beta-amyloid fragment.



- Abnormal depositions of β-amyloid (plaques Aβ or senile plaques) proteins around the neurons → block the normal transport of electrical messages between the neurons.

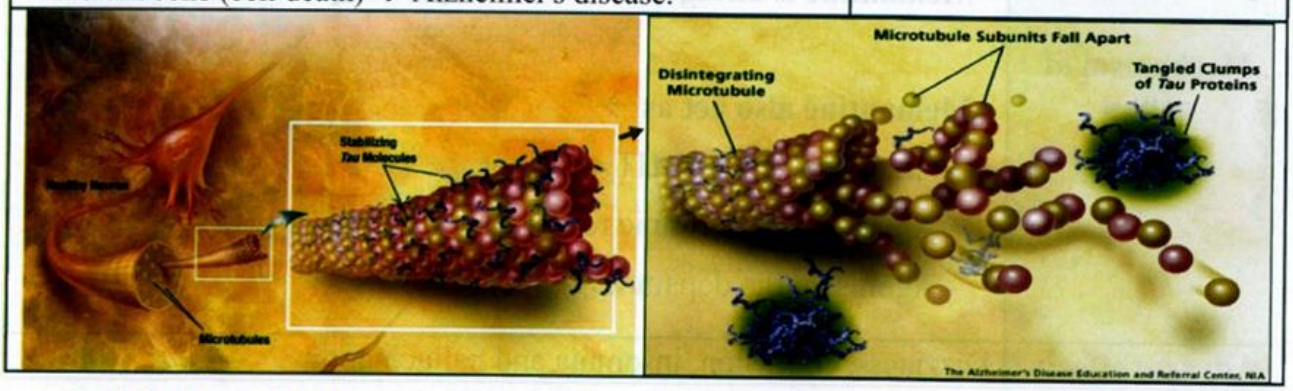
N.B →

- New study found the deposition of amyloid plaques does not correlate well with the loss of brain cells.
- Neuron loss may be due to form neurofibrillary tangles from tau protein inside nerve cell (Tau hypothesis) →



3) Tau hypothesis

- **Tau proteins** → are proteins that stabilize microtubules and they are abundant in neurons of the central nervous system.
- Changes in tau protein lead to formation of neurofibrillary tangles inside nerve cell the → disintegration of microtubules in brain cells (cell death) → Alzheimer's disease.



➢ Management :-

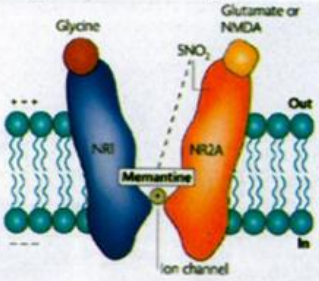
- **There is no cure for AD. The goals of treatment are:**
  - Slow the progression of the disease (although this is difficult to do)
  - Manage symptoms, such as behavior problems, confusion, and sleep problems
  - Change your home environment so you can better perform daily activities
  - Support family members and other caregivers

Anti-alzheimer's drugs

I- Cholinesterase inhibitors

Tacrine	Donepezil (Alzepizil®)
Rivastigmine (Exelon®)	Galantamine (Reminyl®)
Information	- Tacrine was the first to become available, but it has been replaced by others because of its hepatotoxicity.
Mechanism of action	- Binds with cholinesterase enzyme → inactivate cholinesterase enzyme due to conformational change → Increase Ach concentration in Synapse
Adverse effects	**GI distress** - Abdominal cramps - Nausea - Vomiting 

II- NMDA receptor antagonist

Memantine (Ebixa®)	
Mechanism of action	- Glutamate is a useful excitatory neurotransmitter of the nervous system, although excessive amounts in the brain cause → neuronal excitotoxicity → can lead to cell death. - **Memantine is antagonist at N-methyl-D-aspartate receptor** - **Memantine also act as →** - Antagonist at the 5-HT_3 receptor - Antagonist at nicotinic receptors - Agonist at the dopamine D_2 receptor. 
Adverse effects	Dizziness, confusion, insomnia and hallucination

III- Supplements

Ginkgo biloba
- Lowers the chance of developing dementia.
Vitamin E
- A diet rich in natural Vitamin E may reduce the risk of developing Alzheimer's disease.

N.B → Other medicines may be needed to control aggressive, agitated, or dangerous behaviors e.g. haloperidol.

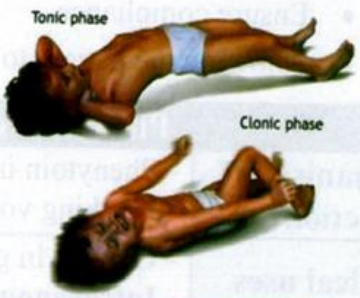
Epilepsy

➢ Definition :-

- Epilepsy is a chronic neurological disorder characterized by disturbances of electrical activity in the brain and recurrent unprovoked seizures.

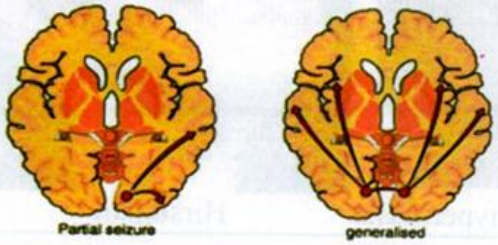
➢ Etiology (Causes) :-

- **About half of all seizures have unknown causes. However, in other cases, the seizures are linked to**
  - Genetic factors.
  - Infections e.g. meningitis.
  - Head trauma e.g. car accidents.
  - Brain tumors and/or stroke.
  - Poisoning e.g. lead poisoning.



➢ Classification of seizures :-

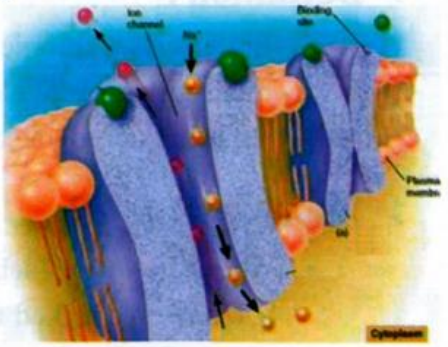
Partial seizures (Focal seizures)	Generalized seizures
- Occur in one part of the brain. - Source of the seizure within the brain is localized. - Consciousness preserved.	- Occur on both sides of the brain. - Source of the seizure within the brain is distributed. - Consciousness lost.
Types	**Types**
1) Simple partial	**1) Generalized Tonic-clonic (grand-mal)**
- No loss of consciousness. - Clonic contraction of single or muscle group - Sensory disturbance.	- Sudden loss of consciousness. - Followed by tonic (continuous contraction) then clonic (rapid contraction and relaxation) convulsion. - The patient often sleeps then recovery.
2) Complex partial	**2) Absence (petit mal) epilepsy**
- Change in or loss of consciousness. - Hallucination and mental distortion. - Motor dysfunction e.g. chewing movement.	- Sudden loss of consciousness for short period - Mild or no motor disturbances.
3) Partial with secondarily generalized	**3) Myoclonic seizures**
- Partial seizure that is followed by generalized attack due to spread of the discharge.	- Jerking of a single or muscle groups. - Without loss of consciousness.
	4) Atonic seizures
	- Sudden loss of muscle tone, causing the person to fall to the ground.
	5) Status epilepticus
	- Sever sustained seizures, without period of recovery → Fatal.



Antiepileptic drugs

➢ Mechanism of action of antiepileptic drugs :-

- Blocking voltage gated channels (Na^+ or Ca^{2+}).
- Enhancing inhibitory GABA NTs.
- Decrease excitatory glutamate NTs.

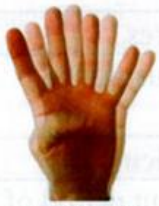


➢ Goal of treatment :-

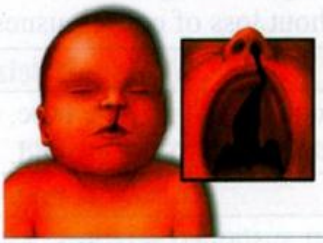
- Control or reduce the frequency of seizures.
- Minimize side effects.
- Ensure compliance.
- Allowing the patient to live as normal life as possible.

Phenytoin or Diphenyl-hydantoin (Epanutin®)		
Mechanism of action	- Phenytoin inhibits the electrical excitability of neurons through blocking voltage gated Na^+ channels.	
Clinical uses	**- Orally:** In grand mal epilepsy and partial seizures. **- Intravenously:** In status epilepsy	
Adverse effects	**Neurologic**	- Diplopia (double vision), ataxia and hallucination.
	Hematologic	- Megaloblastic anemia (due to increase metabolism of folic acid and decrease intestinal absorption).
	Teratogenicity	**- Fetal hydantoin syndrome** (cleft lip and palate, congenital heart disease, slowing of growth and mental deficiency)
	Gingival (Gum)	- Gingival hyperplasia (gum hypertrophy and bleeding of gum).
	Dermatologic	- Rash, dermatitis, pruritis and hirsutism.
	Metabolic	- Hyperglycemia (due to inhibition of insulin release).
	Liver	- Hepatotoxicity
Drug interactions	**- Phenytoin is an LME inducer** so, it increase metabolism of other drugs e.g. anticoagulant, oral contraceptive and Theophylline.	

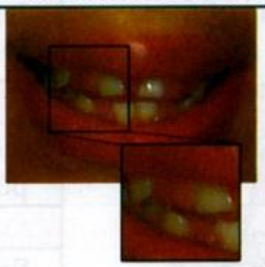
Hydantoin Derivatives		
Mephenytoin (Mesantoin®)	**Ethotoin** (Peganone®)	**Fosphenytoin** (Cerebyx®)
- More toxic than phenytoin	- Less toxic and less effective	- Phenytoin prodrug



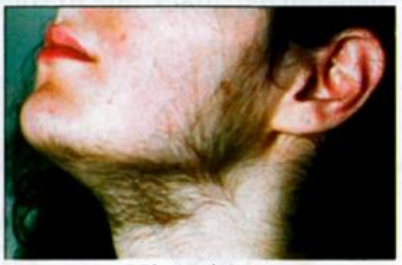
Diplopia



Cleft lip and palate



Gingival hyperplasia



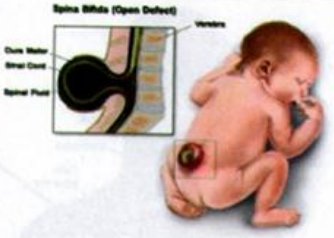
Hirsutism

Carbamazepine (CBZ) (Tegretol®)	
Mechanism	- Acts by blocking of Na^+ channels.
Clinical uses	- **Anticonvulsant** → Grand mal epilepsy and partial seizures. - Also have antidepressant and antipsychotic effects.
Adverse effects	- Allergy, ataxia and anorexia. - Hepatitis (hepatic damage) and anemia (bone marrow depression). - HME (Hepatic/Liver Microsomal Enzyme) inducer.
Drug interactions	- **Carbamazepine** → increase metabolism of other drugs e.g. anticoagulant, oral contraceptive and Theophylline (Decrease it is effect)
Oxcarbazepine (Trileptal®)	- Derivative of Carbamazepine has fewer and less serious side effects.
Barbiturates	
Mechanism	- Acts by potentiating the effect of GABA.
Clinical uses	- Used in grand mal epilepsy and partial seizures.
Adverse effects	- Respiratory depression, dependence and LME inducer.
Benzodiazepines (BDZs)	
Mechanism	- Act by enhancing the GABA transmission.
Clinical uses	- **Diazepam** (Valium®) → Given IV in status epileptics. - **CLonazepam** (Rivotril®) is used orally in absence and myoclonic epilepsy (Not first choice)
Valproic acid (VPA) & Sodium valproate (Depakine®)	
Mechanism of action	- Acts by increase level of GABA by inhibit GABA transaminase enzyme (enzyme breakdown of GABA). - It blocks also Na^+ and T-type Ca^{2+} channels.
Clinical uses	- Grand mal epilepsy, partial seizures and petit male (Not drug of choice). - **Drug of choice** in Myoclonic epilepsy.
Adverse effects	- Allergy, hair loss, nausea and vomiting. - Hepatotoxicity, Teratogenicity (Spina bifida) - LME inhibitors → Increase effect of other drugs e.g. anticoagulant.
Divalproex	- Is a combination of Valproic acid (VPA) & Sodium valproate.


Hair loss


Vomiting


Hepatotoxicity



Spina bifida

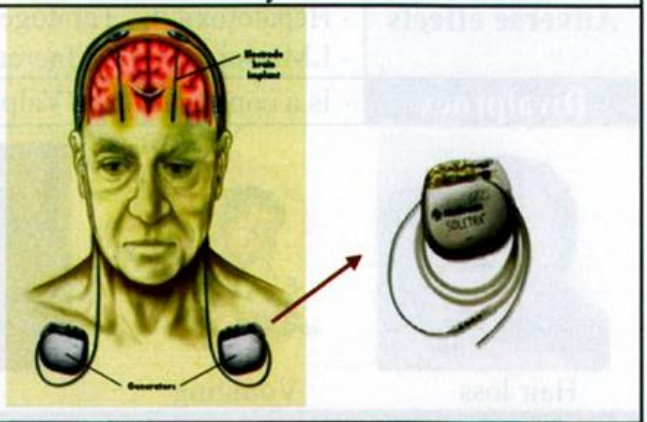
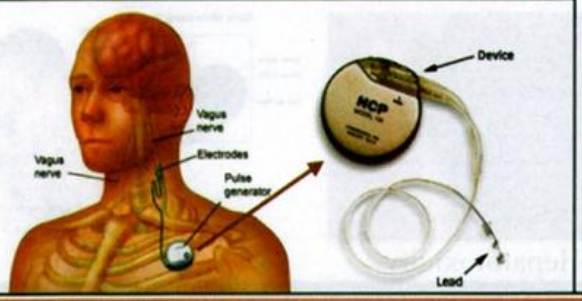
Ethosuximide (Zarontin®)	
Mechanism	- Blocking T-type Ca^{2+} channels especially in thalamic neurons.
Clinical uses	- **Drug of choice** in petit mal (Absence) epilepsy.
Adverse effects	- Allergy, GIT disturbances and drowsiness.

New antiepileptic drugs (Adjunct agents)

- **May be used as mono-therapy or as add-on in resistant case of epilepsy:**

Vigabatrin (Sabril®)	- Irreversible inhibition of GABA transaminase enzyme.
Lamotrigine (Lamictal®)	- Blocks Na^+ channels and antagonists excitatory transmitters as (Aspartate and Glutamate)
Famotrigine (Famotrine®)	
Felbamate (Felbatol®)	- Multiple proposed mechanism (block Na^+ and Ca^{2+} channels, Block NMDA receptor and potentiate GABA)
Gabapentin (Neurontin®)	- Is a GABA analogue enhance GABA release (the exact mechanism is unknown).
Tiagabine (Gabitril®)	- Blocks GABA uptake into neurons.
Levetiracetam (Keppra®)	- Acts by binding to synaptic vesicle protein (SV2A) which is believed to block nerve conduction across synapses (the exact mechanism is unknown).
Pregabalin (Lyrica®)	- Binds to the $\alpha_2\delta$ (alpha-2-delta) subunit of the voltage-dependent Ca^{2+} channel in the CNS. - Inhibit excitatory neurotransmitters.
Topiramate (Topamax®)	- Blocks voltage-dependent Na^+ channels, opening chloride channels by binding $GABA_A$ receptor (the exact mechanism is unknown).

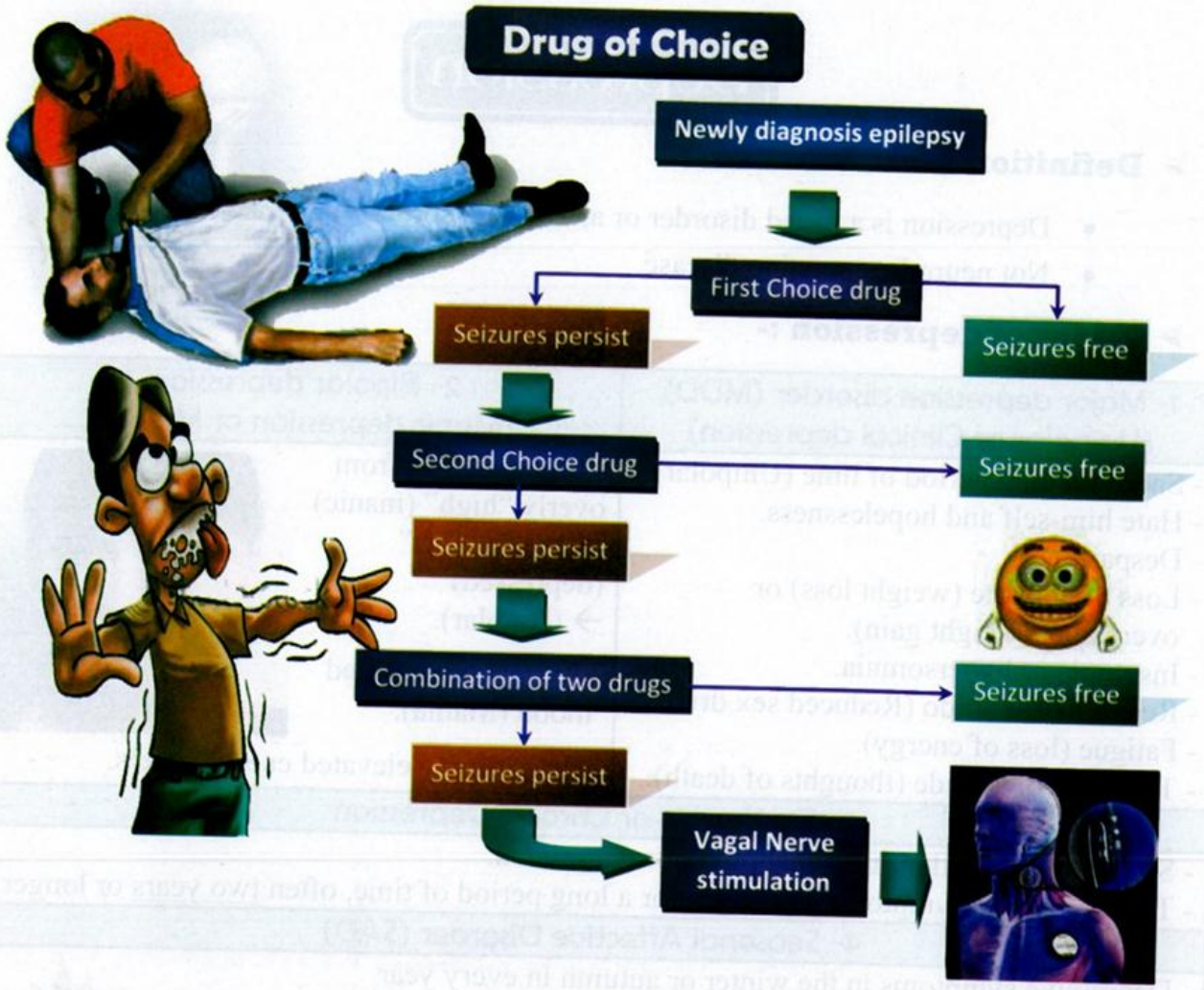
Vagal nerve & Deep brain stimulation

Vagal nerve stimulation (VNS)	Deep brain stimulation (DBS)
- Surgical treatment involving the implantation of a medical device used in treatment for certain type of intractable epilepsy and treatment resistant depression.	- Is a surgical treatment involving the implantation of a medical device called a brain pacemaker, which sends electrical impulses to specific parts of the brain. - Control seizures by electrical stimulation.
- The electrical stimulation prevents the abnormal electrical activity that can cause seizure.	
	

Epilepsy in pregnancy

➔ **Drug should be <u>Avoided</u>** ➔ Divalproex, Barbiturates and Phenytoin.

➔ Women should be monitored regularly by the obstetrician as well as the neurologist.



Choice of Anti-epileptic drugs		
Seizure type	**Drug of choice**	**Recently developed**
Partial Seizures		
Simple partial **Complex partial**	**Carbamazepine → Phenytoin → Valproate**	**Gabapentin** **Lamotrigine** **Vigabatrin**
Partial with secondarily generalized	**Carbamazepine → Phenytoin → Barbiturates → Valproate**	
Generalized Seizures		
Generalized Tonic-clonic (grand-mal)	**Carbamazepine → Phenytoin, Valproate → Barbiturates**	**Lamotrigine** **Levetiracetam** **Topiramate**
Absence (petit mal) epilepsy	**Ethosuximide → Valproate → CLonazepam**	**Lamotrigine**
Myoclonic seizures	**Valproate → CLonazepam**	**Levetiracetam**
Status epilepticus	**Diazepam (IV) → Phenytoin (IV) → Barbiturates (IV)**	

Depression

➢ Definition :-

- Depression is a mood disorder or affective disorder.
- Not neurodegenerative disease.

➢ Types of depression :-

1- Major depression disorder (MDD) (Unipolar or Clinical depression)	2- Bipolar depression (Manic depression or Mania)
- Sad for a long period of time (Unipolar). - Hate him-self and hopelessness. - Despair. - Loss of appetite (weight loss) or overeating (weight gain). - Insomnia or hypersomnia. - Reduction in libido (Reduced sex drive). - Fatigue (loss of energy). - Thoughts of suicide (thoughts of death).	- Mood swings from overly "high" (manic) to overly "low" (depressed) → (Bipolar). - Extremely elevated mood (Mania). - Abnormally elevated energy levels.

3- Dysthymia or Chronic Depression
- Symptoms are milder than that of major depression. - The depression symptoms can linger for a long period of time, often two years or longer.
4- Seasonal Affective Disorder (SAD)
- Depressive symptoms in the winter or autumn in every year. - Due to the lessening of natural sunlight lead to hormone level change. - Light therapy is a common treatment for seasonal affective disorder. - When the depression season ends, they get well and function normally again.
5- Atypical Depression (AD)
- Characterized by over-eating and over-sleeping (Hypersomnia). - This type of depression is mild and can easily be cured compared to other types. - Have a hard time maintaining romantic relationships and are especially afraid of rejection by others (is more common in women than in men).
6- Psychotic major Depression (PMD)
- Severe form of major depression. - Characterized by hallucinations, hears voices and delusional. - If a person with untreated major depression, may suffer from a psychotic depression.
7- Postpartum Depression
- Usually begins in the first few months after childbirth. - Characterized by feelings of extreme sadness, fatigue, loneliness, hopelessness, fears about hurting the baby.

8- Premenstrual Dysphoric Disorder	9- Situational Depression
- End shortly after menstruation begins	- Such as job loss and death of a loved one

Major depression disorder (MDD)

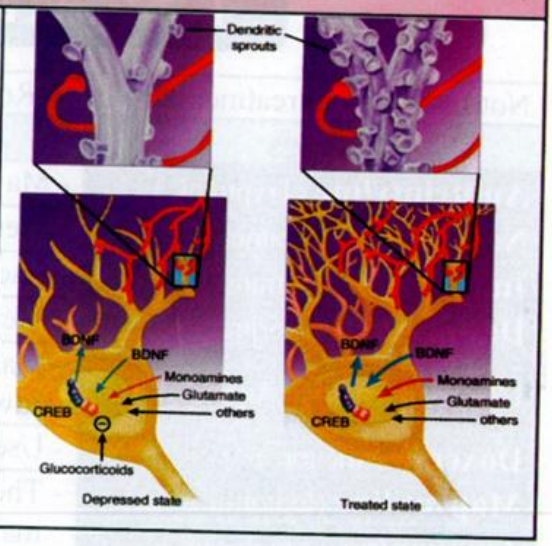
➢ Pathophysiology of Major Depression (Unipolar) :-

Monoamine hypothesis

- Depletion of monoamines (Nor-adrenaline and Serotonin) in certain parts in the brain leads to depression.

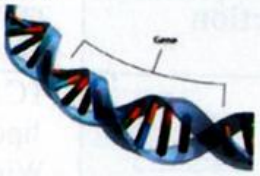
Neurotrophic hypothesis

- Brain-derived neurotrophic factor (BDNF) one of the major neurotrophic factors, plays an important role in neuroprotection, neurogenesis and synaptic connection.
- Exposure to stress and the stress Glucocorticoids hormone → decrease of BDNF.
- Decreasing levels of BDNF in specific areas of the brain, such as the hippocampus, leads to depression and suicide.
- Increase monoamines level → increase BDNF synthesis → Antidepressant effects.
- Time required for synthesize neurotrophic factors takes 2 weeks or longer.



➢ Causes of Major Depression :-

- The exact causes of depression are complex and unknown.
- Some cases have a number of causes are →
  - **Genetic factors:**
    - E.g. → BDNF gene.
  - **Medical conditions:**
    - E.g. → Heart disease, stroke, diabetes, cancer, hypothyroidism, Parkinson's disease, and Alzheimer's disease.
  - **Medications:**
    - E.g. → Antihypertensive agent (used for long periods).
  - **Substance abuse:**
    - Alcohol abuse.
  - **Situations and environmental factors.**
  - **Poor sleep may cause major depression.**
  - **Diet:**
    - Deficiencies in certain vitamins, such as folic acid, vit.B12, and omega-3 fatty acids may cause depression.



➢ Management of Major Depression :-

- Drug therapy (Antidepressant drugs)
- Counseling (Talk therapy or Psychotherapy)
- Treatment using medical devices

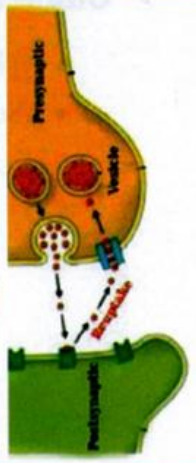
Antidepressant drugs

I - Tricyclic antidepressants (TCAs)

Not first line on treatment due to → Required drug monitoring and severe side effects.

Drugs	Notes
Amitriptyline (Tryptizol®)	- May used as prophylaxis in migraine.
Nortriptyline (Pamelor®)	- Metabolite of **Amitriptyline** used in liver disease.
Imipramine (Tofranil®)	- Used in nocturnal enuresis (Bed wetting in children).
Desipramine (Norpramin®)	- Metabolite of **Imipramine** used in liver disease.
Clomipramine (Anafranil®)	- Mainly used to delay of ejaculation now rarely used in depression.
Doxepin (Silenor®)	- Used in treatment of insomnia.
Maprotiline (ludiomil®)	- The dopaminergic antagonism caused by **amoxapine** may lead to the amenorrhea galactorrhea syndrome.
Amoxapine (Amokisan®)	

Mechanism of action	- TCAs inhibit neuronal reuptake of NE and 5-HT into presynaptic nerve terminal → increase concentration of monoamine in synaptic cleft. - TCAs also block α_1, H_1 and **M** receptors.
Pharmacokinetics	- TCAs are well absorbed from GIT (Oral) due to lipophilic nature. - Widely distributed and → Pass BBB. - Metabolized in liver by HME. - Low therapeutic index → High toxicity. - The elimination half-life ranging from 10 hours to 81 hours. - Once daily dose at night is often preferred.
Antidepressant effect of TCAs	- Effect appears after 2-3 weeks (due synthesize neurotrophic factors takes 2-3 weeks) - Used to treatment psychic depression, acute panic attacks and phobic disorder
Adverse effects	- Sedation → due to Block H_1 receptor. - Weight gain (Increase appetite) → due to Block Serotonin receptor. - Atropine like effect → due to block muscarinic receptor.



	- Sexual dysfunction (Delay of ejaculation). - Postural hypotension, Flushing, Headache, reflex tachycardia and edema formation → due to block α_1 receptor. - Sexual dysfunction (Delay of ejaculation). - Seizers → due to lower seizures threshold. - **Cardiotoxicity** (Fatal arrhythmia) **in over dose** → due Quinidine like effect, blocked NE uptake in the heart and anticholinergic activity.
Contraindication	- Benign Prostatic Hyperplasia (BPH) (Atropine like effect) - Urinary tension (Atropine like effect) - Glaucoma (Atropine like effect) - Epilepsy (Lower seizure threshold)
Drug interactions	**1: Warfarin or Aspirin** - TCAs displace with Aspirin or Warfarin in plasma protein → Increase free drug and activity of Warfarin or Aspirin → lead to toxicity. **2: LME inhibitors or inducers** **3: Clonidine** (Risk of severe hypertension) **4: Quinidine** (Arrhythmia) **5: MAOIs** (Increase release of NE (Severe hypertension crisis). **6: SSRIs** (Serotonin Syndrome)

II - Serotonin/Norepinephrine reuptake inhibitors (SNRIs)

- **Unlike the TCAs, have little side effects.**
- Act by inhibit neuronal reuptake of 5-HT and NE into presynaptic nerve terminal.
- They are effective in treatment of depression associated with neuropathic pain (diabetes).
- **Side effects** → Nausea, vomiting and sexual dysfunction.

Venlafaxine (Efexor®)	**Duloxetine** (Cymbalta®)
- Potent inhibitor of serotonin reuptake and at large dose it inhibit NE reuptake. - Minimal LME inhibitors. - Metabolized to **Desvenlafaxine** (SNRIs).	- Potent inhibitor of serotonin and NE reuptake at all doses.

III - Selective serotonin reuptake inhibitors (SSRIs)

- **First line of treatment** due to fewer side effects.
- Act by inhibit neuronal reuptake of 5-HT into presynaptic nerve terminal.
- Effect appears after 2-3 weeks.

Paroxetine (Seroxat®)	**Citalopram** (Cipram®)	**Escitalopram** (Cipralex®)
Sertraline (Lustral®)	**Fluoxetine** (Prozac®)	**Fluvoxamine** (Faverin®)

Advantage	- No anticholinergic (No atropine like effect) - Little drug interaction. - Less sedative and cardiotoxicity.

Uses	- Depression - Obsessive compulsive disorders (OCD)
Adverse effects	- Sleep disturbance. - Sexual dysfunction (Decrease libido and delayed ejaculation) - SSRI discontinuation syndrome (SSRI withdrawal syndrome) characterized by headache, agitation, flu-like symptoms, change in sleep pattern. - Suicidal attacks especially in children and teenagers.
Drug interactions	- SSRIs with TCAs or MAOIs induce ***Serotonin syndrome*** (See Page 90).

IV - Norepinephrine reuptake inhibitors (NRIs)

Reboxetine (Edronax®)

- Act by inhibit neuronal reuptake of NE into presynaptic nerve terminal.
- It less autonomic side effects.

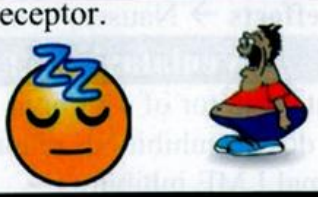
V - Atypical Antidepressants

Bupropion (Wellbutrin®)

- This drug acts as a weak **dopamine** and NE reuptake inhibitors (unique antidepressant).
- Effective in **tobacco smoking quitting** as it prevent reuptake of dopamine.
- No sedation but may cause seizures at high dose.

Mirtazapine (Remeron®)

- Enhance both serotonin and NE by blocking presynaptic α_2 receptor.
- Not act on reuptake.
- Minimal antagonist effect at 5-HT_2.
- Sedative effect (Potent antihistaminic).
- Increase appetite (Weight gain).



Trazodone (Trittico®)

- Block neuronal reuptake of serotonin and block 5-HT_2 receptor.
- Mild to moderate α_1 receptor blocker.
- **Side effects** → Sedation, Priapism (painful erect penis), Orthostatic hypotension, dizziness.

Nefazodone (Serzone®)

- Block neuronal reuptake of serotonin and block 5-HT_2 receptor.
- Less sedation.

Mianserine (Tolvon®)

- Block presynaptic α_2 receptor → Increase release of NE.
- Cause sedation and not cause cardiotoxicity.
- Also inhibits the reuptake of norepinephrine.

VI – Monoamine oxidase inhibitors (MAOIs)

➢ Mechanism of action :-

- **They block the action of both:**
  - MAO-A which metabolizes NE, 5-HT and dopamine.
  - MAO-B which metabolizes dopamine.
- **Examples:**

Non-selective (Block MAO-A & MAO-B) (irreversible)		
Phenelzine (Nardil®)	Isocarboxazid (Marplan®)	Tranylcypromine (Parnate®)
Selective MAO-A inhibitors (Reversible)		
Moclobemide (Aurorix®)	Clorgyline	

➢ Therapeutic uses :-

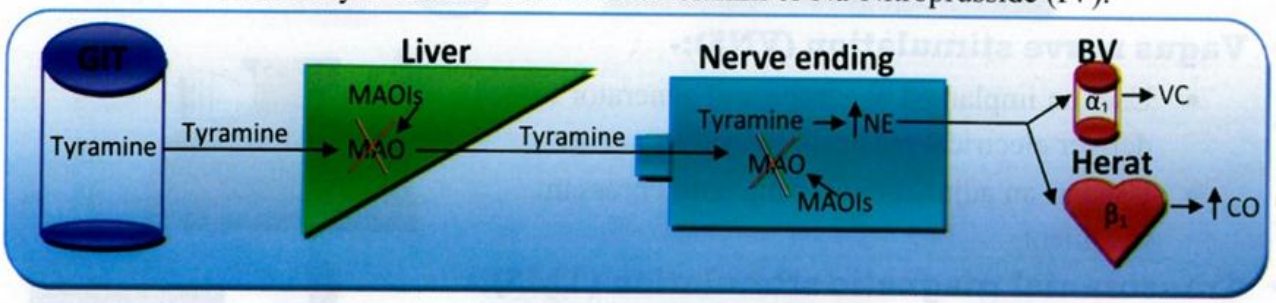
- Depression and phobic disorder (selective MAO-A are preferred).

➢ Side effects :-

- Insomnia, tremors, dry mouth and blurred vision. (Has Atropine like action).

➢ Interactions (Food-Drug) Cheese reaction :-

- With food containing Tyramine e.g. ripe cheese
- Tyramine derived from the amino acid tyrosine.
- Acts as a releasing agent (Increase of catecholamines)
- Tyramine + MAOIs → Increase release of NE → Cause hypertensive crisis.
- Treated by α-blocker such as Phentolamin or Na-Nitroprusside (IV).



Psychotherapy

➢ Counseling (Talk therapy or Psychotherapy):-

- Psychotherapy have a similar training but do not prescribe medication.
- Psychotherapy increases the speed of recovery from a period of depression.
- Successful psychotherapy appears to prevent the recurrence of depression even after it has been terminated.

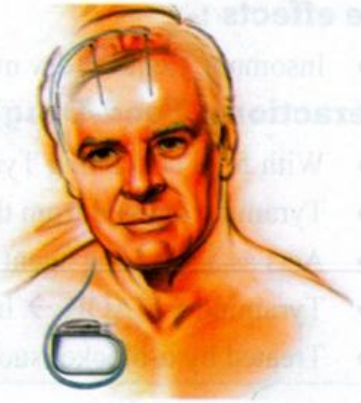
Treatment using medical devices

➢ Electro-convulsion therapy (ECT):-

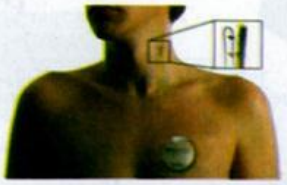
- Used for severe major depression which has not responded to trials of antidepressant.
- It has a quicker effect than antidepressant therapy.
- Electric current is applied while the patient is under general anesthesia.
- The exact mechanism of action of ECT remains elusive (Unknown).

➢ Deep brain stimulation: (DBS):-

- Is a surgical treatment involving the implantation of a medical device called a brain pacemaker, which sends electrical impulses to specific parts of the brain.
- Used in treatment-resistant depression.

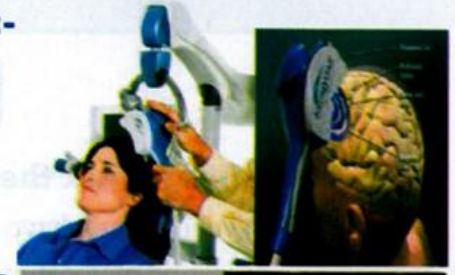


➢ Vagus nerve stimulation (VNS):-



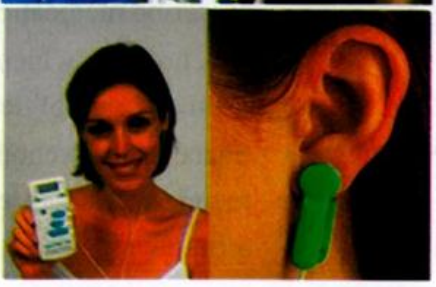
- Uses an implanted electrode and generator to deliver electrical pulses to the vagus nerve.
- Used as an adjunct to existing antidepressant treatment.

➢ Transcranial magnetic stimulation (TMS):-



- Uses electromagnetic induction to induce weak electric currents using a rapidly changing magnetic field; this can cause activity in specific or general parts of the brain.

➢ Cranial Electrotherapy Stimulation (CES):-



- A small, pulsed electric current across a patient's head. has beneficial effects in conditions such as anxiety, depression, insomnia and stress.

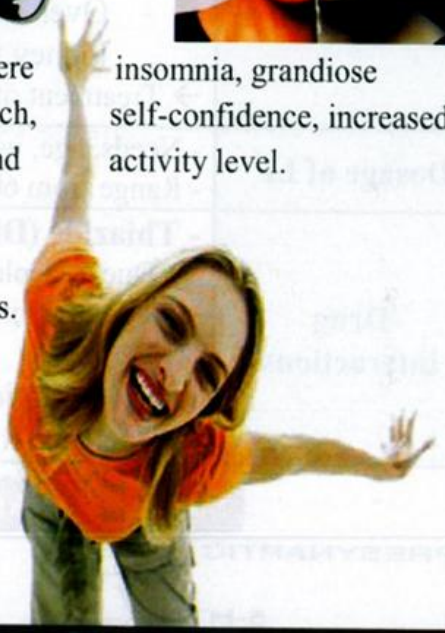
Mania (Manic depression)

➢ Manic depression (Mania or Bipolar depression) :-

- Mood swings from overly "high" (manic) to overly "low" (depressed) → (Bipolar).
- Extremely elevated mood (Mania).
- Abnormally elevated energy levels.

➢ Symptoms:-

- Inappropriate elation, increased irritability, severe insomnia, grandiose notions, increased speed and/or volume of speech, self-confidence, increased sexual desire and markedly increased energy and activity level.



➢ Causes:-

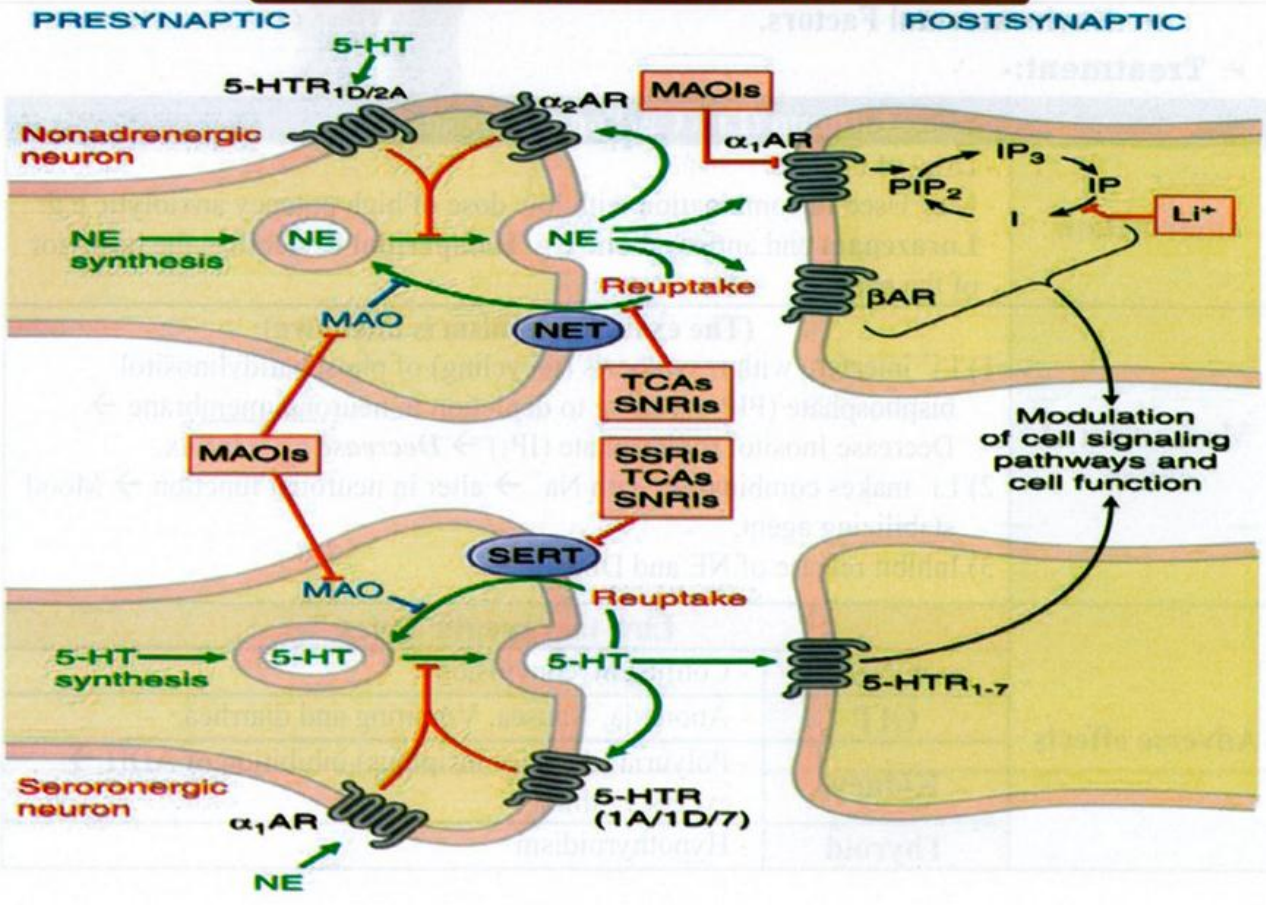
- **Genetic factors:**
  - Manic depression tends to run in families.
- **Neurotransmitters factors:**
  - May due to the dysfunction of certain NTs. or second messengers.
  - Or marked elevation of Norepinephrine.
- **Environmental Factors.**

➢ Treatment:-

Lithium (Li^+) Carbonate (Prianil®)		
Information	- Drug of choice. - May Used in combination with low dose of high potency anxiolytic e.g. **Lorazepam** and antipsychotic e.g. **Haloperidol** to stabilize the behavior of the patient.	
Mechanism of action	**(The exact mechanism is unknown)** 1) Li^+ interfere with resynthesis (recycling) of phosphatidylinositol bisphosphate (PIP_2) leading to depletion in neuronal membrane → Decrease Inositol triphosphate (IP_3) → ***Decrease*** Ca^{2+} influx. 2) Li^+ makes combination with Na^+ → alter in neuronal function → Mood stabilizing agent. 3) Inhibit release of NE and Dopamine.	
Adverse effects	**Low therapeutic index**	
	CNS	- Confusion, convulsion
	GIT	- Anorexia, Nausea, Vomiting and diarrhea.
	Kidney	- Polyuria (diabetes insipidus) inhibition of ADH → excessive thirst
	Thyroid	- Hypothyroidism

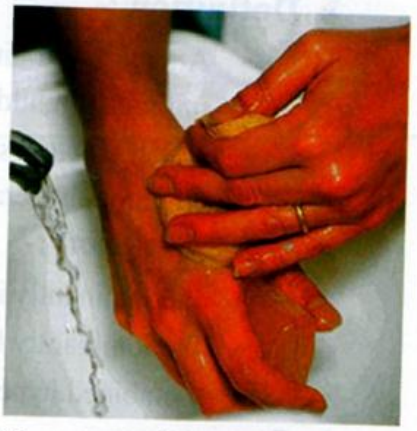
	CVS	- Arrhythmia and hypotension.
	Teratogenicity	- In early pregnancy.
Drug monitoring tests (Li^+ Toxicity)	**1: Serum Li^+ level** - Normal value 0.6-1.2 mEq/L - Higher than 2 mEg/L → Death **2- Thyroid function test (Chronic use)** - Cause hypothyroidism **3- Serum creatinine level** - Over 3 to 5 years of uses may cause kidney failure → Treatment of lithium toxicity by dialysis.	
Dosage of Li^+	- Needs, age, weight and kidney function → affect in the doses of lithium - Range from 600 to 2,400 mg per day.	
Drug interactions	**- Thiazide (Diuretic)** - Due to depletion of Na^+ → Increase reabsorption of Li^+ due to competition of Na^+ and Li^+ → Increase serum Li^+ level. **- NSAIDs** - the excretion of Li^+ is reduced in patient taking NSAIDs this lead to increased plasma concentration of Li^+.	

Summary of Antidepressant mechanism of action



Obsessive compulsive disorder (OCD)

➢ Definition :-



- Obsessive-compulsive disorder (OCD) is an anxiety disorder characterized by unreasonable thoughts and fears (Obsessions) that lead you to do repetitive behaviors (Compulsions).
- Such as a fear of getting contaminated by germs. To ease your contamination fears, you may compulsively wash your hands.

➢ Symptoms :-

- OCD compulsions are repetitive behaviors that feel driven to perform. These repetitive behaviors are meant to prevent or reduce anxiety related to obsessions.

Obsessions symptoms and signs	Compulsion symptoms and signs
Washing and cleaning	Hand washing until your skin becomes raw
Checking	Checking doors repeatedly to make sure they're locked
	Checking the stove repeatedly to make sure it's off
Counting	Counting in certain patterns
Orderliness	Arranging your canned goods to face the same way

➢ Causes :-

- The cause of obsessive-compulsive disorder is not fully understood.
- Main theories include:
  - May be a result of changes in your body's chemistry or brain functions.
  - May have a genetic component, but specific genes have yet to be identified.
  - May stem from behavior-related habits that you learned over time.
  - **May be a result of decrease level of serotonin in the brain.**

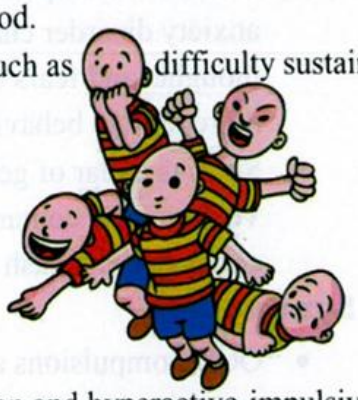
➢ Treatment :-

Psychotherapy	Medications (Drugs)
- A type of therapy called cognitive behavioral therapy (CBT). - This therapy involves gradually exposing you to a feared object or obsession, such as dirt, and teaching you healthy ways to cope with your anxiety.	**Selective Serotonin reuptake inhibitors**
	Fluvoxamine (Faverin®)
	Fluoxetine (Prozac®)
	Paroxetine (Seroxat®)
	Sertraline (Lustral®)
	Other drug effective
	Clomipramine (Anafranil®)
Other treatments	
Electroconvulsive therapy , Transcranial magnetic stimulation and Deep brain stimulation	

Attention Deficit Hyperactivity Disorder (ADHD)

➢ Definition :-

- Attention-deficit/hyperactivity disorder (ADHD) is a chronic condition that affects millions of children and often persists into adulthood.
- ADHD includes some combination of problems, such as difficulty sustaining attention, hyperactivity and impulsive behavior.

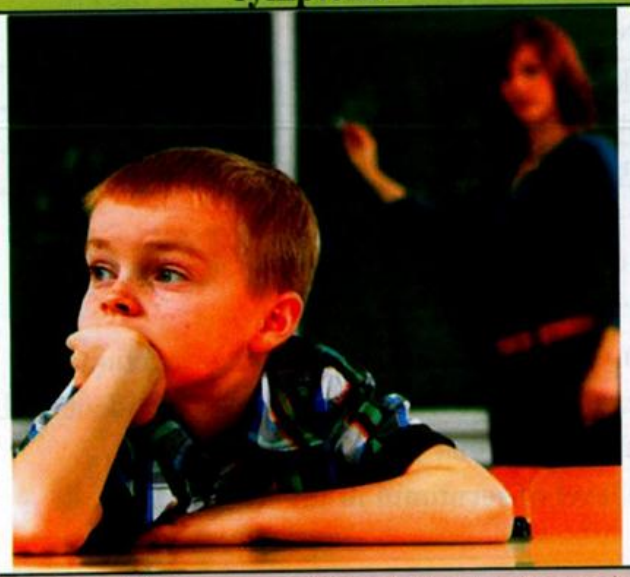
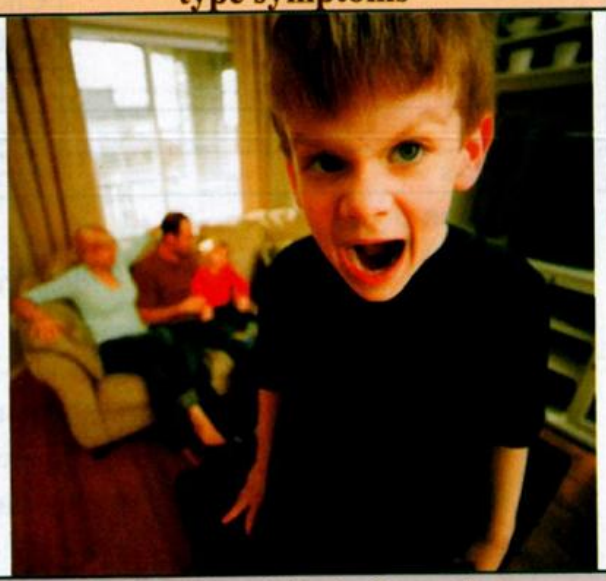


➢ Classification :-

- Predominantly inattentive
- Predominantly hyperactive-impulsive
- Combined hyperactive-impulsive and inattentive

➢ Symptoms :-

- Most children have some combination of inattention and hyperactive-impulsive behavior.

Predominantly inattentive type symptoms	Predominantly hyperactive-impulsive type symptoms
	
Six or more of the following behaviors need to be present for ≥ 6 months	
- Reduced attention span - Poor listener - Careless mistakes - Can't follow instructions - Dislikes chores or home work - Forgetful in daily activities - Difficultly organizing tasks and activity - Have difficulty processing information as quickly and accurately as others	- Cannot remain seated in the classroom - Excessive talking - Uncontrollable/inappropriate restlessness - Difficulty in engaging in play or leisure activities quietly - Touching or playing with anything and everything in sight - Be constantly in motion - Have difficulty waiting for things they want or waiting their turn in games

➢ Causes :-

- The specific causes of ADHD are not known.
- Several factors may cause it:
  - Genetic factors
  - Decrease activity in the areas of the brain that control activity levels or due to brain damage (change in the brain structure specially frontal lobe)
  - **ADHD study showed lower levels of dopamine in the brain.**
  - Environmental factors
  - Food additives such as artificial coloring or food preservatives.
  - Maternal exposure to toxins
  - Smoking, drinking alcohol or using drugs during pregnancy.

➢ Treatment :-

Medications

Stimulant medications (Psychostimulants)	
- Stimulants (Amphetamines) make balance between neurotransmitters in the brain.	
Methylphenidate (Ritalin®)	
Mechanism of action in ADHD	Methylphenidate works in the treatment of ADHD by increasing levels of dopamine in the brain.
Most common side effects	Appetite suppression, Nausea, Abdominal pain, insomnia, Euphoria and CVS side effects (Angina-chest pain)
Methylphenidate is available in a long-acting patch that can be worn on the hip (Daytrana®).	
Amphetamine (Adderall XR®)	
Mechanism of action	- Increase release of nor-adrenaline and dopamine and prevent reuptake. - Powerful CNS stimulant.
Most common side effects	- Psychotic effect (insomnia, anxiety, confusion & hallucination). - Hypertension - Psychological, dependence and addiction (after prolonged use).
Dextroamphetamine (Dexedrine®)	
- Is the dextro isomer of the amphetamine.	
PREGNANCY	Amphetamines should not be used during pregnancy.
Warning	
The FDA issues a "black box" warning on all amphetamines. This means that results from medical studies have indicated that serious and sometimes life threatening adverse reactions have been present. Misuse of Adderall or any other amphetamine can lead to sudden death. This drug is a controlled substance, and addiction is highly probable with prolonged use. It only should be used by the patient for whom it was prescribed. After extended use, the patient may develop a dependence or tolerance to this drug. This drug appears to be effective when proper protocol is followed, but it can be deadly if abused.	

Non-stimulant medications	
Atomoxetine (Strattera®)	
- Is a selective norepinephrine reuptake inhibitor. - Oral administration only. - **The side effects include** → dry mouth, nausea, decreased appetite, constipation, dizziness, sweating, decreased libido and urinary retention.	
Other medications	
Antidepressants	
- These medications are generally used in children who don't respond to stimulants or atomoxetine, or who have a mood disorder as well as ADHD.	
Clonidine (Catapress®)	**Guanfacine** (Intuniv®)
- These are high blood pressure medications shown to help with ADHD symptoms.	

ADHD counseling

- **Psychotherapy and behavior therapy** (With medications)
  - Teachers and parents can learn behavior-changing strategies for dealing with difficult situations.
  - This allows older children with ADHD to talk about issues that bother them, explore negative behavioral patterns and learn ways to deal with their symptoms.

Schizophrenia

➢ Definition :-

- Schizophrenia is a mental disorder characterized by combination of hallucinations, delusions, and disordered thinking and behavior.

➢ Types of Schizophrenia :-

Paranoid Schizophrenia
- Paranoid schizophrenia is the most common form. - With this type of schizophrenia, the primary symptoms are delusions or auditory hallucinations. - Usually do not have thought disorder, disorganized behavior, or affective flattening.
Disorganized (Hebephrenic) Schizophrenia
- People with this schizophrenia type often have unusual thought processes. - Disorganized speech, thinking, and behavior. - The patient may act silly or withdraw socially to an extreme extent.
Catatonic Schizophrenia
- Catatonia is a state of immobility and unresponsiveness that was more common when schizophrenia treatment was not available. Fortunately, catatonia is now rare. - People with this type of schizophrenia can be clumsy (wooden or catalepsy) and uncoordinated. They may also show involuntary movements, or unusual mannerisms.
Residual Schizophrenia
- Can occur in people with long-term schizophrenia. With this schizophrenia type, a person no longer shows positive symptoms, but still shows negative symptoms.
Undifferentiated Schizophrenia
- Person meets the criteria to be diagnosed with schizophrenia, but his symptoms are not consistent with any of the other forms of the disease.

➢ Symptoms :-

Positive symptoms	Negative symptoms
- Delusions - Auditory hallucinations - Thought disorder - Disorganized behavior - Disorganized speech	- Lack of emotional expression - Lack of interest - Speech difficulties - Lack of motivation
Positive and negative symptoms usually occur together	

➢ Causes and Pathophysiology:- (Not completely understood)

- **It is the result of a complex group of →**
  - **Genetic factors**
  - **psychological factors**
  - **Environmental factors**

- **Brain Structure**
  - Differences in brain structures (most commonly occur in the frontal lobes, hippocampus and temporal lobes).
- **Dopamine hypothesis**
  - Increased dopaminergic activity in the mesolimbic pathway of the brain.
- **Other hypothesis**
  - Glutaminergic system abnormalities.
  - May also increase level of Serotonin.

➢ **Treatment :-**

- The first-line psychiatric treatment for schizophrenia is **antipsychotic medication.**

Neuroleptic drugs (Major tranqilizer - Antipsychotics)

➢ **Classification (Most common used) :-**

First generation antipsychotic (Typical neuroleptic)	
- Antipsychotic effects due to blocking D_2 receptors. - Have extrapyramidal side effects.	
Low potency	
Chlorpromazine (CPZ) (Neurazine®)	**Thioridazine** (Thiozin®)
High potency	
Fluphenazine (Modecate®)	**Haloperidol** (Haldol®)
Perphenazine (Trilazine®)	**Zuclopenthixol** (Clopixol® Depot)
Flupenthixol (Fluanxol®)	**Loxapine** (Loxapine®)
Second generation antipsychotic (Atypical neuroleptic)	
- Antipsychotic effects due to blockade of both Serotonin and Dopamine receptors. - Have fewer extrapyramidal side effects and little or no effect on M, H or α receptor. - Current Antipsychotic therapy commonly comprises second generation agents to minimize risk of extrapyramidal side effects associated with first generation drugs.	
Aripiprazole (Abilify®)	**Clozapine** (Clozapex®)
Olanzapine (Zyprexa®)	**Paliperidone** (Invega®)
Quetiapine (Seroquel®)	**Riseridone** (Risperdal®)
Sertindole (Serdolect®)	**Sulpiride** (Dogmatil®)
Ziprasidone (Zeldox®)	
- Approximately 20% of patient will have an insufficient response to all first and second generation antipsychotics.	

➢ Pharmacological action :-

CNS	- **Antipsychotic action** reduces the hallucination and delusions associated with schizophrenia (By blocking D_2 receptors in mesolimbic system) reduce the "positive" symptoms of psychosis and take around 7-14 days. - **Antiemetic action** (By blocking D_2 receptors in CTZ of the medulla) - **Hypothermic action** (By depression the heat regulating center in hypothalamus. - Large dose cause Parkinsonian symptoms by blocking D_2 receptors in the basal ganglia.
CVS	**- Hypotension due to :** o α-blocking effect o Direct vasodilatation o Inhibition of Vasomotor center (VMC) **- Tachycardia due to :** o Atropine like effect and Reflex from hypotension
Endocrine	- Increase prolactin hormone (blocking D_2 receptors in pituitary gland).

➢ Therapeutic uses :-

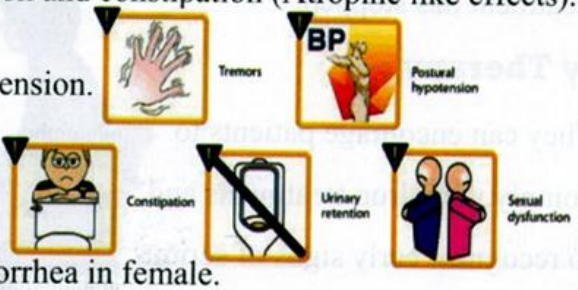
- Used to treat schizophrenia or bipolar disorder (Mania)
- Antiemetic in small dose (Not used in pregnancy).
- Pre-anesthetic medication.

➢ Adverse effects :-

- **Extrapyramidal side effects :**

	Stages	Symptoms	Time of treatment
1	Acute dystonia reactions	Movement disorders in which sustained muscle contractions	Hours to days
2	Akathisia	A feeling of motor restlessness	Days to weeks
3	Parkinson-like symptoms	Reversible Tremors, rigidity and bradykinesia	Weeks to months
4	Tardive dyskinesia	Irreversible involuntary movement of the tongue and face.	Months to years

- **Anti-muscarinic effects :**
  - Dry mouth, blurred vision and constipation (Atropine like effects).
- **α_1-adrenoceptor blockade :**
  - Leads to postural hypotension.
- **H_1-receptor blockade** :
  - Sedation.
- **Endocrine effects :**
  - Amenorrhea and galactorrhea in female.
  - Gynecomastia and impotence in male.



Chlorpromazine is the most likely choice of the agents for causing this adverse effect.

- **Other side effect :**
  - **Clozapine** causes agranulocytosis (Complete absence of circulation neutrophils - White blood cells) in 1-2 % of patients.
  - Weekly blood cell count must be done in patients taking **Clozapine**.
  - **Clozapine** it can induce seizures in non-epileptic patients

➢ Contraindications :-

- Hypersensitivity.
- Glaucoma as it has atropine-like action → Increase IOP.
- Parkinson's disease.
- Cardio vascular disease.

➢ Drug interaction :-

- Enhance sedative effects of (alcohols, barbiturates and BDZs.).
- Block α-receptors, so can reverse the hypertensive effect of adrenaline.

Psychotherapy

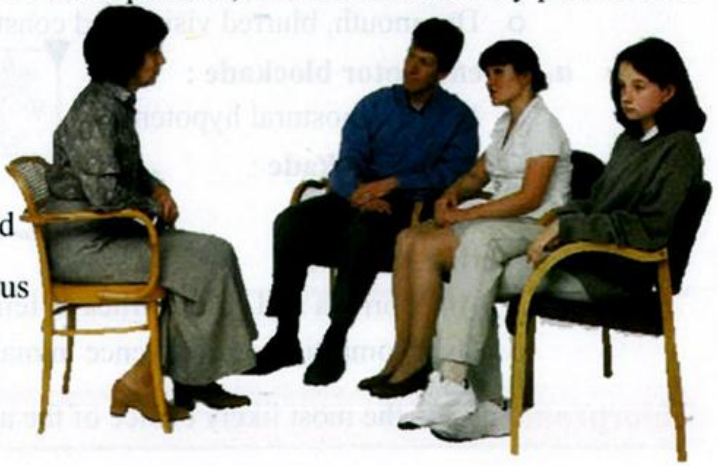
- One-fifth to one-third of all patients with schizophrenia do not respond adequately to drug treatment.
- Sychological therapies can be helpful for many patients.

➢ Cognitive-Behavioral and Other Psychosocial Therapies :-

- The use of cognitive-behavioral therapy (CBT) is showing improvement in both positive and negative symptoms in some patients, and the benefits may persist after treatment has stopped.

➢ Family Therapy :-

- They can encourage patients to comply with drug treatments and to recognize early signs of serious treatment side effects.



CNS stimulants

(A) - Psychomotor stimulant

1- Methylxanthines

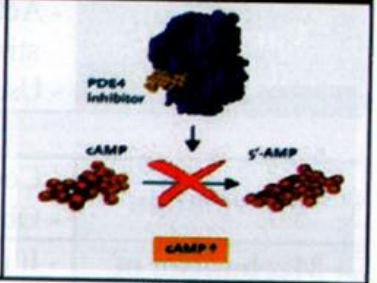
Information

- Natural alkaloids of plant origin e.g. → Tea leaves, coffee bean, cola seeds, Coca and chocolate.
- The Methylxanthines include →

Caffeine	Theophylline	Theobromine

Mechanism of action

- It inhibits (Phosphodiesterase enzyme type-4) PDE4 → accumulation of cAMP responsible for vasodilatation in smooth muscle (SM).
- Block adenosine receptor.
- **N.B:** Unlike cardiac muscle, increased cAMP in smooth muscle causes relaxation.



Pharmacological action

CNS	- Caffeine is more selective and potent on CNS. - Stimulation of cerebral cortex → Increase mental activity and alertness. - Stimulation of medulla → Stimulate RC, VMC and CIC. - Stimulation of spinal cord in large doses.
CVS	- +ve inotropic and chronotropic effect on the heart.
Kidney	- Diuretic effect due to inhibition of Na^+ reabsorption.
SM	- Spasmolytic effect on bronchi, GIT and urinary bladder.
Secretion	- Increase release of catecholamine and gastric HCl.

Therapeutic uses

- Bronchial asthma e.g. **Theophylline** → (Minophylline®)
- Simple headache e.g. (**Caffeine** + **Aspirin**) → (Excedrin®)
- Migraine headache e.g. (**Caffeine** + **Ergotamine**) → (Metograine®)

Adverse effects

- **CNS side effect** → Insomnia, restlessness, tremors and convulsions.
- **CVS side effect** → Increase HR (Direct acting on the heart) and decrease BP (Central acting → inhibition of CIC).
- **GIT side effect** → Ulceration.

Drug interactions of Theophylline

- **Drugs increase metabolism of Theophylline** (Enzyme inducers) e.g. Phenytoin and barbiturates → Decrease therapeutic effect.
- **Drugs decrease metabolism of Theophylline** (Enzyme inhibitors) e.g. Ketoconazole and Erythromycin → Increase toxicity.

2- Nicotine

Information

- Nicotine is active ingredient in tobacco.
- Not currently used therapeutically (Except in smoking).

Mechanism of action

- In low dose → Stimulate ganglia.
- In high dose → Block ganglia.

Pharmacological action	**CNS**	- Nicotine is high lipid soluble → Cross BBB. - During smoking of low dose of nicotine → Produce some degree of euphoria and arousal. - It improves attention, learning and problem solving. - High dose of nicotine → Inhibition of RC and VMC. - Nicotine is also an appetite suppressant.
	Peripheral effects	- Stimulation of sympathetic ganglia and adrenal medulla → Increase heart rate and blood pressure.
	- Nicotine is an addictive substance and physical dependence develops rapidly and can be severe (Withdrawal Syndrome).	
Varenicline (Chantix®)	- Acting as a partial agonist of the nicotinic receptor, and partially stimulates, the receptor without producing a full effect like nicotine. - Used to quit smoking.	
3- Cocaine		
Information	- Cocaine is a widely available and highly addictive drug. - Obtained from the leaves of the coca plant.	
Mechanism of action	- It inhibits reuptake of the monoamines (NE, Serotonin and Dopamine). - Block Na^+ channels (Local anesthetic)	
Pharmacological action	**CNS**	- Powerful stimulation of the cortex and brain stem. - Increase mental awareness and produces a feeling of wellbeing and euphoria. - Can produce hallucination and delusions. - High dose of Cocaine → It causes tremors, convulsions and inhibits RC and VMC.
	Peripheral effects	- Adrenergic stimulation → Tachycardia, VC and Mydriasis.
Side effects	- Agitation, Convulsion, Hypertension, Sweating and Dependence. - **Toxic effects** → Fatal cardiac arrhythmia and respiratory failure.	
4- Amphetamine		
Mechanism of action	- Increase release of nor-adrenaline and dopamine and prevent reuptake. - Powerful CNS stimulant.	
Uses	- Treatment of narcolepsy (Hypersomnia) and Obesity. - Attention Deficient Hyperactivity Disorder (ADHD).	
Side effects	- Dependence and Tolerance.	
Methylphenidate (Ritalin®)	- As amphetamine but less side effects	

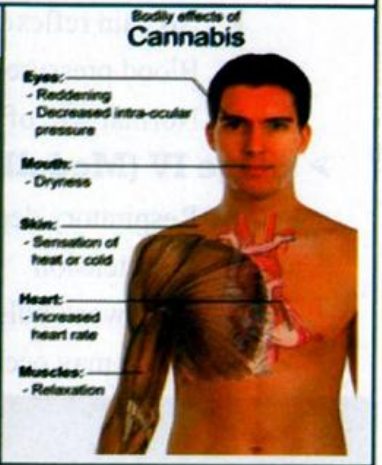
(B) - Brain stem stimulants (Analeptics)

- Stimulate RC and VMC in medulla.
- Produce convulsion in high doses.
- Can be used in respiratory failure e.g. → **Doxapram** and **Amiphenazole**.
- **Cardiozole** and **Picrotoxin** → Cause convulsion and have no clinical uses.

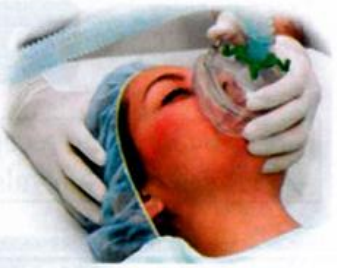
(C) - Spinal cord stimulation (Strychnine)

- Acts by blocking receptors for the inhibitory NT Glycine.
- It causes tonic convulsion which is characterized by being symmetrical and reflex in origin.

(D) - Psychomimetic drugs (Hallucinogens)

LSD (Lysergic acid diethylamide)	
Information	- Synthetic from ergotamine (Ergot alkaloid).
Mechanism	- Stimulate 5-HT_1 and 5-HT_2 receptors in CNS.
Pharmacological action	- Mydriasis, Visual hallucination. - Mood change, Depression and suicide.
Side effects	- Tolerance (True dependence is rare)
Tetrahydrocannabinol (Cannabis or Hashish)	
Mechanism of action	- Stimulate cannabinoid receptors → Decrease release of NTs. - Types of Cannabinoid (CB) receptor → Cannabinoid receptor type 1 (CB1) & Cannabinoid receptor type 2 (CB2) - Both CB1 and CB2 cannabinoid receptors are coupled to inhibitory G-proteins → Inhibits the activity of adenylyl cyclase. - The CB1 receptors are highly expressed throughout the peripheral and central nervous systems.
Effects	- Produces loss of sense of time, distance and sound. - Antiemetic effect. - Stimulate appetite. - Produce euphoria. - Red conjunctiva. - Decrease IOP. - Increase HR  
Side effects	- Tolerance (True dependence is rare)
Phencyclidine (PCP)	
Mechanism of action	- Inhibit reuptake of Dopamine, NE and Serotonin. - It has anticholinergic activity. - NMDA antagonist effects.
Effects	- Phencyclidine, an analog of ketamine, causes dissociative anesthesia and analgesia. - It produces numbness of extremities, staggered gait, slurred speech, and muscular rigidity.

General anesthesia



➢ Definition :-

- Is a stage of reversible inhibition of CNS characterized by loss of consciousness, loss of reflexes and muscle relaxant.

Stages of anesthesia

➢ Stage I (Induction) :-

- Patient is conscious
- Increase sense of hearing
- Analgesia

➢ Stage II (delirium/Excitement) :-

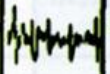
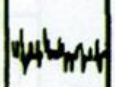
- Patient is unconscious
- Respiration is irregular
- Vomiting may occur

➢ Stage III (Surgical anesthesia) :-

- Patient is unconscious
- Respiration is regular
- No vomiting
- No pain reflexes
- Blood pressure is normal
- Normal size of pupil

➢ Stage IV (Medullary paralysis) :-

- Respiratory depression
- Hypotension
- Very weak pulse
- Death may occur

STAGE	PUPIL		RESP.	PULSE	B.P.
	USUAL SIZE	REACTION TO LIGHT			
1ST INDUCTION				IRREGULAR	NORMAL
2ND EXCITEMENT				IRREGULAR & FAST	HIGH
3RD OPERATIVE				STEADY SLOW	NORMAL
4TH DANGER				WEAK & THREADY	LOW

Stage	Description
I	Amnesia, induction of anesthesia to loss of consciousness
II	Delirium, excitation, potential for vomiting, laryngeal spasm, hypertension, tachycardia, uncontrolled movements, dilated pupils
III	Surgical anesthesia, constricted pupils, regular respiration, adequate anesthetic depth, prevention of hypotension and tachycardia, absence of movement
IV	Overdosage; shallow or no respiration; dilated, nonreactive pupils; hypotension

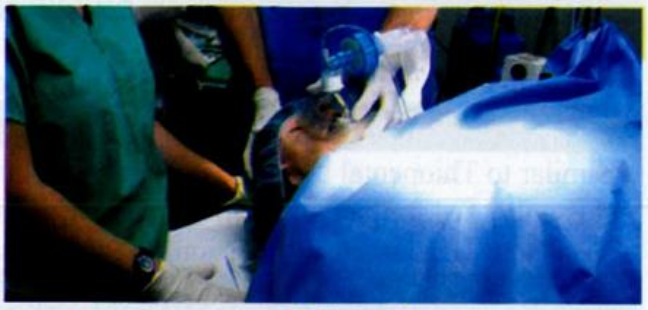
Preanaesthetic medication

➢ Sedative and hypnotic :-

- **Example :**
  - Short-acting barbiturates e.g → **Secobarbital** (Seconal®)
  - BDZs e.g. **Diazepam** (Valium®) - **Midazolam** (Dormicum®)
- **Advantages :**
  - Decrease anxiety
  - Induce sleep after operation
  - Reduce amount of anesthesia

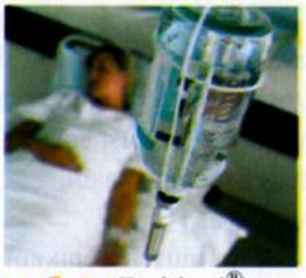
➢ Tranquilizer :-

- **Example :**
  - **Chlorpromazine (CPZ)** (Neurazine®) - **Promethazine** (Sparine®)
- **Advantages :**
  - Remove anxiety
  - Produce hypotension
  - Decrease vomiting



➢ Narcotic analgesics :-

- **Example :**
  - **Morphine** (MST®) - **Fentanyl** (Duragesic®) - **Meperidine** (Demerol®)
- **Advantages :**
  - Produce analgesia and sedation.
  - Reduce amount of anesthesia.



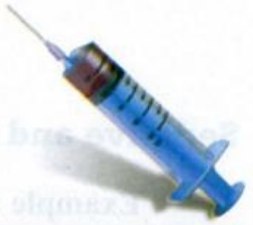
➢ Parasympatholytics :-

- **Example :**
  - **Atropine** - **Hyoscine** and **Glycopyrrolate** (Robinul®).
- **Advantage :**
  - Reduce salivary and bronchial secretion.
  - Protect the heart from bradycardia.
  - Counteract respiratory depressant action of morphine.

➢ Anaesthetic adjuvants :-

- **Neuromuscular blockers:** E.g. **Succinylcholine, Curare** and **Gallamine**
- **Antiarrhythmics: E.g. Lidocaine** (Xylocaine®)

(A) - Intravenous anaesthetics



➢ **Advantages :-**

- Rapid induction (20-30 sec.) and recovery.
- No irritant to respiratory tract.
- No post-operative nausea and vomiting.

Thiopental (Anapental®)

- Ultra-short acting barbiturate.
- Enhances the effect of inhibitory neurotransmitters GABA.
- Given IV and rapidly crosses the BBB.
- Terminated by redistribution from brain to other organs.

➢ **Disadvantages :-**

- o May cause respiratory complication e.g. Apnea and bronchospasm.
- o Passes through the placenta and may cause respiratory depression to fetus.

Benzodiazepines

- See Page (109)

Propofol (Diprivan®)

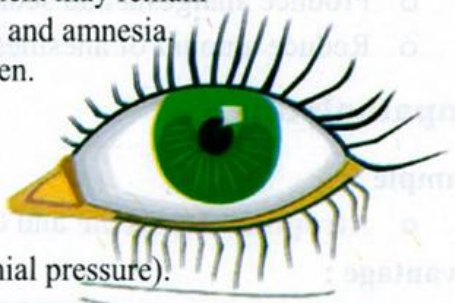
- Similar to Thiopental in its mechanism of action.
- Has antiemetic action and may cause pain at site of injection.

Etomidate (Amidate®)

- Similar to Thiopental but more rapidly metabolized.
- It is only used for patients with coronary artery disease or cardiovascular dysfunction.
- May cause pain at site of injection and involuntary movement during induction.

Ketamine (Ketalar®)

- Antagonist of the excitatory neurotransmitter glutamic acid at its NMDA receptor.
- Given IM or IV to produce dissociated state.
- Ketamine is a **dissociative anesthesia** → Patient may remain conscious (Open eye) with marked analgesia and amnesia.
- Used for minor operation especially in children.
- It rarely induces bronchospasm.



➢ **Disadvantages :-**

- o Has no muscle relaxant action.
- o Increase BP and HR.
- o Increase IOP and ICP (Intra-cranial pressure).
- o Causes hallucination during recovery.
- o Contraindication in pregnancy because of its oxytocic effect.

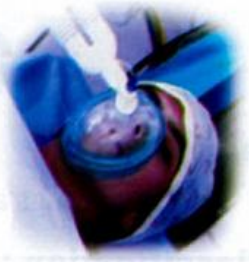
Innovar

- A neuroleptic analgesic.
- Composed of **Droperidol** (Neuroleptic) and **Fentanyl** (Opioid analgesic).

➢ **Disadvantages**

- o Bradycardia
- o Hypotension
- o Respiratory depression

(B) - Inhalational anaesthetics



➢ Information :-

- Either volatile liquids or gases.
- Usually delivered using an anesthetic machine.

➢ Mechanism of action (Unclear) :-

- May dissolve in membrane lipid and affect its physical state.
- They inhibit nicotinic receptors and may affect GABA and Glycine.
- They depress the reticular activating system and cortex.

➢ Pharmacokinetics :-

- Drugs with low solubility in blood (low blood : gas partition coefficient)
  - **Nitrous Oxide** → Rapid rate of induction and recovery.
- Drugs with high solubility in blood (high blood : gas partition coefficient)
  - **Halothane** → Slow rate of induction and recovery.

➢ N.B.

- **Minimum Alveolar Concentration (MAC) :**
  - It is the minimum concentration of the drug in the lung that produces anesthesia in 50% of patients.
  - The lower (MAC) → The more potent anesthetic.
  - MAC measures the potency of anesthetics.

Nitrous oxide (N_2O)	Halothane (Fluothane®)
- Colorless volatile gas	- Colorless volatile liquid
- Has a rapid onset of action and recovery → low blood gas PC = 0.47	- Has a slower onset of action and recovery → High blood gas PC = 2.3
- Weak anesthetic (MAC > 100%)	- More potent than N_2O (MAC = 0.75%)
- Has an analgesic activity	- Has a weak analgesic activity
- Weak skeletal muscle relaxant	- Weak skeletal muscle relaxant
Adverse effects	**Adverse effects**
- Hallucination, Postoperative nausea and vomiting, leuckopenea and megaloplastic anemia.	- Respiratory depression, bradycardia, hypotension, severe hepatic necrosis (damage) and malignant hyperthermia in Patients with a genetic defect in muscle calcium regulation).

Enflurane (Ethrane®)	Desflurane (Suprane®)	
Isoflurane (Forane®)	Sevoflurane (Sevorane®)	Methoxyflurane (Penthrox®)
- They drugs are volatile liquids at room temperature. - They produce better muscle relaxant. - They are less hepatotoxic and cardiotoxic than halothane. - **Enflurane** may cause epilepsy-like syndrome. - **Desflurane** is irritant and may cause bronchospasm.		

(C) - Local anaesthetics (LAs)

➢ Information :-

- These drugs are used to prevent pain in specified areas in the body.

➢ Classification :-

- ***Esters :***
  - E.g. **Cocaine**, **Procaine**, **Tetracaine** and **Benzocaine**.
  - They are metabolized by Pseudo-cholinesterase so, they have short duration.
- ***Amides :***
  - E.g. **Lidocaine** (Xylocaine®), **Mepivacaine** (Mepacaine®) and **Bupivacaine** (Marcaine®).
  - They are metabolized by liver microsomal enzyme.

➢ Mechanism of action :-

- LAs block Na^+ channels to prevent the rapid influx of Na^+ ion essential for the transmission of the nerve impulse across the nerve cell membrane.

➢ Pharmacokinetics :-

- Addition of the vasoconstrictor epinephrine to the LAs → decrease the absorption of LAs and this cause reduce systemic toxicity and increase the duration of action.

➢ Clinical uses :-

- Surface anesthesia → e.g. Skin and cornea.
- Regional anesthesia → e.g. Limbs.
- Less common use → e.g. Arrhythmia.

➢ Toxicity :-

- ***Systemic :***
  - Abdominal pain
  - Confusion
  - Allergy
  - Myocardial depression
  - Skin rashes
- ***Local :***
  - Oedema
  - Hematoma
  - Pain at the site of injection

Questions

➢ Coose the best answer

66: Which one of the following combinations of antiparkinson drugs is an appropriate therapy?

a. Amantadine, carbidopa, and entacapone
b. Levodopa, carbidopa, and entacapone
c. Pramipexole, carbidopa, and entacapone
d. Ropinirole, selegiline, and entacapone
e. Ropinirole, carbidopa, and selegiline

67: A former heroin addict is maintained on methadone, but succumbs to temptation and buys an opioid on the street. He takes it and rapidly goes into withdrawal. Which opioid did he take?

a. Meperidine
b. Heroin
c. Pentazocine
d. Codeine
e. Propoxyphene

68: Akathisia, Parkinson-like syndrome, galactorrhea, and amenorrhea are side effects of perphenazine, caused by

a. Blockade of muscarinic receptors
b. Blockade of α-adrenergic receptors
c. Blockade of dopamine receptors
d. Supersensitivity of dopamine receptors
e. Stimulation of nicotinic receptors

69: Peripheral adverse effects of levodopa, including nausea, hypotension, and cardiac arrhythmias, can be diminished by including which of the following drugs in the therapy?

a. Amantadine
b. Bromocriptine
c. Carbidopa
d. Entacapone
e. Ropinirole

70: Which of the following is an antidepressant agent that selectively inhibits serotonin (5-HT) uptake with minimal effect on norepinephrine uptake?

a. Protriptyline
b. Maprotiline
c. Fluoxetine
d. Desipramine
e. Amoxapine

71: Which of the following inhalation anesthetics is most likely to produce hepatotoxicity?

a. Isoflurane
b. Enflurane
c. Methoxyflurane
d. Halothane
e. Nitrous oxide

72: Carbidopa is useful in the treatment of Parkinson's disease because it

a. Is a precursor of levodopa
b. Is a dopaminergic receptor agonist
c. Prevents peripheral biotransformation of L-dopa
d. Prevents a breakdown of dopamine
e. Promotes a decreased concentration of L-dopa in the nigrostriatum

73: Modest improvement in the memory of patients with Alzheimer's disease may occur with drugs that increase transmission at which of the following receptors?

a. Adrenergic
b. Cholinergic
c. Dopaminergic
d. GABAergic
e. Serotonergic

74: Which of the following is described as a competitive benzodiazepine receptor antagonist?

a. Ketamine
b. Chlordiazepoxide
c. Flumazenil
d. Midazolam
e. Triazolam

75: A 45-year-old man who has been injured in a car accident is brought into the emergency room. His blood alcohol level on admission is 275 mg/dL. Hospital records show a prior hospitalization for alcohol-related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal?

a. None b. Lorazepam c. Pentobarbital
d. Phenytoin e. Buspirone

76: The preferred treatment of status epilepticus is intravenous administration of

a. Chlorpromazine b. Diazepam c. Succinylcholine
d. Tranylcypromine e. Ethosuximide

77: Which of the following is a selective inhibitor of monoamine oxidase type B (MAO-B) and, therefore, useful in treating parkinsonism?

a. Bromocriptine b. Carbidopa c. Selegiline
d. Phenelzine e. Tranylcypromine

78: Halogenated anesthetics may produce malignant hyperthermia in:

a. Patients with poor renal function. b. Patients allergic to the anesthetic.
c. Pregnant women. d. Alcoholics.
e. Patients with a genetic defect in muscle calcium regulation.

79: Which one of the following is most likely to require administration of a muscle relaxant?

a. Ethyl ether b. Halothane c. Methoxyflurane
d. Benzodiazepines e. Nitrous oxide

80: A dopamine receptor agonist that is useful in the therapy of Parkinson's disease is

a. Selegiline b. Bromocriptine c. Apomorphine
d. Amantidine e. Belladonna

81: In addition to its use in the treatment of schizophrenia, chlorpromazine is effective

a. In reducing nausea and vomiting b. As an antihypertensive agent c. As an antihistaminic
d. In the treatment of depression e. For treating bipolar affective disorder

82: Haloperidol may best be characterized by which of the following statements?

a. It is classified as a phenothiazine b. It is a selective D_2 receptor agonist
c. Its mechanism of action is completely different from that of chlorpromazine d. It is more potent as an antipsychotic drug than is chlorpromazine
e. It produces a lower incidence of extrapyramidal reactions than does chlorpromazine

83: Phencyclidine may best be characterized by which of the following statements?

a. It has opioid activity b. Its mechanism of action is related to its anticholinergic properties
c. It can cause significant hallucinogenic activity d. It causes significant withdrawal symptoms
e. Treatment of overdose is with an opiate

84: In comparing the following neuroleptics, which is most likely to cause marked sedation?

a. Chlorpromazine b. Haloperidol c. Resperidone
d. Ziprasidone e. Sertindole

85: A drug that specifically enhances metabolically the activity of brain dopamine is

a. Benztropine b. Selegiline c. Trihexyphenidyl
d. Bromocriptine e. Chlorpromazine

86: Which of the following may cause nephrogenic diabetes insipidus?

a. Fluoxetine b. Haloperidol c. Lithium
d. Phenytoin e. Diazepam

87: A 36-year-old male with a bipolar disorder is treated with lithium. Among the following adverse effects, which is associated with lithium treatment?

a. Browning of the vision b. Hypothyroidism c. Agranulocytosis
d. Neuroleptic malignant syndrome e. Pseudodepression

88: A 40-year-old male with repetitive obsessive behavior that prevents him from carrying out simple tasks is treated with fluoxetine. How is fluoxetine classified?

a. As an MAO inhibitor (MAOI)
b. As a tricyclic nonselective amine reuptake inhibitor
c. As a heterocyclic nonselective amine reuptake inhibitor
d. As a selective serotonin reuptake inhibitor
e. As an α2-adrenergic receptor inhibitor
f. As a muscarinic receptor inhibitor

89: A patient with intractable itching would best respond to which of the following?

a. Chlorpromazine b. Pimozide c. Haloperidol
d. Risperidone e. Clozapine

90: Which of the following antipsychotics requires weekly blood counts?

a. Chlorpromazine b. Clozapine c. Haloperidol
d. Olanzapine e. Molindone

91: Which of the following is not associated with enhancement of the activity of γ-aminobutyric acid (GABA)

a. Chlordiazepoxide b. Phenobarbital c. Diazepam
d. Valproic acid e. Chlorpromazine

92: A 55-year-old teacher began to experience changes in mood. He was losing interest in his work and lacked the desire to play his daily tennis match. He was preoccupied with feelings of guilt, worthlessness, and hopelessness. In addition to the psychiatric symptoms, the patient complained of muscle aches throughout his body. Physical and laboratory tests were unremarkable. After 6 weeks of therapy with fluoxetine, the patient's symptoms resolved. However, the patient complains of sexual dysfunction. Which of the following drugs might be useful in this patient?

a. Fluvoxamine b. Sertraline c. Citalopram
d. Mirtazapine e. Lithium

93: A 26-year-old female with reactive depression complains of missing her period and having milk discharge from her breasts. She has no signs of pregnancy, including a negative pregnancy test. Which of the following might have caused these findings?

a. Fluvoxamine b. Amoxapine c. Fluoxetine
d. Mirtazapine e. Sertraline

94: A 20-year-old female with a history of grand mal seizures who is well controlled on seizure medication complains of losing her balance. Which of the following agents could account for this adverse effect?

a. Valproic acid b. Phenytoin c. Carbamazepine
d. Diazepam e. Phenylephrine

95: A 51-year-old woman with symptoms of major depression also has narrow-angle glaucoma. Which of the following antidepressants should be avoided in this patient?

a. Amitriptyline b. Sertraline c. Bupropion
d. Mirtazepine e. Fluvoxamine

96: At a follow-up visit one month after a 22-year-old male was newly diagnosed with schizophrenia and started on chlorpromazine, he has several complaints, listed below. Which of the following cannot be attributed to chlorpromazine?

a. Restless feeling b. Sexual dysfunction c. Urinary hesitancy
d. Vomiting

97: For each patient, select the drug of choice:

a. Midazolam b. Diazepam c. Alprazolam
d. Ethosuximide e. Oxazepam

I: A 38-year-old male with a 15-year history of grand mal seizures is brought to the ED (Emergency Department) with generalized tonic-clonic seizures that are unremitting.

a	b	c	d	e

II: A 16-year-old female is brought to the ED by her mother, who has observed that her daughter has abruptly experienced an impairment of consciousness associated with clonic jerking of the eyelids and staring into space lasting approximately 30 s.

a	b	c	d	e

98: A 20-year-old male with absence seizures is treated with ethosuximide. What is the principal mechanism of action of ethosuximide?

a. Sodium channel blockade
b. Increase in the frequency of the chloride channel opening
c. Increase in GABA
d. Calcium channel blockade
e. Increased potassium channel permeability
f. NMDA receptor blockade

99: A 30-year-old female with partial seizures is treated with vigabatrin. What is the principal mechanism of action of vigabatrin?

a. Sodium channel blockade
b. Increase in the frequency of the chloride channel opening
c. Increase in GABA
d. Calcium channel blockade

100: A 36-year-old man presents with symptoms of compulsive behavior. If anything is out of order, he feels that "work will not be accomplished effectively or efficiently." He realizes that his behavior is interfering with his ability to accomplish his daily tasks but cannot seem to stop himself. Which of the following drugs would be most helpful to this patient?

a. Imipramine b. Fluvoxamine c. Amitriptyline
d. Tranylcypromine e. Lithium

101: A pediatric patient treated for grand mal seizures develops abnormal values on liver function tests. Which of the following antiepileptic agents would cause this to occur?

a. Carbamezine b. Valproic acid c. Phenytoin
d. Phenobarbital e. Gabapentin

102: A 19-year-old female whose roommate is being treated for depression decides that she is also depressed and secretly takes her roommate's pills "as directed on the bottle" for several days. One night, she makes herself a snack of chicken liver paté and bleu cheese, accompanied by a glass of red wine. She soon develops headache, nausea, and palpitations. She goes to the ED, where her blood pressure is found to be 200/110 mmHg. What antidepressant did she take?

a. Sertraline b. Phenelzine c. Nortriptyline
d. Trazodone e. Fluoxetine

103: A 41-year-old female is seen in the psychiatric clinic for a follow-up appointment. She has been taking an antidepressant for three weeks with some improvement in mood. However, she complains of drowsiness, palpitations, dry mouth, and feeling faint on standing. Which antidepressant is she taking?

a. Amitriptyline b. Trazodone c. Fluoxetine
d. Venlafaxine e. Bupropion

104: A 36-year-old male unemployed dishwasher with no history of seizures presents with difficulty thinking coherently and claims that he is an astronaut. Following treatment, he suddenly has a grand mal seizure. Which neuroleptic agent was administered?

a. Haloperidol b. Fluphenazine c. Clozapine
d. Molindone e. Loxapine

105: A 31-year-old female is treated with an antipsychotic agent because of a recent history of spontaneously removing her clothing in public places and claiming that she hears voices telling her to do so. Her blood pressure is normally 130/70 mmHg. Since being treated with a drug, she has had several bouts of syncope. Orthostatic hypotension was noted on physical examination. Which drug most likely caused this?

a. Haloperidol b. Olanzapine c. Fluphenazine
d. Chlorpromazine e. Sertindole

106: Neural tube defects may occur with which of the following antiseizure drugs?

a. Ethosuximide b. Vigabratin c. Phenobarbital
d. Valproic acid e. Primidone

107: An adolescent male is newly diagnosed with schizophrenia. Which of the following neuroleptic agents may improve his apathy and blunted affect?

a. Chlorpromazine b. Fluphenazine c. Haloperidol
d. Risperidone e. Thioridazine

108: A young man is brought into the emergency room. He is unconscious, and he has pupillary constriction and depressed respiration. You note needle marks on his legs. You administer naltrexone, and he awakens. This agent was effective because:

a. The patient was suffering from an overdose of a benzodiazepine
b. Naltrexone antagonizes opiates at the receptor site
c. Naltrexone is a stimulant of the CNS
d. Naltrexone binds to the opioid and inactivates it
e. The was was suffering from an overdose of meperidine

109: Which of the following is an IV anesthetic with dissociative anesthesia?

a. Ketamine b. Etomidate c. Propofol
d. Innovar e. Thiopental

110: Memantine used in treatment of Alzheimer's disease due to antagonist effect at

a. NMDA receptors b. ACh receptors c. GABA receptors
d. Glycine receptors e. Dopamine receptors

Answers

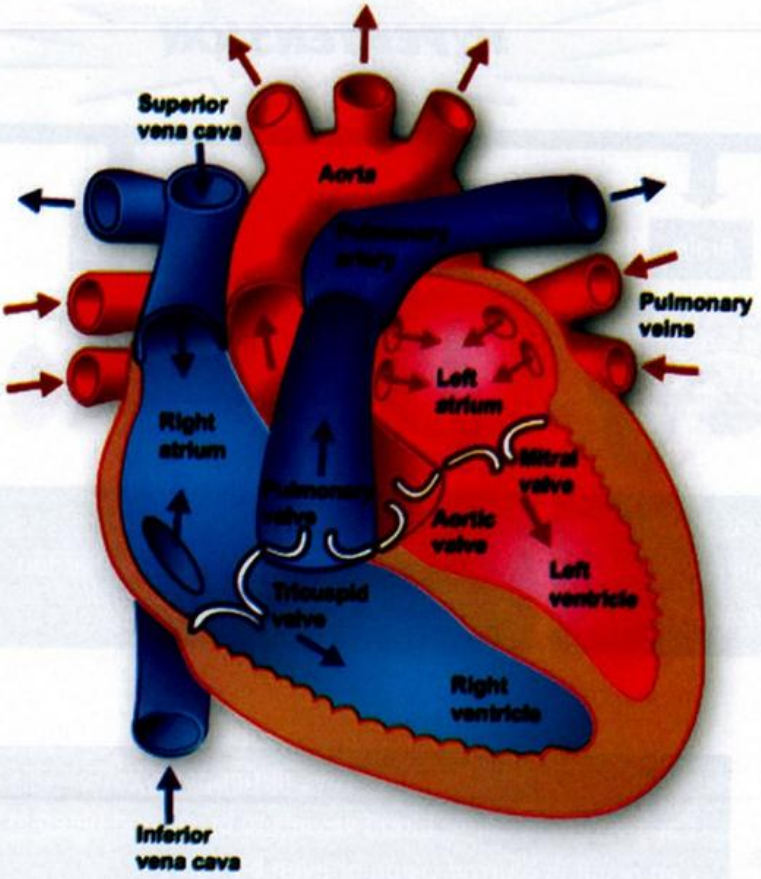
66	67	68	69	70	71	72	73	74	75
b	c	c	c	c	d	c	b	c	b
76	77	78	79	80	81	82	83	84	85
b	c	e	e	b	a	d	c	a	b
86	87	88	89	90	91	92	93	94	95
c	b	d	a	b	e	d	b	b	a
96	97	98	99	100	101	102	103	104	105
d	I: b, II: d	d	c	b	b	b	a	c	d
106	107	108	109	110					
d	d	b	a	a					

Questions and answers from (References):

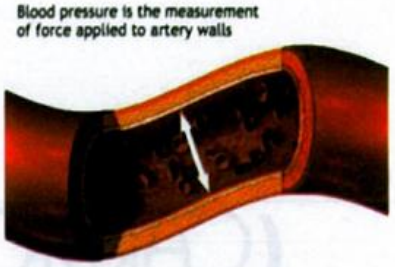
Basic and Clinical Pharmacology 12th edition, Katzung-Lange
Pharmacology 5th edition Lippincott Williams & Wilkins
Pharmacology 12th edition PreTest Self-Assessment and Review

CVS

(CARDIO VASCULAR SYSTEM)



Hypertension

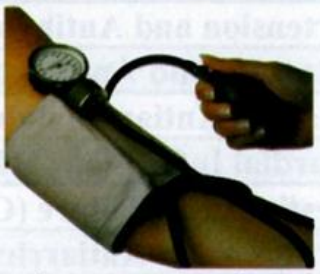


➢ Blood pressure (BP) control :-

- **BP** → Pressure generated when the heart Contrast against the resistance of the blood vessels.
- **Cardiac output (CO)**:
- **CO** = Stroke volume (**SV**) X Heart rate (**HR**)

BP = Cardiac output (CO) X Peripheral vascular resistance (PVR)

- Increase CO → Increase BP.
- Increase PVR → Increase BP.
- Increase CO and PVR → Increase BP.

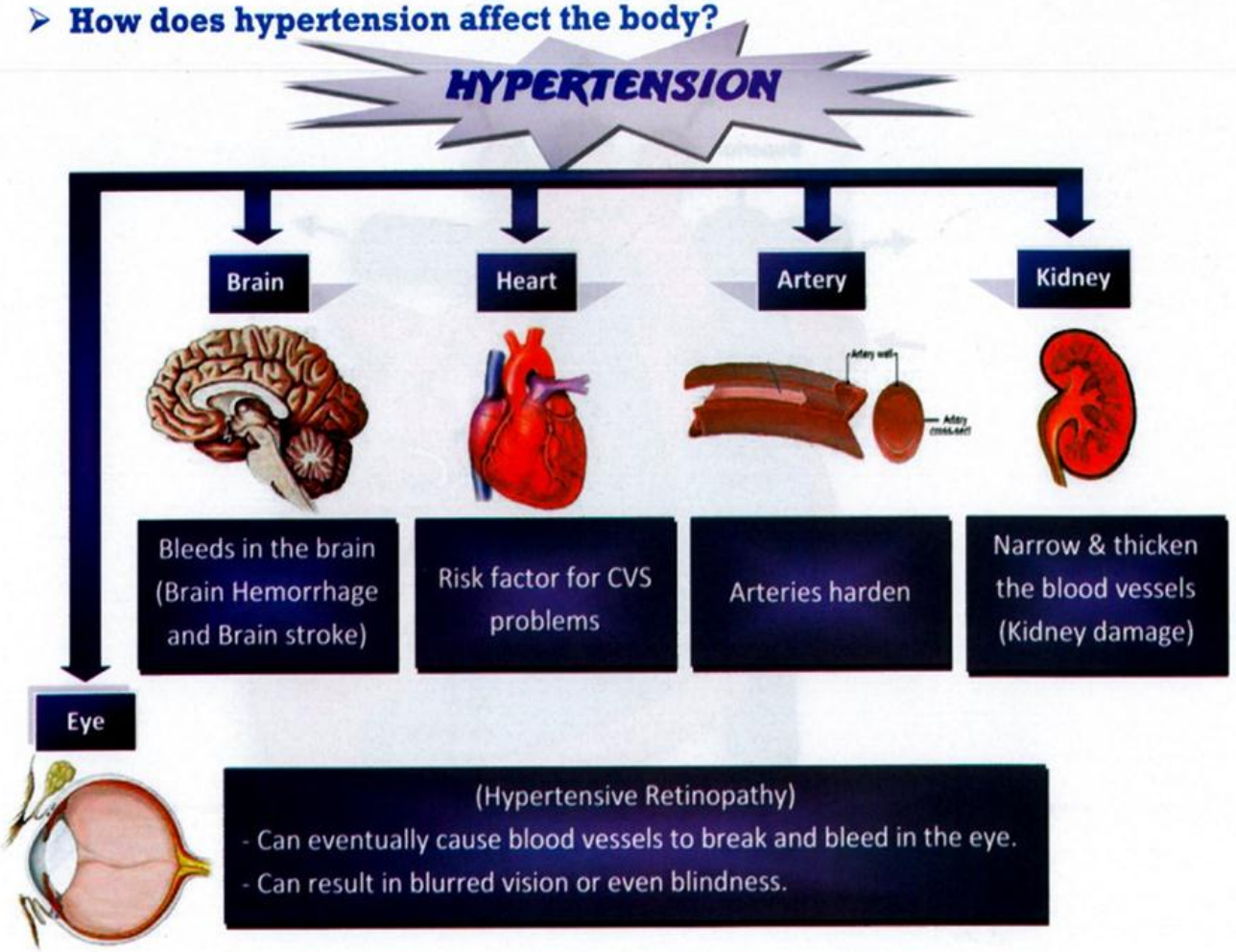


- **Drugs decrease BP :**
  - Drug decrease CO, PVR or decrease both.

➢ Definition of hypertension :-

- It is a condition in which both systolic and diastolic blood pressure rise above normal levels.

➢ How does hypertension affect the body?



➢ Normal resting blood pressure :-

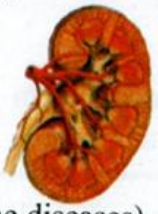
Blood pressure value	Male Age (year)			Female Age (year)		
	10-15	20-30	50-60	10-15	20-30	50-60
Systolic blood pressure SBP (mmHg)	100	120	134	84	120	130
Diastolic blood pressure DBP (mmHg)	60	80	84	40	74	84
Mean arterial pressure MAP (mmHg)	73	93	97	55	88	92

➢ Classification of hypertension based on blood pressure:-

Category	SP	DP	Follow-up
Optimal	Under 120	Under 80	Recheck in 2 years.
Normal	Under 130	Under 85	Recheck in 2 years.
High-normal (Pre-Hypertensive)	130-139	85-89	Recheck in 1 year.
Stage 1	140-159	90-99	Confirm within 2 months.
Stage 2	160-179	100-109	See your healthcare provider within a month.
Stage 3	180-209	110-119	See your healthcare provider immediately.
Stage 4	210 or over	120 or over	Go to the intensive care unit immediately.

➢ Classification of hypertension based on Causes :-

- **Essential hypertension (Primary hypertension or Idiopathic) hypertension :**
  - The majority of cases about 95%.
  - No specific medical causes.
  - Unknown etiology but some environmental factors may interfere e.g. smoking, obesity, stressful lifestyle, high dietary intake of sodium, family story and alcohol intake.
  - It occurs more often among middle aged males than among middle aged females.
- **Secondary (Inessential) hypertension :**
  - Few cases about 5%.
  - Result from →
    - Hormonal disturbances (Endocrine diseases)
    - Kidney disease
    - Medical causes



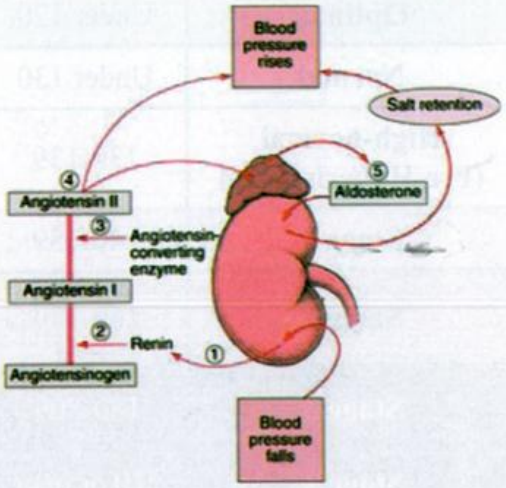
➢ Hypertension risk factors :-

- **Risk factors that can be controlled are :**
  - High cholesterol level
  - Tobacco use (Smoking)
  - Diabetes mellitus
  - Overweight (obesity)
  - Physical inactivity
  - High salt intake
  - Coarctation of the aorta
  - Sleep apnea

- **Risk factors beyond our control are :**
  - Age
  - Family history of heart disease

➢ Regulation of Blood Pressure :-

- **Endocrine Factors**
  - Renin, Angiotensin, ADH, Aldosterone
- **Neural Factors**
  - Sympathetic & Parasympathetic
- **Blood Volume**
  - Sodium, Mineralocorticoids
- **Cardiac Factors**
  - Heart rate & Contractility



➢ Causes of hypertension :-

Nature causes	Chemical causes
- Salt sensitivity - Insulin resistance - Sleep apnea - Genetics - Stressful situations, obesity, smoking and other lifestyle - Renal hypertension - Hypercalcemia - **Endocrine causes :** o Primary hyperaldosteronism o Pheochromocytoma o Hyperthyroidism o Cushing's syndrome (high levels of cortisol in the blood)	- Salt - Alcohol - Oral contraceptives - NSAIDs - Glycyrrhiza glabra (Liquorice) - Decongestants - Antidepressants - Sympathomimetics - Many industrial chemical - Corticosteroids - Ergotamine alkaloids - Cyclosporine - Cocaine - Caffeine

➢ Treatment of hypertension :-

Lifestyle modification	Medications (Antihypertensive drugs)
- DASH eating plane - Weight loss - Regular exercise - Quite smoking - Dietary sodium (salt) - Reduction of environmental stressors 	- Diuretics - β-blockers - ACE Inhibitors (ACEIs) - Angiotensin receptor blockers - Renin inhibitors - α-blockers - Calcium channel blockers - Centrally-acting sympathetic inhibitors - Peripherally-acting sympathetic inhibitors - Ganglionic blockers - Vasodilators - Antihypertensive of natural sources

➢ Dietary Approaches to Stop Hypertension (DASH) eating plane :-

- **Is a diet that is low in:**
  - Saturated fat, Cholesterol and Total fat.
- **It also includes:**
  - Fruits, Vegetables, Grain products, Fish.
- **It encourages fewer servings of:**
  - Red meat, Sweets and Sugar.
- **It is rich in:**
  - Magnesium, Potassium, Calcium, As well as Protein and fiber.

➢ Analysis needed to diagnose Hypertension :-

- **Complete Blood Count (CBC)**
- **Erythrocyte sedimentation rate (ESR)**
- **Plasma electrolytes**
- **Blood glucose**
- **Cholesterol**
- **Urea and Creatinine**
- **Urine analysis**
- **Chest X-ray**
- **Examination of eyes**

Antihypertensive drugs

1 – Diuretics

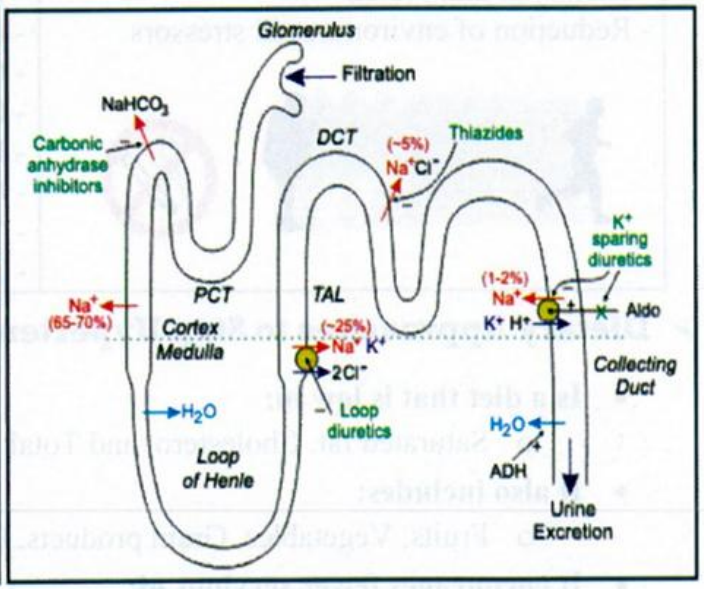
➢ Information :-

- Reduction in blood volume by facilitates sodium and water excretion.

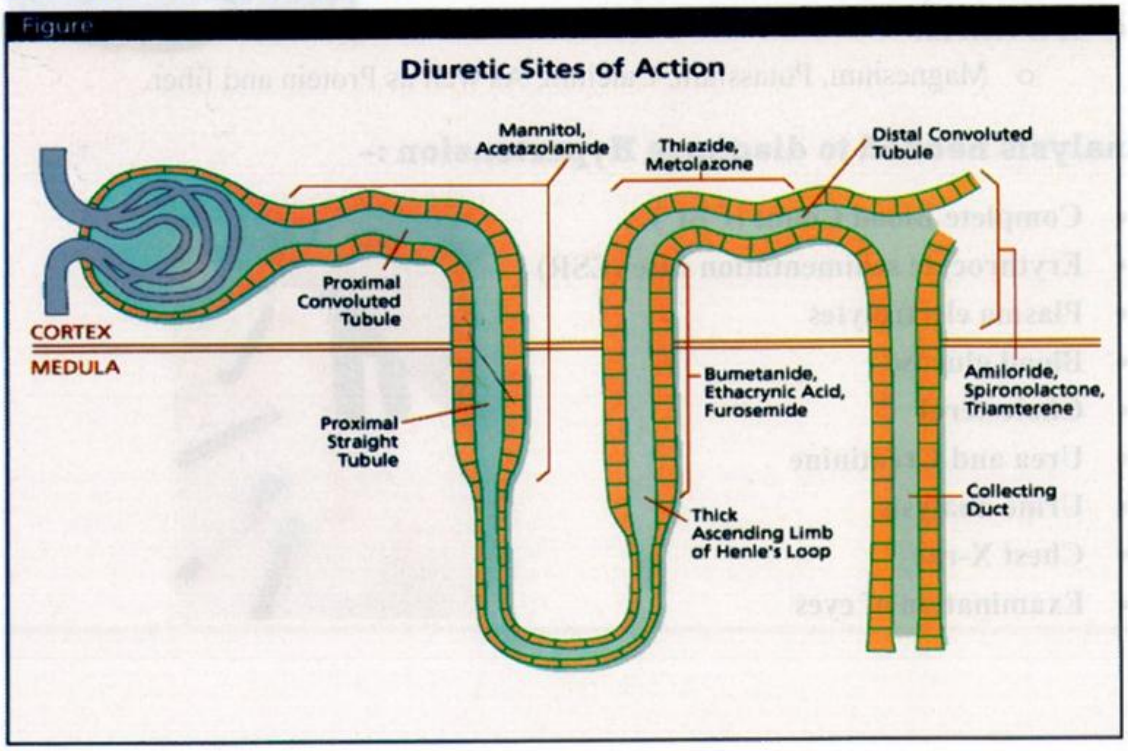
➢ Classification of diuretics :-

Extra-Renal (Pre-renal)
- Water and Ethyl alcohol (↓ADH).
- Digitalis only in Heart failure.
- Albumin only in Hypoalbuminemia.
- Dobutamine and Dopamine.
- Methylxanthines e.g. Theophylline.
Renal
- K^+ Sparing diuretics
- Thiazide (Low ceiling)
- Loop diuretics (High Ceiling)
- Carbonic anhydrase inhibitors e.g. Acetazolamide
- Osmotic diuretics e.g. Mannitol
- Acidifying diuretics e.g. NH4Cl

➢ Advanced Mechanism of Diuretics :-



➢ Diuretic sites of action :-



A- Thiazides (Moderate Efficacy)

Hydrochlorothiazide (Hydretic®)

Mechanism of action	- Decrease BP by increasing sodium and water excretion by reducing reabsorption of sodium and chloride at the **early (proximal) part of the distal convoluted tubule** of the kidney. - Resulting in decrease extracellular volume, cardiac output and renal blood flow.
Therapeutic uses	- Thiazide diuretics decrease blood pressure. - They are useful in treatment of black and elderly patients. - They are not effective in patients with inadequate kidney function.

Side effects	Contraindication
* **Hypokalemia** - Hypercalcaemia - Hyperuricemia - Hyperlipidemia - Hyperglycemia - Hypersensitivity (Allergy) - Hypomagnesemia - Hyponatremia - GIT Disturbances - Fetotoxic	- Digitalis toxicity ($\downarrow K^+$ and $\uparrow Ca^{2+}$) - Hypokalemia - Advanced liver disease - Advanced kidney disease - Arrhythmia - Diabetes mellitus (Hyperglycemia) - Gout (Hyperuricemia) - Atherosclerosis (Hyperlipidemia) - Allergy - Pregnancy (Fetotoxic)

Drug interactions	- Lithium (Decrease its renal excretion), Digitalis (Increase toxcity), NSAIDs (Decrease its diuretic effect) and Oral drugs used for diabetes.

Indapamide (Natrilix®)

- Is a new thiazide diuretic (have a unique mechanism of action). Long acting (Once daily).
- Combining diuretic effects with a direct vasodilatation (Ca^{2+} channels blocker) effect.

B- Loop Diuretics (High Efficacy or High Ceiling)

Bumetanide (Burinex®) | Furosemide (Lasix®) | Torsemide (Examide®)

Mechanism of action	- Decrease BP by increasing sodium and water excretion by reducing reabsorption of sodium, chloride and potassium at the **thick ascending limb of loop of Henle** of the kidney. - Decrease renal vascular resistance and increase renal blood flow.		
Therapeutic uses	- Powerful diuretics (in emergency in severe cases of Hypertension). - Useful in edema caused by → Congestive Heart Failure (CHF), Liver cirrhosis and Nephrotic syndrome. - Acute renal failure (due to increase renal blood flow).		
Side effects	* **Hypokalemia** - Hypocalcaemia - Hypomagnesemia - Hyponatremia	- Hyperuricemia - Hyperglycemia - Hyperlipidemia - Fetotoxic	- **Ototoxicity** (Deafness) - Hypersensitivity (allergy) - Risk of dehydration - GIT Disturbances
Drug interactions	- Aminoglycosides (Ototoxicity), Warfarin (Displacement from PP), Cephalosporins (Nephrotoxicity), Lithium, Digitalis and NSAIDs.		

C- Potassium (K^+) Sparing (Retaining or Conserving) Diuretics
(Low Efficacy or Low Ceiling)

1- Aldosterone Antagonists

	Spironolactone (Aldactone®)	Eplerenone (Eplorefix®)
Mechanism of action	- Aldosterone receptor antagonist at the **late distal convoluted tubule and collecting ducts** → Increase Na^+ and Ca^{2+} excretion and decrease K^+ and H^+ excretion. - Spironolactone has antiandrogenic effects (block androgen receptor).	
Therapeutic uses	- Hyperaldosteronism. - Edema caused by CHF, Liver cirrhosis and Nephrotic syndrome. - Essential Hypertension. - In combination with thiazide or loop diuretics → - Synergistic their diuretic effect. - Correct their hypokalemia. **Spironolactone** 25mg + **Hydrochlorothiazide** 25 mg (Aldactazide®) **Spironolactone** 50mg or 100mg + **Furosemide** 20 mg (Lasilactone®)	
Spironolactone play a role in treatment of hirsutism, androgenic alopecia and acne in females		
Side effects	* **Hyperkalemia** - CNS side effects (Confusion, Drowsiness and Headache) - Allergy and Metabolic acidosis (due to Increase H^+ in blood) - Hormones (In male cause Gynecomastia and Impotence - In female cause Menstrual disturbance).	

2- Non-aldosterone Antagonists

	Amiloride (Midamor®)	Triamterene (Dyrenium®)
Mechanism of action	- Increase Na^+ excretion due to inhibition of Na^+/K^+ exchange and decrease Ca^{2+} and H^+ excretion at the **late distal convoluted tubule and collecting ducts**.	
Therapeutic uses	- Usually used in combination with thiazide or loop diuretics → - Synergistic their diuretic effect. - Correct their hypokalemia. **Amiloride** 5mg + **Hydrochlorothiazide** 50 mg (Moduretic®) **Xipamide** 10mg + **Triamterene** 30mg (Epitens®) → Xipamide → Like the structurally related thiazide diuretics.	
Side effects	* **Hyperkalemia** - GIT Disturbances - Allergy - Metabolic acidosis (Increase H^+ in blood)	

➢ **N.B:-**

- Thiazides or loop diuretics when used only. Patient must take K^+ supplements →

  e.g. - **Potassium Chloride** 300 mg (K-Chlor®)

  - **Potassium Gluconate** 600mg (Slow-K®)

2 – β-Adrenoceptor blocking agents

Propranolol (Inderal®)	Non-selective β-adrenoceptor antagonist	
Nadolol (Corgard®)		
Timolol (Timogel®)		Used in glaucoma
Sotalol (Betacor®)		
Metoprolol (Betaloc®)	Selective β_1-adrenoceptor antagonist	
Atenolol (Atelol®)		
Esmolol (Brevibloc®)		
Nebivolol (Nebilet®)		Stimulate releasing of NO
Betaxolol (Betoptic®)		Used in glaucoma
Bisoprolol (Concor®)		
Pindolol (Visken®)	β-adrenoceptor antagonist with a partial agonist activity	- Not pure blockers. - Weakly stimulate both β_1 and β_2 receptors.
Penbutolol (Levatol®)		
Acebutolol (Sectral®)		
Celiprolol (Celectol®)		- Less bronchoconstriction.
Labetalol (Labipress®)	Mixed adrenoceptor antagonist	- In Pheochromocytoma
Carvedilol (Carlol V®)		- Useful in CHF

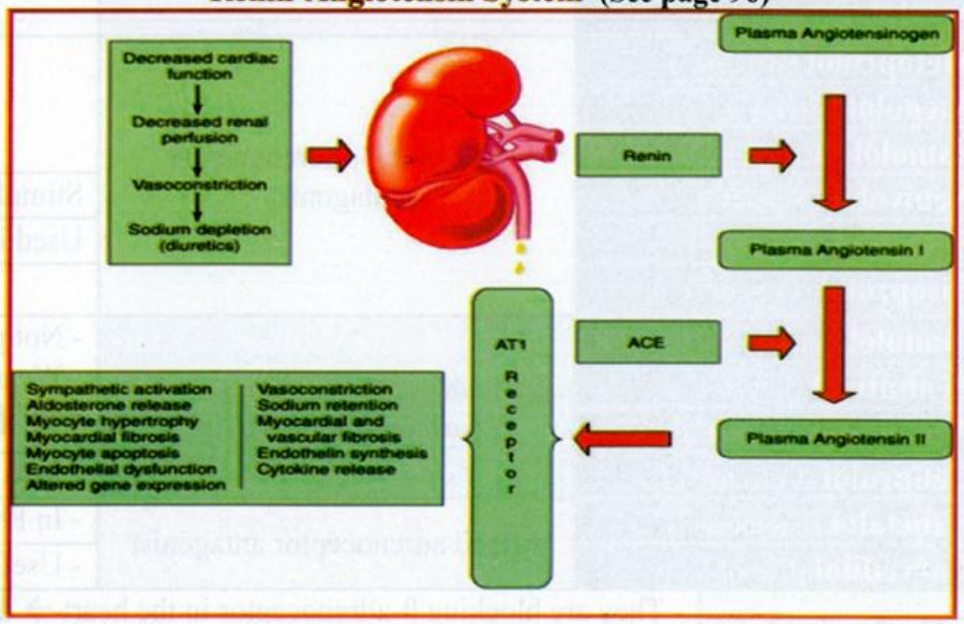
Mechanism of action	- They are blocking β-adrenoceptor in the heart → decrease all heart properties → decrease cardiac output → decrease BP. - They may decrease sympathetic outflow from the CNS.
Uses	- Hypertension, congestive heart failure, arrhythmia and angina.
Side effects	**1:** Bronchoconstriction. **2:** Hypotension. **3:** Bradycardia and heart block. **4:** Heart failure and physical fatigue due to decrease cardiac output. **5:** Increase incidence of hypoglycaemic episodes in type I diabetics. **6:** Cold extremities (symptoms of peripheral vascular disease) due to all adrenaline and nor-adrenaline act only in α receptors especially α1 →VC. **7:** Sexual dysfunction (Decrease libido and Impotence) **8:** CNS effect → cross BBB → sleep disturbance. **9:** Increase plasma conc. of LDL → Atherosclerosis → Angina **10: Sudden Stop β-blockers** → Up-regulation of adrenoceptors → cardiac arrhythmia and hypertension (May cause sudden death).
Contraindication	**1:** Bronchial asthma. **2:** Hypotension. **3:** Heart Failure (Avoid large dose) **4:** Partial heart blocker. **5:** Peripheral vascular diseases (e.g. Raynaud's disease)

3 – Angiotensin converting enzyme inhibitors (ACEIs)

Captopril (Capoten®)	**Fosinopril** (Monopril®)	**Enalapril** (Renitec®)
Benazepril (Cibacen®)	**Lisinopril** (Zestril®)	**Perindopril** (Coversyl®)
Cilazapril (Zapritens®)	**Ramipril** (Tritace®)	**Imidapril** (Tanatril®)

Mechanism of action

Renin-Angiotensin System (See page 96)



- ACE inhibitors block the conversion of angiotensin I to angiotensin II.
  1 : VD and decrease BP
  2 : Decrease Sympathetic outflow
  3 : Decrease Aldosterone release → Decrease Na^+ and H_2O retention
- ACE inhibitors also inhibit the degradation of other substances e.g. Bradykinin (Inflammatory mediator) → accumulation of bradykinin → Dry persistence cough.

Adverse effects

- **Dry persistence cough** and **angioedema** due to increased levels of Bradykinin (treated by NSAIDs).
- **Hyperkalemia** (Due to decrease aldosterone secretion).
- **Renal impairment**
- **Fetopathic potential** (Teratogenicity) → Decrease Organogenesis of lung and fetal abnormalities and may cause fetal death.

Drug interactions

1: K^+ sparing diuretics or K^+ supplements → Hyperkalemia.
2: NSAIDs → due to decrease Prostaglandins (PGs)
- Decrease renin secretion
- Hyperkalemia
- Blocking bradykinin

→ Decrease hypotensive effect

3: Angiotensin receptor blockers (ARBs)
4: Renin inhibitors e.g. **Aliskiren**

Contraindication

- Pregnancy, lactation, Chronic obstructive pulmonary disease (COPD) and Impaired renal function.

4 – Angiotensin II receptor blockers

Losartan (CozAAr®)	Irbesartan (Aprovel®)	Valsartan (Diovan®)
Candesartan (Atacand®)	Eprosartan (Teveten®)	
Telmisartan (Micardis®)	Olmesartan (Erastapex®)	

Mechanism	- These drugs block **AT_1** receptor → Prevents Angiotensin II effects
Adverse effects	- No or less cough and angioedema.
Contraindication	- Pregnancy, lactation and COPD (Less than ACE inhibitors)

5 – Renin inhibitors

Aliskiren (Tekturna®)	
Mechanism of action	- Directly inhibits Renin → Block conversion of plasma angiotensinogen to angiotensin I.
Adverse effects	- Includes cough and angioedema, hyperkalemia and in high dose cause diarrhea.

6 – α-Adrenoceptor blocking agents

Mechanism of action	- **VD** due to **α_1** receptor blocking → decrease peripheral resistance → decrease blood pressure.
Non-selective α-adrenoceptor antagonist	
Tolazoline (Priscoline®) | **Phentolamine** (Rogitine®) | **Phenoxybenzamine** (Dibenzyline®)	
Uses	- Hypertension in patients with pheochromocytoma - Raynaud's phenomenon (peripheral vascular disease) - Impotence (male erectile dysfunction)→ **VD** →Increase erection - Urinary retention associated with benign prostatic hyperplasia (BPH)
Adverse effects	- Postural hypotension, Failure of ejaculation, Reflex tachycardia and Nasal congestion
Selective α_1-adrenoceptor antagonist used in hypertension	
Prazosin (Minipress®)	
Uses	- Primary hypertension - CHF due to decreases preload and afterload - Urinary retention associated with BPH.
Side effects	- **Initial Syncopal Attack** (First dose phenomenon) → ***Severe postural hypotension*** → to overcome that the first dose must be minimized and giving at bed time. - Nasal congestion. - Long use in male → Failure of ejaculation. - Na^+ and water retention used with diuretic drugs.

7 - Calcium channel blockers (CCB)

Information	- Ca^{2+} channels are present in heart, blood vessels & smooth muscle. - Blocking Ca^{2+} channels in the heart → Decrease CO. - Blocking Ca^{2+} channels in the blood vessels → VD → Decrease resistance

Classification of calcium channel blockers (CCB)

Phenylalkylamines

Verapamil (Isoptin®)

- Selective blocker in calcium-channel on cardiac muscle cells
- They have minimal effect on blood vessels (VD)

Dihydropyridines

Nifedipine (Epilat®)	**Amlodipine** (Norvasc®)	**Felodipine** (Plendil®)
Nicardipine (Pelcard®)	**Nimodipine** (Nimotop®)	**Lacidipine** (Lacipil®)

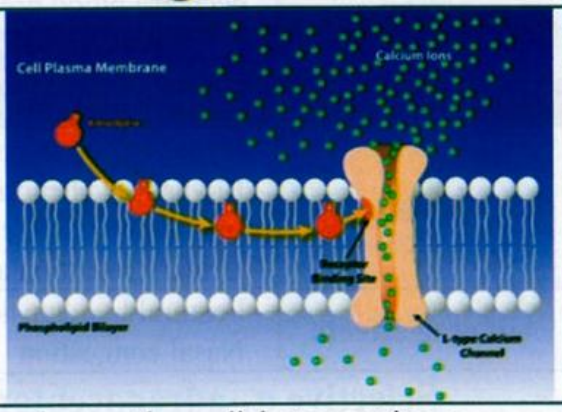
Lercanidipine (CareDipine®)

- Selective blocker in calcium-channel on blood vessels → Cause VD → Decrease Resistance → decrease blood pressure.

Benzothiazepines

Diltiazem (Altiazem®)

- Having both blocker effects on cardiac and vascular smooth muscle calcium-channels.

Mechanism of action	- Block voltage-dependent L-type Ca^{2+} channels present in heart, blood vessels and smooth muscle. - Decrease Ca^{2+} influx into cardiac muscle and blood vessels cause → Cardiac inhibition and VD	
Uses	- Hypertensive patients who also have asthma, diabetes, angina or peripheral vascular disease. - All types of angina. - Acute myocardial infarction - Arrhythmia especially **Verapamil**	
Side effects	- Dizziness, headache, fatigue - Constipation occurs with **Verapamil** - A-V block & heart failure only with **Verapamil** and **Diltiazem** - Reflex Tachycardia with **Nifedipine** (due to VD)	

CCB may called CEB (Ca^{2+} Entry Blocker)

8 – Centrally-acting sympathetic inhibitors

Selective α_2-adrenoceptor agonists	
Clonidine (Catapress®)	
Mechanism of action	**1) Stimulate presynaptic α_2 receptors** → This binding decreases presynaptic Ca^{2+} levels, and inhibits the release of NE → lowering blood pressure. **2) Stimulate central α_2 receptors** → Decrease sympathetic out flow → decreases NE and renin → decrease CO and resistance → lowering blood pressure. **3) Stimulate I_1 (Imidazoline) receptor** → Sympatho-inhibitory action →lower blood pressure.
Uses	- Hypertension - Treatment of withdrawal syndrome in opiates and alcoholics - Treatment of attention deficit hyperactivity disorder (ADHD) - Can be used for migraine
Side effects	- **CNS effect** → sedation, depression and drowsiness. - Constipation. - **Sudden Stop** of clonidine → cause hypertensive crisis (treated by **α_1** and **β** blocker). (Must Stop clonidine **slowly**)
α-Methyldopa (Aldomet®)	
Mechanism of action	**Methyldopa has a dual mechanism of action** **1)** It passes BBB and converting into α-Methyl-norepinephrine (false transmitter) by dopamine beta-hydroxylase (DBH) enzyme → The false transmitter is central α_2-agonist → decrease sympathetic out flow → decreases NE → decrease BP. **2)** It is a competitive inhibitor of dopa decarboxylase enzyme → which converts L-dopa into dopamine. (Dopamine is a precursor for norepinephrine and subsequently epinephrine).
Uses	- Hypertension in **pregnancy**.
Adverse effects	**→ Sympathetic blocked:** - Postural hypotension, failure of ejaculation and nasal congestion. **→ CNS manifestation:** - Sedation, drowsiness, depression and Parkinsonian symptoms. - **Increase prolactin hormone** (Due to inhibition of dopaminergic mechanism → Causing gynecomastia and galactorrhea. - **Allergy** → Bone marrow depression and hepatotoxicity.
Drugs act only on imidazoline receptors (Agonists)	
Rilmenidine (Hyperium®)	**Moxonidine** (Cynt®)
Mechanism of action	- Shows greater selectivity for imidazoline receptors than central α_2 receptors.

9 – Peripherally-acting sympathetic inhibitors

Guanethidine (Ismelin®)	
Mechanism of action	- Act by blocking the release of stored NE → gradual decrease blood pressure and heart rate.
Uses	- Rapid control of blood pressure in a hypertensive emergency.
Adverse effects	- Postural hypotension, Failure of ejaculation and Nasal congestion.
Reserpine (Hypoten®)	
Mechanism of action	- Inhibition of the uptake of NE into vesicle → NE not stored→Increase intra-neuronal degradation of NE by MAO. - This action occurs both centrally and peripherally.
Uses	- Treatment of mild hypertensive

10 – Ganglionic blockers

Trimethaphan (Arfonad®)	Mecamylamine (Inversine®)
- Mono sulfonium (S^+) (Don't pass BBB)	- Secondary amine (Pass BBB)
- Ultra short acting	- Longer action
- Not given orally (IV)	- Given orally
- Treatment of emergency hypertension	- Moderately hypertension
- Histamine release → Flushing & dizziness	- Not histamine release

11 – Direct vasodilators

- Direct vasodilator → Decrease peripheral resistance → Decrease Blood pressure.

Veno-Dilators → Nitrates (See Angina)

Arterio-dilators

- Useful in hypertension and heart failure.

Hydralazine (Apresoline®)	Minoxidil (Rogaine®)
- **Adverse effects include** → headache, flushing, Hypersensitivity reactions (Rheumatoid arthritis and lupus erithematosus like syndrome), Peripheral neuritis and GIT upset	- **Adverse effects include** → Tachycardia (C/I in angina and arrhythmia) and hypertrichosis.
	- Used locally in alopecia for long period.

Mixed Dilators

Sodium Nitroprusside (Nipride®)	
Information	- Given by IV infusion (Not stop suddenly) - Onset of action → ½ minute and Duration of action → 3 minute - Not given orally (Toxic due to hydrolysis into cyanide)
Uses	- Emergency Hypertension - Emergency heart failure

12 – Antihypertensive of natural sources

Hibiscus tea (*Hibiscus sabdariffa*)

- Hibiscus tea is an infusion made from crimson or deep magenta-coloured calyces (sepals) of the ***Hibiscus sabdariffa*** flower.
- Hibiscus flowers contain anthocyanins, which are believed to be the active antihypertensive compounds, acting as ACE inhibitors.
- Hibiscus has a tendency to reduce serum sodium (Na^+) concentrations without modifying potassium (K^+) levels.
- There is no difference between drinking hibiscus cold or hot.

Co-Enzyme Q_{10}

- Present in most food
- coenzyme Q_{10} has the potential in hypertensive patients to lower systolic blood pressure by up to 17 mm Hg and diastolic blood pressure by up to 10 mm Hg without significant side-effects.

➢ Hypertensive urgency and Hypertensive Emergency :-

Hypertensive Urgency	Hypertensive Emergency
- Managed by using oral antihypertensive agents	- Managed by using IV antihypertensive agents
- Treatment is initiated with very low doses of oral agents using incremental doses as needed and avoiding large starting doses that may result in excessive blood pressure reduction.	- Reducing the mean arterial pressure by 10% during the first hour and an additional 15% within the next 2 to 3 hours has been recommended.
- The initial goal is to reduce blood pressure to 160/110 mm Hg over several hours to days. - Mean arterial pressure (MAP) should be reduced by no more than 25% within the first 24 hours	**Specific agents (according to 1st choice)** - Sodium Nitroprusside - Fenoldopam (D_1 receptor agonist) - Nitroglycerin - Enalaprilat IV (active metabolite of enalapril) - Hydralazine - Nicardipine - Esmolol - Labetalol (IV) - Phentolamine
Specific agents (according to 1st choice) - ACE inhibitors - Calcium channel blocker (Nicardipine) - Labetalol (Oral) - Clonidine - Nifedipine	

➢ Drug of choice in hypertensive patients :-

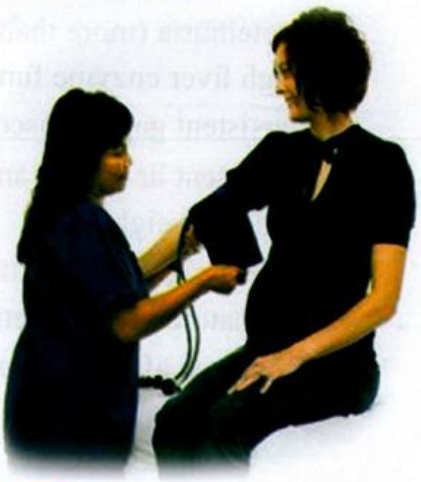
- Diuretics
- β-blockers
- ACE Inhibitors
- AT_1 blockers
- Renin inhibitors
- α-blockers

- Ca^{2+} channel blockers
- Centrally-acting sympathetic inhibitors
- Peripherally-acting sympathetic inhibitors
- Vasodilators

Hypertensive patient with	Drug of choice	Drug to avoid
- African heritage **- Elderly**	- Thiazide diuretics - Calcium channel blockers	
- Pregnancy	- α-Methyldopa - Labetalol - Calcium Channel blockers	- ACE inhibitors - AT_1 receptor blockers
- Angina pectoris	- β-blocker - Calcium Channel blockers	- Hydralazine - Minoxidil
- Asthma **- Coronary obstructive pulmonary disease (COPD)**	- Calcium channel blockers	- β-blockers - ACE inhibitors
- Benign prostatic hyperplasia	- α-blockers	
- Depression	- Calcium channel blockers - ACE inhibitors	- Centrally acting α-adrenoceptor agonist - β-blockers - Reserpine
- Diabetes mellitus	- ACE inhibitors - Calcium channel blockers - AT_1 receptor blockers	
- Gout		Diuretics
- Heart failure	- Diuretics - ACE inhibitors	- β-blockers - Calcium channel blockers
- Hyperlipidemia	- Calcium channel blockers - ACE inhibitors - α-blocker	- β-blockers - Diuretics
- Migraine	- β-blockers - Calcium channel blockers	
- Myocardial infarction	- ACE inhibitors - β-blockers	
- Osteoporosis	- Thiazide diuretics - Spironolactone	- Loop diuretics
- Peripheral vascular disease	- α-blockers - ACE inhibitors	- β-blockers
- Renal Diseases	- Loop diuretics	- Thiazide diuretics

Hypertension during pregnancy

➢ Background:-



- Hypertension can develop during pregnancy or can be pre-existing.
- Although many pregnant women with high blood pressure have healthy babies without serious problems.
- High blood pressure can be dangerous for both the mother and the fetus.
- Women with pre-existing high blood pressure are more likely to have certain complications during pregnancy that those with normal blood pressure.

➢ What are the effects of hypertension in pregnancy?

- The effects of high blood pressure range from mild to severe.
- High blood pressure can harm the mother's kidneys and other organs, and it can cause low birth weight and early delivery.
- In the most serious cases, the mother develops "toxemia of pregnancy" which can threaten the lives of both the mother and the fetus.

➢ Types of Hypertension during pregnancy :-

1 - Gestational hypertension

➢ Characters:-

- Normal BP before marriage
- Confirmed in 20th week of pregnancy
- More than or equal 140/90 mm Hg
- **No proteinuria**
- Gastric discomfort
- Resolved after 12th week of labor

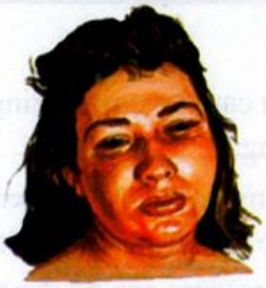
2- Pre-eclampsia

➢ Mild Pre-eclampsia :

- Confirmed in 20th week of pregnancy
- **Proteinuria** (more than or equal 300 mg/day)
- Thrombocytopenia
- Gastric discomfort
- Resolved after 12th week of labor

➢ Sever Pre-eclampsia:

- Confirmed in 20th week of pregnancy
- Proteinuria (more than or equal 2-5 g/day)
- High liver enzyme functions (AST-ALT)
- Persistent gastric discomfort
- Persistent headache and blurred vision
- Sudden weight gain
- Swelling (edema) in the face and hands
- Premature labor or fetus mental retardation
- Resolved after 12th week of labor



Edema in the face

Weight gain

3- Eclampsia

➢ Characters:-

- Sever form of preeclampsia
- Associated with seizure (Generalized tonic-clonic seizures)
- High proteinuria > 5 g/day
- Persistent gastric discomfort
- High liver enzyme functions (AST-ALT)
- Toxemic changes during eclampsia may suffer fetal death.
- Placental bleeding and placental abruption may occur.

4- Chronic hypertension

➢ Characters:-

- Hypertension before marriage
- Not resolved after labor
- Persistent after 12th week of labor
- **Causes** e.g. Obesity, Endocrine disorders and kidney disease

5- Superimposed (Chronic HT + Eclampsia)

➢ Characters:-

- Hypertension before marriage
- Sudden increase in proteinuria, BP and decrease in Platelet count
- Mental retardation and growth restriction may occur
- Placental bleeding and placental abruption may occur

Treatment of Hypertension in pregnancy

➢ Lifestyle Modification :-

- Salt restriction
- Low dose aspirin reduce the incidence of preeclampsia
- Other lifestyle modification

➢ FDA classified drug in pregnancy to 5 categories

A	Most safe
B	Safe
C	Animals adverse effects in fetus
D	Human fetal risk based on marketing experience
X	Fetal risk in animals and humans

➢ Drugs of choice :-

1: α-Methyldopa (Aldomet®)
- Centrally acting antihypertensive agent widely considered the first-line agent for treatment of hypertension during pregnancy (Category B). - Dose (250 mg – 3 g per day)
2: Labetalol (Labipress®)
- Unlike other beta-blockers - Category C
3: Ca^{2+} Channel blockers
- Category C
4: Diuretics
- With caution (Category C)
5: Vasodilators
- Category C

➢ Treatment of Eclampsia seizures (Anticonvulsant) :-

Magnesium sulfate	
- Dose:4-6 g IV load, followed by 2-3 g/h to maintain levels 4-8 mg/dL - Category: A	
Phenytoin (Epanutin®)	- Category C (Not used)

➢ Drugs to avoid during pregnancy

- ACE inhibitors
- AT_1 receptor blockers

Hypotension

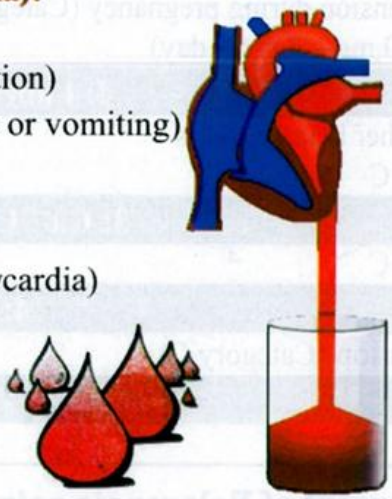
➢ Hypotension (Low blood pressure) :-

- The force of blood pushing by the heart against the walls of the arteries lower than normal
- Hypotension is generally considered as systolic blood pressure less than 90 mm Hg or diastolic less than 60 mm Hg.

➢ Symptoms :-

- Cardinal symptom of hypotension is lightheadedness or dizziness.
- Fainting (syncope)
- Blurred vision
- Headache
- Rapid and short breathing
- Fatigue

➢ Conditions that can cause low blood pressure :-



- **Reduced blood volume (Hypovolemia):**
  - Hemorrhage (blood loss)
  - Insufficient fluid intake (starvation)
  - Excessive fluid losses (diarrhea or vomiting)
  - Excessive use of diuretics
- **Decreased cardiac output:**
  - Extremely low heart rate (bradycardia)
  - Heart failure
  - Heart valve problems
  - Beta blockers
- **Excessive vasodilation**
  - Decrease sympathetic outflow or Increase parasympathetic activity
  - Severe infection (septicemia)
  - Vasodilator medications such as Nitrate, Ca^{2+} channels blockers and ACEIs
- **Endocrine problems**
  - Thyroid hormone disturbances
  - Adrenal insufficiency (Addison's disease) (Impaired aldosterone production)
  - Hypoglycemia
- **Lack of nutrients in diet**
  - lack of the vitamins B_{12} and folate can cause **Anemia**

➢ Types of Hypotension :-

Postural or Orthostatic hypotension (Low blood pressure on standing up)

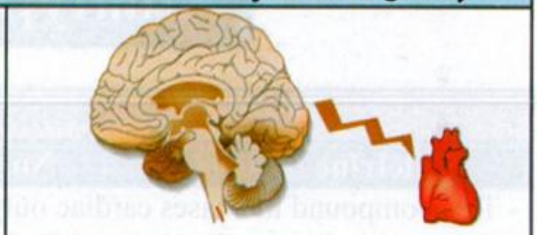
- Sudden drop in blood pressure when stand up from a sitting position (blood pool in legs).
- Increase heart rate by reflex mechanism.
- Postural hypotension occurs → due to dehydration, prolonged bed rest diabetes or other medications.
- Postural hypotension is especially common in older adults.

Postprandial hypotension (Low blood pressure after eating)

- Postprandial hypotension is a sudden drop in blood pressure after eating.
- It affects mostly older adults.
- Large amount of blood flows to your digestive tract after eat.
- Increase heart rate by reflex mechanism.

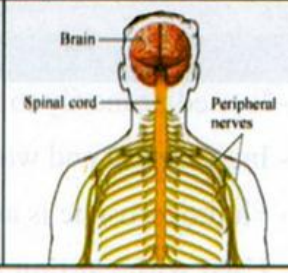
Neurally mediated hypotension (Low blood pressure from faulty brain signals)

- Blood pressure drop after standing for long periods, leading to signs and symptoms such as dizziness.
- Mostly affects young people.
- Occur because of a miscommunication between the heart and the brain.
- stand for extended periods → blood pools in legs → Nerves in the heart send faulty signals to the brain (that blood pressure is too high) → As a result, the brain decrease the heart rate → decreasing blood pressure (Hypotension)



Multiple system atrophy with orthostatic hypotension (Low blood pressure due to nervous system damage)

- Also called Shy-Drager syndrome.
- This rare disorder causes progressive damage to the autonomic nervous system.
- ANS controls involuntary functions such as blood pressure, heart rate, breathing and digestion.



➢ Complications :-

- Even moderate forms of low blood pressure can cause not only dizziness and weakness but also fainting and a risk of injury from falls.
- And severely low blood pressure from any cause can deprive the body of enough oxygen to carry out its normal functions, leading to damage of heart and brain.

➢ **Treatments :-**

Lifestyle Modification

- Use high amount of salt in diet (Increase blood volume)
- Drink enough water (Increase blood volume)
- Wear compression stockings (Reduce the pooling of blood in legs)

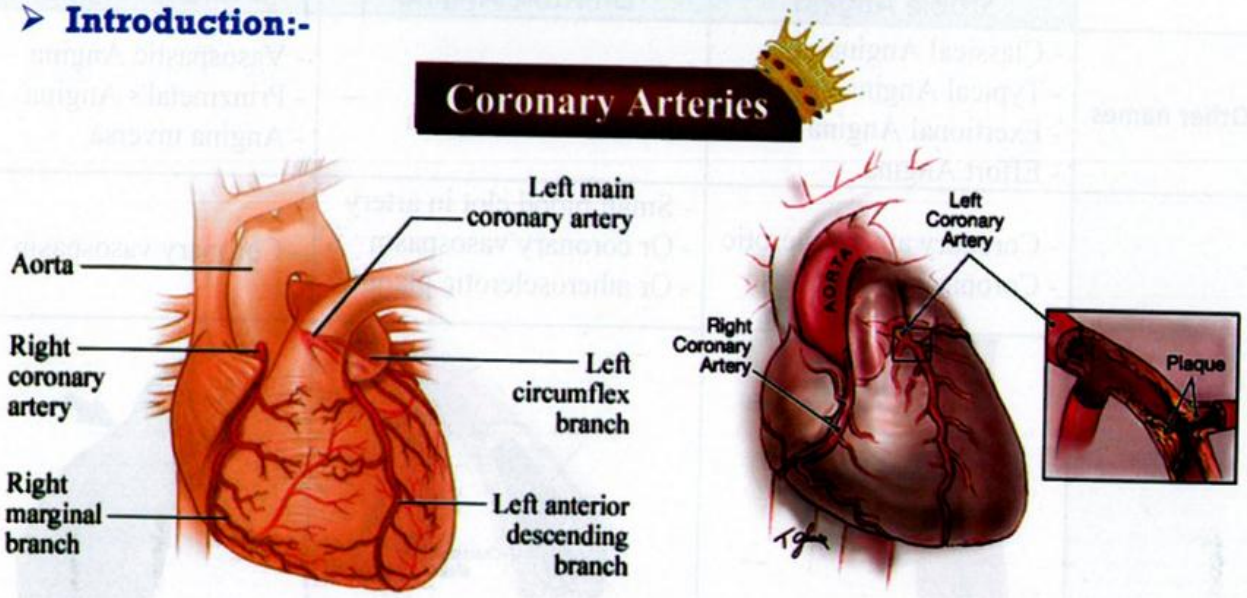
Antihypotensive Drugs

Sympathomimetic agents		
Etilefrine (Effortil®)	**Norfenefrine** (Coritat®)	**Midodrine** (Gutron®)
- This compound increases cardiac output, stroke volume, venous return and blood pressure due to stimulation of both α and β adrenergic receptors. - **Midodrine** selective α_1 receptor agonist (vasopressor). - Used in treating orthostatic hypotension.		
Synthetic corticosteroid		
Fludrocortisone (Astonin-H®)		
- Is used primarily to replace the missing hormone aldosterone in adrenal insufficiency. - Increase salt and water retention → increase blood volume → Increase CO → increase BP. - Fludrocortisone is available in 0.1 mg tablets. - **Used with caution** for Diabetes mellitus, CHF, Kidney and liver diseases, Eye problems, peptic ulcer, Psychosis and pregnancy.		
Other		
Heptaminol (Corasore®)	- Act as vasoconstrictor → Increase resistance.	

Anemia must treated → in hypotensive patient due to anemia

Angina Pectoris

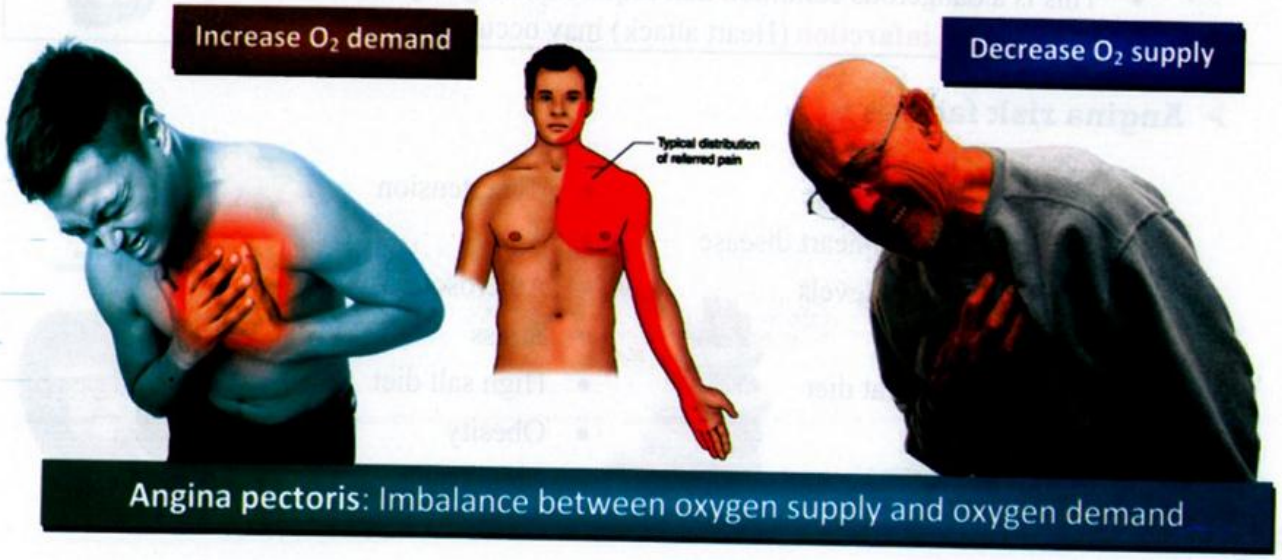
➢ Introduction:-



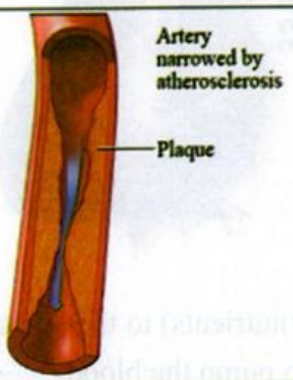
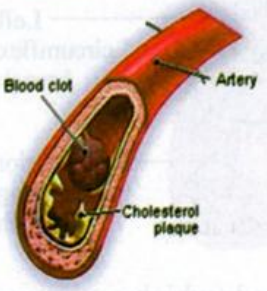
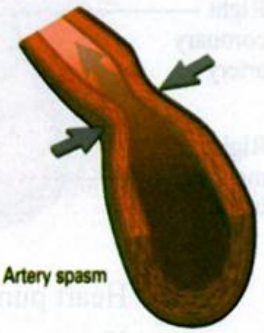
- Heart pump blood (which carry oxygen and nutrients) to the all body tissues.
- Heart need energy (Oxygen and nutrients) to pump the blood.
- Blood which carry oxygen and nutrients (Energy) pumped from the heart to the heart through coronary arteries.
- Increase heart rate due exercise → Heart need more blood through coronary arteries to able to pump the blood to the tissues.
- Coronary artery narrowing → Small amount of blood reached to the heart → decrease heart work → Angina pain.

➢ **Def. →** **Chest pain** caused by transient myocardial ischemia due to an imbalance between myocardial oxygen supply and oxygen demand.

➢ **Pain:** Sudden, severe, pricking chest pain radiating to the neck, jaw, back and arms.



➢ Types of angina :-

	Stable Angina	Unstable Angina	Variant Angina
Other names	- Classical Angina - Typical Angina - Exertional Angina - Effort Angina	- Crescendo Angina - Preinfarction Angina	- Vasospastic Angina - Prinzmetal's Angina - Angina inversa
Cause	- Coronary atherosclerotic - Coronary heart disease	- Small blood clot in artery - Or coronary vasospasm - Or atherosclerotic plaque	- Coronary vasospasm
			
Distribution	- Most common	- Second most common	- Rare
Occurs	- Exertion - Emotion - Exposure to cold weather - Heavy meals	- At rest or minimal exertion	- At rest between midnight and early morning
Relief	- Decreases at rest - Relief by medicine	- Not relieved by rest or medicine	- Relieved by medicine

N.B:

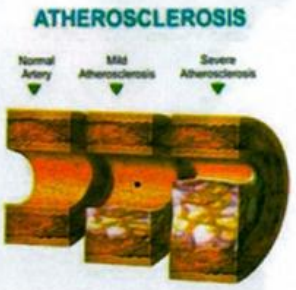
➢ **Unstable Angina** :

- This is a dangerous condition that requires emergency treatment.
- **Myocardial infarction** (Heart attack) may occur in 10-20% of patients.

➢ Angina risk factors :-

- Coronary heart disease
- Family history of heart disease
- High cholesterol levels
- Smoking
- High saturated fat diet
- Diabetes
- Inactivity

- Hypertension
- Age
- Atherosclerosis
- Stress
- High salt diet
- Obesity
- Menopause



➢ Treatments :-

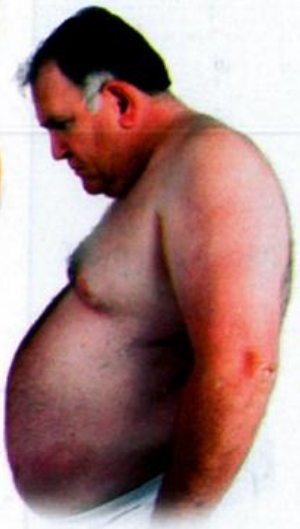
- **Goals of treatment:**
  - **Increase coronary artery blood flow and Decrease O_2 demand on heart:**
    - Vasodilators (Nitrates and Ca^{2+} channel blockers)
  - **Decrease O_2 demand on heart:**
    - β-adrenergic receptor antagonists
  - **Treat coronary artery disease:**
    - Decrease cholesterol level e.g. statins
    - Surgical procedures e.g. stents and angioplasty
  - **Lifestyle modification**

➢ Classification of treatments :-

- **Lifestyle Modification (General measures)**
- **Drug Treatment (Antianginal drugs)**
- **Coronary artery revascularization**

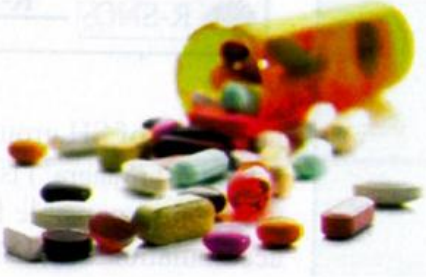
Lifestyle Modification

- Stop smoking
- Reduce weight
- Treat Hypertension
- Treat Hypercholesterolemia and Diabetes
- **Avoid →**
  - Severe exertion
  - Heavy meal
  - Emotions
  - Cold Weather
  - Stress and angry



Antianginal Drugs

1. Organic Nitrates
2. β-Blockers
3. Ca-Channel blockers
4. New antianginal drugs



1- Organic Nitrates

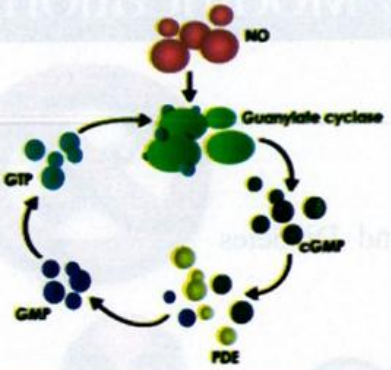
- The prototype of these agents is Nitroglycerin (NG) or Glyceryl Trinitrate (GTN)

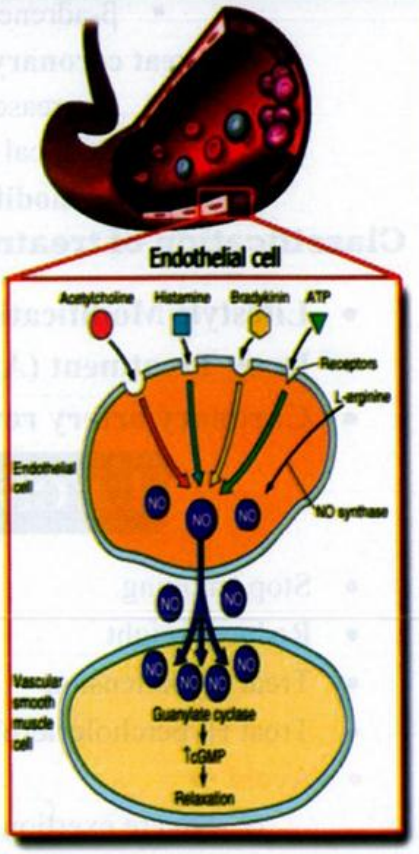
Isosorbide dinitrate (Isordil®) | **Isosorbide mononitrate** (Efox®)

Nitroglycerin (NitromAck®)

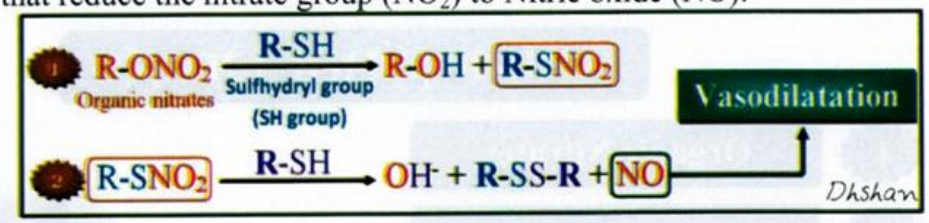
Mechanism of action

- Nitric oxide (NO) is primarily produced by vascular endothelial cells → cause relaxation of vascular smooth muscle (**Vasodilation**).
- NO → Stimulate Guanylate cyclase → Increase cyclic Guanosine monophosphate (cGMP) → Decrease Ca^{2+} influx → Relaxation of vascular smooth muscle → VD.
- NO also activates K^+ channels, which leads to hyperpolarization and relaxation.





- Organic nitrates are drugs that not directly release NO and not form NO within tissues.
- Nitrate group (NO_2) in organic nitrate interact with enzymes (nitric oxide synthase) and intracellular **sulfhydryl group** (R-SH) (**SH group**) that reduce the nitrate group (NO_2) to Nitric oxide (NO).



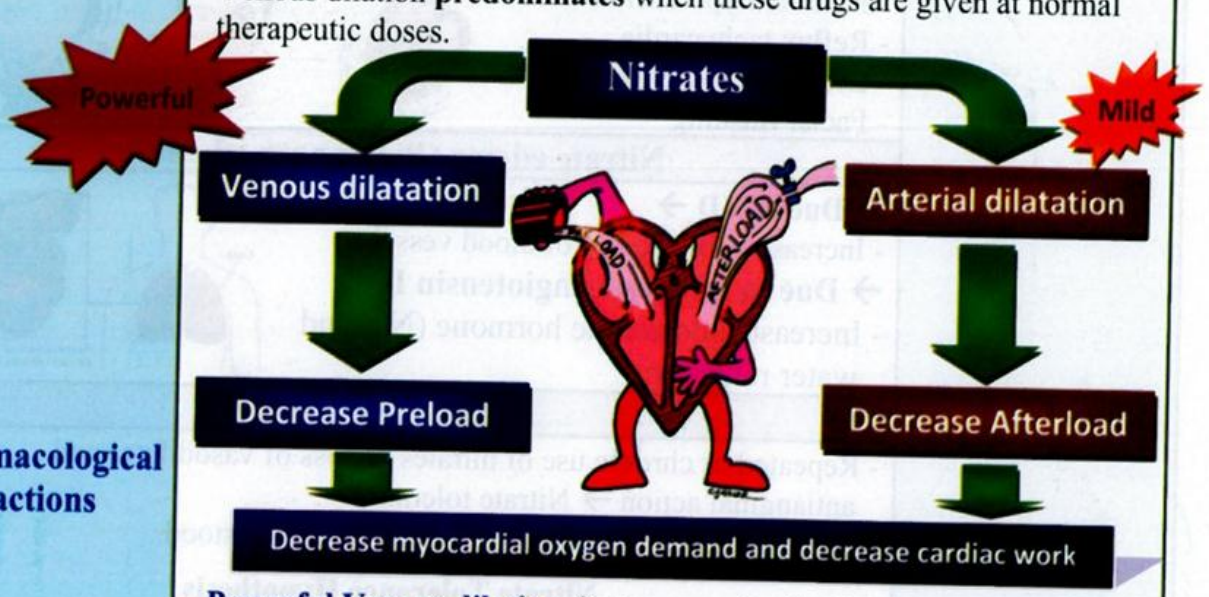
→ N.B:

- Depletion of SH group → Cause **Nitrate tolerance**.
- Sildenafil (Viagra®) is selective inhibitors of Phosphodiesterase (PDE) which is responsible for degradation of cGMP into GMP → accumulation of cGMP → VD of Penis → Erection.

Pharmacological actions

➢ CVS :-

- Although organic nitrates can dilate both arteries and veins
- Venous dilation **predominates** when these drugs are given at normal therapeutic doses.



- Powerful Venous dilation → Decrease Preload
- Decrease myocardial oxygen demand
- Decrease cardiac work

- Mild Arterial dilation → Decrease afterload
- Decrease myocardial oxygen demand
- Decrease cardiac work

Nitrates effective for all types of angina

- Mild coronary artery dilation
- Redistribution of coronary blood flow

➢ Other actions (Minimal action):-

- Inhibit platelet aggregation
- Spasmolytic effect (Smooth muscle relaxant)
- Stimulate respiratory center

Pharmacokinetics

- Well absorbed from Buccal mucosa, Intestine, Skin and Alveoli.
- Low oral bioavailability (Excessive first pass metabolism).
- Excreted in the urine after conjugation with glucuronic acid.

Pharmaceutical preparations

- Short acting (For acute attacks):

- Nitroglycerin (sublingual, spray)
- Isosorbide dinitrate (sublingual, spray)
  - Every 3 to 5 minutes as needed (Maximum 3 doses)

- Long acting (For Angina prophylaxis):

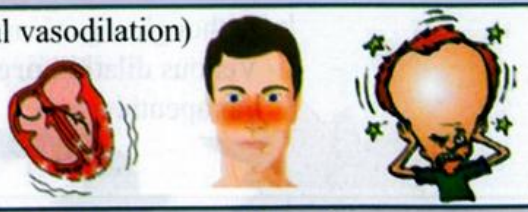
- Nitroglycerin
  - Oral SR (2.5-12.5 mg) 2-4 times/day
  - 2% ointment (1-1.5 inch/8hrs)
  - Patches (1 patch=25mg)/day

- Isosorbide dinitrate (oral) 10-40mg/8hrs.
- Isosorbide mononitrate (oral) 20mg/12hrs

Side effects

Vasodilatation side effects

- Throbbing headache (Cerebral vasodilation)
- Postural hypotension
- Reflux tachycardia
- Drug rash (Allergy)
- Facial flushing



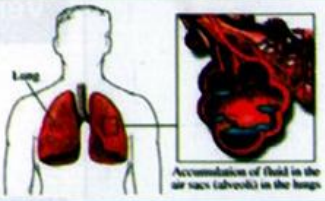
Nitrate edema (Pulmonary edema)

→ Due to VD →

- Increase permeability of blood vessels.

→ Due to increase Angiotensin II →

- Increase aldosterone hormone (Na^+ and water retention).



Nitrate tolerance

- Repeated or chronic use of nitrates → loss of vasodilator and antianginal action → Nitrate tolerance.
- The mechanism for tolerance is not fully understood.

Nitrate Tolerance Hypothesis

- Depletion of SH group.
- Excessive generation of free radicals.
- Dysfunction of endothelial nitric oxide synthase (NOS).
- Decrease sensitivity of guanylate cyclase.
- Activation of renin-angiotensin aldosterone axis.

→ Avoid of tolerance :

1: Giving a drug holiday (Nitrate free interval period) during the day (8-10 hours) e.g. 7am - 5pm → to allow regeneration of SH group.

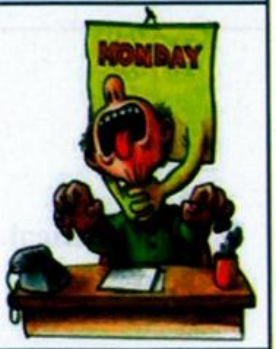
2: Start the treatment with the smallest effective dose

3: Give SH containing compounds as NAC (N-acetyl cysteine), Methionine (Which increase glutathione (source of SH)

4: Replacement of nitrates by another drugs e.g. Ca^{2+} channel blockers and β-blockers.

Monday syndrome

- Industrial disease for workers in nitroglycerin (Monday morning headache) caused by chronic exposure to organic nitrates in the work place.
- Characterized by →
  - Headache
  - Dizziness
  - Tachycardia



Other side effect

- In prolonged drug use convert hemoglobin into met-hemoglobin → (No ability to carry O_2).

2- β- Adrenoceptor blocker

Propranolol (Inderal®) **Nadolol** (Corgard®) **Sotalol** (Betacor®)	Non-selective β-adrenoceptor antagonist	More Bronchoconstriction
Metoprolol (Betaloc®) **Atenolol** (Atelol®) **Esmolol** (Brevibloc®) **Nebivolol** (Nebilet®) **Bisoprolol** (Concor®)	Selective β_1-adrenoceptor antagonist	Less Bronchoconstriction Stimulate releasing of NO
Action	- Decreased requirement for myocardial oxygen	
Uses (in angina)	- **High** effective in Stable angina - **Less** effective in Unstable angina (Without intrinsic sympathomimetic activity). - **Not** effective in vasospastic angina (Variant angina).	
Side effects	- Bronchoconstriction. - Bradycardia and heart block. - Cold extremities. - Sexual dysfunction (Decrease libido and Impotence) - **Sudden Stop β-blockers** → Up-regulation of adrenoceptors → cardiac arrhythmia and hypertension (May cause sudden death).	

3- Calcium channel blockers

Phenylalkylamines		
Verapamil (Isoptin®)		
- Selective blocker in calcium-channel on cardiac muscle cells. - They have minimal effect on blood vessels (VD). 		
Dihydropyridines		
Nifedipine (Epilat®)	**Amlodipine** (Norvasc®)	**Felodipine** (Plendil®)
Nicardipine (Pelcard®)	**Nimodipine** (Nimotop®)	**Lacidipine** (Lacipil®)
Lercanidipine (CareDipine®)		
- Selective blocker in calcium-channel on blood vessels → Cause VD → Decrease Resistance → decrease blood pressure. 		
Benzothiazepines		
Diltiazem (Altiazem®)		
- Having both blocker effects on cardiac and vascular smooth muscle calcium-channels.  		
Uses (in angina)	- Calcium Channels Blockers effective for all types of angina.	

4- New antianginal drugs (Adjunct agents)

Ranolazine (Ranexa®)	
Mechanism of action	- Block sodium-dependent calcium channels → decrease Ca^{2+} influx. - Partial fatty acid oxidation inhibitor.
Uses	- Used in combination with antianginal drugs. - Has no effect on HR (Unlike β-blocker or CCB).
Adverse effects	- Prolonged QT interval → Ventricular arrhythmia.
Trimetazidine (Vastarel®)	
Mechanism of action	- The first cytoprotective anti-ischemic agent. - Increase glucose metabolism. - Improve myocardial glucose utilization. - Decrease fatty acid metabolism (FA oxidation inhibitors). - Decrease O_2 requirement and consumption (Anti-anginal). - Decrease accumulation of lactic acid decrease Angina pain. - Prevent excessive production of free radicals (Antioxidant).
Uses	- Used in combination with antianginal drugs.
Nicorandil (Randil®)	
Mechanism of action	- Vasodilator antianginal agent. - Stimulates guanylate cyclase to increase formation of cGMP → VD. - K^+ATP channel opener → Increase K^+ influx → Hyperpolarization. - This hyperpolarizes the cell, which inactivates voltage-gated calcium channels & reduces intracellular Ca^{2+} (Indirect blocking Ca^{2+} channel).
Uses	- Used in combination with antianginal drugs.
Side effects	- Mouth ulcer, Flushing, and perianal ulcer, palpitation and anal ulcer.
Dipyridamole (Persantine®)	
Mechanism of action	- Prophylactic against strock (Decrease thrombus formation) - It acts as a thromboxane synthase inhibitor, therefore lowering the levels of TXA_2 → Decrease platelet aggregation. - Decrease reuptake and metabolism of adenosine. - Inhibition of phosphodiesterase enzyme(PDE) → Increase cAMP
Uses	- Used in combination with antianginal drugs - Treatment of pulmonary hypertension - Used in combination with aspirin → prevention of stroke
Side effects	- Long use or large dose cause steal structure of the heart (steal phenomenon) → due to VD of healthy blood vessels and No VD of ischemic blood vessels and shift of blood from ischemic to non-ischemic area.
Aspirin (low dose) (Aspocid®)	
Mechanism of action	- Aspirin inhibit formation of Thromboxane-A_2 (TXA_2) → Decrease platelet aggregation (Antiplatelet).
Uses	- Used with antianginal drugs → prophylactic against blood clotting.

➢ Combination therapy and drug-drug interaction :-

Good Combination	
Nitrate + β-blockers	- Avoid Bradycardia and Tachycardia
β-blockers + Thiazide	- Synergistic effect and decrease edema.
Nitrate + Verapamil	- Avoid Bradycardia and Tachycardia
β-Blockers + Nifedipine	- Avoid Bradycardia and Tachycardia
Bad Combination	
Insulin + β-blockers	- Hypoglycemic coma
β-blockers +Verapamil	- Severe bradycardia and heart block
Nifedipine + Nitrates	- Severe reflex tachycardia

Coronary artery revascularization

Coronary artery bypass graft (CABG)

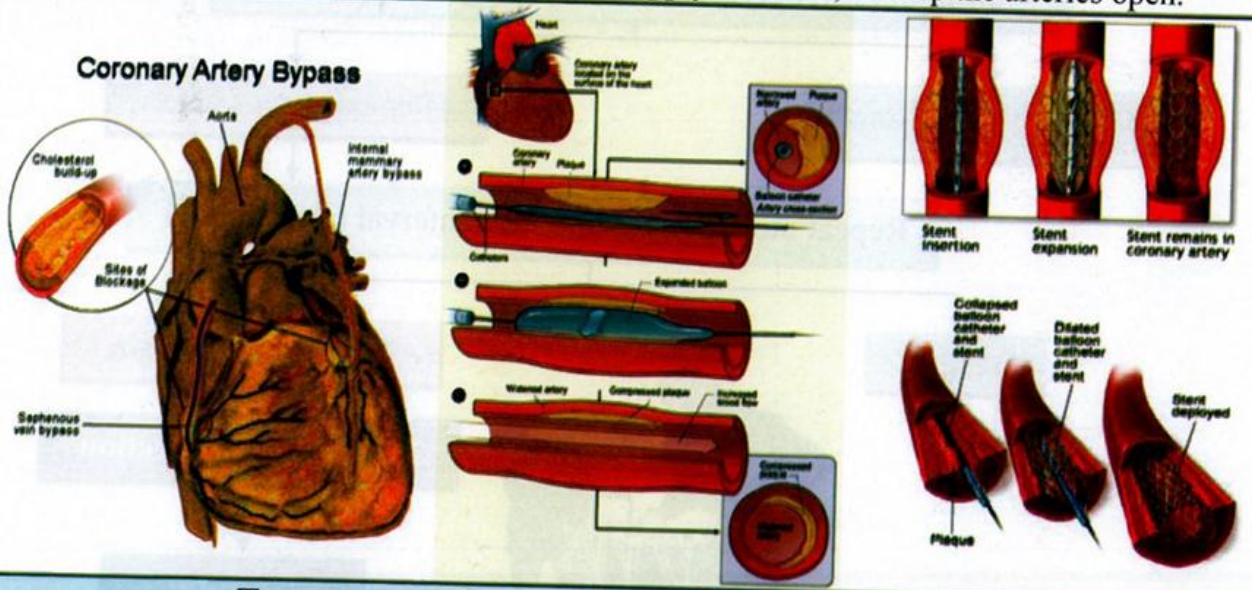
- The surgical procedure places new blood vessels around existing blockages to restore necessary blood flow to the heart muscle.

Coronary Artery balloon Angioplasty

- Coronary angioplasty, also called **Percutaneous coronary intervention (PCI).**
- Is a procedure used to open clogged heart arteries. Angioplasty involves temporarily inserting and blowing up a tiny balloon where your artery is clogged to help widen the artery.

Coronary Artery Stent

- Is a tube placed in the coronary arteries that supply the heart, to keep the arteries open.



Transmyocardial Laser Revascularization (TMR)

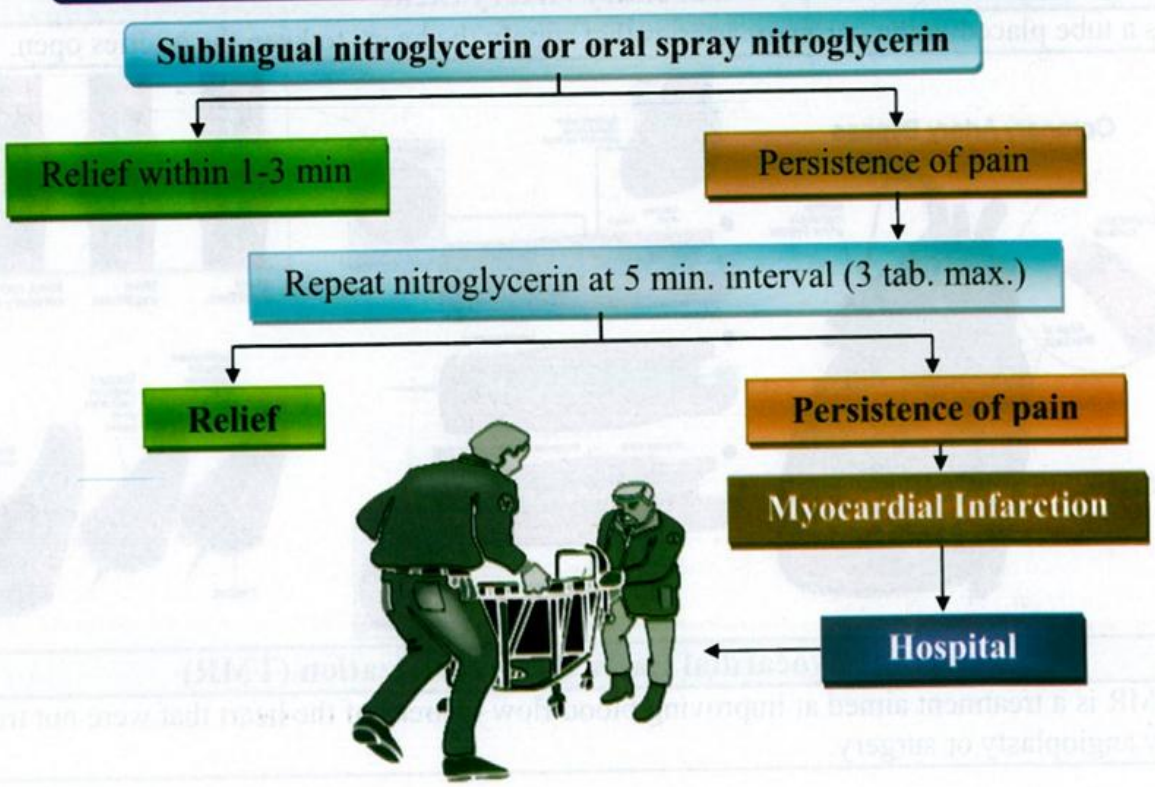
- TMR is a treatment aimed at improving blood flow to areas of the heart that were not treated by angioplasty or surgery.

Strategy of treatments of angina

- **Lifestyle modification:-**
- **Drug Treatments:-**

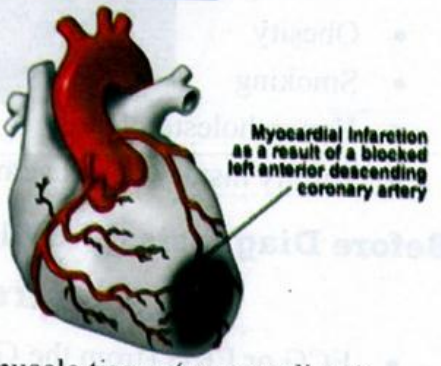
A: Stable Angina	
Short-Acting (Acute attacks)	
Nitroglycerin (sublingual, spray) **Isosorbide dinitrate** (sublingual, spray)	
Repeat the dose every 5 min. till disappearance of pain (Maximum 3 doses).	
Long-Acting (Prophylaxis)	
Nitroglycerin (Oral, Ointment or Patches) **Isosorbide dinitrate** (Oral) **Isosorbide mononitrate** (Oral) **Aspirin** (75-100mg/d)	**Statins** (lower lipid level in the blood) **β-blockers** **Calcium Channel Blockers** **Nicorandil**
Coronary artery revascularization	
B: Variant Angina	
Organic Nitrate Or **Calcium Channel Blockers** (No **β-blockers**)	
C: Unstable Angina	
Organic Nitrate - Antiplatelet - Heparin - Statins - Calcium Channel Blockers - β-blockers (without intrinsic sympathomimetic activity (ISA))	

Treatment of an acute attack of angina



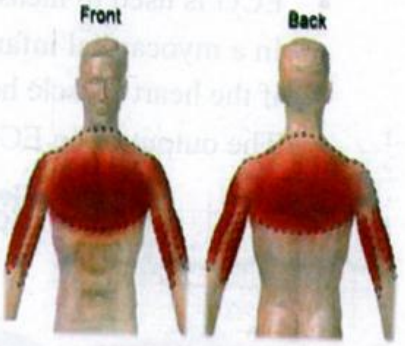
Myocardial Infarction (MI)

➢ Myocardial Infarction:-

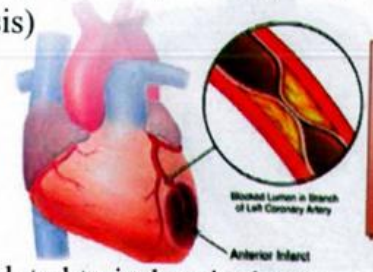


- Commonly known as a **heart attack**.
- Results from the interruption of blood supply to a part of the heart, causing heart cells to die.
- This is most commonly due to blockage of a coronary artery.
- If left untreated for a sufficient period of time, can cause damage or death (infarction) of heart muscle tissue (myocardium).

➢ Symptoms:-



- **Severe chest pain** (due to ischemia)
  - Pain radiates most often to the left arm, but may also radiate to the lower jaw, neck, right arm, back, and epigastrium, where it may mimic heartburn.
- Shortness of breath (dyspnea & pulmonary edema)
- Excessive sweating (diaphoresis)
- Nausea and vomiting
- Sudden death can occur



➢ New classification:-

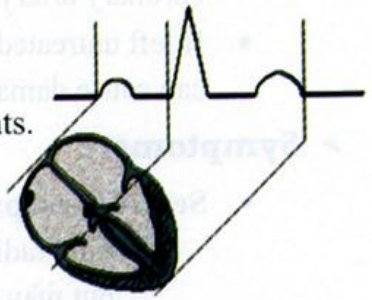
- **Type 1**
  - Myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
- **Type 2**
  - Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
- **Type 3**
  - Sudden unexpected cardiac death before blood samples for biomarkers could be drawn or before their appearance in the blood
- **Type 4**
  - **Type 4a :** MI associated with percutaneous coronary intervention (PCI)
  - **Type 4b :** MI associated with stent thrombosis
- **Type 5**
  - MI associated with coronary artery bypass graft (CABG) surgery

➢ Risk factors :-

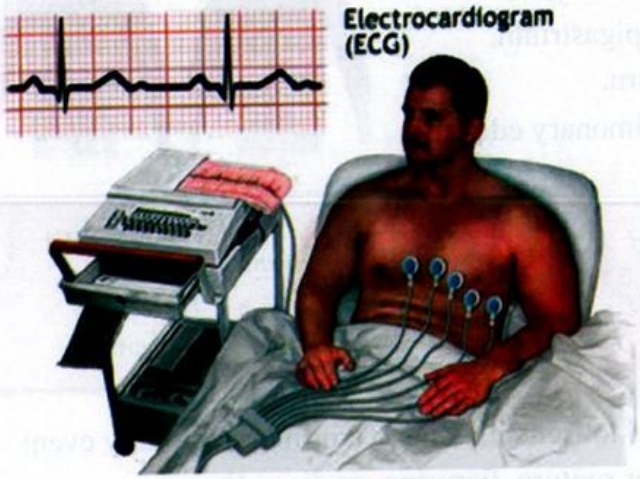
- Older age
- Obesity
- Smoking
- Hypercholesterolemia
- Family history of ischaemic heart disease
- Male gender
- Negative emotions and stress
- Diabetes
- High blood pressure
- Lack of physical activity

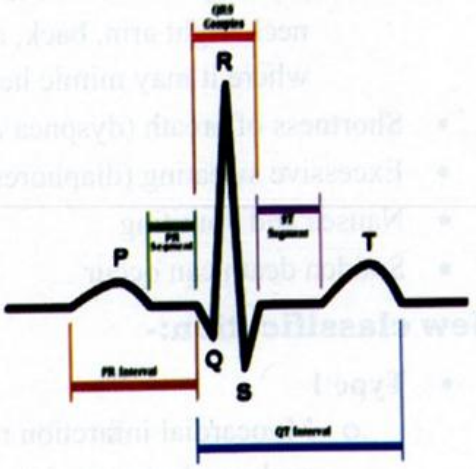
➢ Before Diagnosis, What is the ECG:-

Electrocardiogram (ECG)



- ECG or EKG (from the German Elektrokardiogramm).
- ECG is used to measure the rate and regularity of heartbeats.
- In a myocardial infarction (MI), the ECG can identify if the heart muscle has been damaged in specific areas.
- The output of an ECG recorder is a graph.





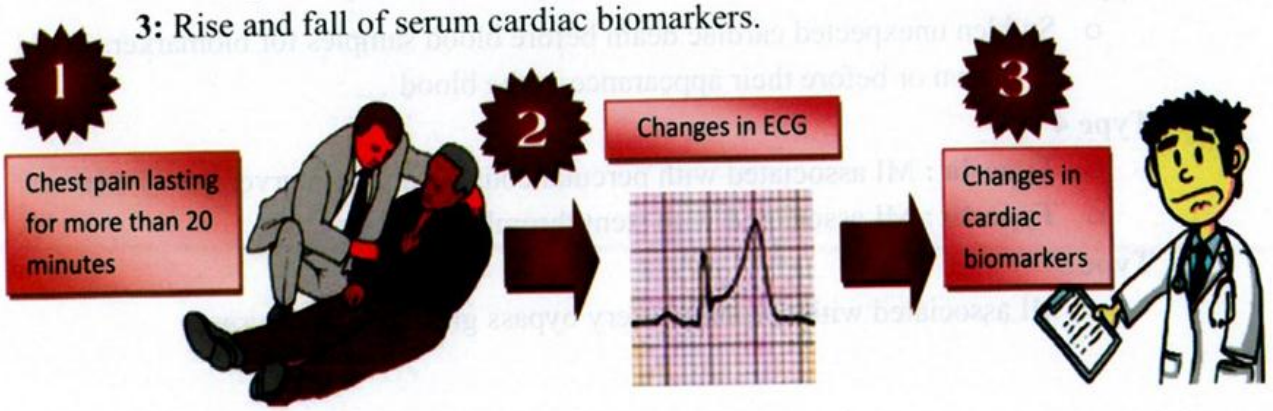
➢ Myocardial infarction diagnosis:-

- A patient is diagnosed with myocardial infarction if two or three of the following criteria are applied:

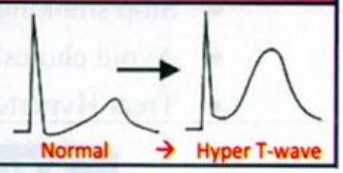
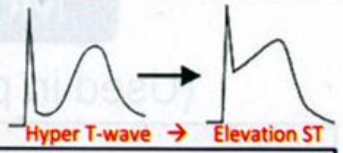
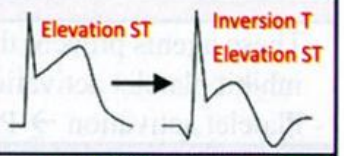
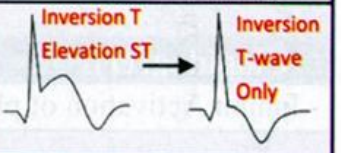
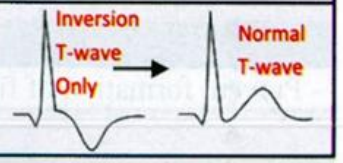
1: Clinical history of ischaemic type chest pain lasting for more than 20 minutes.

2: Changes in serial ECG tracings.

3: Rise and fall of serum cardiac biomarkers.



ECG Evolution of myocardial infarction

Time from onset of symptoms	ECG	Graph
Within Minutes	**- Hyper-acute T-wave** ▪ More Pointer ▪ More taller ▪ More sharper	
Within Hours	**- Elevation of the ST segment** (Hallmark of Myocardial infarction)	
Within days	**- Inversion of T-wave** **- Less ST segment elevation**	
Within one or more weeks	**- ST segment changes revert completely to normal.** **- T-wave inversion may develop.**	
Months after the MI	**- T waves may gradually return to normal**	

Cardiac Biomarkers (Lab Tests)

- Certain blood tests read as "abnormal" after an MI has occurred because when heart muscle cells die, the chemicals in these cells are released into the blood.
- This does not occur instantly and usually takes several hours.
- These chemicals are called markers of MI (Cardiac markers) and include CPK (Creatine Phosphokinase), CPK-MB (Myocardial Creatine Kinase), Troponin, and Myoglobin.

Lab Test	Begins to rise	Peak	Duration	Found in
CPK	4-8 Hours	-	48-72 Hours	Heart, Brain, Skeletal Muscle
CPK-MB	3-4 Hours	12-24 Hours	48 Hours	Heart
Myoglobin	1-2 Hours	4-6 Hours	24 Hours	Heart, Skeletal Muscle
Troponin	3-6 Hours	12-24 Hours	1 week	Heart, Skeletal Muscle

- **Other Diagnosis**
  - Echocardiography
  - Chest radiograph (Chest X-ray)
  - Technetium (^{99m}Tc) sestamibi (Cardiolite®) scan

➢ Myocardial infarction Prevention:-

Lifestyle Modification

- Stop smoking and Reduce weight.
- Avoid cholesterol, fat and salt in diet.
- Treat Hypertension, Hypercholesterolemia and Diabetes.

Medications and Surgery

(Used in prevention and Secondary Prevention)

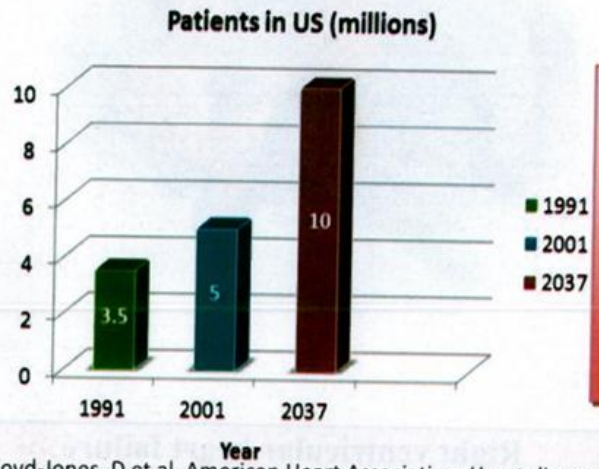
Antithrombotic agents		
- These agents prevent the formation of thrombus associated with myocardial infarction and inhibit platelet activation. - Platelet activation → Prothrombin → Thrombin → Fibrin → Blood Clot		
Antiplatelet agents		
Clopidogrel (Plavix®)	**Aspirin** (low dose) (Aspocid®)	**Dipyridamole** (Persantine®)
- Inhibit Activation of platelet → Decrease platelet aggregation		
Anticoagulants		
Enoxaparin (Clexane®)		
- Prevent formation of fibrin → Clot not formed.		
Thrombolytics (Fibrinolytics)		
Streptokinase (Kabikinase®)	**Alteplase** (Cathflo Activase®)	**Reteplase** (Retavase®)
Dissolve blood clots (Lysis of fibrin).		
Platelet aggregation inhibitors		
Tirofiban (Thrombostat®)	**Abciximab** (Reopro®)	**Eptifibatide** (Integrilin®)
Vasodilators		
Nitroglycerin (NitromAck®)		
β-adrenergic blockers		
Metoprolol (Betaloc®)	**Esmolol** (Brevibloc®)	
Angiotensin-converting enzyme (ACE) inhibitors		
Captopril (Capoten®)	**Enalapril** (Renitec®)	
Cholesterol Lowering Agents		
Simvastatin (Zocor®)	**Pravastatin** (Lipostat®)	
Analgesics (MI pain)	**Morphine** (Morphine Sulphate®)	
Surgery		
Coronary artery bypass graft (CABG) percutaneous coronary intervention (PCI) Coronary Artery Stent	**(See Angina)**	

Congestive Heart Failure (CHF)

➢ Introduction :-

- **Definition of Heart Failure (HF):**
  - HF is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
  - **Or:** The heart is unable to pump enough blood with each beat.

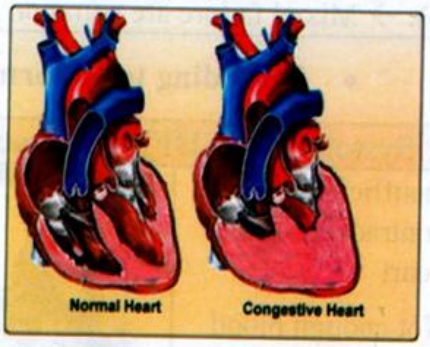
- **Heart Failure Prevalence in the United States:**



- 6 million patients1; estimated 10 million in 2037
- Incidence: about 660,000 new cases each year
- Costs in excess of $39 billion to the U.S. health care system in 2010
- ~50% of patients with HF die within 5 years after diagnosis
- ~35% with class IV HF die within 1 year

1. Lloyd-Jones, D et al. American Heart Association. Heart disease and stroke facts 2010 update. Circulation 2010; 121 (7): 948-954.
2. Croft JB et al. J Am Geriatr Soc. 1997;45:270–275.

- **Ejection fraction (EF):**
  - A measurement of how much blood the left ventricle pumps out with each contraction.
  - 60 % of the total amount of blood in the left ventricle is pushed out with each heartbeat.
    - Normal EF between 55% - 70%
    - Heart failure = Less than 40%



➔ **Symptoms of abnormal EF:**

- Less blood goes to the brain that may make you feel confused.
- Lungs may fill up with fluid making you feel short of breath.
- Kidneys may not be able to get rid of the fluid.
- Ankles and feet may swell up.

➢ Risk factors:-

- Coronary artery disease
- Diabetes
- Infections (Septicaemia)
- Severe anemia
- Hyperthyroidism
- Cardiac arrhythmia
- Myocardial infarct: damaged tissue
- Alcoholism
- Faulty heart valves
- Lung disease
- Cardiomyopathy (Heart muscle disease)
- Untreated high blood Pressure
- Ischemic heart disease: most prevalent
- Toxic drugs

➢ Symptoms of CHF:-

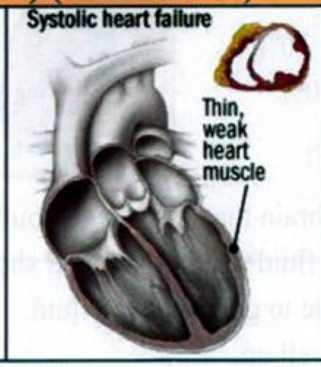
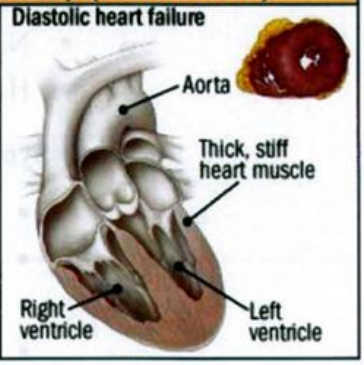
- Shortness of breath
- Persistent coughing
- Increased heart rate
- Edema (excess fluid build-up in body tissues)
- Tiredness and fatigue
- Lack of appetite and nausea
- Confusion and impaired thinking

➢ Classification :-

- **According to side of the heart:**

Left ventricular heart failure	Right ventricular heart failure
- First common	- Left heart failure often leads to right heart failure in the longer term.
- Less pumping by lift ventricle	- Less pumping by right ventricle.
- less aortic flow to the body and brain	- Less pulmonary flow to the lungs
N.B: → Mixed failure are common (Lift and right failure)	

- **According to abnormality of contraction and relaxation:**

Systolic HF (SHF) (Contraction)		Diastolic HF (DHF) (Relaxation)	
- insufficient contraction of the heart - Not enough blood is pumped from the chambers - Thin, Weak heart muscle		- Insufficient relaxation of the heart - Not enough blood fills the chambers - Thick, stiff heart muscle	

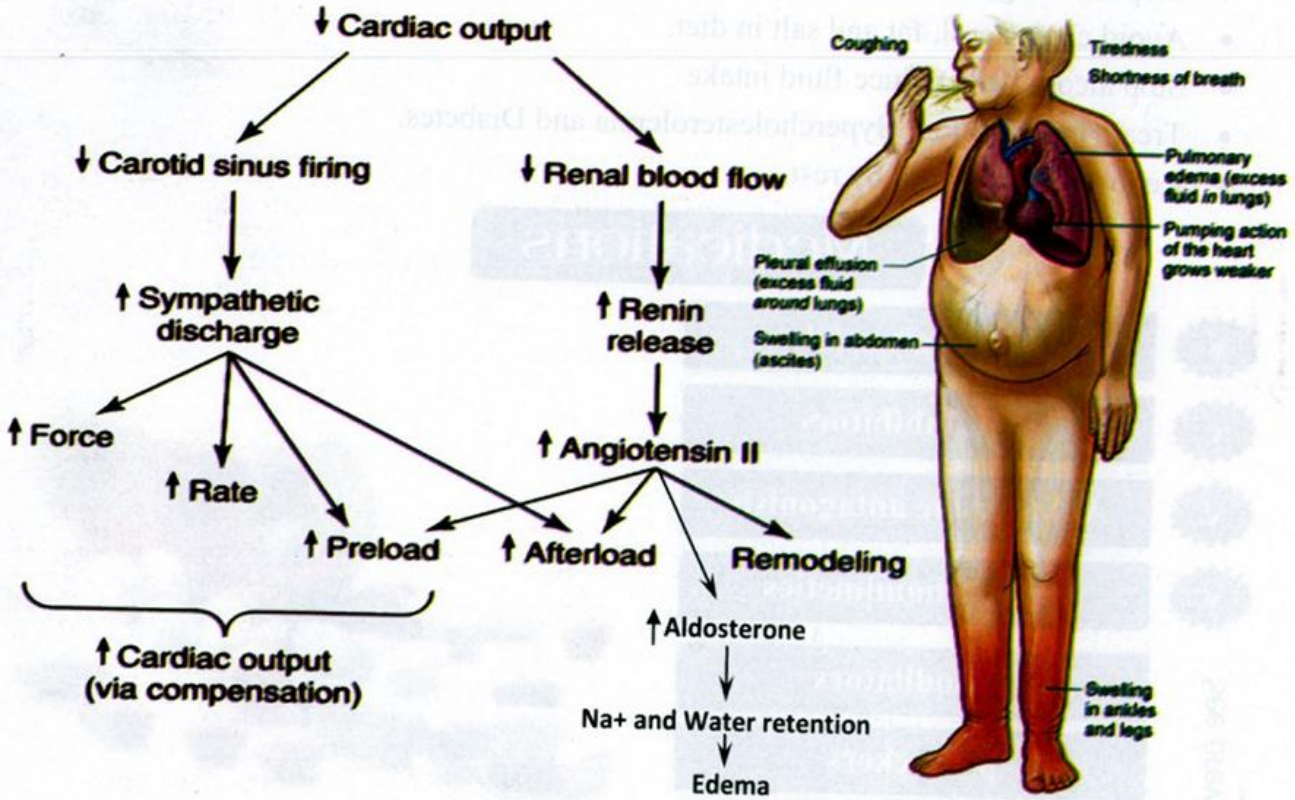
- **Functional classification** (New York Heart Association Classification):

Class I	- Patients have no limitation of physical activity
Class II	- Patients have slight limitation of physical activity
Class III	- Patients have marked limitation of physical activity
Class IV	- Patients have symptoms even at rest and are unable to carry on any physical activity without discomfort

- **According to Stages** (In its 2001 guidelines the American College of Cardiology/American Heart Association working group introduced four stages of heart failure):

Stage A	- Patients are at high risk for heart failure but have no structural heart disease or symptoms of heart failure
Stage B	- Patients have structural heart disease but have no symptoms of heart failure
Stage C	- Patients have structural heart disease and have symptoms of heart failure
Stage D	- Patients have refractory heart failure requiring specialized interventions

➢ Compensatory mechanisms of heart failure(Pathophysiology) :-



➢ Diagnosis :-

- Echocardiography
- Chest radiograph (Chest X-ray)
- Electrocardiogram (ECG)
- Blood tests
  - Electrolytes
  - Renal function,
  - Liver function tests,
  - Thyroid function tests,
  - Complete blood count (CBC)

➢ Treatments :-

- Lifestyle modification
- Medications
- Surgery and medical devices

Lifestyle Modification

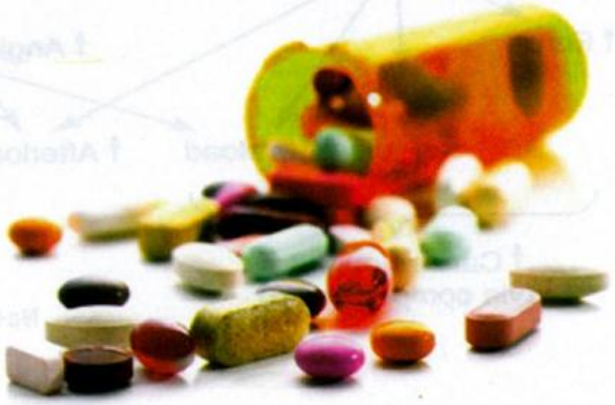
- Stop smoking and Reduce weight.
- Avoid cholesterol, fat and salt in diet.
- Stop alcohol and reduce fluid intake
- Treat Hypertension, Hypercholesterolemia and Diabetes.
- Reduce cardiac work by rest.

Medications

- √ Cardiac glycosides
- √ PDE inhibitors
- √ Aldosterone antagonists
- √ Sympathomimetics

See previous topics

- Vasodilators
- β-Blockers
- ACEIs and AT Blockers
- Diuretics



Cardiac Glycosides

Digitalis lanata

➢ Derived from plants :-

Plant origin	Drug name
Strophanthus	Ouabain (Uabanin®)
Digitalis lanata	Digoxin (Lanoxin®)
Digitalis purpurea	Digitoxin (Unidigin®)

➢ Pharmacokinetics :-

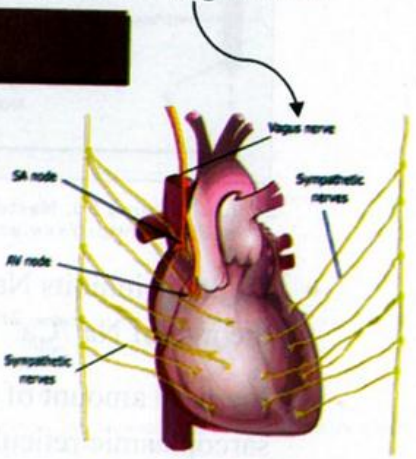
	Digitoxin	Digoxin	Ouabain
Administration	Orally only	Orally & IV	IV only
Oral Bioavailability	90-100%	75%	0%
Half-life ($T_{1/2}$)	7 days	36 hours (1.5 days)	21 hours
Lipid solubility	High	Moderate	Less
Plasma protein binding	95%	25%	0%
Potency	High	Moderate	Less
Elimination	Liver	Kidneys	Kidneys
Excretion	Urine and feces	Urine only	Urine only
Kidney dysfunction	Safe	Not safe	Not safe
Liver dysfunction	Not safe	Safe	Safe
Optimal plasma Conc.	10-25 ng/ml	0.5-2 ng/ml	
Very Low Therapeutic Index			

➢ Effect on the Heart :-

- +ve inotropic effect (Increase force of contraction) by direct effect on the heart
- -ve chronotropic effect (Decrease Heart rate) by direct effect and vagal effect

Strong Short Systole & Long Diastole

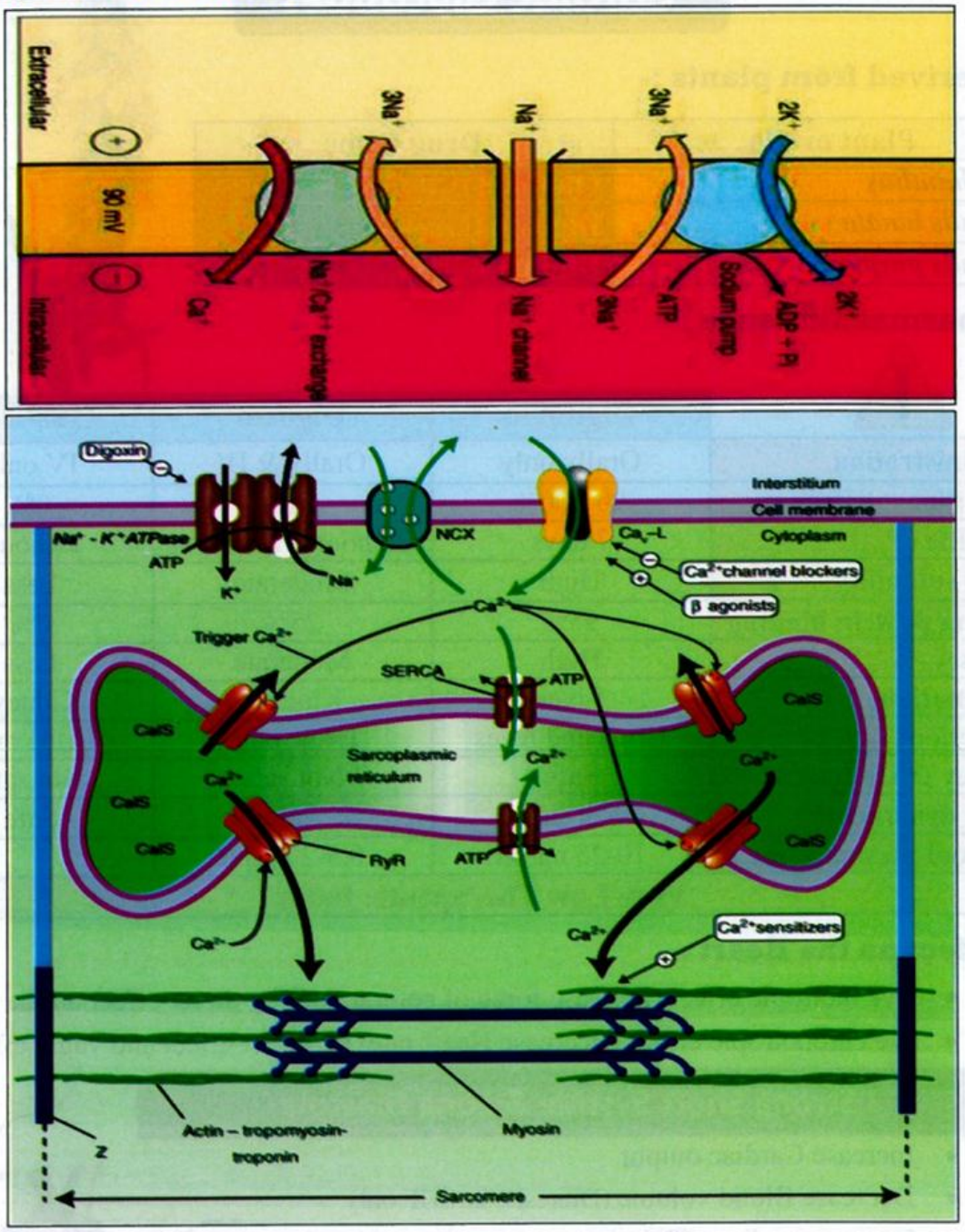
- Increase Cardiac output
- Decrease Blood volume (Diuresis) in CHF only
- Increase cardiac efficiency



➢ Other effects :-

- **Kidney** → Diuretic effect on CHF only (Due to increase renal blood flow and decrease renin → Decrease Aldosterone → No Na^+ retention)
- **CNS** → Stimulate VMC, CTZ and vagal center
- **Endocrine** → Gynecomastia in male (rare) due to ability to bind to estrogen receptor (Steroid similarity structure)

➢ Mechanism of action :-

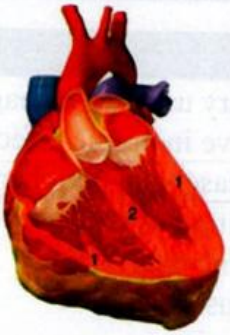


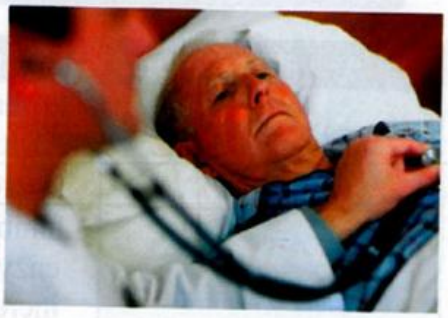
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

- Digitalis inhibits Na^+/K^+ ATPase pump → Increase intracellular Na^+ → Increase the rate of Na^+/Ca^{2+} exchange mechanism →Increase Ca^{2+} inside the cell.
- Increase amount of Ca^{2+} inside the cell leads to increase storage of Ca^{2+} in sarcoplasmic reticulum (SR) → Causing a corresponding increase in the release of calcium during each action potential.
- This leads to increase the force of contraction of the heart (+ve inotropic).

➢ Therapeutic uses:-

- **Heart failure**
  - Increase cardiac output
  - Increase diuresis
  - Decrease cardiac size
  - Decrease heart rate
  - Decrease venous pressure
  - Decrease edema
- **Atrial Arrhythmia**
  - Atrial fibrillation
  - Atrial flutter
  - Paroxysmal atrial tachycardia





➢ Dose:-

- **Initial dose (Initial digitalizing dose):**
  - **Digoxin** → 0.4-0.6 mg initially followed by 0.1-0.3 mg / 6-8 hours.
  - **Digitoxin** → 0.2-0.3 mg / 6 hours for 4 doses.
- **Maintenance dose:**
  - **Digoxin** → 0.125-1.5 mg/day (Orally)
  - **Digitoxin** → 0.05-0.2 mg/day (Orally)

➢ Side effects & toxicity:-

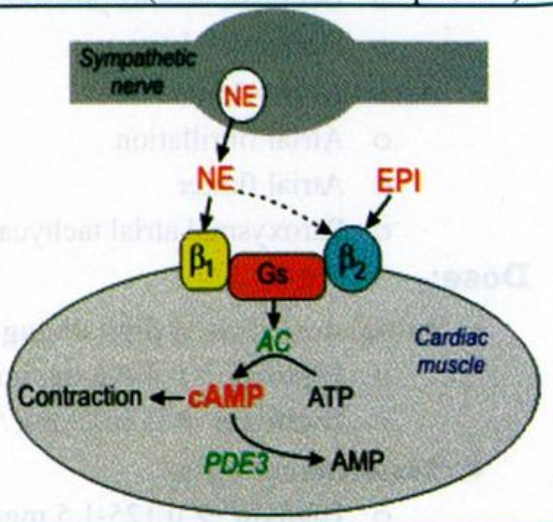
- **Early manifestation of toxicity :**
  - Anorexia, Nausea & Vomiting
  - Bradycardia (< 60 beat/min.)
- **Late manifestation of toxicity :**
  - **Eye** → Visual disturbance and colored vision called **Chromatopsia** (Yellow-tinted vision)
  - **CVS** → Bradycardia, Heart block and **Arrhythmia**.
  - **GIT** → Anorexia, Nausea, Vomiting and Diarrhea
  - **CNS** → Headache, Hallucination, Convulsions, Confusion & Delusions.
  - **Hormonal** → Gynecomastia (rare)

➢ Factors increase digitalis toxicity:-

- **Drugs increase toxicity** e.g. Sympathomimetic drugs, Thiazide and loop diuretic
- **Organ dysfunction** e.g. Renal failure and hepatic failure
- **Dosing errors**
- **Old age**
- **Serum electrolytes disturbances**
  - Hypokalemia
  - Hypercalcemia

Digoxin Immune Fab (Ovine) (Digibind®)
- Antidote for overdose of digitalis.
- It works by binding to the digoxin, rendering them unable to bind to their action sites on target cells.

Phosphodiesterase type 3 (PDE3) Inhibitors

Amrinone (Inocor®)	Milrinone (Primacor®)
Information	- Primary used for management of acute heart failure. - Positive inotropic effects. - Decrease total peripheral resistance (Decrease after and preload).
Mechanism of action	- Inhibition of PDE enzyme type 3 → increase cyclic adenosine monophosphate (cAMP) → increase Ca2+ influx → contraction of the heart → +ve inotropic effect. - increase cAMP → in smooth muscle → relaxation 
Therapeutic uses	- IV (short duration of action) in acute heart failure.
Side effects	- Ventricular arrhythmia - Hypotension - Thrombocytopenia

Aldosterone Antagonists

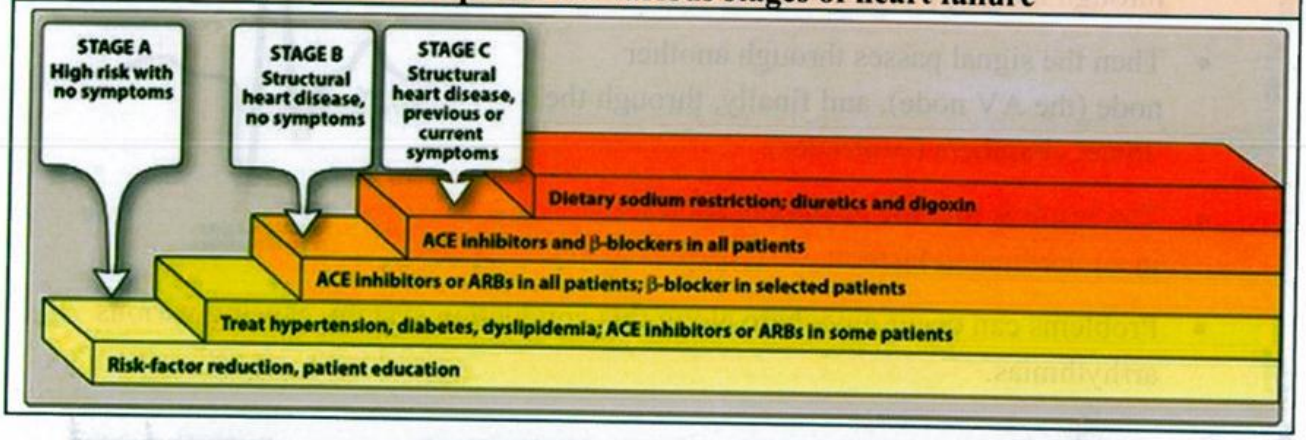
Spironolactone (Aldactone®)	Eplerenone (Eplorefix®)
Mechanism of action	- Spironolactone is a competitive with aldosterone in mineralocorticoid receptors in renal epithelial cells in kidney - It is increase water and sodium excretion.
Uses	- Edema caused by CHF - Essential Hypertension.
Side effect	* **Hyperkalemia** - CNS side effects - Confusion - Drowsiness - Headache - Allergy and Metabolic acidosis (due to Increase H^+ in blood) - Hormones - In male cause Gynecomastia and Impotence. - In female cause Menstrual disturbance.

Direct Sympathomimetics

	Dopamine (Intropin®)	Dobutamine (Dobutrex®)
Action	- Cause immediate +ve inotropic effects - Dopamine used in small or moderate dose (in high dose stimulate α receptor → VC)	

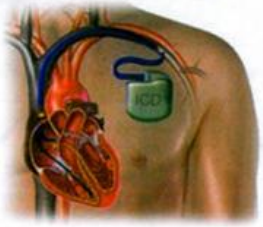
Management	
Acute Herat Failure (Acute pulmonary edema)	**Chronic Heart Failure**
- Sit the patient up - Give oxygen by face mask - Analgesia and sedation (Morphine) - Nitrates are first-line vasodilators - Furosemide 20-40 mg IV (slowly) - Milrinone IV	- Treatment of the underlying causes - Non-Pharmacological treatment - Pharmacological treatment - Cardiac Glycosides - Diuretics - Vasodilators and other agents

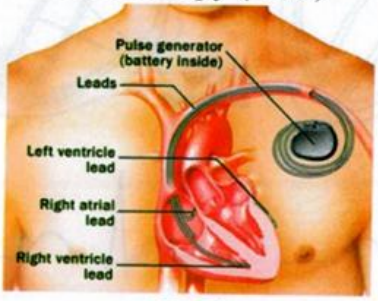
Treatment options for various stages of heart failure



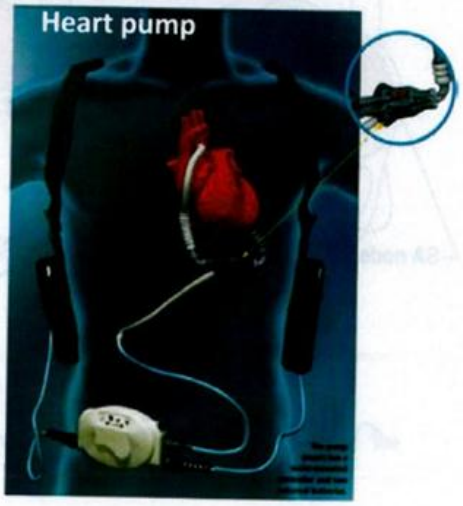
Surgery and medical devices

- Coronary bypass surgery
- Heart valve repair or replacement
- Implantable cardioverter-defibrillators (ICDs)
- Cardiac resynchronization therapy (CRT)
- Heart pumps
- Heart transplant



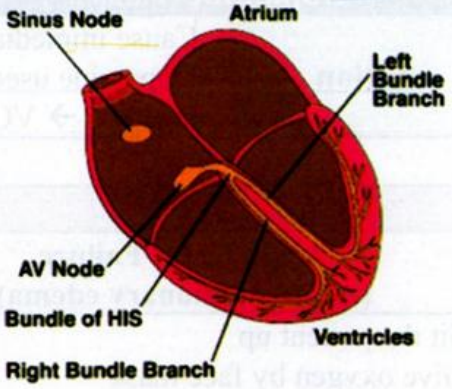


(CRT)



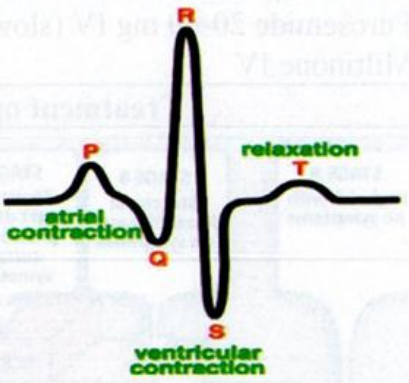
Arrhythmia

➢ **Def.** → Abnormality in the normal rhythmic contraction of the heart.
→ Also known as Cardiac dysrhythmia

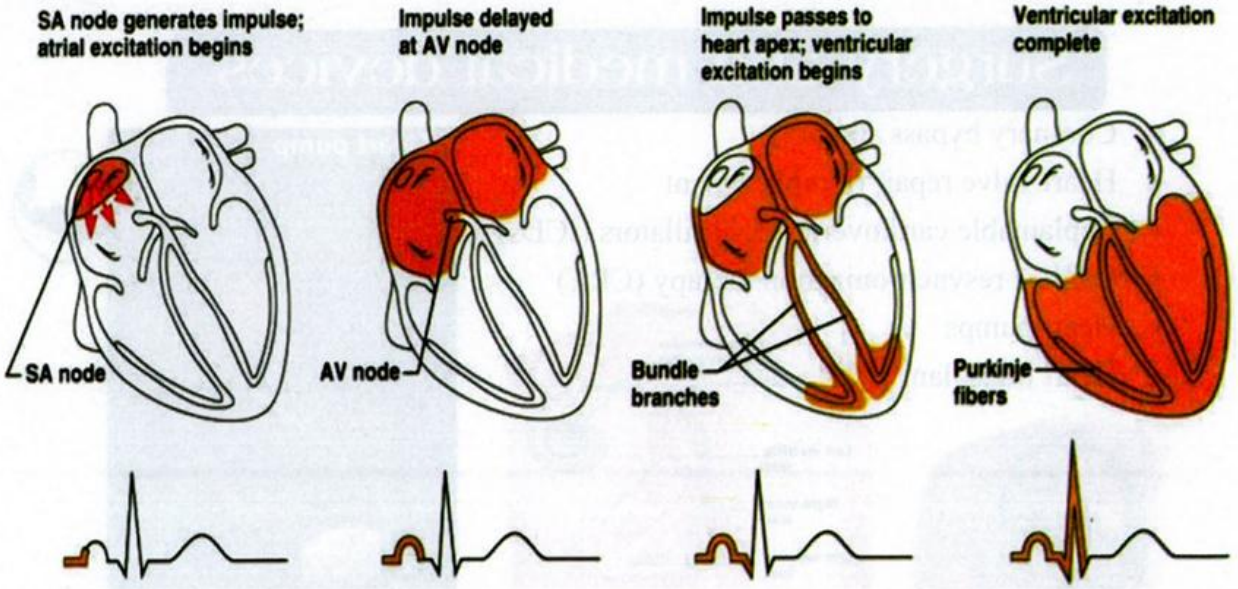


➢ **Conduction in the heart :-**

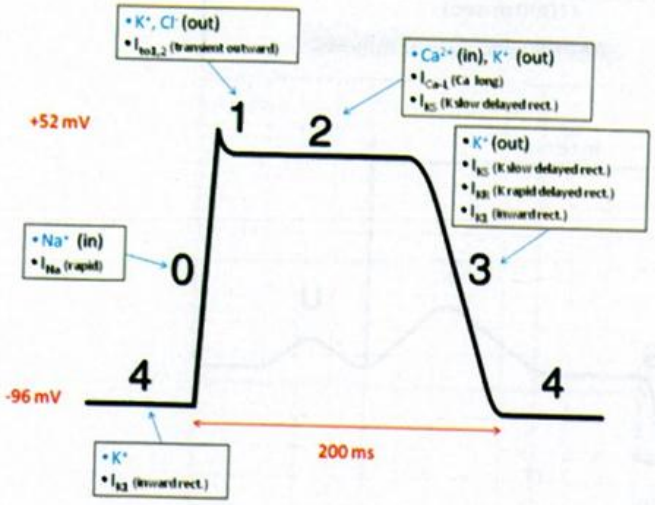
- Normally, the 4 chambers of the heart (2 atria and 2 ventricles) contract in a very specific, coordinated manner.
- The electrical impulse that signals your heart to contract in a synchronized manner begins in the sinoatrial node (SA node), which is your heart's natural pacemaker.
- The signal leaves the SA node and travels through the 2 upper chambers (atria).
- Then the signal passes through another node (the AV node), and finally, through the lower chambers (ventricles).
- The result is that the chambers contract in a coordinated fashion.

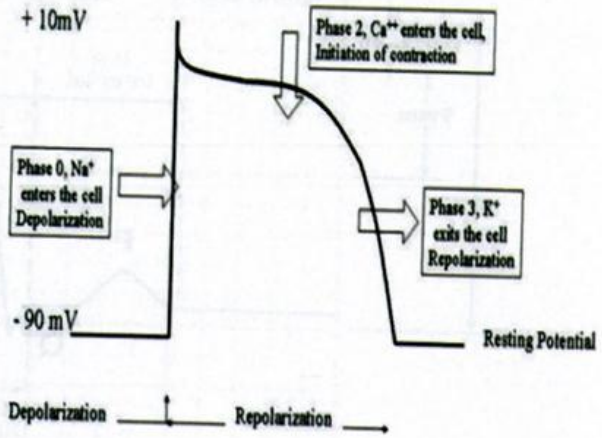


- Problems can occur anywhere along this conduction system, causing various arrhythmias.



➢ Cardiac Action Potential :-



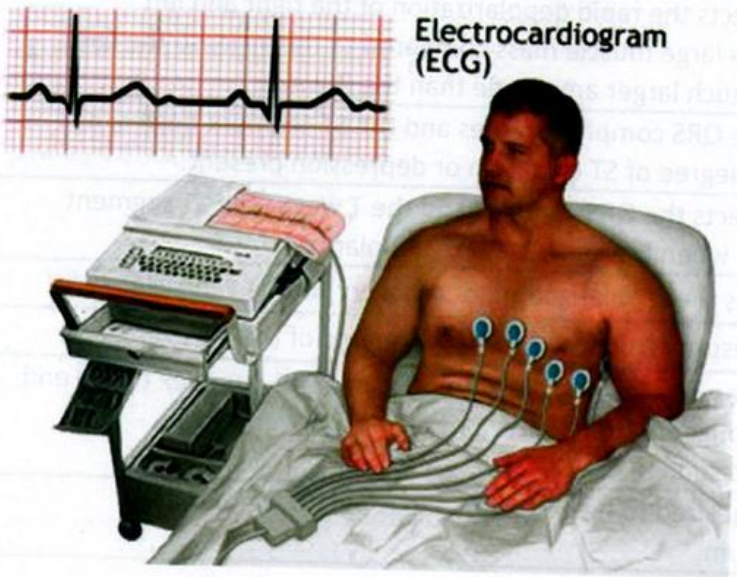


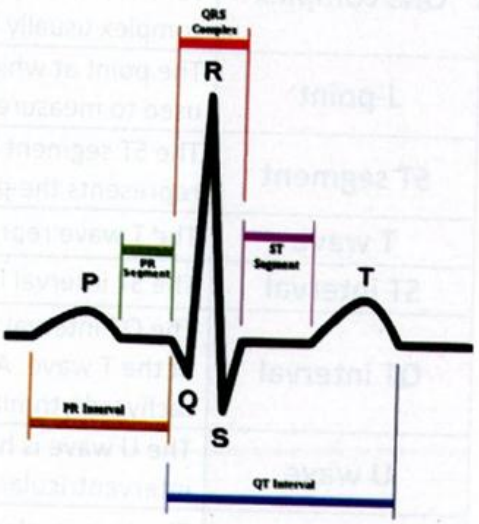
Phases of action potential

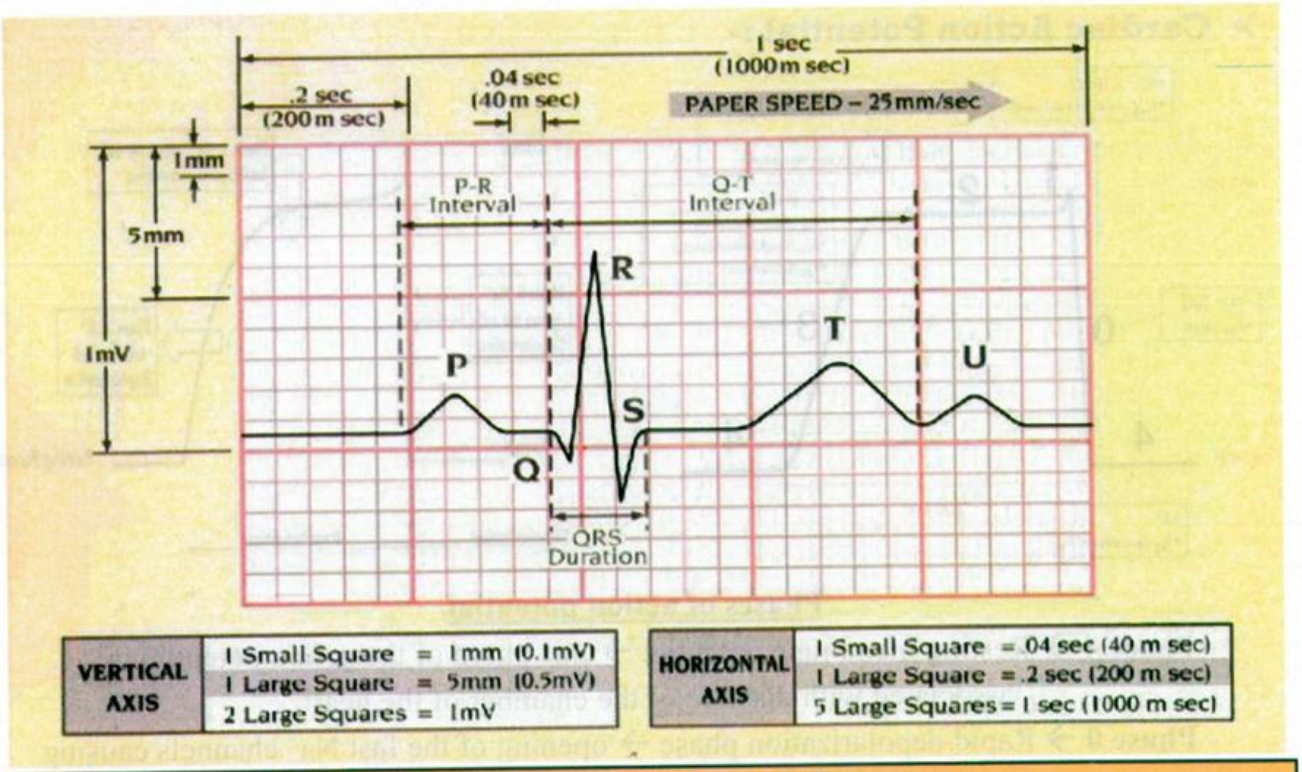
- **Phase 4** → Resting membrane potential → this phase of the action potential is associated with diastole of the chamber of the heart.
- **Phase 0** → Rapid depolarization phase → opening of the fast Na^+ channels causing a rapid increase in the membrane conductance.
- **Phase 1** → Inactivation of the fast Na^+ channels → due to lose of K^+ and Cl^- ions.
- **Phase 2** → (Plateau phase) → Influx of Ca^{2+} and efflux of K^+ (slow and partial).
- **Phase 3** → (Rapid repolarization phase) → K^+ channels opener (Rapid and complete).

➢ Electrocardiogram (ECG)

- ECG or EKG (from the German Elektrokardiogramm).
- ECG is used to measure the rate and regularity of heartbeats.

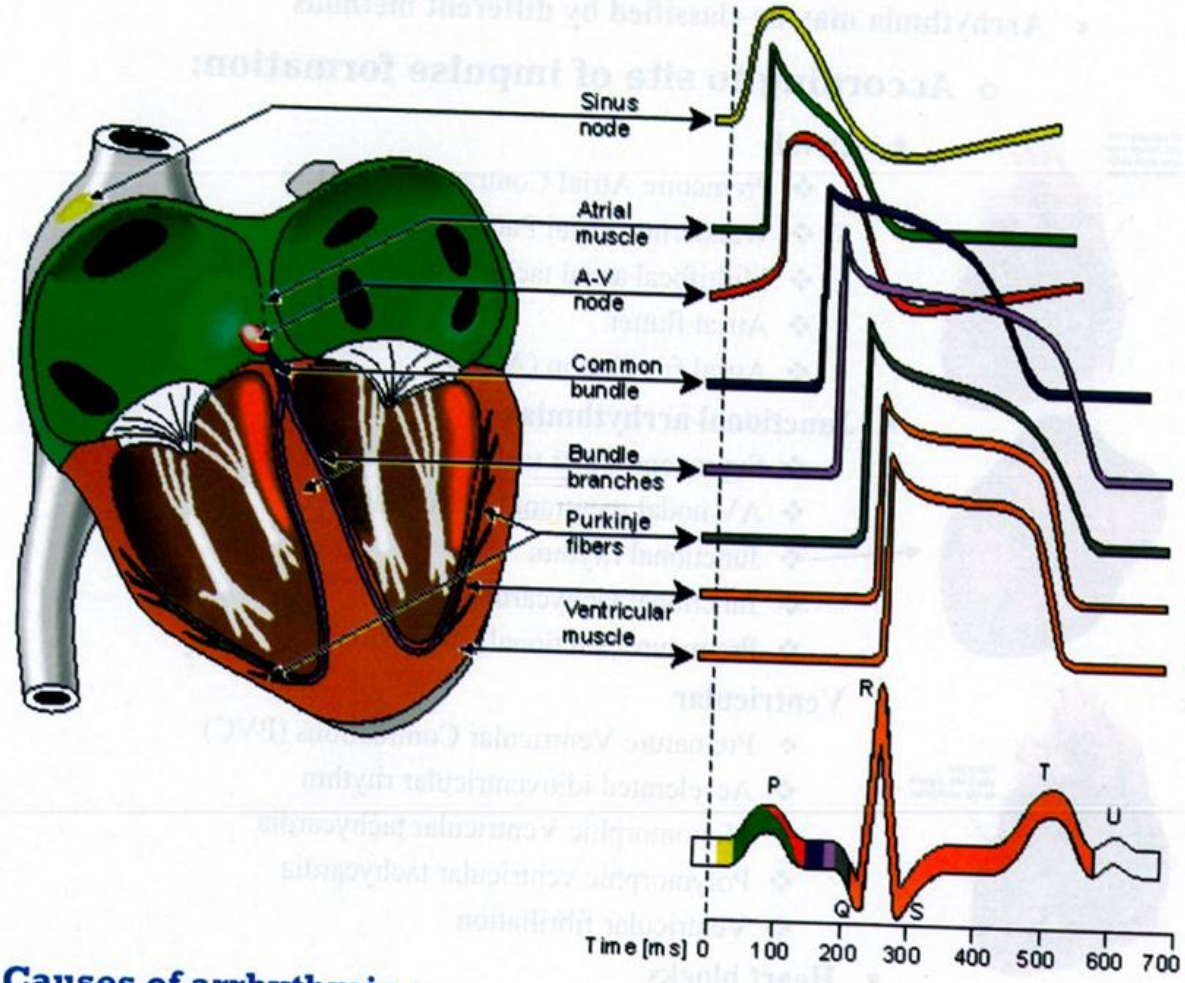






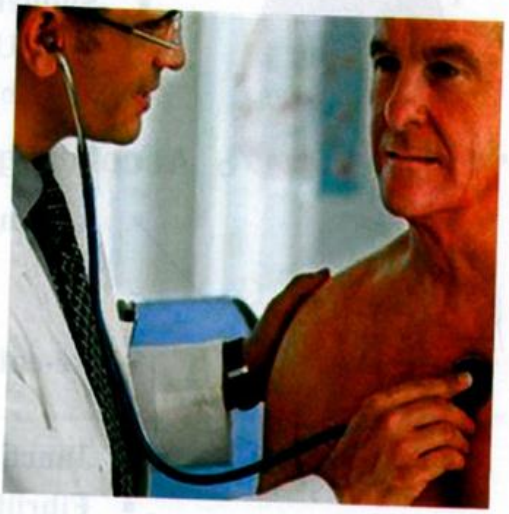
Feature	Description
RR interval	The interval between an R wave and the next R wave
P wave	During normal atrial depolarization, the main electrical vector is directed from the SA node towards the AV node, and spreads from the right atrium to the left atrium. This turns into the P wave on the ECG.
PR interval	The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex. The PR interval reflects the time the electrical impulse takes to travel from the sinus node through the AV node and entering the ventricles.
PR segment	The PR segment connects the P wave and the QRS complex.
QRS complex	The QRS complex reflects the rapid depolarization of the right and left ventricles. They have a large muscle mass compared to the atria, so the QRS complex usually has much larger amplitude than the P-wave.
J-point	The point at which the QRS complex finishes and the ST segment begins, it is used to measure the degree of ST elevation or depression present.
ST segment	The ST segment connects the QRS complex and the T wave. The ST segment represents the period when the ventricles are depolarized.
T wave	The T wave represents the repolarization (or recovery) of the ventricles
ST interval	The ST interval is measured from the J point to the end of the T wave.
QT interval	The QT interval is measured from the beginning of the QRS complex to the end of the T wave. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.
U wave	The U wave is hypothesized to be caused by the repolarization of the interventricular septum.
J wave	The J wave, elevated J-point.

➢ Relation between ECG and cardiac action potential:-



➢ Causes of arrhythmia :-

- Scarring of heart tissue (such as from a heart attack)
- Changes in heart structure (such as from cardiomyopathy)
- Coronary artery disease
- High blood pressure
- Diabetes, Smoking and Stress
- Overactive thyroid gland (hyperthyroidism)
- Drinking too much alcohol or caffeine
- Drug abuse and electrolytes imbalance



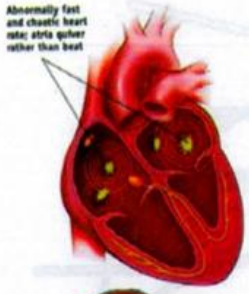
➢ Symptoms of arrhythmia :-

- Fast or slow heart beat (palpitation)
- Skipping beats and Cardiac arrest
- Fainting
- Lightheadedness, Dizziness and Chest pain
- Shortness of breath, Paleness and Sweating

➢ Classification of arrhythmia :-

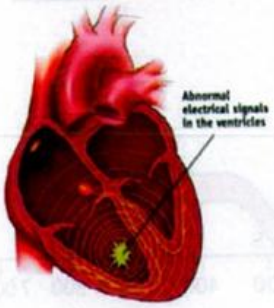
- **Arrhythmia may be classified by different methods**

o According to site of impulse formation:

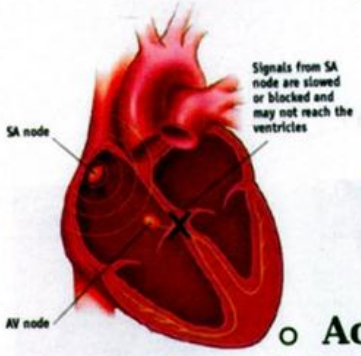


- **Atrial**
  - ❖ Premature Atrial Contractions (PACs)
  - ❖ Wandering Atrial Pacemaker
  - ❖ Multifocal atrial tachycardia
  - ❖ Atrial flutter
  - ❖ Atrial fibrillation (A-fib)

- **Junctional arrhythmias**
  - ❖ Supraventricular tachycardia (SVT)
  - ❖ AV nodal reentrant tachycardia
  - ❖ Junctional rhythm
  - ❖ Junctional tachycardia
  - ❖ Premature junctional contraction

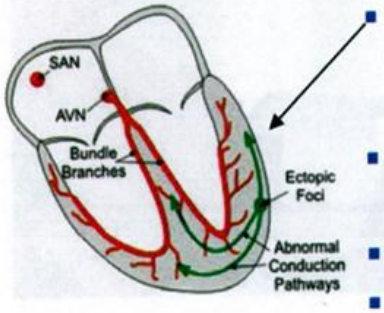


- **Ventricular**
  - ❖ Premature Ventricular Contractions (PVC)
  - ❖ Accelerated idioventricular rhythm
  - ❖ Monomorphic Ventricular tachycardia
  - ❖ Polymorphic ventricular tachycardia
  - ❖ Ventricular fibrillation



- **Heart blocks**
  - ❖ First degree
  - ❖ Second degree
  - ❖ Third degree
- **Sudden arrhythmic death syndrome (SADS)**
  - ❖ Used to describe sudden death due to cardiac arrest brought on by an arrhythmia.

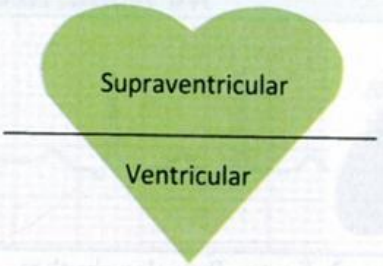
o According to Mechanism:



- **Automaticity (Ectopic pacemaker or Ectopic focus)** → excitable group of cells that causes a premature heart beat outside the normally functioning SA node
- **Re-entry** (electrical impulse recurrently travels in a tight circle within the heart)
- **Junctional**
- **Fibrillation** (Atrial fibrillation or Ventricular fibrillation)

o According to heart rate:

- **Tachycardia**
- **Bradycardia**
- **Premature heartbeats**
- **Heart Block**



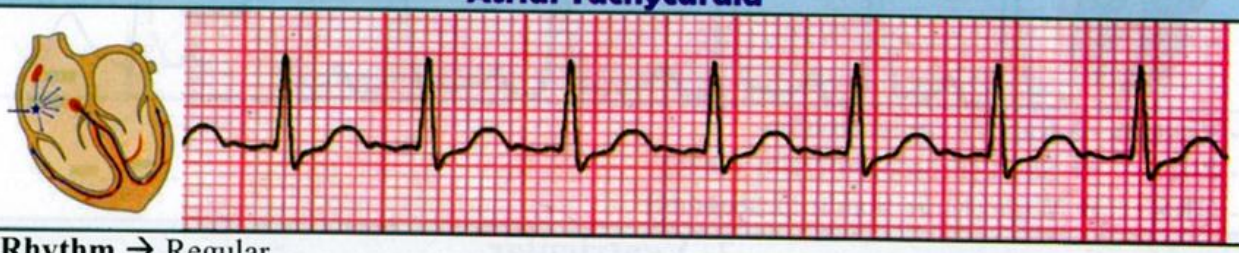
A- Tachycardia

- This refers to a fast heartbeat → a resting heart rate greater than 100 beats a minute.

1- Supraventricular

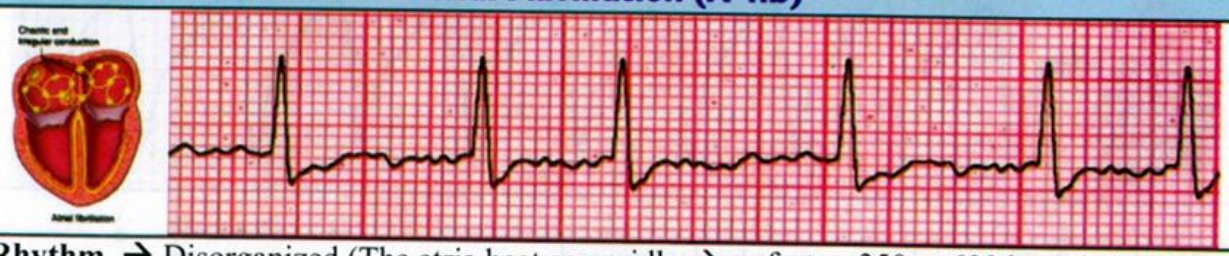
- This is a type tachycardia that originates from above the ventricles, such as the atria.
- It is sometimes known as paroxysmal atrial tachycardia (PAT).
- Several types of supraventricular tachycardia.

Atrial Tachycardia



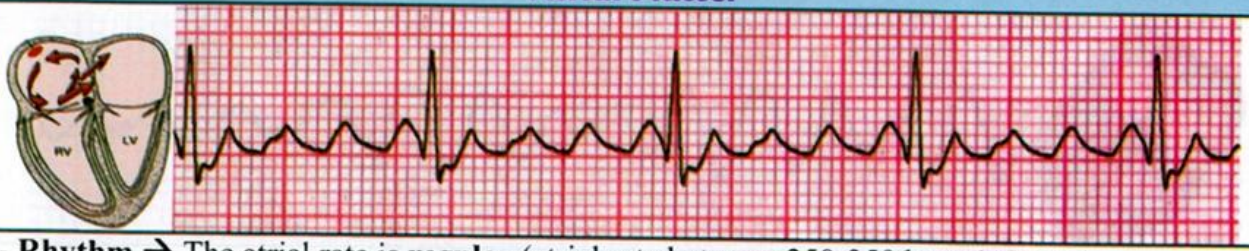
- **Rhythm** → Regular
- **P-Wave** → Deficult to see due to rabid rate

Atrial Fibrillation (A-fib)



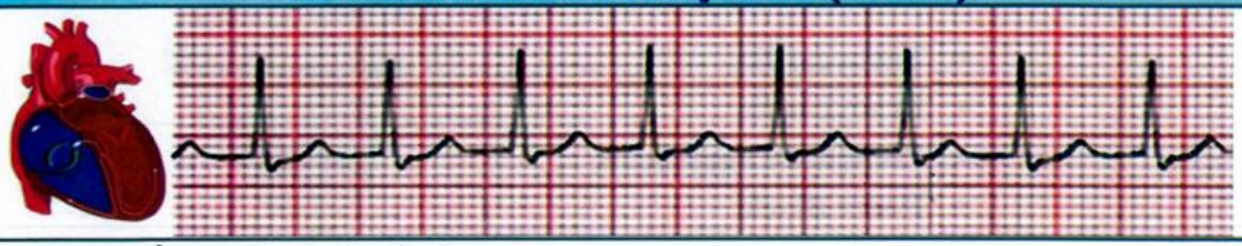
- **Rhythm** → Disorganized (The atria beat so rapidly → as fast as 350 to 600 beats/minute)
  → Pulse is irregularly irregular/irregular rhythm
- **P-Wave** → No P wave
- **QRS** → Irregular (Slow or Rapid) less than 0.12 seconds (Narrow)

Atrial Flutter



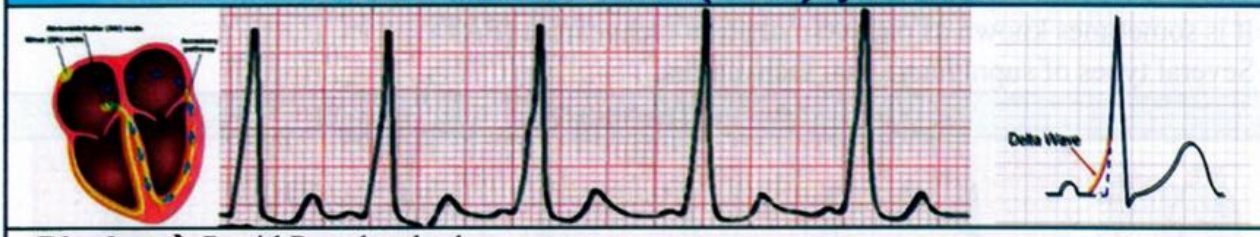
- **Rhythm** → The atrial rate is **regular** (atrial rate between 250-350 beats/minute)
- **P-Wave** → Will be well defined and have a "Saw tooth" pattern to them
- **QRS** → Narrow (Less than 0.12 seconds)

AV Nodal Reentrant Tachycardia (AVNRT)



- **Rhythm** → Faster Regular rhythm
- **P-Wave** → No P-wave
- **QRS** → Narrow (Less than 0.12 seconds)

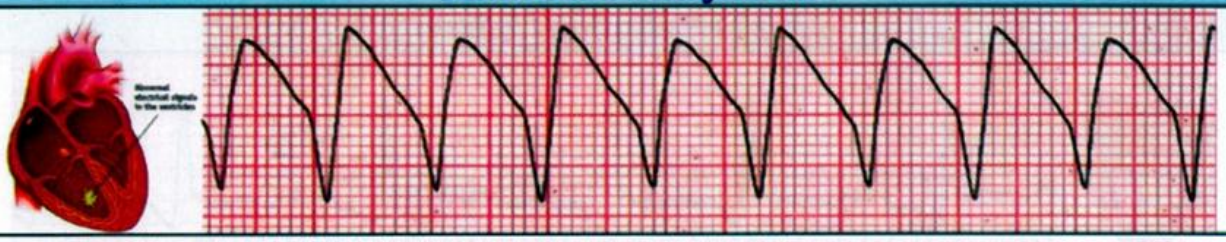
AV Reciprocating Tachycardia (AVRT)
Wolff Parkinson White (WPW) syndrome



- **Rhythm** → Rapid Regular rhythm
- **P-R** → Short (Present of Delta Wave)
- **QRS** → Wide (More than 0.12 seconds)

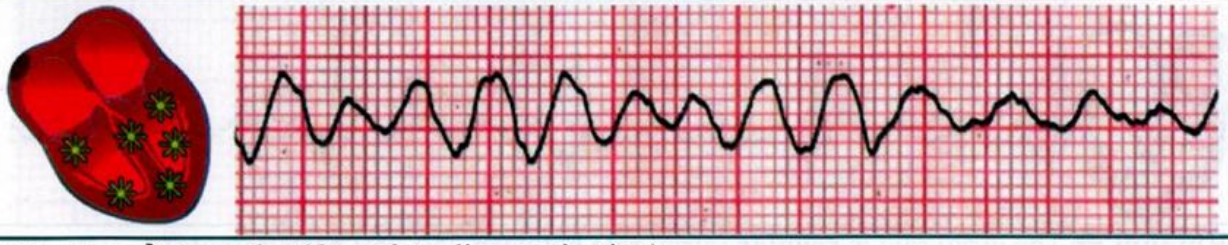
2- Ventricular

Ventricular Tachycardia



- **Rhythm** → The atrial rate cannot be determined.
  → Ventricular rate is usually between 150 and 250 beats/min.
- **P-Wave** → No P-wave
- **QRS** → Wider (More than 0.12 seconds)

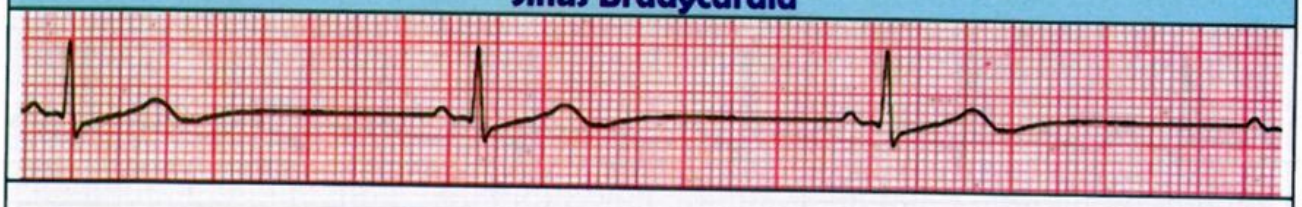
Ventricular Fibrillation



- **Rhythm** → Irregular (Complete disorganization)
- **P-Wave** → No P-wave
- **QRS** → No QRS complexes

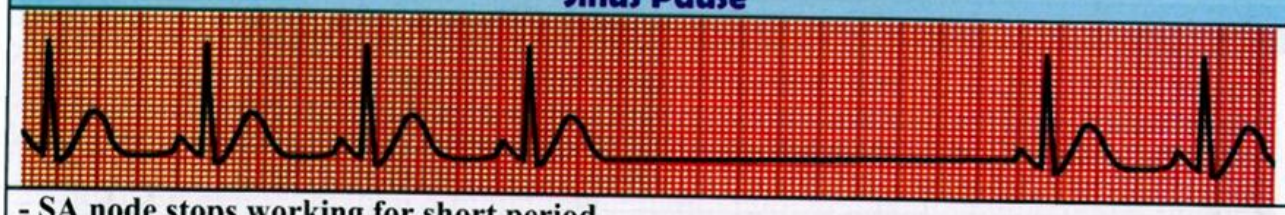
B- Bradycardia

Sinus Bradycardia



- **Rhythm** → Rate is less than 60 beats/min (Normal rhythm, but slow).
- **P-Wave** → P wave is present
- **QRS** → Narrow (less than 0.12 seconds)

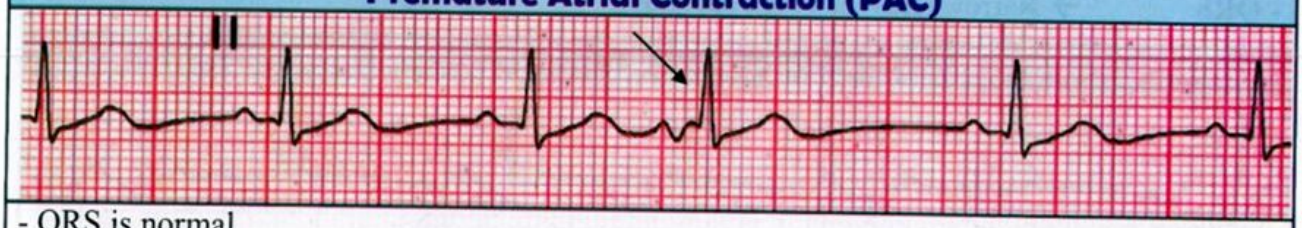
Sinus Pause



- **SA node stops working for short period**
- **Pause in heart beat for 6-8s**

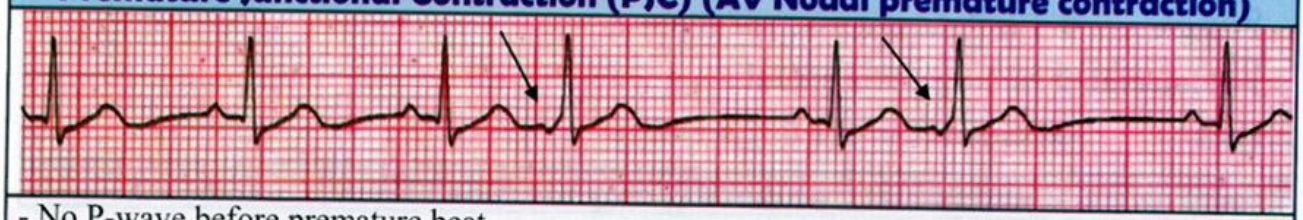
C- Premature heartbeats

Premature Atrial Contraction (PAC)



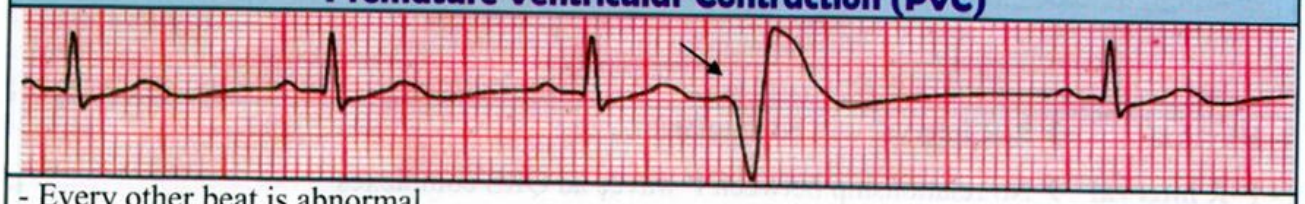
- QRS is normal
- P-wave is present but looks different on the premature beat

Premature Junctional Contraction (PJC) (AV Nodal premature contraction)



- No P-wave before premature beat
- QRS is normal

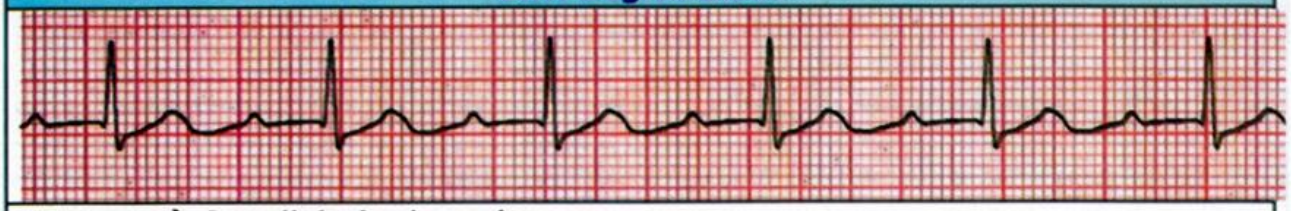
Premature Ventricular Contraction (PVC)



- Every other beat is abnormal
- One QRS complex and P-wave are normal
- Next QRS is wide and T-wave is inverted

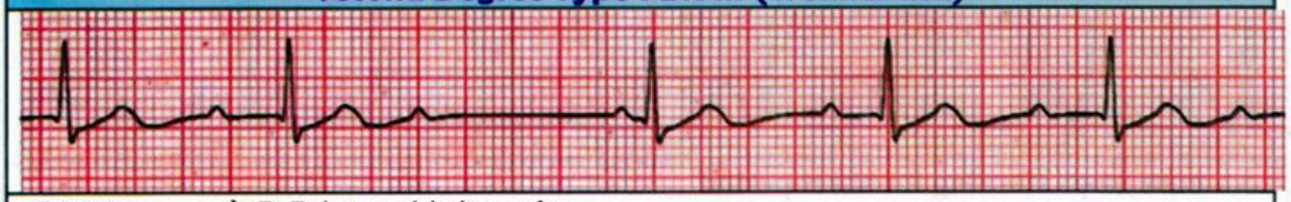
D- Heart Block

First Degree Block



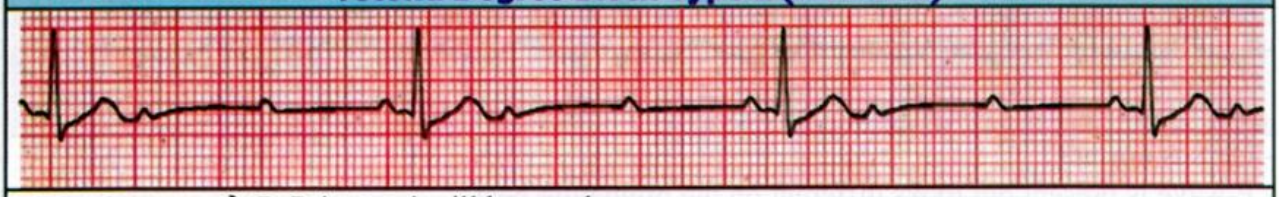
- **Rhythm** → Overall rhythm is regular
- **P-Wave** → The P waves appear uniform
- **QRS** → Narrow (less than 0.12 seconds)

Second Degree Type 1 Block (Wenkebach)



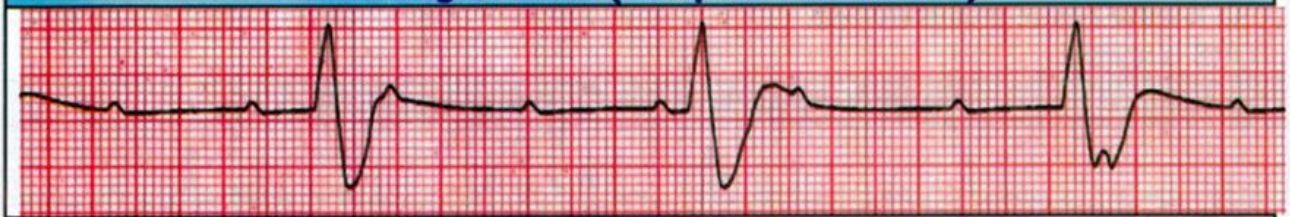
- **Rhythm** → R-R interval is irregular
- **P-R interval** → Progressively longer
- **QRS** → Narrow (less than 0.12 seconds)

Second Degree Block Type 2 (Mobitz II)



- **Rhythm** → R-R interval will be regular
- **P-Wave** → The P waves appear uniform
- **P-R interval** → No longer than normal
- **QRS** → Narrow (less than 0.12 seconds)

Third Degree Block (Complete Heart Block)



- **Rhythm** → R-R interval will be regular
- **P-R interval** → No relationship between P waves ad QRS complexes
- **QRS** → Wide (More than 0.12 seconds)

Antiarrhythmic Drugs

➢ Goal of antiarrhythmic drugs :-

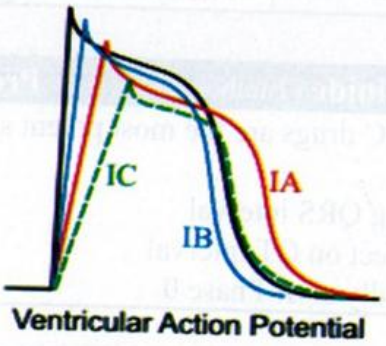
- The ultimate goal of antiarrhythmic drug therapy is to restore normal rhythm and conduction of the heart.

➢ Antiarrhythmic drugs are used to :-

- Decrease or increase conduction velocity
- Alter the excitability of cardiac cells by changing the duration of the effective refractory period
- Suppress abnormal automaticity

➢ Antiarrhythmic drug classes :-

- Class I - Sodium-channel blockers.
- Class II - β-blockers.
- Class III - Potassium-channel blockers.
- Class IV - Calcium-channel blockers.



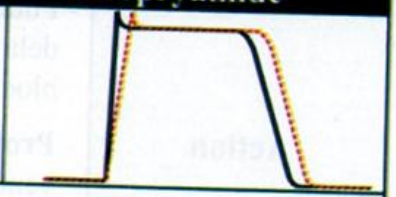
Ventricular Action Potential

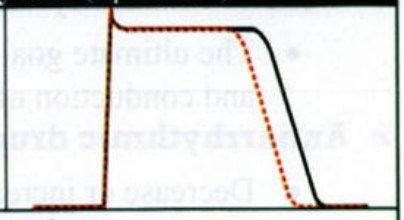
- **Class IA:** e.g., quinidine
  - Moderate Na^+-channel blockade
  - ↑ ERP
- **Class IB:** e.g., lidocaine
  - Weak Na^+-channel blockade
  - ↓ ERP
- **Class IC:** e.g., flecainide
  - Strong Na^+-channel blockade
  - → ERP

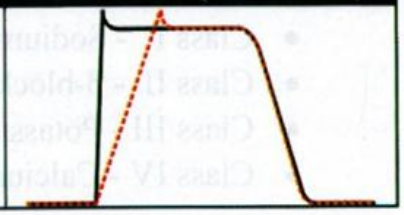
Sodium-Channel Blockers (Class I Antiarrhythmic)

➢ Mechanism of action :-

- Sodium-channels blockers affected in action potential by blocking Na^+ channels in the heart.
- Also called Membrane stabilizing agents.

Class IA		
Quinidine (Quinacard®)	Procainamide (Pronestyl®)	Disopryamide
- Class IA drugs have moderate potency as sodium channel blockers → prolong QRS interval. **(Slow Phase 0)** - Also usually prolong repolarization (prolong QT interval) through blockade of potassium channels.		
Uses	→ **Quinidine** - Atrial tachycardia, atrial Flutter and atrial fibrillation → **Procainamide** & **Disopryamide** → Atrial and ventricular arrhythmia	
Major adverse effects	→ **Quinidine** → **Cinchonism** (blurred vision, tinnitus, headache, psychosis, cramping and nausea). → **Procainamide** → lupus-like syndrome and Rheumatoid-like reaction. → **Disopryamide** → (-ve) inotropic effect.	

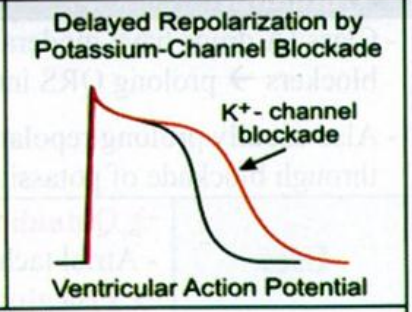
Class IB		
Lidocaine (Xylocaine®)	**Tocainide** (Tonocard®)	**Mexiletine** (Mexitil®)
Lignocaine (Xylocard®)	**Phenytoin** (Epanutin®)	
- Class IB drugs have the lowest potency as sodium channel blockers - No effect on QRS interval - Decrease QT interval - Shortens Phase 3		
Uses	- Ventricular arrhythmia during myocardial infarction. - **Phenytoin** → Digitalis induced arrhythmia (drug of choice).	

Class IC		
Flecainide (Tambocor®)	**Propafenone** (Rythmol®)	**Moricizine** (Ethmozine®)
- Class IC drugs are the most potent sodium channel blocking agents - Prolong QRS interval - No effect on QT interval - Markedly slow Phase 0		

β-blockers (Class II Antiarrhythmic)

Propranolol (Inderal®)
- Decreasing sympathetic activity on the heart. - Useful in the treatment of supraventricular tachycardia. - Inhibit Phase 4 depolarization in SA and AV nodes. - Slow rhythm, prolong PR interval, no effect on QRS or QT intervals.

Class III – Potassium-channel blockers

Amiodarone (Cardarone®)	**Dronedarone** (Multaq®)	**Ibutilide** (Corvert®)
Bretylium (Bretylate®)	**Sotalol** (Betacore®)	**Dofetilide** (Tikosyn®)
Action	- Potassium-channels blockers → cause delayed the action potential by blocking K^+ channels in the heart. - **Prolongs Phase 3** repolarization in ventricular muscle fibers. - Prolong QT interval	
Uses	- Supraventricular and Ventricular Arrhythmia	
Major adverse effects	- **Amiodarone** → Pulmonary toxicity, Photosensitivity, Thyroid dysfunction, Hepatotoxicity and Constipation. - **Bretylium** → Postural Hypotension.	

Class IV - Calcium-channel blockers

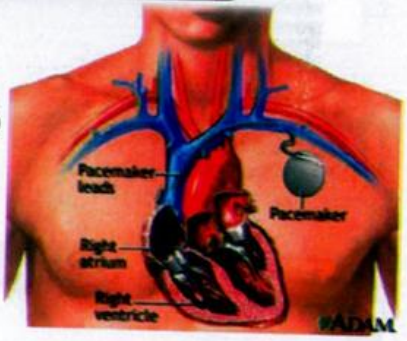
Verapamil (Isoptin®)	Diltiazem (Altiazem®)
Action	- They decrease conduction through the AV node. - Shorten phase 2 (Plateau) of the cardiac action potential.
Uses	- Supraventricular arrhythmia

Other Agents

Digoxin (Lanoxin®)	
Action	- Used in atrial fibrillation (AF) due to Decreases conduction of electrical impulses through the AV node.
Adverse effects	- May Cause Ventricular tachycardia and fibrillation (Treated by Phenytoin).
Adenosine (Regenerate®)	
Action	- Adenosine is a naturally occurring nucleoside, - But at high doses, the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node. - Intravenous adenosine is the Drug of choice for abolishing **acute supraventricular tachycardia.**
Magnesium sulfate	
Uses	- In digitalis induced arrhythmia if hypomagnesaemia is present

Surgery and medical devices

- **Medical devices:**
  - Pacemaker
  - Implantable cardioverter-defibrillators (ICD)



- **Surgical treatments:**
  - Maze procedure:
    - This involves making a series of surgical incisions in the upper half of your heart (atria).
  - Ventricular aneurysm surgery:
    - In some cases, a bulge (aneurysm) in a blood vessel leading to the heart is the cause of an arrhythmia.
    - It involves removing the aneurysm.
  - Coronary bypass surgery:
    - If have severe coronary artery disease

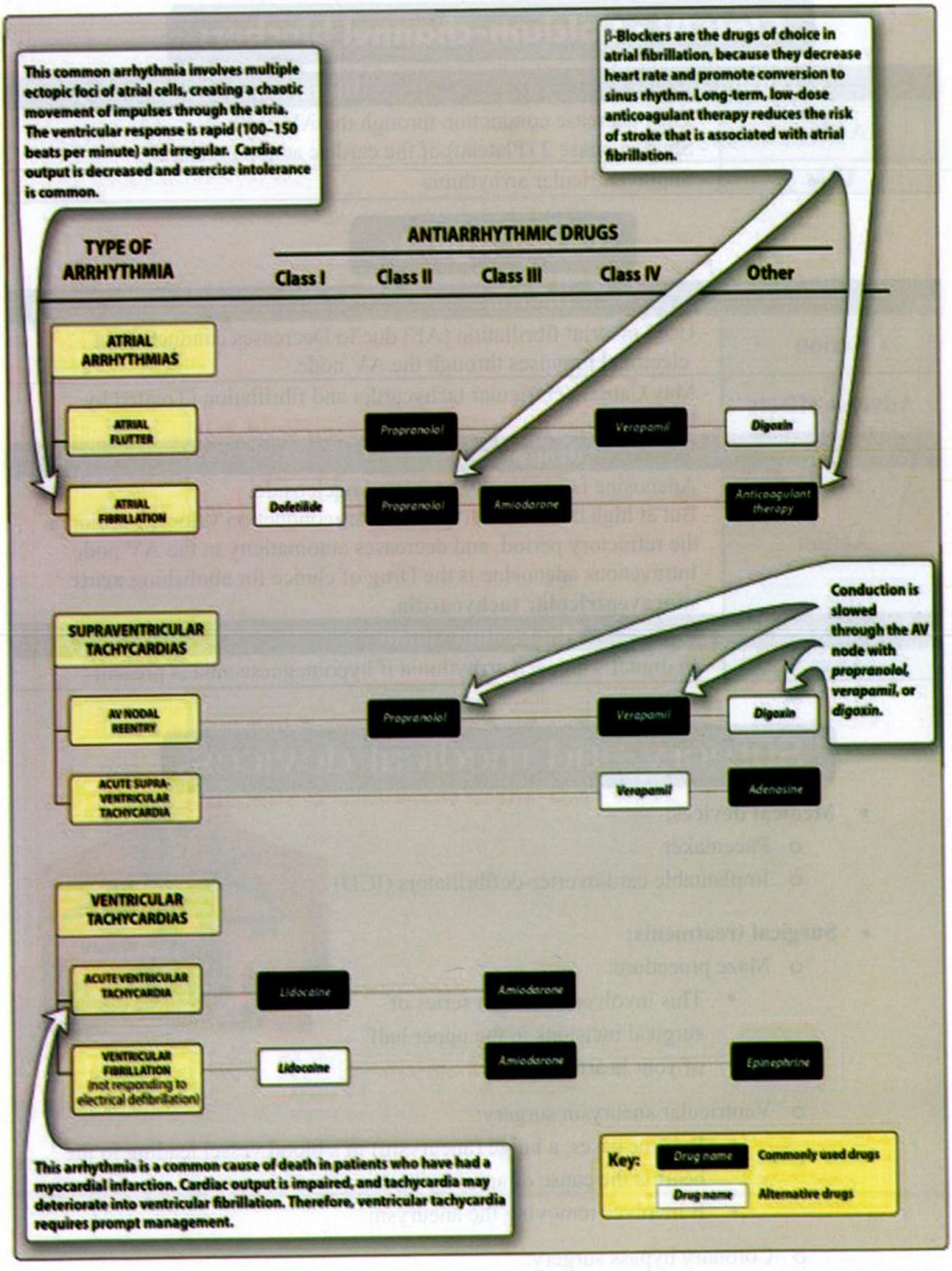


Table from Pharmacology 5th edition Lippincott Williams & Wilkins, 2012, p 208

Questions

➢ Coose the best answer :-

111: A 75-year-old female in congestive heart failure (CHF) is unable to climb a flight of stairs without experiencing shortness of breath. Digoxin is administered to improve cardiac muscle contractility. Within two weeks, she has a marked improvement in her symptoms. What cellular action of digoxin accounts for this?

a. Inhibition of cAMP synthesis
b. Inhibition of Ca^{2+} release
c. Inhibition of the Na^+/K^+ ATPase pump
d. Inhibition of β-adrenergic stimulation
e. Inhibition of ATP degradation

112: In a patient who has had attacks of Paroxysmal atrial tachycardia, an ideal prophylactic drug is

a. Adenosine
b. Procainamide
c. Lidocaine
d. Nifedipine
e. Verapamil

113: The therapeutic action of β-adrenergic receptor blockers such as propranolol in angina pectoris is believed to be primarily the result of

a. Reduced production of catecholamines
b. Dilation of the coronary vasculature
c. Decreased requirement for myocardial oxygen
d. Increased peripheral resistance
e. Increased sensitivity to catecholamines

114: A 59-year-old female with mild CHF is treated with furosemide. What is its primary mechanism of action?

a. Inhibition of Na^+,K^+ ATPase
b. Inhibition of Na^+, K^+, Cl^- co-transporter
c. Inhibition of Na^+,Cl^- co-transporter
d. Inhibition of Cl− transporter
e. Inhibition of Ca^{2+} transporter

115: A 59-year-old male with a history of rheumatic heart disease is found to have atrial fibrillation (AF), for which he is treated with digoxin. Treatment with digoxin converts his AF to a normal sinus rhythm and most likely results in a decrease in which of the following?

a. The length of the refractory period
b. The velocity of shortening of the cardiac muscle
c. The conduction velocity in the AV node
d. The atrial maximum diastolic resting potential

116: A 65-year-old female receives digoxin and furosemide for CHF. After several months, she develops nausea and vomiting. Serum K^+ is 2.5 mEq/L. Electrocardiogram (EKG) reveals an AV conduction defect. What cellular effect is causing these new findings?

a. Increased intracellular K^+
b. Increased intracellular cGMP
c. Increased intracellular Ca^{2+}
d. Increased intracellular norepinephrine
e. Increased intracellular nitric oxide (NO)

117: The EKG of a patient who is receiving digitalis in the therapeutic dose range would be likely to show

a. Prolongation of the QT interval
b. Prolongation of the PR interval
c. Symmetric peaking of the T wave
d. Widening of the QRS complex
e. Elevation of the ST segment

118: In a hypertensive patient who is taking insulin to treat diabetes, which of the following drugs is to be used with extra caution and advice to the patient?

a. Hydralazine b. Prazosin c. Guanethidine
d. Propranolol e. Methyldopa

119: Which of the following drugs is considered to be most effective in relieving and preventing ischemic episodes in patients with variant angina?

a. Propranolol b. Nitroglycerin c. Sodium nitroprusside
d. Nifedipine e. Isosorbide dinitrate

120: If quinidine and digoxin are administered concurrently, which of the following effects does quinidine have on digoxin?

a. The absorption of digoxin from the GI tract is decreased
b. The metabolism of digoxin is prevented
c. The concentration of digoxin in the plasma is increased
d. The effect of digoxin on the AV node is antagonized
e. The ability of digoxin to inhibit the Na^+ K^+ ATPase is reduced

121: A 64-year-old male with arteriosclerotic heart disease (AHD) and CHF who has been treated with digoxin complains of nausea, vomiting, and diarrhea. His EKG reveals a bigeminal rhythm. The symptoms and EKG findings occurred shortly after another therapeutic agent was added to his regimen. A drug-drug interaction is suspected. Which agent was involved?

a. Lovastatin b. Hydrochlorothiazide c. Phenobarbital
d. Nitroglycerin e. Captopril

122: Compensatory increases in heart rate and renin release that occur in heart failure may be alleviated by which of the following drugs?

a. Milrinone b. Digoxin c. Dobutamine
d. Enalapril e. Metoprolol

123: A 69-year-old male with angina develops severe constipation following treatment with

a. Propranolol b. Captopril c. Verapamil
d. Dobutamine e. Nitroglycerin

124: A 58-year-old man is admitted to the hospital with acute heart failure and pulmonary edema. Which one of the following drugs would be most useful in treating the pulmonary edema?

a. Digoxin b. Dobutamine c. Furosemide
d. Minoxidil e. Spironolactone

125: Angiotensin converting enzyme (ACE) inhibitors are associated with a high incidence of which of the following adverse reactions?

a. Hepatitis b. Hypokalemia c. Agranulocytosis
d. Proteinuria e. Hirsutism

126: Patients with genetically low levels of N-acetyltransferase are more prone to develop a lupus erythematosus–like syndrome with which of the following drugs?

a. Propranolol b. Procainamide c. Digoxin
d. Captopril e. Lidocaine

127: A 46-year-old man is admitted to the emergency department. He has taken more than 90 digoxin tablets (0.25 mg each), ingesting them about 3 hours before admission. His pulse is 50 to 60 beats per minute, and the electrocardiogram shows third-degree heart block. Which one of the following is the most important therapy to initiate in this patient?

a. Digoxin immune Fab b. Potassium salts c. Lidocaine
d. Phenytoin e. DC cardio version

128: The preferred agent to combat extreme digoxin overdose is

a. K^+ b. Ca^{2+} c. Phenytoin
d. Fab fragments of digoxin antibodies e. Magnesium (Mg^{2+})

129: Significant relaxation of smooth muscle of both venules and arterioles is produced by which of the following drugs?

a. Hydralazine b. Minoxidil c. Diazoxide
d. Sodium nitroprusside e. Nifedipine

130: The first-line drug for treating an acute attack of reentrant supraventricular tachycardia (SVT) is

a. Adenosine b. Digoxin c. Propranolol
d. Phenylephrine e. Edrophonium

131: A 57-year-old man is being treated for an atrial arrhythmia. He complains of headache, dizziness, and tinnitus.

Which one of the following antiarrhythmic drugs is the most likely cause?

a. Amiodarone b. Procainamide c. Propranolol
d. Quinidine e. Verapamil

132: An 83-year-old male has been effectively treated with hydrochlorothiazide to control his elevated blood pressure. He has had a recent onset of weakness. Blood chemistry analysis reveals a K^+ of 2.5 mEq/L. Another drug is added, and one month later his serum K^+ is 4.0 mEq/L.

a. Acetazolamide b. Amiloride c. Furosemide
d. Hydrochlorothiazide e. Mannitol

133: A 76-year-old male with a combined history of bronchiogenic carcinoma and CHF is maintained on a diuretic to control pulmonary and peripheral edema. Recent measurement of blood electrolytes reveals an elevated serum Ca^{2+}.

a. Acetazolamide b. Amiloride c. Furosemide
d. Hydrochlorothiazide e. Mannitol

134: A 66-year-old female with CHF and hearing loss is given a diuretic as part of a regimen that includes digoxin and an ACE inhibitor. In the course of treatment, she develops an AV conduction defect and is found to be hypomagnesemic. She also has worsening hearing loss, which is reversed when the drug is stopped.

a. Acetazolamide b. Amiloride c. Furosemide
d. Hydrochlorothiazide e. Mannitol

135: Administration of which of the following antianginal agents results in antianginal effects for only 10 hours, despite detectable therapeutic plasma levels for 24 hours?

a. Atenolol b. Transdermal nitroglycerin c. Amlodipine
d. Amyl nitrite

136: A 56-year-old female has recently developed essential hypertension, for which she is receiving chlorothiazide to lower her blood pressure. Which of these ions would not increase in concentration in her urine?

a. K^+ b. Cl^- c. Ca^{2+}
d. Na^+ e. Mg^{2+}

137: A 56-year-old patient complains of chest pain following any sustained exercise. He is diagnosed with atherosclerotic angina. He is prescribed sublingual nitroglycerin for treatment of acute chest pain. Which of the following adverse effects is likely to be experienced by this patient?

a. Hypertension b. Throbbing headache c. Bradycardia
d. Sexual dysfunction e. Anemia

138: A 45-year-old man has recently been diagnosed with hypertension and started on monotherapy designed to reduce peripheral resistance and prevent Na^+ and water retention. He has developed a persistent cough. Which of the following drugs would have the same benefits but would not cause cough?

a. Losartan b. Nifedipine c. Prazosin
d. Propranolol

139: A 36-year-old male is seen in the ED with tachycardia, a respiratory rate of 26 breaths per minute (BPM), and EKG evidence of an arrhythmia. An intravenous bolus dose of an antiarrhythmic agent is administered, and within 30 s, he has a respiratory rate of 45 BPM and complains of a burning sensation in his chest.

a. Adenosine b. Captopril c. Clonidine
d. Digoxin e. Dobutamine

140: A 50-year-old male with a two-year history of essential hypertension well controlled on hydrochlorothiazide is found on a recent physical examination to have a blood pressure of 160/105 mmHg. The hydrochlorothiazide is substituted with another agent. Two weeks later, he returns for follow-up complaining of a loss of taste.

a. Adenosine b. Captopril c. Clonidine
d. Digoxin e. Dobutamine

141: A 54-year-old female is treated for essential hypertension with an antihypertensive that controls her blood pressure. One day, she comes to the ED with chest pain, tachycardia, anxiety, and a blood pressure of 240/140 mmHg. She has not taken her medication for two days. Which antihypertensive can account for her findings?

a. Clonidine b. Propranolol c. Doxazosin
d. Minoxidil e. Prazosin

142: Which one of the following drugs may cause a precipitous fall in blood pressure and fainting on initial administration?

a. Atenolol b. Hydrochlorothiazide c. Nifedipine
d. Prazosin e. Verapamil

143: Which one of the following antihypertensive drugs can precipitate a hypertensive crisis following abrupt cessation of therapy?

a. Clonidine b. Diltiazem c. Enalapril
d. Losartan e. Hydrochlorothiazide

144: For each patient, select the drug most likely to have caused the adverse effect.

a. Adenosine	b. Amiodarone	c. Bretylium
d. Flecainide	e. Procainamide	f. Propafenone
g. Quinidine	h. Sotalol	i. Tocainide
j. Verapamil		

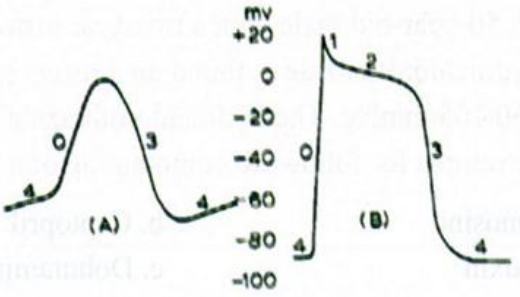
A: A 68-year-old female has AF, which is treated with an antiarrhythmic agent that blocks Na+ channels. On a recent office visit, she complained of recurrent attacks of feeling faint and of experiencing an episode of loss of consciousness. An EKG showed marked prolongation of the QT interval. Plasma concentration of the drug was in the therapeutic range.

a	b	c	d	e
f	g	h	i	j

B: A 55-year-old male has recurrent ventricular arrhythmias after an MI, for which he is given an antiarrhythmic agent that blocks Na+ channels and prolongs the action potential. One year later, a blood test is positive for circulating antinuclear antibodies.

a	b	c	d	e
f	g	h	i	j

145: It is customary today to classify antiarrhythn drugs according to their mechanism of action. This is best defined by intracellular recordings that yield monophasic action potentials. In the accompanying figure, the monophasic action potentials of (A) slow response fiber (SA node) and (B) fast Purkinje fiber are shown. For each description that follows, choose the appropriate drug with which the change in character of the monophasic action potential is likely to be associated.



a. Digoxin	b. Amiodarone	c. Mexiletine
d. Nifedipine	e. Propranolol	f. Flecainide
g. Disopyramide	h. Verapamil	

A: Moderate phase 0 depression and slow conduction; prolonged repolarization

a	**b**	**c**	**d**	**e**
f	**g**	**h**	**i**	**j**

B: Affects mainly phase 3, prolonging repolarization

a	**b**	**c**	**d**	**e**
f	**g**	**h**	**i**	**j**

Answers

111	112	113	114	115	116	117	118	119	120
c	e	c	b	c	c	b	d	d	c
121	122	123	124	125	126	127	128	129	130
b	e	c	C	d	b	a	d	d	a
131	132	133	134	135	136	137	138	139	140
d	b	d	c	b	c	b	a	a	b
141	142	143	144-A	144-B	145-A	145-B			
a	d	a	g	e	g	b			

Questions and answers from (References):

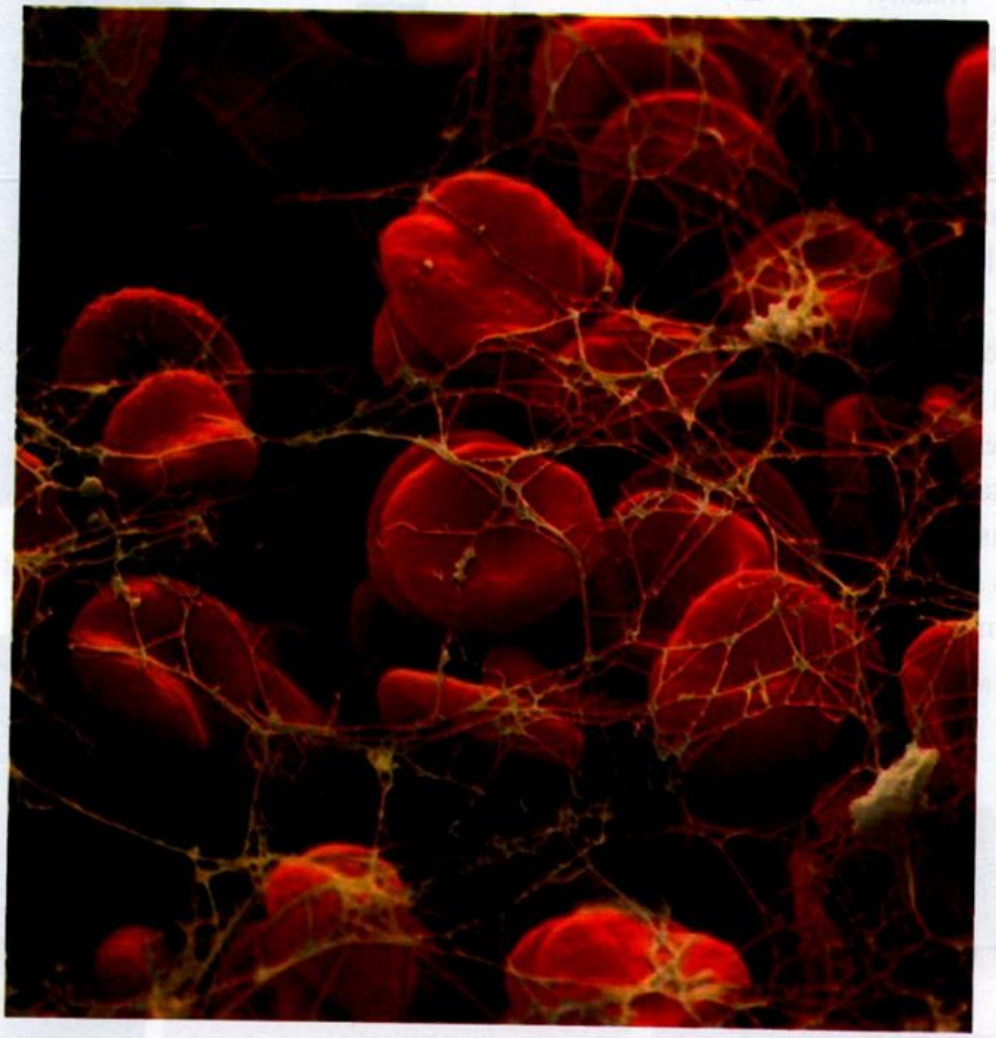
Basic and Clinical Pharmacology 12th edition, Katzung-Lange

Pharmacology 5th edition Lippincott Williams & Wilkins

Pharmacology 12th edition PreTest Self-Assessment and Review

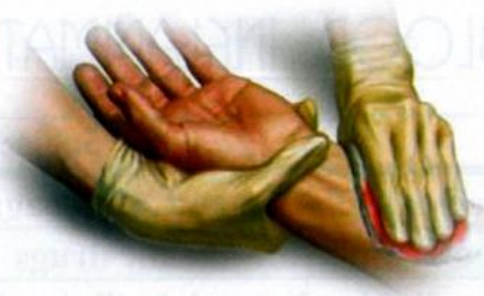
Blood, Inflammation and gout diseases

(BLOOD, INFLAMMATION AND GOUT DISEASES)



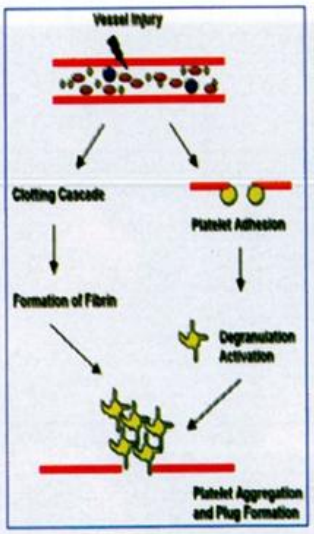
Blood Coagulation

➢ Introduction :-



- In normal situation a delicate balance prevents thrombosis and hemorrhage.
- Disorders of coagulation can lead to an increased risk of bleeding (hemorrhage) or obstructive clotting (thrombosis).
- Inside the vascular system the blood must remain in fluid form but when exposed to non-endothelial surface outside the vascular system, it clots quickly as in case of vascular injury.
- When intravascular thrombi do occur, a system of fibrinolysis is activated to restore fluidity.

➢ Main steps of clot formation:-



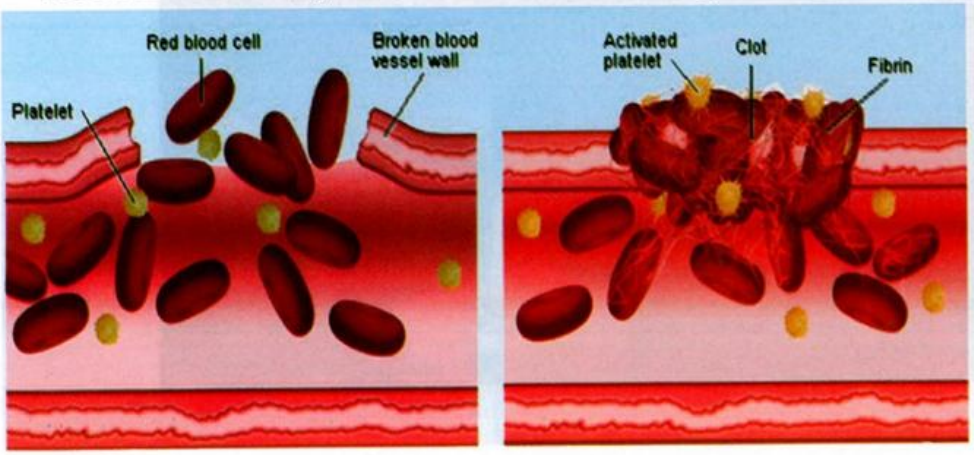
1: Vasoconstriction (VC)→ To decrease the blood flow in injured area.

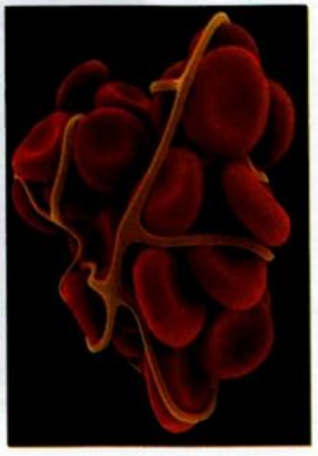
2: Platelet adheres to macromolecules in the subendothelial regions of the injured blood vessels.

3: Release of intracellular granules containing chemical mediators.

4: The platelets aggregate to form the primary haemostatic plug, plug which composed of the viscous content of lysed platelets.

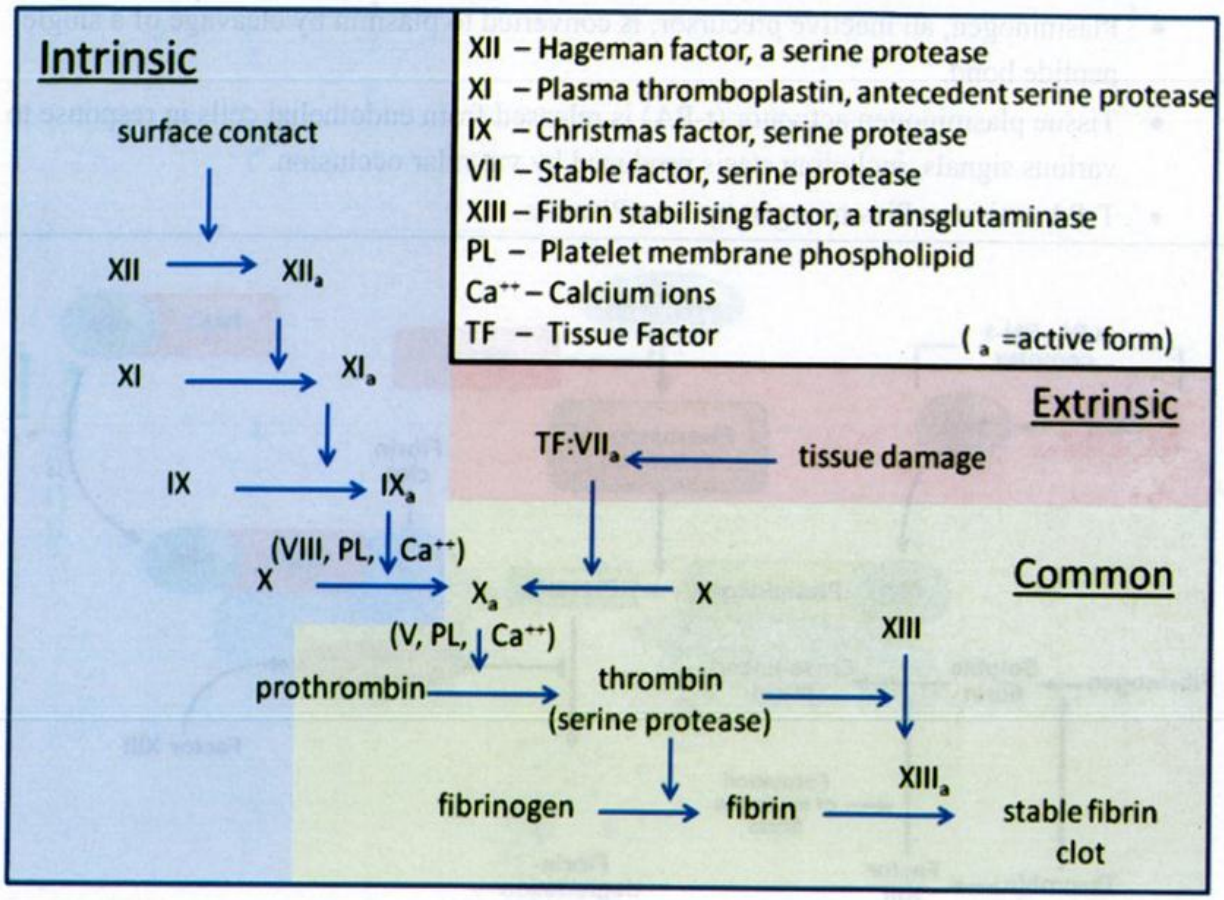
5: Platelets stimulate local activation of plasma **coagulation factors**, leading to generation of thrombin which catalysis the conversion of fibrinogen to fibrin.





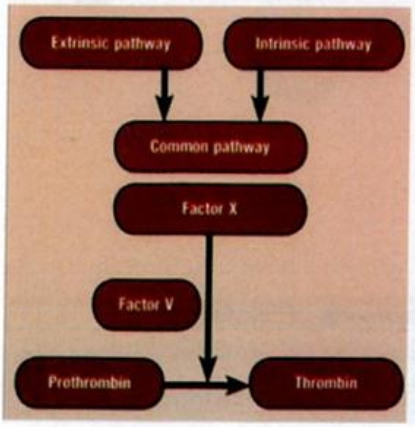
➢ Coagulation factors and Coagulation pathway:-

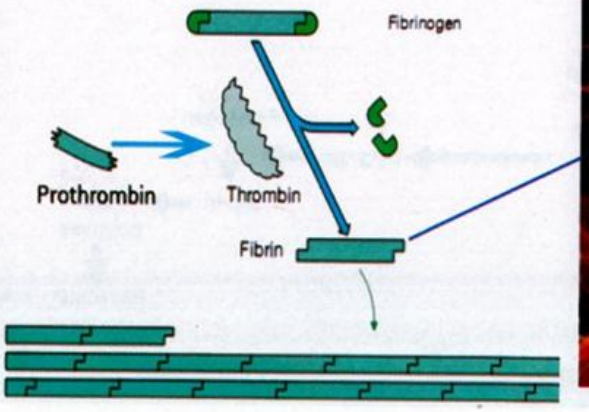
The three pathways that makeup the classical blood coagulation pathway

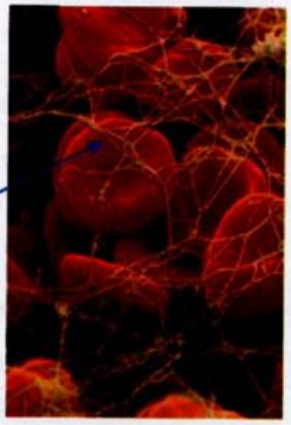


➢ Conversion of fibrinogen to fibrin :-

- Thrombin converts fibrinogen to fibrin
- Fibrin monomers bind together (bound to each other non-covalently) to form a gel.
- Fibrin act as **network** which collect RBCs to form clot.

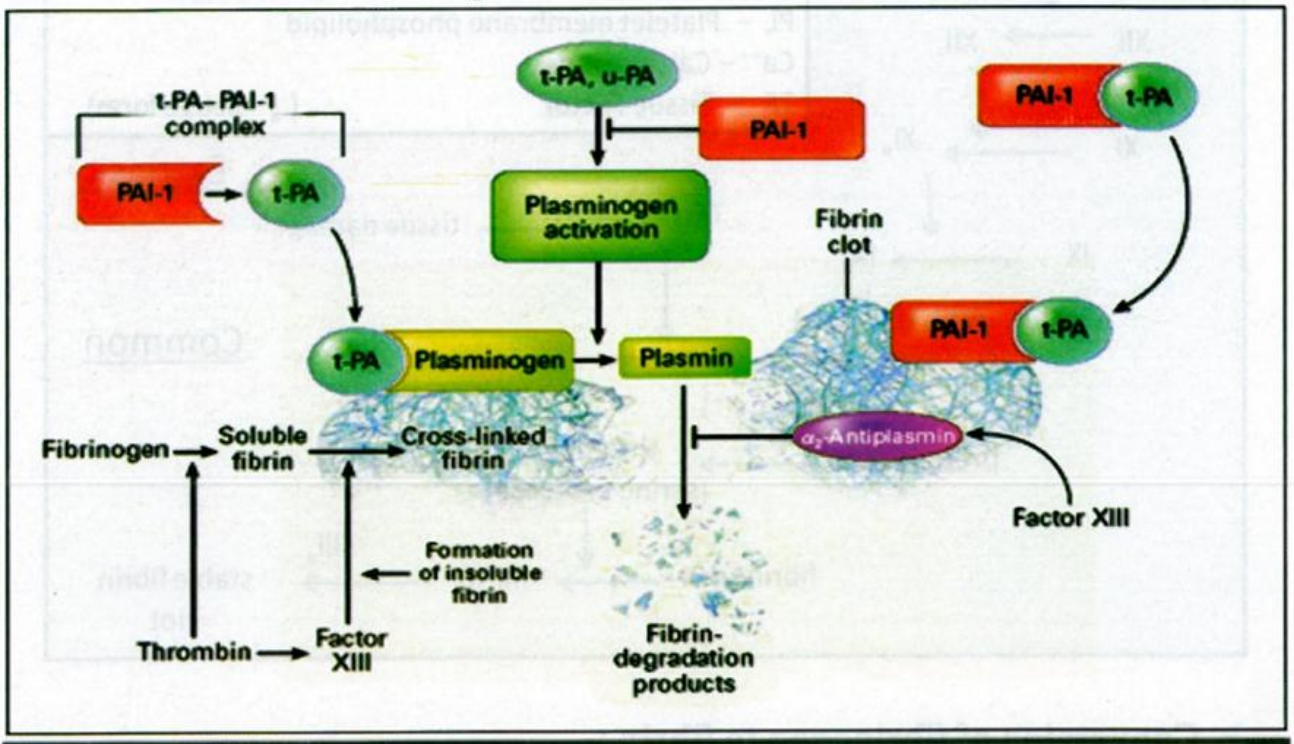


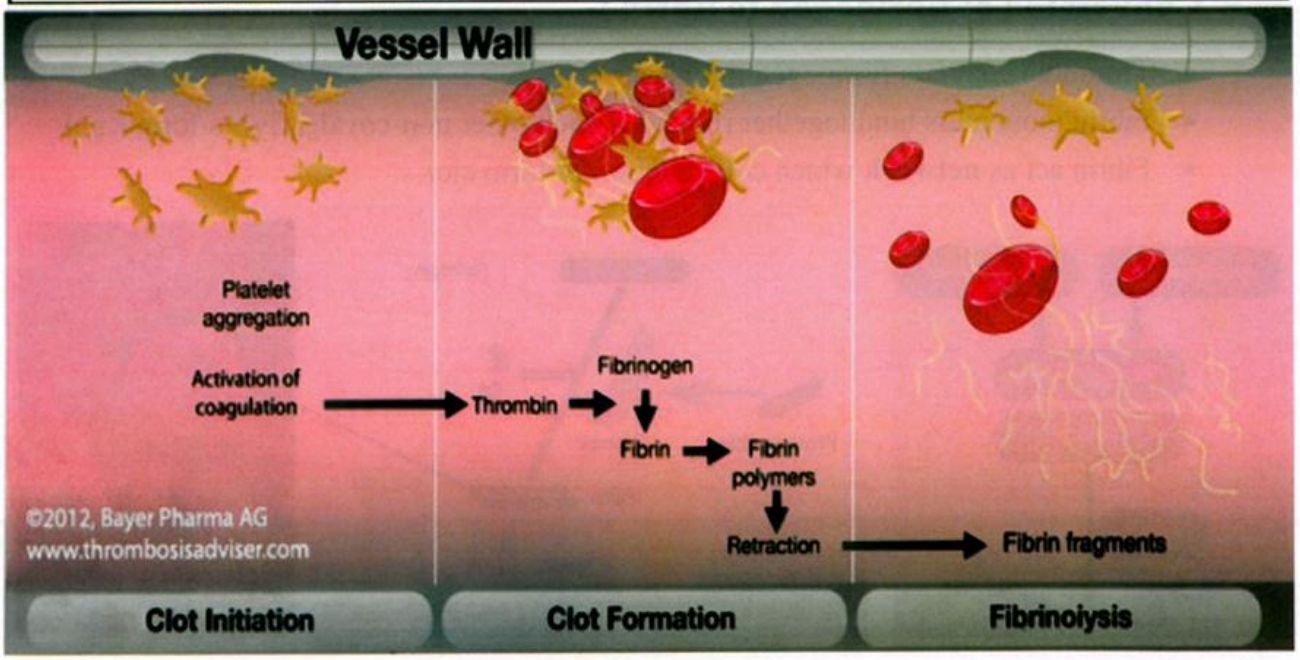




➢ Fibrinolysis (Breakdown of fibrin) :-

- The fibrinolytic system dissolves intravascular clots as a result of the action of plasmin, (fibrinolysin) an enzyme that digests fibrin network.
- Plasminogen, an inactive precursor, is converted to plasmin by cleavage of a single peptide bond.
- Tissue plasminogen activator (t-PA) is released from endothelial cells in response to various signals, including stasis produced by vascular occlusion.
- T-PA activates Plasminogen to form Plasmin.

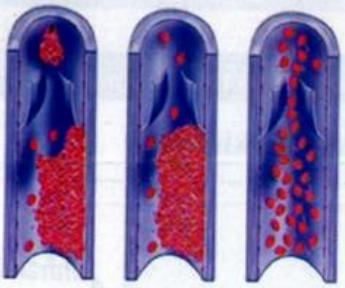




Anticoagulant drugs

➢ **Drug classes :-**

- Anticoagulants
- Antiplatelet drugs (Inhibitors of platelet aggregation)
- Thrombolytic agents (Fibrinolytics)



Anticoagulants

- **Heparin** (Parenteral anticoagulants)
- **Vitamin K antagonists** (Oral anticoagulants)
- **Direct Thrombin inhibitors** (DTIs)
- **Selective Factor Xa inhibitors**

N.B: The main goal of anticoagulant drugs → Prevent formation of fibrin → Clot not formed.

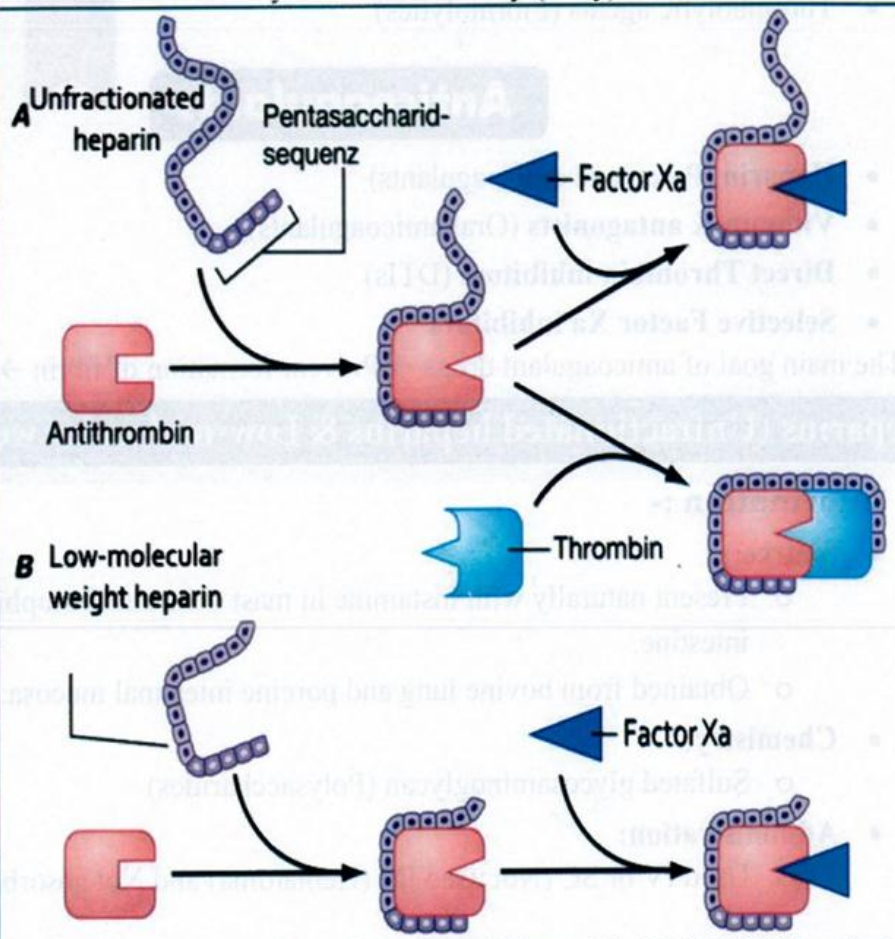
Heparins (Unfractionated heparins & Low-molecular weight heparins)

➢ **Information :-**

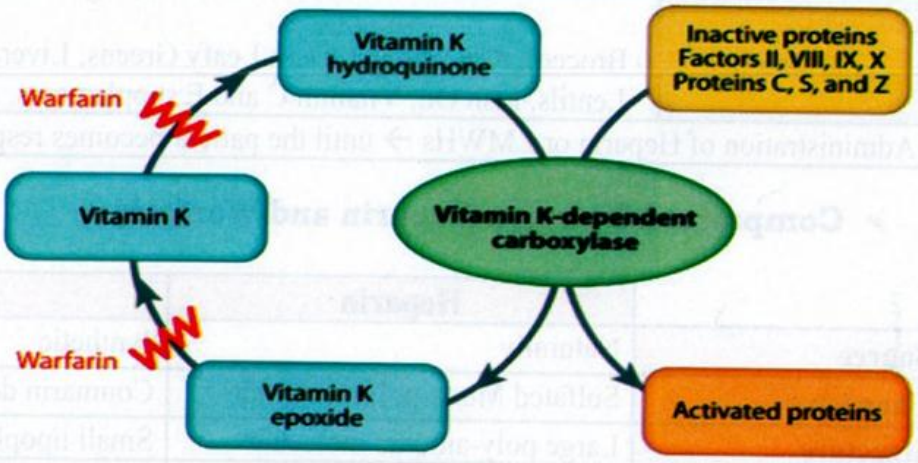
- **Source:**
  - Present naturally with histamine in mast cells and Basophils in lung liver and intestine.
  - Obtained from bovine lung and porcine intestinal mucosa.
- **Chemistry:**
  - Sulfated glycosaminoglycan (Polysaccharides)
- **Administration:**
  - Used IV or SC (Not used IM (Hematoma) and Not absorbed orally)

➢ **Comparison between UFH & LMWH :-**

	Unfractionated heparins (UFH)	Low-molecular weight heparins (LMWHs)
Molecular weight	High Mwt. (Higher than 30000 Da)	Low Mwt. (Less than 8000 Dalton)
Bioavailability	Low	High
Dose	Un fixed dose	Fixed dose
T-half	Short	Long
Price	Cheep	Very expensive
Anti-factor Xa activity	Less	More
Bleeding	Cause bleeding	Less cause bleeding
Antidote	Protamine sulfate high specific	Protamine sulfate less specific

Unfractionated heparins		
Heparin calcium (Calciparine®)		
Low-molecular weight heparins		
Nadroparin (Fraxiparine®)	Enoxaparin (Clexane®)	Tinzaparin (Innohep Anti-Xa®)
Pharmacokinetics	- Rapid onset of action & short half-life. - Given intravenously or subcutaneously (Only).	
Mechanism of action	 - **Heparin** enhance the action of Anti-Thrombin III (AT-III) by binds to AT-III and cause a ***conformational change*** → Activation of AT-III → AT-III rapidly combine with and thrombin and Factor Xa. - **LMWHs** complex with AT-III and inactivate Factor Xa.	
Uses	- Prevention and treatment of Deep Venous Thrombosis. - Pulmonary embolism. - Acute coronary syndromes (Myocardial Infarction).	
Adverse effects	- Bleeding (Hemorrhage) → Monitoring the bleeding time - Hypersensitivity reaction (Fever, Urticaria, Rash & Anaphylactic shock) - Thrombosis (Chronic administration of Heparin lead to reduction in AT-III activity) - Thrombocytopenia (Small number of platelet) and Osteoporosis	
Antidote	**Protamine sulfate** (Protamine®)	
- Ionically combines with heparin		

Vitamin K antagonists (Oral Anticoagulants)

Coumarin Anticoagulants	
Commonly used	
Warfarin (Marevan®)	
Rarely Used (Not clinically used)	
Dicumarol	
Derivatives	
Phenindione (Dindevan®)	
Pharmacokinetics	- Well absorbed orally → 100% Bioavailability. - Distributed all over the body and passes BBB and placental barrier. - Highly bound to plasma protein (99%) → long duration of action. - Metabolized slowly by Hepatic microsomal enzyme. - Excreted in urine (Not milk). - Onset of action delayed after 1-2 days. - Duration of action 5-7 days.
Dosage	- Initial dose → 5-10 mg/day - Maintenance dose → 2-10 mg/day (according to Prothrombin time (Normally 12-15 seconds)
Mechanism of action	 - Several of the protein coagulation factors (Including Factors II, VII, IX, and X require vitamin K as a cofactor for their synthesis by the liver. - Warfarin inhibits vitamin K epoxide reductase → blocks the vitamin K-dependent glutamate carboxylation of precursor clotting factors II, VII, IX and X. - Inhibit activation of prothrombin (coagulation factor II) into thrombin.
Uses (Prophylaxis and treatment)	- Deep venous thrombosis - Pulmonary embolism - Thromboembolic disorders - Atrial fibrillation with risk of embolism - Prophylaxis of systemic embolism post myocardial infarction After initial heparin treatments Start by both heparin & warfarin

Adverse effects	- Bleeding - Warfarin Necrosis → Warfarin induced skin necrosis especially in breast area (Increased in patients with protein C or S deficiency) - Cholesterol microembolization - Osteoporosis
Contraindication	- In pregnancy risk foetal haemorrhage and teratogenicity
Drug Interaction	- Antibiotics can suppress production of vitamin K by the gut flora. - Use of high doses of vitamin K (10-15mg) may cause resistance to warfarin for more than a week. - Enzyme inducer drugs e.g. Phenobarbital → Increase metabolism of warfarin → Decrease effect of warfarin. - Enzyme inhibitors drugs e.g. Erythromycin → Decrease metabolism of warfarin → Increase toxicity of warfarin. - Displacement from plasma protein binding sites (Increase toxicity of warfarin) e.g. Aspirin.
N.B:	**The good food list for people on anticoagulant (Low vit.K)** - Snap peas, Red cabbage, Avocado, Asparagus, Kiwi, Cranberries, Kidney beans, Soybeans, Mackeral and Soymilk. **Food to avoid (High vit.K)** - Broccoli, Cauliflower, Dark Leafy Greens, Liver, Seaweed, Chickpeas, Lentils, Fish Oil, Vitamin C and E supplements, Alcohol, Caffeine.
- Administration of Heparin or LMWHs → until the patient becomes responsive to warfarin.	

➢ Comparison between Heparin and Warfarin :-

	Heparin	Warfarin
Source	Naturally	Synthetic
Chemistry	Sulfated Muco-polysaccharide	Coumarin derivatives
Structure	Large poly-anionic molecule	Small lipophilic molecule
Administration	Parenteral IV or SC	Orally
Distribution	**Not** pass BBB or Placenta	Pass BBB or Placenta
Metabolism	Rapid	Slow
Onset	Rapid	Delayed 72 hours
Duration	Few hours (4-6)	Several days (4-7 days).
Mechanism	Inhibit thrombin by activates antithrombin III	Inhibit synthesis of factors II, VII, IX & X
Antidote	Protamine Sulfate	Vit. K
Uses	Acute cases e.g.→ for 1-2 weeks.	Chronic cases → for > 3 months

Direct thrombin inhibitors (DTIs)

- Direct Thrombin Inhibitors are a class of medication that act as anticoagulants (delaying blood clotting) by directly inhibiting the enzyme thrombin.
- **Hirudin** : is a naturally occurring peptide in the salivary glands of medicinal leeches (***Hirudo medicinalis***)
- There are two types of DTIs.

Bivalent

Bivalirudin (Angiomax®)	Lepirudin (Refludan®)

- Lepirudin is produced in yeast cell by recombinant DNA technology.

Univalent

Argatroban (Argatroban®)	Dabigatran (Pradax®)

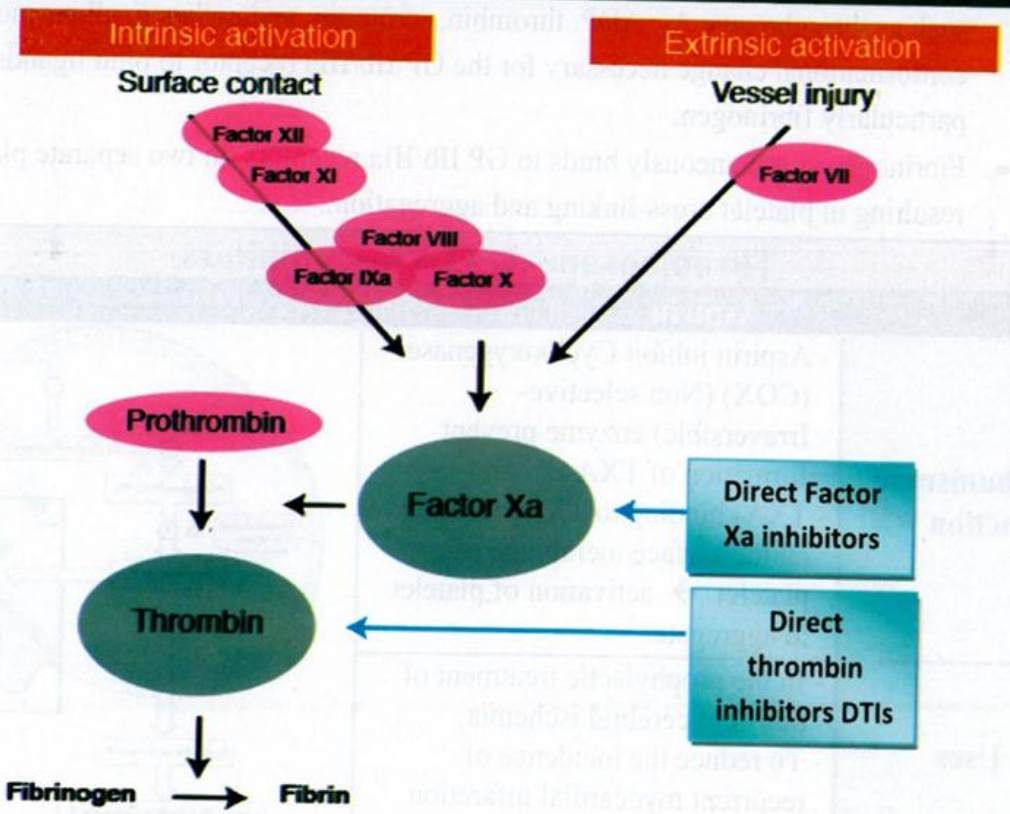
Melagatran or Ximelagatran (Exanta®)

Direct Factor Xa inhibitors

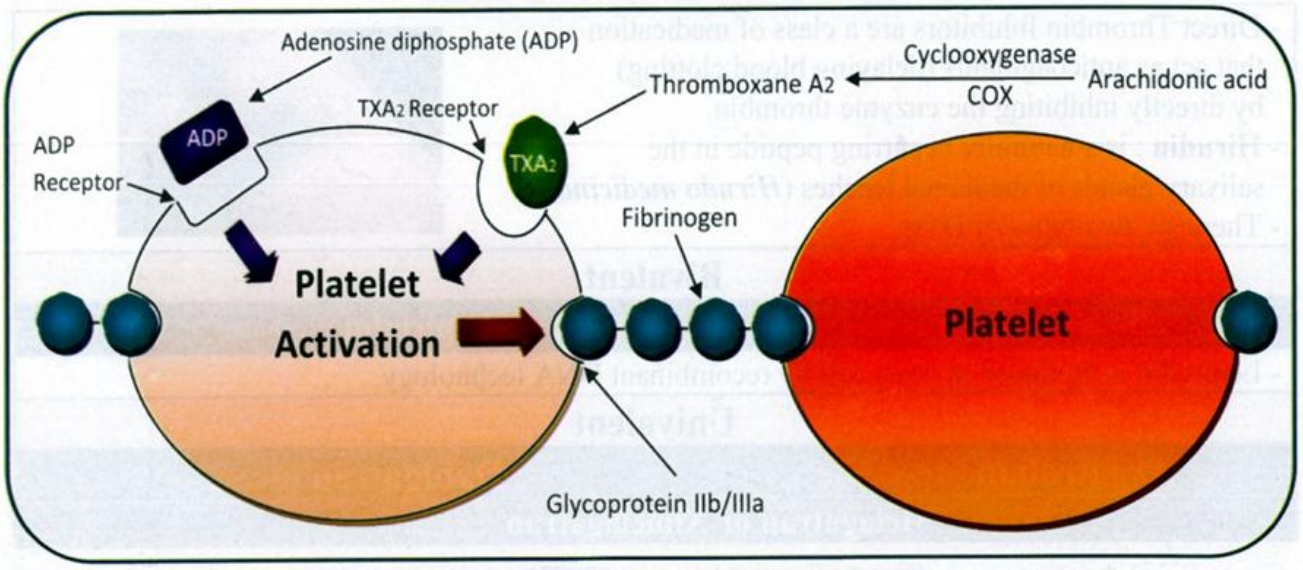
Fondaparinux (Arixtra®)	Apixaban (Eliquis®)

Fondaparinux (fawn-da-PEAR-eh-nux) is the first in a new class of pentasaccharide anticoagulant.

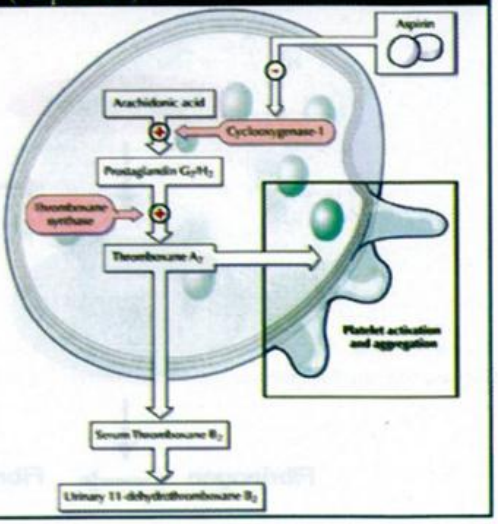
Rivaroxaban (Xarelto®)



Antiplatelet drugs



- Platelet aggregation inhibitors decrease the formation or the action of chemical signals that promote platelet aggregation.
- The last step in this response to vascular trauma depends on a family of membrane GP receptors that after activation can bind adhesive proteins, such as fibrinogen
- The most important of these is the GP IIb/IIIa receptor that ultimately regulates platelet-platelet interaction and thrombus formation. Thus, platelet activation agents, such as thromboxane A_2, ADP, thrombin, serotonin, and collagen, all promote the conformational change necessary for the GP IIb/IIIa receptor to bind ligands, particularly fibrinogen.
- Fibrinogen simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and aggregation.

Thromboxane-A_2 (TXA_2) inhibitors		
Aspirin in small dose (75-150mg) (Aspocid®)		
Mechanism of action	- Aspirin inhibit Cyclooxygenase (COX) (Non selective-Irreversible) enzyme prevent formation of TXA_2. - TXA_2 binding to TXA_2 receptor on the surface membrane of platelet → activation of platelet to aggregate.	
Uses	- In the prophylactic treatment of transient cerebral ischemia, - To reduce the incidence of recurrent myocardial infarction.	

Dipyridamole (Persantin®)	Dazoxiben
- It acts as a thromboxane synthase inhibitor, therefore lowering the levels of TXA_2. - Dipyrdamole decrease reuptake and metabolism of adenosine.	
Uses	- Used in combination with antianginal drugs - Treatment of pulmonary hypertension - Used in combination with aspirin → prevention of stroke

Adenosine diphosphate (ADP) receptor inhibitors			
Clopidogrel (Plavix®)	**Ticlopidne** (Ticlopide®)	**Prasugrel** (Effient®)	**Ticagrelor** (Brilinta®
- These drugs irreversibly inhibit the binding of ADP to its receptors on platelets and, thus, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen an to each other.			
Uses	- Used for the prevention of transient ischemic attacks and strokes for patients with prior cerebral thrombotic event. - It is also used as adjunct therapy with aspirin		

Glycoprotein IIB/IIIA inhibitors	
Abciximab (ReoPro®)	**Eptifibatide** (Integrilin®)
Tirofiban (Thrombostat®)	
Uses	- Used (IV) during percutaneous coronary intervention (angioplasty)

Fibrinolytics drugs (Thrombolytic drugs)

➢ **Information :-**

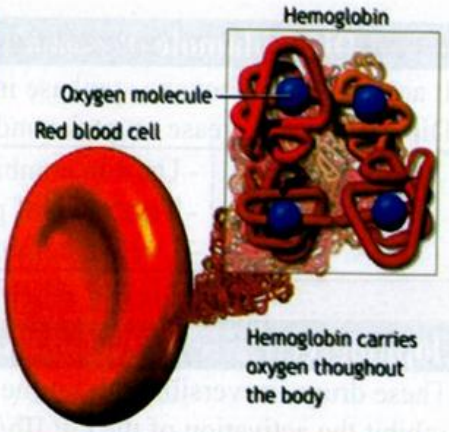
- Degrades fibrin clots.
- Converts plasminogen to plasmin→ Plasmin is a serine protease which split fibrin products and dissolves clots.

Streptokinase (Kabikinase®)	
Mechanism of action	- Streptokinase forms a complex with plasminogen → Converts plasminogen to plasmin. - Plasmin breaks down clot by  cut fibrin network.
Uses	- Acute pulmonary embolism, Deep vein thrombosis and Acute MI
Side effect	- Systemic bleeding and Drug allergy

Urokinase (Angikinase®)	Anistreplase (Eminase®)
Mechanism	- It cleaves the Arg-Val bond in plasminogen to produce active plasmin. Plasmin degrades fibrin clots as well as fibrinogen and other proteins.
Uses	- Pulmonary embolism and deep vein thrombosis
Side effect	- Bleeding complications

Tissue Plasminogen Activator		
Alteplase (Cathflo Activase®)	**Reteplase** (Retavase®)	**Tenecteplase** (TNKase®)
Mechanism of action	- It binds to plasminogen and converts it to plasmin and so this way it decreases the risk of systemic bleeding	

Anemia

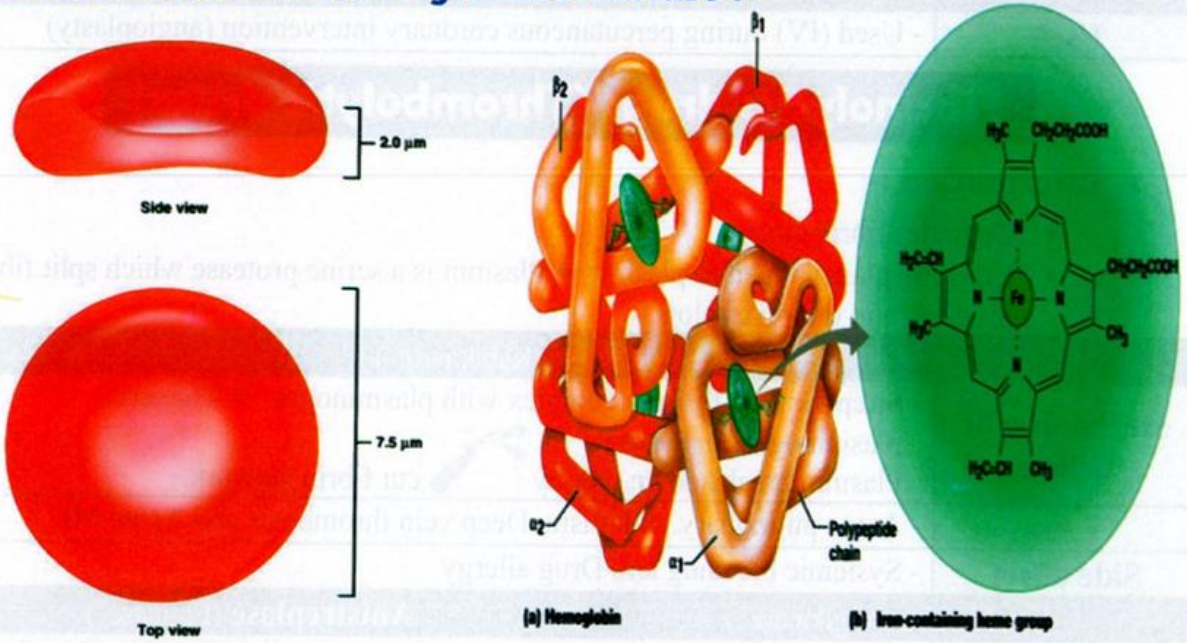


➢ **Def.:** Anemia is a condition in which don't enough healthy red blood cells to carry adequate oxygen to tissues due to decrease in the number of R.B.Cs or their hemoglobin content or decreases in both.

➢ **Red blood cell size :-**

Normocytic cells	**Normal** size of RBCs
Macrocytic cells	**Larger** size of RBCs
Microcytic cells	**Smaller** size of RBCs
Normochromic cells	**Normal** concentration of hemoglobin
Hyperchromic cells	**Higher** concentration of hemoglobin
Hypochromic cells	**Lower** concentration of hemoglobin

➢ **Red blood cell and Hemoglobin structure :-**



- **Hemoglobin (Hb or Hgb):** is found only in RBCs and its main function is transport of oxygen from lungs to tissues and carbon dioxide from tissues to lung.
- **Structure of hemoglobin:** its conjugated protein consists of specialized protein called globin tightly bound to 4 heme molecules.
- **A heme group:** consists of an iron (Fe^{2+}) ion (charged atom) held in a heterocyclic ring, known as a **Porphyrin**. This porphyrin ring consists of four pyrrole molecules cyclically linked together with the **iron ion** bound in the center.

➢ Types of normal Hemoglobin:-

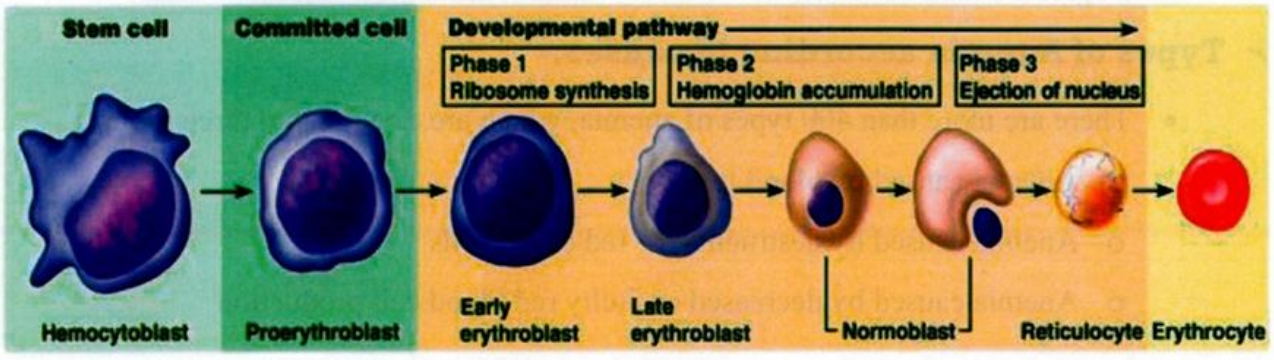
- **Hemoglobin A**: It is the major hemoglobin in adult 97% consists of 4 Polypeptide chains (2-Alpha and 2-Beta).
- **Hemoglobin A2**: Accounts about 2% of adult human hemoglobin and consists of (2-alpha and 2-delta chains).
- **Fetal hemoglobin (HbF)** : Present in fetus during inter-uterine fetal life accounts about 1% of adult human hemoglobin and consist of 2-alpha and 2-gamma chains
- **Hemoglobin A1c (Glycated hemoglobin):**
  Hemoglobin A reacts non-enzymatically with glucose to form Hemoglobin A1c.

➢ Abnormal derivatives of hemoglobin:-

- **Met-hemoglobin (Met-Hb):** It is oxidized hemoglobin in which Fe^{2+} oxidized to Fe^{3+}, Oxidation may occur by some drugs, hydrogen peroxide and free radicals. Met-Hb bind oxygen irreversibly thus cannot act as oxygen carrier.
- **Carboxy-hemoglobin (COHb):** It is hemoglobin combined with carbon monoxide instead of oxygen (Carbon monoxide have 200 times greater affinity to Hb than oxygen). Increase in COHb more than 40% results in unconsciousness and may be fatal.
- **Sulf-hemoglobin (S-Hb):** Hemoglobin combined with sulfur as a result of exposure of Hb to toxic effect certain drugs as sulfonamides. S-Hb produce anoxia and cyanosis (Cannot carry oxygen)
- **Hematin:** It is hemoglobin without iron.

➢ Formation of RBCs (Erythropoiesis):-

- **Kidneys** respond to a lower than normal oxygen concentration in the blood by releasing the hormone **erythropoietin**.
- **Erythropoietin** travels to the bone marrow and stimulates an increase in the production of red blood cells (RBCs).
- The **heart** and **lungs** work to supply continuous movement and oxygenation of RBCs.
- Damaged or old RBCs are destroyed primarily by the **spleen**.
- RBCs usually live for about 120 days before they die and need to be replaced.

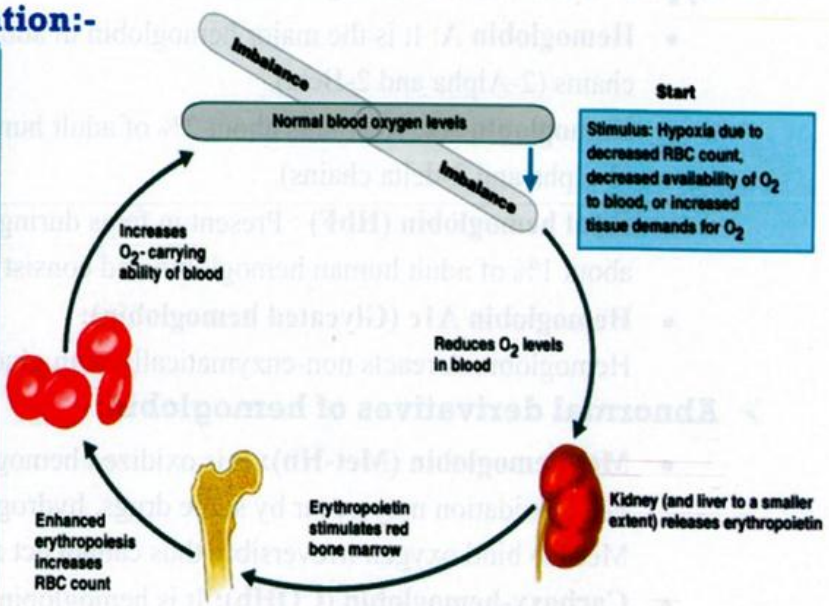


➢ Erythropoiesis Regulation:-

- **Decrease** oxygen supply (Tissue hypoxia) →Release of erythropoietin from kidney which stimulate synthesis of mRNA necessary for formulation of R.B.Cs in bone marrow →increase production of R.B.Cs.

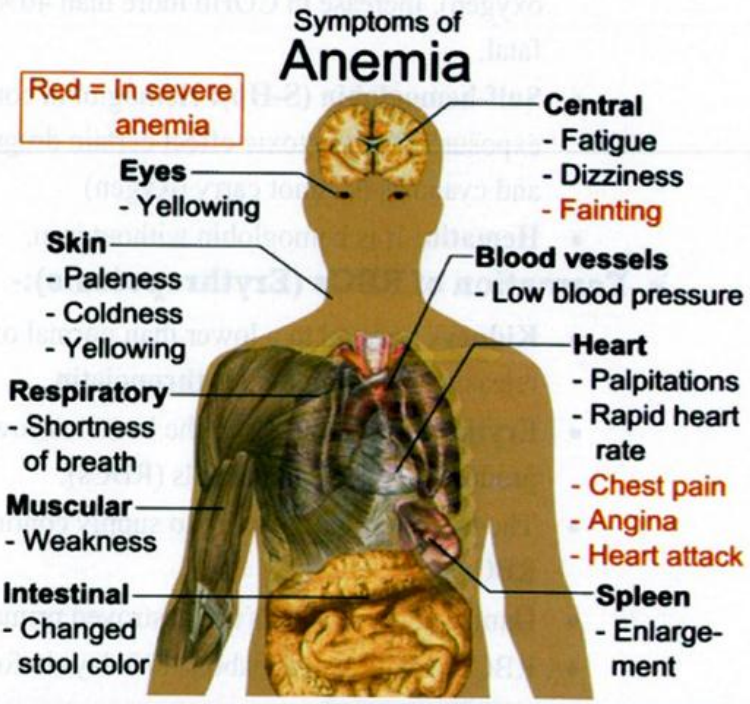
- **Increase** oxygen supply →inhibits erythropoiesis.

- **N.B**→ Thyroxin → Increase rate of Erythropoiesis.



➢ Symptoms of Anemia :-

- Fatigue
- Dyspnea on exertion
- Headache
- Confusion
- Decrease mental activity
- Pale skin
- A fast or irregular heartbeat
- Chest pain
- Dizziness
- Cold hands and feet
- Lethargy
- Loss of energy
- Rapid respiration
- Depressed metabolic rate



➢ Types of Anemia according to causes:-

- There are more than 400 types of anemia, which are divided into three groups:
  - Anemia caused by blood loss
  - Anemia caused by destruction of red blood cells
  - Anemia caused by decreased or faulty red blood cell production

Common types of Anemia

(I) Normochromic Normocytic Anemia

➢ **N.B:-**

- **Normocytic** → Normal size of RBCs.
- **Normochromic** → Normal concentration of hemoglobin.
- Caused by blood loss or destruction of red blood cells.

Hemolytic Anemia

➢ **Definition:**

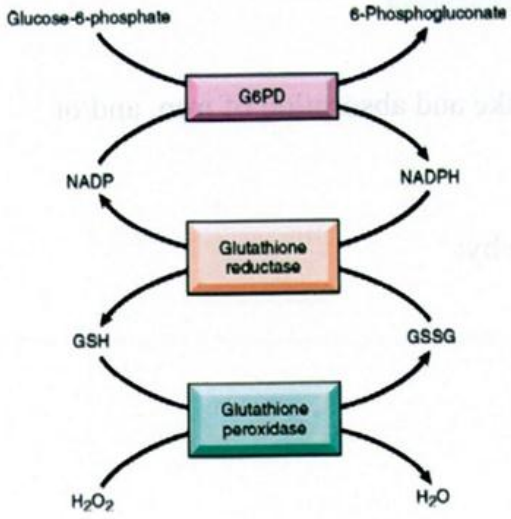
- Is a form of anemia due to hemolysis (abnormal breakdown) of red blood cells (RBCs).

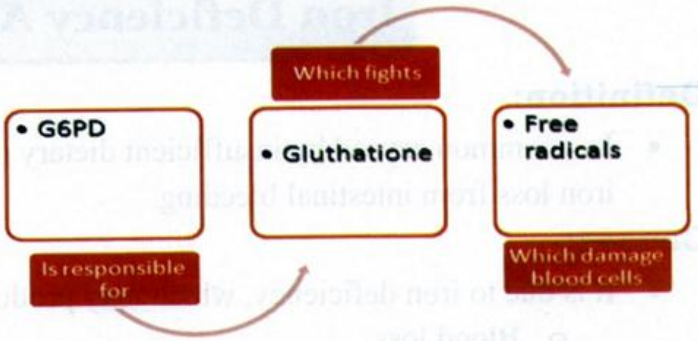
➢ **Causes:**

- Certain genetic defects that cause the blood cells to take on abnormal shapes (such as sickle cell anemia, thalassemia, and hemolytic anemia due to G6PD deficiency)
- Incomputable blood transfusion
- Chemical poisons, Snake venoms and Sensitivity to drugs
- Antibodies against red blood cells
- Infection as some types of malaria

➢ **Hemolytic anemia due to Glucose-6-phosphate dehydrogenase (G6PD) deficiency**

- Fava beans and certain drugs such as Primaquine, Sulfa and chloramphenicol may induce hemolytic anemia (Hemolysis of RBCs) in Patient with G6PD deficiency.
- G6PD enzyme protects RBCs from damage (G6PD enzyme responsible for convert NADP into NADPH which make detoxification of the drugs through glutathione system)





Favism: Form of hemolytic anemia that can occur after eating fava beans → closely related to G6PD deficiency.

Aplastic Anemia

➢ Definition:

- Is a condition where bone marrow does not produce sufficient new cells to replenish blood cells.

➢ Causes:

- Idiopathic (without a known cause)
- Exposure to ionizing radiation from radioactive materials
- Drugs antibiotics e.g. Chloramphenicol
- Viral infections
- Destruction of bone marrow by malignant diseases.

Erythropoietin
(Epoetin®)
- Used IV or SC
- Erythropoietin is available as a therapeutic agent produced by recombinant DNA technology in cell culture.
It is used in treating anemia (deficiency of Erythropoiesis).

Hemorrhagic Anemia

➢ Definition:

- Is a form of anemia due to Excessive loss of blood:

➢ Causes:

- Rapid hemorrhage → Acute
- Bleeding piles → Chronic

(II) Microcytic Hypochromic Anemia

➢ N.B:-

- **Microcytic** → Smaller size of RBCs.
- **Hypochromic** → Lower concentration of hemoglobin.

Iron Deficiency Anemia

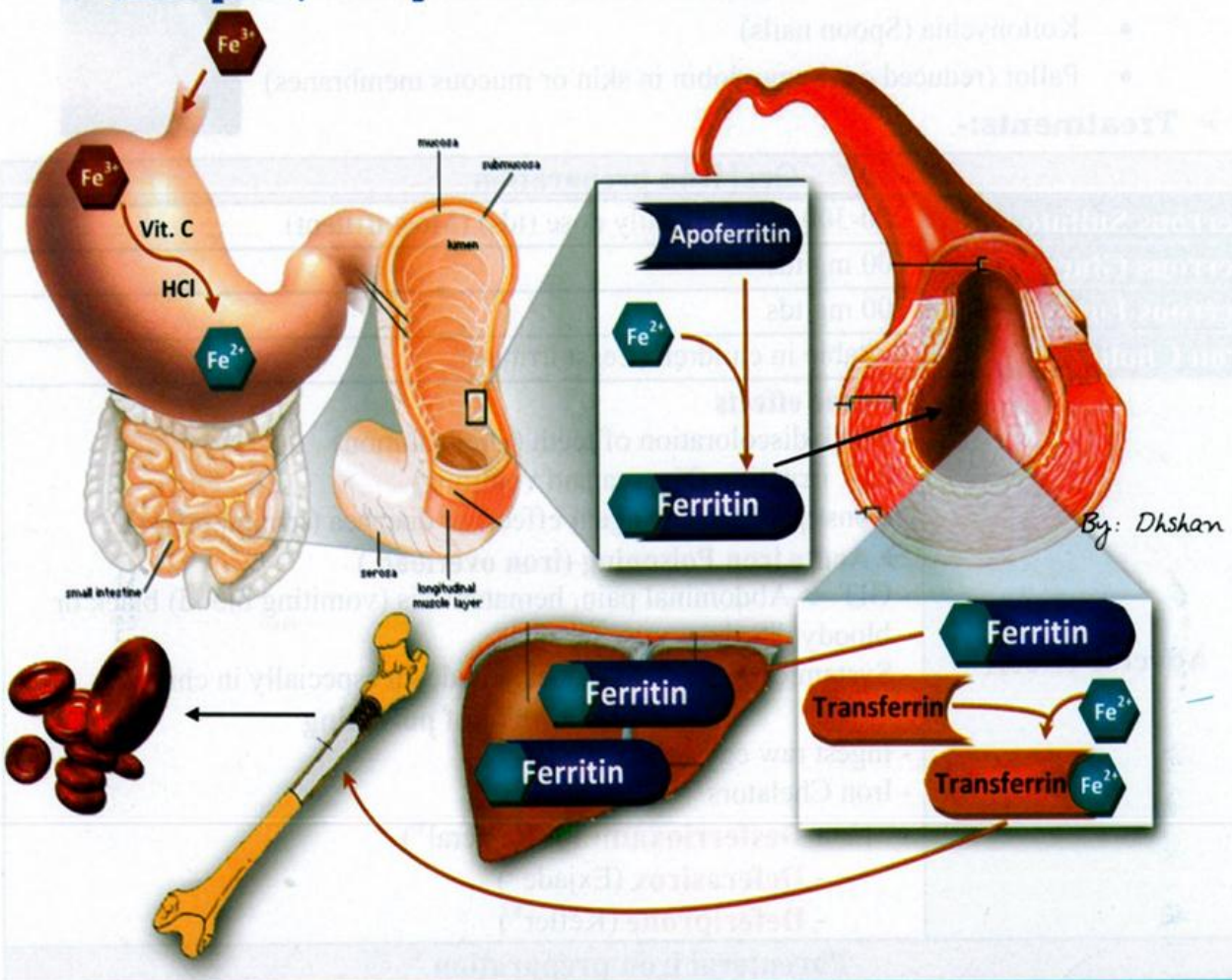
➢ Definition:

- Is a common caused by insufficient dietary intake and absorption of iron, and/or iron loss from intestinal bleeding.

➢ Causes:-

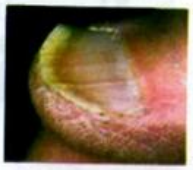
- It is due to iron deficiency, which may produce by:
  - Blood loss
  - lack of iron in the diet
  - Inability to absorb iron.
  - Pregnancy

➢ Absorption, Transport and Store of iron:-



- Iron is absorbed in the ferrous sate (Fe^{2+}) only; Most of diet iron is in the ferric state (Fe^{3+}).
- Ferric is reduced to ferrous in the stomach by HCl and Vitamin C.
- Absorption of iron occurs in upper part of small intestine by active process.
- The intestinal mucosa contains a protein (Apoferritin) which combines with iron to form ferritin.
- Iron absorption stop when all Apoferritin converted to Ferritin.
- When blood hemoglobin decreases, Ferritin gives its iron to blood.
- The blood containing a beta globulin called transferrin, which carries iron to bone marrow to form RBCs.
- Iron is stored in deferent tissues as liver, spleen and bone marrow in the form of ferritin.
- Ca^{2+} helps the absorption of iron because Ca^{2+} combines with oxalates and phosphates.

➢ A Sign of Iron Deficiency:-



- Koilonychia (Spoon nails)
- Pallor (reduced oxyhemoglobin in skin or mucous membranes)

➢ Treatments:-

Oral iron preparation	
Ferrous Sulfate	200-300 mg total daily dose (tds) (Most irritant)
Ferrous Gluconate	600 mg tds
Ferrous Fumarate	200 mg tds
Iron Choline Citrate	Suitable in children (Least irritant)
Adverse effects	**→ Side effects** - Black discoloration of teeth (Oral solution) - GIT irritation (Nausea and vomiting) - Constipation (Astringent effect) or diarrhea (Irritant effect) **→ Acute iron Poisoning (iron overload)** - GIT → Abdominal pain, hematemesis (vomiting blood) black or bloody diarrhea. - Systemic → Acidosis, shock and death especially in children. **Treatment of poisoning** - Ingest raw egg with milk - Iron Chelators - **Desferrioxamine** (Desferal®) - **Deferasirox** (Exjade®) - **Deferiprone** (Kefler®)
Parenteral iron preparation	
Iron Dextran (Imferon®)	50 mg/ml IV or IM
Iron sorbitol citric acid complex (Jectofer®)	50 mg/ml IM
Adverse effects	**Iron Poisoning (iron overload)** **→ Local** → Pain, Pigmentation and inflammation. **→ Systemic** → Headache, encephalopathy, convulsion, fainting, Tachycardia, hypotension, hemolysis and bronchospasm, muscle and joint pains, skin rash and liver cirrhosis.

- **Diet supplement →**
  - Increase iron in the diet (Liver, meat and fish).
  - Diet includes vitamin C and zinc.
  - Decrease tea and coffee consumption.
- **Role of Zinc**
  - Zinc is essential for normal iron metabolism and prevention of anemia, but high levels of zinc can depress iron and lead to anemia.
- **Role of Copper →** Act as cofactor for formation of hemoglobin.

(III) Macrocytic Hyperchromic Anemia

➢ **N.B:-**

- **Macrocytic** → Larger size of RBCs.
- **Hyperchromic** → Higher concentration of hemoglobin.

Megaloblastic Anemia

(Vitamin B_{12}/folate deficiency anemia)

- **Role of folic acid**
  - Folic acid is needed for formation of DNA therefore it is essential for RBCs maturation.
- **Role of Vitamin B_{12}**
  - Vitamin B_{12} contains cobalt and it is important for nuclear maturation and cell division.

➢ **Causes:-** (Results from inhibition of DNA synthesis in red blood cell production)

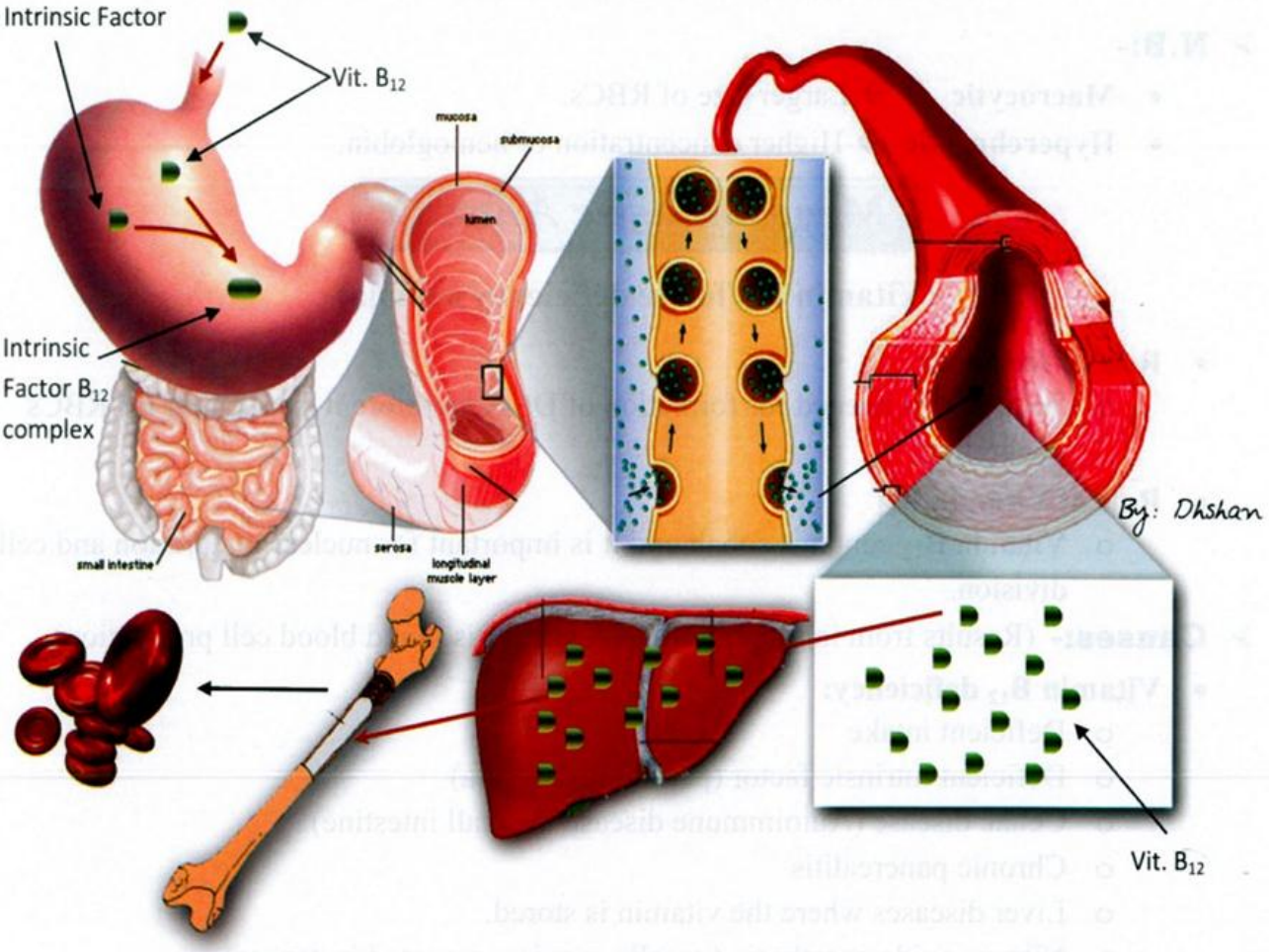
- **Vitamin B_{12} deficiency:**
  - Deficient intake
  - Deficient intrinsic factor (pernicious anemia)
  - Celiac disease (Autoimmune disease in small intestine)
  - Chronic pancreatitis
  - Liver diseases where the vitamin is stored.
  - Nitrous oxide anesthesia (usually requires repeated instances).
- **Folate deficiency:**
  - Alcoholism
  - Deficient intake
  - Increased needs: pregnancy, infant, rapid cellular proliferation, and cirrhosis
  - Malabsorption (congenital and drug-induced)
  - Intestinal and jejunal resection
- **Combined Deficiency: Vitamin B_{12} & folate.**

Pernicious Anemia

(Vitamin B_{12} deficiency anemia)

- Is one of many types of the larger family of megaloblastic anemias.
- It is caused by loss of gastric parietal cells which are responsible, in part, for the secretion of intrinsic factor, a protein essential for subsequent absorption of vitamin B_{12} in the ileum.

➢ Absorption, Transport and Store of Vitamin B_{12}:-



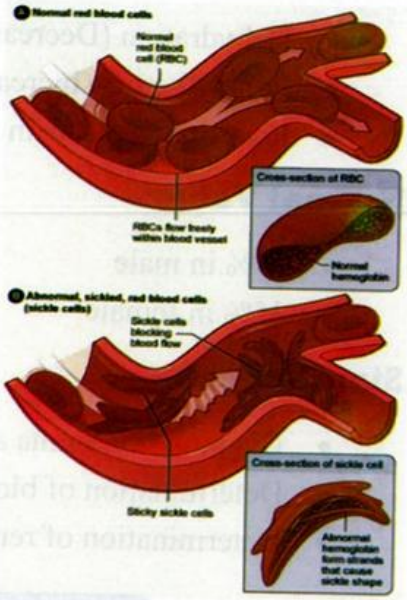
- **Vitamin B_{12}** is called extrinsic factor and for its absorption an intrinsic factor is needed.
- The **intrinsic factor** is secreted by the mucous membrane of the fund of the stomach.
- The intrinsic factor combine with vitamin B_{12} and form **intrinsic factor B_{12} complex** which absorbed by process of pinocytosis in lower part of ileum.
- Vitamin B_{12} is stored in large amount in liver.
- It released slowly from liver as needed by bone marrow for formation of new RBCs.

➢ Treatments:-

Cyanocobalamin (Vitamin B_{12}) (Betolvex®)	
Function	- **RBCs** → Nuclear maturation and cell division. - **Nerve cell** → Myelination (Increase conduction) - **Liver** → Lipotropic
Dose	- 1000 mcg/day for 2 weeks then 100 - 1000 mcg of once per week.
Folic acid (Folicap®)	
Dose	- 10-20 mg/day orally
- Folic acid alone corrects anemia but increase the nervous lesion because folic acid diverts vitamin B_{12} from nervous system to bone marrow, **so folic acid should not be used alone.**	

(IV) Sickle Cell Anemia

- Genetic blood disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape.
- Sickling decreases the cells flexibility and results in a risk of various complications.
- The sickling occurs because of a mutation in the hemoglobin gene.
- Sickle-cell disease may lead to various acute and chronic complications, several of which have a high mortality rate.
- Sickle cells die after only 10 to 20 days.



➢ Adult reference ranges-red blood Cells:-

Measurement (units)	Male	Female
Hemoglobin (gm/dL)	14-17	12-15.5
Red cell count (million/µL)	5-6	4-5
Hematocrit (HCT) (%)	45	35
Mean cell volume (MCV) (fL)	75-96	
Mean corpuscular hemoglobin (pg) (MCH)	26-32	
Mean corpuscular hemoglobin concentration (MCHC) (gm/dL)	32-38	

➢ Diagnosis of anemia (lab tests):-

Hematocrit (HCT)

➢ **Def. →** Is the volume percentage (%) of red blood cells in blood.

➢ **Measurement:-**

- By centrifugation method (not important).

➢ **Decrease hematocrit due to:-**

- Hydration (Increase body water)
- Anemia (Decrease RBCs number)
- After fluid transfusion

➢ **Increase hematocrit due to:-**

- Dehydration (Decrease body water)
- Polycythemia (Increase RBCs number)
- Loss of plasma as in burns.

➢ **Normal Value:-**

- 45% in male
- 35% in female

➢ **Significance:-**

- Diagnosis of anima and polycythemia (Increase formation of RBCs)
- Determination of blood volume
- Determination of renal blood flow

Mean cell volume (MCV)

➢ **Def. →** It the average volume of single RBCs in absolute units (cubic micron).

➢ **Measurement:-**

- MCV = Hematocrit X 10/RBCs count in millions.

➢ **Normal Value:-**

- 75-96 fL (femtoliters)

➢ **Significance:-**

- Less than normal → Microcytic anemia (Iron deficiency anemia)
- More than normal → Macrocytic anemia (Vitamin B12 and/or folic acid deficiency anemia)

Mean Corpuscular Hemoglobin (MCH)

➢ **Def. →** It is the amount of hemoglobin in single RBCs.

➢ **Measurement:-**

MCH = Hemoglobin content X 10/RBCs count in millions.

➢ **Normal Value:-**

- 26-32 pg (picograms)

➢ **Significance:-**

- Less than normal → Microcytic anemia
- More than normal → Macrocytic anemia

Mean Corpuscular Hemoglobin Concentration (MCHC)

➢ **Def. →** It is measure the amount of hemoglobin in 100 ml of packed RBCs.

➢ **Measurement:-**

MCHC= hemoglobin content X 10/hematocrit value.

➢ **Normal Value:-**

- 32-38 gm/dL

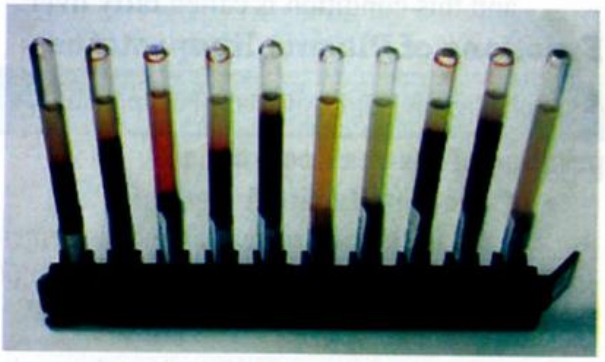
➢ **Significance:-**

- Less than normal → Hypochromic anemia
- More than normal → Hyperchromic anemia

Erythrocyte Sedimentation Rate (ESR)

➢ **Normal Value:-**

- **In Female:**
  - In first hour 8 mm
  - In second hour 16 mm
- **In Male:**
  - In first hour 6 mm
  - In second hour 8 mm



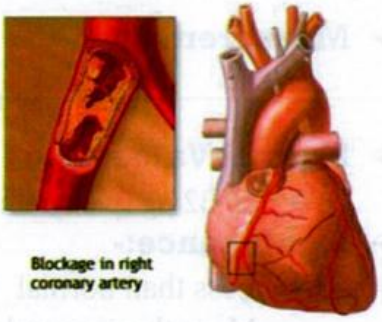
➢ **Significance:-**

- ESR is not a diagnostic test; but its repeated determination indicates the severity, progress of diseases and the effect of treatment.
- **Increase in ESR →** due to tissue break down or when foreign protein enter blood as in infection e.g. Rheumatic fever or increase in fibrinogen and certain globulin in plasma.
- **Decrease in ESR →**due to lack of fibrinogen as in defibrinated plasma.

Hyperlipidemias

➢ Overview:-

- **Hyperlipidemias** → elevated concentrations of any or all of the lipids in the plasma, including Hypertriglyceridemia, hypercholesterolemia, etc..
- **Cholesterol** is a waxy substance that's found in the fats (lipids) in blood. While body needs cholesterol to continue building healthy cells, high cholesterol can increase risk of heart disease.



➢ Plasma Lipids:-

- During fasting, total plasma lipids concentration range from 360-820 mg/dl.
- **They include:**

Cholesterol	140-220 mg/dl	Free cholesterol 30%
		Cholesterol esters 70%
Phospholipids	150-200 mg/dl	
Triacylglycerol	40-160 mg/dl	
Free fatty acids	6-16 mg/dl	

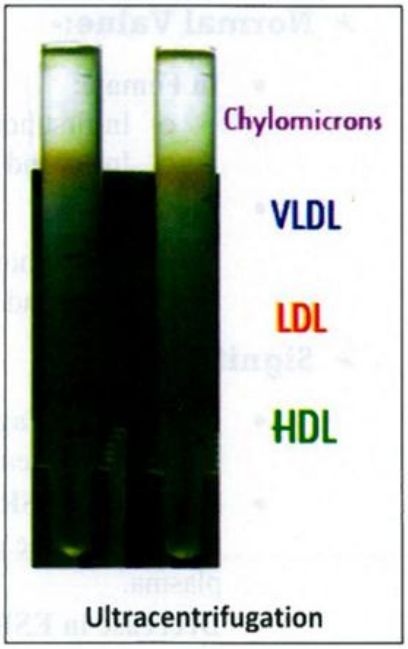
- Lipids alone are water insoluble compounds. Thus, they cannot be transported in plasma.
- Lipids are conjugated to proteins to form **lipoproteins**, which are water soluble and can be transported in plasma.
- These proteins are synthesized by the liver and called Apo-lipoproteins (Apo-proteins) They are five classes: A, B (B100 & B48), C, D and E.
- Failure of liver to synthesize Apo-lipoproteins lead to accumulation of fat in liver and this condition is called **fatty liver**.

➢ Fractions of Plasma lipoproteins:-

Fraction of Plasma Lipoproteins = Plasma Lipid + Apo-proteins

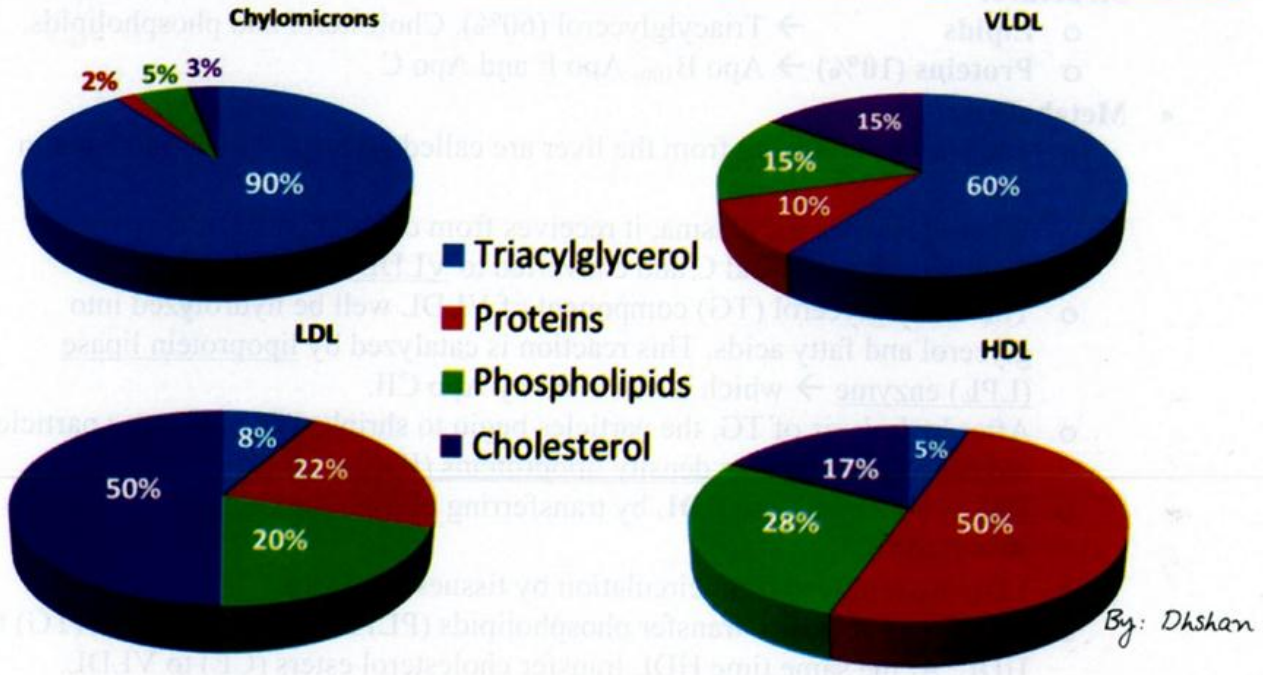
→ Separation of Plasma lipoproteins:-

- **Ultracentrifugation method:**
  - Ultracentrifugation means centrifugation of compounds at high speed ~ 40,000 round per minute (RPM)
  - By Ultracentrifugation plasma lipoproteins are separated according to density
    1: Chylomicrons (**largest**)
    2: Very low density lipoproteins (VLDL)
    3: Low density lipoproteins (LDL)
    4: High density lipoproteins (HDL) (**Smallest**)



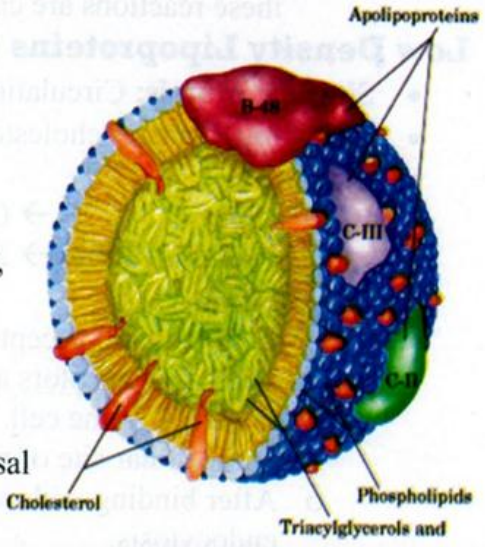
- **Electrophoresis method** (Not important):

Fraction of plasma lipoproteins	Source	Main lipid	Apo-lipoproteins	
Chylomicrons	Intestine	Triacylglycerol (TG)	2%	A, B_{48}, C & E
VLDL	Liver	Triacylglycerol (TG)	10%	B_{100}, C & E
LDL	Blood from VLDL	Cholesterol, Cholesterol esters and phospholipids	22%	B_{100}
HDL	Liver		50%	A, C, D & E
FFA-Albumin	Adipose tissue	FFA	99%	Albumin



➢ Chylomicrons:-

- **Site of synthesis**: Intestinal mucosa
- **Functions:** Chylomicrons transport dietary lipids intestine to blood to the peripheral tissues.
- **Structure:**
  - **Lipids** → Triacylglycerol (90%), Cholesterol and Phospholipids.
  - **Proteins** (2%) → Apo A, B_{48}, E & C.
- **Metabolism:**
  - The particles released by intestinal mucosal cells are called Nascent chylomicrons and contains Apolipoprotein B_{48}.
  - When it reaches the plasma, it receives from circulating HDL two Apolipoproteins E and C and converted into Chylomicrons.



- The triacylglycerol component of chylomicrons well be hydrolyzed into glycerol and fatty acids. This reaction is catalyzed by lipoprotein lipase (LPL) enzyme which is activated by Apo CII.
- After hydrolysis of TG, the chylomicrons particles begin to shrink. In addition, the Apo CII returns to HDL.
- The remaining particles are called Chylomicron remnants.

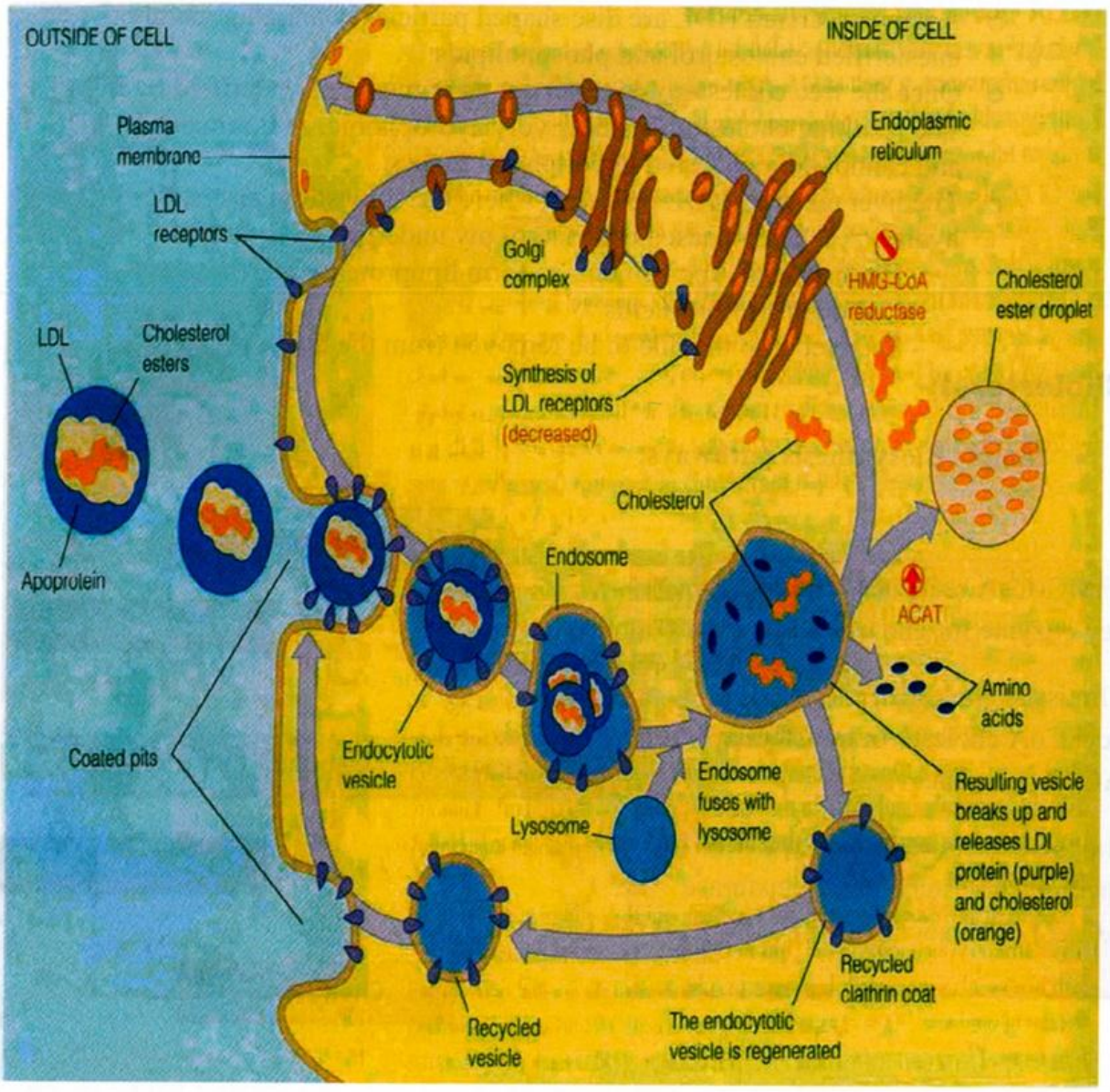
➢ Very Low Density Lipoproteins (VLDL):-

- **Site of synthesis:** Liver
- **Functions:** VLDL carries lipids from liver to the blood to the peripheral tissues.
- **Structure:**
  - **Lipids** → Triacylglycerol (60%), Cholesterol and phospholipids.
  - **Proteins (10%)** → Apo B_{100}, Apo E and Apo C
- **Metabolism:**
  - The particles released from the liver are called Nascent VLDL and contain Apo B_{100}.
  - When it reaches the plasma, it receives from circulation HDL two Apolipoproteins E and C and converted to VLDL.
  - The triacylglycerol (TG) component of VLDL well be hydrolyzed into glycerol and fatty acids. This reaction is catalyzed by lipoprotein lipase (LPL) enzyme → which is activated by Apo CII.
  - After hydrolysis of TG, the particles begin to shrink. The remaining particles are called Intermediate density lipoproteins (IDL)
  - **IDL** is converted into **LDL** by transferring phospholipids, Apo CII and Apo E to HDL.
  - LDL are removed from circulation by tissues as muscle.
  - VLDL particles also transfer phospholipids (PL) and Triacylglycerol (TG) to HDL. At the same time HDL transfer cholesterol esters (CE) to VLDL. these reactions are catalyzed by Cholesterol ester transfer protein.

➢ Low Density Lipoproteins (LDL):-

- **Site of synthesis:** Circulation from VLDL (Derived from VLDL)
- **Function:** Transfer cholesterol from liver to the peripheral tissues.
- **Structure:**
  - **Lipids** → Cholesterol and phospholipids.
  - **Proteins (22%)** → Apo B_{100}
- **Metabolism:**
  - LDL contains receptor on the surface membrane.
  - The LDL receptors are negatively charged glycoprotein molecules, made by the DNA of the cell. They are grouped in pits in cell membranes. The intracellular site of pits coated with a protein called Clathrin.
  - After binding with receptors, the LDL are internalized as intact particles by endocytosis.
  - The vesicle containing the LDL rapidly lose its clathrin coat and fuses with other similar vesicles, forming large vesicle called Endosomes.

- The pH of the contents of endosomes falls, allowing separation of the LDL from its receptors. the receptors then migrate to one side of the endosomes while LDL stays free within the lumen of the vesicle.
- The receptor can be returned to the cell membrane. The lipoprotein remnants are hydrolyzed by Lysosomal enzymes releasing cholesterol, Amino acids, Phospholipids and fatty acids.
- ***Oversupply of cholesterol***
  → Inhibits HMG-CoA reductase activity so that cholesterol synthesis well be decreased.
  → Stimulate a liver enzyme called Acyl CoA cholesterol acyl transferase (ACAT) → Transfer a fatty acid from fatty acyl CoA to form cholesteryl ester that can be stored inside the cell for future use.
  → Inhibit the synthesis of new LDL receptor proteins, so that further entry of LDL cholesterol into the cell is limited.



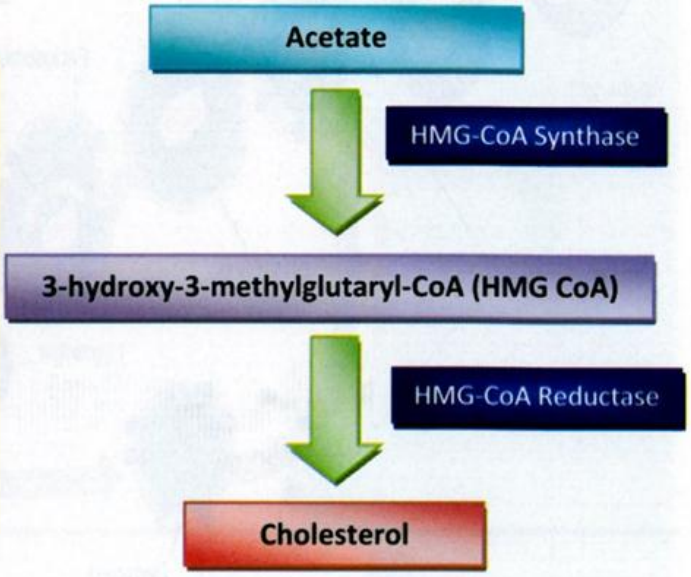
➢ High Density Lipoproteins (HDL):-

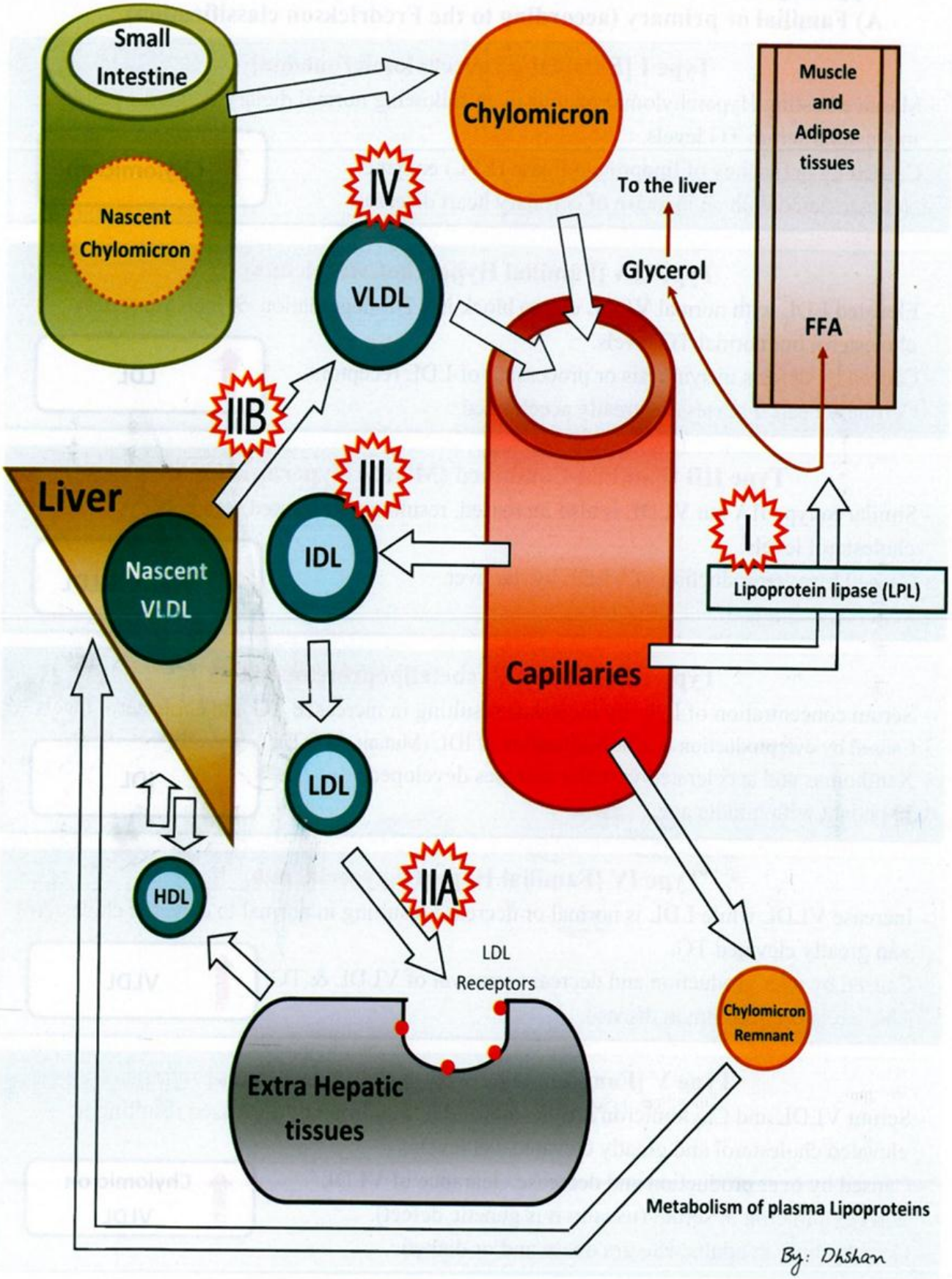
- **Site of synthesis:** Liver
- **Function:** 1- Remove cholesterol from extra hepatic tissues and esterifying it. Using a plasma enzyme called Lecithin Cholesterol Acyl Transferase (LCAT). The Apo A of HDL activates LCAT.
  2- Act as reservoir of Apo C that is transferred to chylomicrons and VLDL to activate Lipoprotein lipase (LPL) enzyme.
  3- HDL particles carry cholesterol esters to
  - VLDL and LDL
  - Liver (HDL is hydrolyzed and cholesterol released)
- **Structure:**
  - **Lipids** → Cholesterol and phospholipids.
  - **Proteins (50%)** → Apo A, C and E
- **Metabolism:**
  - A newly secreted HDL are disc shaped particles containing mainly unesterified cholesterol and phospholipids.
  - Once the free cholesterol is taken up, its immediately esterified by LCAT. The resulting cholesterol ester is very hydrophobic, so it remains in HDL and cannot be transferred to peripheral tissues.
  - The liver takes up HDL particles, where the cholesteryl esters are hydrolyzed. The released cholesterol my undergo:
    - Binding with Apo-proteins to form lipoproteins
    - Converting to bile acids
    - Secreted into the bile to be removed from the body.

➢ Cholesterol:-

- **Simple Biosynthesis pathways:**

- HMG-CoA reductase enzyme is the Key enzyme for cholesterol synthesis.
- In tissue cholesterol is esterified by Acyl CoA cholesterol transferase (ACAT) enzyme.
- In plasma cholesterol is esterified by Lecithin cholesterol acyl transferase (LCAT) → Associated with HDL)



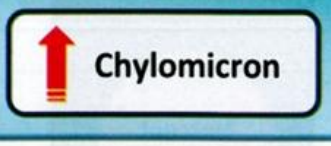

Small Intestine
Nascent Chylomicron
Chylomicron
IV
VLDL
To the liver
Glycerol
Muscle and Adipose tissues
FFA
IIB
Liver
Nascent VLDL
III
IDL
I
Lipoprotein lipase (LPL)
Capillaries
LDL
HDL
IIA
LDL Receptors
Chylomicron Remnant
Extra Hepatic tissues
Metabolism of plasma Lipoproteins
By: Dhshan

➢ Hyperlipidemia classification:-

A) Familial or primary (according to the Fredrickson classification)

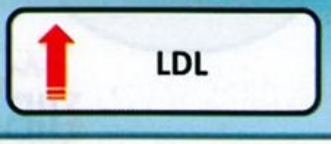
Type I [Familial Hyperchylomicronemia]

- Massive Fasting Hyperchylomicronemia even following normal dietary fat intake resulting in elevated serum TG levels.
- Caused by deficiency of lipoprotein lipase (LPL) enzyme.
- Not associated with an increase of coronary heart disease.



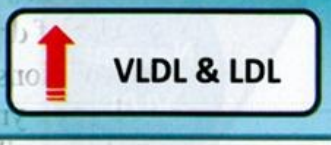
Type IIA [Familial Hypercholesterolemia]

- Elevated LDL with normal VLDL due to block in LDL degradation → increase serum cholesterol but normal TG levels.
- Caused by defects in synthesis or processing of LDL receptors.
- Coronary heart diseases are greatly accelerated.



Type IIB [Familial Combined (Mixed) Hyperlipidemia]

- Similar to type IIA but VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels.
- Caused by overproduction of VLDL by the liver.
- Relatively common.



Type III [Familial Dysbetalipoproteinemia]

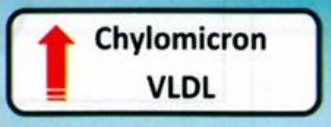
- Serum concentration of IDL are increased resulting in increased TG and cholesterol levels.
- Caused by overproduction or Underutilization of IDL (Mutant APO E).
- Xanthomas and accelerated vascular diseases developed in patient with middle age.

Type IV [Familial Hypertriglyceridemia]

- Increase VLDL while LDL is normal or decrease resulting in normal to elevated cholesterol and greatly elevated TG.
- Caused by over production and decrease removal of VLDL & TG.
- This a relatively common disease.

Type V [Familial Mixed Hypertriglyceridemia]

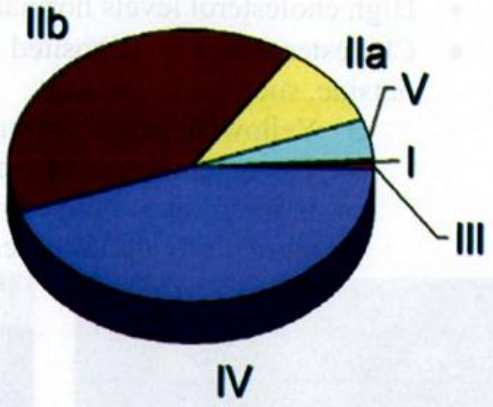
- Serum VLDL and Chylomicron are elevated, LDL in normal or decreased resulting in elevated cholesterol and greatly elevated TG levels.
- Caused by over production and decrease clearance of VLDL and chylomicron in serum (usually it is genetic defect).
- Occur mainly in adults who are obese and/or diabetic.



- **Relative prevalence of familial forms of Hyperlipidemias:-**

  ➔ **According to more relatively :-**

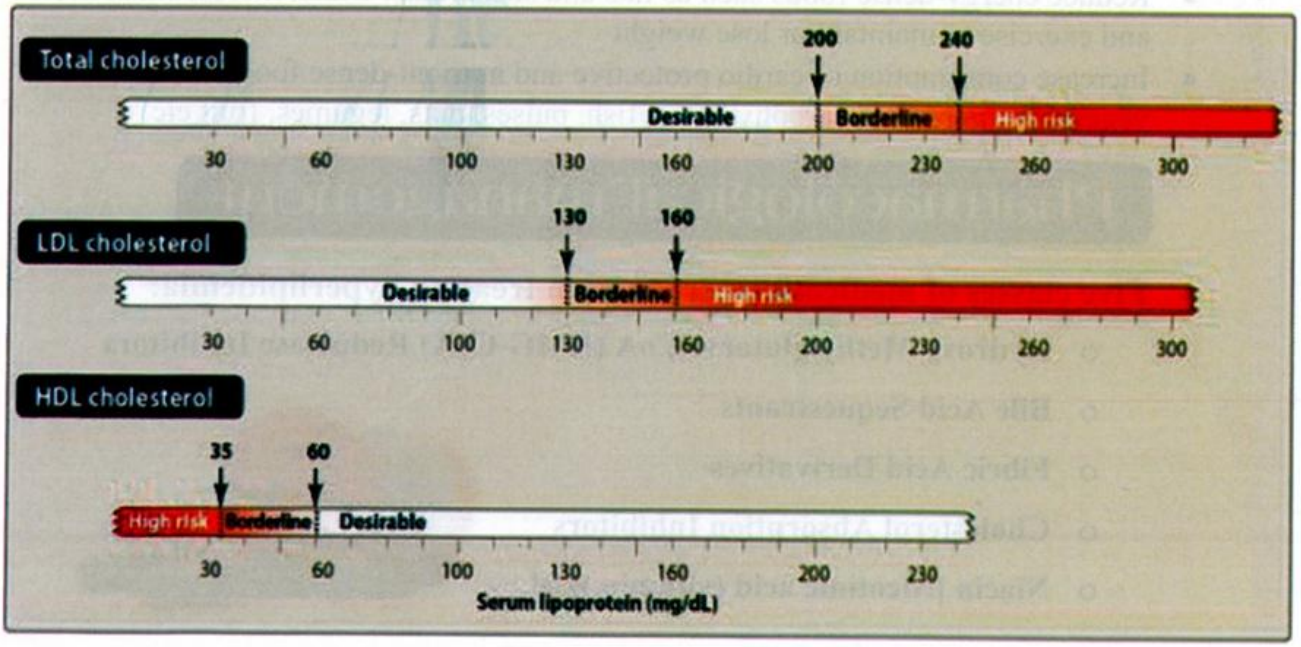
  - Type IV
  - Type IIB
  - Type IIA
  - Type V
  - Type III
  - Type I



B) Acquired hyperlipidemias (also called secondary dyslipoproteinemias)

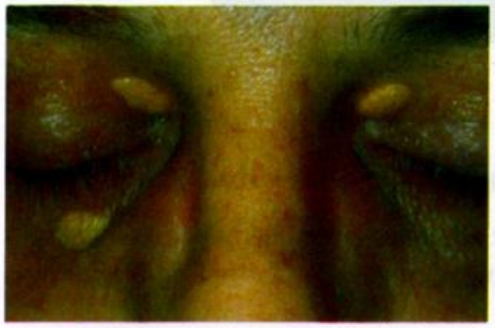
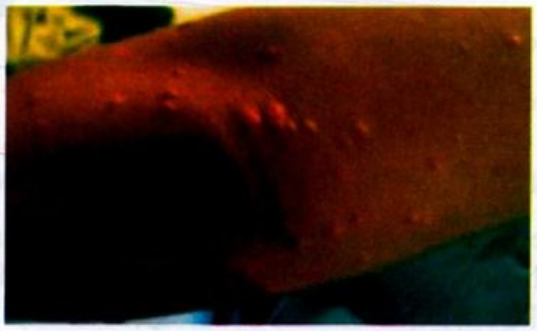
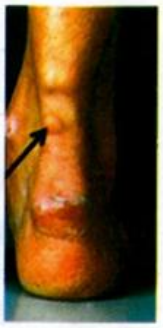
- They may result in increased risk of premature atherosclerosis or, when associated with marked hypertriglyceridemia, may lead to pancreatitis and other complications of the chylomicronemia syndrome.
- The most common causes of acquired hyperlipidemia are:
  - Diabetes mellitus
  - Use of drugs such as diuretics, beta blockers and estrogens.
- Other conditions leading to acquired hyperlipidemia include:
  - Hypothyroidism
  - Renal failure
  - Nephrotic syndrome
  - Alcohol
  - Some rare endocrine disorders and metabolic disorders

➢ Plasma cholesterol levels:-



➢ Symptoms:-

- High cholesterol levels normally do not cause any symptoms.
- Cholesterol may be deposited in various places in the body that are visible from the outside, such as in
  - Yellowish patches around the eyelids (Xanthelasma Palpebrarum).
  - The outer margin of the iris (arcus, senilis or cornea).
  - In the form of lumps in the tendons of the hands, elbows, knees and feet, particularly the Achilles tendon (Tendon Xanthoma).

➢ Management:-

Non-pharmacological management

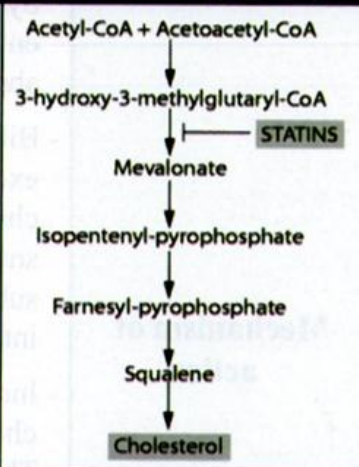
- Reduce intake of saturated and trans-unsaturated fat to less than 7-10% of total energy
- Reduce intake of cholesterol to < 250 mg/day
- Replace sources of saturated fat and cholesterol with alternative foods such as lean meats, low-fat dairy products, polyunsaturated spreads and low glycaemic index carbohydrates
- Reduce energy-dense foods such as fats and soft drinks, whilst increasing activity and exercise to maintain or lose weight
- Increase consumption of cardio protective and nutrient-dense foods such as vegetables, unrefined carbohydrates, fish, pulses, nuts, legumes, fruit etc.

Pharmacological management

- **Five classes of medications are used in treating hyperlipidemia:**
  - **Hydroxy Methylglutaryl-CoA (HMG-CoA) Reductase Inhibitors**
  - **Bile Acid Sequestrants**
  - **Fibric Acid Derivatives**
  - **Cholesterol Absorption Inhibitors**
  - **Niacin [Nicotinic acid (vitamin B3)]**

HMG-CoA Reductase Inhibitors (Statins)

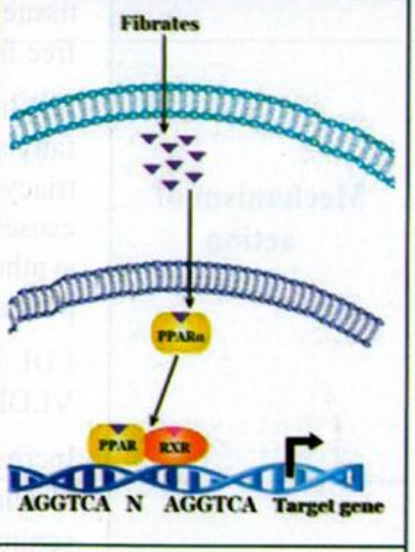
Atorvastatin (Ator®)	Fluvastatin (Lescol XL®)	Lovastatin (Lipdip®)
Pravastatin (Lipostat®)	Rosuvastatin (Crestor®)	Simvastatin (Zocor®)

Mechanism of action	- **Inhibition of HMG CoA reductase** (3-hydroxy-3-methylglutaryl coenzyme-A reductase) → Inhibition of de novo cholesterol synthesis →depletes the intracellular supply of cholesterol. - **Increase LDL receptor** → due to Depletion of intracellular cholesterol → Promotes uptake of LDL from blood. - Can **increase plasma HDL levels** in some patients. 
Potency	- Rosuvastatin and Atorvastatin are the most potent LDL cholesterol lowering statin drugs, followed by Simvastatin, Pravastatin and then Lovastatin and Fluvastatin.
Uses	- Hyperlipidemia and mixed dyslipidemia, reduction of elevated total and LDL cholesterol levels, to slow progression of coronary artery disease (CAD), along with diet and exercise. - Prevention of first MI, to slow progression of CAD, reduce risk of stroke, and MI.
Dose	- Once daily in the evening or at bedtime.
Side effects	**1-**The more common adverse reactions include nausea, vomiting, constipation, abdominal pain or cramps, and headache. **2- Liver:** Biochemical abnormalities in liver function have occurred with the HMG CoA reductase inhibitors (Liver function test monitoring). **3- Muscle:** Myopathy and rhabdomyolysis (damage of skeletal muscle tissue) have been reported only rarely. Myopathy increased in patients usually suffered from renal insufficiency or were taking drugs such as cyclosporine, itraconazole, erythromycin, gemfibrozil, or niacin. (Plasma creatine kinase levels should be determined regularly).
Drug interaction	- Warfarin (Increase Warfarin levels) - Bile acid sequestrants (Additive effect) (take statins at least 2-4 hours after the bile acid sequestrants)
Contraindications	- Pregnancy (Category X) - Lactation - Children or teenagers

Bile acid sequestrants (Bile acid-binding resins)

Cholestyramine (Questran®)	Colesevelam (Cholestagel®)	Colestipol (Colestid®)
Mechanism of action	- Bile salts is manufactured and secreted by the liver and stored in the gallbladder, emulsifies fat and lipids to facilitate absorption in the intestine. - Bile acid sequestrants → They are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine → form an insoluble substance that cannot be absorbed by the intestine, so it is secreted in the feces. - Increased loss of bile acids, the liver uses cholesterol to manufacture more bile. - This is followed by a decrease in cholesterol levels. - Intracellular cholesterol concentration decreases, which activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to a fall in plasma LDL.	**Cholesterol** ↓ **Bile salts** ↓ **Bile salts + Bile acid sequestrants** ↓ **Insoluble complex** ↓ **Feces**
Uses	- The drugs of choice in treating Type IIA and Type IIB hyperlipidemias. - Cholestyramine can also relieve pruritus caused by accumulation of bile acids in patients with biliary obstruction.	
Side effects	- **GIT:** The most common side effects are GI disturbances, such as constipation, nausea, and flatulence. (Colesevelam has fewer GI side effects). - **Impaired absorptions:** impair the absorption of the fat-soluble vitamins (A, D, E, and K) **at high doses**. (Not Colesevelam)	
Drug interaction	- Cholestyramine and colestipol interfere with the intestinal absorption of many drugs for example → Tetracycline, Phenobarbital, Digoxin, Warfarin, Pravastatin, Fluvastatin, Aspirin, and thiazide diuretics **→ Therefore, drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after, the bile acid–binding resins.**	
Contraindications	- Used cautiously during pregnancy (Category C) - In those with complete biliary obstruction - Used cautiously in patients with a history of liver or kidney disease	

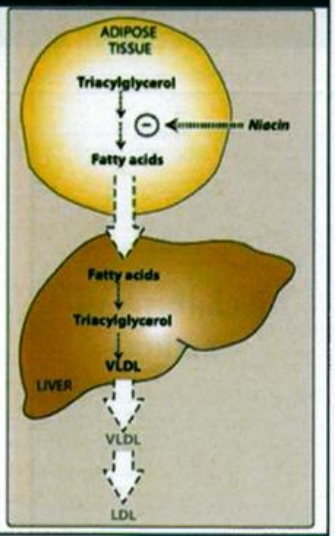
Fibric Acid derivatives (Fibrates)

Bezafibrate (Bezalip®)	Etofibrate (Lipo-Merz®)	Fenofibrate (Finorate®)
Gemfibrozil (Lopid®)		
Mechanism of action	- **Peroxisome proliferator activated receptors alpha (PPARα)** are members of the nuclear receptor supergene family that regulates lipid metabolism. - **Fibrates** → Activate PPARs → decrease triacylglycerol concentrations by increasing the expression of lipoprotein lipase and decreasing Apo-CII concentration - **Fibrates** also increase the level of HDL cholesterol by increasing the expression of Apo-A.	
Uses	- Treatment of hypertriacylglycerolemias, causing a significant decrease in plasma triacylglycerol levels. - Useful in treating Type III hyperlipidemia. - Patients with hypertriacylglycerolemia (Type IV or Type V) who do not respond to diet or other drugs	
Side effects	- **GIT effects:** mild GI disturbances. - **Gall bladder:** Lithiasis due to increase biliary cholesterol excretion, there is a predisposition to the formation of gallstones. - **Muscle:** Myositis (inflammation of muscle), muscle weakness or tenderness (evaluated in patients with renal insufficiency).	
Drug interaction	- Compete with the warfarin for binding sites on plasma proteins.	

Cholesterol Absorption Inhibitors

Ezetimibe (Ezetrol®)	
Mechanism of action	- Selectively inhibits intestinal absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. - Reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. - Ezetimibe lowers LDL cholesterol by 17 percent and triacylglycerols by 6 percent, and it increases HDL cholesterol by 1.3 percent.
Combination	**Ezetimibe + Simvastatin** (Cazet®) - A formulation of ezetimibe and simvastatin has been shown to lower LDL levels more effectively than the statin alone.

Niacin [Nicotinic acid (vitamin B3)]

Niacin (Niaspan®)		
Mechanism of action	- Niacin strongly inhibits lipolysis in adipose tissue the primary producer of circulating free fatty acids. - The liver normally utilizes these circulating fatty acids as a major precursor for triacylglycerol synthesis. Thus, niacin causes a decrease in liver triacylglycerol synthesis, which is required for VLDL production. - LDL is derived from VLDL → decrease in VLDL → leads to decrease LDL. - Increase HDL cholesterol levels.	
Uses	- Niacin is used as adjunctive therapy for the treatment of very high serum triglyceride levels in patients who present a risk of pancreatitis (inflammation of the pancreas). - Niacin lowers plasma levels of both cholesterol and triacylglycerol → useful in the treatment of familial hyperlipidemias.	
Side effects	**Niacin Flush** - An intense cutaneous flush (accompanied by an uncomfortable feeling of warmth, and severe itching or tingling). - Administration of aspirin prior to taking niacin decreases the flush. **Hyperuricemia** - Niacin inhibits tubular secretion of uric acid. **Others** - Impaired glucose tolerance and hepatotoxicity have also been reported.	

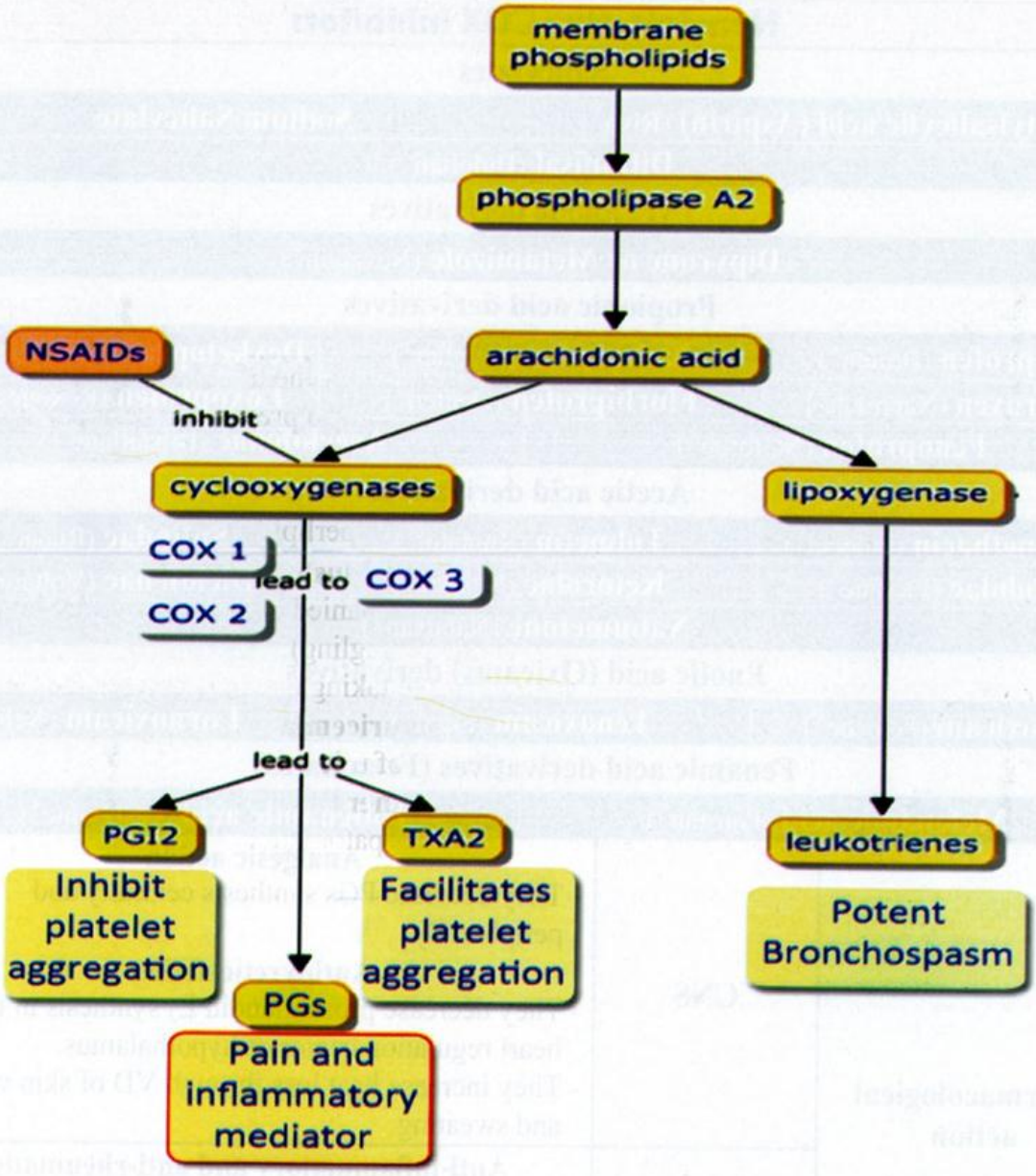
Supplements

Garlic (Tomex®)
- The benefits of garlic on cardiovascular health are the best known. Its benefits include lowering serum cholesterol and triglyceride levels, improving the ratio of HDL to LDL cholesterol, lowering blood pressure, and helping to prevent the development of atherosclerosis.
Omega-3 fatty acid (Fish oil) (BioChol®)
- Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) comprise approximately 30% of the fatty acids in fish oil. - EPA and DHA are potent inhibitors of VLDL and TG formation. - EPA and DHA increase HDL.

Non-steroidal anti-inflammatory drugs (NSAIDs)

- **Def.** → They are drugs that have similar action as Antipyretic and Anti-inflammatory effect but they differ in the chemical structure.

- **Mechanism of action :-**



→ Non-steroidal anti-inflammatory drugs (NSAIDs) inhibits Cyclooxygenase (COX) enzyme →

Decrease synthesis of

- **Prostaglandins (PGs)** → Responsible for → Pain and inflammatory mediator.
- **Prostacyclin (PGI_2)** → Responsible for → Decrease platelet aggregation.
- **Thromboxane-A_2 (TXA_2)** → Responsible for → Facilitates platelet aggregation.

➢ There are 3 isomers of COX enzyme :-

COX-1	Present in platelet, stomach and kidney
COX-2	Found at the site of inflammation
COX-3	Found in brain (CNS)

➢ Types of NSAIDs :-

Non-Selective COX inhibitors		
Salicylates		
Acetylsalicylic acid (Aspirin) (Rivo®)	**Sodium Salicylate**	
Diflunisal (Doloban®)		
Pyrazolone derivatives		
Dipyrone or Metamizole (Novalgin®)		
Propionic acid derivatives		
Ibuprofen (Brufen®)	**Ketoprofen** (Ketofan®)	**Dexketoprofen** (Dextrafast®)
Naproxen (Naprofen®)	**Flurbiprofen** (Ocufen®)	**Loxoprofen** (Roxogesic®)
Fenoprofen (Nalfosab®)	**Aceclofenac** (Bristaflam®)	
Acetic acid derivatives		
Indomethacin (Indocid®)	**Tolmetin** (Rumatol®)	**Sulindac** (Rudac®)
Etodolac (Etodine®)	**Ketorolac** (Ketolac®)	**Diclofenac** (Voltaren®)
Nabumetone (Nabuxan®)		
Enolic acid (Oxicams) derivatives		
Piroxicam (Feldene®)	**Tenoxicam** (Soral®)	**Lornoxicam** (Xefo®)
Fenamic acid derivatives (Fenamates)		
Mefenamic acid (Ponstan®)	**Tolfenamic acid** (Fastgraine®)	

Pharmacological action	**CNS**	**Analgesic action** - They decrease PGs synthesis centrally and peripherally. **Antipyretic action** - They decrease prostaglandin E_2 synthesis in the heart regulation center of hypothalamus. - They increase heat loss through VD of skin vessels and sweating.
	Inflammation	**Anti-inflammatory and anti-rheumatic** - They decrease PGs synthesis → reducing vascular permeability and edema. - Decrease inflammatory mediator
	Blood	- Aspirin in small dose (75-150 mg/day) → decrease platelet aggregation due to inhibit TXA_2.

	GIT	- Ulcers of the stomach or duodenum internal bleeding due to decrease stomach PGs levels.
	Kidney	- Decrease renal blood flow due to decrease Kidney PGs levels.
Therapeutic uses	- Analgesic in headache, toothache and common cold - Antipyretic in fever - Anti-inflammatory in rheumatoid arthritis - Aspirin in small dose used as anti-thrombotic in angina and myocardial infarction	
Adverse effects	→ **GIT** - Nausea, vomiting and ulceration → **Bleeding** → **Hypersensitivity reaction** - Bronchospasm and skin rash. → **Salicylism (Chronic use of salicylate)** - Cause tinnitus (ringing in the ear) - Blurred vision → **Reye's syndrome (Aspirin)** - Fatal hepatic injury and encephalopathy in childeren → **Teratogenic** → **Idiosyncrasy** - Hemolysis in patient with Glucose-6-Phosphate dehydrogenase (G6PD) enzyme deficiency.	
Contraindications	- Peptic ulcer - Allergy - Bronchial asthma - Pregnancy -Renal disease - Bleeding tendency - Aspirin not used in infant and children (<6years).	

Selective COX-2 inhibitors

Meloxicam (Mobic®)	Celecoxib (Celebrex®)	Rofecoxib (Vioxx®)

- Directly inhibit COX-2, an enzyme responsible for inflammation and pain at the site of inflammation.
- Reduces the risk of peptic ulceration.
- Vioxx® (Rofecoxib) was withdrawn voluntarily from the market, due to an increased risk of myocardial infarction and stroke.

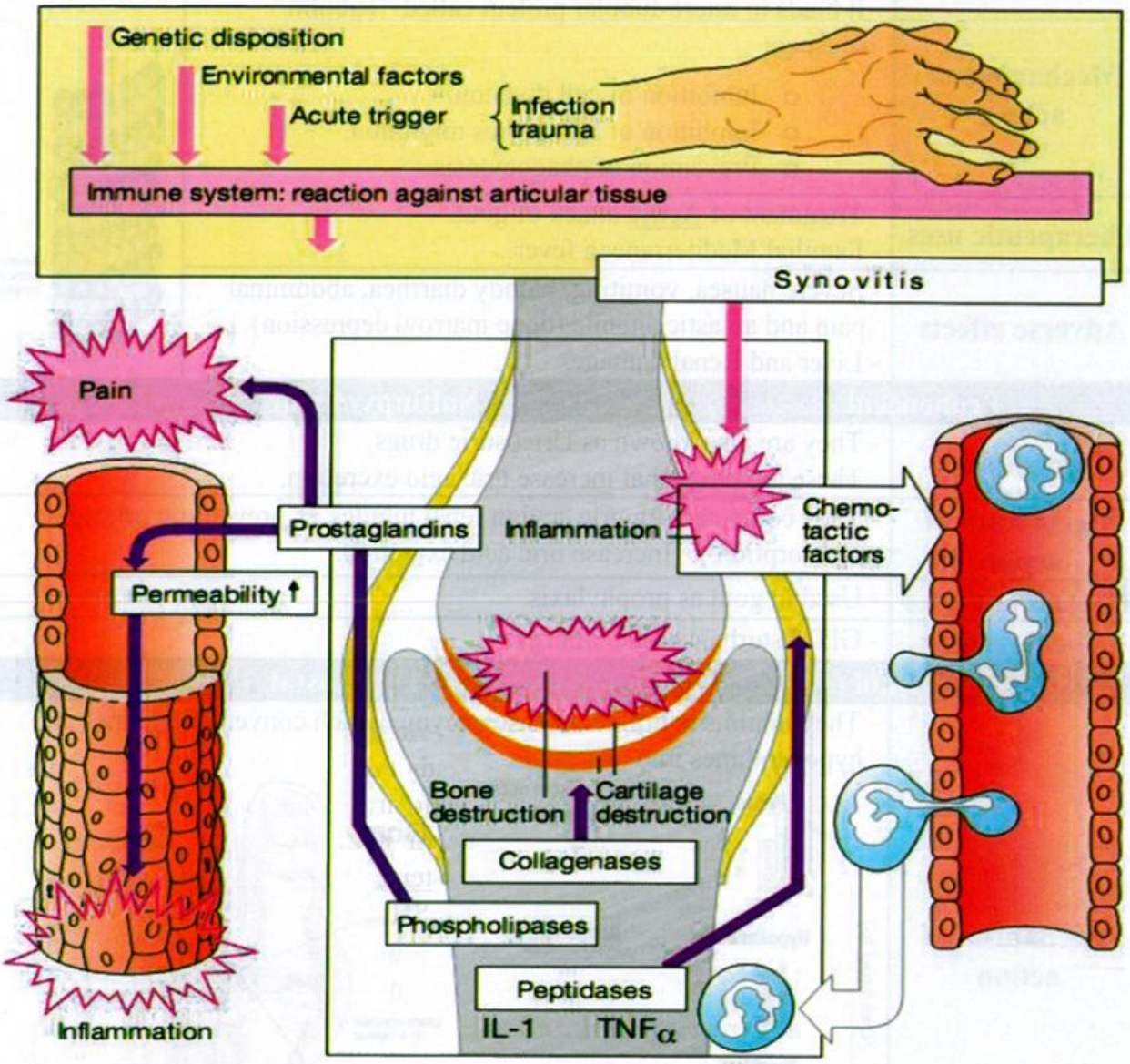
Therapeutic uses	- Sports injuries, osteoarthritis, rheumatoid arthritis, colorectal polyps, and menstrual cramps.

Selective COX-3 inhibitors	
Paracetamol (Phenacetin) {Acetaminophen} (Panadol®)	
Information	- Paracetamol was first marketed in the United States in 1953. It was safe than aspirin to take for children and people with ulcer. - COX-3 was actually discovered in 2002, and been found to be selectively inhibited by Paracetamol (Magic drug).
Pharmacokinetics	- Well absorbed orally - Distributed all over the body - Metabolized in the liver - Phenacetin (Active) → Paracetamol (Active) → Toxic metabolite → Detoxified by Glutathione system → Conjugation with Glucuronic acid and Sulfuric acid → - Excreted in urine
Mechanism	- Inhibit Selectively COX-3 enzyme present mainly in central.
Action	- **Antipyretic analgesic** - **No** Anti-inflammatory - **No** peptic ulcer - **No** bleeding
Uses	- Antipyretic analgesic
Safety	**- Safe in** - Children - Bronchial asthma - Peptic ulcer - Pregnancy
Side effects	**Hepatotoxicity** - **Paracetamol** overdose (10g in adult & 5g in child) → cause acute liver failure due to → Excess toxic metabolite cause depletion of SH group needed in glutathione system in the liver (detoxification). - **Treatment** → Oral N-Acetylcysteine (NAC) → SH donor. → Methionine → → SH donor. **Nephrotoxicity** - Chronic use of **Phenacetin** lead to nephrotoxicity (analgesic nephropathy) → characterized by renal papillary necrosis → Due to destruction of some or all of the renal papillae in the kidneys. **Met-Hemoglobin and hemolytic anemia** - In patient with G6PD enzyme deficiency

Propacetamol	Benorylate or Benorilate
- Prodrug form of paracetamol used by IV injection and converted to paracetamol by plasma esterase enzyme - 2g of propacetamol are equivalent to 1g of paracetamol.	- Ester-linked codrug of aspirin with paracetamol. - Used as an anti-inflammatory and antipyretic.

Disease modifying antirheumatic drugs (DMARDs)

➢ **Def.** → Are not analgesic and don't inhibit COX but they suppress the inflammatory process. They have slow action (4-10 weeks).

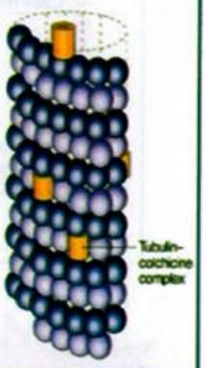


Examples includes

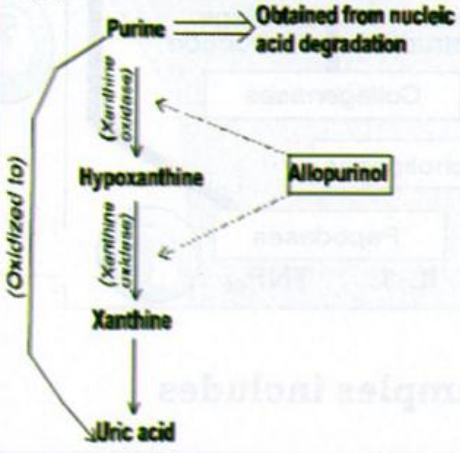
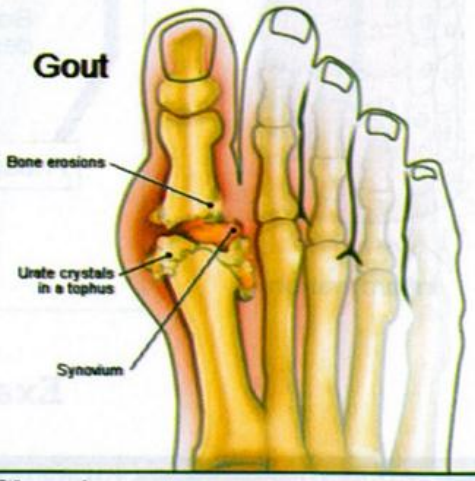
Gold salts	**Sulfasalazine** (Azulfidine®)	**Penicillamine** (Artamine®)
Cyclophosphamide (alkyloxan®)		**Methotrexate** (Methotrexate®)
Cyclosporine (Cyclosporine®)		**Hydroxychloroquine** (Plaquenil®)
Azathioprine (Imuran®)		**Leflunomide** (Avara®)

Drugs used in gout

➢ **Def.** → Gout is a condition in which uric acid crystals are deposited in joints leading to arthritis.

Colchicine (Colchicine®)		
Mechanism of action	- It binds to micro-tubular protein called "Tubulin" causing : o Inhibition of cell division. o Inhibition of leukocytes migration. o Prevention of phagocytosis.	
Therapeutic uses	- Treatment of **Acute** attack of gout. - Familial Mediterranean fever.	
Adverse effects	- Severe nausea, vomiting, bloody diarrhea, abdominal pain and aplastic anemia (bone marrow depression). - Liver and Renal damage.	

Probenecid (Benemid®)	**Sulfinpyrazone** (Novopyrazone®)
Information	- They are also known as Uricosuric drugs. - These are drugs that increase uric acid excretion.
Mechanism of action	- They compete with uric acid in renal tubules → preventing uric acid reabsorption → Increase uric acid excretion.
Therapeutic uses	- Used in gout as prophylaxis.
Adverse effects	- GIT disturbances and allergy.

Allopurinol (Zyloric®)	**Febuxostat** (Uloric®)
Mechanism of action	- They inhibits xanthine oxidase enzyme which converts xanthines and hypoxanthines into uric acid.  
Therapeutic uses	- Treatment of hyperuricemia and **Chronic** gout.
Adverse effects	- Allergy, GIT disturbance, Headache and Hepatic damage.

Rasburicase (Elitek®)	
Mechanism	- Is a recombinant urate oxidase enzyme → Oxidize uric acid

Questions

➢ Coose the best answer :-

146: 22-year-old woman who experienced pain and swelling in her right leg presented at the emergency room. An ultrasound study showed thrombosis in the popliteal vein. The patient, who was in her second trimester of pregnancy, was treated for 7 days with intravenous unfractionated heparin. The pain resolved during the course of therapy, and the patient was discharged on Day 8. Which one of the following drugs would be most appropriate out-patient follow-up therapy for this patient, who lives 100 miles from the nearest hospital?

a. Warfarin
b. Aspirin
c. Alteplase
d. Unfractionated heparin
e. Low-molecular-weight heparin

147: A 60-year-old man is diagnosed with deep-vein thrombosis. The patient was treated with a bolus of heparin, and a heparin drip was started. One hour later, he was bleeding profusely from the intravenous site. The heparin therapy was suspended, but the bleeding continued. Protamine was administered intravenously, and the bleeding resolved. The protamine:

a. Degraded the heparin
b. Inactivates antithrombin
c. Activates the coagulation cascade
d. Activates tissue-plasminogen activator
e. Ionically combines with heparin

148: A 44-year-old obese male has a significantly high level of plasma triglycerides. Following treatment with one of the following agents, his plasma triglyceride levels decrease to almost normal. Which agent did he receive?

a. Neomycin
b. Lovastatin
c. Cholestyramine
d. Gemfibrozil

149: Nicotinic acid in large doses used to treat hyperlipoproteinemia causes a cutaneous flush. The vasodilatory effect is due to

a. Release of histamine
b. Production of local prostaglandins
c. Release of platelet-derived growth factor (PDGF)
d. Production of NO
e. Ca^{2+} channel blockade

150: One type of hyperlipoproteinemia is characterized by elevatedplasma levels of chylomicra, normal plasma levels of β-lipoproteins, and the inability of any known drug to reduce lipoprotein levels. This is which of the following types of hyperlipoproteinemia?

a. Type I
b. Type IIa, IIb
c. Type III
d. Type IV
e. Type V

151: A 45-year-old male post–myocardial infarction (post-MI) for one week is being treated with intravenous (IV) heparin. Stool guaiac on admission was negative, but is now 4+, and he has had an episode of hematemesis. The heparin is discontinued, and a drug is given to counteract the bleeding. What drug was given?

a. Aminocaproic acid
b. Dipyridamole
c. Factor IX
d. Protamine
e. Vitamin K

152: Precautions advisable when using lovastatin include

a. Serum transaminase measurements
b. Renal function studies
c. Acoustic measurements
d. Monthly complete blood counts
e. Avoidance of bile acid sequestrants

153: A 60-year-old male, following hospitalization for an acute myocardial infarction, is treated with warfarin. What is the mechanism of action of warfarin?

a. Increase in the plasma level of factor IX
b. Inhibition of thrombin and early coagulation steps
c. Inhibition of synthesis of prothrombin and coagulation factors VII, IX, and X
d. Inhibition of platelet aggregation in vitro
e. Activation of plasminogen
f. Binding of Ca^{2+} ion cofactor in some coagulation steps

154: A 39-year-old pregnant female requires heparin for thromboembolic phenomena. What is the mechanism of action of heparin?

a. Increase in the plasma level of factor IX
b. Inhibition of thrombin and early coagulation steps
c. Inhibition of synthesis of prothrombin and coagulation factors VII, IX, and X
d. Inhibition of platelet aggregation in vitro
e. Activation of plasminogen
f. Binding of Ca^{2+} ion cofactor in some coagulation steps

155: A 42-year-old male with an acute MI is treated with alteplase. What is the mechanism of action of alteplase?

a. Inhibition of platelet thromboxane production
b. Antagonism of ADP receptor
c. Glycoprotein IIb/IIIa antagonist
d. Inhibition of the synthesis of vitamin K–dependent coagulation factors
e. Activation of plasminogen from plasmin

156: A 65-year-old male with a previous history of a stroke is treated with ticlopidine as prophylaxis for preventing further stroke. What is the mechanism of action of ticlopidine?

a. Inhibition of platelet thromboxane production
b. Antagonism of ADP receptor
c. Glycoprotein IIb/IIIa antagonist
d. Inhibition of the synthesis of vitamin K–dependent coagulation factors
e. Activation of plasminogen from plasmin

157: A 40-year-old female is to have angioplasty following an acute MI. As part of her treatment, she is given intravenously administered eptifibatide. What is the mechanism of action of eptifibatide?

a. Inhibition of platelet thromboxane production
b. Antagonism of ADP receptor
c. Glycoprotein IIb/IIIa antagonist
d. Inhibition of the synthesis of vitamin K–dependent coagulation factors
e. Activation of plasminogen from plasmin

158: A 47-year-old female comes to the emergency department (ED) with severe crushing chest pain of one hour's duration. Electrocardiogram and blood chemistries are consistent with a diagnosis of acute MI. Streptokinase is chosen as part of the therapeutic regimen. What is its mechanism of action?

a. It activates the conversion of fibrin to fibrin-split products
b. It activates the conversion of plasminogen to plasmin
c. It inhibits the conversion of prothrombin to thrombin
d. It inhibits the conversion of fibrinogen to fibrin

159: A 40-year-old male with markedly elevated cholesterol, diagnosed as having heterozygous familial hypercholesterolemia, is treated with cholestyramine. What is the mechanism of action of cholestyramine?

a. Sequestration of bile acids
b. Decreased hepatic secretion of VLDL
c. Increased lipoprotein lipase activity
d. Inhibition of HMG-CoA reductase
e. Decreased oxidation of plasma lipids

160: A 35-year-old male with markedly elevated plasma triglyceride and LDL levels, and low plasma HDL levels, is treated with gemfibrozil. What is the mechanism of action of gemfibrozil?

a. Sequestration of bile acids
b. Decreased hepatic secretion of VLDL
c. Increased lipoprotein lipase activity
d. Inhibition of HMG-CoA reductase
e. Decreased oxidation of plasma lipids

161: A 65-year-old male post-MI with an elevated LDL level is treated with atorvastatin. What is the mechanism of action of atorvastatin?

a. Sequestration of bile acids
b. Decreased hepatic secretion of VLDL
c. Increased lipoprotein lipase activity
d. Inhibition of HMG-CoA reductase
e. Decreased oxidation of plasma lipids

162: Which one of the following is the most common side effect of antihyperlipidemic drug therapy?

a. Elevated blood pressure
b. Gastrointestinal disturbance
c. Neurologic problems
d. Heart palpitations
e. Migraine headaches

163: Which one of the following hyperlipidemias is characterized by elevated plasma levels of IDL?

a. Type I
b. Type II
c. Type III
d. Type IV
e. Type V

164: Which one of the following drugs causes a decrease in liver triacylglycerol synthesis by limiting available free fatty acids needed as building blocks for this pathway?

a. Niacin
b. Fenofibrate
c. Cholestyramine.
d. Gemfibrozil
e. Lovastatin

165: Which one of the following drugs binds bile acids in the intestine, thus preventing their return to the liver via the enterohepatic circulation?

a. Niacin
b. Fenofibrate
c. Cholestyramine
d. Fluvastatin
e. Lovastatin

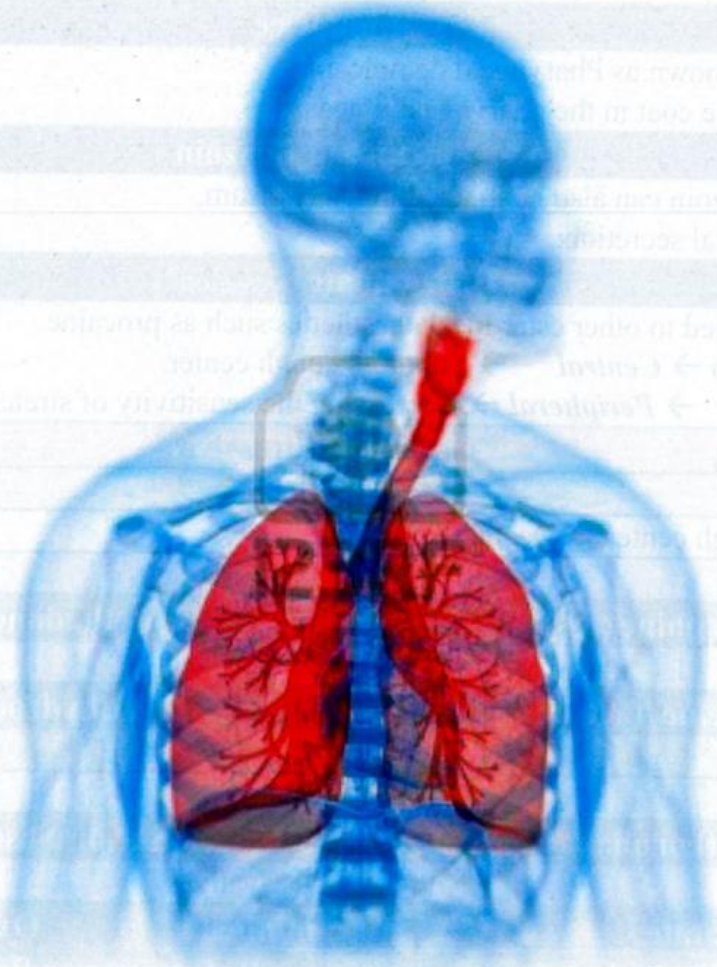
Answers

146	147	148	149	150	151	152	153	154	155
e	e	d	b	a	d	a	c	b	e
156	157	158	159	160	161	162	163	164	165
b	c	b	a	c	d	b	c	a	c

Questions and answers from (References):
Pharmacology 5th edition Lippincott Williams & Wilkins
Pharmacology 12th edition PreTest Self-Assessment and Review

Respiratory System

(RESPIRATORY SYSTEM)



Cough Therapy

➢ Definition:-

- Cough is a protective mechanism to expel secretions and foreign bodies outside the respiratory tract.

➢ Types of Cough :-

- **Dry (unproductive or useless)** → Treated by **Antitussives**
- **Productive cough (Useful)** → Treated by **Expectorant** and/or **Mucolytic agents**.

Antitussives

Peripheral Antitussives		
Stop Smoking		
- Smoker's Cough.		
Liquorice		
- Liquorice also known as Pharyngeal demulcent. - Form a protective coat in the pharyngeal mucosa.		
Tincture of Benzoin		
- Tincture of Benzoin can also be inhaled in water steam. - Increase bronchial secretion.		
Benzonatate (Tessalon®)		
- Chemically related to other ester local anesthetics such as procaine. - Dual mechanism → ***Central*** → Suppress cough center. → ***Peripheral*** → Decreasing the sensitivity of stretch receptors.		
Central Antitussives		
A- Narcotic		
- Suppresses cough center → Decrease cough.		
Highly additive		
Morphine (MST®)	**Methadone** (Amidone®)	
Less additive		
Codeine (Codaphen®)	**Dihydrocodeinone**	
B- Non-Narcotic		
Opiate derivatives		
Dextromethorphan (Codiphan®)	**Narcotine or Noscapine** (Tusscapine®)	
Non-opiate derivatives		
Benzonatate	**Caramiphen**	**Oxeladine** (Paxeladine®)
Diphenhydramine	**Butamirate or Brospamin** (Sinecod®)	
Clobutinol (Silomat®)	**Pipazetate or Pipazethate** (Selgon®)	
- Studies in 2004 had indicated that Clobutinol has the potential to prolong the QT interval.		

Mucolytics

➢ Mucolytic agents:-

- A mucolytic agent is an agent which dissolves thick mucus by dissolving various chemical bonds within secretions (liquefy mucous secretions).
- They are not expectorant, but they help the action of expectorants.

Bromhexine (Bisolvine®)
- It breaks mucopolysaccharide of the mucous. - The effect appears after 3 days of treatments. - Useful in bronchitis and bronchial asthma.
Ambroxol (Bronchopront®)
- It is the active metabolite of Bromhexine.
CarboxyMethylCysteine (Mucolase®)
- Break the Bisulfide bridge (S-S) of sputum → decrease surface tension → Mucolytic. - Increase volume of sputum but decrease viscosity. - Useful in bronchitis and bronchial asthma.
AcetylCysteine (ACC®)
- Same as CarboxyMethylCysteine. - Used in bronchitis. - Used Paracetamol over dose and Nitroglycerin tolerance (S-H donor).
Erdosteine (Mucotec®)
- 300 mg twice daily → Reduced cough.

Expectorants

➢ Expectorants:-

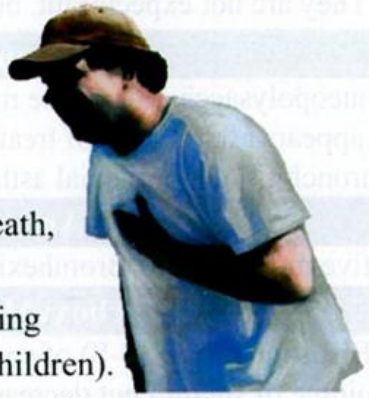
- Works by signaling the body to increase the amount or hydration of secretions, resulting in more yet clearer secretions and as a byproduct lubricating the irritated respiratory tract.

Sedative Expectorant
- Increase secretion of thin, soothhing and protective bronchial mucous → Sedate acutely inflammed mucosa. - Usedespecially in the early stage (Acute).
1- Alkaline Expectorants → Na^+ (or K^+) Acetate, Benzoate, Bicarbonate or citrate. **2- Nauseant Expectorants** → Emetine (Sub-emetic dose). **3- Saline Expectorants** → Na^+ (or K^+) Iodide.
Stimulant Expectorant
- Stimulate the healing of chronically inflamed mucosa.
Guaiacol
- Used in chronic productive cough (acute ineffective).

Bronchial Asthma

➢ Definition :-

- Is the common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm.



➢ Symptoms:-

- Shortness of breath.
- Chest tightness or pain.
- Trouble sleeping caused by shortness of breath, coughing or wheezing.
- A whistling or wheezing sound when exhaling (wheezing is a common sign of asthma in children).
- Coughing or wheezing attacks that are worsened by a respiratory virus, such as a cold or the flu.

➢ Causes:-

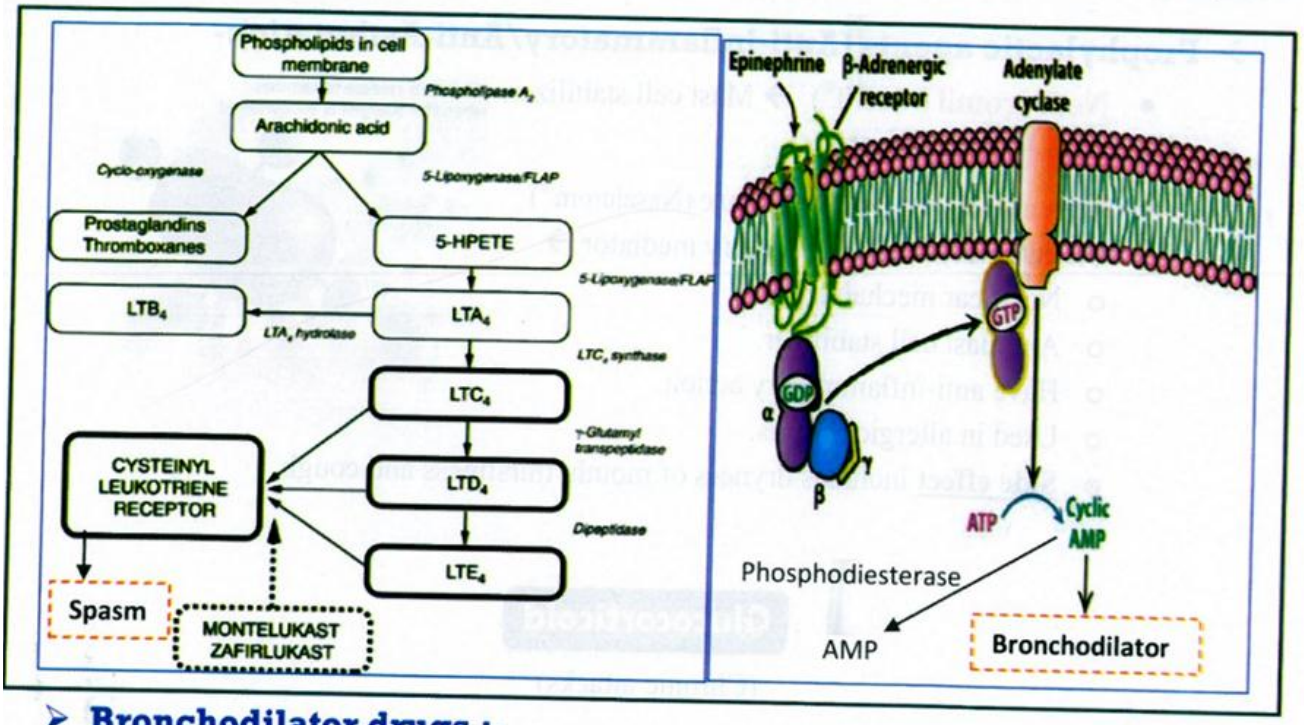
→ Exposure to various allergic substances (allergens) and irritants can trigger signs and symptoms of asthma.

→ Asthma triggers are different from person to person and can include:

- Airborne allergens, such as pollen.
- Air pollutants and irritants, such as smoke.
- Allergic reactions to some foods, such as peanuts or Strawberries.
- Respiratory infections, such as the common cold.
- Physical activity (exercise-induced asthma).
- Cold air.
- Strong emotions and stress.
- Certain medications, including beta blockers and aspirin.
- Gastroesophageal reflux disease (GERD) (a condition in which stomach acids back up into your throat).

→ That the rise in the prevalence of allergies and asthma is a direct and unintended result of reduced exposure to a wide variety of different bacteria and virus types.

→ Study in 2005, 25 genes had been associated with asthma. Many of these genes are related to the immune system or to modulating inflammation.



➢ Bronchodilator drugs :-

- ***β_2 agonist*** → **Increase cAMP → Bronchodilatation** (Acute attack)
  - **Salbutamol** (Ventolin®) - **Terbutaline** (Bricanyl®)
    → Short acting→ Inhalation or oral.
  - **Formoterol** (Foradil®) - **Salmeterol** (Serevent®)
    → Long acting → Inhalation.
  - **Isoprenaline** & **Adrenaline** are rarely used now.

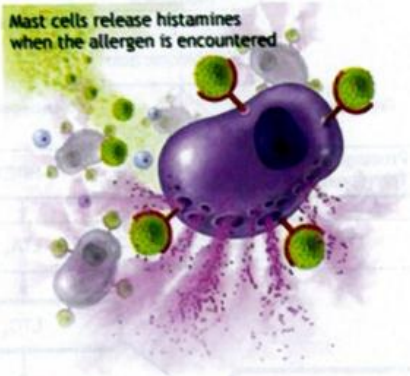
- ***Muscarinic antagonist :***
  - **Tiotropium** (Spiriva®)
  - **Ipratropium** (Atrovent®) (Bronchodilator without effect in mucous secretion).
- ***Methyl xanthines*** → **Phosphodiesterase inhibitors → Increase cAMP**
  - **Theophylline** (Theo-SR®)
  - **Aminophylline** (Aminophylline®)
- ***Leukotriens Pathway inhibitors:***
  - **Zileuton** → inhibits 5-Lipoxygenase enzyme.
  - **Zafirleukast** (Ventair®) - **Montelukast** (Clear air®)
    → Leukotriene receptor (**$CysLT_{1,2}$**) antagonist.

➢ Prophylactic agents (Anti-inflammatory/Anti-Asthmatic):-

- **Nedocromil** (Alocril®) → Mast cell stabilizer.
- **Ketotifen** (Zaditen®)
- **Cromolyn or Cromoglycate** (Nasalcrom®)

→ Prevent release of inflammatory mediator →

- Not clear mechanism.
- Are mast cell stabilizer.
- Have anti-inflammatory action.
- Used in allergic rhinitis.
- **Side effect** includes dryness of mouth, thirstiness and cough.



Glucocorticoid

(Chronic attacks)

- **Hydrocortisone** (Solu-cortef®)
- **Prednisone** (Hostacortin®)
- **Prednisolone** (Hostacortin-H®)
- **Methyl-Prednisolone** (Depo-Medrol®)
- **Betamethasone** (Deprofos®)
- **Dexamethasone** (Epidron®)

Mechanism as anti-inflammatory	- They inhibit antigen/antibody (Ag/Ab) reaction. - Increase effect of stimulate β_2. - Decrease release of Phospholipase A_2 and arachidonic acid.
Side effects	- Disturbance in electrolyte balance which include sodium retention and potassium excretion. - Mobilization of calcium and phosphate with osteoporosis and spontaneous fractures, growth retraction in children is reported. - Hyperglycemia due to inhibit insulin release. - Delayed wound healing and increased liability to infectious. - Acute adrenal insufficiency may be occurring during prolonged treatment.
N.B	- They must be stopped gradually to avoid adrenal insufficiency. - They are contraindication during pregnancy and lactation.

➢ Antibiotics:-

- Broad spectrum antibiotics must be used to treat respiratory infection.

Questions

➢ Coose the best answer :-

166: A 12-year-old girl with a childhood history of asthma complained of cough, dyspnea, and wheezing after visiting a riding stable. Her symptoms became so severe that her parents brought her to the emergency room. Physical examination revealed diaphoresis, dyspnea, tachycardia, and tachypnea. Her respiratory rate was 42 breaths per minute, pulse rate 110 beats per minute, and blood pressure 132/65 mm Hg. Which of the following is the most appropriate drug to rapidly reverse her bronchoconstriction?

a. Inhaled cromolyn b. Inhaled beclomethasone c. Inhaled albuterol
d. Intravenous propranolol

167: A 9-year-old girl has severe asthma, which required three hospitalizations in the last year. She is now receiving therapy that has greatly reduced the frequency of these severe attacks. Which of the following therapies is most likely responsible for this benefit?

a. Albuterol by aerosol b. Cromolyn by inhaler c. Fluticasone by aerosol
d. Theophylline orally e. Zafirlukast orally

168: A 60-year-old male with chronic obstructive lung disease is given ipratropium as part of his therapeutic regimen. What is the mechanism of action of ipratropium?

a. Inhibition of airway muscarinic receptors b. Inhibition of 5-lipoxygenase
c. Breakdown of mucus d. Inhibition of mediator release
e. Inhibition of phosphodiesterase f. Activation of β-adrenergic receptors

169: A 10-year-old female with allergy-induced asthma is treated with cromolyn. What is the mechanism of action of cromolyn?

a. Inhibition of airway muscarinic receptors b. Inhibition of 5-lipoxygenase
c. Breakdown of mucus d. Inhibition of mediator release
e. Inhibition of phosphodiesterase f. Activation of β-adrenergic receptors

170: A one-year-old male develops decreased breath sounds, and wheezing during a febrile episode, which is relieved by albuterol. What is the mechanism of action of albuterol?

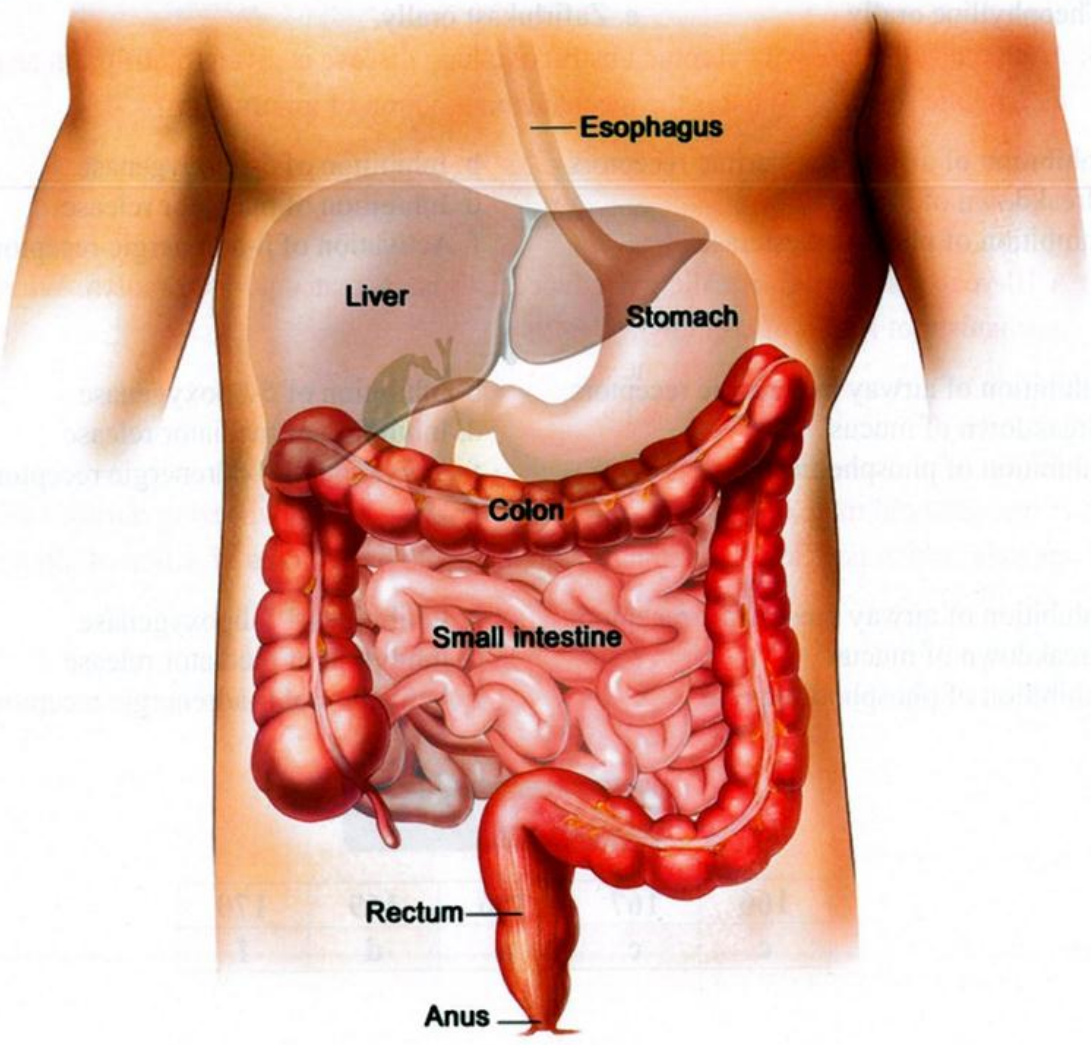
a. Inhibition of airway muscarinic receptors b. Inhibition of 5-lipoxygenase
c. Breakdown of mucus d. Inhibition of mediator release
e. Inhibition of phosphodiesterase f. Activation of β-adrenergic receptors

Answers

166	167	186	169	170
c	c	a	d	f

GIT

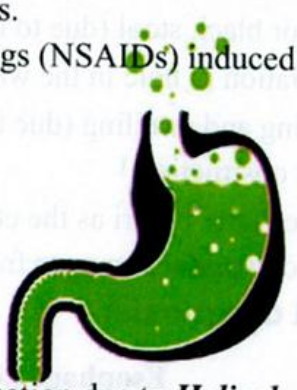
(GASTROINTESTINAL TRACT)



Peptic Ulcer Disease (PUD)

➢ Definition:-

- Is the most common ulcer of an area of the gastrointestinal tract that is usually acidic and thus extremely painful.
- It is defined as mucosal erosions equal to or greater than 0.5 cm. As many as 60–90% of such ulcers are associated with ***Helicobacter pylori***, a spiral-shaped bacterium that lives in the acidic environment of the stomach.
- **The three common forms of peptic ulcers include:**
  - ***Helicobacter pylori*** associated ulcers.
  - Non-steroidal anti-inflammatory drugs (NSAIDs) induced ulcers.
  - Stress-related ulcers.



➢ Classification according to location:-

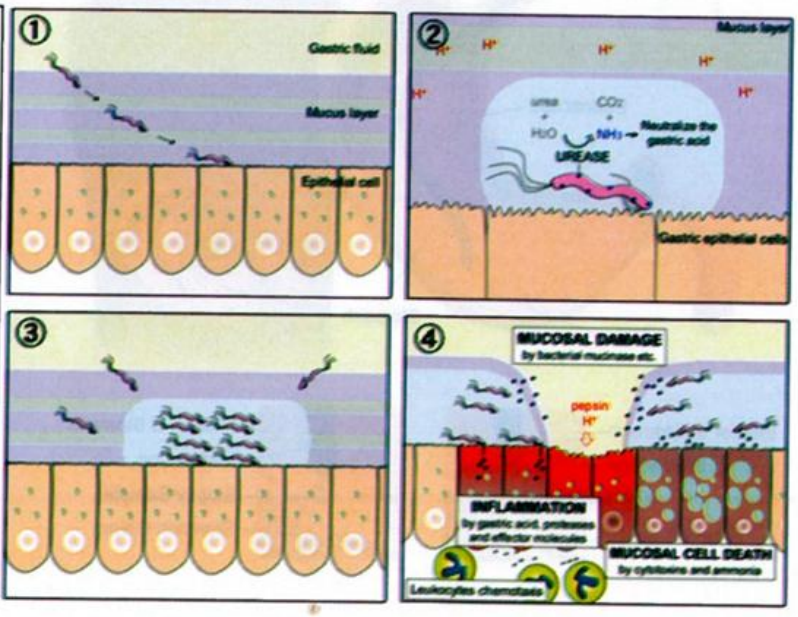
- Stomach (Gastric ulcer)
- Duodenum (Duodenal ulcer)
- Esophagus (Esophageal ulcer)

➢ Causes:-

- A major causative factor is chronic inflammation due to ***Helicobacter pylori***.
- Another major cause is the use of NSAIDs (inhibit the prostaglandins and the mucous layer formation).
- Stress in the psychological sense can influence the development of peptic ulcers.
- Some studies have found correlations between smoking and ulcer formation.
- Zollinger-Ellison syndrome (Increased levels of the gastrin hormone due to a small tumor (Gastrinoma) in the pancreas).

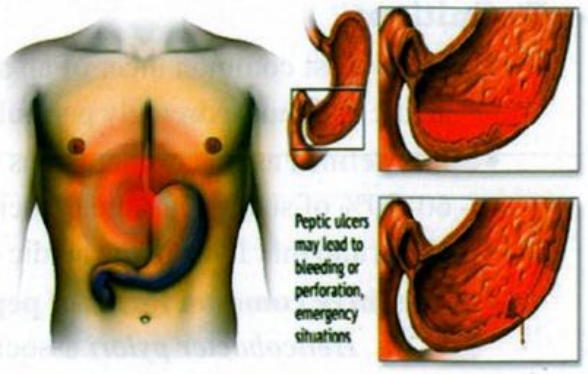
Helicobacter pylori

- ***H. pylori*** attaches to mucus-secreting cells of gastric mucosa, but does not invade the tissue.
- It releases urease enzyme which produces large amounts of NH_3 from urea.
- Organism causes inflammation and ulcers; ammonia has damaging effect on gastric epithelium leading to gastritis and peptic ulcer.



➢ Symptoms:-

- Abdominal pain.
- Bloating and abdominal fullness.
- Nausea and lots of vomiting.
- Loss of appetite and weight loss.



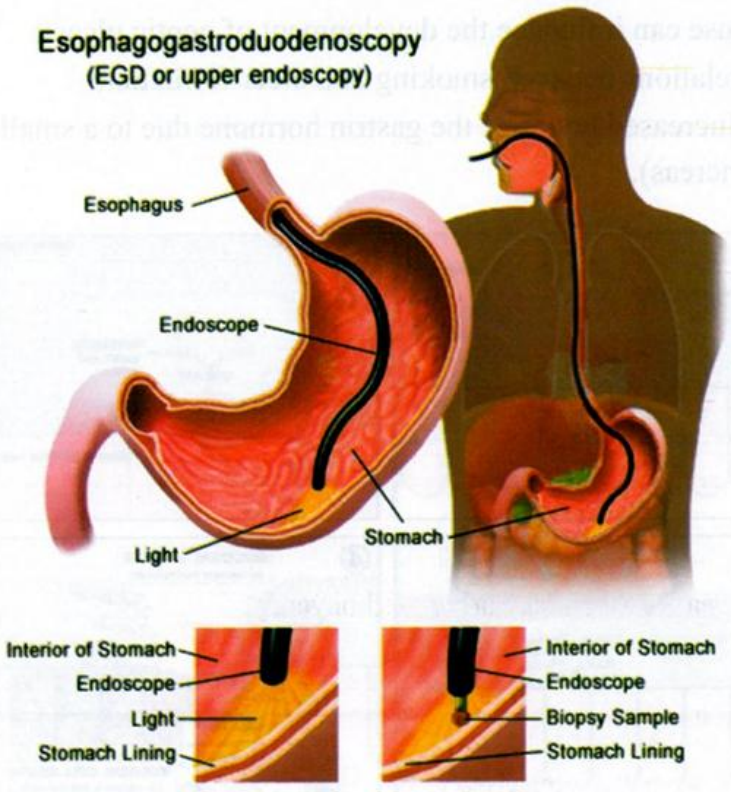
➢ Complications:-

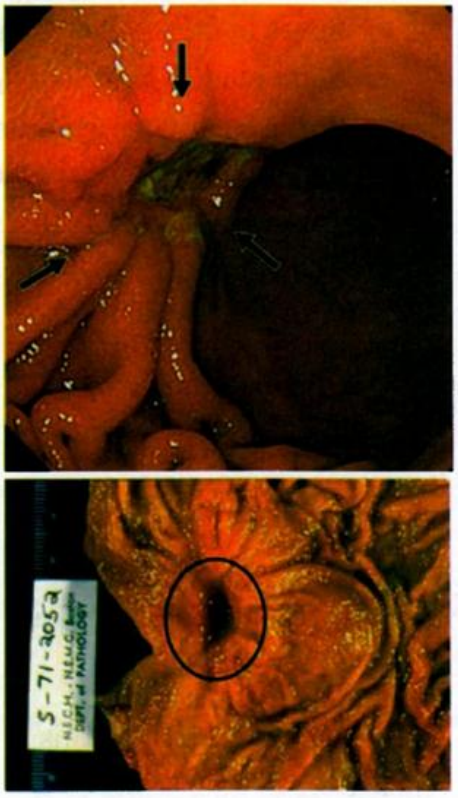
- Gastrointestinal bleeding.
- Hematemesis (vomiting of blood).
- Dark or black stool (due to bleeding).
- Perforation (a hole in the wall)
- Scarring and swelling (due to ulcers) causes narrowing in the duodenum and gastric outlet obstruction.
- Helicobacter pylori as the etiological factor making it 3 to 6 times more likely to develop **stomach cancer** from the ulcer.

➢ Tests and diagnosis:-

Esophagogastroduodenoscopy (EGD)

- A Form of endoscopy, also known as a gastroscopy, is done when a peptic ulcer is suspected. by direct visual identification, the location and severity of an ulcer can be described.





Diagnosis to detect *Helicobacter pylori*

- ***H. pylori*** may be detected in a blood test, a stool test or a breath test.

1- Urea Breath Test

- The breath test uses radioactive carbon atom to detect ***H. pylori***.
- To perform this exam the patient will be asked to drink a tasteless liquid which contains the carbon as part of the substance that the bacteria breaks down.
- After an hour, the patient will be asked to blow into a bag that is sealed.
- If the patient is infected with ***H. pylori***, the breath sample will contain radioactive carbon dioxide.
- This test provides the advantage of being able to monitor the response to treatment used to kill the bacteria.

2- Rapid urease test

- Also known as the CLO test (Campylobacter-like organism test) is a rapid test for diagnosis of ***Helicobacter pylori***.
- Samples of cells or tissues (biopsy specimen) may be collected through the endoscope. These samples are then sent to laboratory for testing.
- Samples placed into a medium containing urea and an indicator such as phenol red.
- The urease produced by ***H. pylori*** hydrolyzes urea to ammonia, which raises the pH of the medium, and changes the color of the specimen from yellow (Negative) to red (Positive).

3- Direct culture from an EGD biopsy specimen

- This is difficult to do and can be expensive

4- Measurement of antibody levels in blood

- Does not require EGD

5- Stool antigen test

➢ Treatments:-

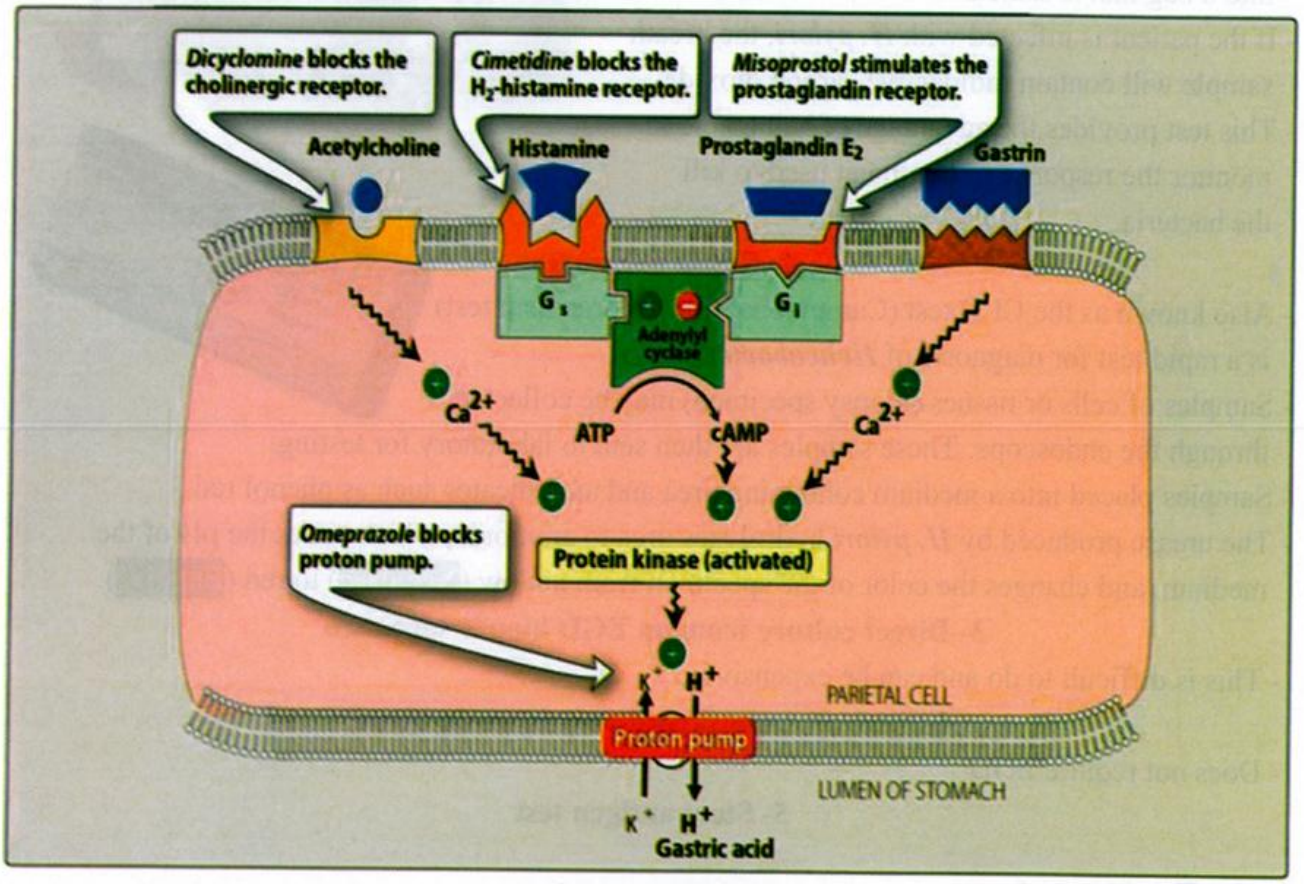
Non-Pharmacological

- **Decrease** → Spice food, Heavy meals, Tea, Coffee and Carbonated beverage (Pepsi).
- **Control** → Stress.
- **Stop** → Smoking.
- **Avoided** →Non-Steroidal anti-inflammatory drugs (NSAIDs).

Pharmacological

➢ Classification of drugs :-

- Antacids
- Mucosal Protective (Cytoprotective) agents
- H_2 receptor blockers
- Proton pump inhibitors (PPIs)
- Muscarinic blockers
- Prostaglandins analogous
- Eradication of ***Helicobacter Pylori (H. pylori).***



Antacids

Calcium carbonate $CaCO_3$	Aluminum hydroxide $Al(OH)_3$
Sodium bicarbonate $NaHCO_3$	Magnesium hydroxide $Mg(OH)_3$
Mechanism of action	- Antacids are weak bases that react with gastric acid to form water and a salt → Neutralize gastric HCl.
Side effects	- Aluminum hydroxide → Constipating. - Magnesium hydroxide → Diarrhea.

Cytoprotective Agents

- These compounds, known as **Mucosal Protective agents**.
- Have several actions that enhance mucosal protection mechanisms, preventing mucosal injury, reducing inflammation, and healing existing ulcers.

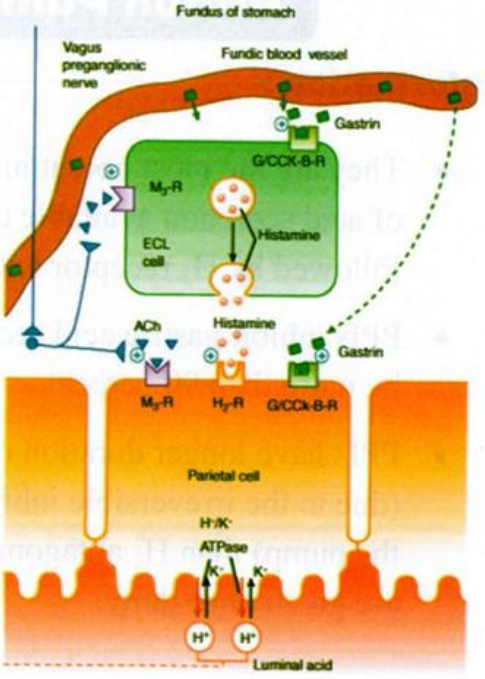
Sucralfate compound (Gastrofait®)	
Mechanism of action	- Sucralfate → complex of aluminium hydroxide and sulfated sucrose. - Forming complex gels with epithelial cells → prevents degradation of mucus by pepsin and acid. - It also stimulates prostaglandin release. - Increase release of mucus (Dilute acidity) and bicarbonate (Neutralize acidity). - Effective in heals duodenal ulcers.
- Used in long-term maintenance therapy to prevent their recurrence. - Should not be administered with H_2 antagonists or antacids. - Not prevent NSAID-induced ulcers.	
Bismuth compound	
- Effective in heal peptic ulcers. - Have antimicrobial activity. - Inhibits the activity of pepsin. - Increase secretion of mucus.	

H_2 Receptor Blockers

➢ Information :-

- H_2 receptor one type of histaminic receptor located in gastric mucosa which coupled by Gs (Excitatory effect) → When histamine binding by H_2 → Increase secretion of HCl.
- H_2 receptor blocker prevents HCl release.

Drug	Potency
Cimetidine (Not used)	1
Ranitidine (Zantac®)	4-10
Nizatidine (Ulcfree®)	4-10
Famotidine (Antodine®)	20-50



➢ Mechanism of action :-

4) H_2 receptor blocker → block the actions of histamine at all H_2 receptors.
5) Decrease histamine release from enterochromaffin-like (ECL) cell.
6) Reduce effect of other substances that promote acid secretion such as gastrin and acetylcholine.

➢ Clinical uses :-

- **Peptic ulcer disease (PUD)**
- **Gastroesophageal reflux disease (GERD)**
  - **But** proton pump inhibitors (PPIs) are more potent and preferentially used in the treatment of this disorder.
- **Non-ulcer dyspepsia**
- **Prevention of stress ulcer**

N.B: Tolerance to the effects of H_2 antagonists can be seen within 2 weeks of therapy.

➢ Adverse effects :-

- **Adverse effect of Ranitidine, Nizatidine** and **Famotidine** Occurring in less than 3% of patient include diarrhea, headache and fatigue.
- **Adverse effect of Cimetidine :**
  - Cimetidine inhibits binding of dihydrotestosterone to androgen receptors (Anti-androgenic effect) and increase serum prolactin cause→
    - Gynecomastia in male (Increase prolactin).
    - Impotence in male (Anti-androgenic effect).
    - Galactorrhea in female (Increase prolactin).

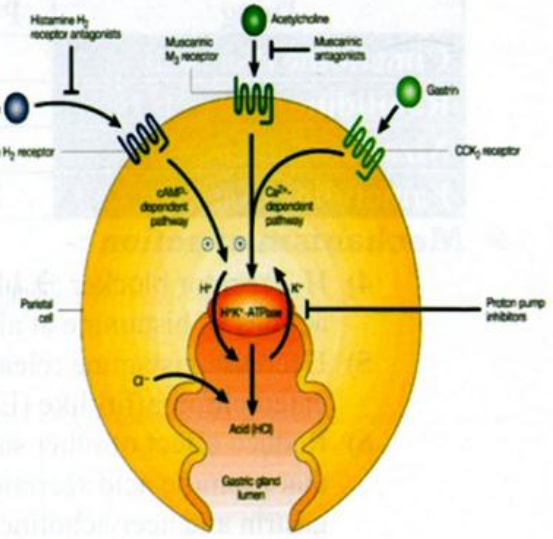
➢ Drug interactions :-

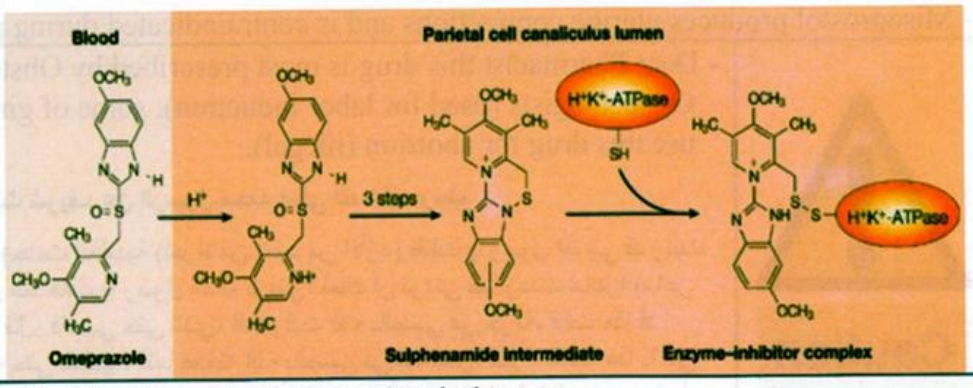
- Cimetidine is LME inhibitor (Inhibit Cytochrome P450) → Increase effect of other drug e.g. **warfarin**.
- All of H_2-blocker except **Famotidine** inhibit gastric first pass metabolism of **ethanol** (**Alcohol**) especially in women resulting in increased bioavailability of ethanol → increase blood ethanol level.

Proton Pump Inhibitors (PPIs)

➢ Information :-

- They are the most potent inhibitors of acid secretion available today, followed by H_2 receptor antagonists.
- PPIs inhibit gastric acid secretion by more than 90 percent.
- PPIs have longer duration of action (due to the irreversible inhibition of the pump) than H_2 antagonists and are given once daily.



Omeprazole (Omez®)	Lansoprazole (Lanzor®)
Pantoprazole (Controloc®)	Rabeprazol (Pariet®)
Esomeprazole (Nexium®)	
Mechanism of action	- Proton pump inhibitors act by irreversibly (covalent binding) blocking the H^+/K^+ ATPase enzyme → Prevent pump of proton (H^+). - Body takes about 18 hours for the enzyme to be resynthesized. - PPIs suppress acid production and healing peptic ulcers. 
Uses	- Esophagitis and active duodenal ulcer. - **Zollinger-Ellison syndrome** (long time therapy). - **Gastroesophageal reflux disease (GERD).** - Reduce the risk of bleeding from an ulcer caused by aspirin and other NSAIDs. - They are also successfully used with antimicrobial regimens to eradicate ***H. pylori***.
Dose and activity	- 20-40 mg (Orally) Once daily. - For maximum effect→ taken 30 minutes before largest meal of the day. - If an H_2-receptor antagonist is also needed, it should be taken well after the PPI for best effect, because The H_2 antagonists will reduce the activity of the proton pump, and PPIs require active pumps to be effective.
Drug Interaction	- Omeprazole is LMEIs → inhibits the metabolism of other drugs such as warfarin.

Muscarinic Antagonist

Pirenzepine (Gastrozepin®)	Telenzipine
Action	- They are selective M_1 antagonist → Decrease acid secretion with less adverse effect than atropine. - Reduce acid production by 40%. - Rarely are used today, because of their relatively poor efficacy.
Adverse effects	- Dry mouth, blurred vision, constipation and headache.

Prostaglandins Analogues

Misoprostol (Misotac®)

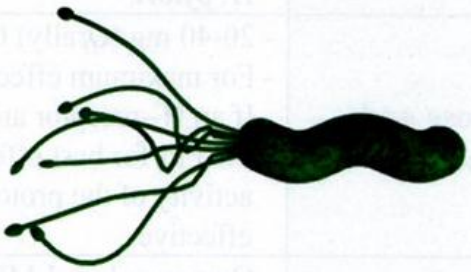
- Prostaglandin E_2, produced by the gastric mucosa, inhibits secretion of HCl and stimulates secretion of mucus and bicarbonate.
- Misoprostol is a synthetic Prostaglandin E_1 analogue that inhibits gastric acid secretion by direct action on partial cells and it also increase secretion of bicarbonate and mucus.
- Used mainly in **NSAIDs associated ulcer**.
- Misoprostol produces uterine contractions and is contraindicated during pregnancy.

- Dear Pharmacist this drug is most prescribed by Obstetricians and Gynecologists (used for labor induction); some of girls (Prostitutes) may use this drug for abortion (illegal).

حديث شريف عن الرسول محمد صلى الله عليه وسلم

عن بريدة رضي الله عنه قال: (جاءت الغامدية (امرأة من غامد من الأزد) فقالت يا رسول الله إني قد زنيت فطهرني وإنه ردَّها فلما كان الغد قالت يا رسول الله لم تردني؟ لعلك أن تردني كما رددت ماعزاً (ماعز بن مالك)، فو الله إني لحبلى قال: فاذهبي حتى تلدي، فلما ولدت أتته بالصبي في خرقة، قالت هذا قد ولدته، قال: اذهبي فأرضعيه حتى تفطميه، فلما فطمته أتته بالصبي في يده كسرة خبز، فقالت هذا يا نبي الله قد فطمته وقد أكل الطعام، فدفع الصبي إلى رجل من المسلمين، ثم أمر بها فحفر لها إلى صدرها وأمر الناس فرجموها) رواه مسلم

Eradication of *H. Pylori*



- Eradication of this infection use triple therapy **or** quadruple therapy usually results in a 90 percent or greater eradication rate

Triple therapy (2-week course)

- Consisting of a PPI with either metronidazole or amoxicillin plus clarithromycin

Quadruple therapy (2-week course)

- Consisting of a bismuth subsalicylate and metronidazole plus tetracycline plus a PPI

Preparation	(Heli-cure®)
	Clarithromycin 250mg + **Omeprazole** 20mg + **Tinidazole** 500 mg

Nausea and Vomiting

➢ Definition (Not Disease) :-

- **Nausea**
  - The inclination to vomit or as a feeling in the throat or epigastric region alerting an individual that vomiting is imminent.
- **Vomiting (Emesis)**
  - The ejection or expulsion of gastric contents through the mouth, often requiring a forceful event.

➢ Causes:-

- Nausea and vomiting may occur separately or together.

- **Common causes include:**

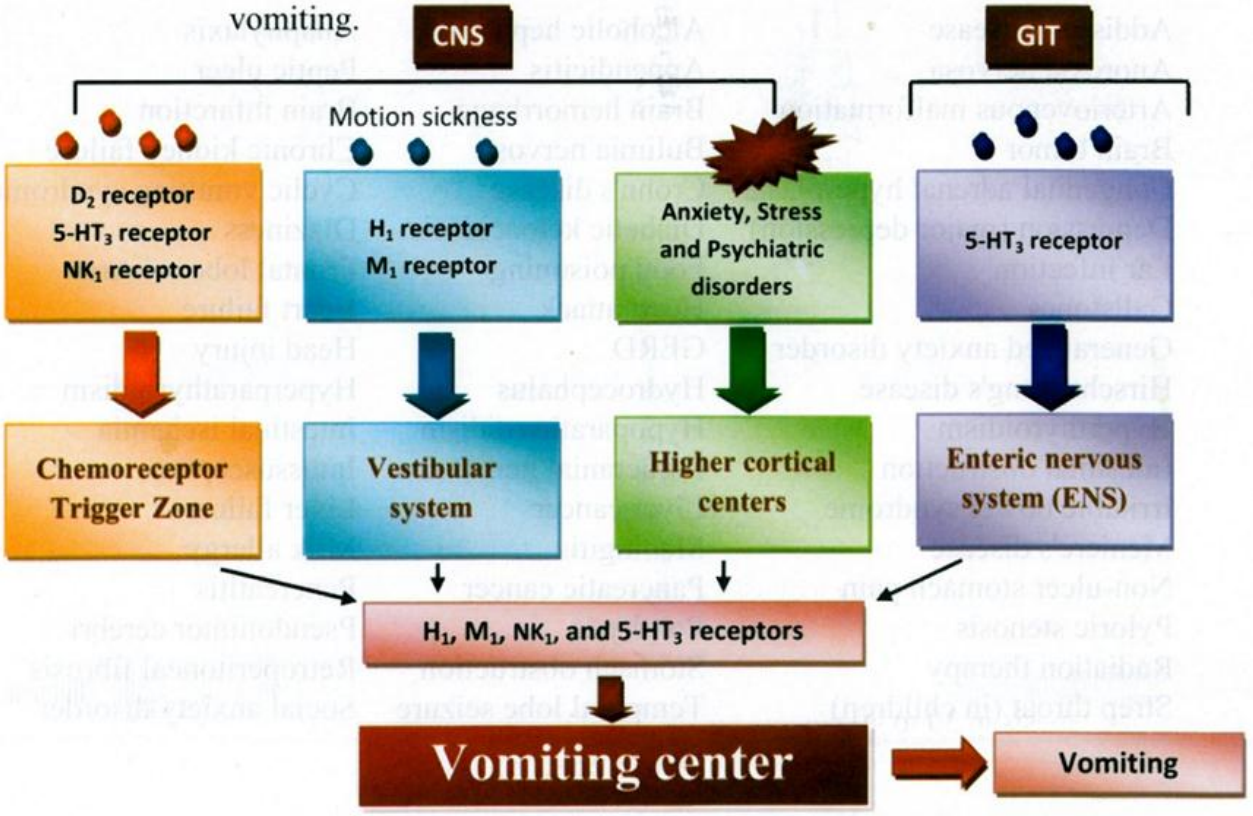
Chemotherapy	Gastroparesis	Overdose of alcohol
General anesthesia	Migraine	Vertigo
Viral gastroenteritis	Motion sickness	Rotavirus

- **Other possible causes:**

Addison's disease	Alcoholic hepatitis	Anaphylaxis
Anorexia nervosa	Appendicitis	Peptic ulcer
Arteriovenous malformation	Brain hemorrhage	Brain infarction
Brain tumor	Bulimia nervosa	Chronic kidney failure
Congenital adrenal hyperplasia	Crohn's disease	Cyclic vomiting syndrome
Depression (major depression)	Diabetic ketoacidosis	Dizziness
Ear infection	Food poisoning	Frontal lobe seizures
Gallstones	Heart attack	Heart failure
Generalized anxiety disorder	GERD	Head injury
Hirschsprung's disease	Hydrocephalus	Hyperparathyroidism
Hyperthyroidism	Hypoparathyroidism	Intestinal ischemia
Intestinal obstruction	Intracranial hematoma	Intussusception
Irritable bowel syndrome	Liver cancer	Liver failure
Meniere's disease	Meningitis	Milk allergy
Non-ulcer stomach pain	Pancreatic cancer	Pancreatitis
Pyloric stenosis	Porphyria	Pseudotumor cerebri
Radiation therapy	Stomach obstruction	Retroperitoneal fibrosis
Strep throat (in children)	Temporal lobe seizure	Social anxiety disorder

➢ Mechanisms that trigger vomiting:-

- **Chemoreceptor Trigger Zone (CTZ):**
  - Lies outside the blood–brain barrier; it can therefore be stimulated by blood-borne drugs that can stimulate vomiting or inhibit it.
  - Have numerous dopamine D_2 receptors, serotonin 5-HT_3 receptors and substance P receptors (NK_1).
  - Stimulation of receptors leading to emesis.
- **Vestibular system**
  - Sends information to the brain.
  - Plays a major role in **motion sickness**.
  - Rich in muscarinic receptors and histamine H_1 receptors.
- **Enteric nervous system (ENS)**
  - ENS inputs transmit information regarding the state of the gastrointestinal system to the brain.
  - Irritation of the GI mucosa by chemotherapy, radiation, distention, or acute infectious gastroenteritis activates the 5-HT_3 receptors of these inputs.
- **Higher cortical centers**
  - Anxiety, psychiatric disorders and stress stimulate cerebral cortex lead to vomiting.



Vomiting center located in the medulla and coordinates the motor mechanisms of vomiting.

➢ **N.B:-**

- Common conditions of nausea and vomiting in **motion sickness**, **pregnancy** and **hepatitis**.
- Nausea and vomiting produced by many **chemotherapeutic agents**.
  - Called → Chemotherapy-Induced Nausea and Vomiting (CINV).
  - Nearly 70 to 80 percent of all patients who undergo chemotherapy experience nausea or vomiting.
  - Chemotherapeutic agents can directly activate the CTZ or vomiting center.
  - Chemotherapeutic agents can also act peripherally by causing cell damage in the gastrointestinal tract and releasing serotonin from the enterochromaffin cells of the small intestinal mucosa serotonin activates 5-HT_3 receptors.
- Uncontrolled vomiting can produce dehydration, metabolic imbalances, and nutrient depletion.

Antiemetic drugs

Drug effective in Motion sickness

M_1 receptor antagonists	
Hyoscine (Scopolamine) (Transderm scop®)	
H_1 receptor antagonists	
Dimenhydrinate (Dramamine®)	**Diphenhydramine** (Dramenex®)
Cyclizine (Emetrex®)	**Meclizine** (Navidoxine®)
- Are very useful in **Motion sickness**. - But are ineffective against substances that act directly on the CTZ.	

D_2 Receptor Blockers

Phenothiazines compounds	
- The first group of drugs shown to be effective antiemetic agents. - Phenothiazines acts by blocking dopamine receptors.	
Prochlorperazine (Emedrotec®)	
Side effects	- Hypotension, restlessness, Extrapyramidal symptoms and sedation. - Effective against moderately emetogenic chemotherapeutic agents.
Substituted Benzamides	
Metoclopramide (Primperan®)	
- Preventing emesis in 30 to 40 percent of patients and reducing emesis in the majority.	
Side effects	- Anti-dopaminergic side effects, including sedation, diarrhea, and extrapyramidal symptoms, limit its high-dose use.

Butyrophenones	
Droperidol (Inapsine®)	**Haloperidol** (Haldol®)
Uses	- Moderately effective anti-emetics. - High-dose haloperidol effective in preventing Cisplatin (Anticancer drugs) induced emesis.
Other D_2 Receptor blockers	
Domperidone (Motilime®)	
Uses	- Nausea and vomiting (block D_2 receptors are found in CTZ) - Restore motility and tone to the upper GIT and facilitate gastric emptying, regulates esophageal and duodenal function.
Side effects	- Anti-dopaminergic side effects and Increase level of prolactin hormone.

5-HT_3 Receptor Blockers

Ondansetron (Zofran®)	**Granisetron** (Kytril®)
Tropisetron (Navoban®)	**Dolasetron** (Anzemet®)
Palonosetron (Aloxi®)	
Administration	- IV or Orally
Uses	- Prevention of nausea and vomiting **associated with surgery and cancer chemotherapy**.
Side effects	- Headache and diarrhea.

Benzodiazepines

Lorazepam (Ativan®)	**Alprazolam** (Xanax®)
- The antiemetic potency of is **low (Not useful)**. - Their beneficial effects may be due to their sedative and anxiolytic. - These same properties make benzodiazepines useful in treating anticipatory vomiting.	

Corticosteroids

Methyl-Prednisolone (Depo-Medrol®)	**Dexamethasone** (Epidron®)
- Are effective against moderately emetogenic chemotherapy. - Their antiemetic mechanism is not known, but it may involve blockade of prostaglandins.	

Cannabinoids

Dronabinol	**Nabilone**
- Are effective against moderately emetogenic chemotherapy. - Not used due to serious side effects, including hallucinations, sedation, vertigo, and disorientation.	

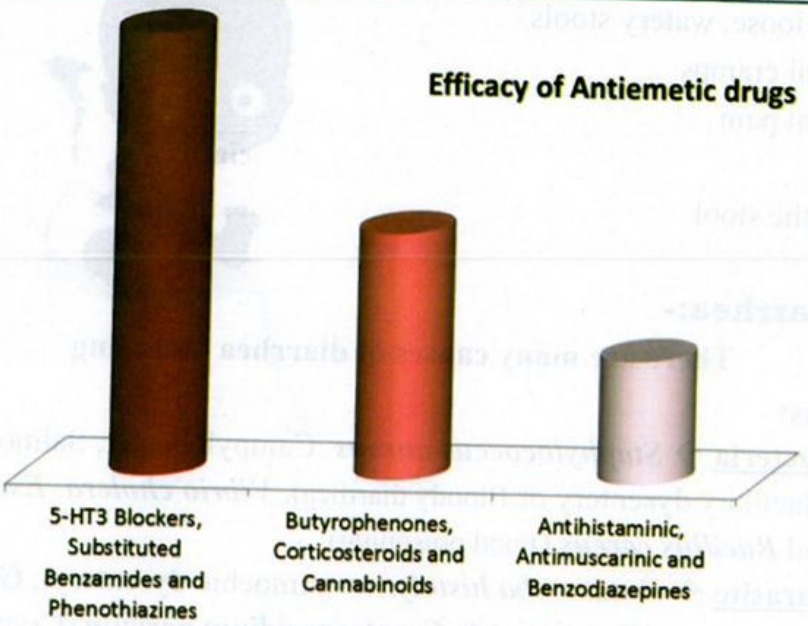
NK_1 receptor blockers

Aprepitant (Depo-Medrol®)

- New class of drugs called substance P antagonists (SPA).
- It mediates its effect by blocking the Neurokinin 1 (NK_1) receptor.
- Aprepitant is metabolized primarily by CYP3A4.
- It can affect the metabolism of other drugs such as Warfarin.
- Side effects → Constipation and fatigue.

Combination Regimens

- Antiemetic drugs are often combined to increase antiemetic activity or decrease toxicity.
- **Dexamethasone** increase antiemetic activity when given with metoclopramide or a 5-HT3 antagonist.
- **Diphenhydramine** is combined with metoclopramide to reduce extrapyramidal side effects.



➢ Antiemetic used during pregnancy :-

- Pyridoxine (10 to 25 mg one to four times daily) is recommended as first line therapy.
- If symptoms persist, addition of antihistaminic such as Meclizine.

Meclizine + (Pyridoxine) Vitamin B_6 (Navidoxine®)

➢ Antiemetic used in children :-

Corticoadrenal extract + (Pyridoxine) Vitamin B_6 (Cortigen-B6®)

➢ Antiemetic from natural sources:-

Ginger extract (Ginger®) for prophylaxis of motion sickness

Diarrhea

➢ Definition :-

- Increased frequency of bowel evacuation, with the passage of abnormally soft or watery faeces.
- It is a common cause of death in developing countries and the second most common cause of infant deaths worldwide.
- The loss of fluids through diarrhea can cause dehydration and electrolyte disturbances such as potassium deficiency or other salt imbalances.
- In 2009 diarrhea was estimated to have caused 1.1 million deaths in people aged 5 and over and 1.5 million deaths in children under the age of 5.
- Diarrhea can be a sign of a serious disorder, such as inflammatory bowel disease, or a less serious condition, such as irritable bowel syndrome.

➢ Signs and symptoms may include:-

- Frequent, loose, watery stools
- Abdominal cramps
- Abdominal pain
- Fever
- Blood in the stool
- Bloating

➢ Causes of diarrhea:-

There are many causes of diarrhea including

- **Infections:**
  - **Bacteria** → ***Staphylococcus aureus***, Campylobacter, Salmonella, Shigella (Bacillary dysentery or Bloody diarrhea), ***Vibrio cholera***, ***Escherichia coli*** and ***Bacillus cereus*** (Food poisoning).
  - **Parasite** → ***Entamoeba histolytica*** (Amoebic dysentery), ***Giardia lamblia*** (Giardiasis) & ***Cryptosporidium parvum*** (Cryptosporidiosis).
  - **Virus** → Rotavirus is a common cause of acute childhood diarrhea.
- **Malabsorption:**
  - Enzyme deficiencies or mucosal abnormality.
  - Pernicious anemia, or impaired bowel function
  - Loss of pancreatic secretions.
  - Other drugs, including agents used in chemotherapy.
- **Inflammatory bowel disease:**
  - Ulcerative colitis
  - Crohn's disease (is an inflammatory disease of the intestines)
- **Irritable bowel syndrome.**

➢ Management of Diarrhea:-

- **Antimicrobial agents:**
  - Antimicrobial help treat diarrhea caused by bacteria or parasites.
  - Antibiotics destroy both good and bad bacteria, which can disturb the natural balance of bacteria in intestines.
  - Most common antiparasitics and antibiotics used in diarrhea.
    - **Metronidazole** (Flagyl®) → Amoebic dysentery and Giardiasis.
    - **Ornidazole** (Tibezole®) → Amoebic dysentery (Amebiasis).
    - **Secnidazole** (Senidal®) → Amoebic dysentery (Anti-protozoa).
    - **Tinidazole** (Fasigyn®) → Amoebic dysentery (Amoebiasis).
    - **Nifuroxazide** (Antinal®) → Wide range of bactericidal activity.
    - **Nitazoxanide** (Cryptonaz®) → Cryptosporidiosis & Giardiasis.
    - **Neomycin – Streptomycin - Cephalosporines** (Antibiotics).
- **Oral Rehydration Therapy (ORT)** (Rehydran-N®)
  - Risk of dehydration is greatest in babies, and rehydration therapy is the standard treatment for acute diarrhea in babies and young children.

  - Sachets may be used with antidiarrheal in older children and adults.
  - Sachets of powder contain sodium chloride and bicarbonate, glucose and potassium.
  - Dose and administration
    - Dissolve the content of one sachet in a 200 ml glass of water to form Oral Rehydration Solution (ORS).
    - Give the small amount of the solution to the child to drink.
  - The solution can be kept for 24 h if stored in a refrigerator.
- **Antidiarrheal Drugs**

Antimotility agents	
Loperamide (Imodium®)	**Diphenoxylate + Atropine** (Lomotil®)
- This are most effective antidiarrheal drugs	
Stool modifiers	
Kaolin + Pectin (Kapect®)	
- **Kaolin** absorb the enterotoxin and bacteria and form a protective coat on the intestinal mucosa. - **Pectin** decrease the stool softness and absorb toxins.	
Adsorbents	
- Adsorbent agents, such as bismuth subsalicylate, methylcellulose, and aluminum hydroxide are used to control diarrhea.	

Constipation

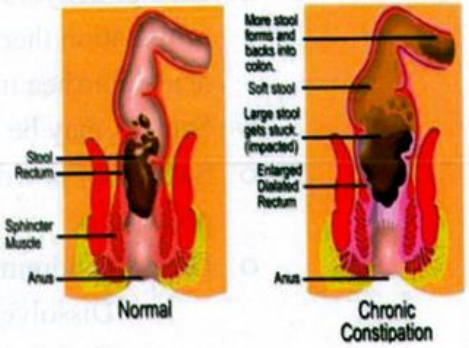
➢ Definition :-

- Also known as costiveness or dyschezia.
- Constipation is infrequent bowel movements or difficult passage of stools (typically three times or fewer per week).

➢ Symptoms :-

- Pass fewer than three stools a week.
- Hard stools.
- Strain excessively during bowel movements.
- Rectal blockage.
- Incomplete evacuation.
- Resisting the urge to have a bowel movement, which is sometimes cause anal pain (hemorrhoids or anal fissures).

➢ Causes:-



- Inadequate water intake.
- Inadequate fiber in the diet.
- A disruption of regular diet or routine; traveling.
- Inadequate activity or exercise or immobility.
- Eating large amounts of dairy products.
- Stress.
- Overuse of laxatives (stool softeners) which, over time, weaken the bowel muscles.
- Hypothyroidism.
- Neurological conditions such as Parkinson's disease
- Antacid medicines containing calcium or aluminium.
- Medicines (especially strong pain medicines, such as narcotics, antidepressants, or iron pills).
- Depression.
- Eating disorders.
- Irritable bowel syndrome.
- Pregnancy.
- Colon cancer.

➢ Non-Pharmacological treatments:-

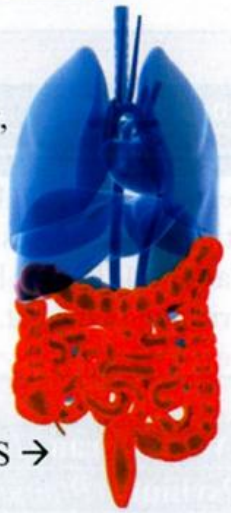
- High-fiber diet (fresh fruits and vegetables), Regular exercise (stimulate intestinal activity), Adequate fluid intake (stool softness) and Take the time for bowel movement.

➢ Pharmacological treatments:-

Laxative Drugs

Stimulant and Irritant Laxative		
Senna extract (*Cassia angustifolia*) (Diolax®)		**Cascara** (*Rhamni purshiani*)
Aloe (*Aloe vera*)	**Bisacodyl** (Bisadyl®)	**Castor oil** (*Ricinus communis*)
- Senna, Cascara and Aloe (Stimulant laxative) containing Anthraquinone as active ingredient. - Stimulant laxatives act on the intestinal mucosa, altering water and electrolyte secretion. - Castor oil (Irritant laxative) is broken down in the small intestine to ricinoleic acid very irritating to the gut. - **Contraindication → Pregnancy** (**Only** Bisacodyl used during pregnancy category B).		
Bulk Forming Laxative		
Wheat bran (*Triticum aestivum*) (Bran®)		**Linseed** (*Linum usitatissimum*)
Psyllium (*Plantago psyllium*) (Regumucil®)		**Ispaghula** (*Plantago ovata*) (Agiolax®)
Polycarbophil (Evaculax®)		**Methylcellulose**
- Also called fiber laxatives. - Hydrophilic colloids (swelling factor). They form gels in the large intestine. - Causing water retention and intestinal distension, increasing peristaltic activity.		
Saline & Osmotic Laxatives		
- Saline cathartics, such as magnesium citrate, magnesium sulfate, sodium phosphate, and magnesium hydroxide. - Electrolyte solutions containing polyethylene glycol (PEG) are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures.		
Glycerin (Glycerin®)		
- Glycerin suppositories have both osmotic and irritant effects (Hyperosmotic action, but also the sodium stearate in the preparation causes local irritation to the colon).		
Lactulose (Lactulose®)		
- Lactulose is a semisynthetic disaccharide sugar that also acts as an osmotic laxative. - Oral doses are degraded in the colon by colonic bacteria into lactic, formic, and acetic acids → increasing colonic peristalsis. - Lactulose is also used in Portal Systemic encephalopathy (Liver failure).		
Emollient or Surfactants Laxatives		
- Surface-active agents (surfactants) that become emulsified with the stool produce softer feces and ease passage. - These include docusate sodium, docusate calcium, and docusate potassium.		
Lubricant Laxatives		
- Mineral oils (e.g. liquid paraffin) are considered to be lubricants. They facilitate the passage of hard stools.		
Others		
Sodium picosulfate (Picolax®)		
- **Safe in Pregnancy**		

Irritable Bowel Syndrome (IBS)



➢ Definition:-

- Is a common disorder that affects in large intestine (colon) characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits (diarrhea and constipation).
- Also called spastic colon, mucous colitis, or irritable colon.
- Mainly occurs in women.
- The problem is in the bowel function not structure.

➢ Pathophysiology:-

- The pathophysiology of IBS remains uncertain.
- There are a number of other factors that may play a role in IBS →
  - Motility of Gastrointestinal tract.
  - Visceral hypersensitivity (increased sensation in response to stimuli).

➢ Causes (Etiology):-

- Although the exact causes of IBS is unknown. It may be due to →
  - Active infection
  - Food sensitivity
  - Neurotransmitters imbalance (abnormal serotonin levels)
  - Stress
  - Genetic tendency
  - Hormones (Because women are more likely to have IBS, researchers believ that hormonal changes play a role in this condition).

➢ Classification:-

- Constipation predominant (IBS-C)
- Diarrhea predominant (IBS-D)
- Alternating constipation and diarrhea (IBS-A)
- Post-infectious IBS (IBS-PI) → characterized by fever, vomiting, diarrhea, or positive stool culture.

➢ Symptoms:-

- Abdominal pain or cramping.
- A bloated feeling and flatulence.
- Diarrhea or constipation (sometimes even alternating bouts of constipation and diarrhea).
- Mucus in the stool.

- **N.B:** Some studies indicate that up to 60% of persons with IBS also have a psychological disorder, typically anxiety or depression.

➢ Different between IBS and Inflammatory bowel disease (IBD):-

Irritable Bowel Syndrome (IBS)	Inflammatory Bowel Disease (IBD)
- Known as spastic colon, mucous colitis, or irritable colon.	- Known as ulcerative colitis and crohn's disease, amoebic dysentery.
- Diarrhea may or may not present - No Bloody diarrhea	- Diarrhea - Bloody diarrhea

➢ Treatments:-

Non-Pharmacological

- **Dietary modifications**
  - Eating light meals
  - Drink plenty of liquids
  - Avoid heavy, spicy foods
  - Avoid gases forming foods as Lentils, Legumes and beans
- **Stress management**

Pharmacological

Constipation Predominant IBS (IBS-C)

Bulking agent (Soluble fibers)
Psyllium (Regumucil®)
- For IBS-C patients - Make stool softer, moister, and more easily passable.
Insoluble fibers
Bran (Bran®)
- Has not been found to be effective for IBS-C.
Osmotic, stimulant and emollient laxatives
- Such as polyethylene glycol, sorbitol, and lactulose may be used but not routinely.
Antidepressant drugs
- SSRIs may be used because of their serotonergic effect, would seem to help IBS, especially patients who are constipation predominant. (TCAs rare to used)
Serotonin Agonists
Tegaserod (Zelmac®)
- Selective 5-HT_4 agonist for IBS-C. - Available for relieving IBS constipation in women and chronic idiopathic constipation (CIC) in men and women. - Removed from the market in 2007 due to FDA concerns about possible adverse cardiovascular effects (Heart attack and stroke).

Mosapride (Fluxopride®)

- Is a gastroprokinetic agent that acts as a selective $5HT_4$ agonist which accelerates gastric emptying.
- Used for the treatment of acid reflux, IBS-C and functional dyspepsia.
- Some common side effects include diarrhea, abdominal pain, dizziness, constipation, headache, insomnia, and nausea.

Others

Itopride (Ganaton®)

- Gastrokinetic agent act by increases acetylcholine concentrations by inhibiting dopamine D_2 receptors and acetylcholinesterase.
- Used in non-ulcer dyspepsia and IBS-C.
- Some common side-effects include rash, diarrhea, increased salivation, constipation, abdominal pain, sleeping disorders, dizziness, galactorrhea, gynecomastia
- Old studies show the itopride may cause cardiac arrhythmia but new studies conducted with healthy adult volunteers, itopride shown as unlikely to cause cardiac arrhythmias or ECG changes.

Lubiprostone (Amitiza®)

- Lubiprostone a prostaglandin E_1 derivative that acts by specifically activating chloride channels on the gastrointestinal epithelial cells, producing a chloride-rich fluid secretion. These secretions soften the stool, increase motility, and promote spontaneous bowel movements (SBM).

Linaclotide (Linzess®)

- Linzess was approved by the FDA on August 30, 2012 for the treatment of Irritable Bowel Syndrome-Constipation (IBS-C) and Chronic Idiopathic Constipation (CIC).
- For more information → www.linzesshcp.com

Antispasmodic drugs

- Some of anti-spasmodic drugs may be used such as **Alverine** (Meteospasmyl®) and **Caroverine** (Spasmium®)
- **Caroverine** acts as N-type calcium channel blocker, competitive AMPA (amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist, and non-competitive NMDA receptor antagonist.

Diarrhea Predominant IBS (IBS-D)

Serotonin Antagonist

Alosetron (Lotronex®)	**Cilansetron** (Calmactin®)

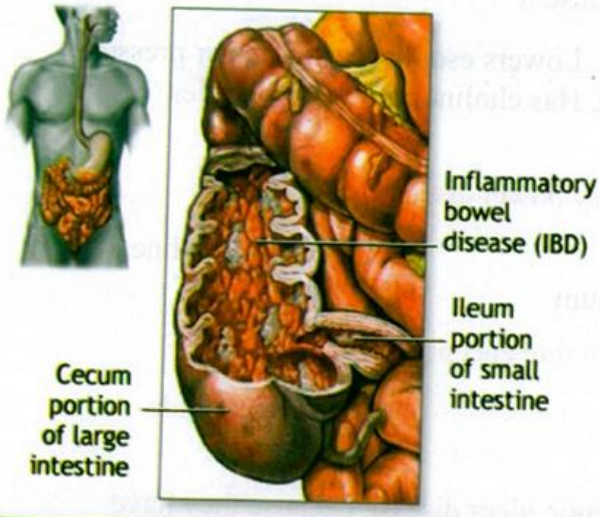
- Selective 5-HT3 antagonist for IBS-D
- Alosetron was withdrawn from the market in 2000 due to severe adverse effects (ischemic colitis and, obstruction or perforation, toxic mega colon and severe constipation. But in 2002 become available again.

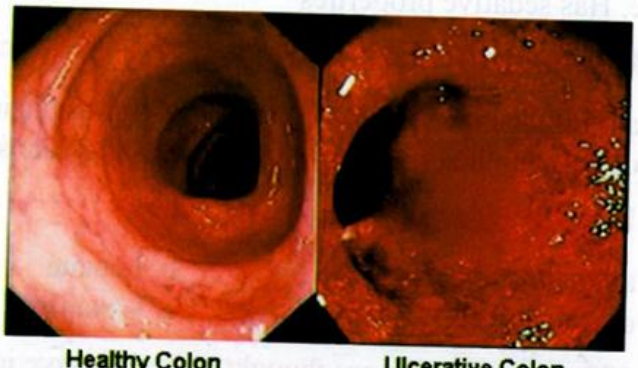
Opioid derivatives	
Loperamide (Imodium®)	**Diphenoxylate** (Lomotil®)
Trimebutine (Debridat®)	
- Act by stimulation of opioid-receptor. - **Diphenoxylate** is formulated with **Atropine** to reduce the risk of abuse. - **Trimebutine** is a drug with anti-muscarinic and weak mu opioid agonist effects. - Side effects → Abdominal pain and bloating, nausea, vomiting and constipation.	

Alternating Constipation & Diarrhea (IBS-A)

Mebeverine (Duspatalin®)
- Mebeverine is a drug with antimuscarinic and weak mu opioid agonist effects. - Used to treats all types of IBS.
Spasmopinaver (Spasmopinaver®)
- Used to treats all types of IBS.
Multicomponent Herbal Mixtures
Chamomile owers (***Matricaria recutita***), Caraway fruits (***Carum carvi***), Peppermint leaves (***Mentha x piperita***) and Fennel (***Foeniculum vulgare***)
(Colostop®) - (Digestion®) - (Gesto®) - (G-star®) - (Regest®)
- Smooth muscle relaxant used to relief IBS symptoms (Antispasmodic).

➢ Treatment of IBD (Inflammatory Bowel Disease):-





Sulfasalazine (Pentasa®)
- Sulfasalazine is a sulfa drug, (a derivative of mesalazine) and is formed by combining sulfapyridine and salicylate with an azo bond. - Used in inflammatory bowel disease and ulcerative colitis. - Has a disease modifying action in rheumatic arthritis.

Questions

➢ Coose the best answer :-

171: Cimetidine slows the metabolism of many drugs because it inhibits the activity of

a. Monoamine oxidase (MAO) b. Cytochrome P450 c. Tyrosine kinase
d. H^+/K^+ ATPase e. Phase II glucuronidation reactions

172: Omeprazole, an agent for the promotion of healing of peptic ulcers, has a mechanism of action that is based on

a. Prostaglandins b. Gastric secretion c. Pepsin secretion
d. H^+/K^+ ATPase e. Anticholinergic action

173: An effective antidiarrheal agent that inhibits peristaltic movement is

a. Clonidine b. Bismuth subsalicylate
c. Oral electrolyte solution d. Atropine
e. Diphenoxylate

174: The approved indication for misoprostol

a. Reflux esophagitis b. Regional ileitis
e. Pathologic hypersecretory conditions such as Zollinger-Ellison syndrome d. Prevention of gastric ulceration in patients using large doses of aspirin-like drugs
c. Ulcerative colitis

175: Metoclopramide has antiemetic properties because it

a. Accelerates gastric emptying time b. Lowers esophageal sphincter pressure
c. Is a CNS dopamine-receptor antagonist d. Has cholinomimetic properties
e. Has sedative properties

176: A drug of choice in the therapy of inflammatory bowel disease is

a. Sulfadiazine b. Sulfasalazine c. Sulfapyridine
d. Sulfamethoxazole e. Salicylate sodium

177: An important drug in the therapy of portal systemic encephalopathy is

a. Lactulose b. Lactate c. Loperamide
d. Lorazepam e. Loxapine

178: Bismuth salts are thought to be effective in peptic ulcer disease because they have bactericidal properties against

a. ***Escherichia coli*** b. ***Bacteroides fragilis*** c. ***Clostridium difficile***
d. ***Helicobacter pylori*** e. ***Staphylococcus aureus***

179: Misoprostol has a cytoprotective action on the gastrointestinal (GI) mucosa because it

a. Enhances secretion of mucus and bicarbonate
b. Neutralizes acid secretion
c. Antagonizes NSAIDs
d. Relieves ulcer symptoms
e. Coats the mucosa

180: The primary pharmacologic action of omeprazole is the reduction of

a. Volume of gastric juice
b. Gastric motility
c. Secretion of pepsin
d. Secretion of gastric acid
e. Secretion of intrinsic factor

181: Preferred drug therapy for Zollinger-Ellison syndrome

a. Ranitidine
b. Metronidazole
c. Omeprazole
d. Sucralfate
e. Misoprostol

182: A 68-year-old patient with cardiac failure is diagnosed with ovarian cancer. She is started on cisplatin but becomes nauseous and suffers from severe vomiting. Which of the following medications would be most effective to counteract the emesis in this patient without exacerbating her cardiac problem?

a. Droperidol
b. Dolasetron
c. Prochlorperazine
d. Dronabinol
e. Ondansetron

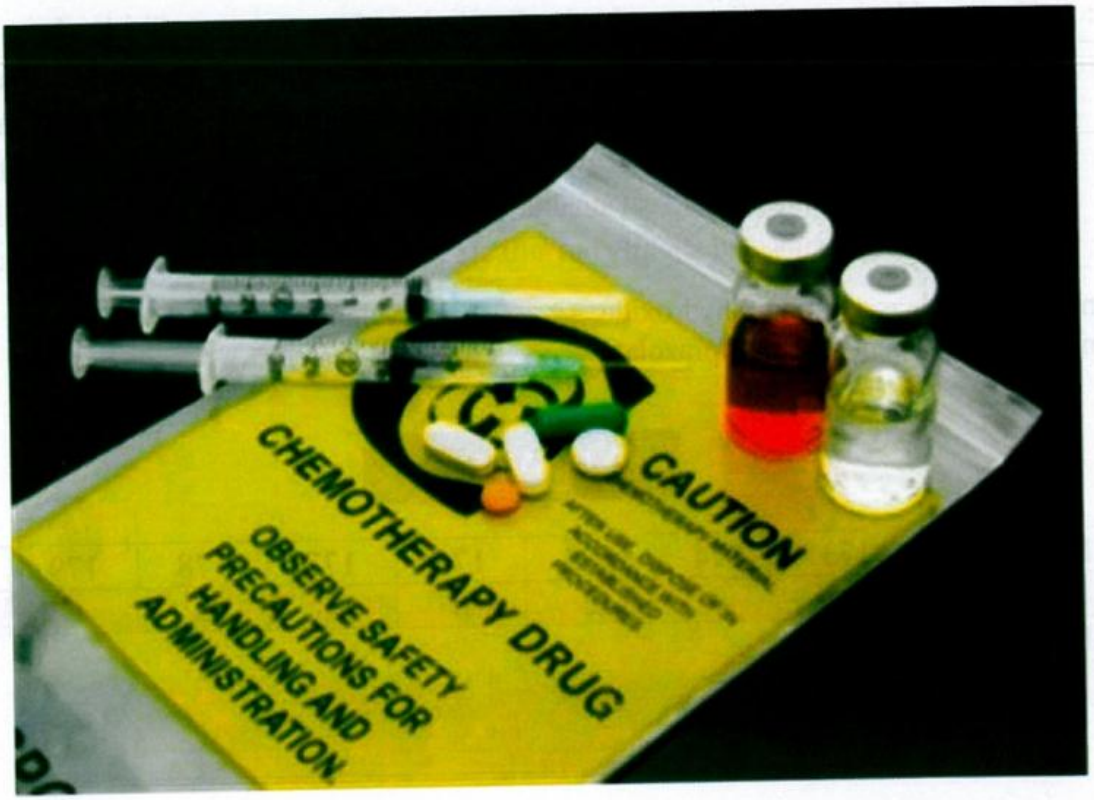
183: A 45-year-old woman is distressed by the dissolution of her marriage. She has been drinking heavily and overeating. She complains of persistent heartburn and an unpleasant, acid-like taste in her mouth. The clinician suspects gastrointestinal reflux disease and advises her to raise the head of her bed 6 to 8 inches, not to eat for several hours before retiring, to avoid alcohol, and to eat smaller meals. Two weeks later, she returns and says the symptoms have subsided slightly but still are a concern. The clinician prescribes:

a. An antacid such as aluminum hydroxide.
b. Dicyclomine
c. An antianxiety agent such as alprazolam.
d. Esomeprazole

Answers

171	172	173	174	175	176	177	178	179	180
b	d	e	d	c	b	a	d	a	d
181	182	183							
c	e	d							

Chemotherapy



Introduction

➢ History of Antimicrobial Agents :-

Paul Ehrlich

- **Paul Ehrlich** (14 March 1854 – 20 August 1915):
  - Was a German scientist in the fields of hematology, immunology, and chemotherapy.
  - End of 1909 Ehrlich is the first one discovering antimicrobial agent (Organic arsenical compound or Salvarsan) limited used in treatment of syphilis.

Sir Alexander Fleming

- **Alexander Fleming** (6 August 1881 – 11 March 1955)
  - Was a Scottish biologist and pharmacologist.
  - In 1929 Fleming is the first one discovering Penicillin from.
  - In Oxford, Ernst Boris Chain and Howard Walter Florey worked out how to isolate and concentrate penicillin.
  - After the team had developed a method of purifying penicillin to an effective first stable form in 1940.
  - Several clinical trials ensued, and their amazing success inspired the team to develop methods for mass production and mass distribution in 1945.

➢ Chemotherapeutic agent for infectious diseases (Antimicrobial agents):-

- Are chemical substances used in treatment of infectious diseases or for their prevention.
- Antimicrobial agents are among the most commonly used and misused of all drugs.
- Misused lead to development of resistance.

➢ Classification of Antimicrobial Agents according to spectrum of activity :-

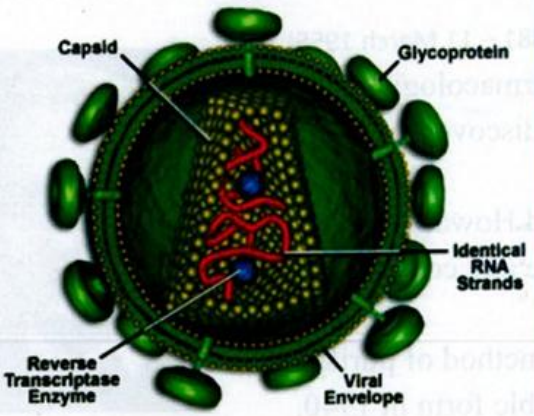
Antibacterial (Antibiotics)	307
Antifungal	334
Antiviral	336
Anti-Parasitic	342

Before Study the antibiotics we must remember some topics from Microbiology →

- Types of Microorganism (MO)
- Function of each component of MO
- Classification of Bacteria

Microorganism

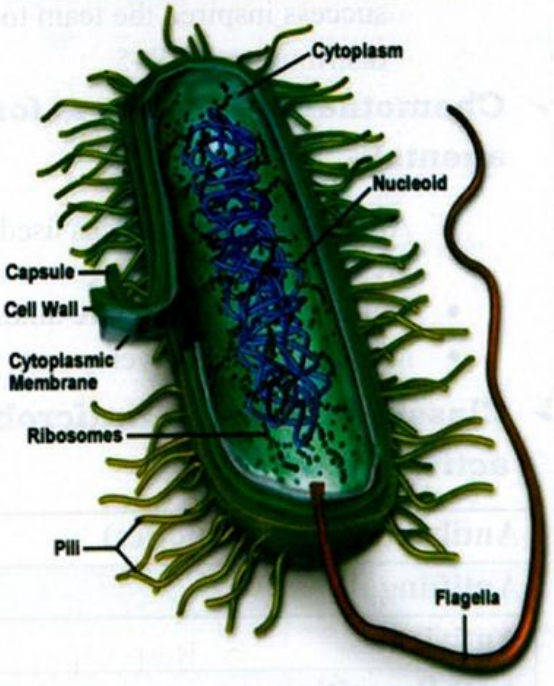
Non-cellular	Cellular	
Viruses	Prokaryotic	Eukaryotic
	- Bacteria	- Fungi - Protozoa
	Cell wall composed of Peptidoglycan	Cell wall composed of Cellulose



Morphology of Bacteria

- **Shape:**
  - Cocci ○ or Bacilli ▭
- **Arrangement:**
  - Chain ○○○○ or Clusters
- **Gram stain:**
  - Gm -ve (Pink/Red)
  - Gm +ve (Purple/Blue)

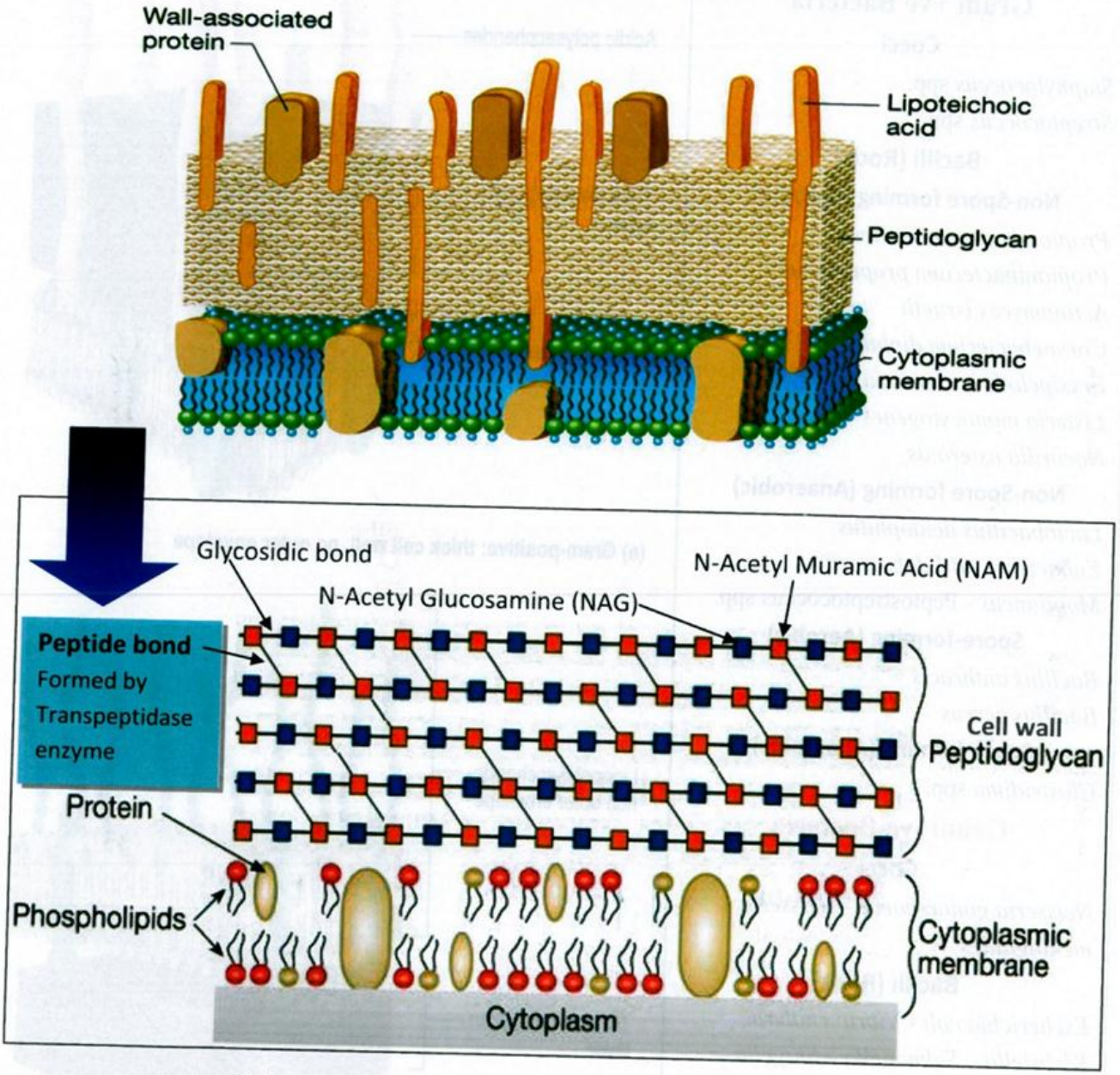
➢ Bacterial cell composition :-



- **Appendage :-**
  - **Flagella**
    - Responsible for movement of bacteria.
  - **Pili**
    - Responsible for adhesion and transfer of genetic material.
- **Cell envelopes :-**
  - **Capsule**
    - Virulence factor and resist phagocytosis.

- **Cell wall**
  - Responsible for rigidity of bacterial cell.
  - Protection of cell protoplasm from mechanical damage.

Cell Wall Structure



- **Cell membrane (Cytoplasmic Membrane)**
  - Control passage of substance into and out the cell.

- **<u>Cytoplasmic regions</u>**
  - **DNA**
  - **Ribosome**
    - Responsible for protein synthesis (See later).
  - **Inclusions granules (Metabolite) e.g. Folic acid**
    - Folic acid enters in nucleotide synthesis.

Classification of Bacteria

➢ According to Gram stain :-

Gram +ve Bacteria

Cocci

Staphylococcus spp.
Streptococcus spp.

Bacilli (Rods)

Non-Spore forming (Aerobic)

Propionibacterium acnes
Propionibacterium propionicum
Actinomyces israelii
Corynebacterium diphtheria
Erysipelothrix rhusiopathiae
Listeria monocytogenes
Nocardia asteroids

Non-Spore forming (Anaerobic)

Lactobacillus acidophilus
Eubacteria - Bifidobacterium
Mobiluncus - Peptostreptococcus spp.

Spore-forming (Aerobic)

Bacillus anthracis
Bacillus cereus

Spore forming (Anaerobic)

Clostridium spp.

Gram -ve Bacteria

Cocci

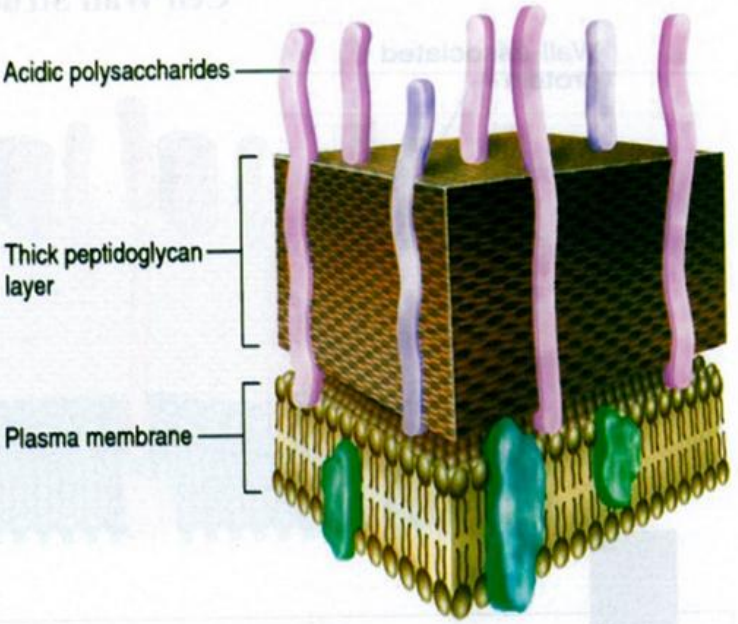
Neisseria gonorrhoeae - Neisseria meningitides

Bacilli (Rods)

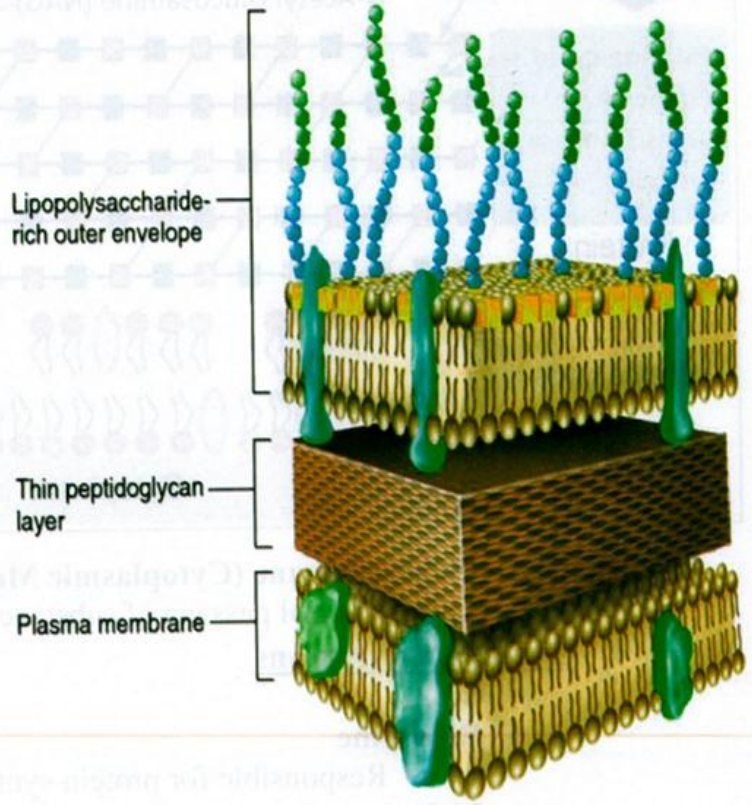
Escherichia coli - Vibrio cholerae- Klebsiella – Salmonella – Shigella – Proteus- Pseudomonas aeruginosa - Helicobacter pylori - Legionella pneumophilia - Haemophilus influenza Brucella - Bordetella pertussis

Mycobacterium

Treponema pallidum (Syphilis)
Mycobacterium tuberculosis
Mycobacterium leprae



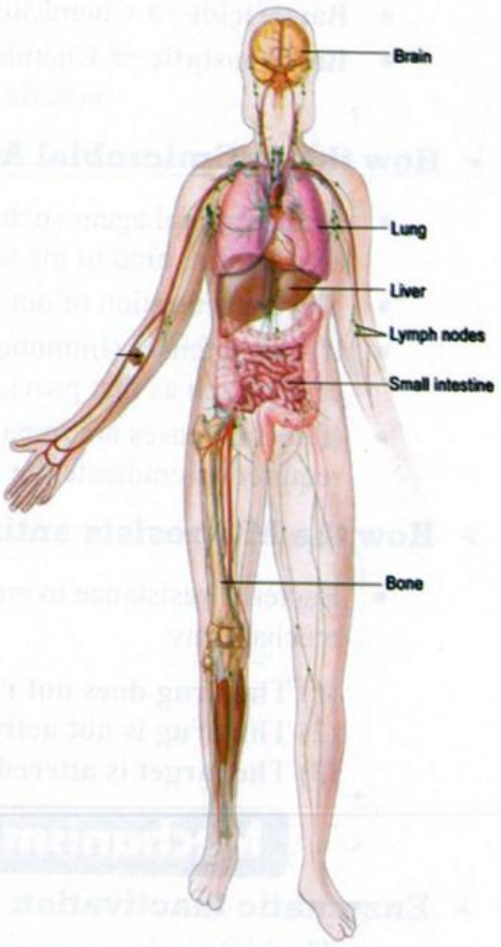
(a) Gram-positive: thick cell wall, no outer envelope

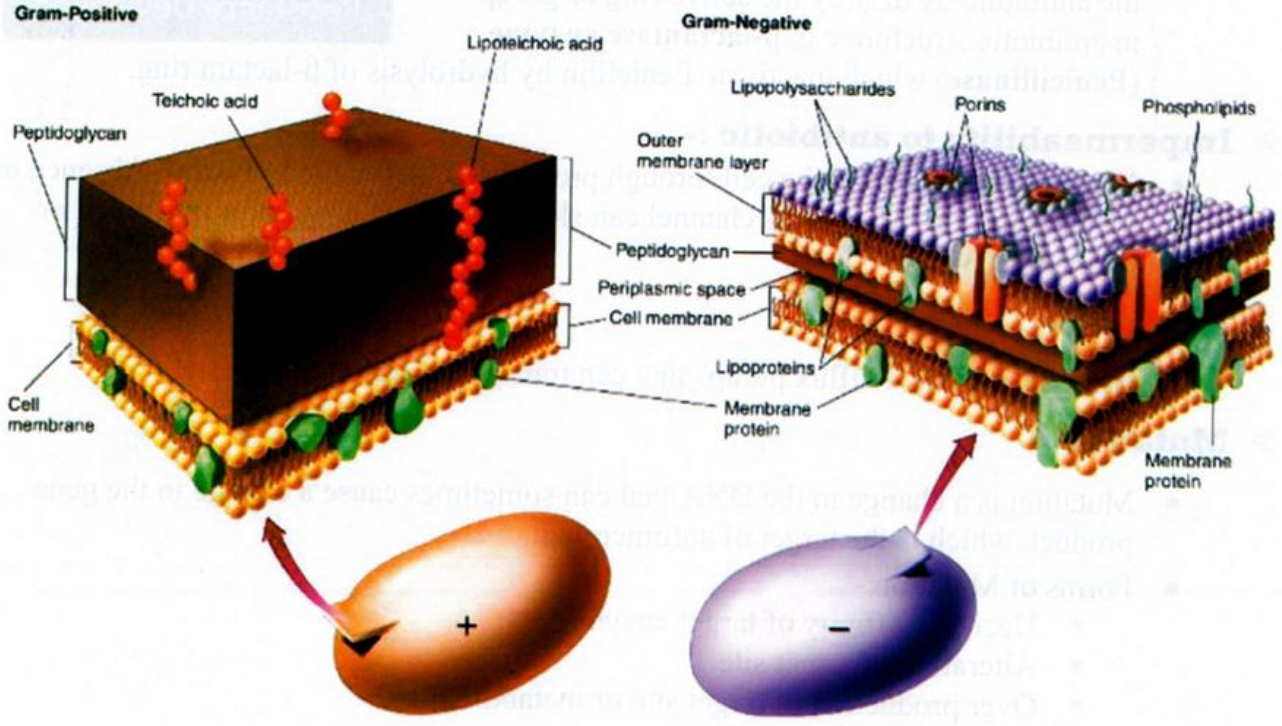


(b) Gram-negative: thinner cell wall, with outer envelope

➢ According to site of infection :-

CNS (Meningitis)	*Neisseria meningitides* *Haemophilus influenza* *Streptococcus pneumoniae*
Mouth	*Peptostreptococcus* spp. *Actinomyces israelii*
Upper Respiratory Tract	*Streptococcus pneumoniae* *Haemophilus influenza* *Streptococcus pyogenes*
Lower Respiratory Tract	*Streptococcus pneumoniae* *Staphylococcus aureus* *Pseudomonas aeruginosa* *Klebsiella pneumoniae* *Haemophilus influenza*
Abdomen and Urinary tract	*Escherichia coli* *Klebsiella* spp. *Proteus* spp.
Skin and Soft tissue	*Staphylococcus aureus* *Staphylococcus epidermidis* *Streptococcus pyogenes*
Bone and Joints	*Staphylococcus aureus* *Streptococcus* spp. *Neisseria gonorrhoeae* Gram -ve rods





➢ Important terms :-

- **Bactericide** → Chemical substance used for killing of bacteria (Irreversible).
- **Bacteriostatic** → Chemical substance used for inhibiting or stopping the growth of bacteria (Reversible).

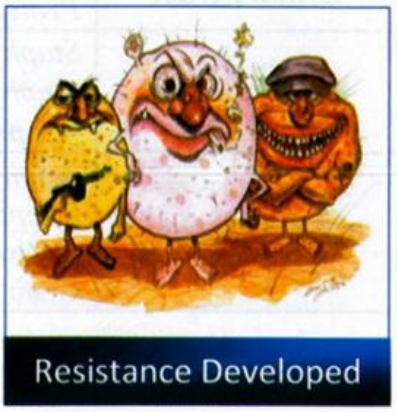
➢ How the Antimicrobial Agents kill MO?

- Antimicrobial agent such as antibiotic to be effective, it must reach its target in an active form, bind to the target, and interfere with its function.
- The concentration of antibiotic must be sufficient to inhibit growth of MO.
- If host defenses (Immune system) are intact and active, a minimum inhibitory effect, such as that provided by ***bacteriostatic agents*** may be sufficient.
- If host defenses are impaired, antibiotic-mediated killing (***Bactericide***) may be required to eradicate the infection.

➢ How the MO resists antimicrobial agents according to misused?

- Bacterial resistance to an antimicrobial agent is attributable to three general mechanisms:

(1) The drug does not reach its target
(2) The drug is not active
(3) The target is altered



Mechanism of Resistance

➢ Enzymatic inactivation :-

- The MO produces special enzyme to inactivate the antibiotic by destroy the active ring or group in antibiotic structure e.g. **β-lactamase enzyme** (**Penicillinase**) which inactivate Penicillin by hydrolysis of β-lactam ring.

➢ Impermeability to antibiotic :-

- Many antibiotics enter the cell through protein channels called **"Porin"** Absence or mutation or loss of a porins channel can slow the rate of drug entry into a cell or prevent entry.

➢ Efflux :-

- Bacteria also have efflux pumps that can transport drugs out of the cell.

➢ Mutation :-

- Mutation is a change in the DNA that can sometimes cause a change in the gene product, which is the target of antimicrobial.
- Forms of Mutation:-
  - Decrease affinity of target enzyme.
  - Alteration of target site.
  - Over production of target site or metabolite.

Antibiotics

➢ Definition :-

- Antibacterial substances produced by various species of microorganisms (bacteria, fungi, and actinomycetes) that suppress the growth of other microorganisms (MO).

➢ Ideal Antibiotic :-

- Have the appropriate spectrum of activity for the clinical setting.
- Have no toxicity to the host, be well tolerated.
- Low development of resistance.
- Not induce hypersensitivity reaction in the host.
- Have rapid and extensive tissue distribution
- Have a relatively long half-life.
- Be free of interactions with other drugs.
- Be convenient for administration.
- Be relatively inexpensive.

Classification of Antibiotics

➢ According to their source :-

- **Natural**: from Fungi e.g. Penicillin, from Bacteria e.g. Gentamycin or from Actinomycetes e.g. Streptomycin.
- **Synthetic**: e.g. Chloramphenicol.
- **Semi-synthetic**: e.g. Ampicillin.

➢ According to Chemical structure :-

- Difficult to classified

➢ According to Mechanism of action :-

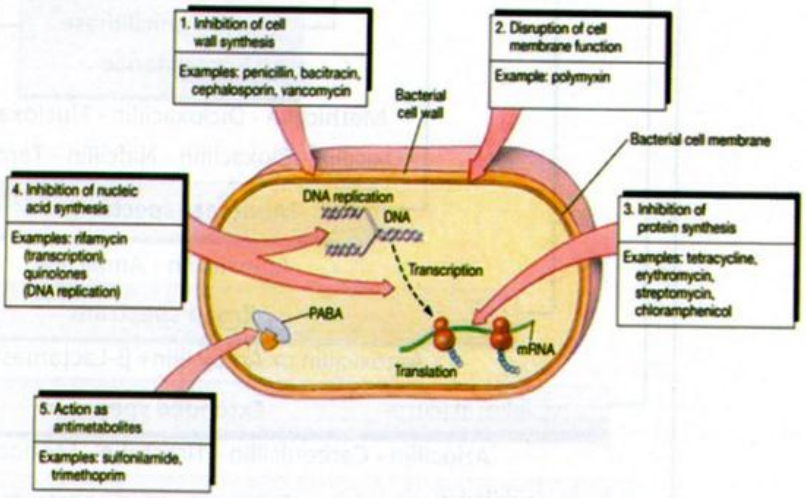
1: Agents that inhibit synthesis of cell wall or repair.

2: Agents that disruption of cell membrane functions.

3: Agents that inhibit protein synthesis.

4: Agents that inhibit of nucleic acid synthesis.

5: Agents that act as antimetabolite.



Antibiotics that Inhibit cell wall synthesis

β-Lactam (Similar Agents)

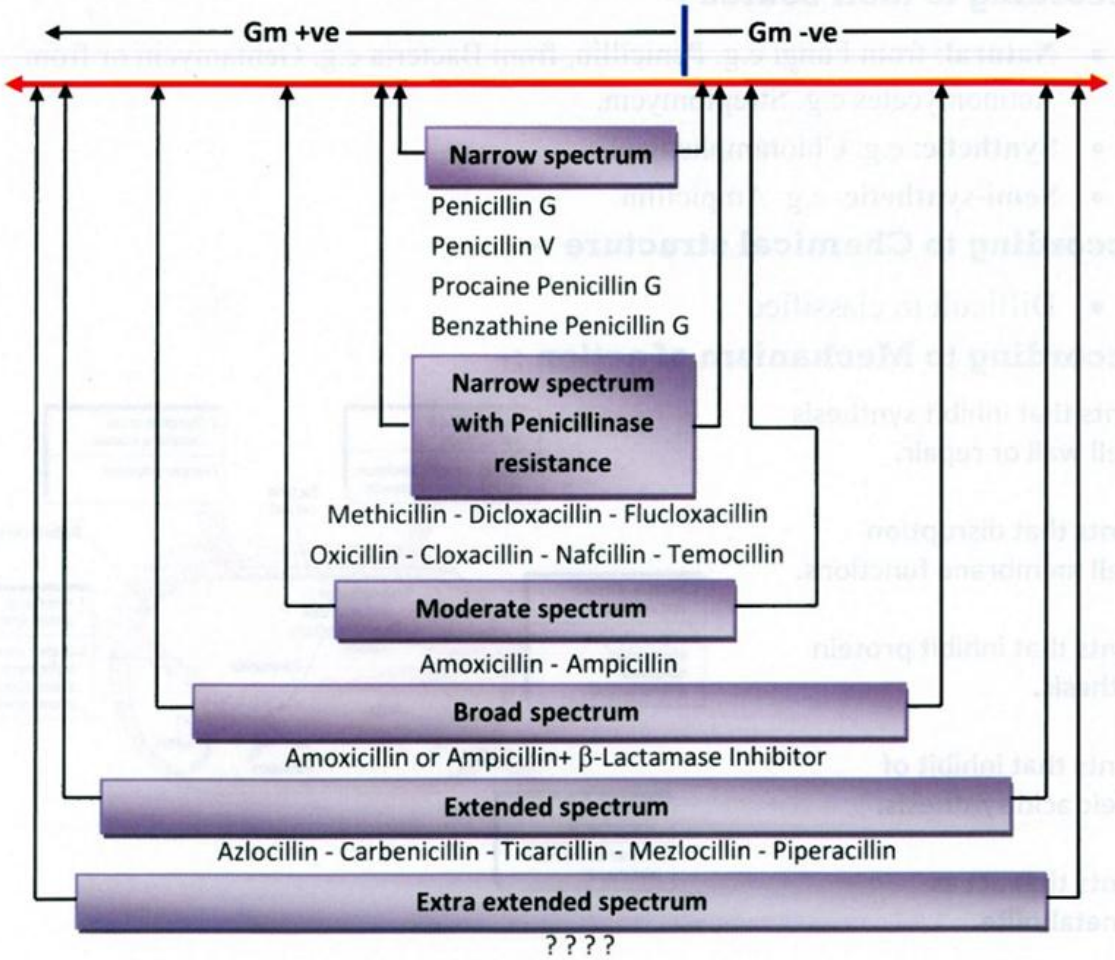
- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems

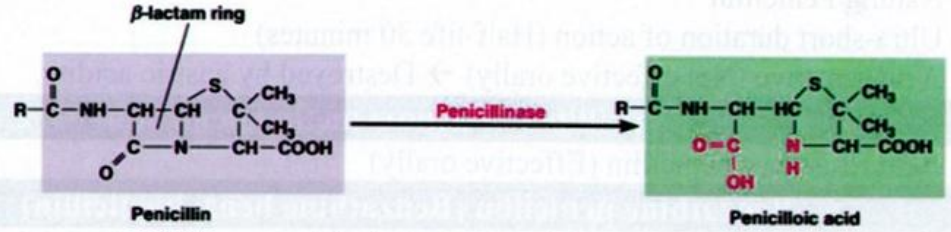
Non-β-Lactam (Dissimilar Agents)

- Vancomycin
- Cycloserine
- Bacitracin

Penicillins (PCN)

➢ **Penicillins according to spectrum of activity :-**



Information	- Isolated naturally from *Penicillium notatum* or *penicillium chrysogenum*. - Derivatives of 6-aminopenicillanic acid (6-APA).
Pharmacokinetics	- **Routes of administration** → is determined by the stability of drug - **Absorption** → Most of the Penicillins are incompletely absorbed after oral administration (Amoxicillin is almost completely absorbed). - **Distribution** → Distribute well throughout the body - Pass easily placental barrier → (Not teratogenic). - Not penetrate CSF in normal meninges → (Pass easily in inflamed meninges) - **Excretion** → Active renal excretion (Inhibited by Probenecid).
Mechanism of action	- Penicillins act by binding with **Penicillin binding protein (PBP)** on transpeptidase enzyme → Inactivation of **Transpeptidase enzyme** which is responsible for formation of peptide bond during formation or repair of peptidoglycan → Decrease rigidity of cell wall → the cell wall can't able to protect bacterial cell from high internal osmotic pressure → cytolysis → death (Bactericidal).
Uses	- Cellulitis - Bacterial endocarditis - Gonorrhea - Meningitis. - Pneumonia - Septicemia in children - Syphilis - Anthrax. - Diphtheria - Clostridial infections (Combined with Anti-toxins). - Surgical procedures in patients with valvular heart disease.
Bacterial resistance to Penicillins	- Enzymatic inactivation by β-lactamase enzyme (Penicillinase).  - Impermeability to antibiotic (mutational loss of Porin) - Efflux - Modification of target PBPs.
Adverse Reactions	**1- Hypersensitivity reaction** - 5% of patients will develop a hypersensitivity reaction. - Hypersensitivity test must be applied <u>at all time of injection</u>. - Hypersensitivity test <u>may give false negative result</u>. → Rash, Itch, Fever, Asthma → Anaphylactic shock. <u>- **Treatment**:- (Triple Therapy)</u> - By Injection of physiologic specific antidote (Epinephrine) + Glucocorticoid + Antihistaminic

	- Management of the Patient Potentially Allergic to Penicillin :- **(Desensitization)** - Occasionally is recommended for patients who are allergic to penicillin and who must receive the drug. - This procedure consists of administering gradually increasing doses of penicillin in the hope of avoiding a severe reaction and should be performed only in an intensive care setting. **2- Super infection** (Kill good bacteria in mouth and colon) - **Diarrhea** → Pseudomembranous colitis → Treated by (Vancomycin or Metronidazole) - **Candida (Oral thrush)** → Treated by Nystatin or Miconazole **3- Neurotoxicity** - Penicillins are irritating to neural tissue and they can provoke seizures **4- Acute Interstitial nephritis** (With Methicillin) **5- Stevens Johnson Syndrome (Rare)** - Painful Blistering of the skin and mucous membrane. - In many cases proceeded with flu like symptoms and high fever. - Severe conjunctivitis, iritis, palpebral edema, conjunctival and corneal blisters and erosions, and corneal perforation.

➢ Narrow Spectrum Penicillins :-

Penicillin G (Benzylpenicillin) (Penicillin-G sodium®)	
- Natural Penicillin - Ultra-short duration of action (Half-life 30 minutes) - Acid sensitive (Not effective orally) → Destroyed by gastric acidity.	
Penicillin V (Phenoxymethyl penicillin) (Ospen®)	
- Acid resistance penicillin (Effective orally)	
Benzathine penicillin (Benzathine benzylpenicillin) (Retarpen®)	
- Long acting penicillin (over 2-4 weeks) - Slowly absorbed into the blood. - 55% bound to plasma proteins. - Used as a single agent in the treatment and prevention of many disease condition.	
Uses	- Prophylaxis of rheumatic fever. - Early or latent syphilis.
Procaine penicillin (Procaine benzylpenicillin)	
- Is a form of penicillin which is a combination of benzylpenicillin and the local anaesthetic agent procaine → reducing the pain. - IM injection, it is slowly absorbed into the circulation.	
Uses	- Syphilis - Respiratory tract infections - Cellulitis and anthrax.

➢ Narrow Spectrum with Penicillinase resistance :-

Methicillin	Oxicillin	Cloxacillin	Dicloxacillin
Flucloxacillin	Nafcillin	Temocill	
- Known as **Antistaphylococcal penicillins**. - Developed to overcome the penicillinase enzyme of ***S. aureus*** that inactivates natural Penicillins. - Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci (Methicillin-susceptible ***S. aureus*** **(MSSA)).**			
Cloxacillin + Ampicillin (Ampiclox®) - Dicloxacillin + Ampicillin (Cloxapen®) Flucloxacillin + Ampicillin (Amoflux®)			

➢ Moderate Spectrum (Aminopenicillin) :-

Ampicillin (Ampicillin®)	**Amoxicillin** (Amoxil®)
- Highly affected by foods taken after meal by 2hours or before meals by 1 hour.	- Less effected by food
- Short duration	- Long duration
- Less effective in Gram -Ve (e.g. Shigella & Salmonella)	

➢ Broad Spectrum Penicillins :-

Ampicillin + Sulbactam (Unasyn®)	**Amoxicillin + Clavulanic acid** (Augmentin®)
- Broad Spectrum penicillins = Aminopenicillin + β-lactamase enzyme inhibitors. - Sulbactam, Tazobactam and Clavulanic acid are β-lactamase enzyme inhibitors. - Developed to gain or enhance activity against β-lactamase producing organisms. - **Drug of choice in** Respiratory Tract Infections, Otitis Media, Sinusitis and Skin infection.	

➢ Extend Spectrum Penicillins (Anti-pseudomonal penicillins):-

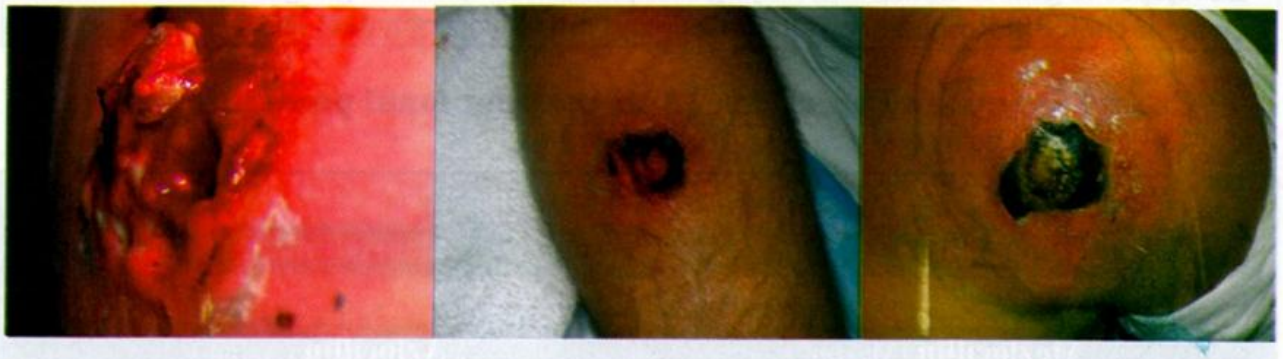
Carboxypenicillin Group	
Carbenicillin (Geocillin®)	**Ticarcillin** (Ticar®)
Ureidopenicillins Group	
Mezlocillin (Mezlin®)	**Azlocillin** (Azlin®)
Piperacillin (Pipril®)	
- Extend Spectrum Penicillins = Broad Spectrum + ***Pseudomonas aeruginosa*** - Are called antipseudomonal penicillins because of their activity against ***Pseudomonas aeruginosa*** **(Drug of choice in *Pseudomonas*** Infections) - Developed to further increase activity against resistant gram-negative aerobes. - Piperacillin is the most potent of these antibiotics. - Ticarcillin and Piperacillin are formulated with β-lactamase enzyme inhibitors.	

➢ Summary for Specific treatment :-

Narrow Spectrum	Penicillin G Penicillin V Benzathine Penicillin Procaine Penicillin	*Streptococcus* *Neisseria meningitidis*
Penicillinase resistant	Methicillin Oxacillin Nafcillin Cloxacillin Dicloxacillin	*Staphylococcus aureus*
Aminopenicillins	Ampicillin Amoxicillin	*Haemophilus influenzae* *Proteus mirabilis* *E. coli* *Neisseria*
Carboxypenicillins and Ureidopenicillins	Carbenicillin Ticarcillin Piperacillin Azlocillin Mezlocillin	*Pseudomonas* *Enterobacter* *Proteus* *Klebsiella*

➢ What is the MRSA Meaning?

- MRSA (Methicillin-Resistance ***Staphylococcus aureus***) is a bacterium responsible for several difficult-to-treat infections in humans.



- MRSA is strain of ***Staphylococcus aureus*** that has devolved resistance to β-lactam antibiotics, which include penicillins (methicillin,dicloxacillin, nafcillin, oxacillin etc..) and cephalosporins.

- Specific treatment → Vancomycin (see later)

Cephalosporins

➢ Information :-

- They are β-Lactam antibiotics.
- First isolated from cultures of ***Cephalosporium acremonium.***
- The cephalosporin nucleus, 7-aminocephalosporanic acid (7-ACA).
- Not acid resistance (Used orally or Injection).

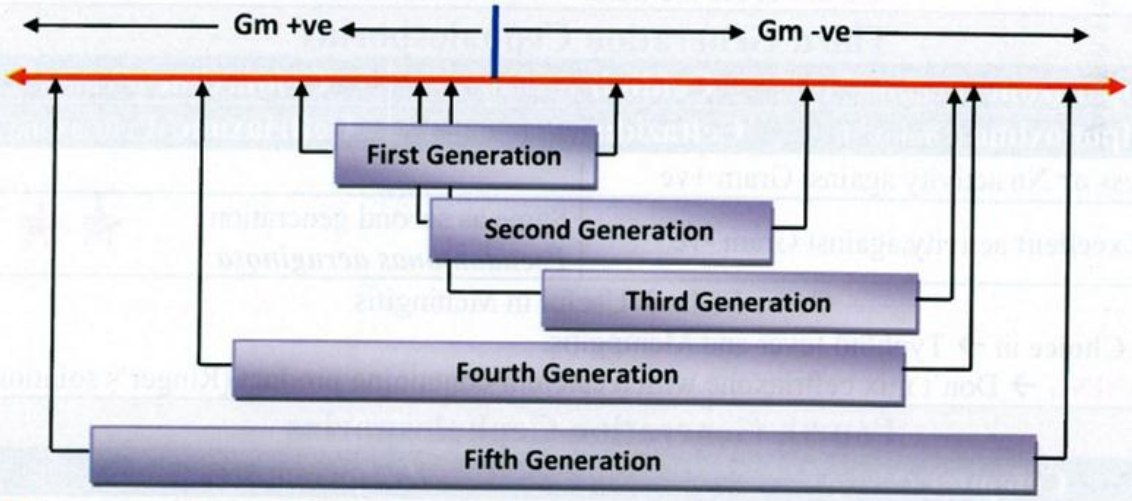
➢ Mechanism of action and bacterial resistance :-

- Mechanism of action as Penicillins (Bactericidal and decrease Cell wall synthesis).
- Mechanism of bacterial resistance as Penicillins.

➢ Activity of Cephalosporins :-

- Not active against →
  - MRSA (Methicillin-Resistance ***Staphylococcus aureus***)
  - **Enterococci**
  - ***Clostridium difficile***
  - ***Listeria monocytogenes***

➢ Classification of Cephalosporins :-



➢ Adverse effect of Cephalosporins :-

- Because the Cephalosporins are structurally similar to the Penicillins, some patients allergic to Penicillins may be allergic to a cephalosporin antibiotic. The incidence of cross-sensitivity is approximately 5–10%.
- **Nephrotoxicity** → If administrated with nephrotoxic drug such as furosemide (Loop Diuretic).
- Mild stomach cramps or upset nausea, vomiting, and diarrhea.
- Super infection (as Penicillins).

First Generation Cephalosporins

Cefadroxil (Duricef®)	**Cefazolin** (Zinol®)	**Cephapirin** (Cefatrexyl®)
Cephalaxin (Ceporex®)	**Cephradine** (Velosef®)	
Some activity against Gram +ve	***Staphylococcus aureus**** ***Staphylococcus epidermidis*** ***Streptococcus pyogenes*** ***Streptococcus pneumoniae*** ***Anaerobic streptococci***	★
Some activity against Gram -ve	***Escherichia coli & Klebsiella pneumoniae***	

Do not cross the blood-brain barrier (BBB) → Not effective in Meningitis

Second Generation Cephalosporins

Cefaclor (Bacticlor®)	**Cefprozil** (Cefzil®)	**Cefixime** (Ximacef®)
Cefuroxime (Zinnat®)	**Cefoxitin** (Mefoxin®)	**Loracarbef** (Lorabid®)
Less activity against Gram +ve	***Streptococcus pyogenes*** ***Streptococcus pneumoniae*** ***Anaerobic streptococci***	
Good activity against Gram -ve	***Escherichia coli*** ***Klebsiella pneumonia*** ***Haemophilus influenza**** ***Neisseria* spp.***	★

Do not cross the BBB **except Cefuroxime**

Third Generation Cephalosporins

Cefoperazone (Cefazone®)	**Cefdinir** (Cefdin®)	**Cefotaxime** (Cefotax®)
Cefpodoxime (Orelox®)	**Ceftazidime** (Fortum®)	**Ceftriaxone** (Ceftriaxone®)
Less or No activity against Gram +ve		
Excellent activity against Gram -ve	Same as second generation ***Pseudomonas aeruginosa***	★★

Cross BBB → Useful in Meningitis

- **First Choice** in → Typhoid fever and Meningitis.
- **WARNING** → Don't mix ceftriaxone with a calcium-containing product (Ringer's solution).

Fourth Generation Cephalosporins

Cefepime (Maxipime®)	**Cefpirome** (Cefrom®)
Excellent activity against **Gram -ve** and **Gram +ve** - These are comparable to third-generation but more resistant to β-lactamases.	★★★

Fifth Generation Cephalosporins

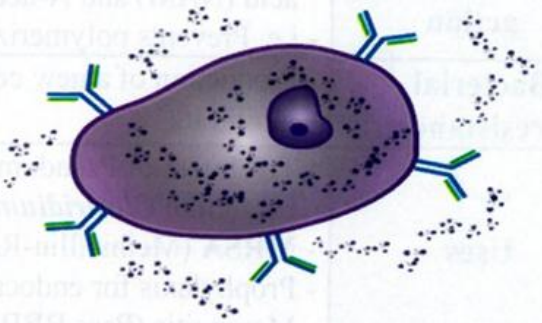
Ceftobiprole (Zeftera®)

- Ceftobiprole was approved in Canada in June 2008.
- Treatment of complicated skin and soft tissue infections (cSSTI).
- Commonly used to treat infections caused by MRSA and VRSA. ★★★★★

→ Do you think there will be a sixth generation of cephalosporins group in the future?

☐ Yeas ☐ No

Monobactams

Aztreonam (Azactam®)	
Information	- The only commercially available monobactam antibiotic.
Spectrum of activity	- Narrow spectrum antibiotic. - Has little or **No** activity against Gram + ve and anaerobes. - Also acts against aerobic Gram - ve rods. - They have no cross-hypersensitivity reactions with penicillin.
Uses	***Mast cell*** **Ig-E antibodies on the surface of mast cells, when activated by a medication, cause the mast cell to release chemical mediators into the tissue and blood.**  - Used in patients with IgE-mediated penicillin allergy.
Adverse effects	- Phlebitis (associated with the formation of blood clots), skin rash, and occasionally, abnormal liver function tests.

Carbapenems

Imipenem	
Spectrum of activity	- **Most broad spectrum antibiotics**. - Imipenem are active against Gram +ve, Gram -ve bacteria, and anaerobes. - **Not active** against MRSA.
Combination	**Imipenem + Cilastatin** (Tienam®) - Imipenem is rapidly degraded by the renal enzyme dehydropeptidase when administered alone (Nephrotoxic Metabolite). - Co-administered with cilastatin (Dehydropeptidase enzyme inhibitors) → Prevent this inactivation (Prolong duration of action)
Adverse effects	- Nausea and vomiting, Allergy, Antibiotic associated colitis. And Seizure
Meropenem	
- Similar to Imipenem but not metabolized by dehydropeptidase (Dipeptides) enzyme. - Less produced seizures and less side effects.	
Ertapenem	
- Similar to Meropenem, but has longer half-life.	

Non-β-lactam (Dissimilar agent)

Vancomycin

Vancomycin (Vancocin®)	
History	- Vancomycin was first isolated in 1953 by Edmund Kornfeld from a soil sample collected from the interior jungles of Borneo by a missionary.
Mechanism of action	- It prevents the synthesis of the long polymers of N-acetyl-muramic acid (NAM) and N-acetyl-glucosamine (NAG) - i.e. Prevents polymerization of peptidoglycan
Bacterial resistance	- Production of a new cell wall component that vancomycin doesn't inhibit it.
Uses	- Treatment of Pseudomembranous colitis caused by the bacterium ***Clostridium difficile*** **(Drug of choice)**. - **MRSA** (Methicillin-Resistance ***Staphylococcus aureus***). - Prophylaxis for endocarditis (Penicillin-hypersensitive individuals). - Meningitis (Pass BBB but not drug of choice)
Adverse effects	- **Nephrotoxicity** and **Ototoxicity**. - **Red man syndrome** (Non-specific mast cell degranulation → release of histamine → Redness and hotness in face and neck.
"VRSA"	- **VRSA** (Vancomycin-Resistant ***Staphylococcus aureus***) refers to strains of Staphylococcus aureus that have become resistant to the glycopeptide antibiotic vancomycin

Telavancin (Vibativ®)

- Telavancin is a semi-synthetic derivative of vancomycin.
- The FDA approved the drug in September 2009 for complicated skin and skin structure infections (cSSSI).
- Mechanism of action → like vancomycin.
- Higher rate of kidney failure than vancomycin.
- May prolong QT interval (Arrhythmia).
- Used in **MRSA** (Methicillin-Resistance ***Staphylococcus aureus***).

Cycloserine

Cycloserine (Seromycin®)

- Effective against ***Mycobacterium tuberculosis*** (TB) (Not drug of choice) (2nd line Therapy)
- Cycloserine action as a partial agonist of the neuronal NMDA receptor → Convulsion

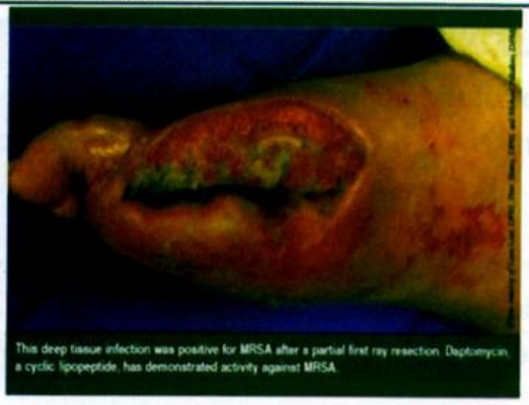
Bacitracin

Bacitracin
- As a toxic and difficult-to-use antibiotic. - Very effective **topically** (ingredient of eye and skin antibiotic preparations). - Its action is on **Gram + ve** cell walls. - Nephrotoxicity (kidney damage potential) if used systemically (Parentally)

Antibiotics that disruption of cell membrane functions

Polymyxin B and E
- Disruption of cell membrane functions → Leakage of cell contents → Death (Bactericidal). - Affects mainly **Gram -ve** bacteria especially ***Pseudomonas aeruginosa***. - Used locally only (Not absorbed) (ingredient of eye and skin antibiotic preparations). - Nephrotoxicity if used systemically.

Daptomycin (Cubicin®)	
- Is a cyclic lipopeptide antibiotic.	
Mechanism of action	- Binding to the bacterial cytoplasmic membrane → rapid depolarization of the membrane → disrupting multiple aspects of membrane function → leading to inhibition of protein, DNA and RNA synthesis → bactericidal (bacterial killing is concentration dependent).
Spectrum of activity	- Is active against Gram +ve bacteria **only**. **- Active against →**  - Methicillin-Susceptible ***S. aureus*** (MSSA) - Methicillin-Resistant ***S. aureus*** (MRSA) - Vancomycin-Resistant ***S. aureus*** (VRSA) - Penicillin-Resistant ***Streptococcus pneumoniae*** - ***Streptococcus pyogenes*** - ***Corynebacterium*** - ***Enterococcus*** ★★★★
Uses	- Used for the treatment of complicated skin and skin structure infections (cSSSI) and bacteremia caused by MRSA



This deep tissue infection was positive for MRSA after a partial first ray resection. Daptomycin, a cyclic lipopeptide, has demonstrated activity against MRSA.

Antibiotics that Inhibit Protein synthesis

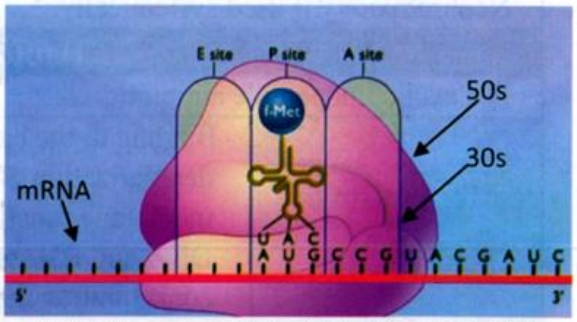
Protein Synthesis in Bacterial Cell

➢ Ribosome in bacterial cell:-

- Bacterial cell (Prokaryotes) have a **70S ribosome** (50S large subunit and 30S small subunit), but human cell (Eukaryotes) have a **80S ribosome** (60S large subunit and 40S small subunit).
- Prokaryotes and Eukaryotes have a different structure to ribosomes so can use antibiotics for selective toxicity against ribosomes of prokaryotes.

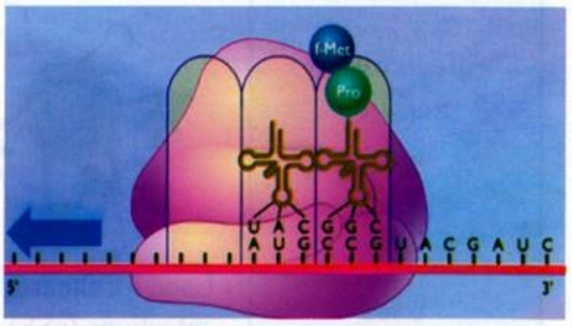
➢ Steps of protein synthesis in bacterial cell:-

- **Initiation:**
  - Initiate formation of 70S ribosome from 30S and 50S.
  - Required initiation (Start) codon (AUG) and initiation factor (IF).
  - AUG corresponds to N-formyl methionine amino acid.



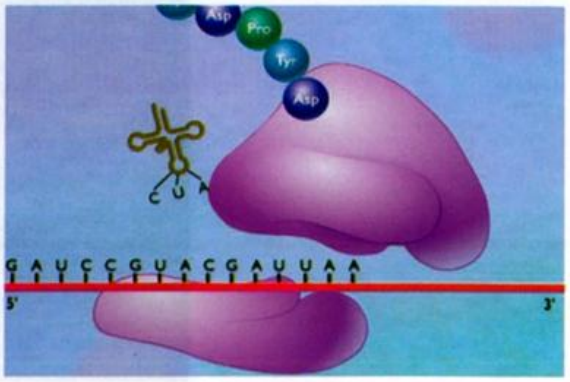
A site (Acceptor site) - P site (Peptidyl site)
E site (Exit site)

- **Elongation :**
  - By formation of peptide bond between amino acids.
  - Required Peptidyl transferase enzyme and elongation factor (EF).



- **Translocation or Propagation:**
  - Movement of the ribosome through mRNA.

- **Termination:**
  - It required termination non-sense codon (UAA - UAG - UGA).

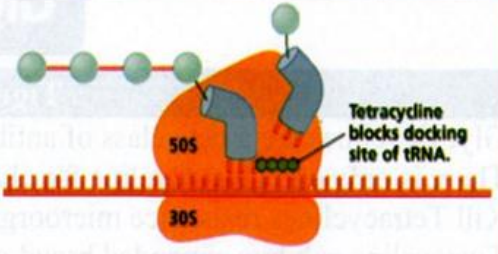


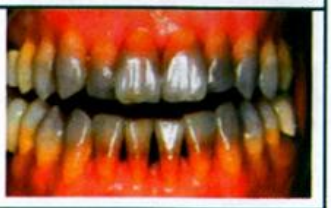
Antibiotics that Inhibit Protein synthesis

- **Tetracyclines**
  - Tetracycline
  - Oxytetracycline
  - Demeclocycline
  - Minocycline
  - Doxycycline
  - Glycylcyclines
- **Aminoglycosides**
  - Streptomycin
  - Neomycin
  - Gentamicin
  - Amikacin
  - Tobramycin
- **Macrolides**
  - Erythromycin
  - Clarithromycin
  - Azithromycin
  - Roxithromycin
  - Spiramycin
- **Others**
  - Chloramphenicol
  - Oxazolidinones
  - Ketolides
  - Lincosamides
  - Streptogramins

Tetracyclines

Low lipid solubility (Slowly absorbed)	High lipid solubility (Rapidly absorbed)
Tetracycline (Tetracid®)	**Doxycycline** (Vibramycin®)
Demeclocycline (Declomycin®)	**Minocycline** (Minocin®)
Oxytetracycline (Oxytetracid®)	
- Due to low lipid solubility they are affected by food. - Make chelation of many metals e.g. Ca, Mg, Fe and Al → Decrease absorption. - Mainly excreted by kidney (Not used in renal failure) → Rarely used now.	- Not affected by food. - Less chelation. - Safe in renal failure.

History	- The first of these compounds Chlortetracycline was introduced in 1948 followed by Oxytetracycline and Tetracycline in 1950 and 1952 respectively.
Mechanism of action	- Quickly **Bacteriostatic** drugs, but at high dosage they are also **Bactericidal**.  - They reversibly bind to the **30S ribosomal subunit** of bacteria, blocking the binding of aminoacyl-tRNA to the site A on the mRNA ribosome complex. - This prevents addition of amino acids to the growing peptide, resulting in inhibition of protein synthesis.

<table>
<tr><td>Spectrum of activity</td><td colspan="2">- Tetracyclines are effective against gram +ve and gram -ve bacteria as well as against organisms other than bacteria.
- High effective against (First choice):
▪ Rickettsia (Rickettsial infection).
▪ Mycoplasma pneumoniae.
▪ Chlamydia infection (Sexually transmitted infection).
▪ Brucella species e.g. (B. abortus).
- Effective against:
▪ Bacillus anthracis (Anthrax).
▪ Vibrio cholera (Cholera).</td></tr>
<tr><td rowspan="6">Adverse effects</td><td>GIT</td><td>Gastrointestinal discomfort
- Anorexia, epigastric pain, abdominal distention, perianal irritation.</td></tr>
<tr><td>Calcified tissues</td><td>- Deposition in fetal and growing bones, stunted growth.
- Discoloration and hypoplasia of teeth.
  </td></tr>
<tr><td>Fatal hepatotoxicity</td><td>- Occur in pregnant women who received high doses of tetracyclines.</td></tr>
<tr><td>Photosensitivity</td><td>- Severe sunburn, occurs when a patient receiving a tetracycline is exposed to sun or ultraviolet rays</td></tr>
<tr><td>Azotemia</td><td>- Increase free nitrogenous compound in the blood due to destroy protein.</td></tr>
<tr><td>Fanconi syndrome</td><td>- Administration of Tetracycline after expire date converted to → 4 epoxy (epi) tetracycline → Cause damage of proximal renal tubules.
- Characterized by :
- Nausea, vomiting, polyuria, polydipsia, proteinuria, acidosis and glycosuria.</td></tr>
</table>

Glycylcyclines

★★★★

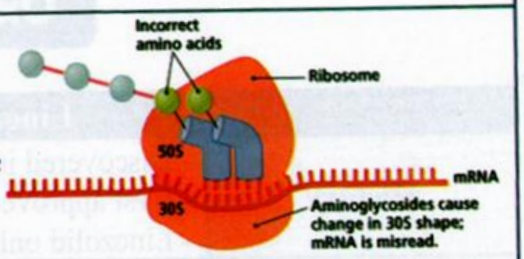
Tigecycline (Tygacil®)

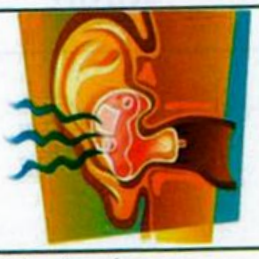
- Glycylcyclines are a new class of antibiotics derived from tetracycline.
- There is only one glycylcycline for clinical use "Tigecycline" [tye-ge-SYE-Kleen].
- Kill Tetracyclines resistance microorganisms.
- Tigecycline exhibits expanded broad-spectrum activity that includes:
  - Methicillin-Resistant ***S. aureus*** (MRSA)
  - Vancomycin-Resistant ***Enterococci*** (VRE)
- **Bacterial resistance** by → Efflux pump and/or Ribosomal protection.
- **Uses → cSSSI** (Complicated skin and skin structure infections).
  → cIAI (Complicated intra-abdominal infection)

Aminoglycosides

Streptomycin	**Gentamicin** (Garamycin®)
Tobramycin (Nebcin®)	**Neomycin** (Neomycin®)
Amikacin (Amikin®)	

Sources	- Aminoglycosides that are derived from ***Streptomyces*** have -mycin suffixes, whereas those derived from ***Micromonospora*** are named with the suffix -micin.
Pharmacokinetics	- Poorly absorbed orally (Highly polar). - Minimal plasma protein binding. - Concentrations in CSF are inadequate. - Excreted mainly in urine.
Mechanism of action	- All aminoglycosides are **Bactericidal**. - Susceptible **Gram -ve** organisms allow aminoglycosides to diffuse through porin channels in the outer membranes. - These organisms also have **Oxygen-dependent system** that transports the drug across cytoplasmic membrane (Not active against anaerobe). - Aminoglycosides binds to 30s ribosome subunit → Misreading of mRNA → Decrease protein synthesis.
Mechanism of bacterial resistance	- Decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides or porin channels are absent. - Enzymatic inactivation by transferase or other enzymes that inactivate aminoglycosides.
Spectrum of activity	- Aerobic gram-negative bacilli, including ***Pseudomonas aeruginosa***, ***Proteus*** and ***Klebsiella***. - Also active against some gram + ve cocci e.g. β-lactamase producing ***Staphylococcus aureus***. - ***Mycobacterium T.B*** is sensitive to Streptomycin.
Side effects	**Ototoxicity**: - The antibiotic accumulates in the endolymph of the inner ear lead to damage of cranial nerve 8th. - Deafness may be irreversible. **Nephrotoxicity**: - Retention of the aminoglycosides by the proximal tubular cells lead to kidney damage **Muscle relaxant**: - Skeletal muscle relaxant (↓ release of ACh) **Allergic reaction**: - Contact dermatitis
Drug interactions	- Cephalosporins, Polymyxins and furosemide





	Aminoglycosides + Penicillin
Combination	**When administered in 2 separate syringe (Good)**
	- Penicillin shows a synergistic effect with aminoglycosides, since the inhibition of peptidoglycan synthesis allows aminoglycosides to penetrate the bacterial cell wall more easily, allowing their disruption of bacterial protein synthesis within the cell. This results in a lowered Minimum Bactericidal Concentration (MBC) for susceptible organisms. - Penicillin acts more on Gm + ve and Aminoglycoside acts more on Gm - ve.
	When administrated in same syringe (Bad)
	- Aminoglycoside + Penicillin in same container → Inactivate each other by chemical interaction.

Oxazolidinones

Linezolid (LZD) (Zyvox®)	
History	- Discovered in the 1990. - First approved for use in 2000. - Linezolid only marketed oxazolidinone in 2009.
Pharmacokinetics	- Oral bioavailability (>90%) and good tissue penetration (orally or parenterally). - Metabolized in the liver, without involvement of the cytochrome P450 system. - Dose 30 mg/kg/day. - Linezolid is quite expensive; a course of treatment may cost one or two thousand U.S.
Mechanism of action	- Linezolid binds to a site on the 50S subunit → inhibiting the formation of the 70S initiation complex → inhibits bacterial protein synthesis.
Spectrum of activity	- Effect against **gram + ve** bacteria that are resistant to several other antibiotics. - It is also moderately active against ***Mycobacterium tuberculosis***. - Has no clinically significant effect on most gram -ve bacteria.
Uses	- Community-acquired pneumonia (***Streptococcus pneumoniae***) - Hospital-acquired pneumonia (***Streptococcus pneumoniae***) - Uncomplicated skin and skin structure infections (uSSSI) - Complicated skin and skin structure infections (cSSSI) - Vancomycin-resistant ***Enterococci*** (VRE) - Vancomycin-resistant ***Staphylococcus aureus*** (VRSA) - ***Clostridium perfringens*** - MRSA also resistant to linezolid and Not better than Vancomycin.
Adverse effects	- Nausea, diarrhea and Headaches (3-10 % of patient) - Rash and constipation (2% of patient) - Thrombocytopenia (2% of patient)

Macrolides

Erythromycin (Erythrocin®) | **Clarithromycin** (Klacid®)
Roxithromycin (Roxicin®) | **Azithromycin** (Zithromax®)
Spiramycin (Rovamycin®)

- Activity stems from the presence of a macrolide ring (large macrocyclic lactone ring)

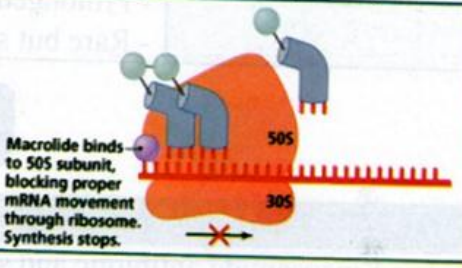
Pharmacokinetics

- Absorbed orally (Erythromycin unstable in acid media so used as enreric coated or in esterified forms).
- Distributed all over the body except CSF.
- Metabolized in liver.
- Excreted in bile.
- Half-life

Erythromycin	Clarithromycin	Azithromycin
2 (hours)	4 (hours)	40 (hours)

Mechanism of action

- **Bacteriostatic**, but at high dosage they are also **Bactericidal**.
- Bind irreversibly to the 50S subunit → Inhibit translocation steps of protein synthesis.



Spectrum of activity

- **Erythromycin**
  - Effective against many of the same organisms as penicillin G.
- **Clarithromycin**
  - Has a spectrum of antibacterial activity similar to that of erythromycin, but higher effective against:
    - ***Helicobacter pylori*** (First choice).
    - ***Haemophilus influenzae.***
    - ***Chlamydia***, ***Legionella*** and ***Moraxella*** species.
- **Azithromycin**
  - More active against respiratory infections due to ***Haemophilus influenzae*** and ***Moraxella catarrhalis***.
  - Now the preferred therapy for urethritis caused by ***Chlamydia trachomatis***.
  - Also has activity against Mycobacteria.

Side effects

GIT	- Nausea, vomiting and diarrhea
Liver	- Cholestatic jaundice especially with the estolate form of erythromycin.
Ototoxicity	- Transient deafness has been associated with erythromycin, especially at high dosages.

Drug interactions

- Erythromycin is a liver microsomal enzyme (LME) inhibitor → Decrease metabolism of other drug such as Warfarin → Increase toxicity of Warfarin.

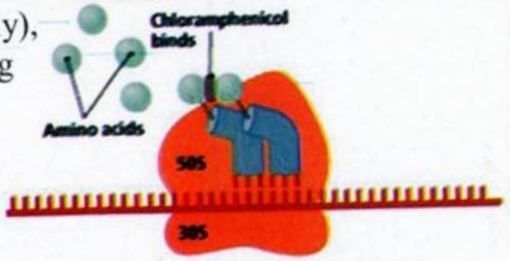
Ketolides

Telithromycin (Ketek®)	
- Ketolides are antibiotics belonging to the macrolide group. - Telithromycin is the first ketolide antibiotic. - Mechanism similar to Erythromycin. - Has an antibacterial spectrum similar to that of Azithromycin.	
FDA Warning	- In 2007, the FDA announced a revision to the labeling of Ketek to improve patient safety. - Ketek remains on the market for the treatment of community acquired pneumonia of mild to moderate severity. - Ketek should not be used in patients with myasthenia gravis.
Side effects	- Visual disturbances - Muscle paralysis - Prolonged QT interval (Arrhythmia) - Rare but severe → Liver damage.

Lincosamides

Clindamycin (Dalacin®-C)	
- Is a Lincosamide antibiotic and structurally related to Macrolides. - Mechanism similar to Erythromycin.	
Pharmacokinetics	- Absorbed orally and parenterally. - Distributed all over the body but **not** CSF and **concentrated in bone and teeth.** - Metabolized in liver. - Excreted in bile.
Spectrum of activity	- More effective against Anaerobes.
Uses	- **Bone infection** (Osteomyelitis) and teeth infection. (drug of choice) - **Intra-abdominal anaerobic infections** (Enteritis). - Combination therapy in acne
Side effects	- **Fatal pseudomembranous colitis** caused by overgrowth of ***Clostridium difficile***. (Treated by Vancomycin or Metronidazole) - Liver and kidney dysfunction - Abdominal pain and cramps - Rash
Lincomycin (Lincocin®)	
- It is rarely used today and reserved for patients allergic to penicillin or where bacteria have developed resistance. - Also effective against other organisms including ***Actinomycetes***, ***Mycoplasma***, and some species of ***Plasmodium***.	

Chloramphenicol

<table>
<tr><th colspan="4">Chloramphenicol (Chloramphenicol®)</th></tr>
<tr><td colspan="4">- An antibiotic produced by Streptomyces venezuelae, an organism first isolated in 1947 from a soil sample collected in Venezuela.
- Active against a wide range of gram +ve and gram -ve organisms. However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.
- Chloramphenicol is still widely used in topical preparations.</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">- Absorbed orally (Complete absorbed) and parenterally.
- Metabolism → Conjugated in liver with glucuronic acid.</td></tr>
<tr><td>Mechanism of action</td><td colspan="3">- Bacteriostatic (more commonly), may be Bactericidal depending on the organism.
- Act by binding to the 50S ribosomal subunit.
 

- Inhibit Peptidyl transferase reaction → Inhibit protein synthesis.</td></tr>
<tr><td>Resistance</td><td colspan="3">- Enzymatic inactivation (Acetyl coenzyme A transferase).
- Decrease Permeability.</td></tr>
<tr><td>Spectrum of activity</td><td colspan="3">- Broad-spectrum bacteriostatic antibiotic.
- Excellent activity against anaerobes.</td></tr>
<tr><td>Uses</td><td colspan="3">- Typhoid and Paratyphoid fever (3rd choice after 3rd generation Cephalosporins and Quinolones)
- Meningitis (2nd choice after 3rd generation Cephalosporins)
- Rickettsial infection (2nd choice after Tetracyclines)</td></tr>
<tr><td rowspan="3">Side effects</td><td rowspan="2">Anemia</td><td colspan="2">"Bone marrow suppression"
1: Hemolytic anemia occurs in patients with low levels of glucose 6-phosphate dehydrogenase.</td></tr>
<tr><td>2: Aplastic anemia
- Irreversible
- Non dose dependent
- Rare and fatal
- Idiosyncratic</td><td>3: Other anemia
- Reversible
- Dose dependent</td></tr>
<tr><td>Blood</td><td colspan="2">- Thrombocytopenia (decrease of platelets)
- There is an increased risk of childhood leukemia (is a type of cancer of the blood or bone marrow characterized by an abnormal increase of immature white blood cells) risk increases with length of treatment.</td></tr>
</table>

	Gray baby syndrome	- This phenomenon occurs in newborn infants because they do not yet have fully functional liver enzymes. - Deficiency of Gluco-Uridyl transferase enzyme which responsible for glucuronidation (metabolism) of chloramphenicol. - Accumulation of chloramphenicol due to decrease metabolism and excretion. - The manifestations in the first 24 hours are vomiting, refusal to suck, irregular and rapid respiration, abdominal distention, periods of cyanosis, and passage of loose, green stools. Soon they become flaccid, turn an ashen-gray color, and become hypothermic. - **Treatments** → Artificial respiration, Blood transfusion and liver microsomal enzyme inducers.
Drug interactions	- Chloramphenicol is a liver microsomal enzyme (LME) inhibitor → Decrease metabolism of other drug such as Warfarin → Increase toxicity of Warfarin. - Antagonizes the bactericidal action of Aminoglycosides (Inhibit transport system)	

Streptogramins

Quinupristin/Dalfopristin (Synercid®)

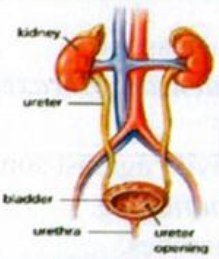
- They are combined in a weight-to-weight ratio of 30% Quinupristin to 70% Dalfopristin.
- Quinupristin and dalfopristin are protein synthesis inhibitors in a synergistic manner. While each of the two is only a bacteriostatic agent, the combination shows bactericidal activity.
- **Administration** → IV, usually 7.5 mg/kg every 8-12 hours.
- **Uses** → used to treat certain serious bacterial infections that have not responded e.g. Complicated skin and skin structure infections (cSSSI).
- **Adverse effects** → Venous irritation, Arthralgia (Joint aches), myalgia (muscle aches) and Hyperbilirubinemia.

Fusidic Acid

Fusidic Acid (Fucidin®)

- Fusidic acid acts as a bacterial protein synthesis inhibitor by preventing the turnover of elongation factor G (EF-G) from the ribosome (Bacteriostatic).
- often used topically in creams and eye drops.

Antibiotic that Inhibit nucleic acid synthesis



Quinolones and Fluoroquinolones

Classification according to Generation

First	Second	Third	Fourth
Nalidixic acid **Cinoxacin**	**Norfloxacin** **Ciprofloxacin** **Enoxacin** **Ofloxacin** **Lomefloxacin**	**Levofloxacin** **Sparfloxacin** **Grepafloxacin**	**Trovafloxacin** **Gatifloxacin** **Moxifloxacin** **Gemifloxacin**
- First generation → Quinolones. - Second, Third and Fourth → Fluoroquinolones. - First generation less used today. - Moderate activity against Gram - ve.	- Expanded activity against Gram - ve. - Some activity against Gram + ve. - Some activity against atypical bacteria such as Mycoplasma and Chlamydia.	- Retain expanded Gram - ve activity - Improve activity against gram +ve and atypical bacteria.	- Maintains Gram -ve activity. - Improved Gram + ve coverage. - Gains anaerobic coverage.

This is a new classification, there is another classification includes only Trovafloxacin in fourth generation.

- The first generation of the quinolones begins with the introduction of nalidixic acid in 1962 for treatment of urinary tract infections in humans.
- Fluoroquinolones (2nd, 3rd and 4th generation) more potent than Quinolones (1st generation).

Pharmacokinetics	- Absorbed orally (Bioavilability 80% - 90%). - Distributed all over the body and **concentrated intracellular especially prostatic tissue and kidney**, but low CSF level. - Metabolized in the liver. - Excretion in urine and bile.
Mechanism of action	- Inhibit bacterial DNA synthesis by inhibiting DNA gyrase (Topoisomerase II) and Topoisomerase IV → Rapid cell death. - In gram -ve organisms the inhibition of DNA gyrase is more significant than that of topoisomerase IV, in gram +ve organisms the opposite is true.

Resistance	- Mutations in the bacterial DNA gyrase and Topoisomerase IV. - Reduced intracellular concentration of the drugs in the bacterial cell.
Spectrum of activity	- All the fluoroquinolones are bactericidal. - They are effective against gram - ve organisms such as the ***E.coli***, ***Pseudomonas*** species, ***Haemophilus influenzae***, ***Moraxella catarrhalis***, ***Legionellaceae*** and ***chlamydia***. - Third generation fluoroquinolones have good activity against some gram + ve organisms, such as ***Streptococcus pneumoniae***. - Fourth generation have activity against many anaerobes.

Ciprofloxacin (Ciprofar®)

- This is the most frequently used fluoroquinolone.
- Effective against many systemic infections (Not effective against MRSA).
- Ciprofloxacin is also particularly useful in treating infections caused by Gram - ve →
  - **Traveler's diarrhea** caused by ***E. coli***.
  - Complicated and uncomplicated **Urinary tract infections** (UTIs) and **prostatitis**.
  - **Typhoid fever**
  - Drug of choice for prophylaxis and treatment of **anthrax**.
  - It is the most potent of the fluoroquinolones for ***Pseudomonas aeruginosa***.
- Used as an alternative to more toxic drugs, such as the aminoglycosides.

Norfloxacin (Noracin®)

- Isomer of Ofloxacin (Tarivid®).
- Used in the treatment of prostatitis due to E. coli and of sexually transmitted diseases (Not syphilis).
- Has excellent activity against respiratory infections due to ***S. pneumoniae***.
- Has activity against skin infections.

Moxifloxacin (Avalox®)

- Enhanced activity against gram + ve organisms
- Has excellent activity against many anaerobes.
- It has very poor activity against ***P. aeruginosa***.

Gemifloxacin (Flobiotic®)

- Used in **Chronic bronchitis** and **Community-acquired pneumonia**.

Side effects	**GIT**	- Nausea, vomiting, and diarrhea
	CNS	- Headache, dizziness and may cause seizures.
	Photosensitivity	- Avoid excessive sunlight and to apply sunscreens.
	Gatifloxacin	- Serious diabetes
	Grepafloxacin	- Prolong QT interval (withdrawal from market)
	Trovafloxacin	- Fatal liver damage (withdrawal from market)
Contraindication	- Pregnancy, lactation and Children under 18 years of age. - Epilepsy patient.	
Drug interaction	- Theophylline increases concentration of ciprofloxacin. - Decrease cations (Al, Mg, Ca, Zn, Fe) absorption.	

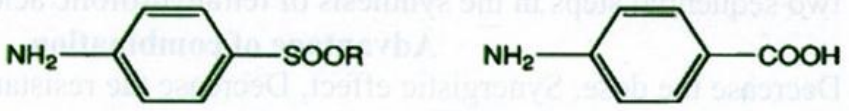
Antibiotic that act as Anti-metabolite

Sulfonamides (Sulfa drugs)

➢ History of sulfonamides :-

- The best example of antibacterial agents acting as anti-metabolites are the sulfonamides
- The sulfonamide story began in 1935 when it was discovered that a red dye called prontosil had antibacterial properties in vivo (i.e. when given to laboratory animals).
- Instead, it was found that the dye was metabolized by bacteria present in the small intestine of the test animal, and broken down to give a product called sulfanilamide.
- The sulfa drugs are seldom prescribed alone except in developing countries (low cost) and their efficacy urinary tract.
- **Cotrimoxazole** was introduced in the 1970 and used now widely than sulfa drugs alone.

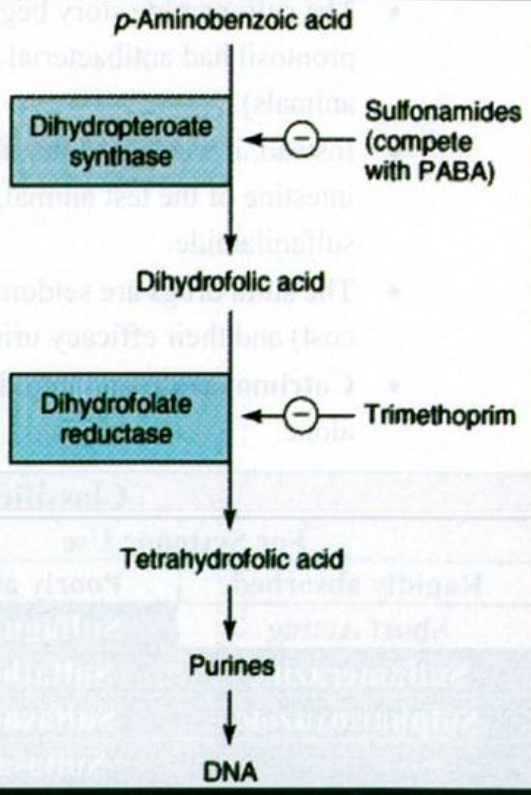
Classification of Sulfonamides		
For Systemic Use		**For Topical Use**
Rapidly absorbed	**Poorly absorbed**	**For ophthalmic infection**
Short Acting	**Sulfaguanidine**	**Sulfacetamide** (Isopto Cetamide®)
Sulfamerazine	**Sulfathalidine**	**For skin burns**
Sulphaisoxazole	**Sulfasuccidine**	**Silver Sulfadiazine** (Dermazine®)
Sulfaisodimidine	**Sulfasalazine** Used → Ulcerative colitis	**Mafenide** (Sulfamylon®)
Intermediate Acting		
Sulfadoxine		
Sulfamethoxazole		
Long Acting		
Sulfamethoxydiazine		
Sulfadoxine		



Sulfonamide **p-Aminobenzoic acid**

Pharmacokinetics	**Absorption** - Most sulfa drugs are well absorbed via the small intestine. - Sulfasalazine not absorbed used in treatment of chronic inflammatory bowel disease. - Silver sulfadiazine or mafenide are effective in reducing burn associated sepsis, because they prevent colonization of bacteria.

	Distribution - Highly bound to plasma proteins, Displace bilirubin → increase serum bilirubin → Kernicterus (in newborns). **Metabolism** - In the liver by Acetylation → Acetyl sulfa (Insoluble in acid media) **Excretion** - Acetyl sulfa crystallization in the urine (Acidic media) → Produce crystaluria. - May also excreted in milk.
Mechanism of action	- Sulfa drugs are **Bacteriostatic**. - Due to structural similarity between sulfonamide and P-Amino-benzoic acid (PABA) → Compete with PABA → Inhibition of Dihydropteroate synthase. - Inhibition of folic acid synthesis which is essential for synthesis of DNA. - **Trimethoprim** inhibits Dihydrofolate reductase enzyme → Inhibit DNA.



Co-Trimoxazole (Trimethoprim/Sulfamethoxazole) (Septrin-D.S.®)

- The synergistic antimicrobial activity of cotrimoxazole results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid.

Advantage of combination

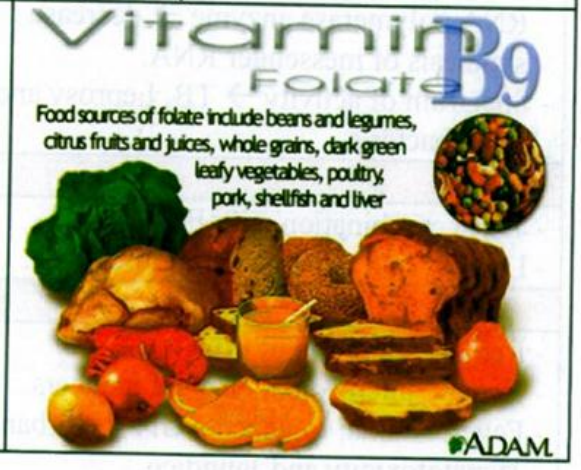
- Decrease the dose, Synergistic effect, Decrease the resistance, Increase spectrum of activity, The combination has bactericidal action.

Spectrum of activity	- **Cotrimoxazole** has a broader spectrum of antibacterial action than the sulfa drugs. - It is effective in treating UTIs and respiratory tract infections - It is effective in ampicillin or chloramphenicol resistant systemic salmonella infections. - **Silver Sulfadiazine** and **Mafenide** used in Skin burn and wounds. - **Sulfacetamide** used topically in eye infections. - **Sulfasalazine** → Inflammatory bowel disease (Ulcerative colitis).

Adverse effects	**Skin Allergy**	- Photosensitivity, Fever and skin rash. - The reaction is severe in the elderly.
	GIT	- Nausea and vomiting.
	Crystalurea	- Due to low solubility of sulfa. - Avoided by: - Plenty fluid intake. - Alkalinization of urine. - Use triple sulfa (Sulfonamide mixture) → Decrease dose of each one. - Sulfadiazine - Sulfamerazine - Sulfamethazine
	Blood	- **Hemolytic anemia** in patient with Glucose-6-phosphate dehydrogenase (G6PD) deficiency. - **Aplastic anemia** (Bone marrow depression) - **Agranulocytosis**
	Kernicterus	- This disorder may occur in newborns because sulfa displace bilirubin from Binding sites of serum plasma protein.
	Stevens johnson syndrome (SJS)	- Is a life-threatening condition affecting the skin. - Stevens-Johnson syndrome is marked by a blistering purple or red rash that progresses to cover large parts of the body.
Contraindication	- Infant under 2 months. - Pregnancy and lactation. - Kidney disease. - Liver Problems. - Blood problems. - Deficiency of glucose-6-phosphate dehydrogenase (G6PD).	
Drug interactions	- Increase concentration of Phenytoin, warfarin and Methotrexate is placement from albumin binding sites by sulfamethoxazole.	

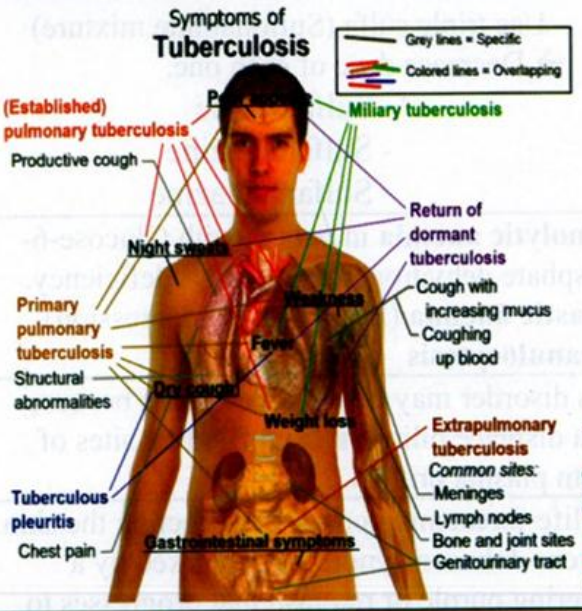
- Why sulfa drug nontoxic in human?

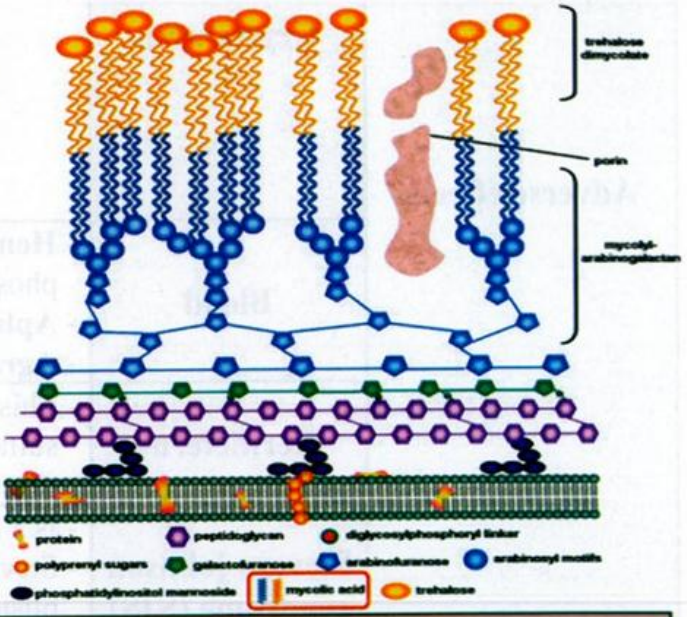
- The human organism does not have the enzymes necessary for synthesizing folic acid which it needs.
- Folic acid not biosynthesis in the human and get it from diet.
- Folic acid in human cell converted to Tetrahydrofolic acid by folic acid reductase enzyme.



Anti-Mycobacterial

Anti-Tuberculous drugs





First Line drugs (High Efficacy)	
Rifampicin (Rimactane®)	**Isoniazid** (INH) (Iso-Nicotinic acid Hydrazine)
Pharmacokinetics	
- Well absorbed orally. - Distributed all over the body. - Deacetylated in liver. - Excreted in urine and bile.	- Well absorbed orally. - Distributed all over the body. - Acetylated in liver. - Excreted in urine.
Mechanism of action	
- Bactericidal by decrease DNA dependent RNA polymerase enzyme → decrease synthesis of messenger RNA. - Spectrum of activity → TB, Leprosy and other bacteria.	- Bacteriostatic and Bactericidal by decrease mycolic acid synthesis present in cell wall of TB. - Decrease utilization of Vit. B6 in TB. - Spectrum of activity → TB only.
Uses	
- TB in combination with INH. - Leprosy and other bacterial infections.	- TB in combination with rifampicin.
Side effects	
- Red discoloration of urine. - Hepatic microsomal enzyme inducers. - Fever, Ataxia, Headache, GIT disturbance, Hepatotoxicity and Jaundice.	- Peripheral neuropathy (Deficiency Vit B6) - Hepatic microsomal enzyme inhibitors. - MAO inhibitor. - Hepatotoxicity and Hypersensitivity.

Pyrazinamide (P.T.B®)

- Pyrazinamide (Prodrug) diffuses into ***M. tuberculosis***, where the enzyme pyrazinamidase converts pyrazinamide to the active form pyrazinoic acid → inhibit the fatty acid synthase (FAS) enzyme → Inhibit fatty acid in the bacteria (Bacteriostatic, but can be bactericidal)
- **Side effects** → Hepatotoxicity, Hyperuricemia and joint pains (arthralgia).

Ethambutol (EMB) (Etibi®)

- Ethambutol is bacteriostatic against. It works by obstructing the formation of cell wall.
- **Side effects** → Optic neuritis, Peripheral neuropathy and Hyperuricemia.

Second Line drugs (Less Efficacy)

Aminoglycosides

- Streptomycin is the first antibiotic effective in the treatment of tuberculosis.
- Is no longer considered as a first line drug by because of high rates of resistance.

Para-Amino Salicylic acid

- Amino group abolish the analgesic effect of salicylic acid and important to act as anti TB.
- **Side effects** → Allergy, GIT disturbance, Hepatotoxicity and nephrotoxicity.

Cycloserine

- It act as antimetabolite → Inhibit alanine amino acid → which is important in cell wall.

Side effects → Allergy, GIT disturbance and CNS disorders (Psychosis)

Ethionamide

- This is a structural analog of isoniazid.
- The action may be through disruption of mycolic acid.

Side effects → Allergy, GIT disturbance and Hepatotoxicity.

Fluoroquinolones

- The fluoroquinolones, such as moxifloxacin and levofloxacin, have an important place in the treatment of multidrug-resistant tuberculosis.

Macrolides

- The macrolides, such as azithromycin and clarithromycin, are part of the regimen that includes ethambutol and rifabutin used for the treatment TB.

Standard treatment of TB

- INH, Rifampicin, Pyrazinamide and Ethambutol for 2 months → Followed by INH, Rifampicin for 4 months.

Anti-Lepral drugs

- Infection dose of **leprosy** (Hansen's disease) → Small number of ***Mycobacterium leprae.***
- Approximately 70 percent of all cases in the world are located in India.

Dapsone (Dapsone®)

- Is structurally related to the sulfonamides and similarly inhibits folate synthesis via dihydropteroate synthetase inhibition.

Clofazimine (Lamprene®)

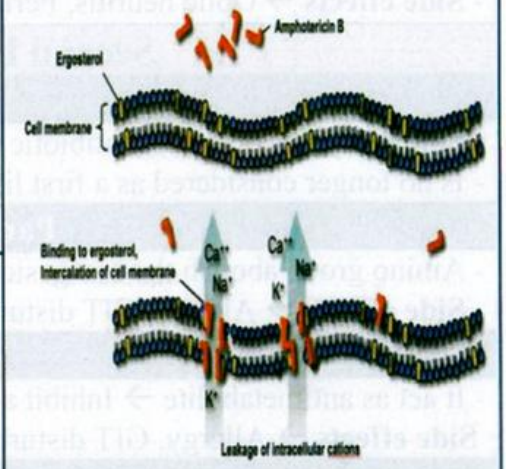
- Clofazimine is a phenazine dye that binds to DNA and prevents it from serving as a template for future DNA replication.

Antifungal Drugs

A) Systemic antifungal for systemic infection

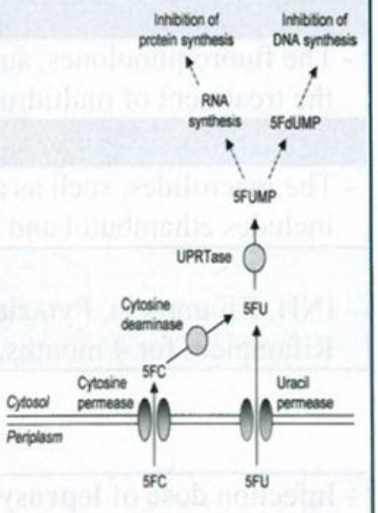
Amphotericin B (Fungizone®)

Pharmacokinetics	- Poorly absorbed orally (Given IV infusion). - Poor penetrate to CSF (penetrate CSF by intrathecal injection).
Mechanism of action	- Bind to ergosterol in the cell membrane → forming pores → the electrolytes and cell constituents leak from the cell → Cell death. - Broad spectrum antifungal (Fungicidal or Fungistatic).
Side effects	- Low therapeutic index - Hypotension and Hypokalemia - Fever, convulsion - **Nephrotoxicity** - Anemia and Anaphylaxis - Irritant → Thrombophlebitis



Flucytosine (Ancobon®)

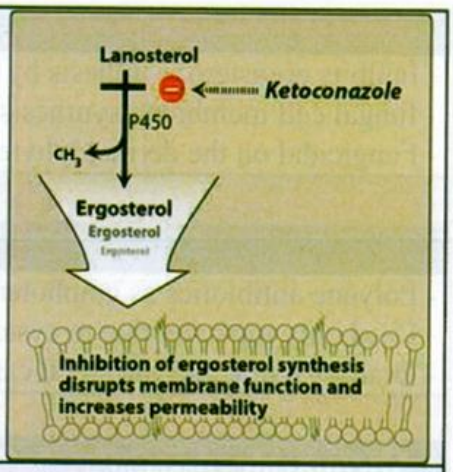
Pharmacokinetics	- Absorbed orally and pass BBB.
Mechanism of action	**Two major mechanisms of action have been elucidated (fungistatic) :** **1:** Drug is intrafungally converted into the **cytostatic fluorouracil** that undergoes further steps of activation and finally interacts as **5-fluorouridinetriphosphate** with RNA biosynthesis and disturbs the building of certain essential proteins. **2:** Drug is intrafungally converted into conversion into → **5-fluorodeoxyuridinemonophosphate** which inhibits fungal DNA synthesis.
Side effects	- GIT disturbance and sever entero-colitis - Hepatic dysfunction. - Neutropenia and thrombocytopenia



Azoles

Ketoconazole (Nizoral®)	**Itraconazole** (Sporanox®)
Fluconazole (Diflucan®)	**Voriconazole** (Vfend®)
Pharmacokinetics	- Ketoconazole and Itraconazole → Orally and Topically - Fluconazole and Voriconazole → Orally and IV - Fluconazole Penetrate CNS (Drug of choice in Fungal meningitis)

Mechanism of action	- Block cytochrome P450 which is responsible for demethylation of lanosterol into ergosterol → Decrease ergosterol synthesis → Disruption of cell membrane function. - Some of research suggests ketoconazole (2%) shampoo may be beneficial in men suffering from androgenic alopecia. - Itraconazole used in Aspergillosis.
Side effects	**→ Side effects of Ketoconazole** - Allergy, GIT disturbance, Gynecomastia and Impotence. - Hepatic dysfunction and Liver microsomal enzyme inhibitor. **→ Side effects of other Azoles** - Less side effects than ketoconazole. - Fluconazole → No endocrine side effects.



Flucytosine + Ketoconazole → Additive effect
Flucytosine + Amphotericin B → Antagonism effect

Echinocandins

Caspofungin (Cancidas®)

- It is a member of a new class of antifungals termed the echinocandins.

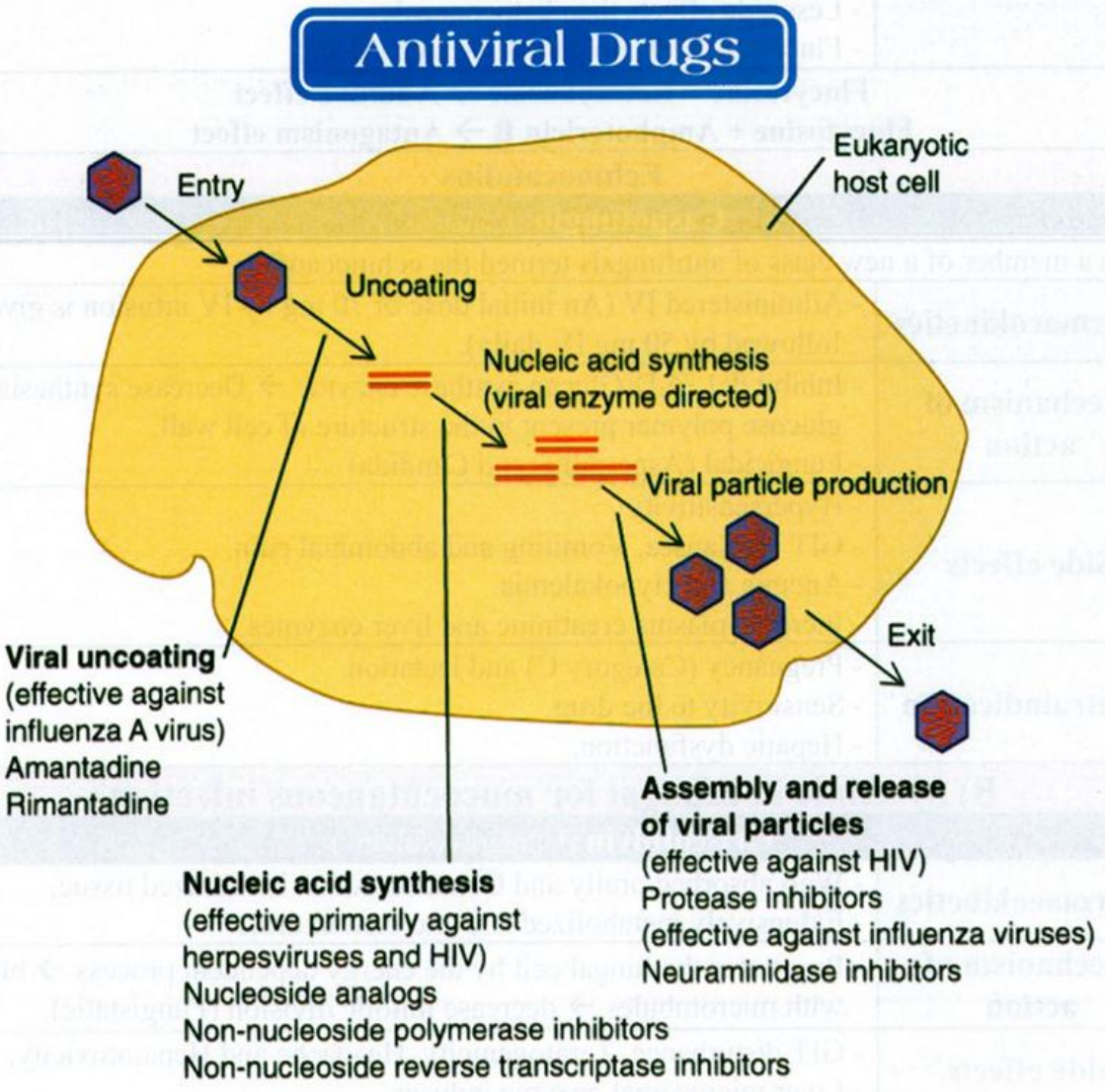
Pharmacokinetics	- Administered IV (An initial dose of 70 mg by IV infusion is given followed by 50 mg IV daily).
Mechanism of action	- Inhibit β(1,3)-D-Glucan synthase enzyme → Decrease synthesis of glucose polymer present in the structure of cell wall. - Fungicidal (Aspergillus and Candida)
Side effects	- Hypersensitivity - GIT → Nausea, Vomiting and abdominal pain. - Anemia and Hypokalemia - Increase plasma creatinine and liver enzymes.
Contraindication	- Pregnancy (Category C) and lactation. - Sensitivity to the drug. - Hepatic dysfunction.

B) Systemic antifungal for mucocutaneous infection

Griseofulvin (Ultragriseofulvin®)

Pharmacokinetics	- Well absorbed orally and Concentrated in keratinized tissue. - Extensively metabolized and excreted in urine.
Mechanism of action	- Penetrates the fungal cell by the energy dependent process → bind with microtubules → decrease mitotic division (Fungistatic).
Side effects	- GIT disturbance, Teratogenicity, Headache and Hepatotoxicity. - Liver microsomal enzyme inducer.

Terbinafine (Lamisil®)		
- Inhibits ergosterol synthesis by inhibiting squalene epoxidase, an enzyme that is part of the fungal cell membrane synthesis pathway (not act on P450). - Fungicidal on the dermatophytes group of fungi.		
C) Topical antifungal drugs		
Nystatin (Mycostatin®)		
- Polyene antibiotics as amphotericin B. - Used only topically due to systemic toxicity. - Orally for oral and intestinal candidiasis and locally on skin or vagina.		
Topical Azoles		
Miconazole (Daktarin®)	**Econazole**	**Clotrimazole**
Others		
Tolnaftate	**Whitfield ointment**	**Undecylenic acid**



A) For respiratory virus infection

1- Neuraminidase inhibitors

Oseltamivir (Tamiflu®) | **Zanamivir** (Relenza®)

- Orthomyxoviridae are a family of RNA viruses that includes five genera: Influenzavirus A, Influenzavirus B, Influenzavirus C, Isavirus and Thogotovirus.
- Orthomyxoviruses that cause influenza contain the enzyme neuraminidase, which is essential to the life cycle of the virus.
- **Mechanism** → inhibits neuraminidase enzyme.
- Administered within the first 24 to 48 hours after the onset of infection.
- **Side effects of Oseltamivir** → GIT discomfort and nausea.
- Zanamivir not used in asthmatic patient due to bronchospasm effect.

2- Inhibitors of viral uncoating

Amantadine (Adamine®) | **Rimantadine** (Rymanta®)

- Amantadine is no longer recommended for treatment of influenza A infection.
- For the 2008/2009 flu season, the United States' Centers for Disease Control and Prevention (CDC) found that 100% of seasonal H3N2 and 2009 pandemic flu samples tested have shown resistance to Amantadine.
- The CDC issued an alert to doctors to prescribe the neuraminidase inhibitors oseltamivir and zanamivir instead of amantadine and rimantadine for treatment of current circulating flu

3- Ribavirin

Ribavirin (Riba®)

- Ribavirin is a synthetic guanosine analog.
- Effective orally, aerosol and intravenously.
- It is effective against a broad spectrum of RNA and DNA viruses.
- Ribavirin is also effective in chronic hepatitis C infections when used in combination with interferon.
- **Mechanism** → drug is first converted to the 5'-phosphate derivatives, the major product being the compound ribavirin-triphosphate, which exerts its antiviral action by inhibiting guanosine triphosphate formation, preventing viral mRNA capping, and blocking RNA-dependent RNA polymerase (This mechanism in influenza viruses only).
- **Side effects** → Dose-dependent transient anemia, increase bilirubin in serum and teratogenic effect.

B) For Hepatic Viral Infections

- The hepatitis viruses thus far identified A, B, C, D, and E. each have a pathogenesis specifically involving replication in and destruction of hepatocytes.
- Hepatitis B and hepatitis C are the most common causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma and are the only hepatic viral infections for which therapy is currently available.
- Hepatitis A is a commonly encountered infection, but it is not a chronic disease.

Interferon (Avonex®)

- Interferons (IFNs) are proteins made and released by host cells in response to the presence of pathogens such as viruses, bacteria, parasites or tumor cells.
- Interferons are named after their ability to "interfere" with viral replication within host cells.
- The interferons are synthesized by recombinant DNA technology.
- At least three types of interferon exist, α, β, and γ.
- **Mechanism** → incompletely understood. It appears to involve the induction of host cell enzymes that inhibit viral RNA translation, ultimately leading to the degradation of viral mRNA and tRNA.
- Not active orally (Administrated IV, IM or SC - 3 times weekly).
- **Side effects** →
  - Flu-like symptoms on injection (fever, chills, myalgias, arthralgias, and GIT disturbances).
  - Fatigue, mental depression and weight loss.
  - Bone marrow suppression.
  - Autoimmune disorders such as thyroiditis (Rare).
  - Cardiovascular problems (Rare).
  - Acute hypersensitivity reactions and hepatic failure (Rare).

Lamivudine (Zeffix®)

- Well absorbed orally.
- For the treatment of adults with **Hepatitis B Virus** (HBV), the dose is 100mg once daily.
- For adults with **Human Immunodeficiency Virus** (HIV), the dose is 300mg once daily or 150mg twice a day (never used on its own in the treatment of HIV).
- This cytosine analog is an inhibitor of both HBV DNA polymerase and HIV reverse transcriptase.

Adefovir (Hepsera®)

- Well absorbed orally (Once daily).
- It is used for treatment of hepatitis B.
- Is a nucleotide analog that is phosphorylated to adefovir diphosphate, which is then incorporated into viral DNA → this leads inhibition of DNA synthesis and prevents viral replication.

Entecavir (Baraclude®)

- Well absorbed orally (Once daily).
- It is used for treatment of hepatitis B and HIV.
- Effective against lamivudine-resistant strains of HBV.
- Is a Guanosine analog → effectively phosporylated to the active triphosphate form → competes with the natural substrate deoxyguanosine triphosphate → inhibiting reverse transription actions of HBV polymerase.

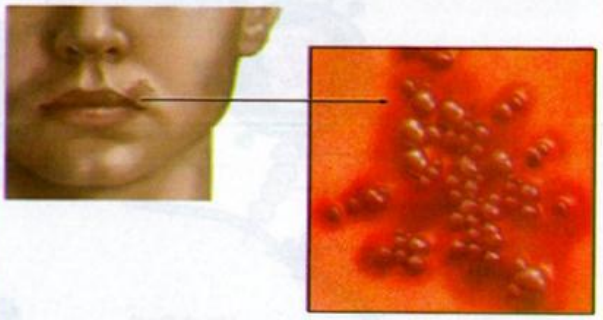
Telbivudine (Tyzeka®)

- Well absorbed orally (Once daily).
- It is used for treatment of hepatitis B.
- is a thymidine analog.

B) For Herpes Virus Infections

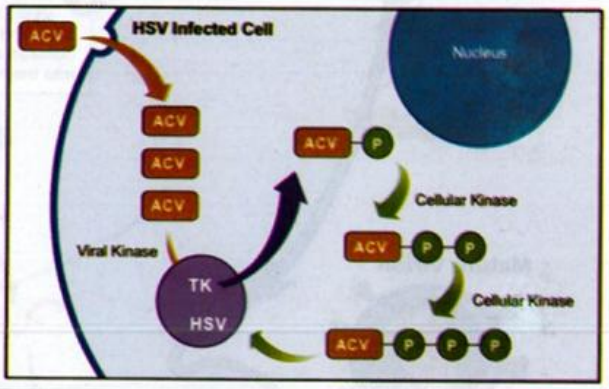
Acyclovir (ACV) (Zovirax®)

- Acyclovir (Acycloguanosine) is the prototypic antiherpetic therapeutic agent.
- It has a greater specificity than vidarabine against herpesviruses. Herpes simplex virus (HSV), varicella-zoster virus (VZV), and some Epstein-Barr virus.
- Drug of choice in HSV encephalitis.
- most common used in genital herpes infections



- Administration → IV, oral or topically.
- Distribution → All over the body (including CSF).

- **Mechanism of action (Activation of Acyclovir)** → Acyclovir is a guanosine analog → monophosphorylated in the viral cell by the Thymidine kinase enzyme (Acyclovir monophosphate) → converted to the di- and triphosphate by Cellular kinase → Acyclovir tri-phosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase and is itself incorporated into the viral DNA.



- **Adverse effects** (Depend on the route of administration) → local irritation (topical), headache, diarrhea, nausea, and vomiting (Oral)

Cidofovir (Vistide®)

- Injectable antiviral medication for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS.
- **Adverse effects** → Nephrotoxic (Probenecid is prescribed to prevent this nephrotoxicity.

Fomivirsen (Vitravene®)

- Limited used in treatment of cytomegalovirus (CMV).

Foscarnet (Foscavir®)

- Unlike most of the antiviral agents (Not required to activation).
- Used to treat herpes viruses, including drug resistant cytomegalovirus (CMV)

Ganciclovir (Cymevene®)

- Ganciclovir is an analog of acyclovir that has 8- to 20-times greater activity against CMV.
- Used in treatment or prevent CMV retinitis in patients with AIDS.
- **Adverse effects** (severe) → dose-dependent neutropenia, carcinogenic and teratogenic.

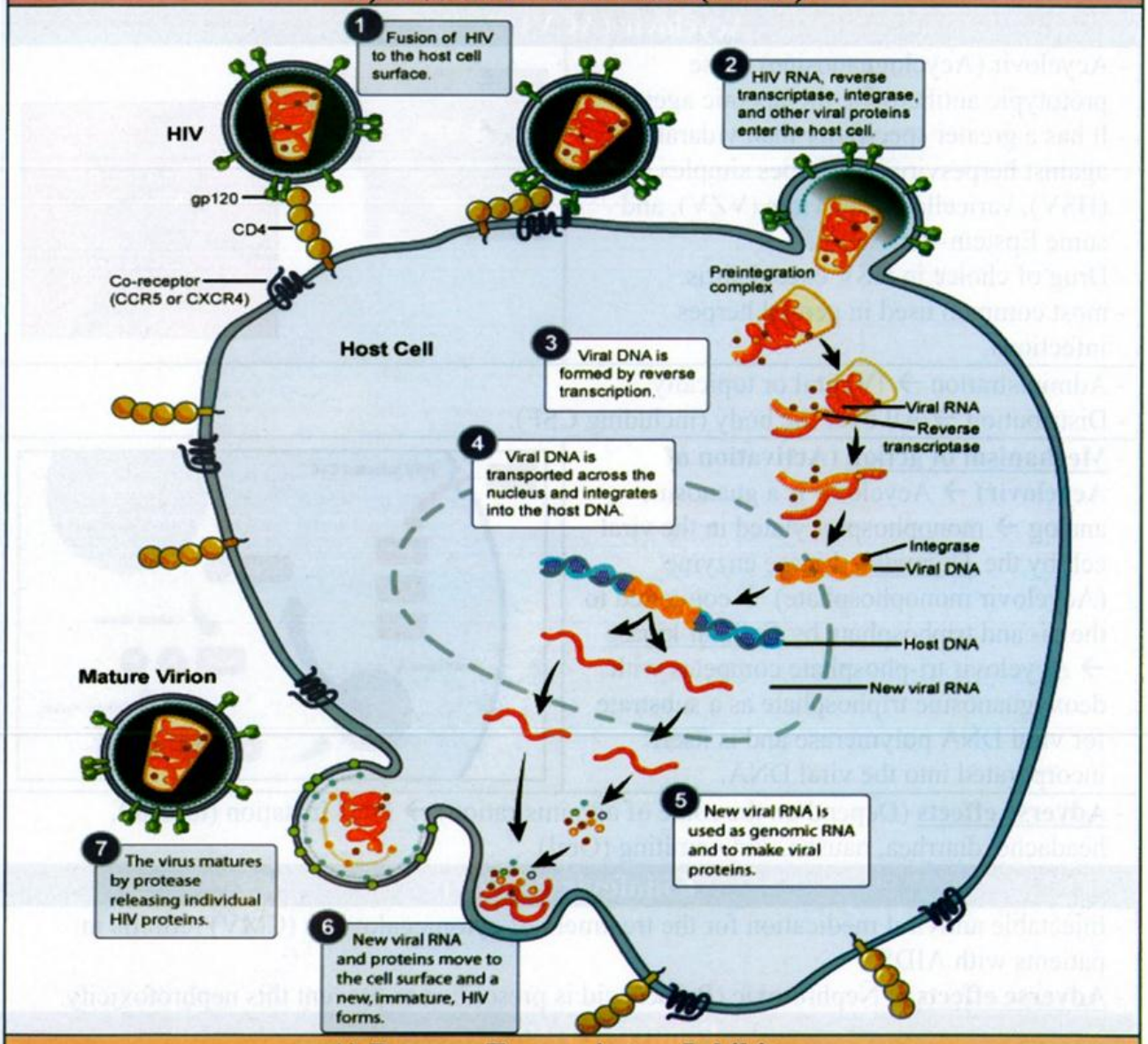
Famciclovir (Famvir®)

- Famciclovir is indicated for the treatment of herpes zoster and treatment of herpes simplex.

Vidarabine (Vira-A®) | Trifluridine (Viroptic®)

- Used to treat herpes viruses

B) For HIV Infections (AIDS)



A) Reverse Transcriptase Inhibitors

1- Nucleoside reverse-transcriptase inhibitors (NRTIs)

Zidovudine (Retrovir®)	- The first drug approved by the FDA for the treatment of HIV.
Didanosine (Videx®)	- The second FDA-approved antiretroviral drug.
Zalcitabine (Hivid®)	- This drug has been discontinued by the manufacturer.
Stavudine (Zerit®)	- Is an analog of thymidine.
Abacavir (Ziagen®)	- Is an analog of guanosine.
Lamivudine (Zeffix®)	- It is approved for the treatment of both HIV and hepatitis B.
Emtricitabine (Emtriva®)	- Approved for the treatment of HIV and undergoing clinical trials for hepatitis B.
Entecavir (Baraclude®)	- It is approved for the treatment of both HIV and hepatitis B.
Apricitabine	- FDA approval in 2011.

2- Nucleotide reverse-transcriptase inhibitors (NtRTIs)		
Tenofovir (Viread®)	- It is approved for the treatment of HIV.	
3-Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)		
Efavirenz (Sustiva®)	**Delavirdine** (Rescriptor®)	**Etravirine** (Intelence®)
Nevirapine (Viramune®)	- Approved by the FDA in 2008.	
Rilpivirine (Edurant®)	- Approved by the FDA in May 2011.	

B) Protease Inhibitors

- All the drugs in this group are reversible inhibitors of the HIV aspartyl protease the viral enzyme responsible for cleavage of the viral polyprotein into a number of essential enzymes and several structural proteins.

Saquinavir (Invirase®)	**Ritonavir** (Norvir®)	**Indinavir** (Crixivan®)
Nelfinavir (Viracept®)	**Amprenavir** (Agenerase®)	**Lopinavir** (Kaletra®)
Atazanavir (Reyataz®)	**Fosamprenavir** (Telzir®)	**Tipranavir** (Aptivus®)
Darunavir (Prezista®)		

C) Entry Inhibitors

Enfuvirtide (Fuzeon®)

- Enfuvirtide is the first of new class of antiretroviral drugs known as entry inhibitors.
- Enfuvirtide is a fusion inhibitor.
- Used in combination therapy for the treatment of HIV.

Maraviroc (Selzentry®)

- Maraviroc is the second entry inhibitor.
- Well absorbed orally.
- Maraviroc blocks the CCR5 coreceptor that works together with gp41 to facilitate HIV entry through the membrane into the cell.

D) Integrase Inhibitors

Raltegravir (Isentress®)

- Raltegravir is the first of new class of antiretroviral drugs known as integrase inhibitors.
- Ragtegravir specifically inhibits the final step in integration of stand transfer of the viral DNA into our own host cell DNA.

E) Combination therapy

Two nucleotide/nucleoside Reverse Transcriptase Inhibitors

Plus

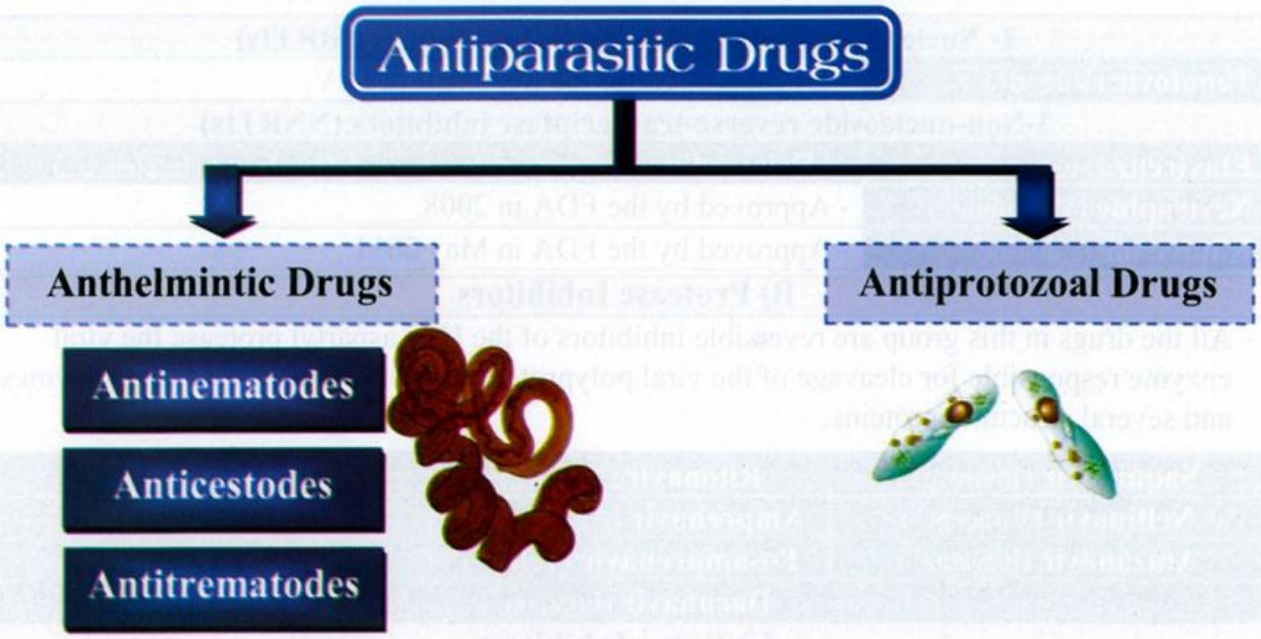
One protease inhibitor

OR

One non-Nucleoside Reverse Transcriptase Inhibitors

OR

One Integrase Inhibitors



- Parasite infection caused by pathogenic protozoa or helminths (Worms).
- Antiparasitics are a class of medications which are indicated for the treatment of parasitic diseases such as nematodes, cestodes, trematodes, infectious protozoa, and amoebas.
-Three major groups of helminths (worms) the nematodes, trematod, and cestodes infect humans.

Anti-Nematodes

- Drugs used to kill Nematode (Round Worm).

Nematode (Round Worm)			
	Type of worm	**Name of worm**	**Disease**
Intestinal Nematode	**Hookworms**	***Ancylostoma duodenale***	Ancylostomiasis
		Necator americanus	Necatoriasis
	Roundworms	***Ascaris lumbricoides***	Ascariasis
	Pinworms	***Enterobius vermicularis***	Enterobiasis
	Threadworms	***Strongyloides stercoralis***	Strongyloidiasis
	Whipworms	***Trichuris trichiura***	Trichuriasis
Tissue Nematode		***Trichinella Spiralis***	Trichinosis
		Wuchereria bancrofti	Filariasis, Wuchereriasis or Elephantiasis
		Brugia malayi	
		Loa loa	
		Dipetalonema perstans	
		Mansonella ozzardi	
		Dracunculus medinensis	Dracunculiasis

Mebendazole (Antiver®)

- Synthetic benzimidazole compound and effective against a **wide spectrum of nematodes**.
- Mebendazole acts by binding to and interfering with the assembly of the parasites microtubules and also by decreasing glucose uptake → Depletion of energy in the worm.
- Drug of choice in the treatment of infections by whipworm, pinworm, hookworms, and roundworm.
- Contraindicated in Pregnancy.

Flubendazole (Fluvermal®)

- It is an analogue of Mebendazole (Same uses and mechanism)

Pyrantel pamoate

- Effective in the treatment of infections caused by roundworms, pinworms, and hookworms.
- It acts as a depolarizing, neuromuscular-blocking agent, causing sudden contraction, followed by paralysis → Paralysis of worm.

Thiabendazole (Mintezol®)

- Synthetic benzimidazole is effective against strongyloidiasis caused by ***Strongyloides stercoralis*** (Threadworm) and early stages of trichinosis.
- **Adverse effects** → dizziness, anorexia, nausea, vomiting and Stevens-Johnson syndrome.
- Contraindicated in Pregnancy.

Ivermectin (Ivactin®)

- Ivermectin [eye-ver-MEK-tin] is the drug of choice for the treatment of onchocerciasis (river blindness) caused by ***Onchocerca volvulus.***
- First choice for cutaneous larva migrans and strongyloides.
- The drug binds and activates glutamate-gated chloride channels (GluCls) → Chloride influx and hyperpolarization occurs → resulting in paralysis of the worm.
- Contraindicated in Pregnancy.

Diethylcarbamazine (Hetrazan®)

- Used in the treatment of filariasis.
- Inhibit arachidonic acid metabolism in filarial microfilaria. This makes the microfilaria more susceptible to immune attack.

Anti-Cestodes

Cestode (Tapeworms)			
	Type of worm	**Name of worm**	**Disease**
Intestinal Cestoda	**Fish worm**	***Diphyllobothrium latum***	Diphyllobothriasis
	Beef tapeworm	***Taenia saginata***	Taeniasis saginata
	Pork tapeworm	***Taenia solium***	Taeniasis solium
	Dwarf tapeworm	***Hymenolepis nana***	Hymenolepiasis
	Rat tapeworm	***Hymenolepis diminuta***	Hymenolepiasis
Tissue Cestoda		***Echinococcus granulosus***	Hydatid disease or Hydatidosis
		Coenurus cerebralis ***Coenurus serialis***	Coenurus disease

Niclosamide (Yomesan®)

- Is the drug of choice for most cestode (tapeworm) infections.
- Niclosamide uncouples oxidative phosphorylation in the tapeworm (Block respiration).

Albendazole (Bendax®)

- Inhibits microtubule synthesis and glucose uptake in nematodes.
- Effective against many types of worm (Broad spectrum).
- Treatment of cestodal infestations, such as cysticercosis (tissue infection after exposure to eggs of ***Taenia solium***) and hydatid disease.
- **Therapy :**
  - 1-3 days for nematodal infestations.
  - 3 months for hydatid disease (risk of hepatotoxicity)
- Contraindicated in Pregnancy.

Anti-Trematodes

Trematoda (Flukes) Flatworms (Leaf-shaped)		
Type of worm	**Name of worm**	**Disease**
Liver flukes	***Fasciola gigantic***	Fascioliasis or liver rot.
	Fasciola hepatica	
Intestinal flukes	***Heterophyes heterophyes***	Heterophyiasis
Blood flukes	***Schistosoma haematobium***	(Schistosomiasis) Urinary bilharziasis
	Schistosoma mansoni	(Schistosomiasis) Intestinal bilharziasis

Praziquantel (Biltricide®)

- Drug of choice for treatment of all forms of schistosomiasis.
- Used in treatment of Cestode infections.
- Act by increase membrane permeability of Ca^{2+} in the worm → Increase contraction → Paralysis of the worm.
- Rapidly absorbed by oral route.
- Distributed at all over the body and CSF.
- Extensively metabolized (Short half-life).
- **Side effects** → Drowsiness, dizziness, malaise, anorexia and GIT disturbance.
- **Dose** (taken with food or a few minutes before a meal)

→ For Schistosomiasis, the dose is 20 mg/kg every 4-6 hours for one day.
→ For liver fluke, the dose is 25 mg/kg every 4-6 hours for one day.
→ For tapeworms, the dose is 5–25 mg/kg once.

- **Drug interaction** → Rifampicin, Carbamazepine, phenytoin, Chloroquine and Cimetidine.

Levamisole (Katrex®)

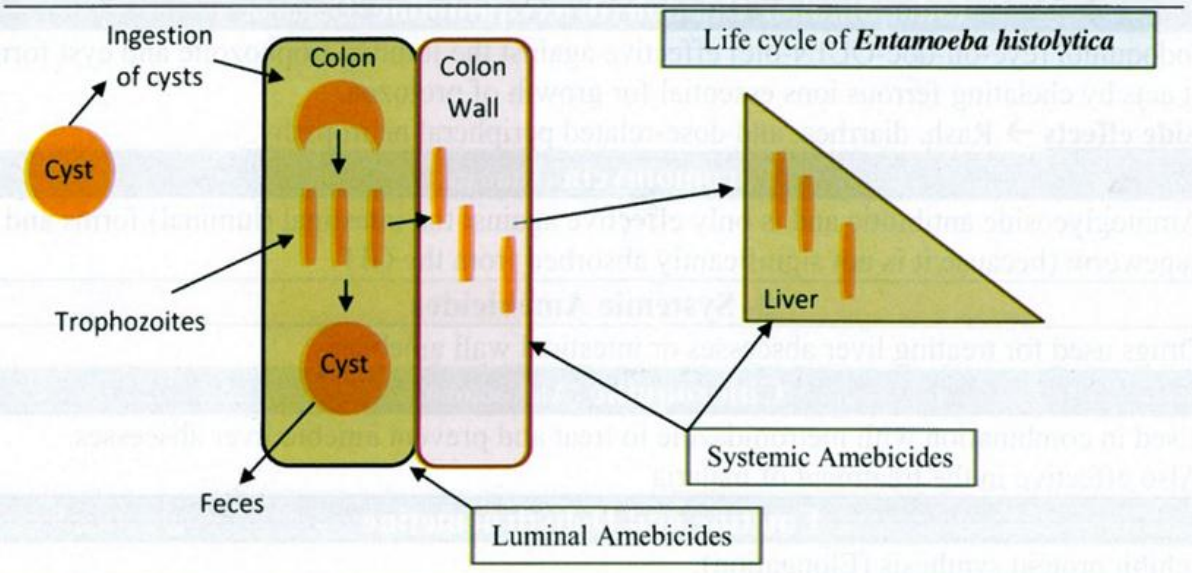
- Is an Anti-helminthic and immunostimulant used in colon cancer.

Anti-Protozoals

Protozoa (Unicellular microorganism)	
Name of Protozoa	**Disease**
Entamoeba histolytica	Amoebiasis
Giardia lamblia	Giardiasis
Trichomonas vaginalis	Vaginitis or Trichomoniasis
Trypanosoma brucei gambiense	Gambian Trypanosomiasis or West African sleeping sickness.
Trypanosoma brucei rhodesiense	Rhodesian Trypanosomiasis or East African sleeping sickness.
Trypanosoma cruzi	American Trypanosomiasis (Chagas disease)
Leishmania donovani	Visceral leishmaniasis
leishmania infantum	Cutaneous leishmaniasis
Plasmodium	Malaria
Toxoplasma Gondii	Toxopasmosis

A) For Amebiasis

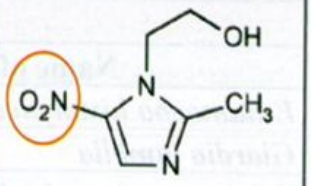
- Amebiasis (Amebic dysentery or Amoebiasis) is an infection of the intestinal tract caused by ***Entamoeba histolytica***.
- **Classification of Antiamoebic drugs**
  - **Luminal amebicides:**
    - These drugs get their name because they act on organisms within the inner cavity (lumen) of the bowel.
  - **Systemic amebicides:**
    - Effective against amebas in the colon wall and liver.
  - **Mixed amebicides:**
    - Effective against both the luminal and systemic.



1- Mixed Amebicides

Metronidazole (Flagyl®)

- Drug of choice for →
  - Amebiasis (***Entamoeba histolytica)***
  - Giardiasis (***Giardia lamblia)***
  - Trichomoniasis or Vaginitis (***Trichomonas vaginalis)***
  - Pseudomembranous colitis ***(Clostridium difficile)***
  - Anaerobic cocci, and anaerobic gram -ve bacilli.



- **Pharmacokinetics:**
  - Well absorbed orally
  - Distributed all over the body
    - Concentrated in CSF, Saliva, Milk, Vaginal secretion, Seminal fluid.
  - Metabolized in liver
  - Excreted in urine
- **Mechanism of action:**
  - The nitro group reduced by the protozoal "pyruvate ferredoxin oxidoreductase enzyme" → The reduced form interact with DNA resulting → breakage of helical structure of DNA.
- **Adverse effects:**
  - GIT disturbance and Allergy
  - Metallic taste
  - Headache, dizziness and vertigo
  - Neutropenia
  - Disulfiram like reaction

Tinidazole (Fasigyn®)

- Similar to metronidazole in spectrum of activity, absorption and adverse effects.
- Used for treatment of amebiasis, amebic liver abcess, giardiasis, and trichomoniasis.

2- Luminal Amebicides

Iodoquinol or Diiodohydroxyquinoline (Diquinol®)

- Iodoquinol [eye-oh-doe-QUIN-ole] effective against the luminal trophozoite and cyst forms.
- It acts by chelating ferrous ions essential for growth of protozoa.
- **Side effects** → Rash, diarrhea, and dose-related peripheral neuropathy.

Paromomycin (Humatin®)

- Aminoglycoside antibiotic and is only effective against the intestinal (luminal) forms and tapeworm (because it is not significantly absorbed from the GIT.

3- Systemic Amebicides

- Drugs used for treating liver abscesses or intestinal wall amebiasis.

Chloroquine (Alexoquine®)

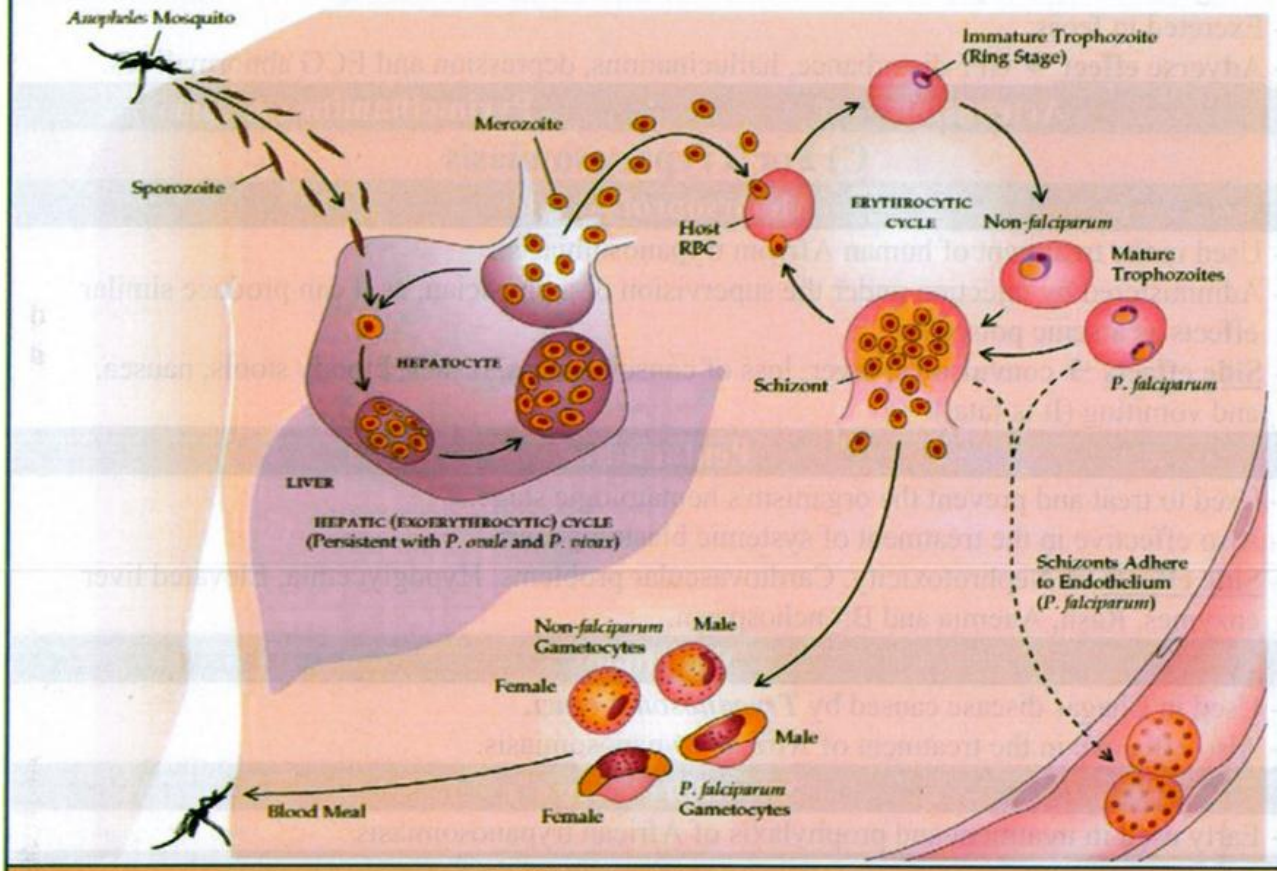
- Used in combination with metronidazole to treat and prevent amebic liver abscesses.
- Also effective in the treatment of malaria

Emetine and Dehydroemetine

- Inhibit protein synthesis (Elongation).

B) For Malaria

- Malaria is an acute infectious disease caused by four species of the protozoal genus Plasmodium.
- The parasite is transmitted to humans through the bite of a female Anopheles mosquito.
- ***Plasmodium malariae*** → Is common.
- ***Plasmodium ovale*** → Is rarely.
- ***Plasmodium falciparum*** → Capillary obstruction and death.
- ***Plasmodium vivax*** → Milder form of the disease.



1- Tissue schizonticide

Primaquine

- is a synthetic **8-aminoquinoline**.
- Primaquine is not effective against the erythrocytic stage of malaria.
- **Adverse effects** → Hemolytic anemia in patients with genetically deficiency of glucose-6-phosphate dehydrogenase.

2- Blood schizonticide

Chloroquine (Alexoquine®)

- is a synthetic **4-aminoquinoline**.
- Drug of choice in the treatment of **Erythrocytic *Plasmodium falciparum*** malaria.
- Chloroquine specifically binds to heme, preventing its polymerization to hemozoin. The increased pH and the accumulation of heme result in oxidative damage to the membranes, leading to lysis of both the parasite and the red blood cell.

- **Adverse effects** →
  - GIT disturbance, Dermatitis, Headache, Peripheral neuritis and Blurred vision.

Quinine

- Mechanism same as → Chloroquine
- **Adverse effect of Quinine** → **Cinchonism**, GIT disturbance and fetotoxic.

Mefloquine (Malariquin®)

- Well absorbed orally and concentrates in the liver and lung.
- Long half-life (17 days).
- Excreted in feces.
- **Adverse effect** → GIT disturbance, hallucinations, depression and ECG abnormalities.

Artemisinin | **Pyrimethamine** (Daraprim®)

C) For Trypanosomiasis

Melarsoprol (Mel B®)

- Used in the treatment of human African trypanosomiasis.
- Administered by injection under the supervision of a physician, as it can produce similar effects as arsenic poisoning.
- **Side effects** → convulsions, fever, loss of consciousness, rashes, bloody stools, nausea, and vomiting (It is fatal)

Pentamidine

- Used to treat and prevent the organism's hematologic stage.
- Also effective in the treatment of systemic blastomycosis.
- **Side effects** → Nephrotoxicity, Cardiovascular problems, Hypoglycemia, Elevated liver enzymes, Rash, Anemia and Bronchospasm.

Nifurtimox

- Used in Chagas disease caused by ***Trypanosoma cruzi.***
- Also effective in the treatment of African trypanosomiasis.

Suramin (Antrypol®)

- Early used in treatment and prophylaxis of African trypanosomiasis.

Benznidazole (Rochagan®)

- Inhibits protein synthesis.
- Used in Chagas disease caused by ***Trypanosoma cruzi***.

D) For Leishmaniasis

Sodium stibogluconate (Pentostam®)

- Used to treat leishmaniasis.
- Administration → Slow IV infusion only (100 ml multi-dose glass bottles)

E) For Toxoplasmosis

Pyrimethamine (Daraprim®)

- Inhibit dihydrofolate reductase (DHFR) enzyme → Decrease folic acid synthesis.

F) For Giardiasis

Metronidazole (Flagyl®) | **Tinidazole** (Fasigyn®) | **Nitazoxanide** (Nitaxide®)

Cancer Chemotherapy

➢ Definition :-

- Cancer is one of a large number of diseases characterized by the development of abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal body tissue. Cancer also has the ability to spread throughout the body.

➢ Symptoms :-

- Fatigue
- Thickening under the skin
- Weight changes
- Skin color changes
- Changes in bowel or bladder habits
- Persistent cough
- Difficulty swallowing
- Hoarseness
- Discomfort after eating
- Muscle or joint pain
- Unexplained and persistent fevers or night sweats

Lung Cancer Symptoms

➢ Causes :-

- Chemical carcinogen e.g. Smoking and Alcohol
- Infection
- Radiation
- Genetically
- Hormones

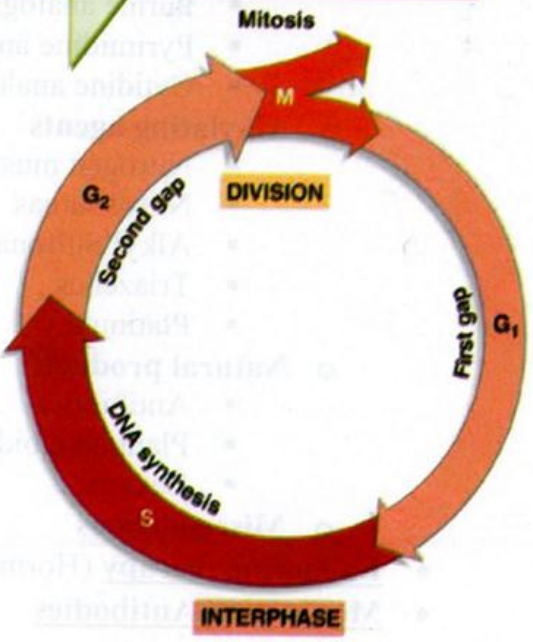
All of these lead to → **Gene mutations**

➢ Gene Mutation :-

- Rapid growth cell and divide more rapidly.
- Uncontrolled cell growth.
- Mistakes (Errors) in DNA repairing.

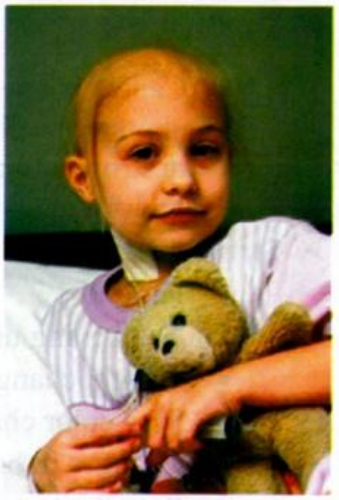
➢ Cell cycle regulation :-

G_1	Cells increase in size in Gap 1. The G1 checkpoint control mechanism ensures that everything is ready for DNA synthesis.
S	DNA replication occurs during this phase.
G_2	The G2 checkpoint control mechanism ensures that everything is ready to enter the M phase.
M	A checkpoint in the middle of mitosis ensures that the cell is ready to complete cell division.



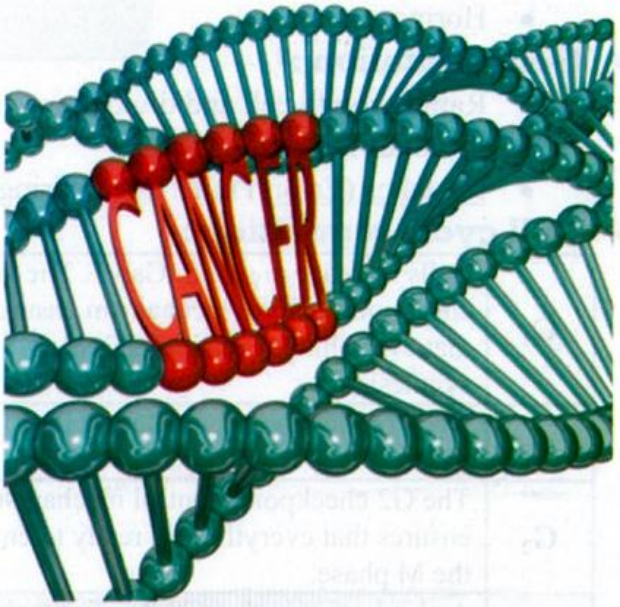
➢ Problems associated with cancer chemotherapy :-

- **Resistance** → Some of cancer (neoplastic) cell are resistant to most anticancer drugs.
- **Toxicity of chemotherapeutic agents:**
  - Affect in normal cells especially rapid proliferation cells → e.g. →
    - Buccal mucosa cell
    - Bone marrow
    - GI mucosa
    - Hair follicles
  - Common adverse effects →
    - Sever vomiting (treated by Ondansetron)
    - Stomatitis
    - Alopecia
    - Bone marrow suppression → Anemia.
  - Specific adverse effects
    - Pulmonary toxicity with Bleomycin
    - Allergy and pancreatitis with L-Asparaginase
    - Bladder toxicity (Cystitis) with Cyclophosphamide
    - Cardiac toxicity with Doxorubicin
    - Hepatotoxicity with Cisplatin
    - Neurotoxicity with Vincristine
    - Immunosuppression with Methotrexate and Cyclophosphamide



➢ Anti-neoplastic (Anti-Cancer) Drugs :-

- **Cytotoxic Drugs :**
  - **Antimetabolites**
    - Folic acid analogs
    - Purine analogs
    - Pyrimidine analogs
    - Cytidine analogs
  - **Alkylating agents**
    - Nitrogen mustard
    - Nitrosoureas
    - Alkyl Sulfonates
    - Triazenes
    - Platinum
  - **Natural products**
    - Antibiotics
    - Plant alkaloids
    - Enzymes
  - **Miscellaneous**
- **Endocrine therapy** (Hormone agonist and antagonists)
- **Monoclonal Antibodies**



Cytotoxic Drugs

A) Antimetabolites

- Antimetabolites are structurally related to normal compounds that exist within the cell.
- They generally interfere with normal purine or pyrimidine nucleotide → inhibiting DNA or RNA synthesis. Their maximal cytotoxic effects in S-phase.

1- Folic acid analogs

Methotrexate (Methotrexate®)

- Methotrexate (MTX) is structurally related to folic acid and acts as an antagonist of the folic acids by inhibiting dihydrofolate reductase (DHFR) enzyme.
- Used in combination in lymphocytic leukemia (Cancer in the white blood cells called lymphocytes), Choriocarcinoma (Cancer in placenta), Burkitt's lymphoma (Cancer of the lymphatic system) in children, breast cancer, and head and neck carcinomas (Cancer).
- Low-dose of MTX effective as a single agent against certain inflammatory diseases.

2- Purine analogs

- Inhibits purine nucleotide synthesis and metabolism. This alters the synthesis and function of RNA and DNA.

6-Mercaptopurine (Purinethol®)

- Used in Acute lymphocytic leukemia.
- Also beneficial in the treatment of Crohn's disease (inflammatory bowel disease).

6-Thioguanine (Lanvis®)

- Used in the treatment of Acute leukemia in combination with daunorubicin and cytarabine.

Fludarabine (Fludara®)

- Treatment of Chronic lymphocytic leukemia.

Cladribine (Litak®)

- Effective against hairy cell leukemia, Chronic lymphocytic leukemia (CLL), and non-Hodgkin's lymphoma.

Pentostatin (Nipent®)

- Used to treat hairy cell leukemia.

3- Pyrimidine analogs

5-Fluorouracil (Nipent®)

- 5FU inhibit Thymidylate synthase enzyme → Inhibit DNA synthesis
- Treatment of slowly growing solid tumors e.g. colorectal, breast, ovarian, pancreatic cancer.

Capecitabine (Xeloda®)

- Is a prodrug, that is enzymatically converted to 5-fluorouracil in the tumor.
- First-line drug in Treatment of colorectal cancer.

Floxuridine (FUDR®)

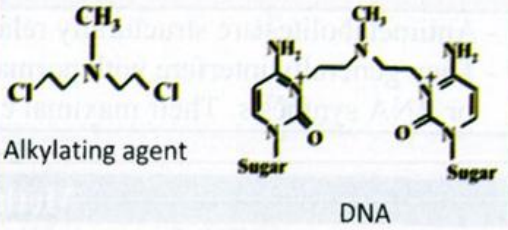
- An analog of 5-fluorouracil used in colorectal cancer.

4- Cytidine analogs

Cytarabine (Aracytin®)	Gemcitabine (Gemzar®)
- Used in acute non-lymphocytic (myelogenous) leukemia.	- First-line treatment of pancreatic cancer. - Used in bladder, lung & breast cancer.

B) Alkylating Agents

- Alkylating agents are very reactive compound → formation of carbocation.
- Carbocation alkylate the important cellular constant e.g. DNA and proteins through the reaction with NH, OH, SH or other group.
- Alkylating agents do not discriminate between cycling and resting cells.



1- Nitrogen mustard

Mechlorethamine

- Mechlorethamine belongs to the group of Nitrogen mustard alkylating agents.
- Used primarily in the treatment of Hodgkin's disease (type of lymphoma) and may use in the treatment of some solid tumors.

Cyclophosphamide (Endoxan®) | Ifosfamide (Holoxan®)

- Treatment of a wide variety of neoplastic diseases e.g. Lymphoma, breast, Lung and ovarian cancer.

Chlorambucil (Leukeran®)

- Mainly used in the treatment of chronic lymphocytic leukemia.

Mephalan (Alkeran®)

- Used to treat multiple myeloma (cancer of plasma cells) and ovarian cancer.

2- Nitrosoureas

- Compounds that include a nitroso (R-NO) group and a urea.
- Inhibit several key enzymatic processes by carbocation of amino acids in proteins in the targeted cells.

Carmustine (BiCNU®) | Lomustine (CeeNU®) | Streptozocin (Zanosar®)

- Cross the blood brain barrier → CNS → Treatment of brain cancer.

3- Alkyl Sulfonates

- Are esters of alkane sulfonic acids with the general formula R-SO2-O-R'.
- They act as alkylating agents.

Busulfan (Myleran®)

- Main uses are in bone marrow transplantation, especially in chronic myelogenous leukemia.

4- Triazenes

- Also known as Triazanylene, is an unsaturated inorganic compound having the chemical formula N_3H_3. It has one double bond.

Dacarbazine (Deticene®)

- Use in the treatment of melanoma (Skin cancers)

Temozolomide (Temodar®)

- The treatment of tumors in the brain (Brain Cancer).
- Recently, Temozolomide has been approved for use against treatment-resistant gliomas and anaplastic astrocytomas (Types of brain tumors).

5- Platinum

Cisplatin (Platinol®) | **Carboplatin** (Paraplatin®) | **Oxaliplatin** (Eloxatin®)

- Cisplatin was the first member of the platinum coordination complex class of anticancer drugs, but because of its severe toxicity, carboplatin was developed.
- Treatment of solid tumors, such as testicular, ovarian and bladder carcinoma.
- **Oxaliplatin** is showing excellent activity against advanced Colorectal cancer.

C) Natural products

1- Cytotoxic Antibiotics

- The antitumor antibiotics → interact with DNA, leading to disruption of DNA function.
- Inhibit topoisomerases (I and II).
- Produce free radicals also play a major role in their cytotoxic effect.

Dactinomycin (Cosmegen®)

- Also known as Actinomycin D.
- First antibiotic to find therapeutic application in tumor chemotherapy.
- Dactinomycin is used in combination with surgery and vincristine for the treatment of Wilms' tumor (cancer of the kidneys that typically occurs in children, rarely in adults).
- In combination with MTX effective in the treatment of gestational choriocarcinoma.

Doxorubicin (Adriamycin®) | **Daunorubicin** (Daunoblastina®)

Epirubicin (Ellence®) | **Idarubicin** (Zavedos®)

- Are classified as anthracycline antibiotics
- Are effective in the S and G_2 phases.
- Doxorubicin is one of the most important and widely used anticancer drugs.
- Daunorubicin and idarubicin are used in the treatment of acute leukemias.
- **Adverse Effects** → Irreversible, dose-dependent **Cardiotoxicity** (more common with Daunorubicin and Doxorubicin.

Bleomycin (Blenoxane®)

- Is a mixture of different copper-chelating glycopeptides that, like the anthracycline.
- Bleomycin is cell-cycle specific and causes cells to accumulate in the G2 phase.
- Cause scission of DNA by an oxidative process.
- Treatment of testicular cancers in combination with Vinblastine or Etoposide.
- Also effective in Squamous cell carcinomas and lymphomas.

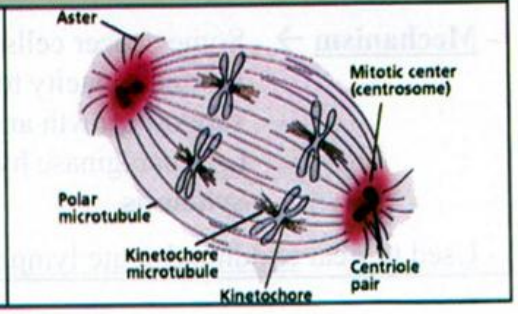
Mitomycin (Mutamycin®)

- Used in solid tumors e.g. bladder, breast, lung and prostate cancer.

2- Plant Alkaloids

I) Microtubule inhibitors

- The mitotic spindle contains system of microtubules composed of the protein tubulin.
- The mitotic spindle is essential for the equal partitioning of DNA.
- Several plant-derived substances used as anticancer drugs disrupt this process by affecting the microtubules.



Vincristine (Oncovin®)	Vinorelbine (Navelbine®)	Vinblastine (Velbe®)

- They are a Vinca alkaloids
- They are generally administered in combination with other drugs.
- **Mechanism** → Tubulin is a structural protein that polymerizes to microtubules. Vinca alkaloid s Binds to tubulin and prevent polymerization.
- **Vincristine (VX)** is used in the treatment of acute lymphoblastic leukemia in children, Wilms' tumor, Ewing's soft-tissue sarcoma, Hodgkin's and non-Hodgkin's lymphomas.
- **Vinblastine (VBL)** is administered with Bleomycin and Cisplatin for the treatment of Testicular cancer and Hodgkin's lymphoma.

Paclitaxel (Taxol®)	Docetaxel (Taxotere®)

- Known as **Taxol**.
- Used in ovarian cancer and breast cancer.
- **Mechanism** →
  - Bind reversibly to the tubulin subunit, but unlike the vinca alkaloids.
  - They promote polymerization and stabilization of the Microtubules.
  - They shift the depolymerization-polymerization process to accumulation of microtubules.
  - The overly stable microtubules formed are nonfunctional.
  - This results in death of the cell.
- Isolated from the wood and bark of Yew tree (***Taxus brevifolia***) which grow in the forests of Western USA and Canada.
- The amount isolated from 3 trees is required for treatment only one cancer patient.
- Docetaxel (Taxotere®) → One vial (2ml) → 3465.90 L.E.

II) Topoisomerase II inhibitors

Etoposide (Lastet®)	Teniposide (Vumon®)

- Known as podophyllotoxin derivatives.
- Inhibits Topoisomerase II → Preventing DNA replication.
- Etoposide is used in lung cancer, testicular cancer, lymphoma and nonlymphocytic leukemia.
- Teniposide is used in the treatment of childhood acute lymphocytic leukemia.

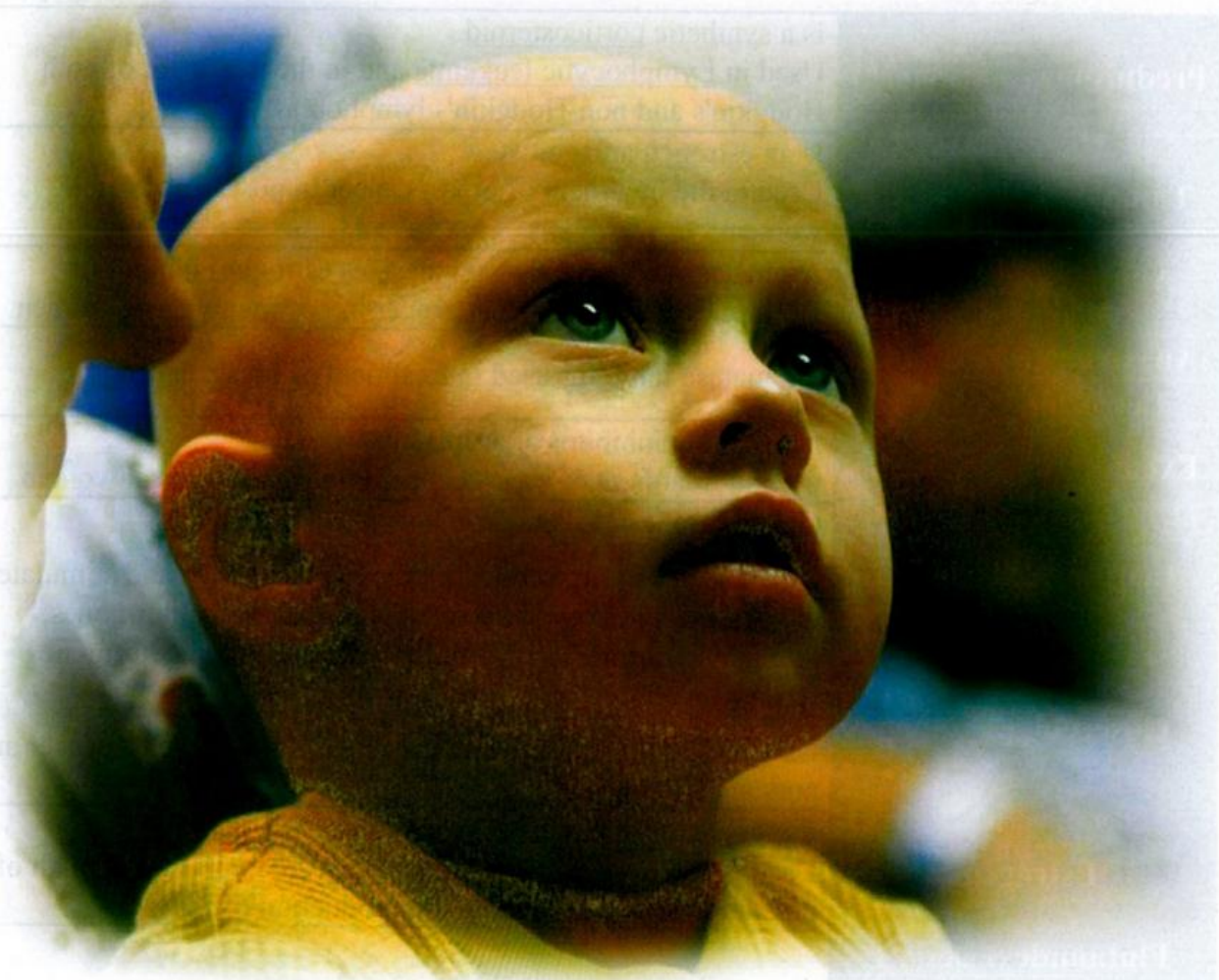
3- Enzymes

L-Asparaginase (Kidrolase®)

- Asparaginase is an enzyme that catalyzes the hydrolysis of asparagine to aspartic acid.
- Asparaginases are naturally produced by microorganisms.
- **Mechanism** →
  - Some cancer cells require an external source of asparagine because of their limited capacity to synthesize sufficient amounts of that amino acid to support growth and function.
  - L-Asparaginase hydrolyzes blood asparagine → Inhibiton of protein synthesis.
- Used to treat childhood acute lymphocytic leukemia in combination with VX.

D) Miscellaneous	
Procarbazine (Natulan®)	Used in the treatment of Hodgkin's disease and other cancers.
Gefitinib (Iressa®)	It is approved for the treatment of non-small cell lung cancer that has failed to respond to other therapy.
Imatinib (Glivec®)	Treatment of chronic myeloid leukemia in blast crisis and GI stromal tumor (Price: 11750 L.E.)
Irinotecan (Campto®)	Used as a first-line drug together with 5-FU and leucovorin for the treatment of colon or rectal carcinoma.
Topotecan (Hycamtin®)	Treatment of ovarian cancer. Also in the treatment of small-cell lung cancer.
Endocrine Therapy	
- Steroid hormones are powerful drivers of gene expression in certain cancer cells, changing the levels or activity of certain hormones can cause certain cancers to cease growing, or even undergo cell death.	
Prednisone (Hostacortin®)	Is a synthetic corticosteroid. Used in Lymphocytic leukemia and in the treatment of both Hodgkin's and non-Hodgkin's lymphomas.
Tamoxifen (Nolvadex®)	Is an estrogen antagonist. Used in the treatment of breast cancer in postmenopausal women.
Aminoglutethimide (Orimeten®)	Aromatase (Enzyme that synthesizes estrogen) inhibitor. Used in treatment of breast cancer in postmenopausal women.
Anastrozole (Arimidex®) **Letrozole** (Femera®)	Aromatase inhibitor used in treatment of breast cancer
Exemestane (Aromasin®)	Irreversible inhibitor of aromatase. used in treatment of breast cancer in postmenopausal women.
Leuprolide (Lupron®)	Gonadotropin-releasing hormone (GnRH) analog. GnRH is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Used in premenopausal women with advanced breast cancer and prostate cancer.
Goserelin (Zoladex®)	
Estrogens	Estrogens are a group of compounds. Used in the treatment of prostatic cancer (inhibit the growth of prostatic tissue by blocking the production of LH).
Flutamide (Eulexin®) **Nilutamide** (Anandron®) **Bicalutamide** (Casodex®)	Are synthetic, non-steroidal anti-androgens. Used in the treatment of prostate cancer.

Monoclonal Antibodies	
- Is the use of monoclonal antibodies (mAb) to specifically bind to target cells or proteins. This may then stimulate the patient's immune system to attack those cells. - Monoclonal antibodies made by fusing cancer cells with the spleen cells from a mouse (Hybridoma).The hybridomas grown in culture medium. By using recombinant technology produce humanized antibodies.	
Rituximab (Mabthera®)	First monoclonal antibody to be approved for the treatment of cancer (Mabthera® 1 Vial 500mg - L.E. 12300.00)
Trastuzumab (Herceptin®)	Its main use is to treat certain breast cancers (Herceptin® 440ml - L.E. 13185.00)
Bevacizumab (Avastin®)	Is the first in a new class of anticancer drugs called antiangiogenesis agents. Use as a first-line drug against metastatic colorectal cancer.



Questions

➢ Coose the best answer :-

184: A 19-year-old male being treated for leukemia develops fever. You give agents that will cover bacterial, viral, and fungal infections. Two days later, he develops acute renal failure. Which drug was most likely responsible?

a. Vancomycin b. Ceftazidime c. Amphotericin B
d. Acyclovir

185: A 26-year-old female with acquired immunodeficiency syndrome (AIDS) develops Cryptococcal meningitis. She refuses all intravenous medication. Which antifungal agent can be given orally to treat the meningeal infection?

a. Ketoconazole b. Amphotericin B c. Fluconazole
d. Nystatin

186: Why is vitamin B6 usually prescribed with isoniazid (INH)?

a. It acts as a cofactor for INH b. It prevents some adverse effects of INH therapy
c. Like INH, it has tuberculostatic activity d. It prevents metabolism of INH

187: The quinolone derivative that is most effective against ***Pseudomonas aeruginosa*** is

a. Norfloxacin b. Ciprofloxacin c. Ofloxacin
d. Enoxacin e. Lomefloxacin

188: A drug primarily used in pneumonia caused by Pneumocystis carinii is

a. Nifurtimox b. Penicillin G c. Metronidazole
d. Trimethoprim/sulfamethoxazole e. Carbenicillin

189: A 19-year-old woman is diagnosed with tuberculosis (TB). Before prescribing a drug regimen, you take a careful medication history because one of the drugs commonly used to treat TB induces microsomal cytochrome P450 enzymes in the liver. Which drug is this?

a. Isoniazid b. Rifampin c. Pyrazinamide
d. Ethambutol e. Vitamin B6

190: The elimination half-life of which of the following tetracyclines remains unchanged when the drug is administered to an anuric patient?

a. Methacycline b. Oxytetracycline c. Doxycycline
d. Tetracycline e. None of the above

191: In the treatment of bacterial meningitis in children, the drug of choice is

a. Penicillin G b. Penicillin V c. Erythromycin
d. Procaine penicillin e. Ceftriaxone

192: In patients with hepatic coma, decreases in the production and absorption of ammonia from the gastrointestinal (GI) tract will be beneficial. The antibiotic of choice in this situation would be

a. Neomycin b. Tetracycline c. Penicillin G
d. Chloramphenicol e. Cephalothin

193: Clavulanic acid is important because it

a. Easily penetrates Gram-negative bacteria
b. Is specific for Gram-positive bacteria
c. Is a potent inhibitor of cell-wall transpeptidase
d. Inactivates bacterial β-lactamases

194: In the treatment of infections caused by *P. aeruginosa*, the antimicrobial agent that has proved to be effective is

a. Penicillin G
b. Piperacillin
c. Nafcillin
d. Erythromycin
e. Tetracycline

195: Ethambutol is administered concurrently with other antitubercular drugs in the treatment of TB in order to

a. Reduce the pain of injection
b. Facilitate penetration of the blood-brain barrier
c. Retard the development of organism resistance
d. Delay excretion of other antitubercular drugs by the kidney
e. Retard absorption after intramuscular injection

196: The most active aminoglycoside against *Mycobacterium tuberculosis* is

a. Streptomycin
b. Amikacin
c. Neomycin
d. Tobramycin
e. Kanamycin

197: Chronic candidiasis infections of the GI tract and oral cavity are treated with which agent in pill form

a. Amphotericin B
b. Nystatin
c. Miconazole
d. Fluconazole
e. Clotrimazole

198: For the treatment of a patient with *Legionella pneumophila*, the drug of choice would be

a. Penicillin G
b. Chloramphenicol
c. Erythromycin
d. Streptomycin
e. Lincomycin

199: The most effective agent in the treatment of *Rickettsia*, *Mycoplasma*, and *Chlamydia* infections is

a. Penicillin G
b. Tetracycline
c. Vancomycin
d. Gentamicin
e. Bacitracin

200: The mechanism of action by which pyrantel pamoate is effective for the treatment of Necator americanus (hookworm) disease is

a. Interference with cell-wall synthesis
b. Interference with cell division
c. Inhibition of neuromuscular transmission
d. Interference with protein synthesis
e. Depletion of membrane lipoproteins

201: Vertigo, inability to perceive termination of movement, and difficulty in sitting or standing without visual clues are some of the toxic reactions that are likely to occur in about 75% of patients treated with

a. Penicillin G
b. Doxycycline
c. Amphotericin B
d. Streptomycin
e. INH

202: Amantadine, a synthetic antiviral agent used prophylactically against influenza A_2, is thought to act by

a. Preventing production of viral capsid protein
b. Preventing virion release
c. Preventing penetration of the virus into the host cell
d. Preventing uncoating of viral DNA
e. Causing lysis of infected host cells by release of intracellular lysosomal enzymes

203: Streptomycin and other aminoglycosides inhibit bacterial protein synthesis by binding

a. Peptidoglycan units in the cell wall
b. Messenger RNA (mRNA)
c. DNA
d. 30S ribosomal particles
e. RNA polymerase

204: A patient with AIDS is treated with a combination of agents, which includes zidovudine. What is the mechanism of action of zidovudine?

a. Inhibition of RNA synthesis
b. Inhibition of viral particle assembly
c. Inhibition of viral proteases
d. Inhibition of nucleoside reverse transcriptase
e. Inhibition of nonnucleoside reverse transcriptase

205: A 39-year-old male with aortic insufficiency and a history of no drug allergies is given an intravenous dose of antibiotic as a prophylaxis preceding the insertion of a valve prosthesis. As the antibiotic is being infused, the patient becomes flushed over most of his body. What antibiotic was given?

a. Vancomycin
b. Gentamicin
c. Erythromycin
d. Penicillin G
e. Tetracycline

206: Which one of the following antimicrobial agents is primarily administered topically?

a. Polymyxin B
b. Penicillin G
c. Dicloxacillin
d. Carbenicillin
e. Streptomycin

207: A 75-year-old woman is hospitalized for pneumonia and treated with an intravenous antibiotic. On day three, she develops severe diarrhea. Stool is positive for ***Clostridium difficile*** toxin. What is the best treatment?

a. Clindamycin
b. Cefaclor
c. Metronidazole
d. Erythromycin
e. Doxycycline

208: A jaundiced one-day-old premature infant with an elevated free bilirubin is seen in the premature-baby nursery. The mother received an antibiotic combination preparation containing sulfamethizole for a urinary tract infection (UTI) one week before delivery. You suspect that the infant's findings are caused by the sulfonamide because of the following mechanism:

a. Enhanced synthesis of bilirubin
b. Competition between the sulfonamide and bilirubin for binding sites on albumin
c. Inhibition of bilirubin degradation
d. Inhibition of urinary excretion of bilirubin

209: Thiabendazole, a benzimidazole derivative, is an antihelminthic drug used primarily to treat infections caused by

a. Ascaris lumbricoides (roundworm)
b. N. americanus (hookworm)
c. Strongyloides
d. Enterobius vermicularis
e. Taenia saginata (flatworm)

210: A 27-year-old female has just returned from a trip to Southeast Asia. In the past 24 hours, she has developed shaking, chills, and a temperature of 104°F. A blood smear reveals Plasmodium vivax. Which of the following agents should be used to eradicate the extraerythrocytic phase of the organism?

a. Primaquine
b. Pyrimethamine
c. Quinacrine
d. Chloroquine
e. Chloroguanide

211: An 86-year-old male complains of cough and blood in his sputum for the past two days. On admission, his temperature is 103°F. Physical examination reveals rales in his right lung, and x-ray examination shows increased density in the right middle lobe. A sputum smear shows many Gram-positive cocci, confirmed by sputum culture as penicillinase-producing ***Staphylococcus aureus***. Which of the following agents should be given?

a. Ampicillin
b. Oxacillin
c. Carbenicillin
d. Ticarcillin
e. Mezlocillin

212: A 40-year-old male is HIV-positive with a cluster-of-differentiation-4 (CD4) count of 200/mm3. Within two months, he develops a peripheral white blood cell count of 1000/mm3 and a hemoglobin of 9.0 mg/dL. Which drug has most likely caused the adverse effect?

a. Acyclovir
b. Dideoxycytidine
c. Foscarnet
d. Rimantadine
e. Zidovudine

213: The mechanism of action of chloroquine in ***Plasmodium falciparum*** malaria is elimination of

a. Secondary tissue schizonts
b. Exoerythrocytic schizonts
c. Erythrocytic stage
d. Asexual forms
e. Sporozoites

- For each patient, select the mechanism of drug action:

a. Inhibition of bacterial cell-wall synthesis
b. Inhibition of bacterial protein synthesis
c. Inhibition of bacterial folic acid synthesis
d. Inhibition of bacterial topoisomerase II.
e. Inhibition of bacterial DNA polymerase

214: A 39-year-old female with a history of chronic UTI develops a new infection with ***Escherichia coli*** that is sensitive to levofloxacin.

a	b	c	d	e

215: A 25-year-old female with a sinus infection caused by ***Haemophilus influenzae*** is treated with trimethoprim-sulfamethoxazole.

a	b	c	d	e

216: A 35-year-old male has recently converted to positive on a purified protein derivative of tuberculin (PPD) test for TB. INH is given as prophylaxis.

a	b	c	d	e

217: The use of chloramphenicol may result in

a. Bone marrow stimulation b. Phototoxicity c. Aplastic anemia
d. Staining of teeth e. Alopecia

218: Which of the following may cause damage to growing cartilage?

a. Fluoroquinolones b. Sulfonamides c. Aminoglycosides
d. Cephalosporins e. Tetracyclines

219: A patient with AIDS is treated with a combination of agents, which includes Efavirenz. What is the mechanism of action of Efavirenz?

a. Inhibition of RNA synthesis
b. Inhibition of DNA synthesis
c. Inhibition of viral particle assembly
d. Inhibition of viral proteases
e. Inhibition of nucleoside reverse transcriptase
f. Inhibition of nonnucleoside reverse transcriptase

220: A patient with AIDS is treated with a combination of agents, which includes Indinavir. What is the mechanism of action of Indinavir?

a. Inhibition of RNA synthesis
b. Inhibition of DNA synthesis
c. Inhibition of viral particle assembly
d. Inhibition of viral proteases
e. Inhibition of nucleoside reverse transcriptase
f. Inhibition of nonnucleoside reverse transcriptase

221: Of the following, the most appropriate statement concerning the reactions caused by aminoglycosides is that these agents

a. Produce ototoxicity
b. Are potent neuromuscular blockers
c. Have little or no effect on kidneys
d. Produce a high incidence of hypersensitivity reactions similar to those of penicillins
e. Produce a high incidence of exfoliative dermatitis

222: The mechanism of action of chloramphenicol as an antibiotic is that it

a. Binds to the 30S ribosome subunit
b. Reversibly binds to the 50S ribosome subunit
c. Prevents cell membrane development
d. Inhibits cell-wall synthesis
e. Inhibits RNA polymerase

223: The drug of choice for the treatment of *T. saginata* (tapeworm) is

a. Mebendazole b. Ceftriaxone c. Primaquine
d. Niclosamide e. Chloroquine

224: The drug of choice for the treatment of *Schistosoma haematobium* is

a. Praziquantel b. Ceftriaxone c. Metronidazole
d. Mebendazole e. Diethylcarbamazine

225: Ampicillin and amoxicillin are in the same group of penicillins. Which of the following statements best characterizes amoxicillin?

a. It has better oral absorption than does ampicillin
b. It can be used in penicillinase-producing organisms
c. It is classified as a broad-spectrum penicillin
d. It does not cause hypersensitivity reactions
e. It is effective against Pseudomonas

226: A 60-year-old male with AIDS develops a systemic fungal infection that is treated with fluconazole. What is the mechanism of action of fluconazole?

a. It inhibits ergosterol synthesis
b. It inhibits DNA synthesis
c. It inhibits peptidoglycan synthesis
d. It inhibits protein synthesis

227: A 50-year-old male diabetic develops an external otitis from which ***Pseudomonas*** organisms are cultured. Topical therapy with polymyxin is effective. What is the mechanism of action of polymyxin?

a. Inhibition of cell-wall synthesis
b. Formation of reactive cytotoxic products that interfere with DNA synthesis
c. Disruption of membrane permeability
d. Inactivation of protein sulfhydryl groups
e. Inhibition of protein synthesis by binding to transfer RNA (tRNA)

228: A 75-year-old male develops a cough that produces blood-tinged sputum. He has a fever of 104°F. Gram-positive cocci in clusters are found in sputum smear. A chest x-ray shows increased density in the right upper lobe. Of the following penicillins, which is most likely to be ineffective?

a. Oxacillin
b. Cloxacillin
c. Ticarcillin
d. Nafcillin
e. Dicloxacillin

229: A 40-year-old female with a history of AIDS develops a herpes simplex keratitis of the eye. Which of the following antiviral agents should be administered in this case?

a. Zanamivir
b. Trifluridine
c. Zidovudine
d. Amantadine
e. Indinavir

230: A 45-year-old female being treated for a chronic UTI develops acute alcohol intolerance. Which of the following agents could have caused this intolerance?

a. Cefoperazone
c. Sulfamethoxazole-trimethoprim
b. Amoxicillin
d. Norfloxacin
e. Tetracycline

231: A 65-year-old male with a pneumonia has a sputum culture that is positive for a staphylococcal strain that is β-lactamase-positive. Which is the best choice of penicillin therapy in this patient?

a. Ampicillin
b. Oxacillin
c. Ticarcillin
d. Penicillin G
e. Carbenicillin

232: A 35-year-old female complains of itching in the vulval area. Hanging drop examination of the urine reveals trichomonads. What is the preferred treatment for trichomoniasis?

a. Doxycycline
b. Pyrimethamine
c. Pentamidine
d. Emetine
e. Metronidazole

233: A 40-year-old female with duodenal ulcers is treated with a combination of agents that includes clarithromycin. Of the following enzymes, which is inactivated by clarithromycin?

a. Dihydrofolate reductase
b. Glucose-6-phosphate dehydrogenase
c. Cytochrome P450
d. Na^+,K^+ATPase
e. Na^+,K^+,Cl^- co-transporter

234: A 30-year-old type I diabetic with renal complications develops acute pyelonephritis. ***P. aeruginosa*** is found in urine cultures and blood cultures. Combined therapy is instituted with an aminoglycoside and which of the following?

a. Clavulanic acid b. Vancomycin c. A second-generation cephalosporin
d. Azithromycin e. Piperacillin

235: A 35-year-old male is diagnosed with primary syphilis. Which of the following agents is the best choice for treating this patient?

a. A first-generation cephalosporin b. Oxacillin c. Imipenen
d. Benzathine penicillin G e. Vancomycin

236: A 20-year-old male has a urethral discharge. Culture of the discharge shows ***Neisseria gonorrhoeae***. Which of the following agents is the best choice for treating this patient?

a. Ceftriaxone b. Benzathine penicillin G c. Imipenen
d. Amikacin e. Sulfamethoxazole-trimethoprim

237: A 36-year-old female with a chronic UTI treated with ciprofloxacin is not responsive to the antibiotic. Which of the following agents that she might have been taking for other reasons would decrease the effectiveness of ciprofloxacin?

a. An antacid b. An antihistamine c. A nonsteroidal anti-inflammatory
d. An anxiolytic e. A multivitamin not containing iron

138: An infant with severe respiratory syncytial virus (RSV) bronchiolitis is best treated with

a. Amantadine b. Indinavir c. Efavirenz
d. Famciclovir e. Ribavirin

139: A 20-year-old male with herpes simplex of the lips is treated with famciclovir. What is the mechanism of action of famciclovir?

a. Cross-linking of DNA b. Strand breakage of DNA
c. Inhibition of viral DNA synthesis d. Inhibition of nucleotide interconversions
e. Inhibition of a viral kinase

240: A patient being treated with a combination of drugs for pulmonary tuberculosis develops a decrease in visual acuity and red-green color blindness resulting from retrobulbar neuritis. Which of the following agents is responsible for these findings?

a. INH b. Streptomycin c. Rifampin
d. Pyrizinamide e. Ethambutol

241: A 26-year-old young man presents with the symptoms of gonorrhea. Because this condition is often associated with an infection due to ***Chlamydia trachomatis***, which of the following quinolones would be the best choice for treating him?

a. Ciprofloxacin b. Nalidixic acid c. Norfloxacin
d. Levofloxacin

242: Sulfonamides increase the risk of neonatal kernicterus, because they:

a. Diminish the production of plasma albumin. b. Increase the turnover of red blood cells.
c. Inhibit the metabolism of bilirubin. d. Compete for bilirubin-binding sites on plasma albumin.
e. Depress the bone marrow.

243: A 25-year-old male patient with acquired immunodeficiency syndrome has a fever of 102°F and complains of severe headaches during the past week. Staining of his CSF with India ink reveals ***Cryptococcus neoformans***. The patient is admitted to the hospital and is treated with:

a. Intravenous amphotericin B plus flucytosine
b. Oral ketoconazole
c. Intrathecal amphotericin B
d. Oral fluconazole
e. Intravenous amphotericin B plus ketoconazole

244: The antineoplastic chemotherapeutic agent that is classified as an alkylating agent is

a. Thioguanine
b. Busulfan
c. Bleomycin
d. Vincristine
e. Tamoxifen

245: Cardiotoxicity limits the clinical usefulness of which one of the following antitumor antibiotics?

a. Dactinomycin
b. Doxorubicin
c. Bleomycin
d. Plicamycin
e. Mitomycin

246: Binding to the enzyme dihydrofolate reductase is the mechanism of action for

a. Procarbazine
b. Paclitaxel
c. Methotrexate
d. Ifosfamide
e. Cladribine

247: Which of the following is considered to be the effective mechanism of action of the vinca alkaloids?

a. Inhibition of the function of microtubules
b. Damage and prevention of repair of DNA
c. Inhibition of DNA synthesis
d. Inhibition of protein synthesis
e. Inhibition of purine synthesis

248: A 50-year-old female is treated with paclitaxel. Of the following, how is paclitaxel classified?

a. An alkylating agent
b. An antimetabolite
c. A plant alkaloid
d. An antibiotic
e. A hormonal agent

249: A 41-year-old female is treated for endometrial cancer with tamoxifen. Of the following, how is tamoxifen classified?

a. An alkylating agent
b. An antimetabolite
c. A plant alkaloid
d. An antibiotic
e. A hormonal agent

250: A 35-year-old female is being treated for cervical cancer with cisplatin. Of the following, how is cisplatin classified?

a. An alkylating agent
b. An antimetabolite
c. A plant alkaloid
d. An antibiotic
e. A hormonal agent

251: A 45-year-old female treated for ovarian cancer develops difficulty hearing. Which of the following agents most likely caused these findings?

a. Paclitaxel
b. Doxorubicin
c. Bleomycin
d. 5-FU
e. Cisplatin

252: A 16-year-old male treated for acute lymphocytic leukemia develops severe lumbar and abdominal pain. His serum amylase is markedly elevated. Which of the following agents most likely caused these findings?

a. 6-MP
b. Asparaginase
c. Doxorubicin
d. Methotrexate
e. Vincristine

Answers

184	185	186	187	188	189	190	191	192	193
c	c	b	b	d	b	c	e	a	d
194	195	196	197	198	199	200	201	202	203
b	c	a	d	c	b	c	d	d	d
204	205	206	207	208	209	210	211	212	213
d	a	a	c	b	c	a	b	e	c
214	215	216	217	218	219	220	221	222	223
d	c	a	c	a	f	d	a	b	d
224	225	226	227	228	229	230	231	232	233
a	a	a	c	c	b	a	b	e	c
234	235	236	237	238	239	240	241	242	243
e	d	a	a	e	c	e	d	d	c
244	245	246	247	248	249	250	251	252	
b	b	c	a	c	e	a	e	b	

Questions and answers from (References):

Basic and Clinical Pharmacology 12th edition, Katzung-Lange
Pharmacology 12th edition PreTest Self-Assessment and Review
Pharmacology 5th edition Lippincott Williams & Wilkins

الحمدُ لله الذي هدانا لهذا وما كنَّا لنهتدي لولا أن هدانا الله.. وبعد فهذه محاولة مخلصة لتقريب علم الأدوية للمعنيين بعلوم الطب والصيدلة، قصدتُ بها وجه الله تعالى، فإن وُفِّقْتُ فمن الله، وإن كانت الأخرى فحسبي أنني اجتهدت وبحثت..والله من وراء القصد، وهو الهادي إلى سواء السبيل،،

D. Ahsha
25/9/2012

Drug Index

(DRUG INDEX)