



General Pharmacology

CHAPTER

1

PHARMACOLOGY

Definition

- Science of drugs

Branches

- 2 Branches →
 - 1) Pharmacokinetics
 - 2) Pharmacodynamics

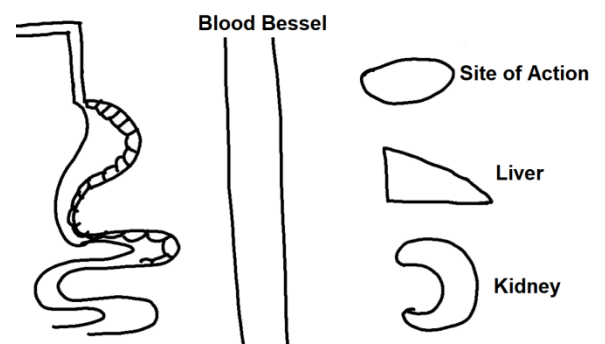


1. Pharmacokinetics

- What the body does to the drug
- Includes →
 - Absorption
 - Distribution
 - Biotransformation (metabolism)
 - Excretion of the drug

2. Pharmacodynamics

- What the drug does to the body
- Includes →
 - Physiological and biochemical effects of drugs
 - Their mechanism of action at organ system

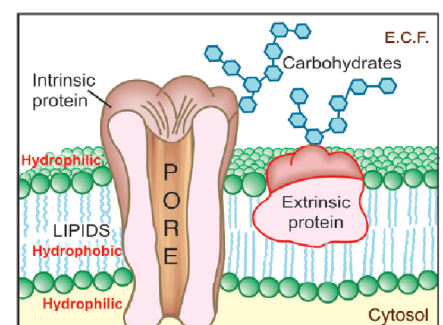


BIOLOGICAL MEMBRANE AND DRUG TRANSPORT

- All pharmacokinetic processes involve transport of the drug across biological membranes.

Biological membrane

- A bilayer (about 100 Å thick)
- Consist of → Phospholipid and cholesterol molecules
 - Polar groups → oriented at two surfaces
 - Nonpolar groups → embedded in matrix



Drug Transport

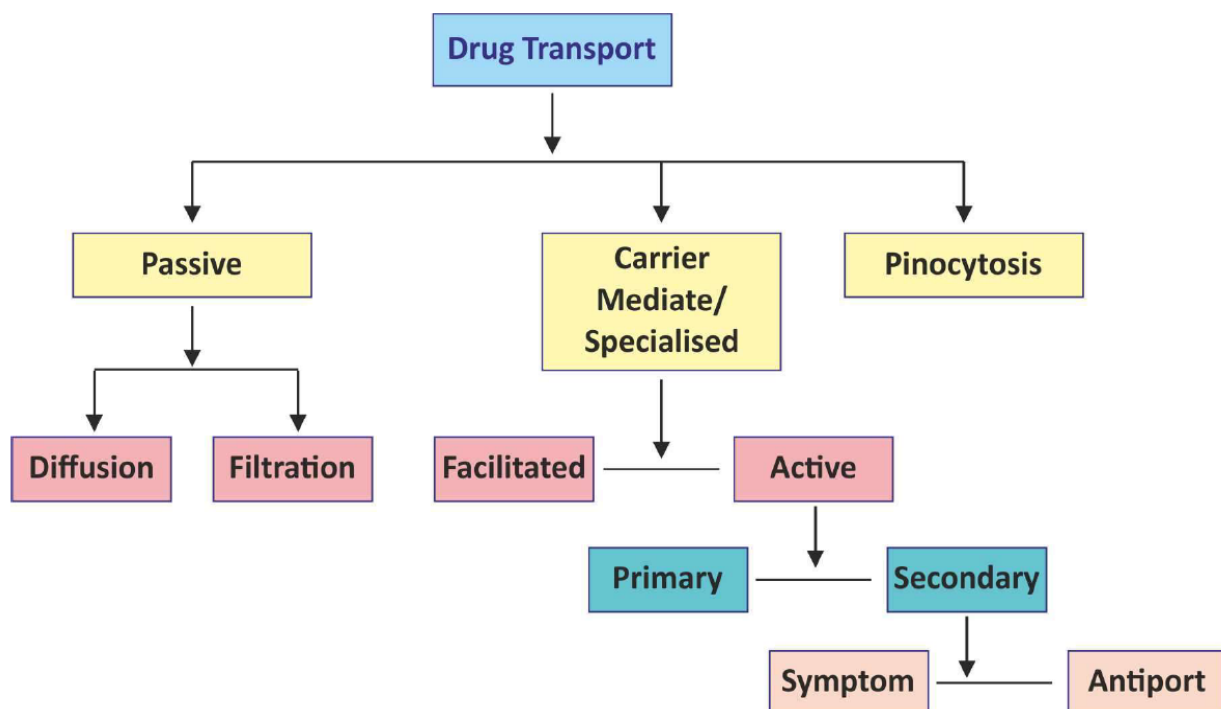
1. Passive transfer

- (a) Diffusion
- (b) Filtration

2. Carrier mediated transport/Specialized transport

- (a) Facilitated transport
- (b) Active transport
 - Primary active transport
 - Secondary active transport

3. Pinocytosis

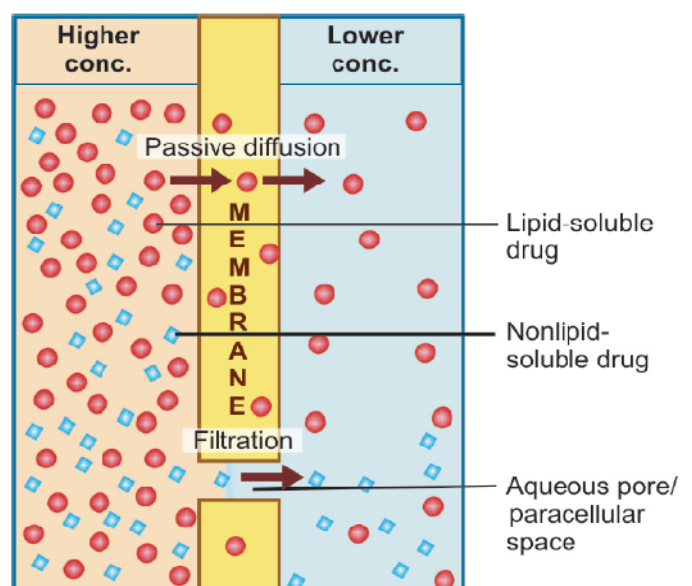


I. Passive transfer

- Through membrane itself
- No carrier molecules or transporters are required

Types

- **2 Types** →
- 1) Diffusion
- 2) Filtration



(1) Diffusion

- Most common mechanism
- Passage of a substance → across a cell membrane in direction of its concentration gradient (high to low)
- No energy requirement
- Bi-directional
- Rate of transport $\propto$ Difference in concentration of drug on 2 sides of membrane
- Rate of transport $\propto$ Lipid solubility (Lipid : water partition coefficient) of drug

(2) Filtration

- **Passage of drugs** → through aqueous pores or through paracellular spaces in cell membrane
- **Lipid** - insoluble drugs cross if their molecular size is smaller than diameter of pores

II. Carrier mediated transport / Specialized transport

- Specific carrier or transporter → Required
- Selectivity, saturability and competitive inhibition
- Located to a particular site → maximum absorption at that site

Transporters combine transiently with their substrate



Undergo a conformational change



Carrying substrate to other side of membrane

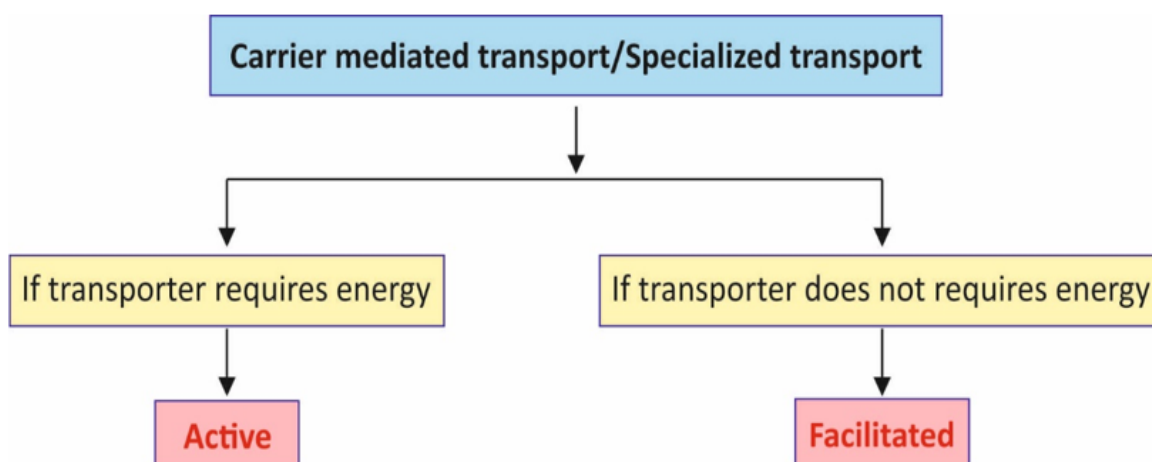


Substrate dissociates



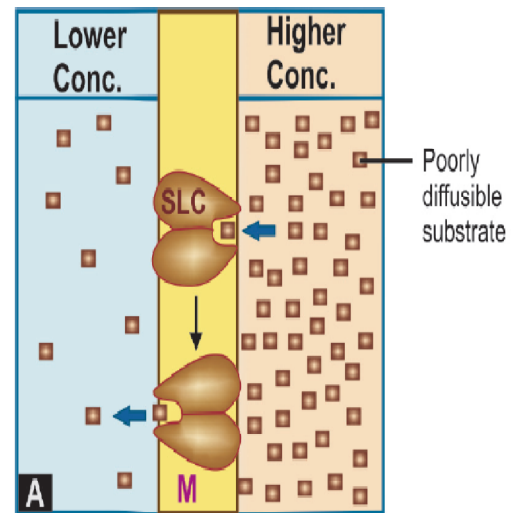
Transporter returns back to its original state

Types



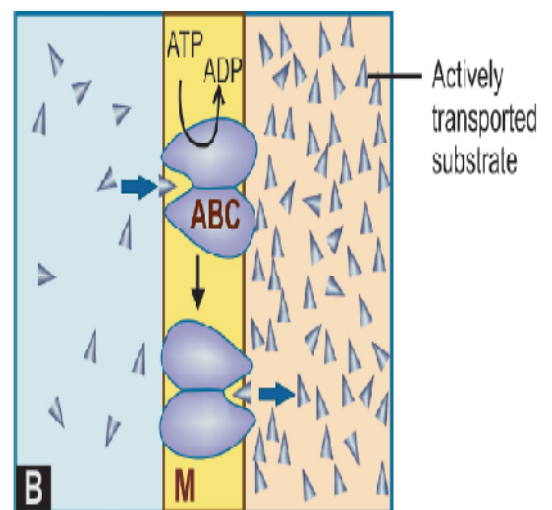
(1) Facilitated transport (diffusion)

- Energy independence (Passive)
- Transports substrate in direction of its electrochemical gradient (high to low)
- Transporter → super-family of solute carrier (SLC) transporters
- e.g. → Entry of glucose into muscle and fat cells by GLUT 4

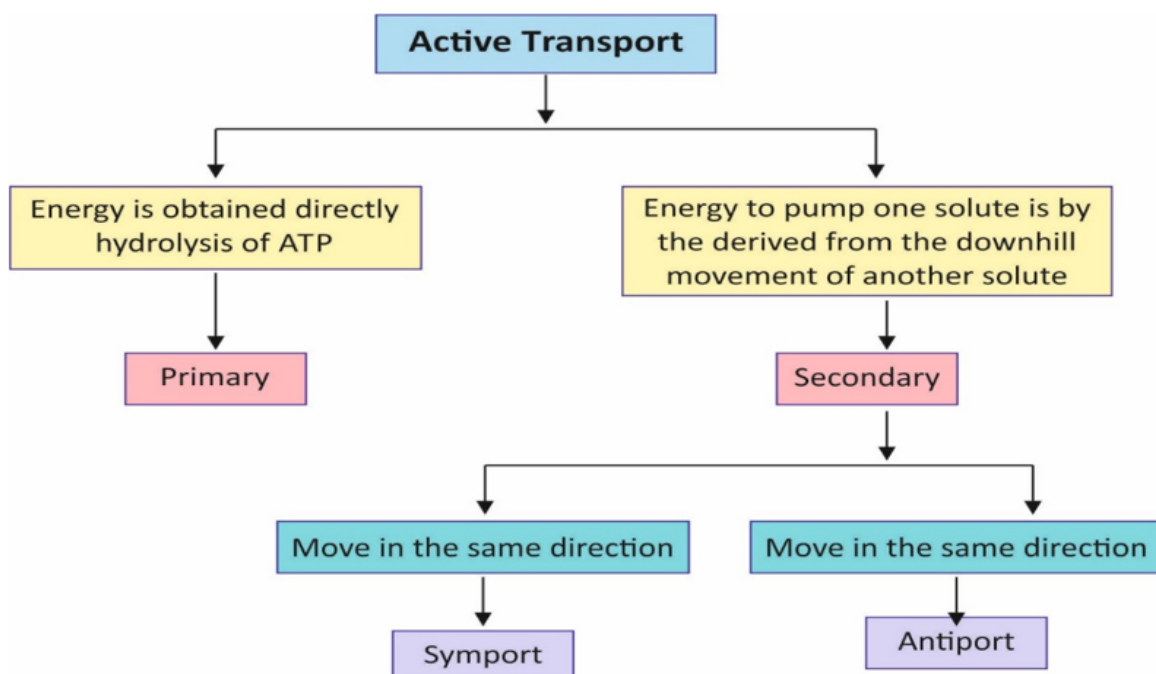


(2) Active transport

- Energy dependence
- Transports substrate against its electrochemical gradient (low to high)
- Unidirectional
- 2 types

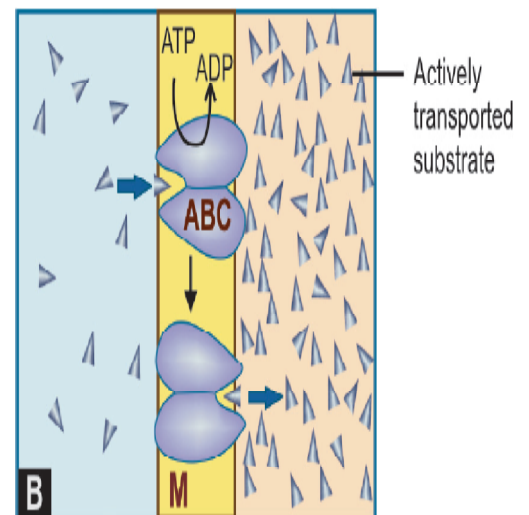


Types



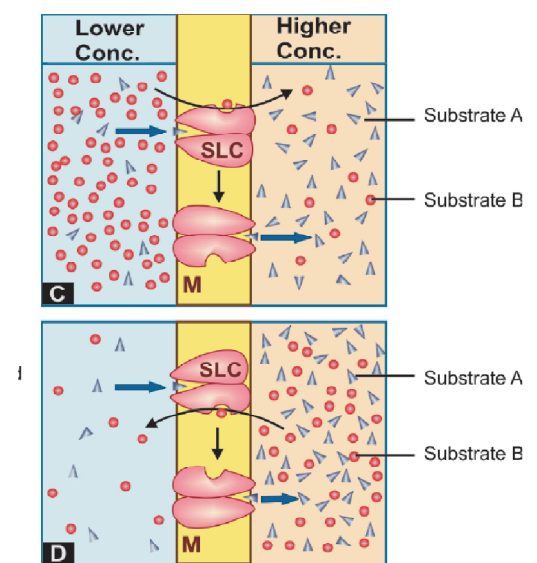
(a) Primary transport

- Energy is obtained → directly by hydrolysis of ATP
- Transporters → superfamily of ATP binding cassette (ABC) transporters (Eg. → P- glycoprotein)
- Mediate → only efflux of drugs (molecular vacuum cleaner)



(a) Secondary transport

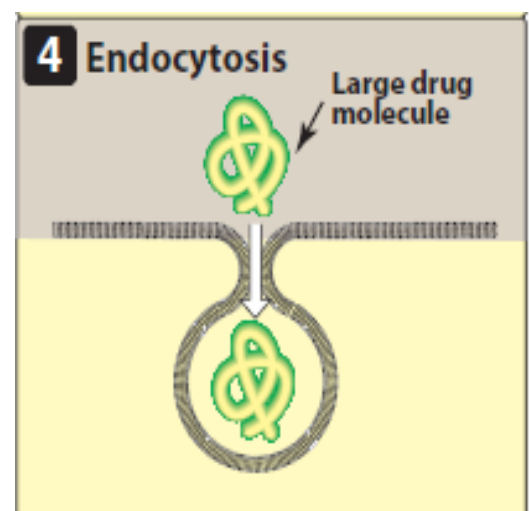
- Energy is obtained (For transfer of one substance) → by transport of another substance
- Transporters → SLC transporters
- Mediate → both uptake and efflux of drugs

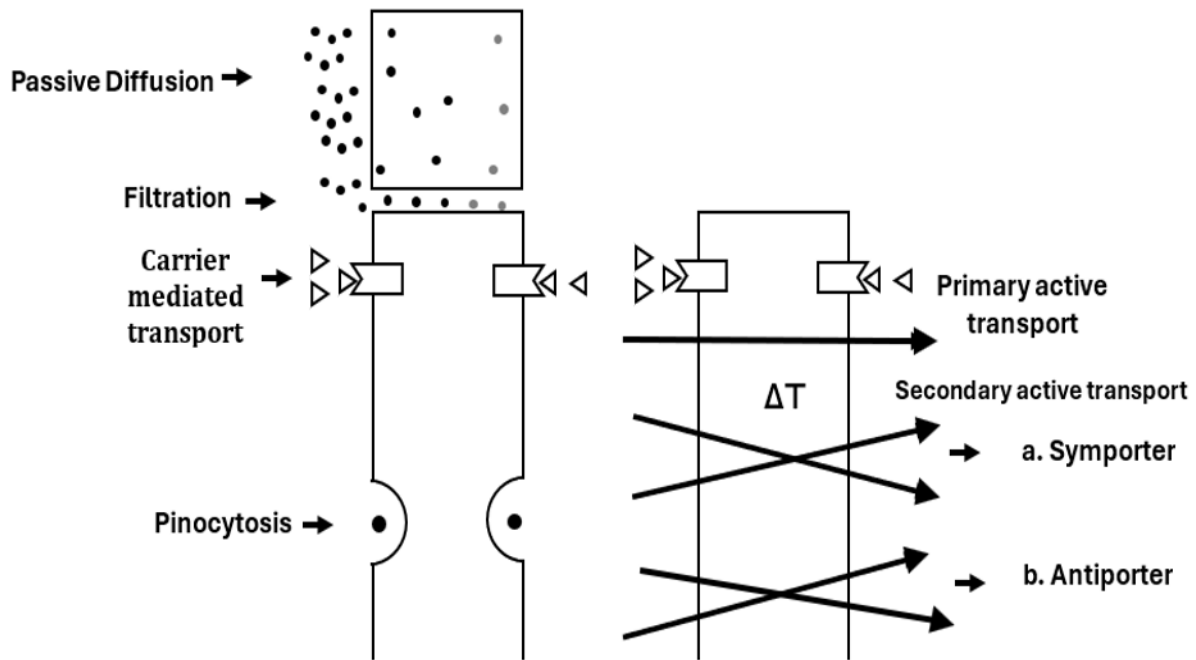


- **Symporters or co-transporter** → carries two substances in the same direction
- **Antiporters or exchanger** → carries two substances in the opposite direction

III. Pinocytosis or vesicular transport

- Engulfing by cell membrane
- By formation of vesicles

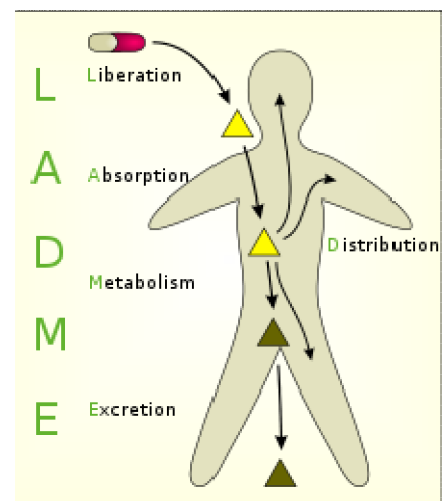




PHARMACOKINETICS

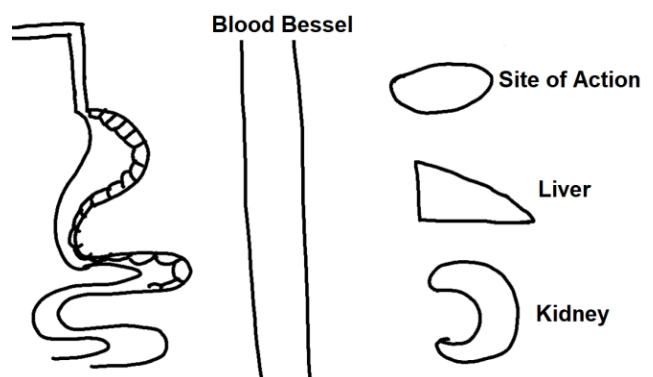
Definition

- What the body does to the drug
- Pharmacokinetics is quantitative study of → Drug movement → in, through and out of body



Includes

1. Absorption
2. Distribution
3. Metabolism
4. Excretion of the drug



DRUG ABSORPTION

Definition

- Movement of drug from its site of administration into circulation

Factors affecting absorption

1. Aqueous solubility
2. Formulation
3. Concentration of drugs
4. Lipid solubility
5. Surface area
6. Motility of GIT
7. Presence of other substances in GIT
8. Vascularity of the absorbing surface
9. Ionization of drugs and local pH

Aqueous solubility

- Rate of absorption $\propto$ Aqueous solubility
- When drug is not in solution its rate of absorption $\rightarrow$ depends on process of solution
- Tablets which rapidly disintegrate $\rightarrow$ rapidly absorb



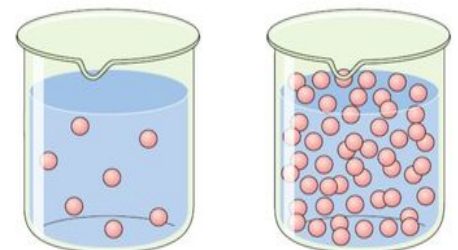
Formulation

- Rate of absorption $\propto$ Aqueous solubility Inert substance used to make tablet (lactose, sucrose, starch, calcium, lactate) $\rightarrow$ affect absorption



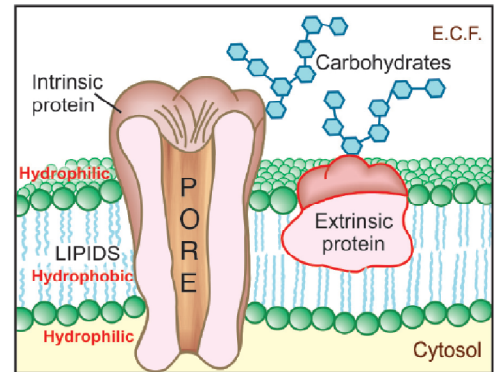
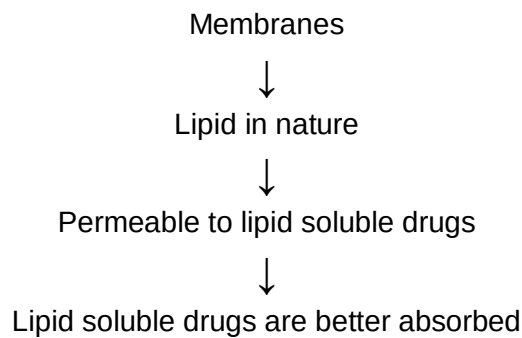
Concentration of drugs

- Rate of absorption $\propto$ Concentration of drugs
- So drug given as concentrated solution is absorbed faster than from dilute solution.



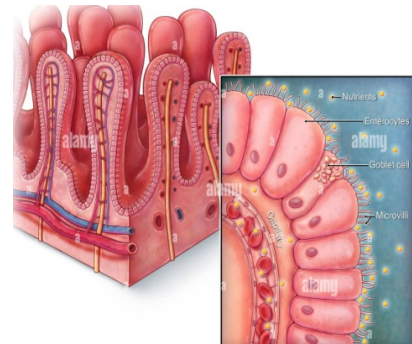
Lipid solubility

- Rate of absorption $\propto$ Lipid solubility



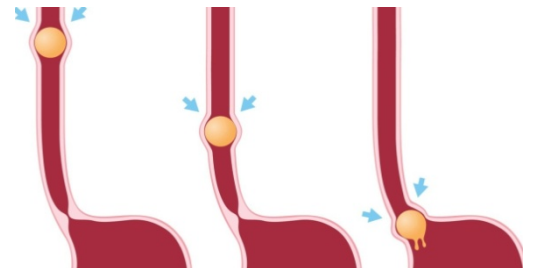
Surface area

- Rate of absorption $\propto$ Surface area
- Eg. small intestine $\rightarrow$ presence of villi



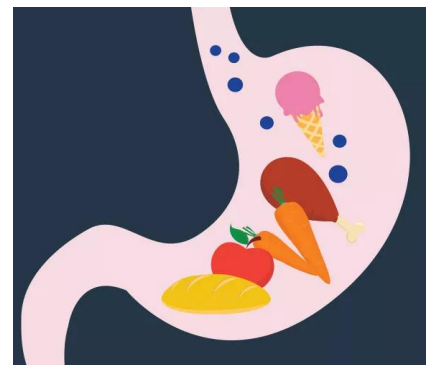
Motility of GIT

- Rate of absorption $\propto$ Motility of GIT
- Motility bring drug rapidly in contact with extensive surface area.



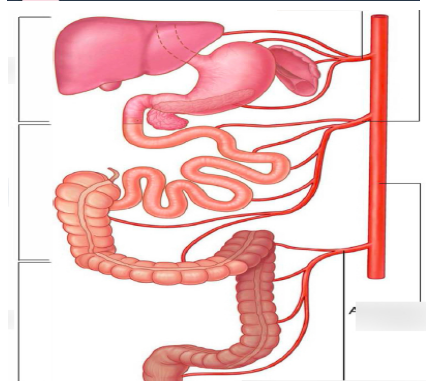
Presence of other substances in

- Food delays absorption
- Grape fruit juice increases absorption by inhibiting p-glycoprotein mediated drug efflux
- Vitamin C increases absorption of Iron



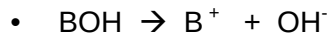
Vascularity of absorbing surface

- Rate of absorption $\propto$ Blood flow to GIT



Ionization of drugs and local pH

- Non- electrolyte drugs → lipid soluble → better – absorbed
- Strong electrolytes → completely ionized at acidic as well as alkaline
- Weak electrolytes → ionization is Ph dependent
- Most drugs are weak electrolytes → their ionization is pH dependent



$$\text{pH} = \text{pKa} + \log \frac{[\text{A}^-]}{[\text{HA}]} \quad \text{pH} = \text{pKa} + \log \frac{[\text{B}^+]}{[\text{BOH}]}$$

- Unionized form → Absorbed
- Ionised form → Excreted
- Ionization of a weak acid (HA)



$$\text{pH} = \text{pKa} + \log \frac{[\text{A}^-]}{[\text{HA}]}$$

If the concentration of ionized drug $[\text{A}^-]$ is equal to concentration of unionized drug $[\text{HA}]$, then

$$\frac{[\text{A}^-]}{[\text{HA}]} = 1$$

Since $\log 1$ is 0, under this condition

$$\text{pH} = \text{pKa}$$

Thus, pKa is numerically equal to pH at which drug is 50% ionized if PH is increased by 1 scale, then –

$$\log \frac{[\text{A}^-]}{[\text{HA}]} = 1 \text{ or } \frac{[\text{A}^-]}{[\text{HA}]} = 10$$

Similarly, if pH is reduced by 1 scale, then –

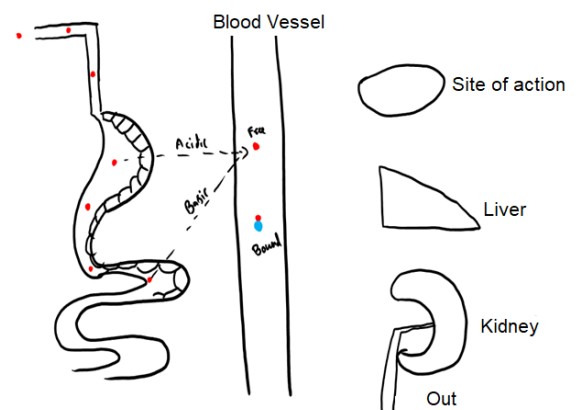
$$\frac{[\text{A}^-]}{[\text{HA}]} = 1/10$$

Remember

- **For absorption** → Same pH is required
- **For excretion** → Opposite pH is required

Implications

1. Site of absorption
2. Urinary PH for excretion



Aqueous solubility

- **Acidic drugs** → e.g. aspirin → unionized at acid gastric pH → absorbed from stomach
- **Basic drugs** → e.g. atropine → unionized at basic pH → absorbed from intestines

Urinary PH for excretion

- **Acidic drugs** → excreted faster → if urine is alkaline (basic)
- **Basic drugs** → excreted faster → if urine is acidified
 - **Alkalinization of urine** → done by IV infusion of sodium bicarbonate
 - **Acidification of urine** → done by IV infusion of arginine hydrochloride followed by ammonium chloride (NH₄Cl)

PH of Medium	Nature of Drug	(pH-pKa)	Ionized Form	Non-ionized Form
3.0	Acidic	2	1%	99%
4.0	Acidic	1	10%	90%
5.0	Acidic	0	50%	50%
6.0	Acidic	1	90%	10%
7.0	Acidic	2	99%	1%
8.0	Acidic	3	99.9%	0.1%

PH of Medium	Nature of Drug	(pH-pKa)	Ionized Form	Non-ionized Form
3.0	Basic	2	99%	1%
4.0	Basic	1	90%	10%
5.0	Basic	0	50%	50%
6.0	Basic	1	10%	90%
7.0	Basic	2	1%	99%
8.0	Basic	3	0.1%	99.9%

Summary

- Weakly acidic drugs →
 - Ionize / excreted more at → basic pH
 - Unionize / absorbed more at → acidic Ph
- Weakly basic drugs →
 - Ionize / excreted more at → acidic pH
 - Unionize / absorbed more at → basic pH

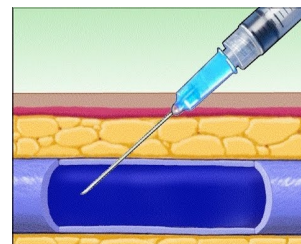
Bioavailability

Definition

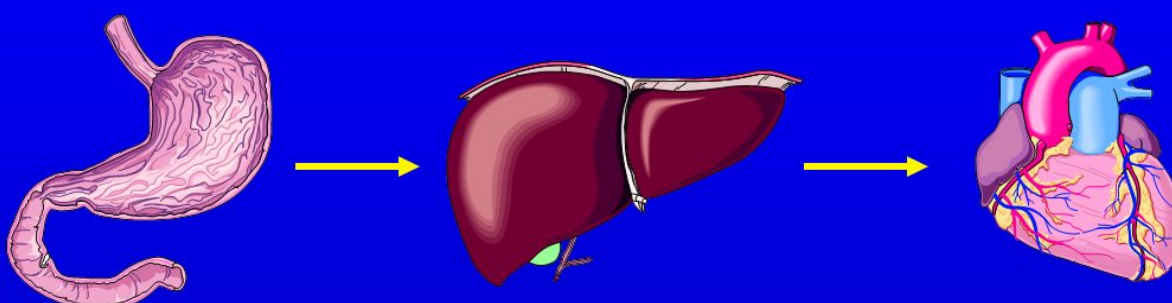
- Measure of fraction (F) of administered dose of a drug that reaches the systemic circulation in the unchanged form.

Routes

1. Bioavailability of drug injected I.V. is 100%
2. Bioavailability after oral ingestion is lower because→
 - (a) Drug may be incompletely absorbed.
 - (b) Absorbed drug may undergo first pass metabolism



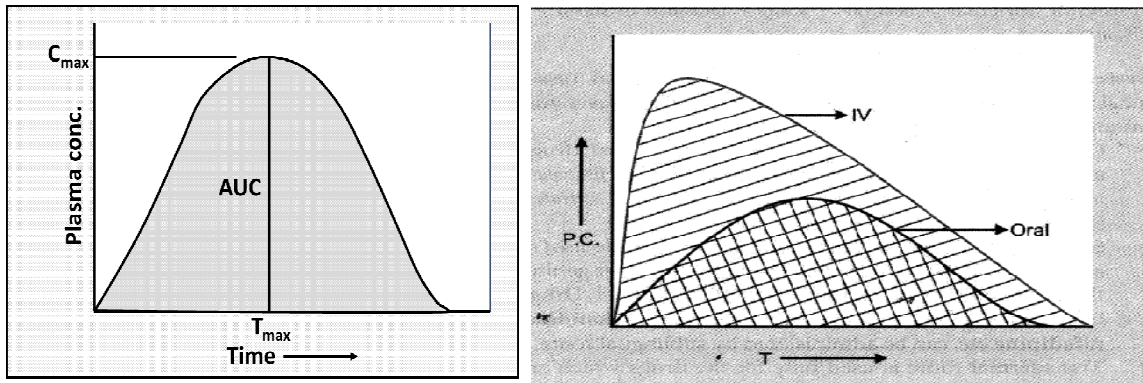
First-pass metabolism



Route of Administration	General characteristics	Bioavailability
• Intravenous	• Onset of action is fastest	• 100%
• Intramuscular	• Painful	• 75-100%
• Subcutaneous	• Lesser volumes can be given compared to intramuscular route	• 75-100%
• Per oral	• Most convenient from patients perspective MC used route	• 5% to <100% First pass metabolism limits blood levels
• Per rectal	• Less first pass metabolism than peroral	• 30 to <100%
• Transdermal	• Very slow absorption Lack of first pass effect Prolonged duration of action	• 80-100%

Calculation

- Area under curve (AUC) of time and plasma concentration.
- T_{max} → time to reach maximum concentration, i.e. rate of absorption
- C_{max} → maximum concentration of a drug that can be obtained



Bioequivalent vs Biologically inequivalent

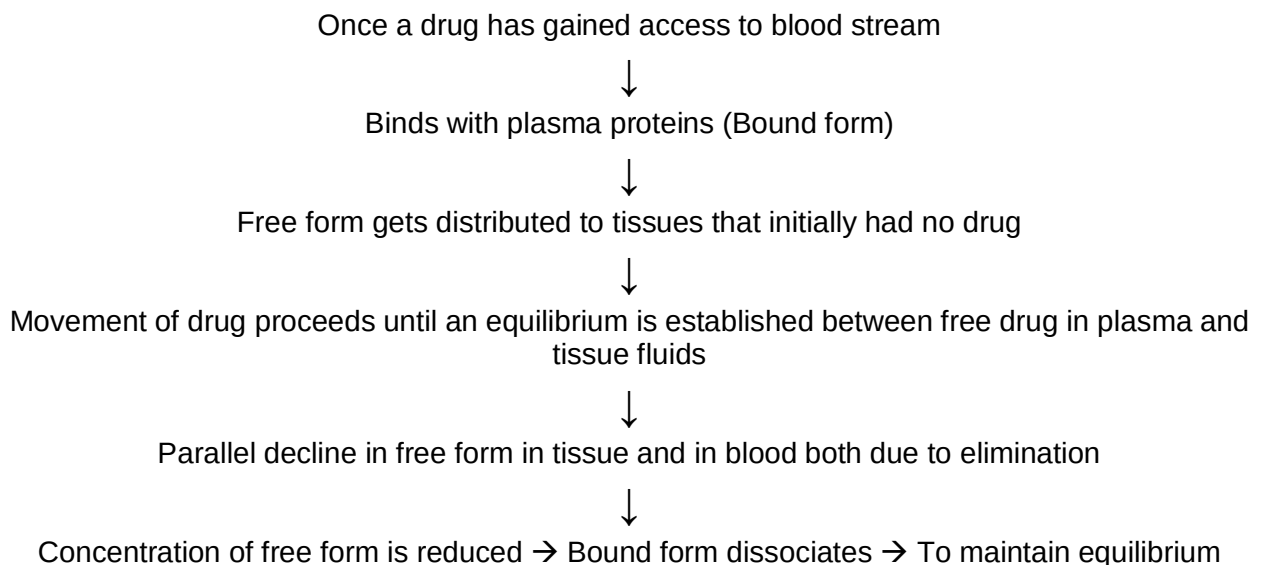
- E.g. phenytoin is available as tab. Dilantin as well as Tab. Eptoin
- Bioequivalent → If difference in bioavailability of these two preparations < 20%
- Biologically inequivalent → If difference in bioavailability of these two preparations > 20%

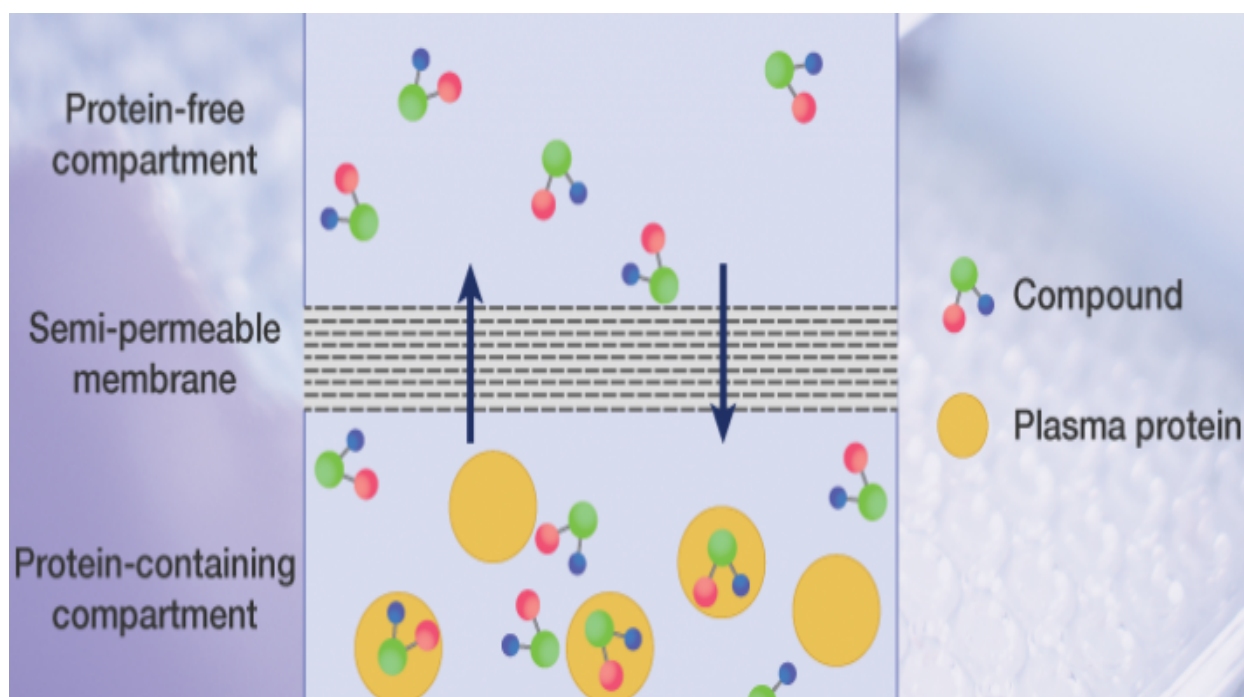


DRUG DISTRIBUTION

Definition

- Delivery of drug to tissues

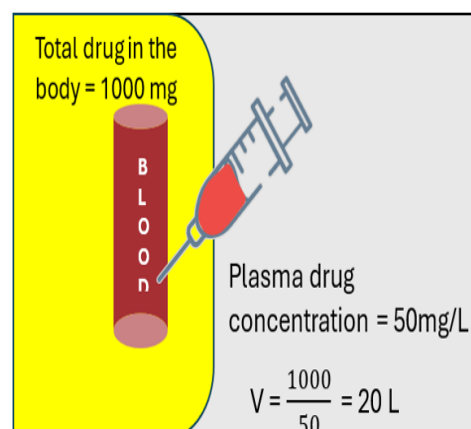




Free (unbound) drug	Bound form
• Active (shows MOA)	• Inactive (acts as a circulating reservoir)
• Metabolized	• Not metabolized
• Excreted	• Not excreted

- Bound drug is in equilibrium with free drug in plasma → It dissociates when concentration of free form is reduced due to elimination → act as temporary storage of drug
 - **Acidic drugs** → bind with albumin
 - **Basic drugs** → bind with α_1 acid glycoprotein

Drugs Highly Bound to Plasma Protein	
To albumin	To α_1 -acid glycoprotein
Barbiturates	β -blockers
Benzodiazepines	Bupivacaine
NSAIDs	Lidocaine
Valproic acid	Disopyramide
Phenytoin	Imipramine
Penicillins	Methadone
Sulfonamides	Prazosin
Tetracyclines	Quinidine
Tolbutamide	Verapamil
Warfarin	



1000 mg of drug injected i.v. produces steady-state plasma concentration of 50 mg/L. apparent volume of distribution is 20 L

Implications

- **Drugs extensively bound to plasma proteins** → high plasma conc. → low V
- **Drugs sequestered in other tissues** → plasma conc. is low → high V.

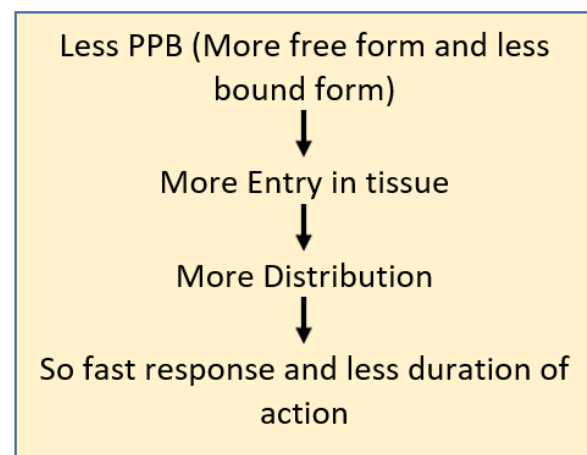
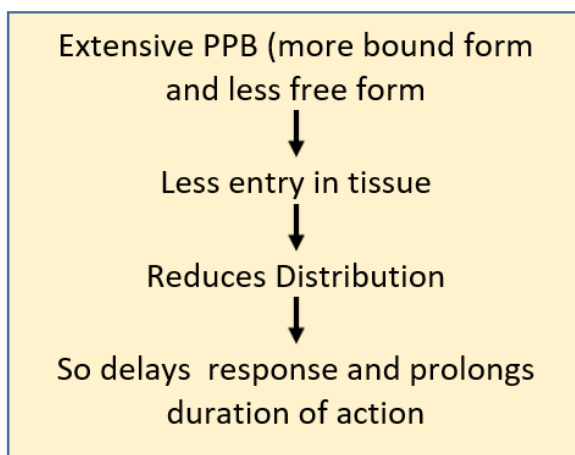
Factors Affecting Distribution

1. Rate of tissue blood flow (perfusion)
2. Onset and duration of action
3. Haemodialysis in case of poisoning
4. Certain Diseases
5. More than one drug

Rate of tissue blood flow (perfusion)

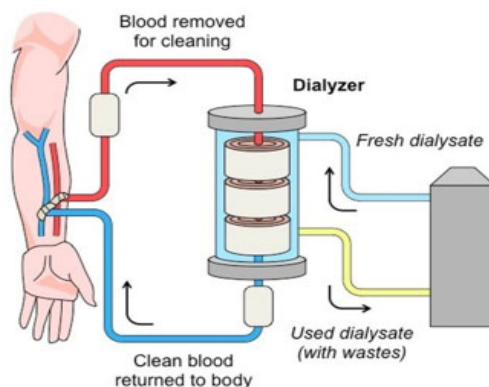
- **Organs with greater perfusion** → such as heart, brain, liver, kidney and lungs → receive most of drugs within few minutes → More susceptible for drug toxicities
- **Organs with poor perfusion** → like muscles, other viscera, skin, and fat → receive drug slowly → Less susceptible for drug toxicities

Onset and duration of action



Haemodialysis in case of poisoning

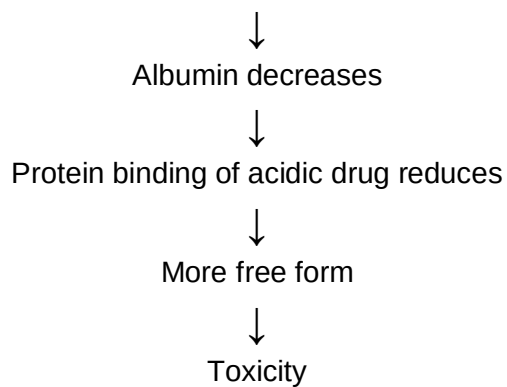
- Drugs with high PPB → not effectively removed by dialysis (because dialysis does not filter proteins)



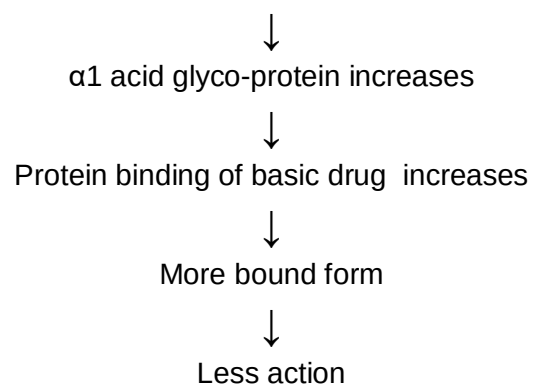
Mnemonic		
Dialysis is not effective in poisoning of		
A	-	Amphetamines
V	-	Verapamil
O	-	Organophosphates
	-	Opioids
I	-	Imipramine
D	-	Digitalis
Dialysis	-	Diazepam

Certain Diseases

In hypoalbuminemia and nephritic syndrome



In acute- phase reactions (MI, surgery, RA, burns)



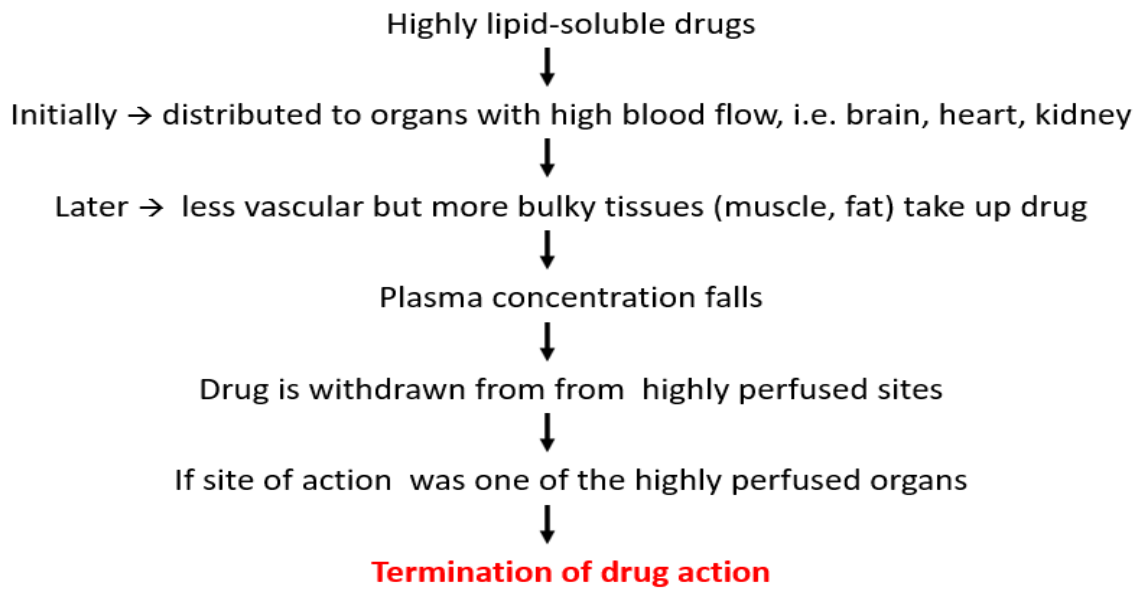
More than one drug

- More than one drug Can bind to same site on albumin
- Displacement among drugs when multiple drugs given together
 - Drug bound with higher affinity → displace that bound with lower affinity.
 - Acidic drugs do not displace basic drugs and vice versa.

Eg.

- Salicylates displace sulfonylureas.
- Indomethacin, phenytoin displace warfarin.
- Sulfonamides and vit K displace bilirubin (kernicterus in neonates)
- Salicylates displace methotrexate

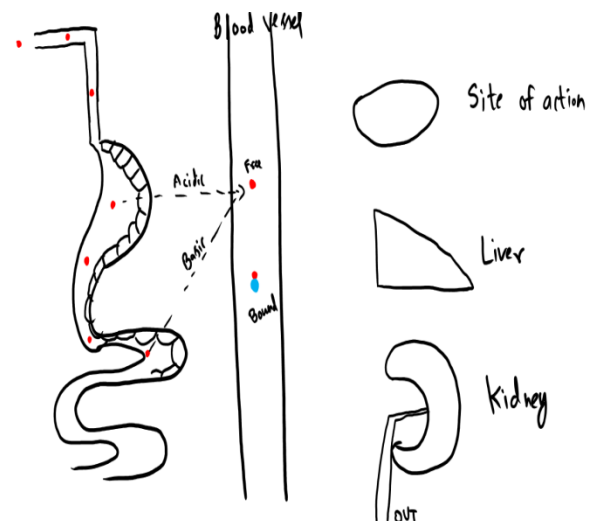
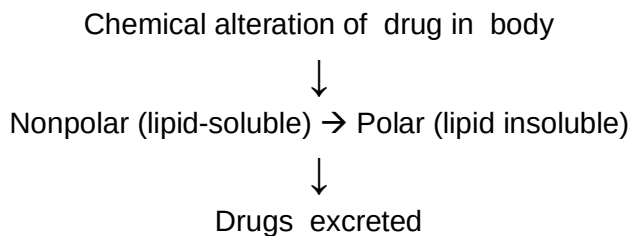
Redistribution



- Eg. → Anaesthetic action of thiopentone sod. Injected i.v. is terminated in few minutes due to redistribution.

METABOLISM = BIOTRANSFORMATION

Introduction

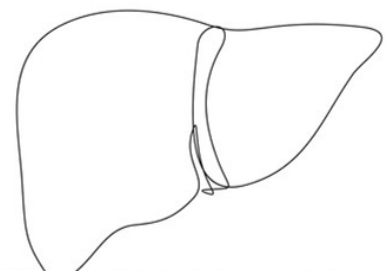


Site of metabolism

Main site → Liver

Extra hepatic sites →

- Kidney → vitamin D
- GIT → penicillin, insulin
- Lungs → 5HT
- Plasma → succinylcholine
- Skin → 7-dehydrocholesterol to chole- calciferol (D3)



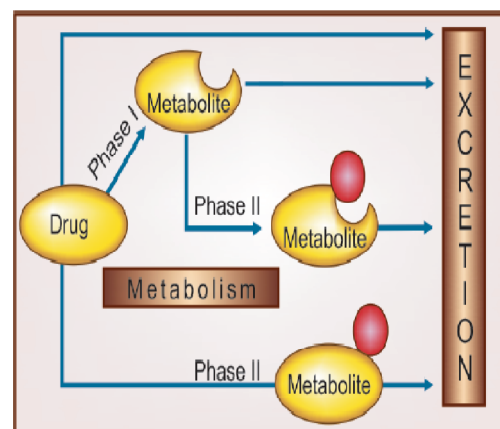
Lead to

1. Active drug → Inactive drug
2. Active drug → Active metabolite
3. Inactive drug → Active metabolite → Prodrug

Mnemonic → PRODRUGS		
All	-	ACE inhibitors (except captopril and lisinopril)
Prefer	-	Prednisone
	-	Proton pump inhibitors
	-	Proguanil
Doing	-	Dipivefrine
M	-	Mercaptopurine
	-	Methyldopa
	-	Minoxidil
D	-	Levo-dopa
In	-	Irinotecan
Clinical	-	Cyclophosphamide
	-	Clopidogrel
	-	Carbimazole
Subjects	-	Sulfasalazine

Classification

- A. Phase I / Nonsynthetic / Functionalization reactions
- B. Phase II / Synthetic / Conjugation reactions



Phase I reaction (Non polar → polar)

- Convert parent drug to a more polar metabolite by introducing or exposing a functional group such as -OH, -NH₂, -SH₂
 1. Oxidation
 2. Reduction
 3. Hydrolysis
 4. Cyclization
 5. Decyclization

Oxidation

- Incorporation of oxygen or removal of hydrogen
- 3 Microsomal enzymes →
 - i) CYPs (cytochrome P 450)
 - ii) FMOs (flavin containing monooxygenase)
 - iii) EH (epoxide hydroxylase)

i) CYPs (cytochrome P 450)

- About 2/3rd drugs are metabolized by CYPs.
- Reduced isozyme gives a special peak of maximum light absorption with pink color at 450 nm when treated with carbon monoxide → Cytochrome P 450
- Induced and inhibited by a number of drugs → Drug – drug interactions
- CYP followed by
 - Number → family
 - Letter → subfamily
 - Another number → CYP gene number
- Eg. CYP 3A4 is family 3, subfamily A and gene number 4.

ii) FMOs (flavin containing monooxygenase)

- FMO3 is most abundant in liver.
- Neither induced nor inhibited → No drug-drug interactions
- Eg. → Metabolizes nicotine, H blockers, clozapine and itopride.

iii) EH (epoxide hydroxylase)

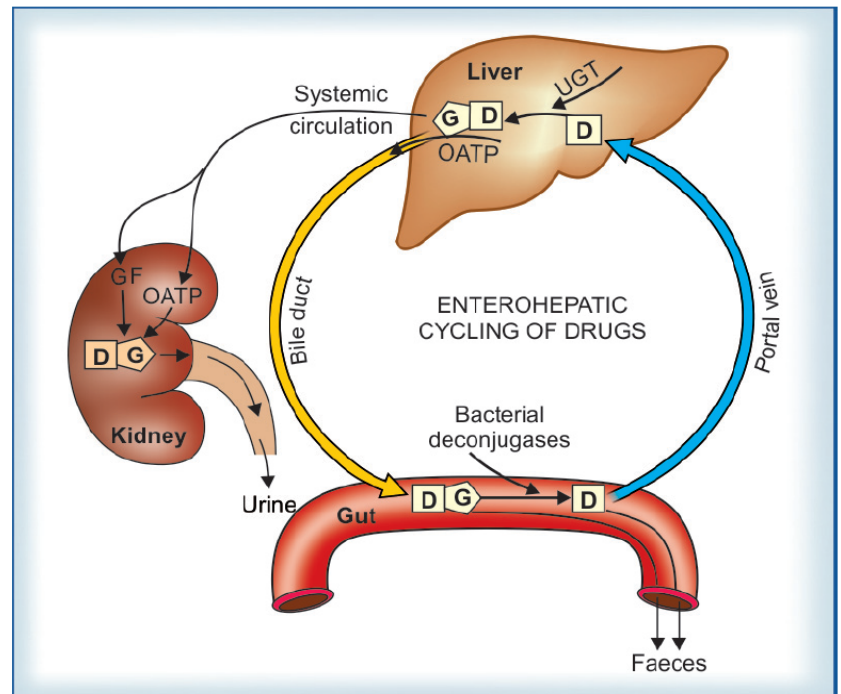
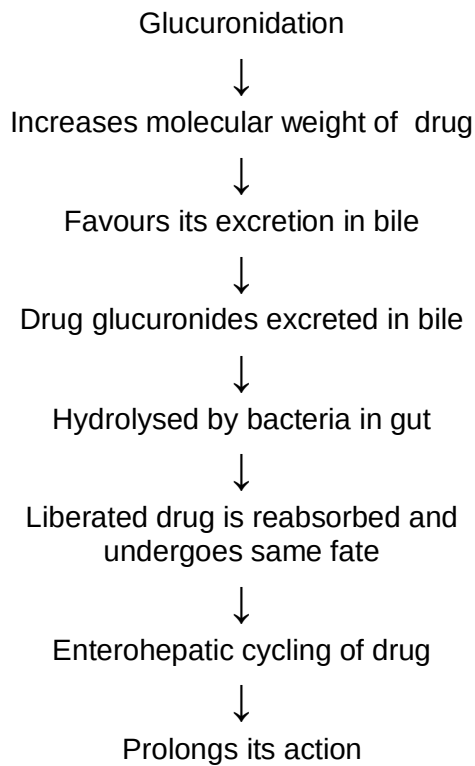
- Deactivate potentially toxic derivatives, epoxide, generated by CYPs.
- Eg. → Carbamazepine is activated to its epoxide form by CYP, which is then deactivated by EH.

B. Phase II reaction (Non polar → polar)

- Coupling between drug and an endogenous hydrophilic substrate such as glucuronic acid, sulfuric acid etc. to create more polar conjugates
 1. Glucuronide conjugation
 2. Glycin conjugation
 3. Glutathion conjugation
 4. Sulfate conjugation
 5. Methylation
 6. Acetylation

Glucuronide conjugation

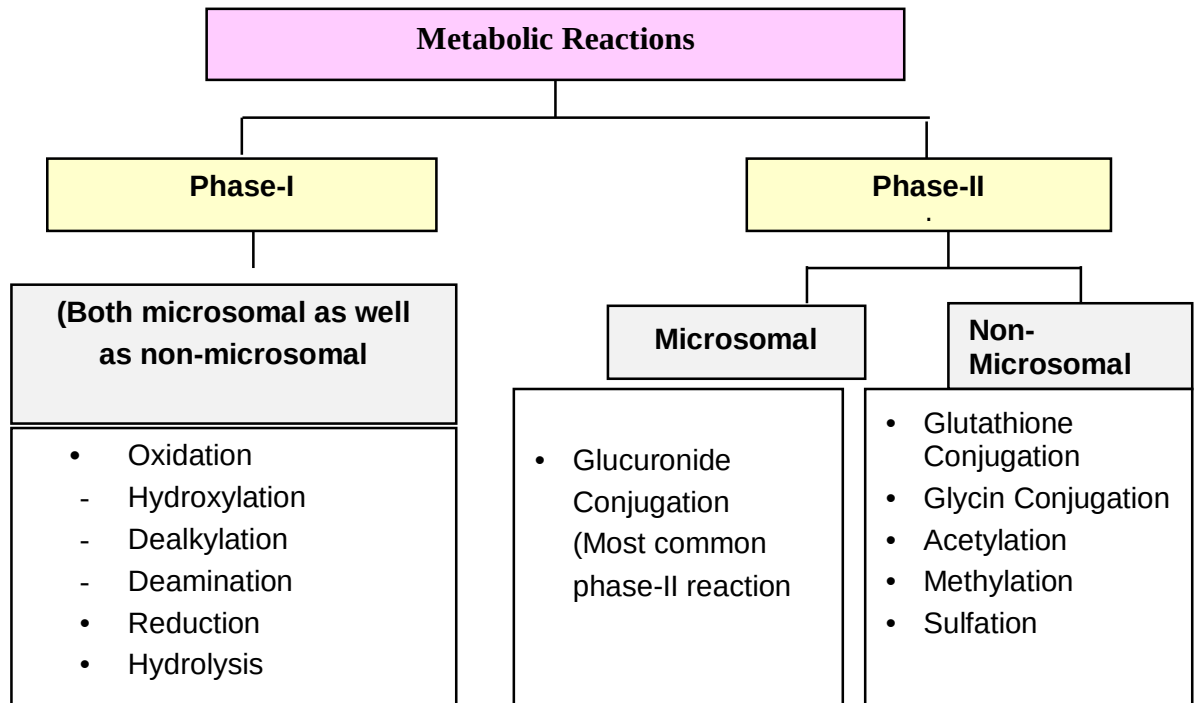
- Carried out by UDP-glucuronosyl transferases (UGTs).
- Eg. → chloramphenicol, aspirin, paracetamol, lorazepam, morphine, metronidazole.



Acetylation

- Compounds having amino or hydrazine residues conjugated with acetyl coenzyme-A
MNEMONIC- **CHIPS – ABC**
 - **C**lonazepam
 - **H**ydralazine
 - **I**soniazid
 - **P**rocaainamide
 - **S**ulfonamides
 - **A**cebutalol, **A**mrinone
 - **B**enzocaine
 - **C**affeine

Mechanism of metabolism

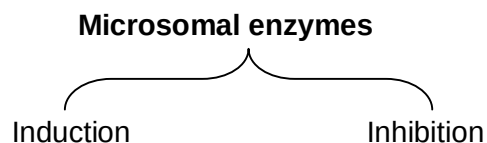


Non-microsomal enzymes

- **Present in** → cytoplasm and mitochondria.
- **Catalyse** → oxidations and reductions, Hydrolytic reactions and all conjugations except glucuronidation
- Not inducible but show genetic polymorphism

Microsomal enzymes

- **Present in** → endoplasmic reticulum.
- **Catalyse** → oxidations, reductions, hydrolysis and glucuronide conjugation
- Induced and inhibited by drugs



Microsomal Enzyme Inhibition

- **Mechanism** → One drug can competitively inhibit the metabolism of another if it utilizes same enzyme
- **Occurs by** → direct effect on the enzyme → fast (within hours)
- **Consequences** → Precipitate toxicity of object drug

Microsomal Enzyme Induction

- **Mechanism** → Many drugs interact with DNA → Increase synthesis of microsomal enzymes
→ Rate of metabolism of inducing drug itself or other drugs is increased
- **Occurs by** → DNA interaction → slow (10 - 14 days)
- **Consequences** → Decreased intensity and duration of action of object drugs

Substrate /Object drug	Enzyme Inhibitors	Enzyme Inducers
C - Cyclosporin, CCB T - Tacrolimus S - Statins C - Cisapride A - Amiodaron, Astemizole N - Navirs (Protease inhibitors)	Vitamin - Valproate K - Ketoconazole Cannot - Cimetidine Cause - Ciprofloxacin Enzyme - Erythromycin Inhibition - INH	G - Griseofulvin P - Phenytoin R - Rifampicin S - Smoking Cell - Carbamazepine Phone - Phenobarbitone Battery - Barbiturate Dead - DDT

Hofmann elimination

- Inactivation of the drug in body fluids by spontaneous molecular rearrangement without the agency of any enzyme
- e.g. Atracurium

EXCRETION

Definition

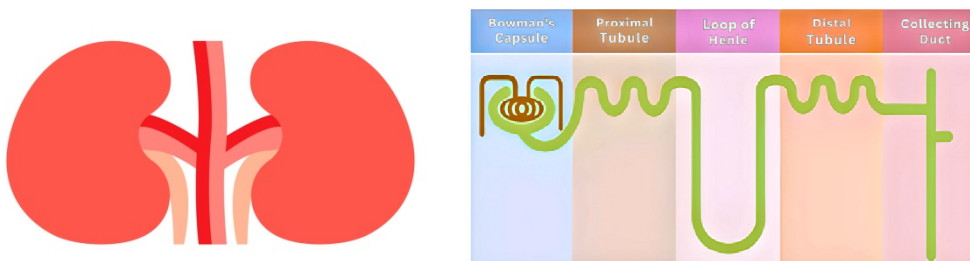
- Passage out of systemically absorbed drug.

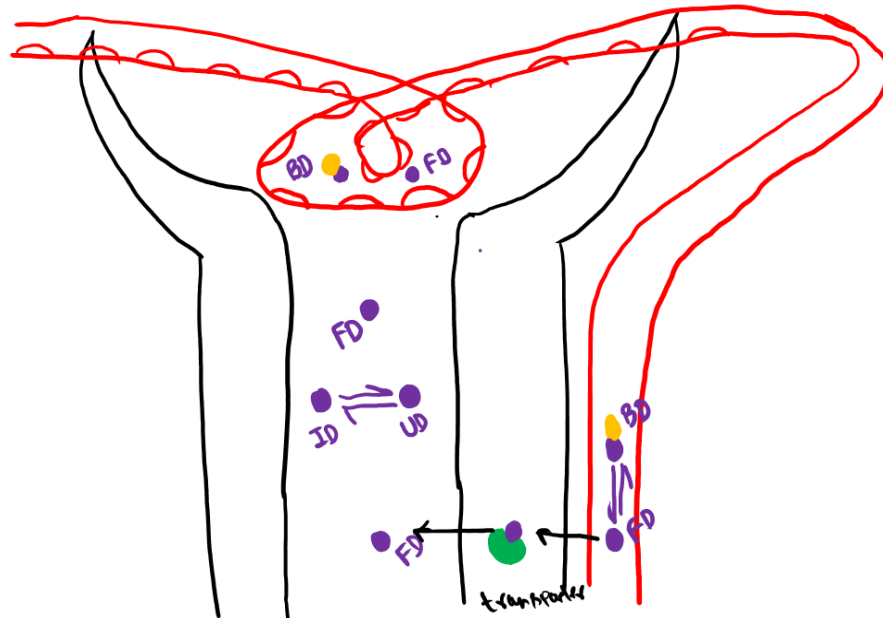
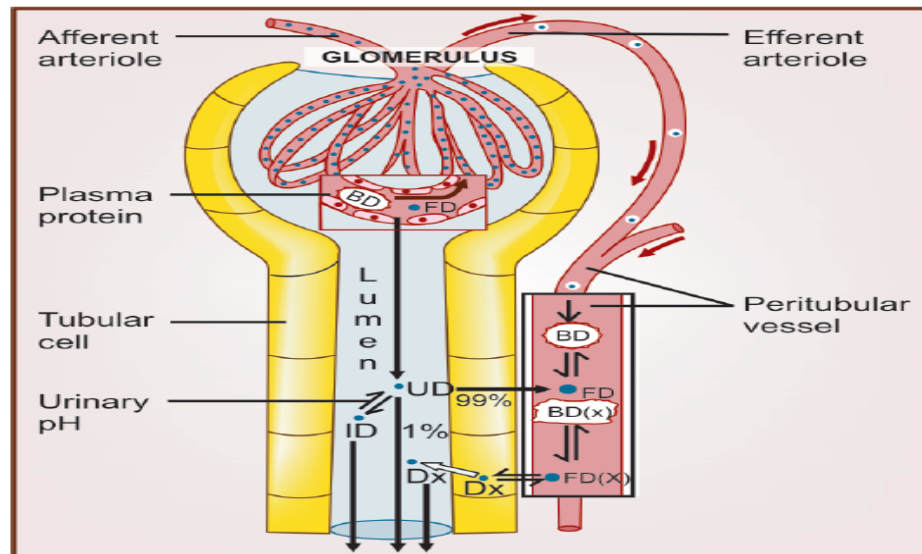
Drugs are excreted in

1. Urine (most important channel)
2. Faces
3. lungs
4. saliva
5. sweat, milk

Renal Excretion

- Net renal excretion = (Glomerular filtration + tubular Secretion) - tubular Reabsorption





1. Microsomal Enzyme Inhibition

- Glomerular capillaries pores → larger than usual
- All free drug (whether lipid-soluble or insoluble) presented to glomerulus is filtered.
- Depends on →
 - a) Plasma protein binding of drug
 - b) Renal blood flow
- Does not depends on → Lipid solubility

2. Tubular reabsorption

- Occurs by passive diffusion
- Depends on →
 - b) Lipid solubility
 - c) Ionization of drug at existing urinary Ph
 - d) Urinary pH

a) **Lipid solubility**

- Lipid-soluble drugs filtered at glomerulus diffuses back
- Non lipid soluble are unable to do so

a) **Ionization of drug at existing urinary Ph**

- Unionised drug filtered at glomerulus back
- Ionized drugs unable to do so

a) **Urinary pH**

- Weak bases ionize more and are less reabsorbed in acidic urine.
- Weak acids ionize more and are less reabsorbed in alkaline urine.

- This principle is utilized for facilitating elimination of drug in poisoning →
 - **Urine is alkalinized in** → barbiturate and salicylate (acidic) poisoning.
 - **Urine is acidified in** → morphine, amphetamine (basic) poisoning

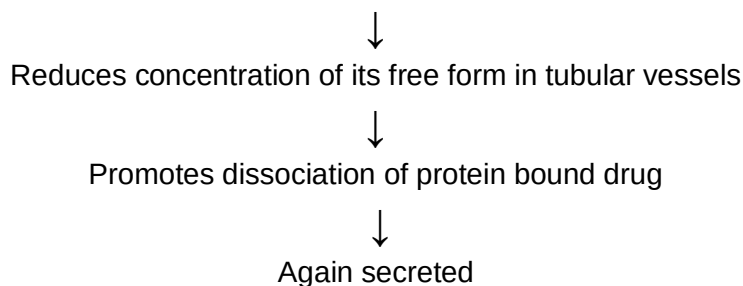
Remember

- **Alkalinization of urine is done by** → IV infusion of sodium bicarbonate
- **Acidification of urine is done by** → IV infusion of arginine hydrochloride followed by ammonium chloride (NH₄Cl)

3. Tubular secretion

- Occurs by passive diffusion
- Depends on →
 - e) Lipid solubility
 - f) Ionization of drug at existing urinary Ph
 - g) Urinary pH

Active transport of drug across tubules by Nonspecific transporters (OAT , OCT)



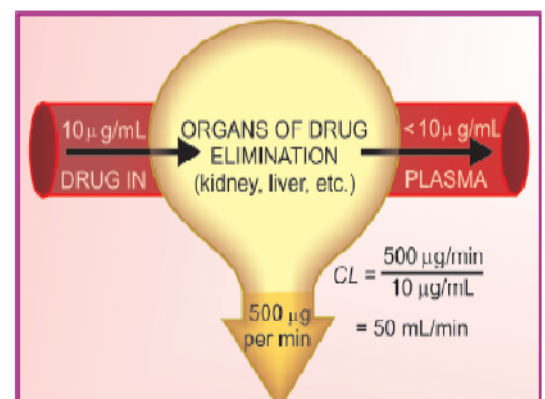
- Bidirectional
- Does not depend on protein binding

Kinetics of Elimination

- Rate of elimination
- Clearance

Rate of Elimination

- Amount of drug eliminated per unit time



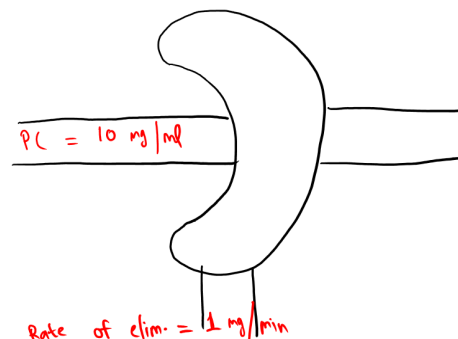
Clearance (CL)

- Volume of plasma from which the drug is completely removed in unit time
- Clearance is measure of → body's ability to eliminate the drug
- It is the ratio of rate of elimination to the concentration of drug.

$$CL = \frac{\text{Drug elimination rate}}{\text{Plasma drug concentration}}$$

Order of Kinetics

- Rate of Elimination $\propto$ (Plasma Concentration)^{order}
- Zero order kinetics
- First order kinetics



1. Zero order kinetics

- Rate of Elimination $\propto$ (Plasma Concentration)⁰
- (Plasma Concentration)⁰ = 1
- Rate of elimination is independent of plasma concentration
- Rate of elimination is constant.
- CL decreases with increase in concentration
- A constant amount of the drug is eliminated in unit time

Mnemonic

Zero	-	Zero order kinetics shown by
W	-	Warfarin
A	-	Alcohol and Aspirin
T	-	Theophylline
T	-	Tolbutamide
Power	-	Phenytoin

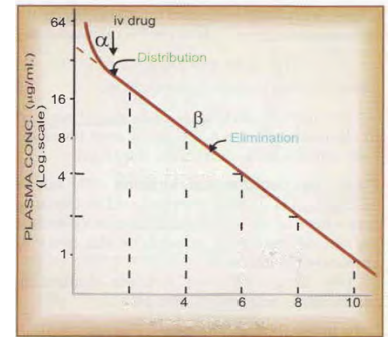
2. First order kinetics

- Rate of Elimination $\propto$ (Plasma Concentration)¹
- Rate of elimination is proportional to plasma concentration for drugs
- CL remains constant
- A constant fraction of drug present in body is eliminated in unit time.

Zero Order Kinetics	First Order Kinetics
• (Plasma Concentration) ⁰ = 1	• (Plasma Concentration) ¹
• Rate of elimination is constant	• Rate of elimination is proportional to plasma concentration for the drugs
• CL decreases with increase in concentration	• CL remains constant
• A constant amount of the drug is eliminated in unit time	• A constant fraction of the drug present in the body is eliminated in unit time.
• t _{1/2} increases with dose	• t _{1/2} remains constant

Plasma half-life

- Time taken for its plasma concentration to be reduced to half of its original value.
- Plasma concentration-time plot → 2 slopes →
 - Initial rapidly declining (α) phase-due to distribution.
 - Later less declined (β) phase-due to elimination.



- **First order kinetics** → $t_{1/2}$ remains constant (because V and CL do not change with dose)
- **Zero order kinetics** → $t_{1/2}$ increases with dose (because CL progressively decreases as dose increased)

First order kinetics ($t_{1/2}$ remains constant)

- 1 $t_{1/2}$ → 50% drug is eliminated.
 - 2 $t_{1/2}$ → 75% (50 + 25) drug is eliminated.
 - 3 $t_{1/2}$ → 87.5% (50+ 25 + 12.5) drug is eliminated
 - 4 $t_{1/2}$ → 93.75% (50 + 25 + 12.5 + 6.25) drug is eliminated
 - 5 $t_{1/2}$ → 96.875% (50 + 25 + 12.5 + 6.25 + 3.125) drug is eliminated.
- Nearly complete drug elimination occurs in 4-5 half lives

Repeated Drug Administration

Plateau principle

When constant dose of a drug is repeated before $4 t_{1/2}$



It would achieve higher peak concentration, because some remnant of previous dose will be present in body



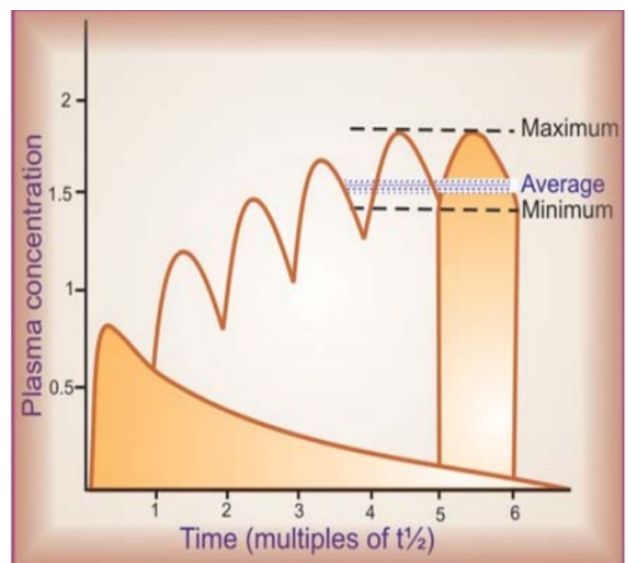
This continues with every until progressively increasing
Rate of elimination = Rate of administration



Subsequently plasma concentration plateaus and fluctuates about an average steady-state level.



Plateau principle of drug accumulation
Steady-state is reached in 4-5 $t_{1/2}$



Example→

- A drug with half- life 6 hours, given i/v in dose of 100 mg and same dose is repeated every 6 hours.
- Concentrations of the drug in blood will be:
 - At 6 hour (1 $t/2$) → 50 +100 =150mg
 - At 12 hour (2 $t/2$) → 75 +100 =175mg

- At 18 hour ($3 t/2$) → $87.5 + 100 = 187.5\text{mg}$
- At 24 hour ($4 t/2$) → $93.75 + 100 = 193.75\text{mg}$
- At 30 hour ($5 t/2$) → $96.88 + 100 = 196.88\text{mg}$

When a drug is repeated at relatively short intervals
↓
It accumulates in body until **elimination = administration**
↓
A steady state plasma concentration (C_{pss}) is attained

Target Level Strategy

- A. Drugs with short $t_{1/2}$
- B. For drugs with longer $t_{1/2}$

A. Drugs with short $t_{1/2}$ (upto 2-3 hr)

Steady state is achieved after about $4 t_{1/2}$ (short time)
↓
Clinically acceptable
↓
Administered at conventional intervals (6-12 hr)

B. For drugs with longer $t_{1/2}$

Steady state is achieved after about $4 t_{1/2}$
↓
Clinically unacceptable
↓
Such drugs administered by initial loading and subsequent maintenance doses

Monitoring of plasma concentration of drugs / Therapeutic drug monitoring (TDM)

A. TDM required for

1. Drugs with low safety margin - digoxin, anticonvulsants, antiarrhythmics, theophylline, aminoglycoside, lithium, tricyclic antidepressants.
2. Potentially toxic drugs used in the presence of renal failure aminoglycoside antibiotics, vancomycin.
3. In case of poisoning
4. In case of failure of response without any apparent reason-antimicrobials.
5. To check patient compliance- psychopharmacological agents



TDM is required for		
A	-	Aminoglycosides (e.g. Gentamicin)
Drug	-	Digitalis
Possessing	-	Phenytoin (Anti-epileptics)
Low	-	Lithium
Therapeutic	-	Tricyclic antidepressants
Index	-	Immunomodulators

B. TDM not required for

1. Drugs whose response is easily measurable (antihypertensives, hypoglycaemics, diuretics)
2. Drugs activated in the body (levodopa)
3. 'Hit and run drugs' (reserpine, guanethidine, MAO inhibitors, omeprazole)
4. Drugs with irreversible action (organophosphate anticholinesterases, phenoxybenzamine)



PHARMACODYNAMICS

Definition

- What drug does to body
- Deals with biochemical and physiological effects of drugs and their mechanism of actions

Principles of Drug Action

- Drugs do not create new functions.
- They modify inherently possessed functions of concerned tissues

Types of drug actions

1. Stimulation
2. Depression
3. Irritation
4. Replacement
5. Cytotoxic action

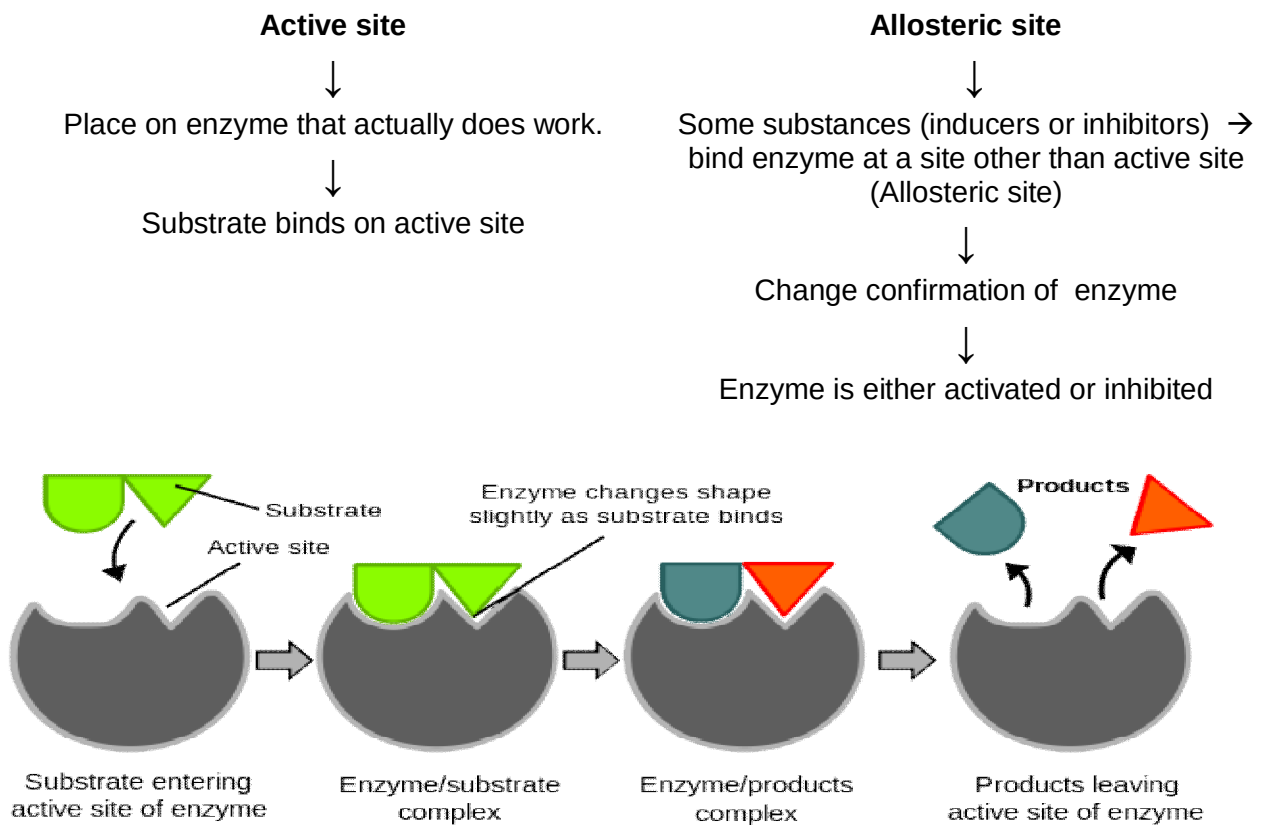
Mechanism of Drug Action

- 4 Mechanisms →
 1. Enzymes
 2. Ion channel
 3. Transporters
 4. Receptors

ENZYMES

Sites

- Enzyme has 2 sites →
 - Active site
 - Allosteric site



Michaelis-Menten Model

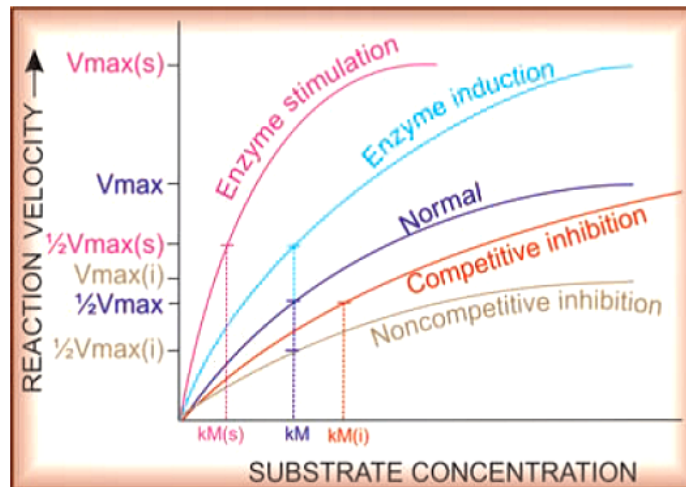
As we increase concentration of substrate

↓

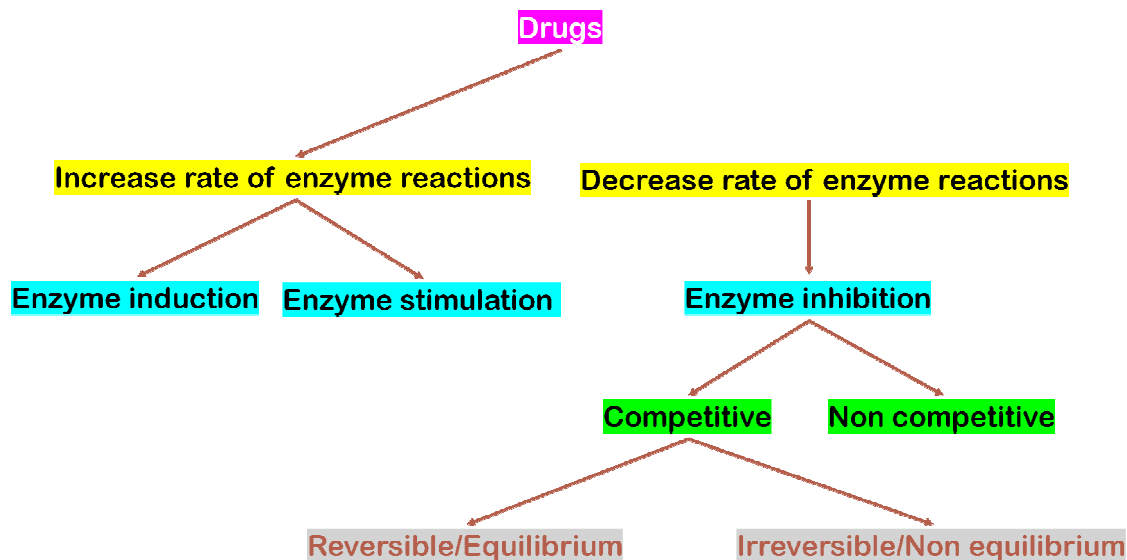
Velocity/rate of reaction goes on increasing linearly up to a point

↓

After that velocity becomes constant



- **K_m (Michaelis menton's constant)** → Amount of substrate required to produce half of maximal velocity
- **V_{max}** → Maximum reaction velocity

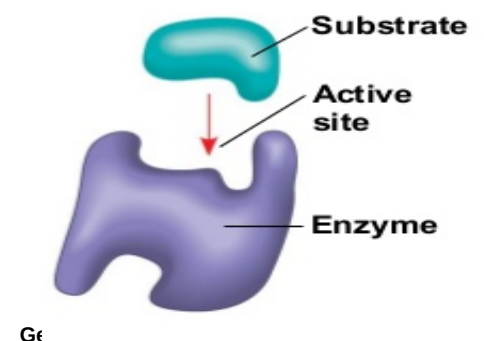


- **K_m (Michaelis menton's constant)** → Amount of substrate required to produce half of maximal velocity

A. INCREASE RATE OF ENZYME REACTIONS

1) Enzyme induction → Synthesis of more enzyme protein

- **k_M** → Same
- **V_{max}** → Increased



2) Enzyme Stimulation → Increases its affinity for substrate

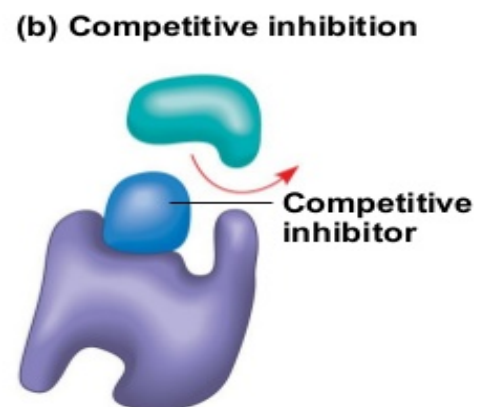
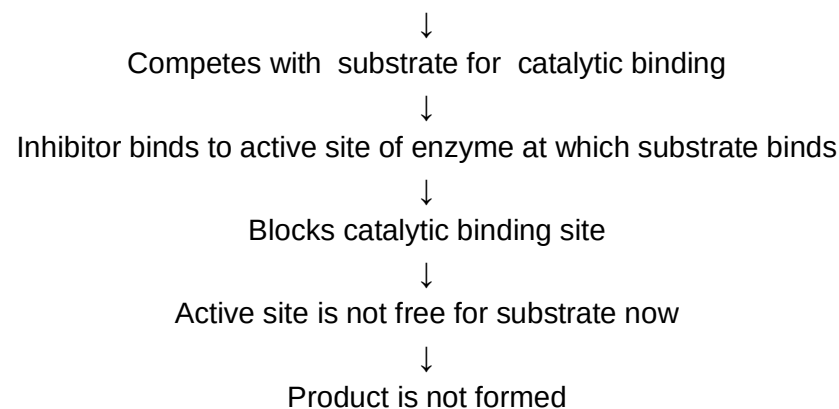
- K_M → Lowered
- V_{max} → increased

B. DECREASE RATE OF ENZYME REACTIONS

- 1) Competitive Inhibition
- 2) Noncompetitive Inhibition

1) Competitive Inhibition

Inhibitor have similar structure as that of substrate of enzyme



a) Equilibrium / Reversible type Competitive Inhibition

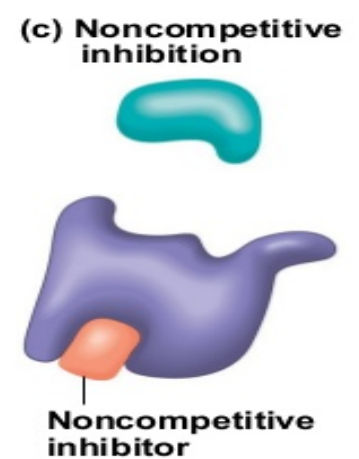
- Surmountable /Reversible → Inhibition can be overcome by increasing dose of substrate
- It results in →
 - K_M → Rise
 - V_{max} → Same

b) Non equilibrium / Irreversible type Competitive Inhibition

- Insurmountable / Irreversible → Inhibition cannot be overcome by increasing dose of substrate
- It results in →
 - K_M → rises
 - V_{max} → decreases

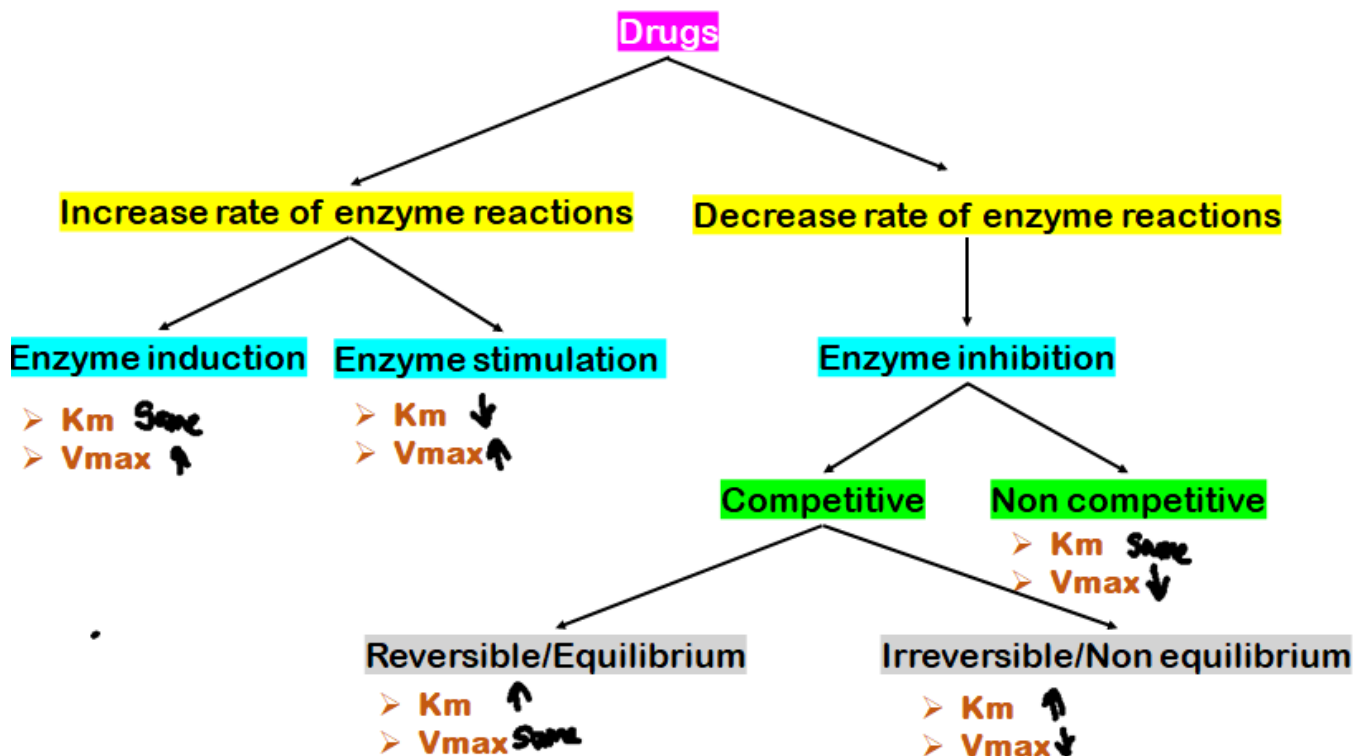
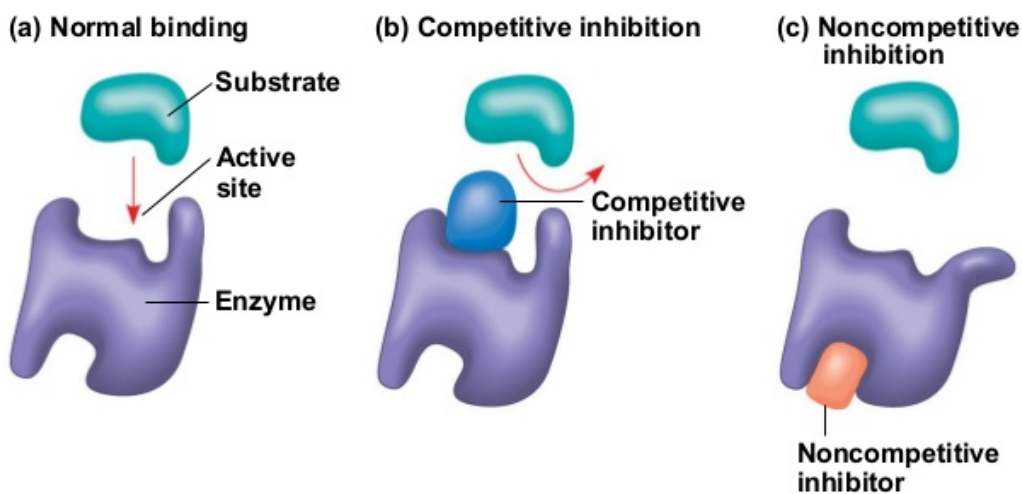
2) Noncompetitive Inhibition

Inhibitor do not have similar structure as that of substrate of enzyme



↓
 Alters enzyme in such a way that it loses its catalytic property
 ↓
 Product is not formed

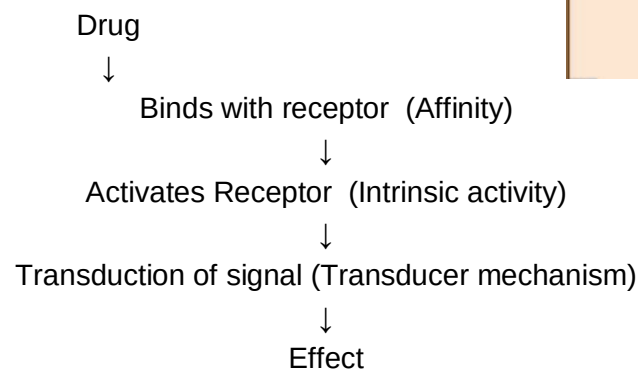
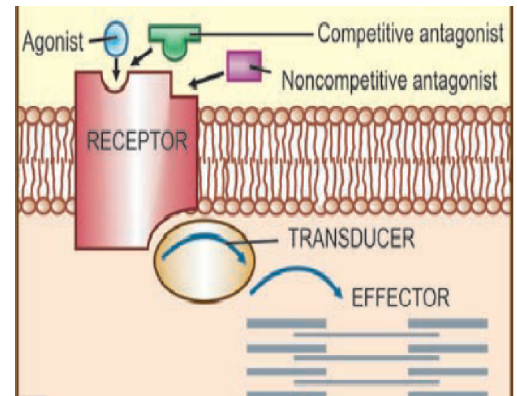
- Insurmountable / Irreversible → Inhibition cannot be overcome by increasing dose of substrate
- It results in →
 - K_m → rises
 - V_{max} → decreases



RECEPTOR

Definition

- Macromolecule located on surface of effector cell that helps to recognize signal molecule/ drug and initiate response to it, but itself has no other function



Properties

- Affinity
- Intrinsic activity

1. Affinity

- RateAbility of a drug to combine with receptor
- If a drug has no affinity, it will not bind to the receptor.
- Drugs with high affinity can be used in low concentrations.

2. Intrinsic activity

- Ability of drug to activate receptor after binding to receptor
- Varies from -1 through zero to +1

Types of Drugs based on intrinsic activity

- Agonist
- Partial agonist
- Antagonist
- Inverse agonist

1. Agonist

- Bind to receptor and activate it maximally similar to that of physiological molecule.
- IA = +1

2. Partial agonist

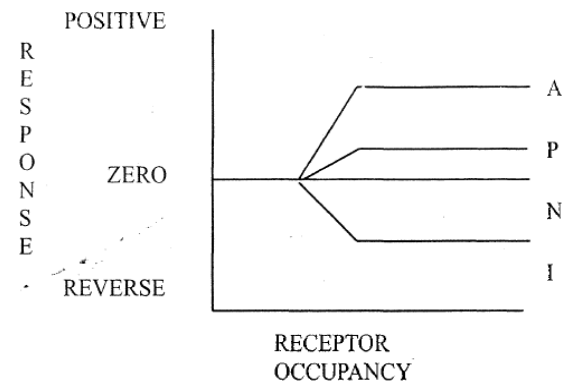
- Bind to receptor and activates it submaximally similar to that of physiological molecule
- IA = between 0 to +1

3. Antagonist

- Binds to receptor but produces no effect
- But now agonist is not able to bind to receptor because these are already occupied by the antagonist.
- Decreases action of agonist but itself has no effect.
- $IA = 0$

4. Inverse agonist

- Bind to receptor and produce opposite effect
- $IA = \text{negative}$



TRANSDUCER MECHANISM

Types

5 Types→

1. G-protein coupled receptors (GPCR)
 - a) Adenylate cyclase/cyclic AMP
 - b) Phospholipase C: IP₃-DAG pathway
2. Receptors with intrinsic ion channel
3. Transmembrane Enzyme-linked receptors
4. Transmembrane JAK-STAT binding receptors
5. Receptors regulating gene expression (Transcription factors)

1. G-protein coupled receptors (GPCR)

- Receptor molecule has 7 α -helical membrane spanning amino acid (AA) segments
- Consist of 3 subunits → α , β and γ

Guanine nucleotide binds to α subunit



In inactive state GDP is bound



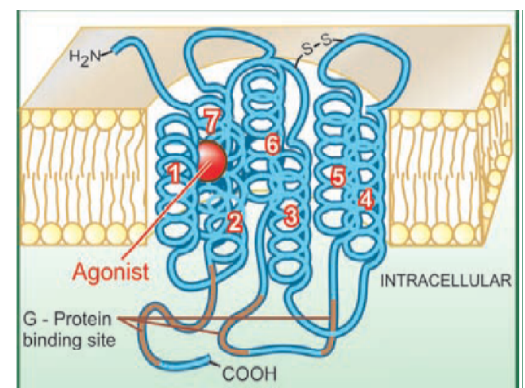
Displacement of GDP by GTP



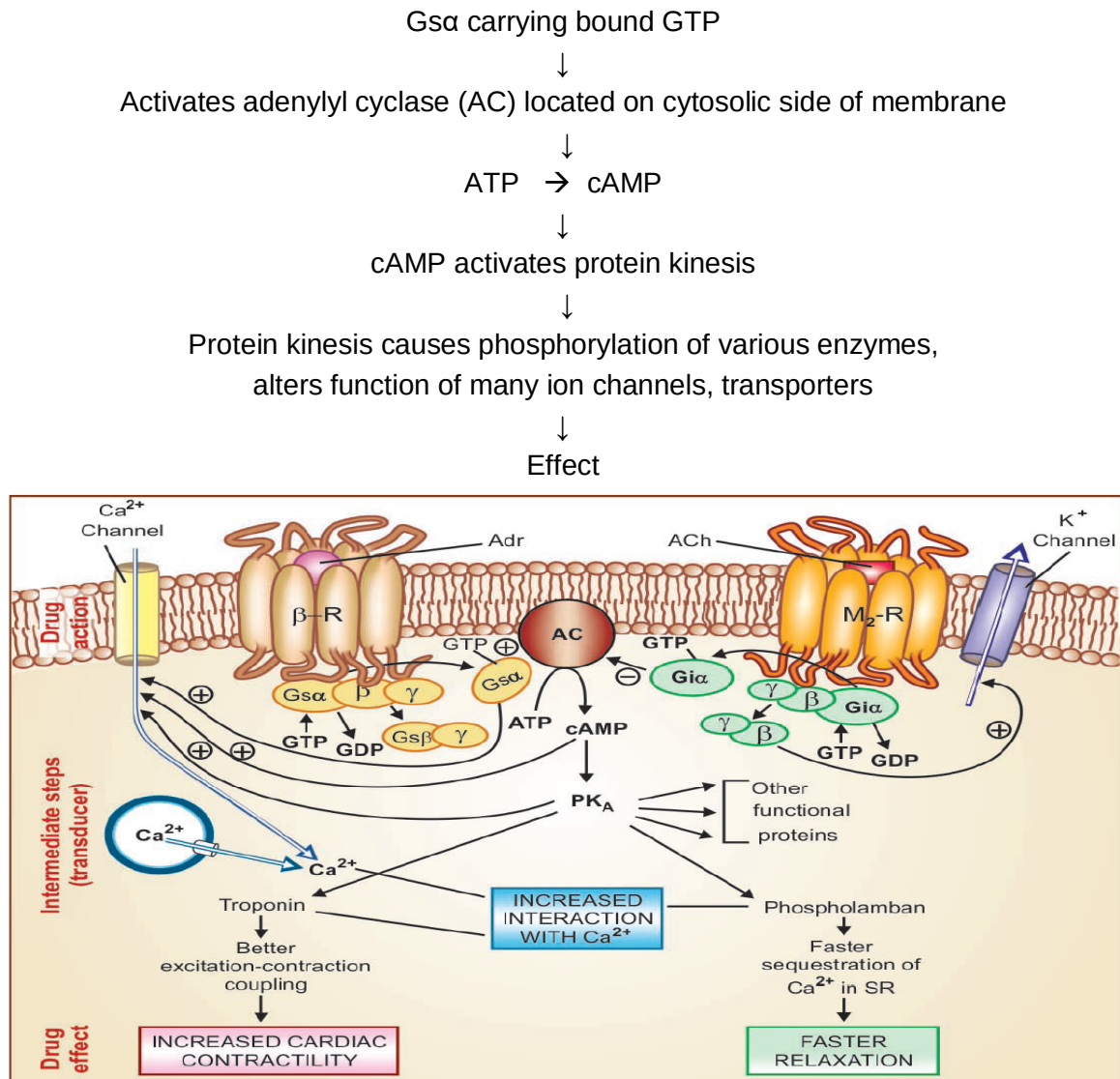
Activation of receptor



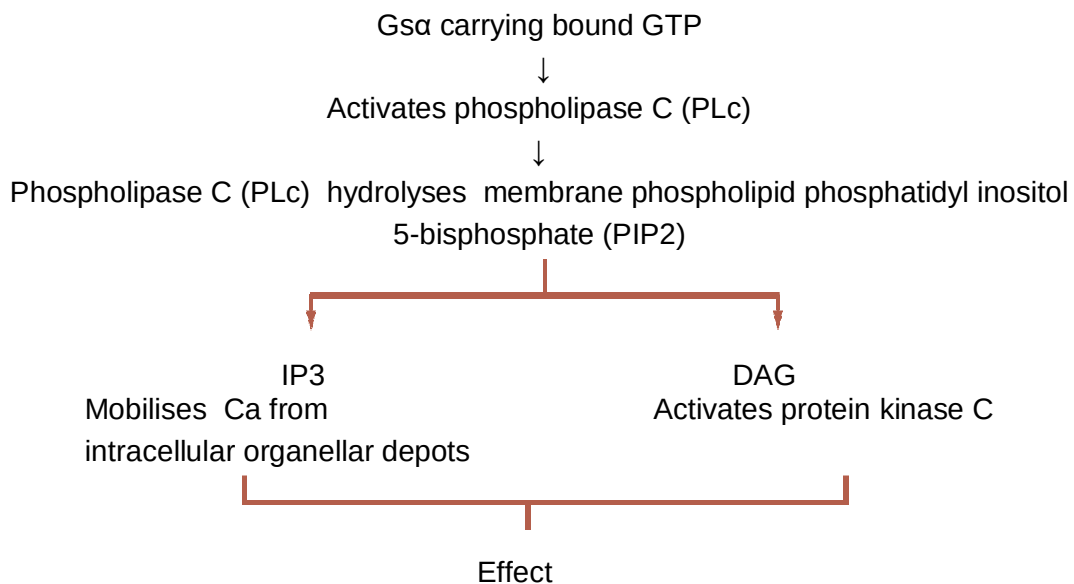
Active α subunit carrying GTP dissociates from other two subunits

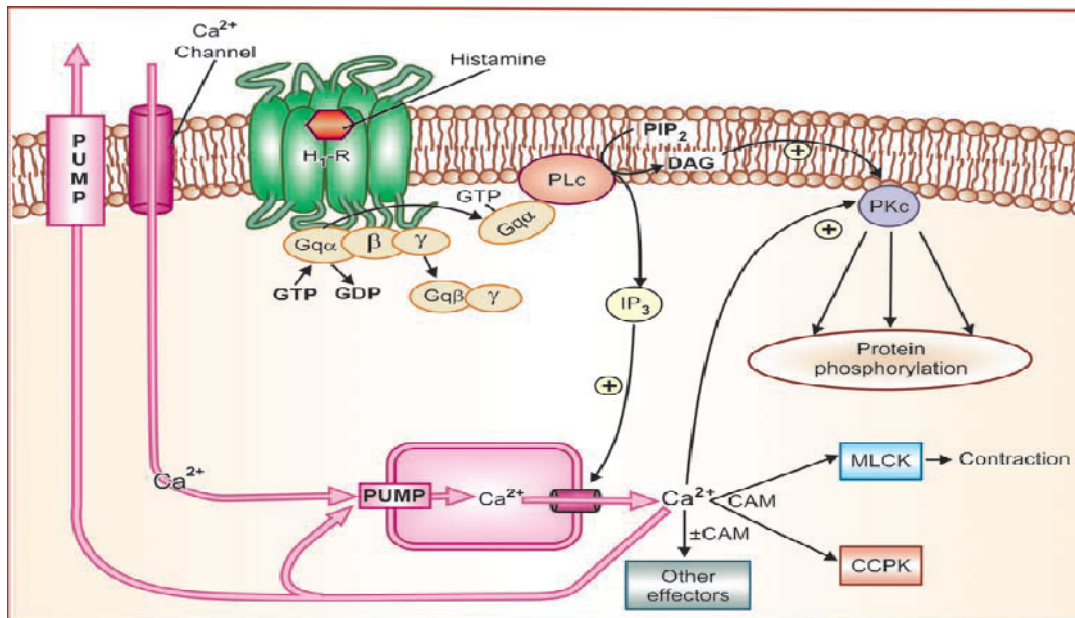


A. Adenylate cyclase/cyclic AMP



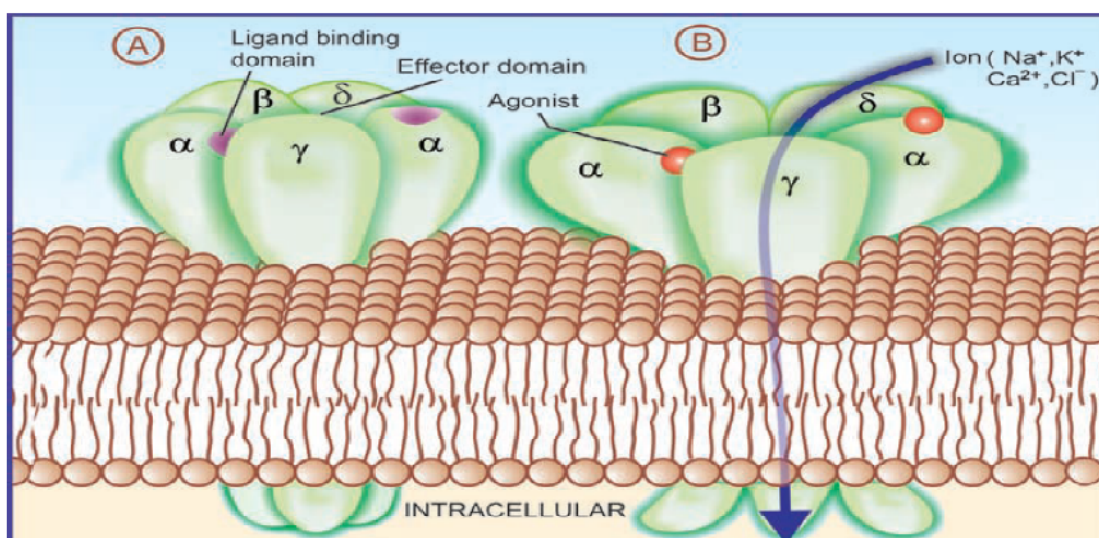
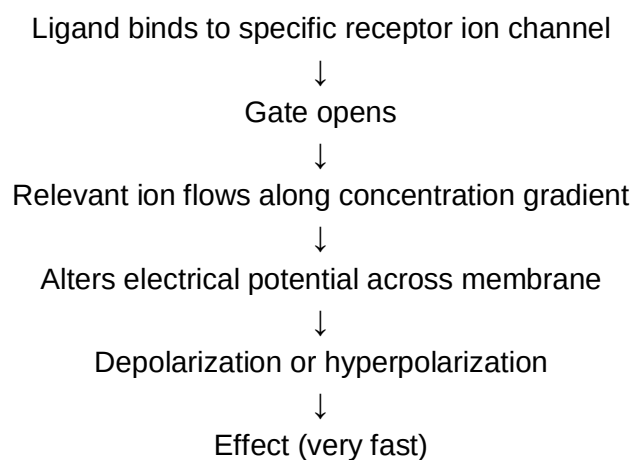
B. Phospholipase C: IP₃-DAG pathway





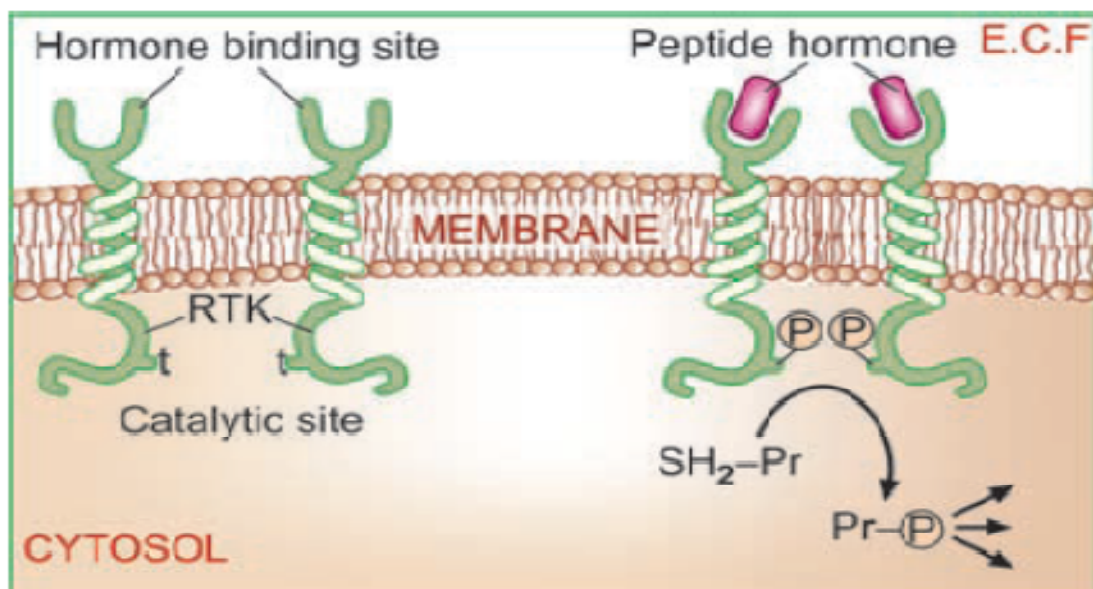
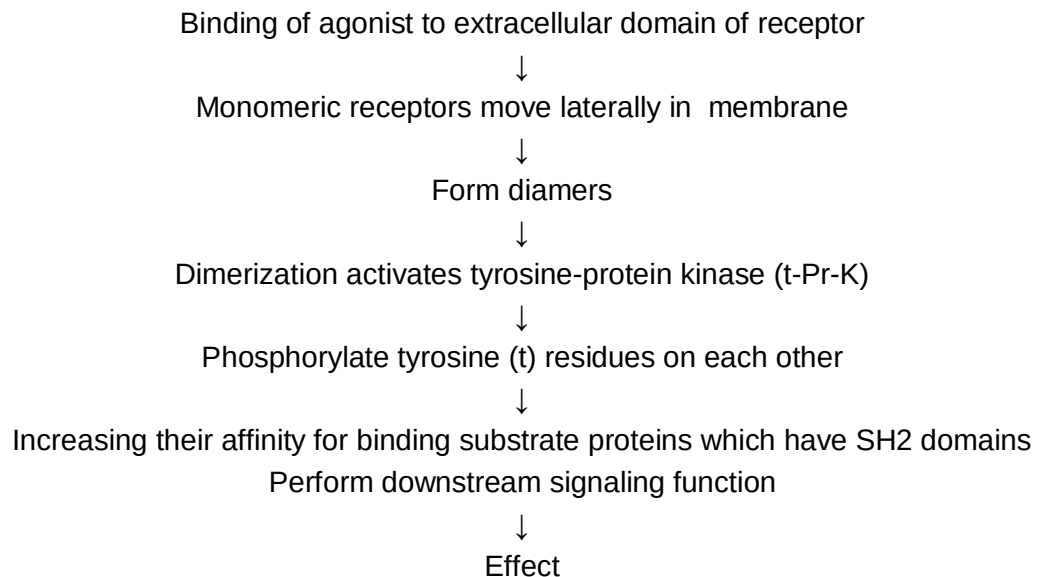
2. Receptors with intrinsic ion channels

- Also called → ligand gated ion channels
- Enclose → ion selective channels (for Na⁺, K⁺, Ca²⁺ or Cl⁻) within their molecules.

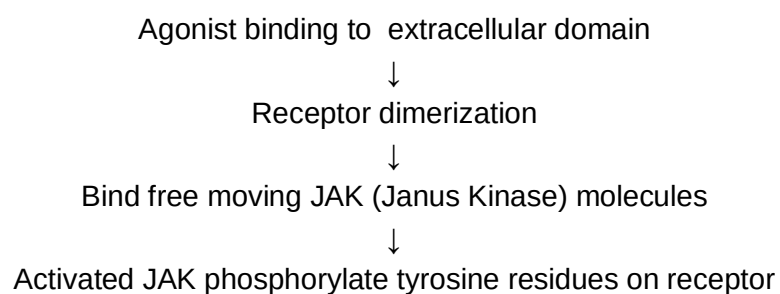


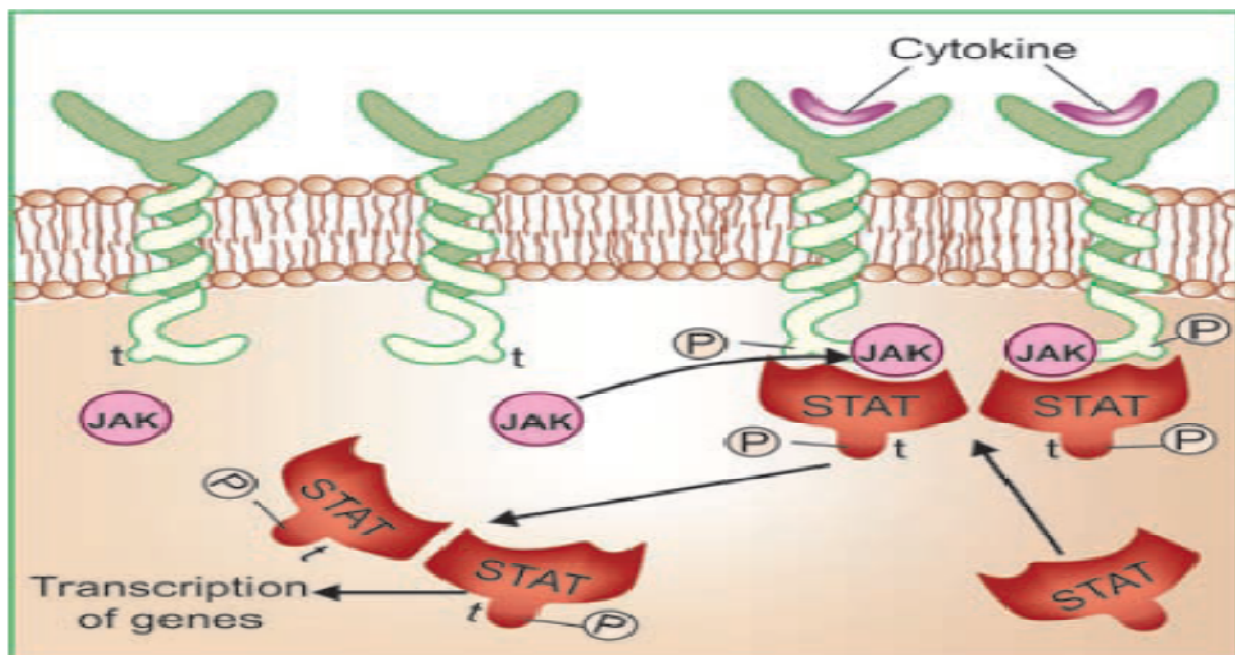
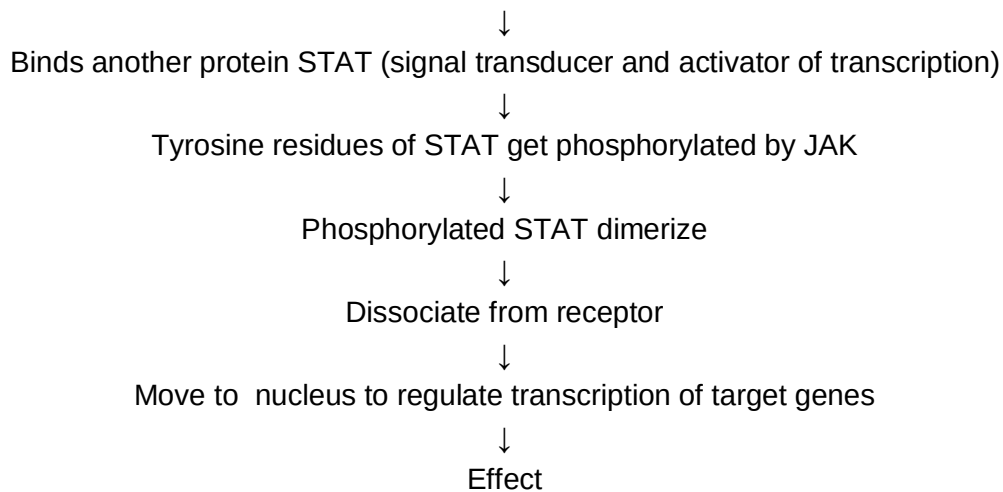
3. Transmembrane enzyme-linked receptors

- Agonist binding site → lie on outer face of plasma membrane
- Catalytic site (having intrinsic protein kinase activity) → lie on inner face of plasma membrane.



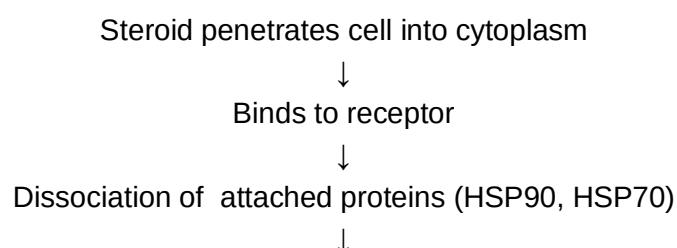
4. Transmembrane JAK-STAT binding receptors

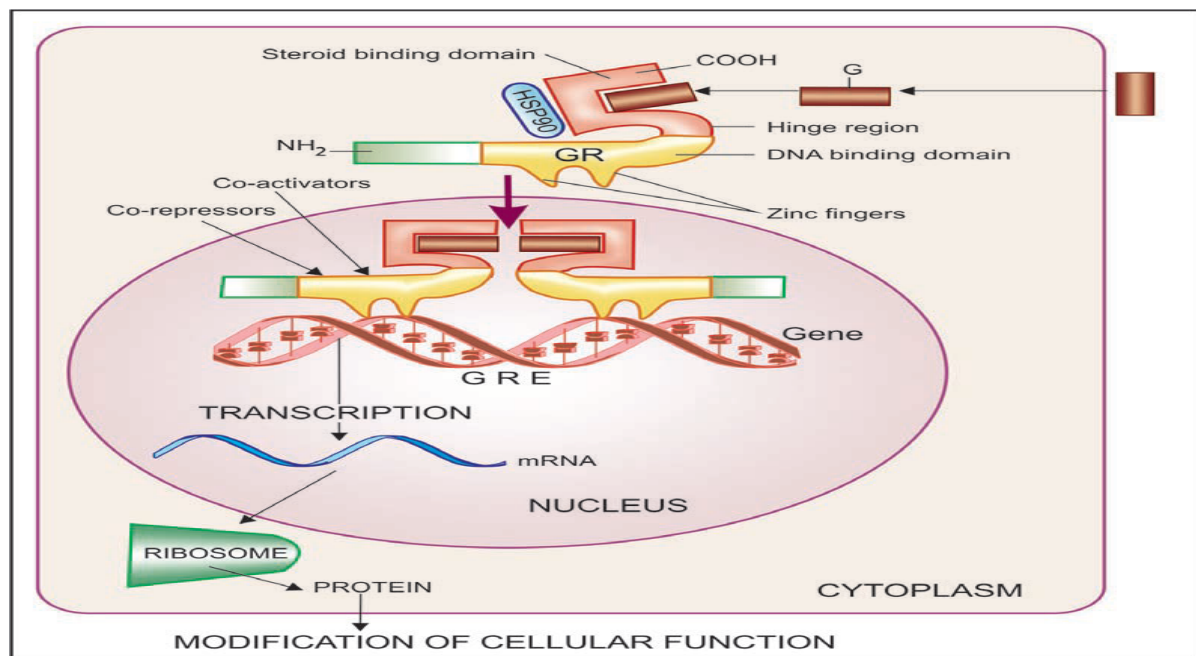
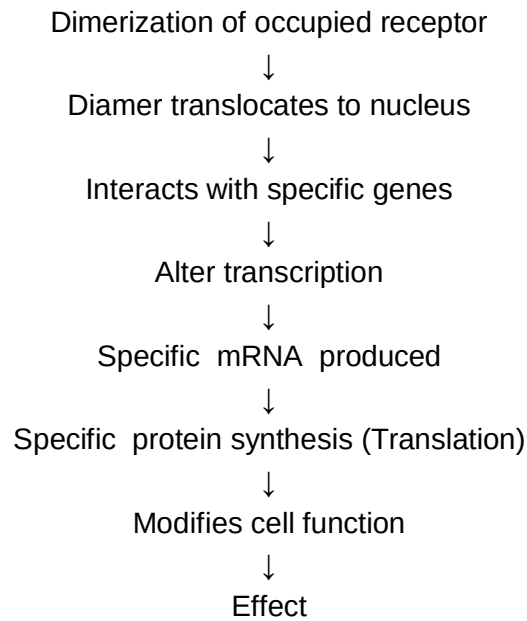




5. Receptors regulating gene expression (Transcription factors)

- Intracellular (cytoplasmic or nuclear) soluble proteins
- Respond to lipid soluble chemical messengers that penetrate cell
- Slowest acting
- Receptor normally resides in cytoplasm in association with 3 other proteins → heat shock protein 90 (HSP 90)
- Receptor has → a steroid binding domain near carboxy terminus and a mid region DNA binding domain having two 'Zinc fingers'





Examples→

Cytosolic

Corticosteroids

- Glucocorticoids
- Mineralocorticoids

D-Vitamin D

Intra-nuclear

P-PPAR

S-Sex Hormones

- Estrogen
- Progesterone
- Testosterone

V-Vitamin A

T-Thyroid hormones

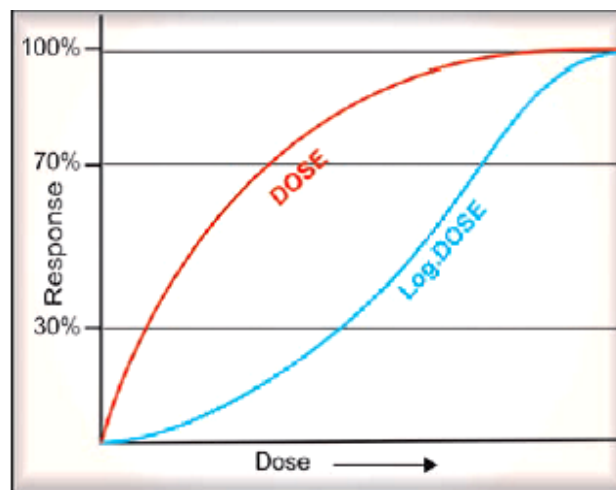
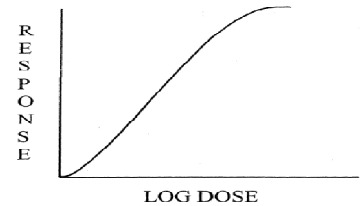
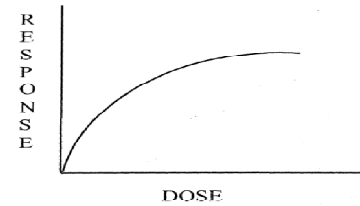
DOSE RESPONSE CURVE (DRC)

Introduction

Graph between →

- **X-axis** → Plasma concentration of drug
- **Y-axis** → Effect/ response produced by drug

- Intensity of response increases with increase in dose
 - **DRC** → Hyperbola (cannot give good mathematical comparisons)
 - **Log DRC** → Sigmoid curve



PARAMETERS

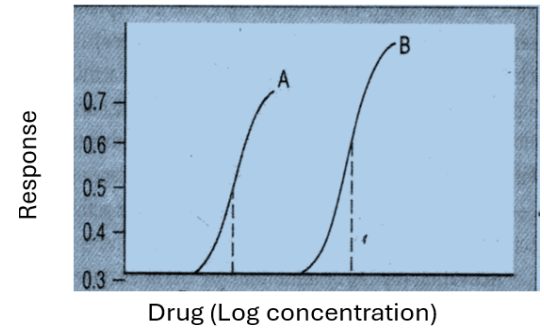
- 4 important parameters determined from DRC →
 1. Potency
 2. Efficacy
 3. Slope
 4. Selectivity, Therapeutic index, Therapeutic range

1) Potency

- Amount of a drug needed to produce response (x axis)
 - Drugs producing same response at **lower dose** → **More potent**
 - Drugs producing same response at **large dose** → **Less potent**
- In DRC →
 - More a drug is on **left side** of graph → **Higher is its potency**
 - More a drug is on **right side** of graph → **Lower is its potency**

2) Efficacy

- Maximum effect produced by a drug (y axis)
 - **More peak** of the curve → **Greater is efficacy**
 - **Less peak** of the curve → **Lesser is efficacy**

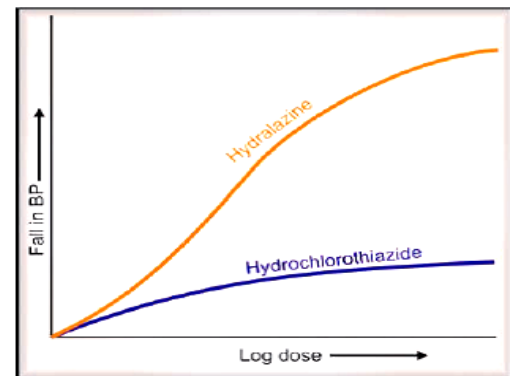


Remember

- Efficacy is clinically more important than potency
- Efficacy is a more decisive factor in the choice of a drug

3) Slope

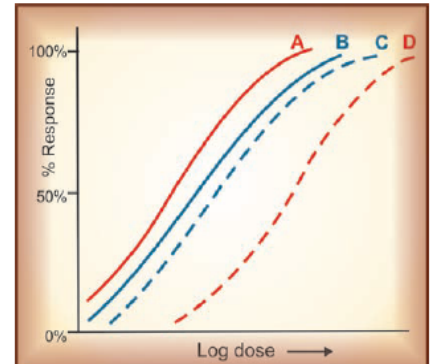
- **A steep slope** → A moderate increase in dose will markedly increase response (dose needs individualization)
- **A flat slope** → A little increase in response will occur over a wide dose range



4) Selectivity, Therapeutic index, Therapeutic range

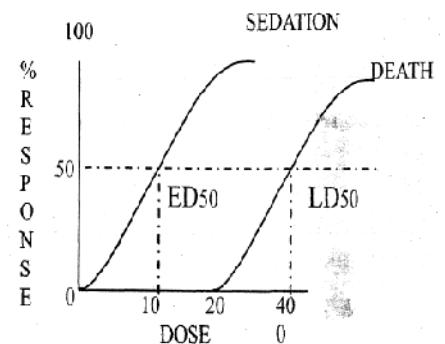
Selectivity

- Single Drug produce many action
- DRCs for different effects of a drug may be different
- Extent of separation of DRCs of a drug for different effects is a measure of its selectivity



Therapeutic index / Safety margin

- Gap between therapeutic effect DRC and adverse effect DRC
- Measure of safety of a drug.
- Median Effective Dose (ED50)**
 - Dose that will produce half of the maximum (50%) response.
 - More is ED50, lower is the potency and vice a versa.



- **Median Lethal Dose (LD50)**

- Dose that will result in death of 50% of animals receiving drug.
- More is LD50 safer is the drug.

$$\text{Therapeutic index} = \frac{\text{median lethal dose}}{\text{median effective dose}}$$

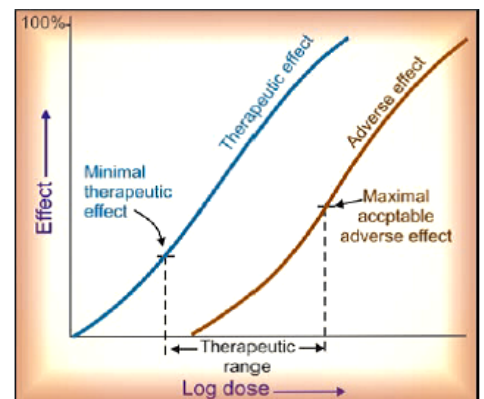
$$\text{or } \frac{LD_{50}}{ED_{50}}$$

- Drugs having **high T.I** → **Safer**
- Drugs having **low T.I** → **Toxic**

Therapeutic range / Therapeutic window

- Difference between →
 - Dose which produces minimal therapeutic effect
 - Dose which produces maximal acceptable adverse effect

Drugs which have low Therapeutic window
 ↓
 Plasma concentration has to be monitored regularly
 ↓
 Therapeutic Dose Monitoring (TDM)



COMBINED EFFECT OF DRUGS

- 1) Synergism
- 2) Antagonism

1) Synergism

- When action of one drug is increased by other
- In a synergistic pair, both drugs can have action in same direction or one may be inactive but still enhance action of other when given together.

Types

- **2 Types** →
 - (a) **Additive**
 - Effect of drugs A + B = effect of drug A + effect of drug B
 - (b) **Supraadditive (potentiation)**
 - Effect of drug A + B > effect of drug A + effect of drug B

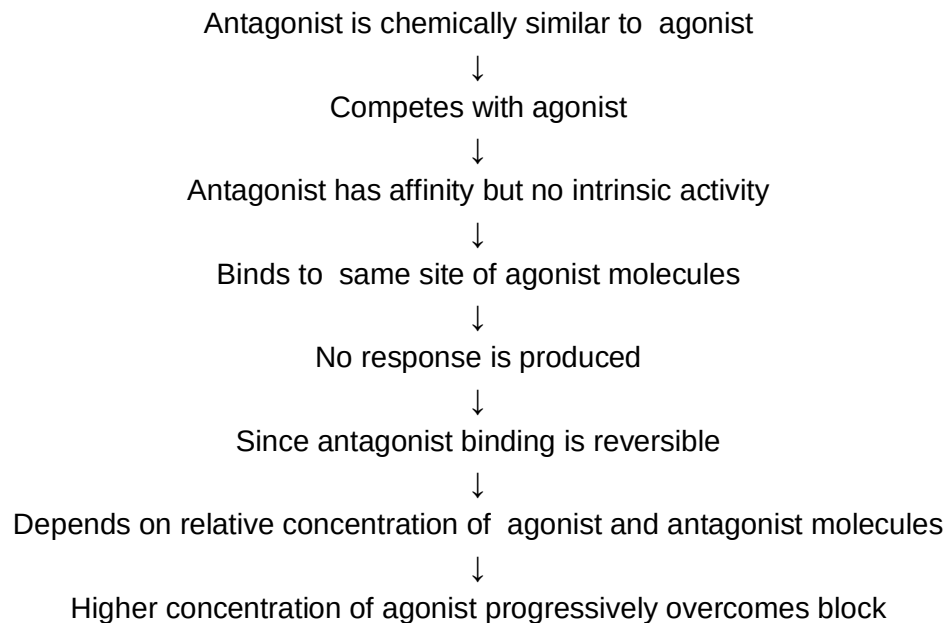
2) Antagonism

- When one drug decreases action of another
- Effect of drugs A + B < effect of drug A + effect of drug B

Types

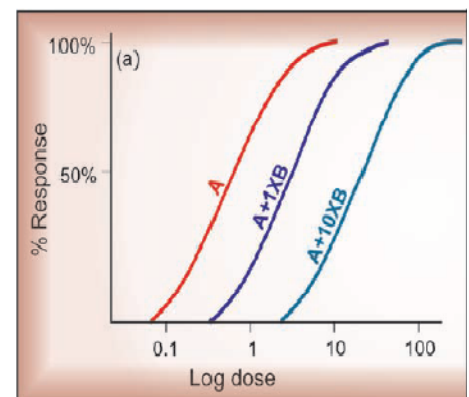
- **2 Types** →
 - a) Competitive antagonism
 - b) Non competitive antagonism

(a) Competitive antagonism

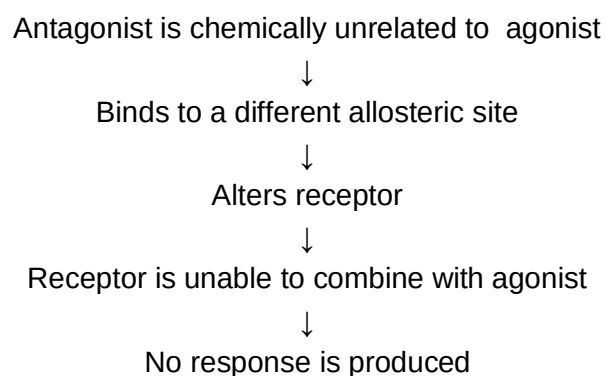


DRC

- Log DRC of agonist is shifted to right.
- Parallel shift of agonist DRC with no suppression of maximal response is obtained



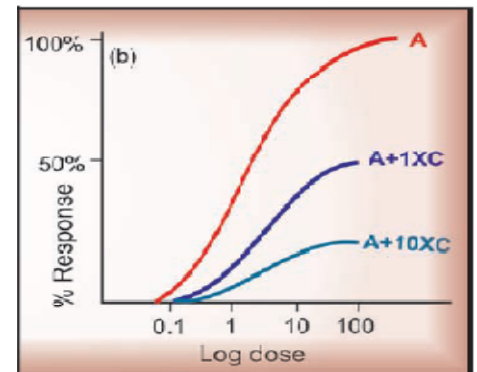
Non Competitive antagonism



↓
Because agonist and antagonist are combining with different sites
↓
No competition between them
↓
Even high agonist dose is unable to reverse block

DRC

- Increasing concentrations of antagonist → flatten agonist DRC



DRUG

WHO definition

"Drug is a substance that is used to → Modify or explore physiological systems or pathological states for the benefit of recipient."



Drug Dosage

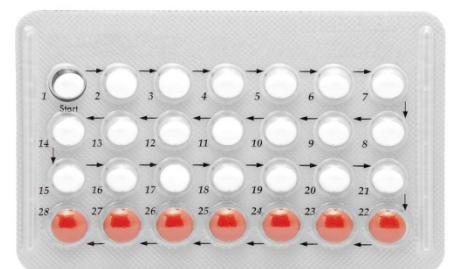
- Appropriate amount of a drug needed to produce a certain degree of response in a patient.
- So dose of a drug has to be qualified in terms of chosen response, e.g.
 - Analgesic dose of aspirin is 0.3-0.6 g
 - Its anti platelet dose is 60-150 mg/ day,
 - Its antiinflammatory dose for RA is 3-5 g per day.

Types

- Standard dose
- Regulated dose
- Target level dose
- Titrated dose

1. Standard dose

- Same dose is appropriate for most patients-individual variations
- e.g. oral contraceptives, penicillin, chloroquine, mebendazole



2. Regulated dose

- Drug modifies a body function which can be easily measured.
- Dosage is accurately adjusted by repeated measurement of affected physiological parameter
- Measurement of plasma drug concentration is not needed.
- e.g. antihypertensives, hypoglycaemics, diuretics



3. Target level dose

- Response is not easily measurable
- An empirical dose is given in beginning → adjustments are made by actual monitoring of plasma concentrations.
- e.g. antidepressants, antiepileptics, digoxin, lithium, theophylline.



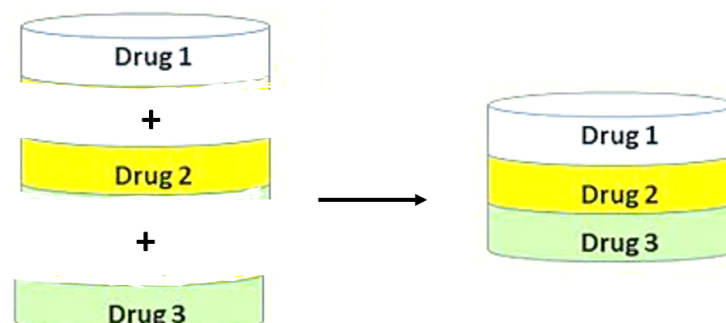
4. Titrated dose

- Dose needed to produce maximal therapeutic effect cannot be given because of adverse effects.
- Optimal dose is calculated by titrating it with an acceptable level of adverse effect.
- Low initial dose and upward titration or high initial dose and downward titration can be practised.
- e.g. anticancer drugs, corticosteroids, levodopa.



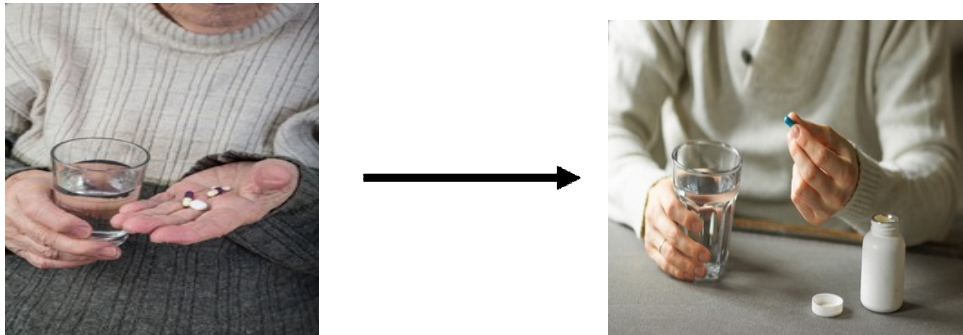
Fixed dose ratio combination preparations

- A large number of pharmaceutical preparations contain two or more drugs in a fixed dose ratio



Advantages

1. Convenience and better patient compliance
2. Certain drug combinations are synergistic, e.g.
e.g. sulfamethoxazole + trimethoprim
3. Therapeutic effect of 2 components being same may add up while side effects being different may not e.g. amlodipine + atenolol as antihypertensive.
4. Side effect of one component may be counteracted by the other
eg. a thiazide + a potassium sparing diuretic
5. Combined formulation ensures that a single drug will not be administered □ important in treatment of tuberculosis and HIV-AIDS.



Disadvantages

1. Patient may not actually need all drugs present in a combination → subjected to additional side effects and expenses.
2. The dose of most drugs needs to be adjusted and individualised → When a combined formulation is used → this cannot be done without altering dose of other components
3. Time course of action of the components may be different → administering them at same intervals may be inappropriate.
4. Altered renal or hepatic function of patient may differently affect pharmacokinetics of components.
5. Adverse effect cannot be easily ascribed to particular drug causing it.
6. Contraindication to one component (allergy) → contraindicates the whole preparation.

Drug Nomenclature

Chemical name

- Follows rules issued by IUPAC
- e.g. 6 R-6 (α-D-phenyl glyceryl amino) penicillin
- **Non-proprietary (official or approved or Generic name or International non proprietary INN) name**
 - Chosen by official bodies (WHO)
 - e.g. ampicillin.
- **Proprietary name (brand name or trade name)**
 - Given by Pharmaceutical company, which is Patented
 - eg. Biocillin

Orphan drugs

- Medicines which are unlikely to be developed by pharmaceutical industry → due to economic reasons but which respond to public health needs.
- An orphan drug → a pharmaceutical agent that has been developed specifically to treat a rare medical condition (fewer than 200,000 people) → orphan disease.
 - Deferipirone to treat iron overload in thalassemia patients
 - N-acetylcysteine to treat paracetamol poisoning
- Since pharmaceutical companies will not like to develop such a drug due to lack of financial benefits, a separate law known as 'The Orphan Drug Act' was passed in 1983.
- Intent of the Orphan Drug Act → to stimulate research, development, and approval of products that treat rare diseases



Me too drug

- Drug similar to already known drug with minor difference
 - Similar → MOA, Indications and adverse effects.
 - Main difference → pharmacokinetic parameters like V , $t_{1/2}$,
- Eg.
 - Enalapril, ramipril, perindopril, captopril
 - Citalopram and escitalopram.



Over-the-counter drugs: (OTC)

- Drugs that do not require a doctor's prescription.
- These drugs are considered safe enough for use without a medical practitioners supervision.

Spurious Drugs

A drug shall be deemed to be spurious if →

- It is manufactured under a name which belongs to another drug
- It is an imitation of another drug
- It has been substituted partly or wholly by another drug or
- It wrongly claims to be product of another manufacturer
- Contaminated and misbranded drugs



Misbranded Drugs

A drug shall be deemed to be misbranded →

- If it is so colored, coated, powdered or polished that damage is concealed or
- if it is made to appear of better or greater therapeutic value than it really is or
- If it is not labelled in the prescribed manner or
- If its label or container or anything accompanying the drug bears any statement, design or device which makes any false claim for the drug or which is false or misleading in any particulars.



NEW DRUG DEVELOPMENT

New drug development involves

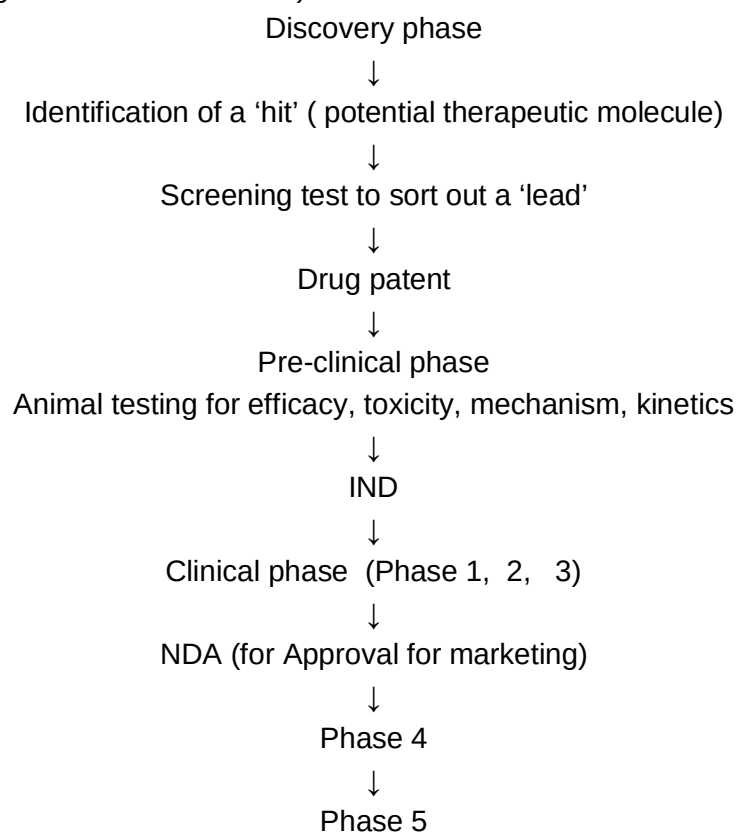
- Designing and synthesis of a substance
- Studies on tissues and animals (Pre-Clinical studies).
- Studies in man (clinical studies).
- Grant of an official license to sell
- Post licensing (marketing) studies of safety and comparison with other drugs

Drug Development

- Before reaching to market a new drug has to pass through a long process of drug development
- Period of preclinical and clinical trials to the approval for marketing by drug authorities.

Administrative body

- Each country has its own administrative body to supervise drug evaluation process and to grant approval for marketing of new drug products.
 - **FDA** (Food and Drug Administration) → in USA
 - **EMA** (European Medicines Evaluation Agency) → in European countries.
 - **CDSCO** (Central Drug Standard Control Organization) → in India that is headed by DCGI (Drug Control General India).



Drug Discovery

- It is the period from → Identification of a potential therapeutic target to selection of a Single molecule for testing in humans.
- Number of compounds passes to process of screening → Hits
- If a compound is found fit for future evaluation it becomes a → Lead
- At the end of discovery phase Drug patent (for 20 years) is taken for lead compound



Preclinical Studies

- Efficacy studies on animals before humans
- Average time 1 - 5 years
- In India → animal handling must be as per the norms regulated by CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals).



Clinical Studies

Once drug is proved effective and safe during preclinical studies

↓

Application is launched before FDA and an institutional review board (IRB)

↓

To register it as an → Investigational New Drug (IND)

↓

Registered as IND (permission to administer a new drug to humans)

↓

Drug has to pass through different stages of clinical trial

↓

Performed in 4 phases (3-6 years)

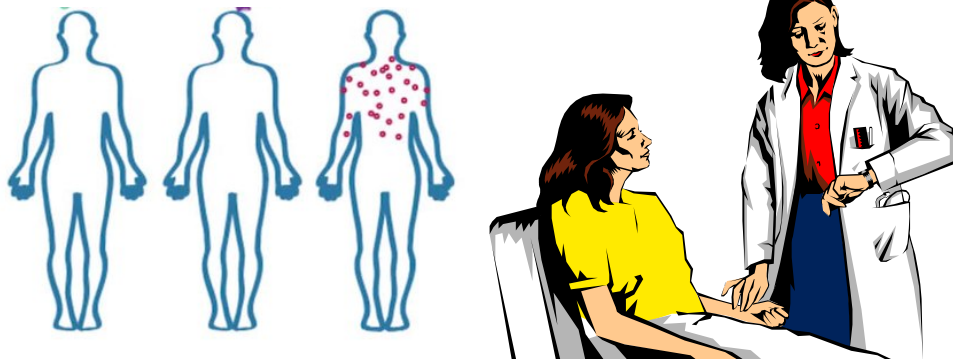


Phases

- **Phase 1:** Efficacy studies on healthy volunteers
- **Phase 2:** Clinical studies on a limited scale
- **Phase 3:** Comparative studies on large number of patients
- **New Drug Application (NDA):** Regulatory review
- **Phase 4:** Continued comparative studies. Registration and market introduction

Phase 1

- **Involves** → 20-100 healthy volunteers (no women of childbearing potential)
- **Emphasis** → on Drug safety
- **Goal** → to identify major side effects, metabolism and routes of excretion
- **Lasts** → 1 year
- About 70% of drugs will pass this phase



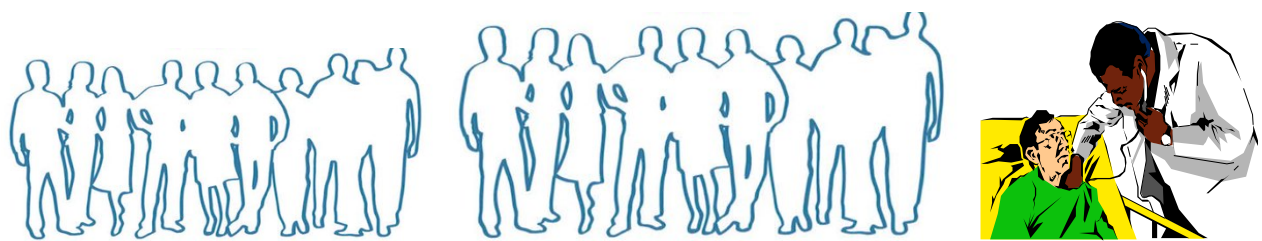
Phase 2

- **Involves** → 100-300 individuals who have target disease
- **Emphasis** → on Effectiveness
- **Goal** → Patients receiving the drug are compared to similar patients receiving a placebo or another drug
- **Lasts** → 2 years
- About 33% of drugs will pass this phase



Phase 3

- **Involves** → 1000-3000 patients
- **Emphasis** → on safety and effectiveness
- **Goal** → Investigates through well-controlled studies different populations and different dosages as well as uses new drug in combination with other drugs
- **Lasts** → 3 years
- 25-30% of drugs will pass this phase



Phase 4

- Post-market surveillance of drug to continually assess safety of the drug
- **Include** →
- Incidence and severity of rare adverse reactions
- Cost-effectiveness analyses
- comparative trials
- Quality of life studies



Phase 5

- Post marketing studies

Once the drug has been given a licence



It can be prescribed for that specific condition only



But after use in market it may help in other similar conditions



So to extend the licence → phase 5 conducted

Different phase of Clinical Trial				
	Phase 1 (Dose escalating design)	Phase 2 (Therapeutic exploring drug)	Phase 3 (Therapeutic Confirmatory drug trial)	Phase 4 (Post marketing Surveillance)
Why	Tolerability Does range Kinetics	Therapeutic efficacy Dose range Kinetics	Confirm safety Efficacy Comparison with other therapy	Long term or new toxicity, economy comparison with others
By whom	Clinical Pharmacologist	Clinical pharmacologist/Clinical investigator	Clinical Investigator	Open for aH Physician



On whom	Healthy volunteers	Selected patients	Patients	Patients
Usual numbers for study	20-100	100-300	1000-3000	Unlimited
Where	Single center well equipped hospital	Specialized clinical center	Multi – centered good hospitals	Any where
Type of study	Open or non-blind	Single blind with inert placebo or positive control	Double blind or cross-over	Open or non-blind



Drugs acting on ANS

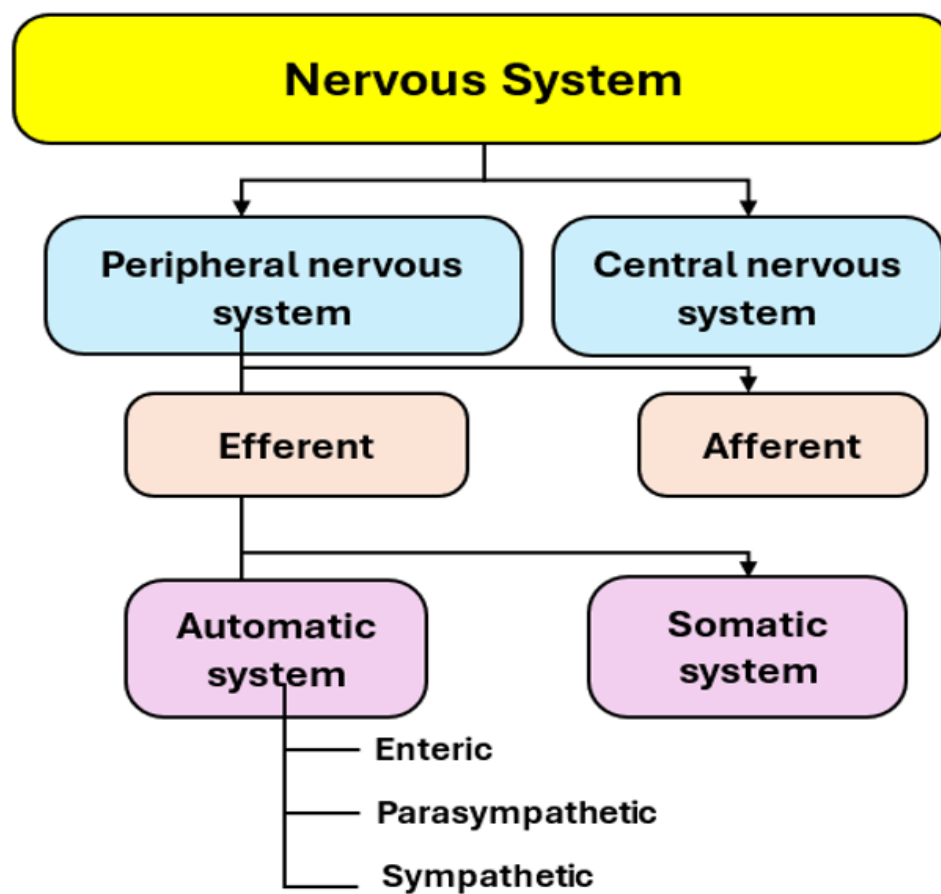
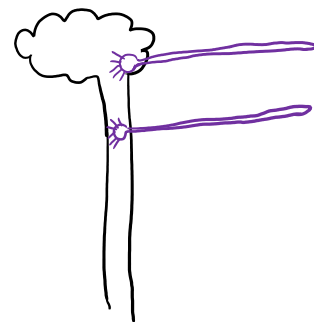
CHAPTER

2

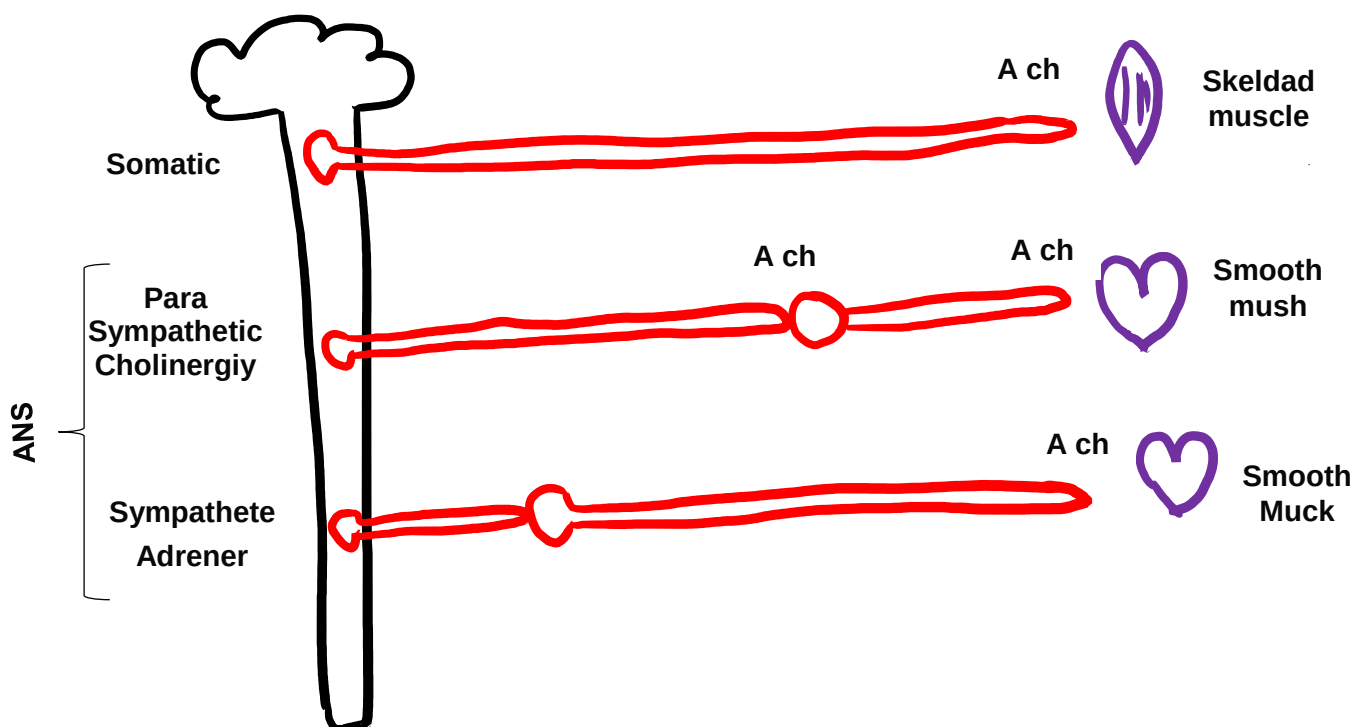
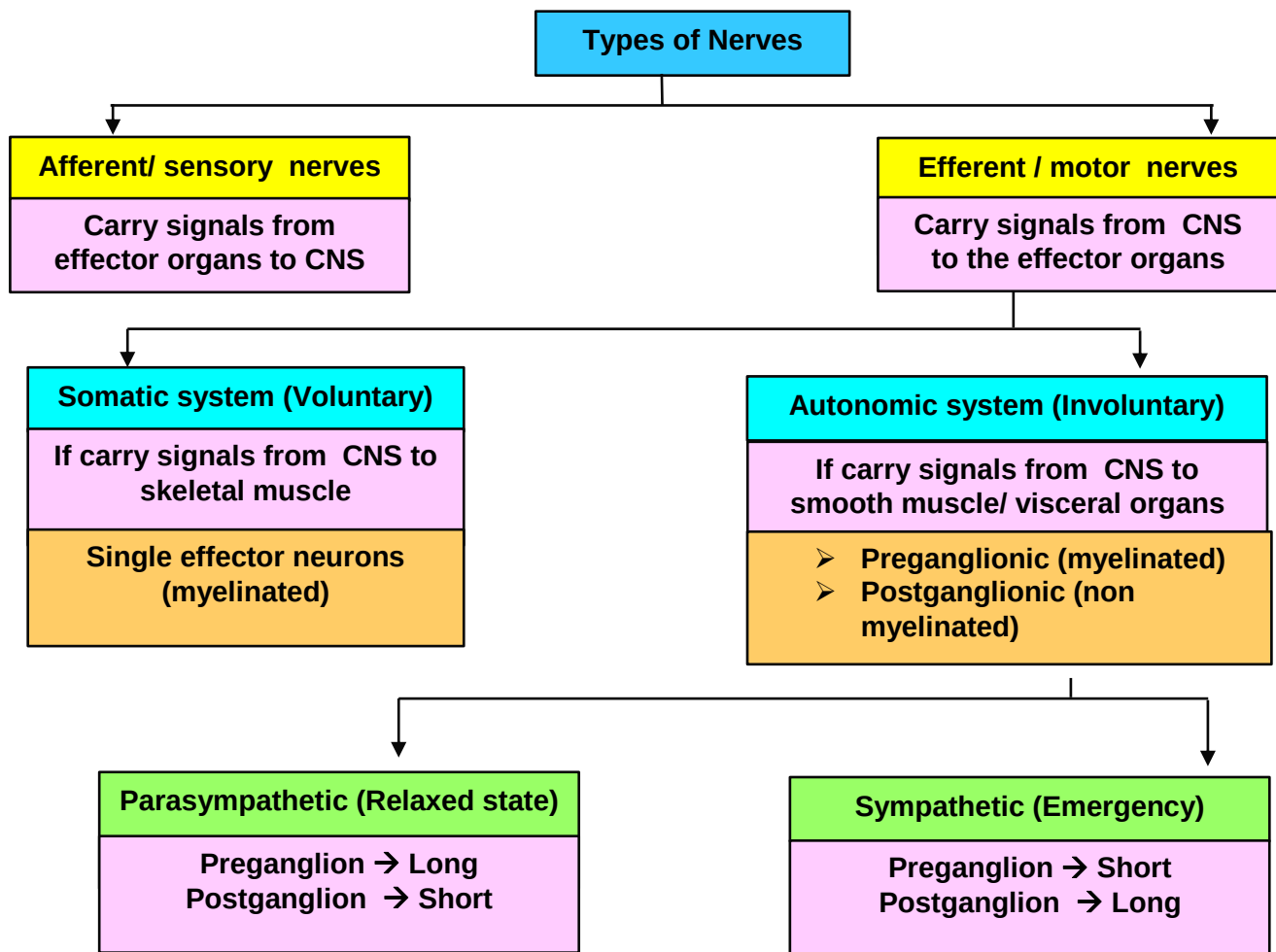
INTRODUCTION TO NERVOUS SYSTEM

Nervous system

- **CNS**
 - Brain
 - Spinal cord
- **PNS**
 - Consists of nerves arising from → brain and spinal cord
 - ❖ 12 pairs of cranial nerves
 - ❖ 31 pairs of spinal nerves



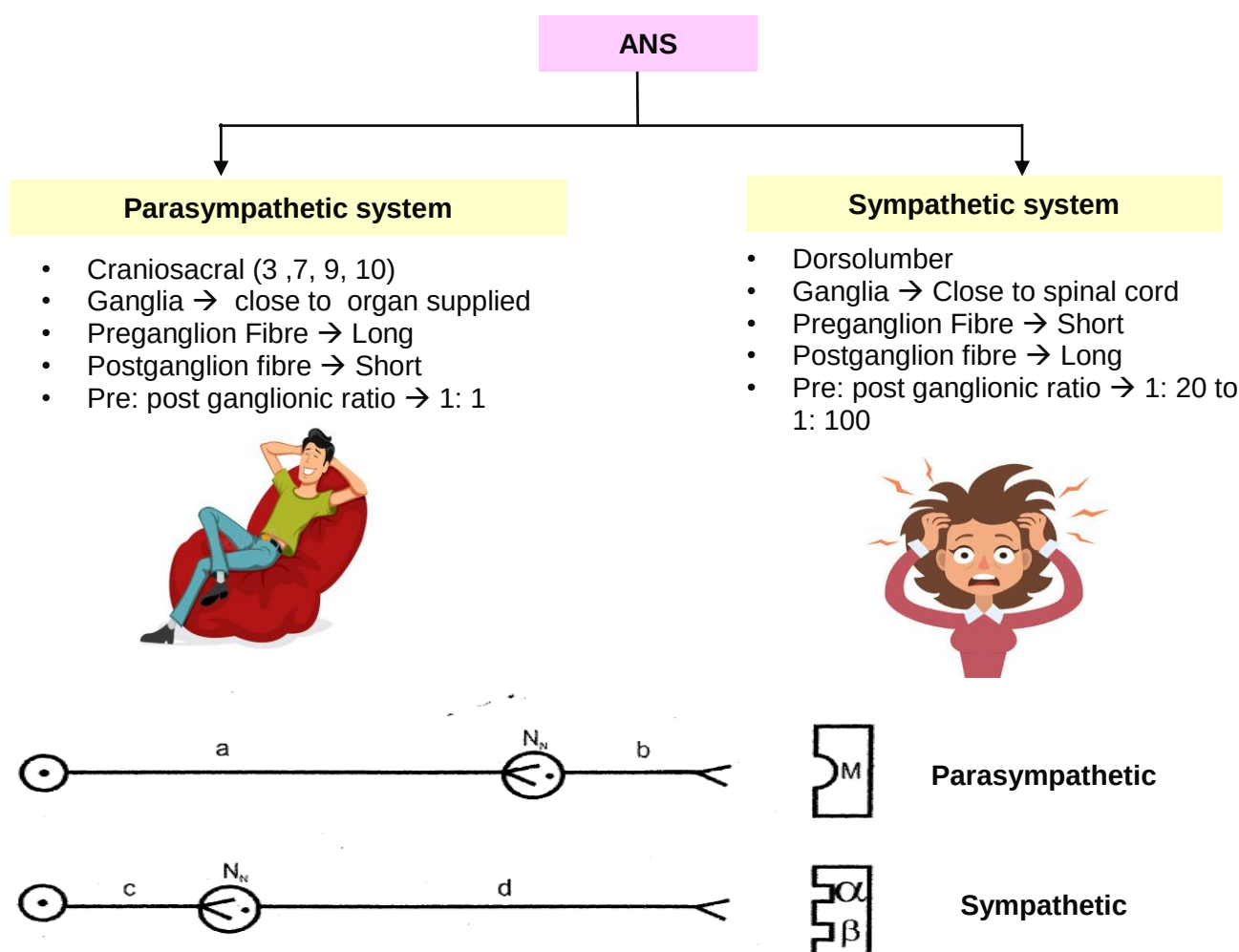
Types of Nerves



Somatic versus Autonomic Nervous System

	Somatic nervous system	Autonomic nervous system
Functions	To control voluntary functions	To control involuntary functions
Target organ	Skeletal muscles	Visceral organs
Neuron	Single myelinated	Two types of neurons connected with a synapse/ganglion. Preganglionic one is non myelinated.
Nerve section	Paralysis or atrophy	No atrophy, activity is maintained, there may be denervation supersensitivity

Autonomic Nervous System (ANS)



Parasympathetic Versus Sympathetic Nervous system

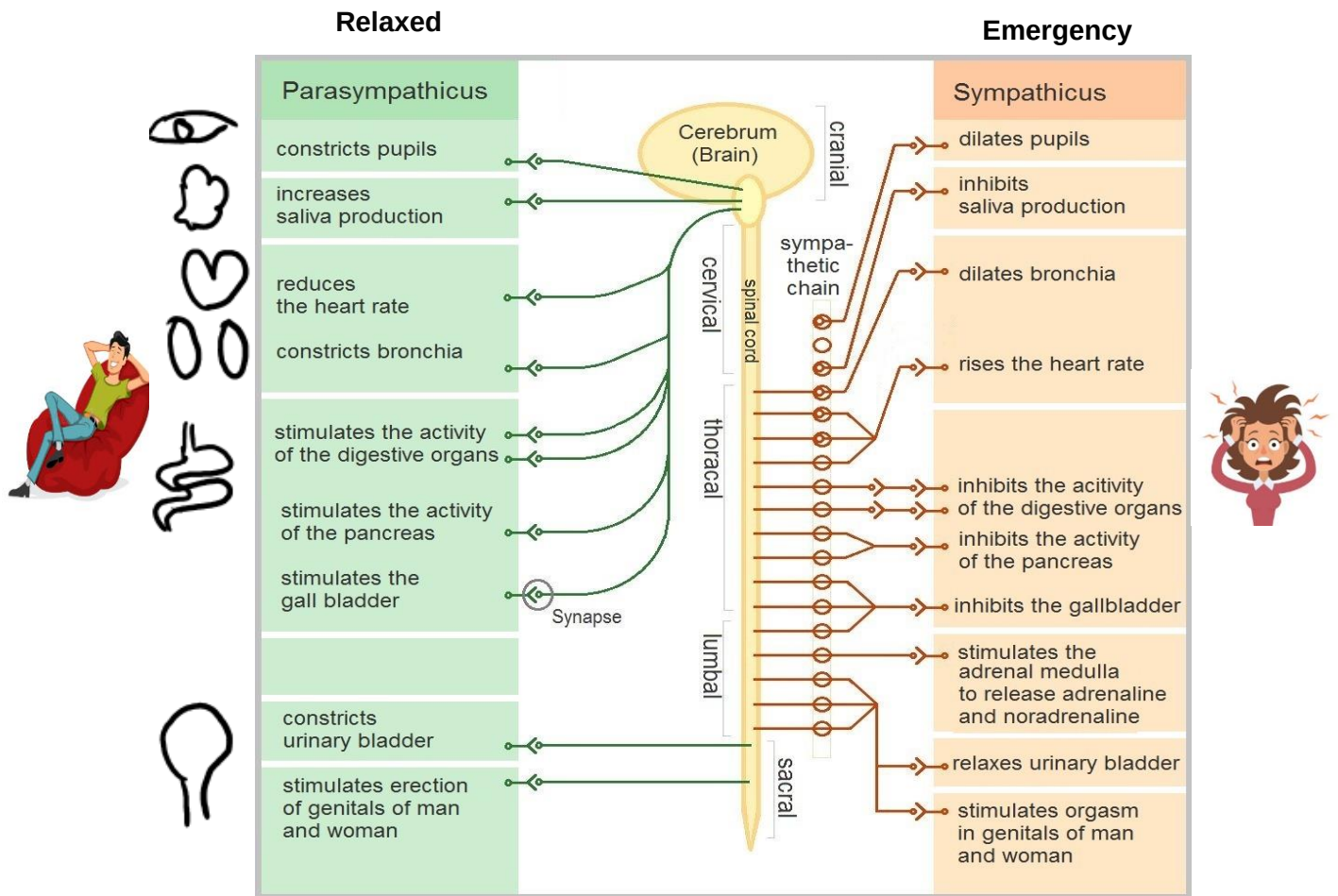
	Parasympathetic	Sympathetic
1. Origin	Cranio-sacral (III, VII, IX, X, S2-S4)	Dorsolumbar (T ₁ to L2 or L3)
2. Ganglia	On or close to the organ supplied	Away from the organs supplied
3. Postgang. Fibre	Short	Long
4. Pre. Post ganglionic fibre ratio	1:1 to 1:2 (except in enteric plexuses)	1:20 to 1:100
5. NT	Major Ach	Major NA

6. Stability of transmitter	Ach- rapidly destroyed locally	NA stable, diffuses for wider actions
7. Important function	Assimilation of food, conservation of energy	Tacking stress and emergency

Actions of Parasympathetic and Sympathetic Nervous system

- Most organs → effect is Opposite
- At some organs → effect is complementary to each other
 - Eg. → sex organ → erection (parasympathetic) and ejaculation (sympathetic)
- At some site → only one system operates
 - Eg. →
 - sweat glands, adrenal medulla, kidney, pilomotor muscles → only Sympathetic innervations
 - Ciliary muscle of eye, gastric and pancreatic glands → only

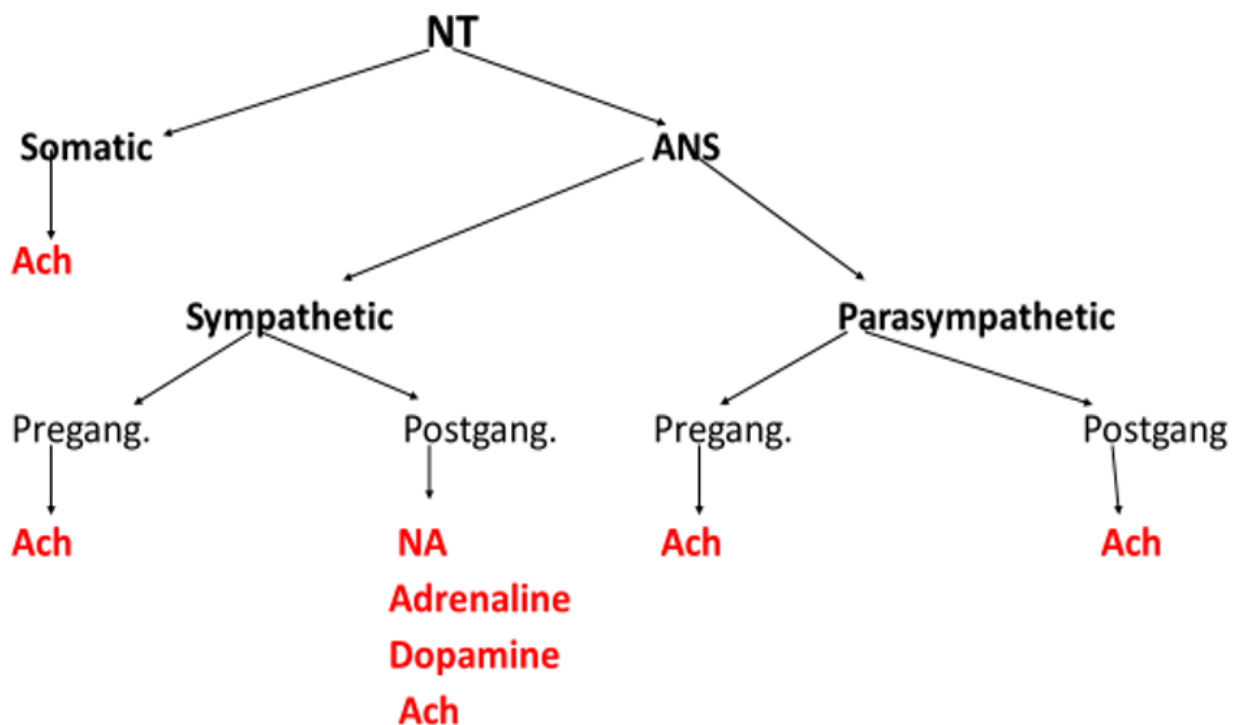
Important actions	Parasympathetic	Sympathetic
Eye	Contraction of constrictor pupillae so Miosis	Contraction of radial muscle (dilator pupillae) so mydriasis
Heart	Reduced rate and contractility	Increase rate and force of contraction
Blood vessels	They have muscarinic receptor but no parasympathetic innervations so respond only to exogenous agonist to produce dilatation.	Skin, mucous membrane, and Splanchnic-constriction Skeletal muscles-dilatation
Smooth muscles	Constriction	Relaxation
Bronchi	Relaxation	Constriction
GIT		
UB, ureter		
Sphincters		
Male Genitalia	Erection	Ejaculation
Uterus		Relaxation
Salivary secretion	Increase	Increase

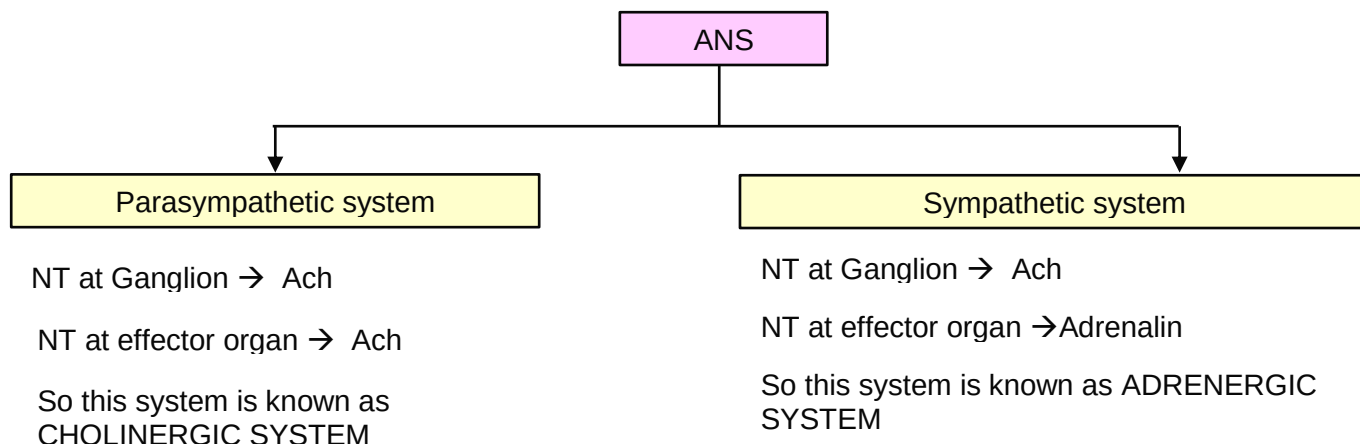


Neurotransmitter (NT)

NT at somatic fibres →

- Acetylcholine (ACh) is principal neurotransmitter (NT)





INTRODUCTION TO CHOLINERGIC SYSTEM

Acetylcholine (ACh)

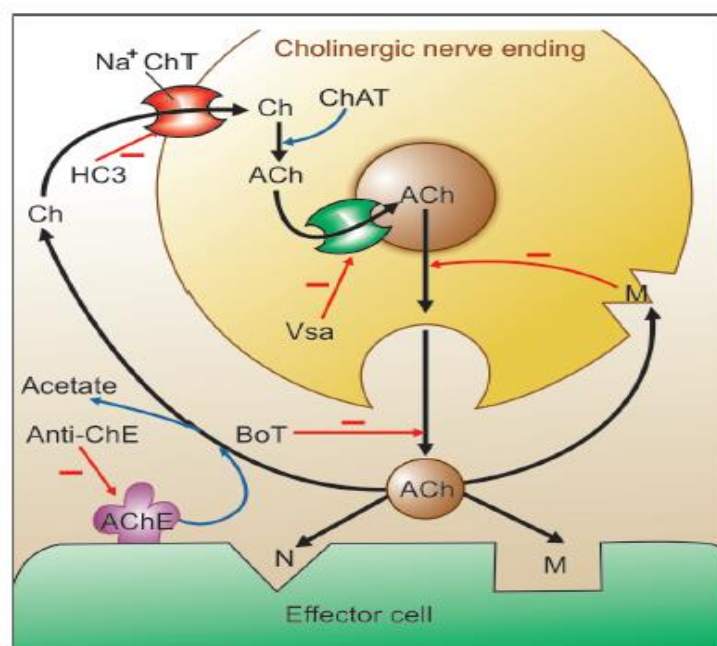
In Cholinergic / Parasympathetic system

↓

Acetylcholine (ACh)

↓

Major neurohumoral transmitter at preganglionic as well as postganglionic fibres



Synthesis and storage of ACh

Choline is taken up by cholinergic neurons by Na⁺: choline cotransporter (Rate limiting step)

↓

Acetyl Co-A donates acetyl group to choline, to form acetylcholine with help of enzyme choline acetyl transferase in axoplasm

↓

Active transport of ACh into synaptic vesicles

↓

Acetylcholine is then stored in vesicles

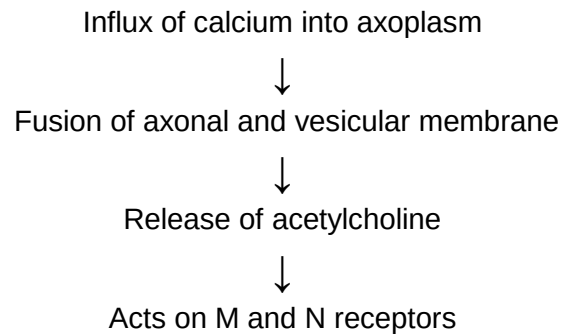
Release of ACh

With arrival of nerve impulse

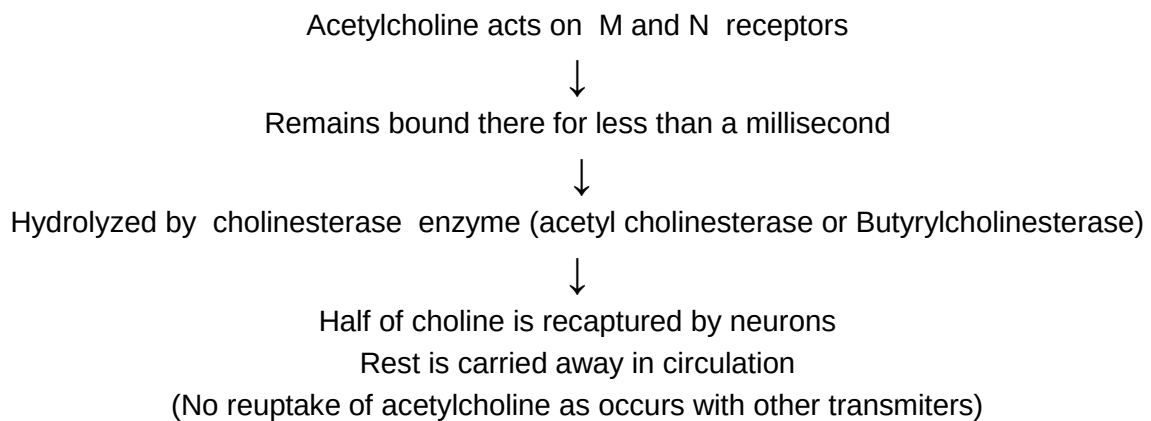
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Depolarization

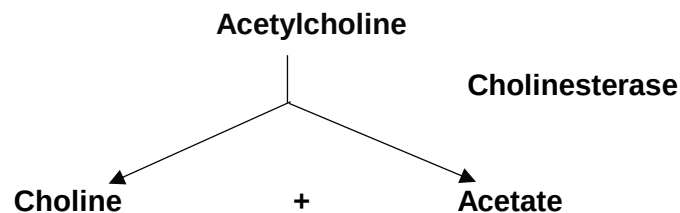
↓



Destruction of ACh



Hydrolysis of Acetylcholine



Remember

- Choline uptake is blocked by → **Hemicholinium**
- Active transport of ACh into synaptic vesicles is inhibited by → **Vesamicol**
- Release is blocked by → **Botulinum and tetanus toxins**
- Release is promoted by → **Latrotoxin, Black widow spider venom**

Cholinoreceptors

1. Muscarinic (M) → G protein coupled receptor

- **Stimulated by** → Muscarine
- **Blocked by** → Atropine
- **5 subtypes** → M1, M2, M3, M4 and M5

2. Nicotinic (N) → Ligand gated cation channel

- **Stimulated by** → Nicotine
- **Blocked by** → Tubocurarine or Hexamethonium

- **2 subtypes** → NM , NN

M1	M2	M3
CNS → • Memory and learning • Vomiting center	Heart → • Myocardial smooth muscles ◦ ↓ Rate ◦ ↓ Contractility ◦ ↓ Velocity	Visceral smooth muscle → • GIT → contraction • Bronchi → contraction • UB → contraction and Sphincters → relaxation • Uterus → contraction
Autonomic ganglia → Stimulation		Eye → • Iris → contraction • Ciliary muscle → contraction
Gastric parietal cells → ↑ acid secretion		Glands → ↑ secretion • ↑ Sweating • ↑ Salivation • ↑ Lacrimation • ↑ Tracheobronchial • ↑ Gastric secretion
		Blood vessels → VD (↓ BP)
		Male sex organ → Erection

NM	NN
Neuromuscular junction → ◦ Contraction of skeletal muscle	Autonomic ganglia → • Depolarisation
	Adrenal medula → • Catecholamine release
	CNS → • Site specific → Excitation or Inhibition

CHOLINERGIC DRUGS (CHOLINOMIMETIC, PARASYMPATHOMIMETIC)

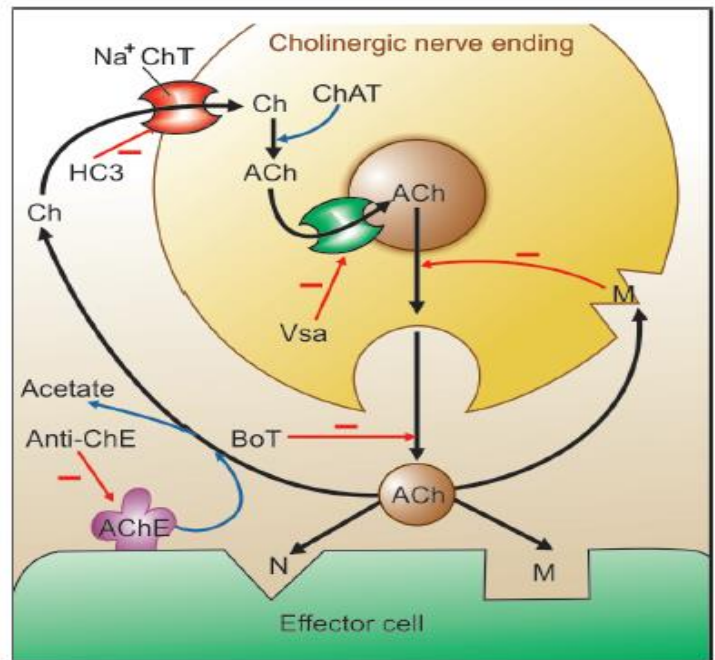
	Cholinergic Drugs	Anticholinergic Drugs
Definition		
Classification		
MOA		
Pharmacological Actions		
Use		
Adverse effects		
Contraindication		

Definition

- Drugs which produce actions similar to that of ACh
 - By directly interacting with cholinergic receptors → Cholinergic agonists
 - By increasing availability of ACh at these sites (by decreasing its destruction) → Anticholinesterases

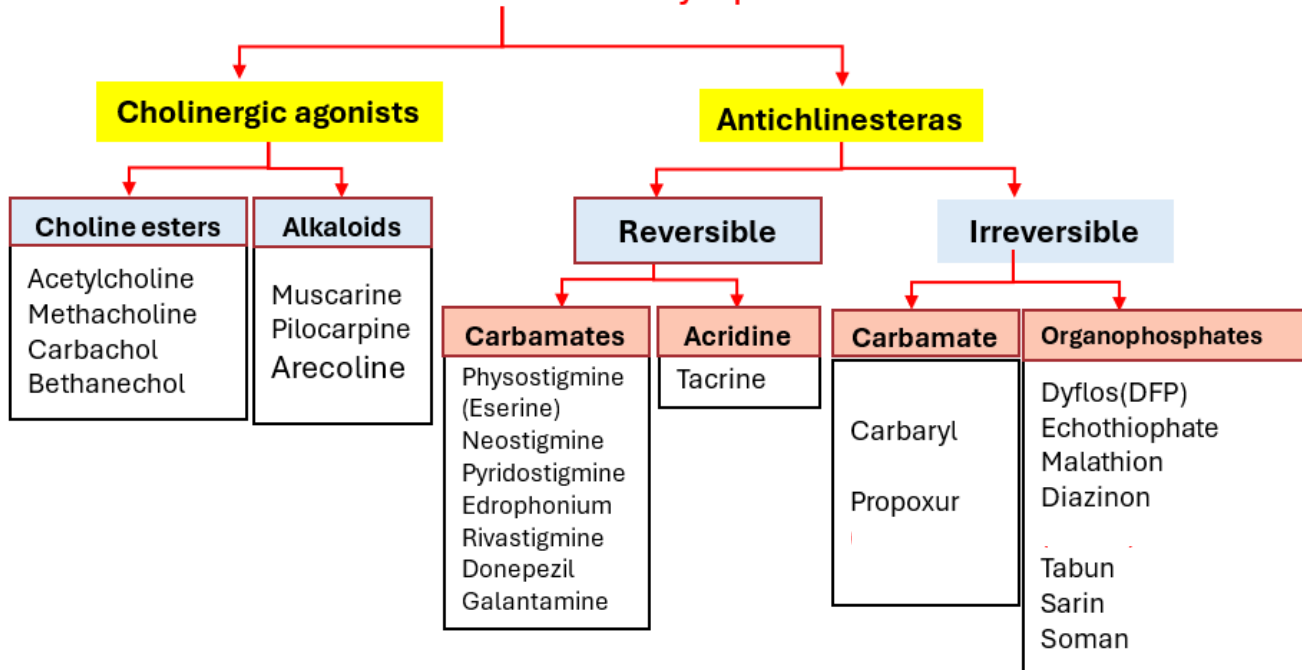
Classification

1. Cholinergic agonists
2. Anticholinesterases → Reversible and irreversible



CHOLINERGIC DRUGS

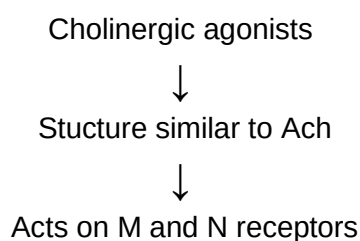
Cholinomimetic Parasympathomimetic

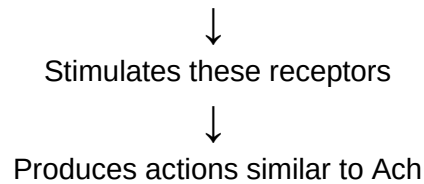


MOA

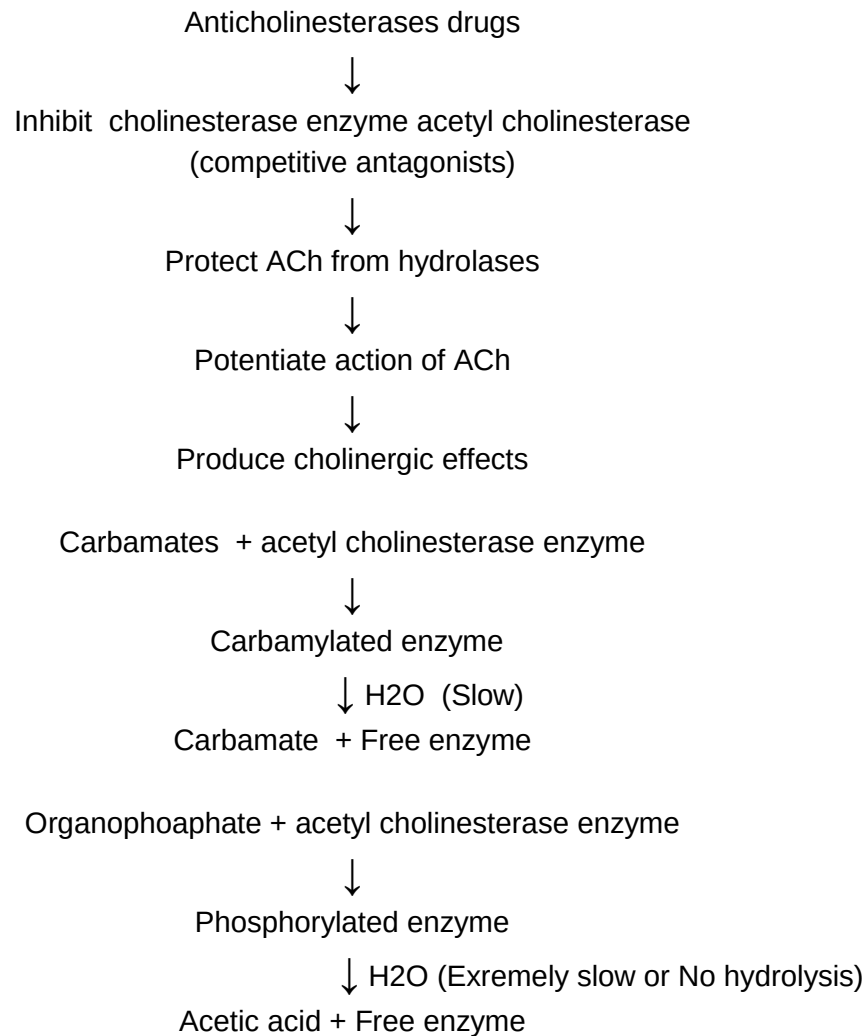
- MOA of Cholinergic agonists
- MOA of Anticholinesterases

MOA of Cholinergic agonists

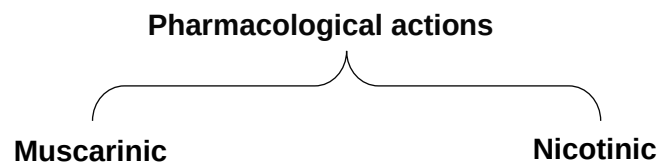




MOA of Anticholinesterases



Pharmacological actions

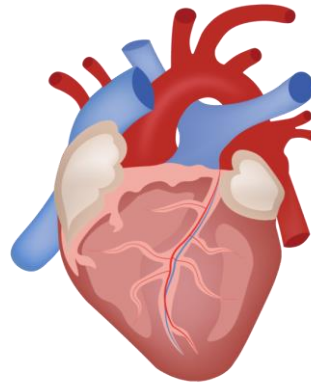


A. Muscarinic Actions

1. Heart (M2)

- M2 activation at S. A. node, atria and A.V. node leads to a→

- **Negative chronotropic** → Reduction in the heart rate (hyperpolarizes the SA node)
- **Negative inotropic** → Reduction in force of contraction (Contraction of atrial fibres is reduced)
- **Negative dromotropic** → Reduction in conduction velocity (At the A-V node RP is increased)



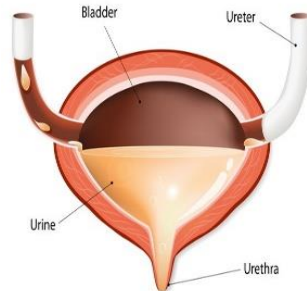
Heart	
Negative	Chronotropic
Negative	Inotropic
Negative	Dromotropic

2. Visceral Smooth muscle (M3)

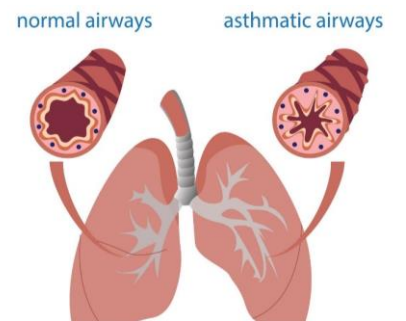
- Smooth muscle Contracted, Sphincter relaxed
- **GIT** → tone and peristalsis increased and sphincters relax → abdominal cramps and evacuation of bowel.
- **Bladder** → Detrusor muscle → contracts while sphincter relaxes → voiding of bladder.
- **Bronchial muscles** → constrict → asthmatics are highly sensitive (dyspnoea, precipitation of and attack of bronchial asthma)



GIT
Contract



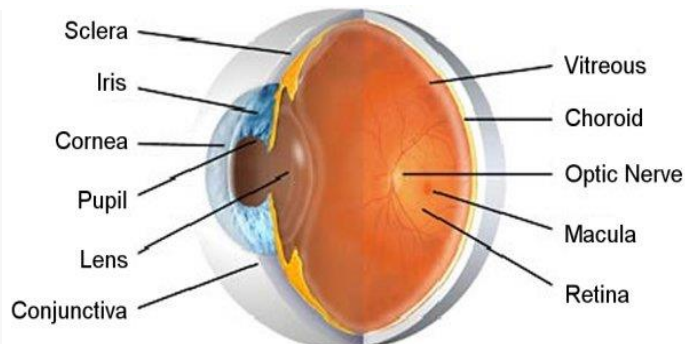
Bladder
Contract



Bronchial muscle
Constricts

3. Eye (M3)

- **Iris muscle** → Contraction → Miosis
- **Ciliary muscle** → Contraction → Decreased IOT



A. Iris Muscle

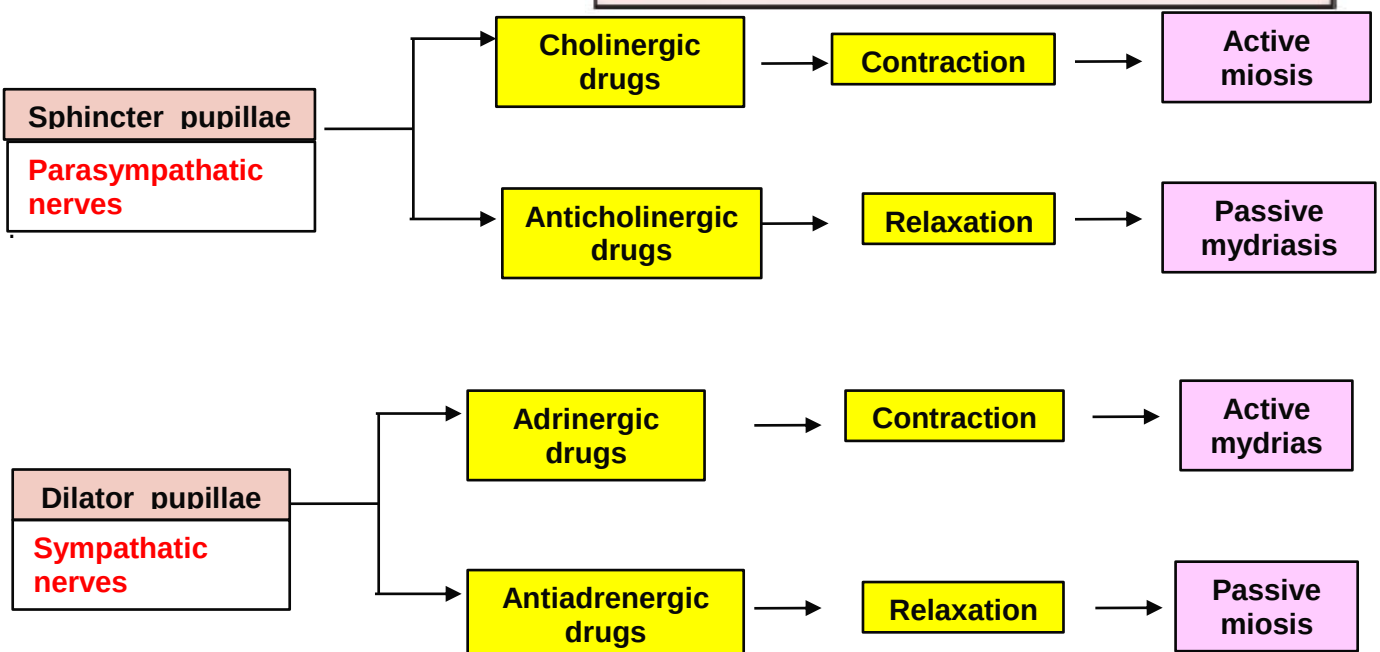
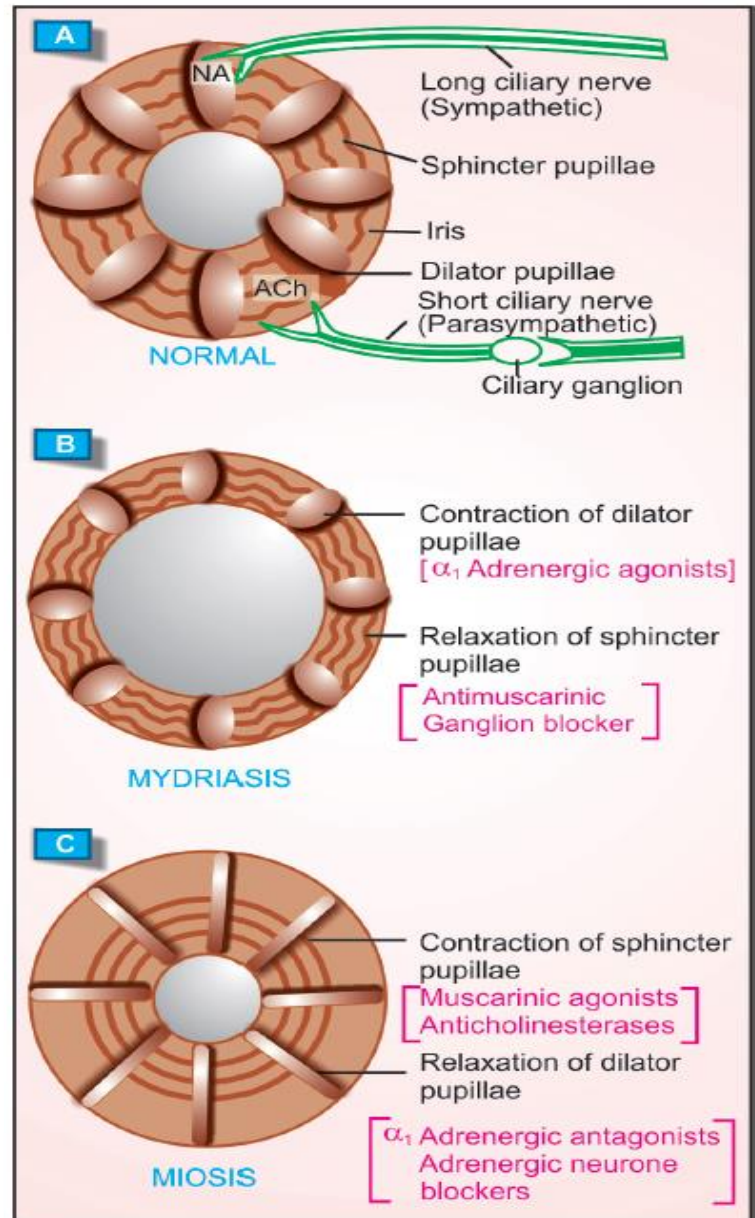
- Contraction of sphincter pupillae → miosis
- Contraction of dilator pupillae → mydriasis
 - **Sphincter pupillae** → Supp. By Parasympathatic nerves
 - **Dilator pupillae** → Supp. By Sympathatic nerves

Miosis →

- **Active miosis** → contraction of sphincter pupillae muscles → Cholinergic / Parasympathomimetics
- **Passive miosis** → blocking action of dilator pupillae muscles → Antiadrenergic / Sympatholytics

Mydriasis →

- **Active mydriasis** → contraction of dilator pupillae → Adrinergetic / Sympathomimetics
- **Passive mydriasis** → blocking action of sphincter pupillae muscles → Anticholinergic / Parasympatholytics

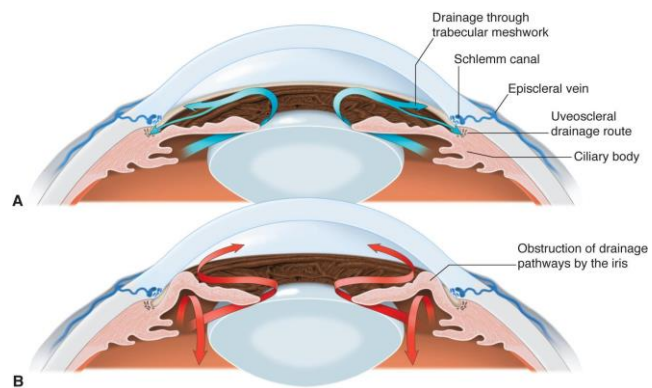
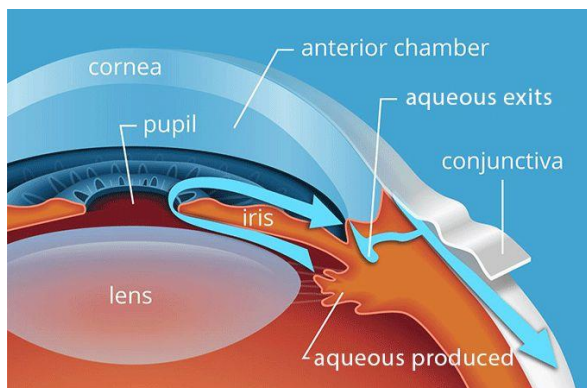
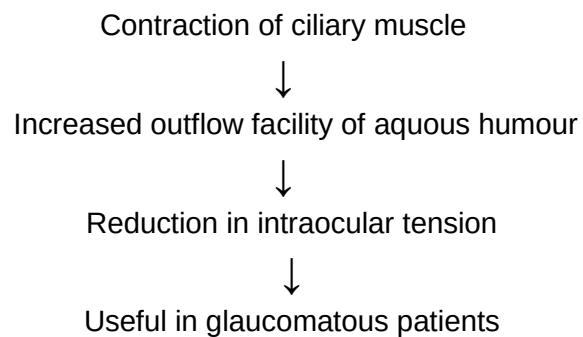


Remember

- **Cholinergic / Parasympathomimetics** → Active miosis → contraction of sphincter pupillae muscles
- **Anticholinergic / Parasympatholytics** → Passive mydriasis → blocking action of sphincter pupillae muscles
- **Adrenergic / Sympathomimetics** → Active mydriasis → contraction of dilator pupillae
- **Antiadrenergic / Sympatholytics** → Passive miosis → blocking action of dilator pupillae muscles



B. Ciliary muscle

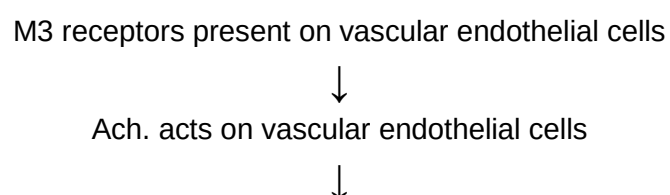


4. Glands (M3)

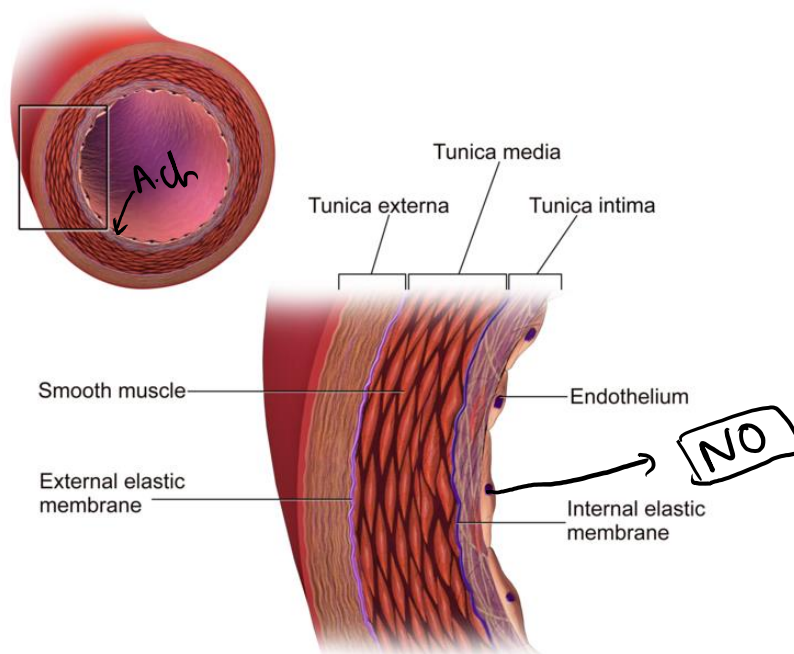
- Secretion from all glands → Increased
 - Sweating
 - Salivation
 - Lacrimation
 - Tracheobronchial
 - Gastric secretion



5. Blood vessels (M3)



Release of EDRF (nitric oxide)
↓
Relaxes muscle
↓
Vasodilatation (fall in BP)



6. Male sex organ (M3)

Erection (M3)



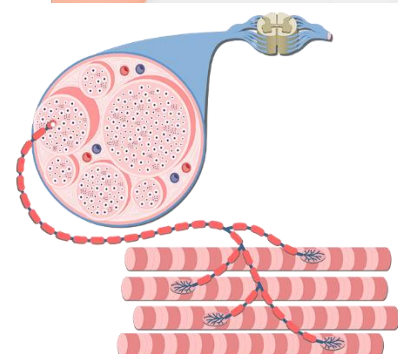
B. Nicotinic Actions

Skeletal muscles

- Contraction of fibre
- Intraarterial injection of high dose can cause twitching and fasciculations

Remember

- Maximum muscarinic action shown by → **Methylcholine > Acetylcholine**
- Maximum nicotinic action shown by → **Carbachol and Acetylcholine.**



Uses

1. GI constipation disorders
2. Urinary retention disorders
3. Xerostomia

4. Eyes – Miosis and decreases IOT
5. Alzheimer's disease
6. Myasthenia gravis
7. Postoperative decuburization
8. Cobra bite
9. Belladonna/ Datura poisoning

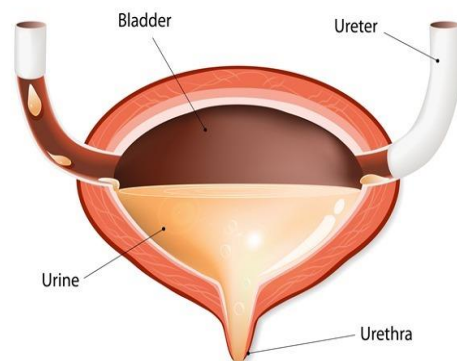
1. GI disorders

- Postoperative abdomen
- Gastric atony or stasis
- Congenital megacolon



2. Urinary retention disorders

- Post operative retention
- Post partum retention
- Neurogenic bladder

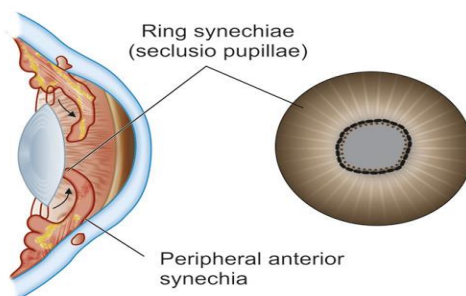


3. Eyes

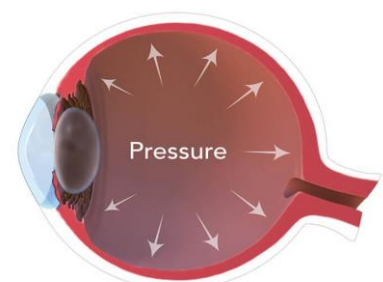
- **Contraction of sphincter pupilla of iris** → Miosis
 - (a) To produce rapid miosis after refraction testing
 - (b) To prevent or to break synechia (Synechia is the adhesion between iris and cornea (anterior synechia) or iris and lens (posterior synechia). The prevention as well as treatment include the alternate use of miotics and mydriatics)
- **Contraction of ciliary muscle** → Decreases IOT
 - (a) To relieve intraocular tension in glaucoma



Rapid miosis after refraction testing



To Prevent and break Synechia



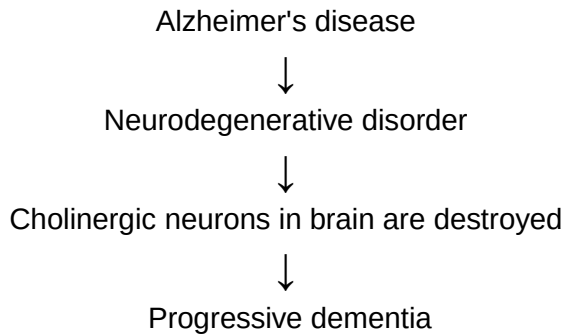
To IOT i5 Glaucoma

4. Glands

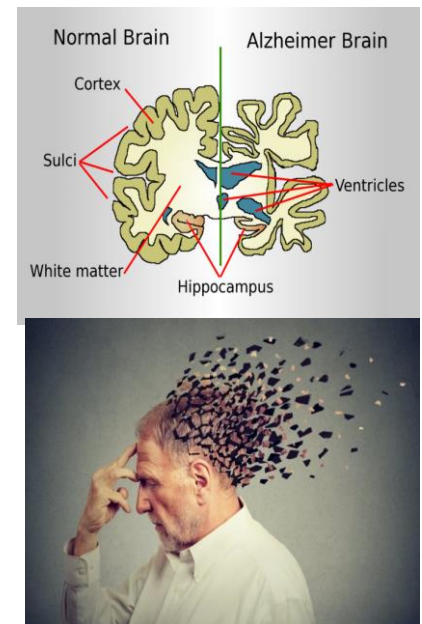
Xerostomia → Pilocarpine is used. It increases salivary secretion



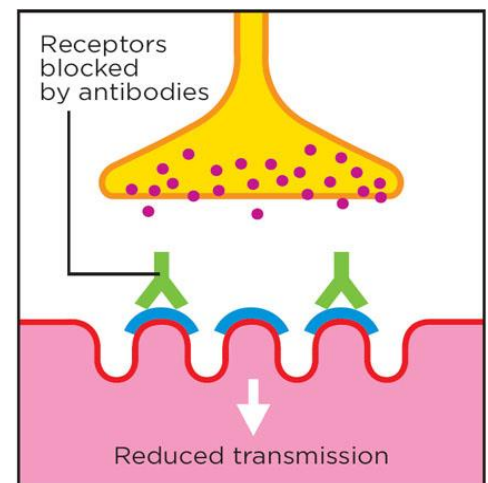
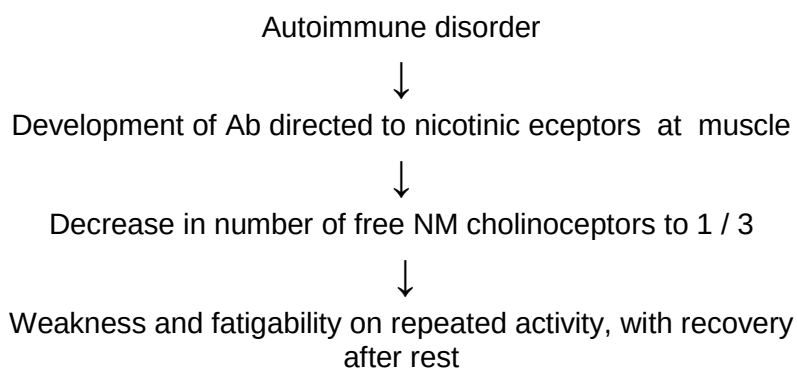
5. Alzheimer's disease



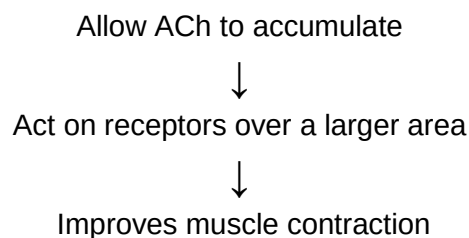
- Relatively cerebroselective anti-ChEs, rivastigmine, donepezil and galantamine are now commonly used.



6. Myasthenia gravis



Neostigmine / Pyridostigmine



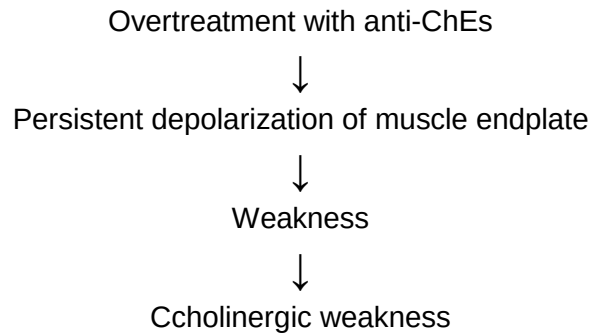
- No effect on the basic disorder which often progresses → Ultimately it may not be possible to restore muscle strength adequately with antiChEs alone.

Myasthenic crisis

- Due to → disease Myasthenia gravis
- Characterized by → acute weakness of respiratory muscles.
- Managed by →
 - Tracheal intubation and mechanical ventilation.
 - IV methylprednisolone pulse

➤ Anti-ChEs

Cholinergic crisis



- Managed by → Withdrawal of anti-ChEs
- Late cases alternately experience → myasthenic and cholinergic weakness.

Edrophonium test

- The two types of weakness require opposite treatments. They can be differentiated by edrophonium test-

- Inject Edrophonium (2 mg i.v.)
 - Improvement - myasthenic crisis
 - Worsening - cholinergic crisis

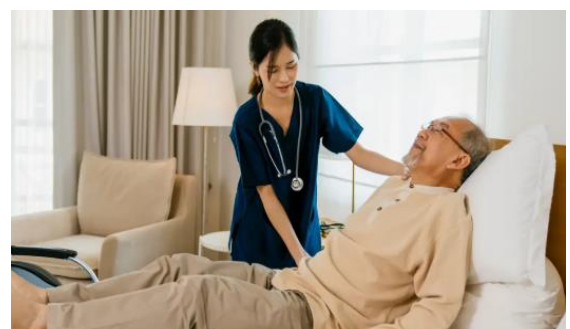


Differences between Myasthenic crisis and Cholinergic crisis

Myasthenic Crisis	Cholinergic Crisis
Under medication	Overmedication
Temporary improvement of symptoms with administration of Edrophonium	Symptoms improve with administration of anticholinergics (Atropine)
Heart rate increased	Heart rate decrease
Respiratory distress	Abdominal cramps
Pupil: Mydriasis	Pupil: Miosis
Increased Blood pressure	Decreased blood pressure
Normal secretion	Increased secretion

7. Postoperative decurarization

- **Postoperative residual curarization (PORC)** → residual paresis after emergence from general anesthesia that may occur with the use of neuromuscular-blocking drugs.
- Neostigmine 0.5-2.0 mg i.v.
- Rapidly reverses muscle paralysis induced by competitive neuromuscular blockers



8. Cobra bite

- Cobra venom → Curare (Neuromuscular blocker) like neurotoxin.
- Though specific antivenom serum is primary treatment
- Neostigmine + atropine prevent respiratory paralysis.



9. Belladonna/ Datura poisoning

- Belladonna/ Datura → anticholinergic drug
- Physostigmine 0.5-2 mg i.v. → specific antidote for poisoning with belladonna or other anticholinergics.



Contraindications

1. Obstructive GI retention → risk of perforation
2. Obstructive urinary retention → risk of perforation
3. Bronchial asthma → since there is bronchospasm.
4. Coronary insufficiency → since a fall in BP can severely reduce coronary blood flow
5. Bradycardia
6. Peptic ulcer → since they increase gastric acid secretions.

ANTICHOLINESTERASE POISONING

Introduction

- Anticholinesterases are easily available as agricultural and household insecticides
- Accidental as well as suicidal, homicidal poisoning is common.



Effects

Muscarinic

- Bradycardia
- Hypotension
- Bronchoconstriction
- Increase bronchial secretions
- Lacrimation
- Sweating
- Miosis, blurring of vision
- Urinary incontinence



Nicotinic

- Muscle paralysis

Death

- Due to respiratory failure.

Management of Organophosphorus Poisoning

- A. Supportive
- B. Specific

A. Supportive measures:

1. Termination of exposure
2. Maintenance of patent airway
3. Artificial respiration and oxygen
4. Diazepam if convulsions
5. Treatment of shock

B. Specific Treatment

1. Atropine
2. Cholinesterase reactivators/ Oximes

1. Atropine

- Specific antidote.
- Required in very high doses → 2-4 mg every 3 to 10 minutes till muscarinic symptoms (bradycardia, miosis) disappear
- Dose up to 200mg may be required
- Atropine has no effect on nicotinic action i.e. neuromuscular paralysis.

2. Cholinesterase reactivators/ Oximes

- (a) Pralidoxime (2-PAM)
- (b) Obidoxime
- (c) DAM (diacetyl monoxide)

- Oximes are used to restore neuromuscular transmission in case of organophosphate anti-ChE poisoning
- Phosphorylated ChE reacts very slowly or not at all with water.
- If more reactive OH groups (oximes) are provided → reactivation occurs more a million times faster
- Contraindicated in carbamate poisoning, because not only it does not reactivate carbamylated enzyme, it has weak anti-ChE activity of its own.

Remember

- **Atropine** → DOC for anticholinesterase poisoning (both for organophosphates and carbamates).
- **Oximes** → can be used in organophosphate poisoning, but are contraindicated in carbamate poisoning

SUMMARY

Cholenergic drugs

Uses

1. GI constipation disorders
2. Urinary retention disorders
3. Xerostomia
4. Eyes – Miosis and decreases IOT
5. Alzheimer's disease
6. Myasthenia gravis
7. Postoperative decurarization
8. Cobra bite
9. Belladonna/ Dhatara poisoning

Adverse effects / C/I

1. Obstructive GI retention
2. Obstructive urinary retention
3. Bronchial asthma
4. Coronary insufficiency
5. Bradycardia
6. Peptic ulcer

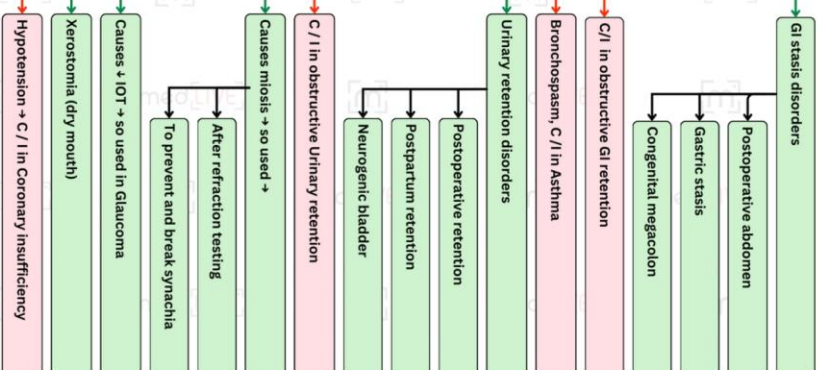


Uses, Adverse effects and Contraindications of CHOLINERGIC DRUGS

based on action of ACh on M and N receptors

Actions of ACh on M ₁ , M ₂ , and M ₃		
M ₁	M ₂	M ₃
CNS → • Memory and learning • Vomiting center	Heart → • Myocardial smooth muscles ◦ ↓ Rate ◦ ↓ Contractility ◦ ↓ Velocity	Visceral smooth muscle → • GIT → contraction • Bronchi → contraction • UB → contraction and sphincters → relaxation • Uterus → contraction
Autonomic ganglia → Stimulation		Eye → • Iris → contraction • Ciliary muscle → contraction
Gastric parietal cells → ↑ acid secretion		Glands → ↑ secretion • ↑ Sweating • ↑ Salivation • ↑ Lacrimation • ↑ Tracheobronchial • ↑ Gastric secretion
		Blood vessels → VD (↓ BP) Male sex organ → Erection
NM		NN
Neuromuscular junction → contraction of skeletal muscle		Autonomic ganglia → depolarization Adrenal medulla → catecholamine release
		CNS → site specific excitation or inhibition

→ Uses
→ Adverse effect / C/I

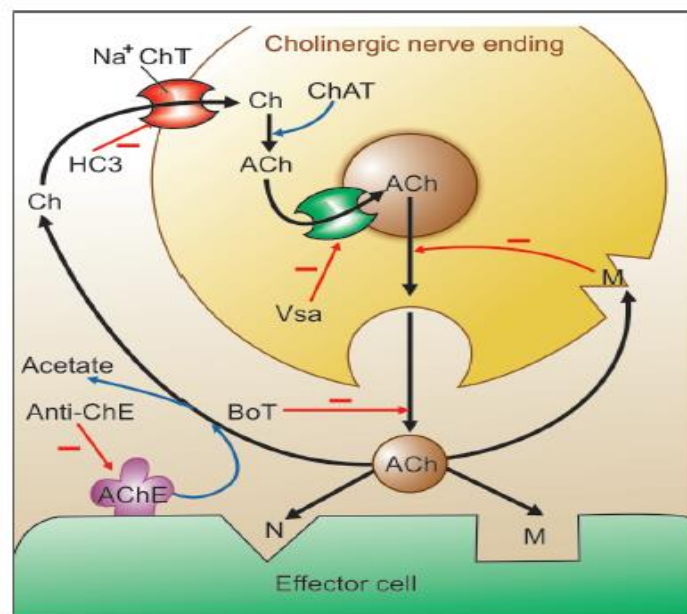


ANTICHOLINERGIC DRUGS (PARASYMPATHOLYTIC DRUGS)

	Cholinergic Drugs	Anticholinergic Drugs
Definition		
Classification		
MOA		
Pharmacological Actions		
Use		
Adverse effects		
Contraindication		

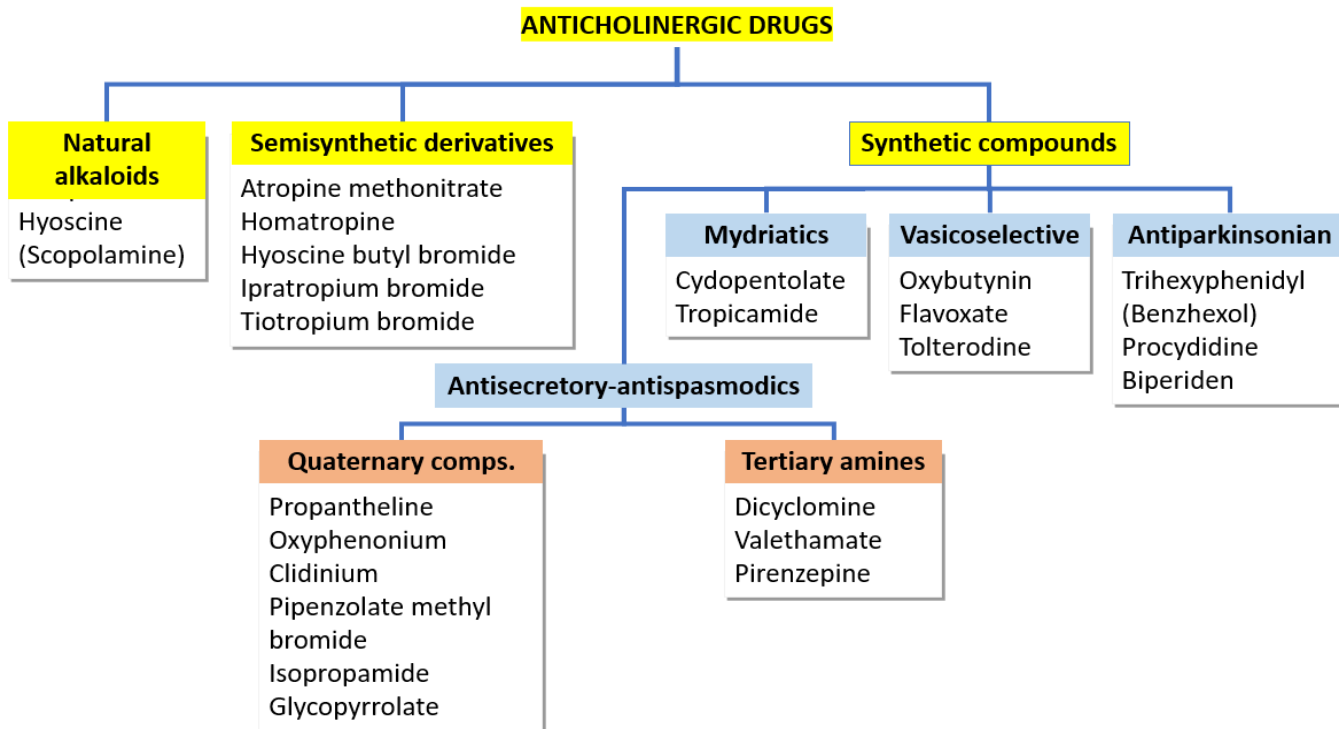
Definition

- Block muscarinic cholinergic receptors → prevent muscarinic effects of acetylcholine
- No effect on Nicotinic receptors
(Nicotinic receptor antagonists → Neuromuscular blockers)



Classification

1. Natural alkaloids
2. Semisynthetic derivatives
3. Synthetic

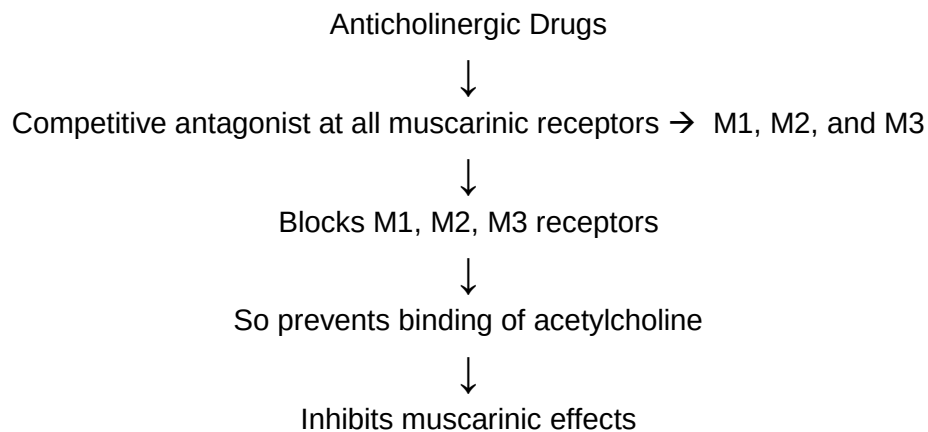


Atropine

- Atropine, an alkaloid from → *Atropa belladonna* / *Datura*
- Prototypical antimuscarinic drug



MOA



Pharmacological actions

1. CNS

- Atropine →
 - Depresses vestibular excitation → Antimotion sickness property.
 - Block relative cholinergic overactivity in basal ganglia → suppresses tremor and rigidity of parkinsonism
 - High doses → cortical excitation, restlessness, disorientation, hallucinations and delirium, respiratory depression and coma.



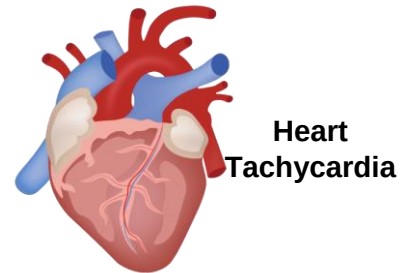
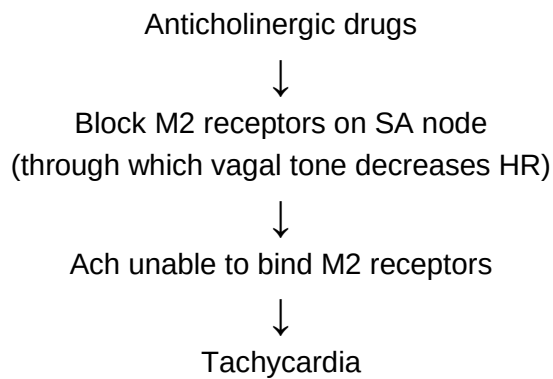
Depresses vestibular excitation



**Acetylcholine
Dopamine**

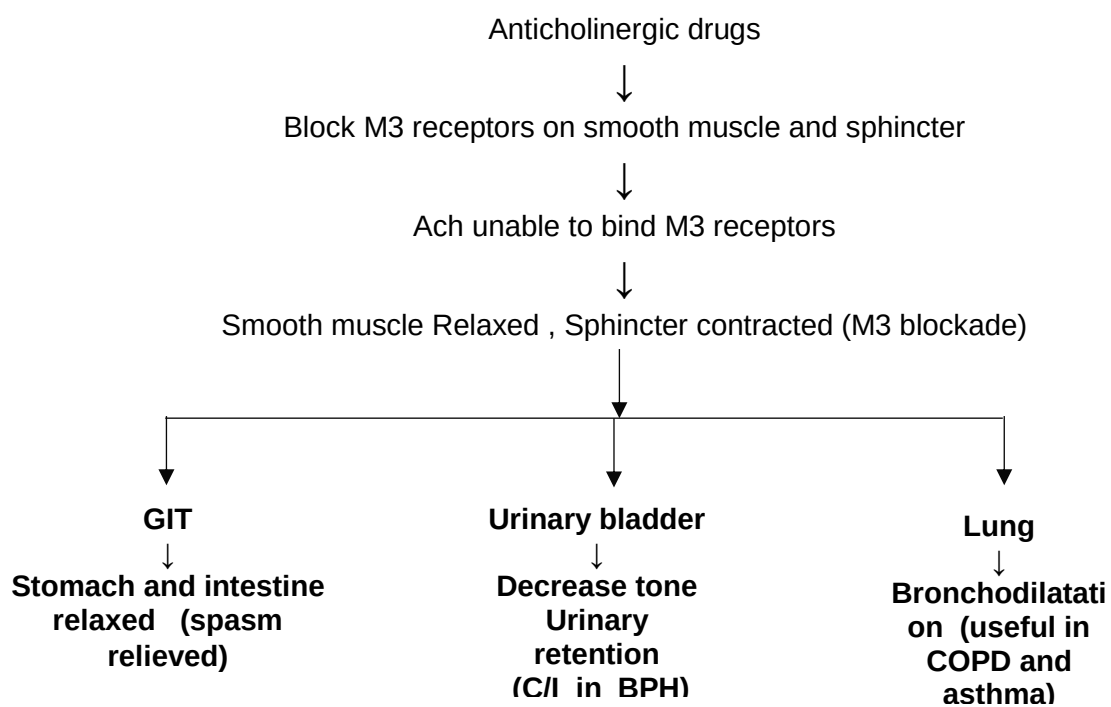
Blocks relative chlinergic

2. Heart



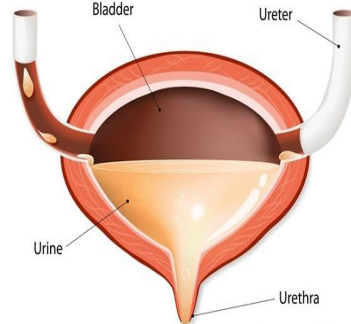
**Heart
Tachycardia**

3. Smooth muscles





**GIT
Relax**



**Bladder
Relax**

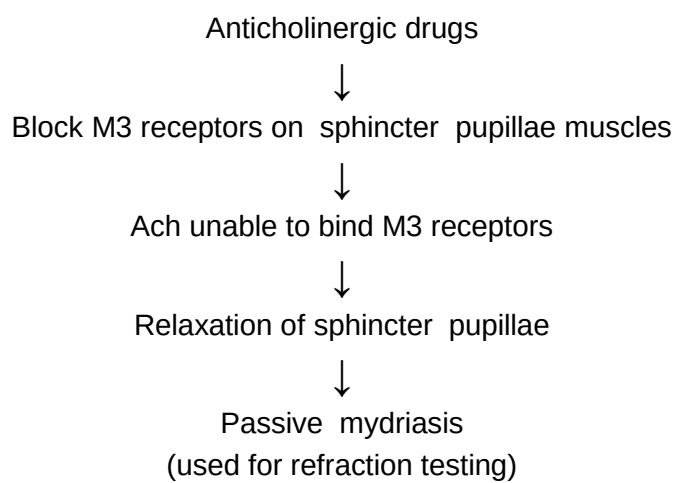
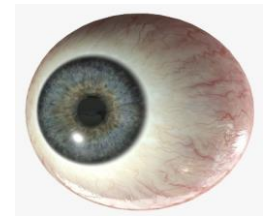


**Bronchial muscle
Bronchodilatation**

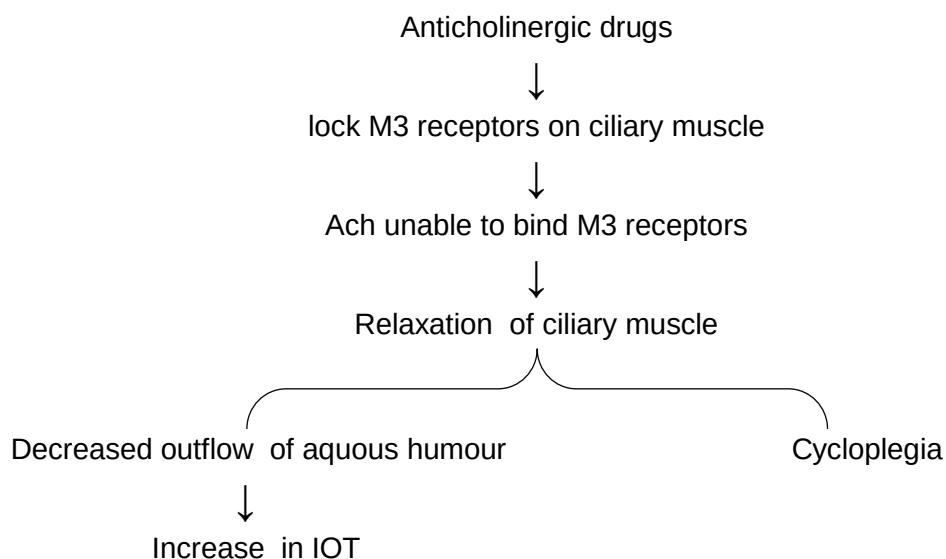
4. Eye

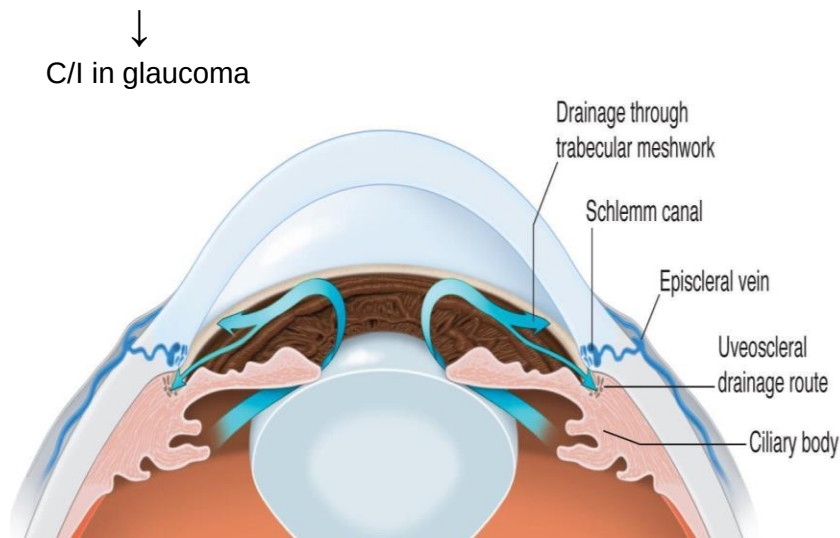
- **Iris muscle** → Relaxation □ Passive mydriasis
- **Ciliary muscle** → Relaxation □ Cycloplegia, IOT rise

A. Iris muscle



B. Ciliary muscle





5. Glands

Anticholinergic drugs
↓
Block M3 receptors on Glands
↓
Ach unable to bind M3 receptors
↓
Decreases secretion



(salivary, tracheobronchial, sweat and lacrimal and gastric secretion)

- **Skin** → Dry, hot
- **Eyes** → Dry
- **Mouth** → Dry, Swallowing difficult

6. Blood vessels

- Atropine blocks vasodilator action of cholinergic agonists

7. Local anaesthetic

- Atropine has an anaesthetic action on cornea

Uses

1. Gastrointestinal conditions
2. Respiratory system
3. Urinary system
4. Uterus
5. Eye
6. Glands
7. CVS
8. CNS
9. Antidote

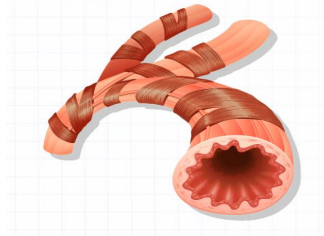
1. Gastrointestinal conditions

- Causes GI relaxation
- Used as Antispasmodic in →
 - Abdominal cramps
 - Intestinal colic
 - Irritable bowel syndrome
 - Gastritis
 - Gastric hypermotility
 - Pylorospasm



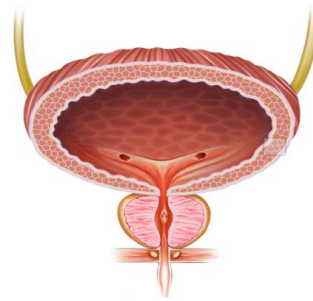
2. Respiratory system

- Causes Bronchodilatation
- Used in →
 - COPD
 - Chronic bronchitis



3. Urinary system

- Causes urinary bladder relaxation
- Used as Antispasmodic in →
 - Renal colic
 - Urinary frequency
 - Urinary urgency
 - Enuresis



4. Uterus

- Causes uterus relaxation
- Used as Antispasmodic in → Dysmenorrhoea



5. Eye

- Causes Relaxation of sphincter pupillae → Mydriasis → used for refraction testing
- Causes Relaxation of ciliary muscle → Cycloplegia → Used in iritis, iridocyclitis, keratitis, corneal ulcer



Causes Mydriasis for refraction testing



Causes Cycloplegia. in Iritis

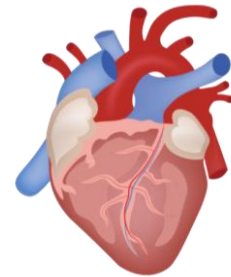
6. Glands

- Decreases secretion
- Used as Antisecretory for →
 - Sialorrhea
 - Preanesthetic medication
 - Excessive salivation in Parkinsonism



7. CVS

- Cause increased Rate and Contractility
- Used as cardiac vagolytic in →
 - Sinus bradycardia
 - Partial Heart block



8. CNS

- Causes sedation and amnesia → used as a lie detector (Scopolamine)
- Suppresses cholinergic system in striatum → Restores balance between DA and Ach → Used in Parkinsonism
- Blocks signals from vestibular system (inner ear) to brain → Used as Antiemetic in motion sickness



Lie detector



Motion sickness



Acetylcholine

Dopamine

Parkinsonism

9. As an antidote in

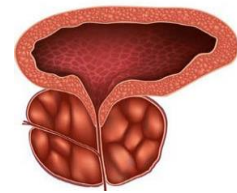
- Organophosphorus/ anticholinesterase poisoning
- Mushroom poisoning (mycetism)

Adverse effects

1. Constipation
2. Difficulty in micturation, urinary retention → C/I in BPH
3. Dilated pupil, photophobia, blurring of vision
4. Increase in IOT → C/I in Glaucoma
5. Dry mouth, difficulty in swallowing and talking.
6. Dry hot skin.
7. Tachycardia, palpitation

Contraindications

- Glaucoma
- BPH



SUMMARY

Anticholinergic drugs

Uses

1. Gastrointestinal conditions
2. Respiratory system
3. Urinary system
4. Uterus
5. Eye
6. Glands
7. CVS
8. CNS
9. Antidote

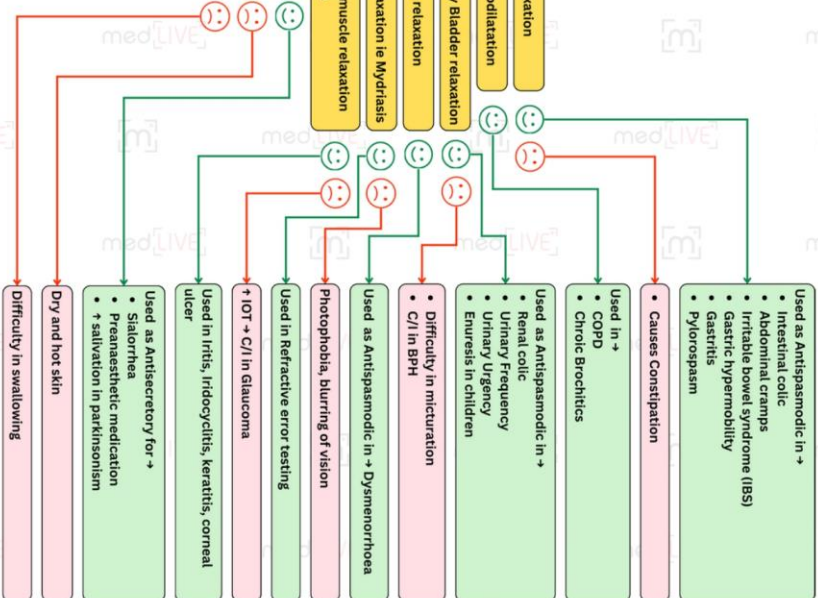
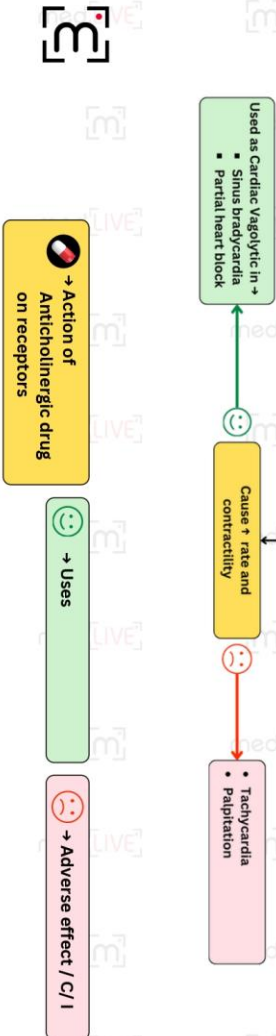
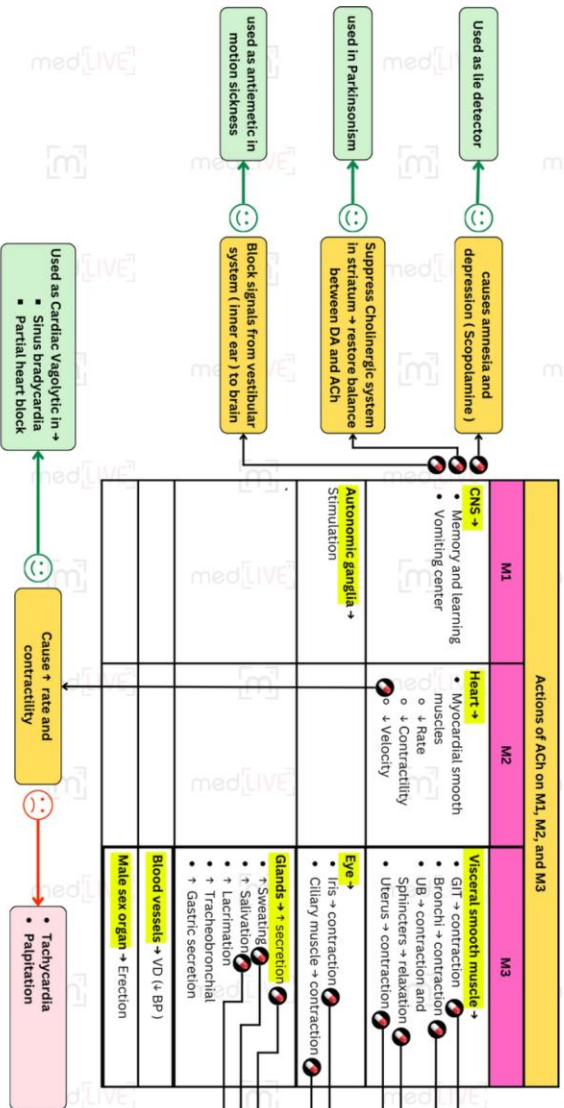
Adverse effects / C/I

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ANTICHOLINERGIC DRUGS

Uses, Adverse effects and Contraindications of
based on action of ACh on M and N receptors



www.medlivebydrpriyanka.com For more details

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PHARMA 2

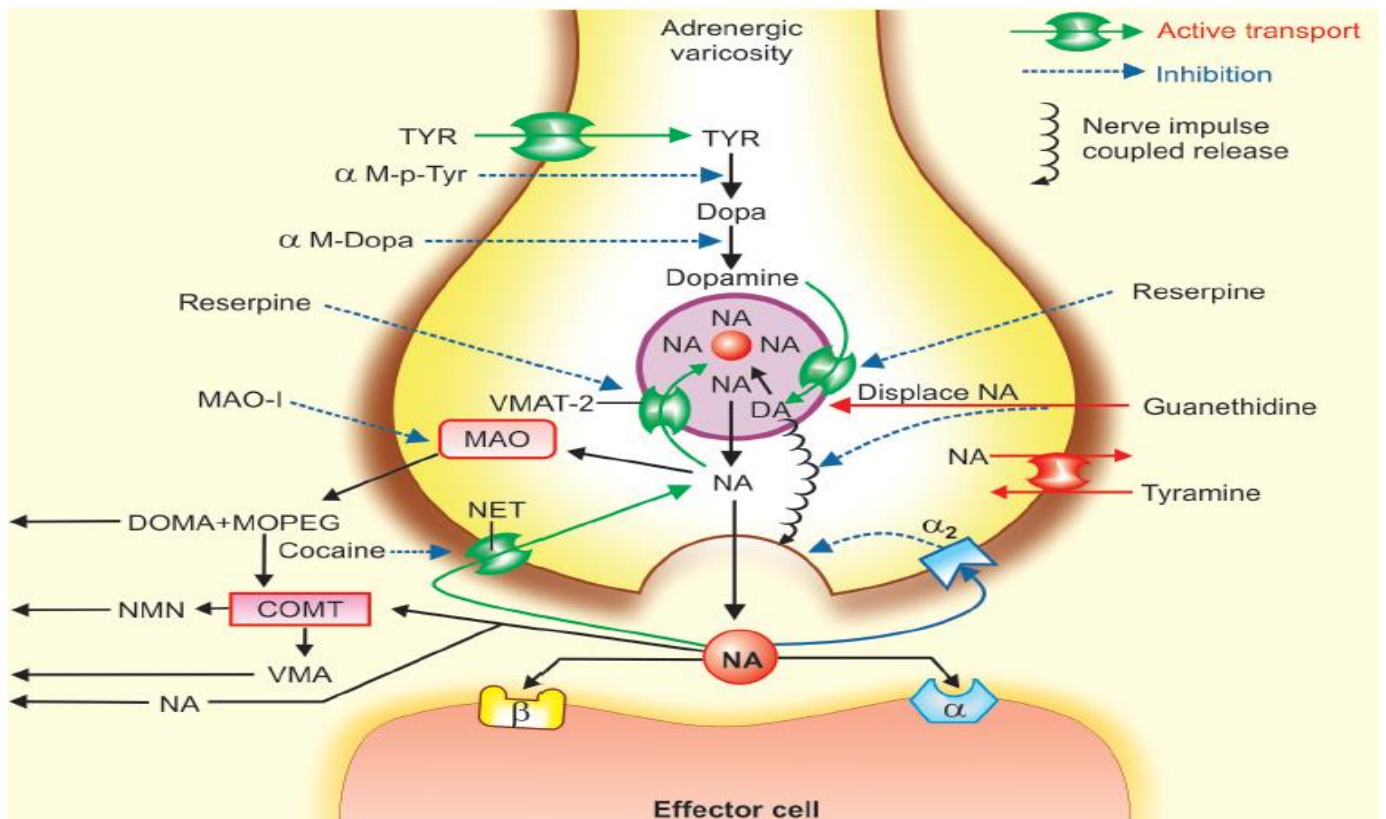
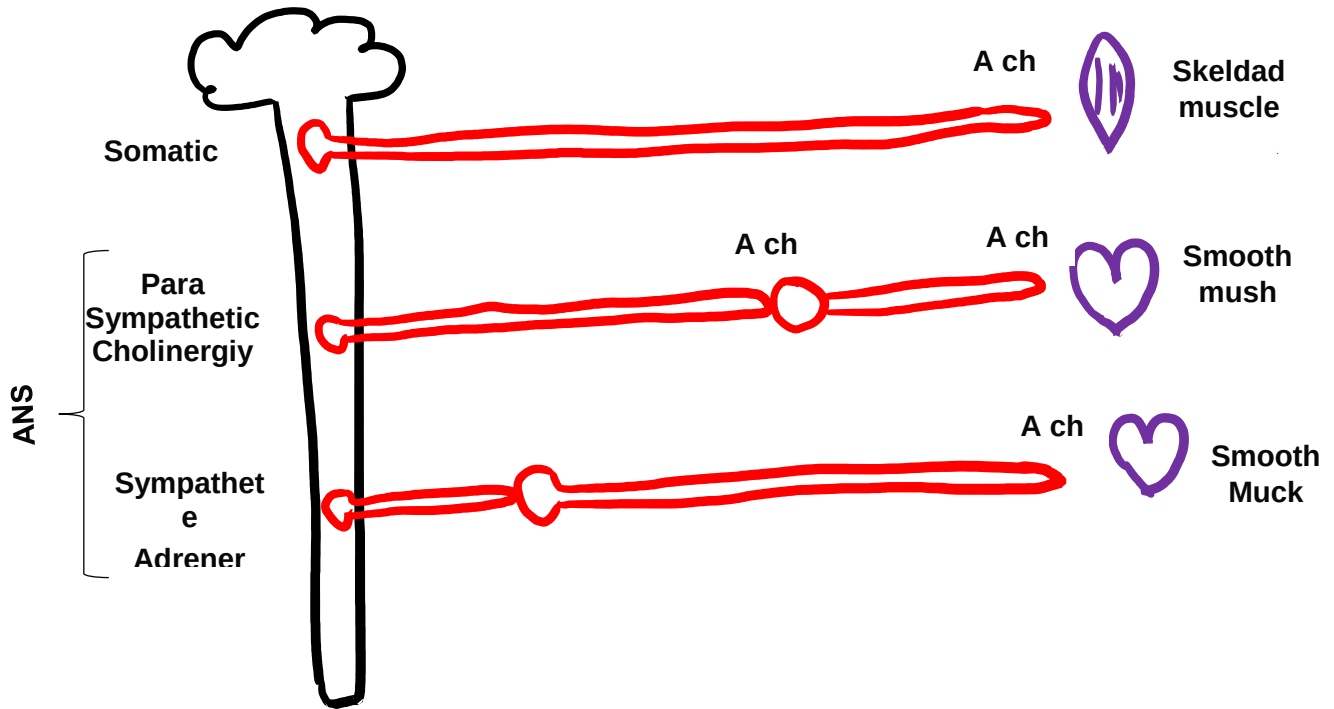
INTRODUCTION TO ADRENERGIC SYSTEM

Noradrenaline (NA)

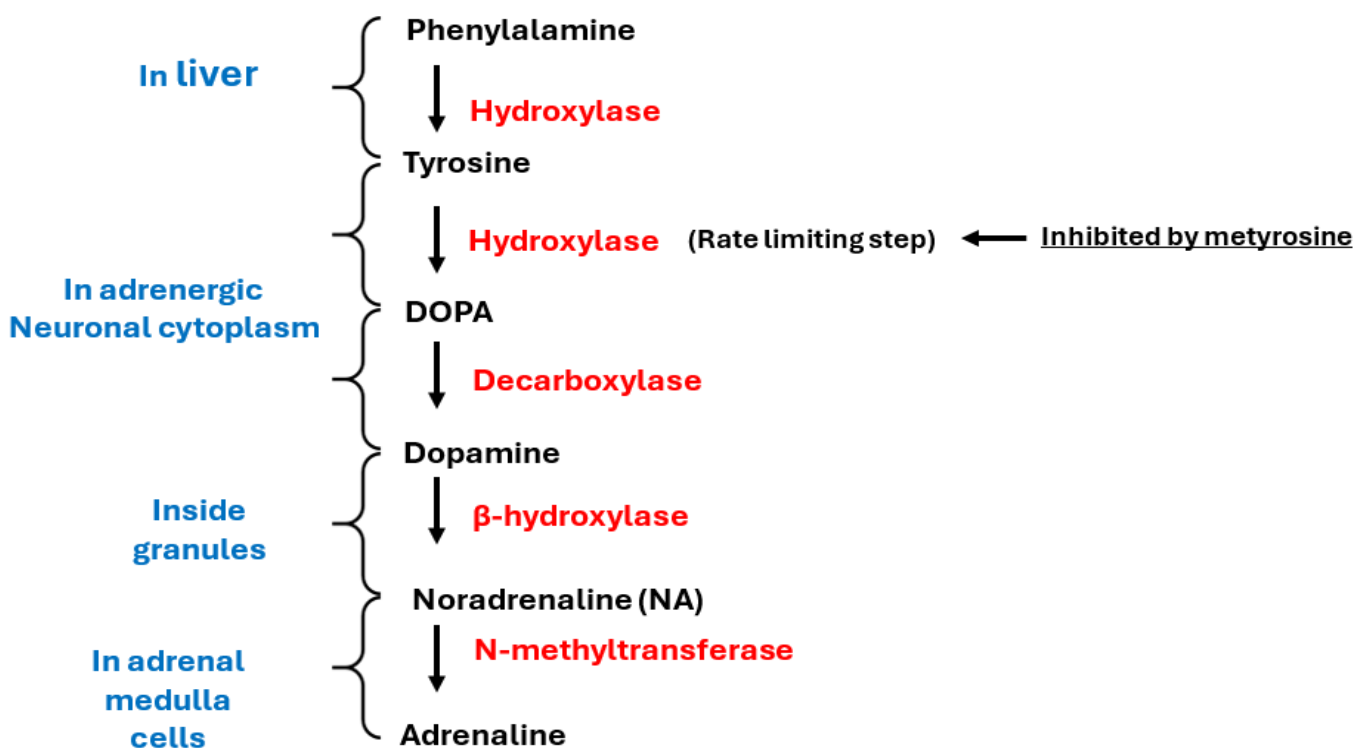
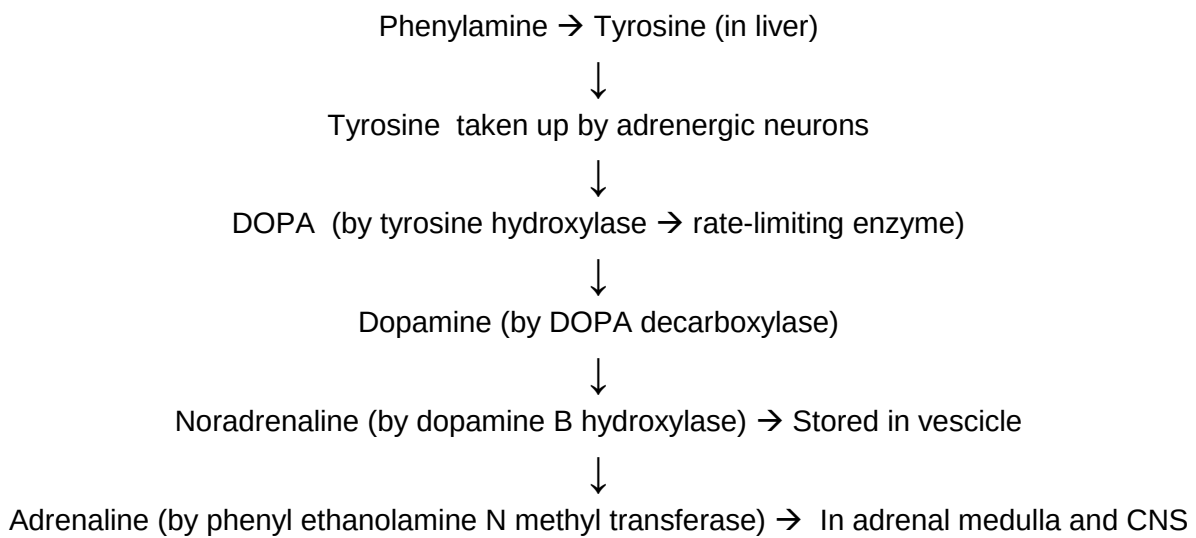
In Adrenergic / Sympathetic system

Noradrenaline (NA)

Major neurohumoral transmitter at postganglionic fibres



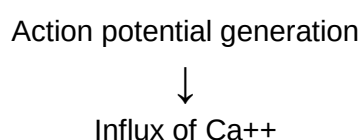
Synthesis and Storage of NA

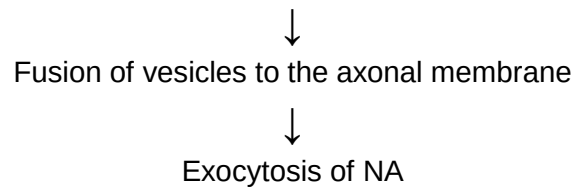


Remember

- Synthesis of NA occurs in → **All adrenergic neurons**
- Synthesis of adrenaline occurs only in → **Adrenal medullary cells**

Release of NA





Uptake of catecholamines

1. Axonal uptake (uptake -1)
2. Vesicular uptake
3. Extraneuronal uptake (uptake-2)

1. Axonal uptake (uptake -1)

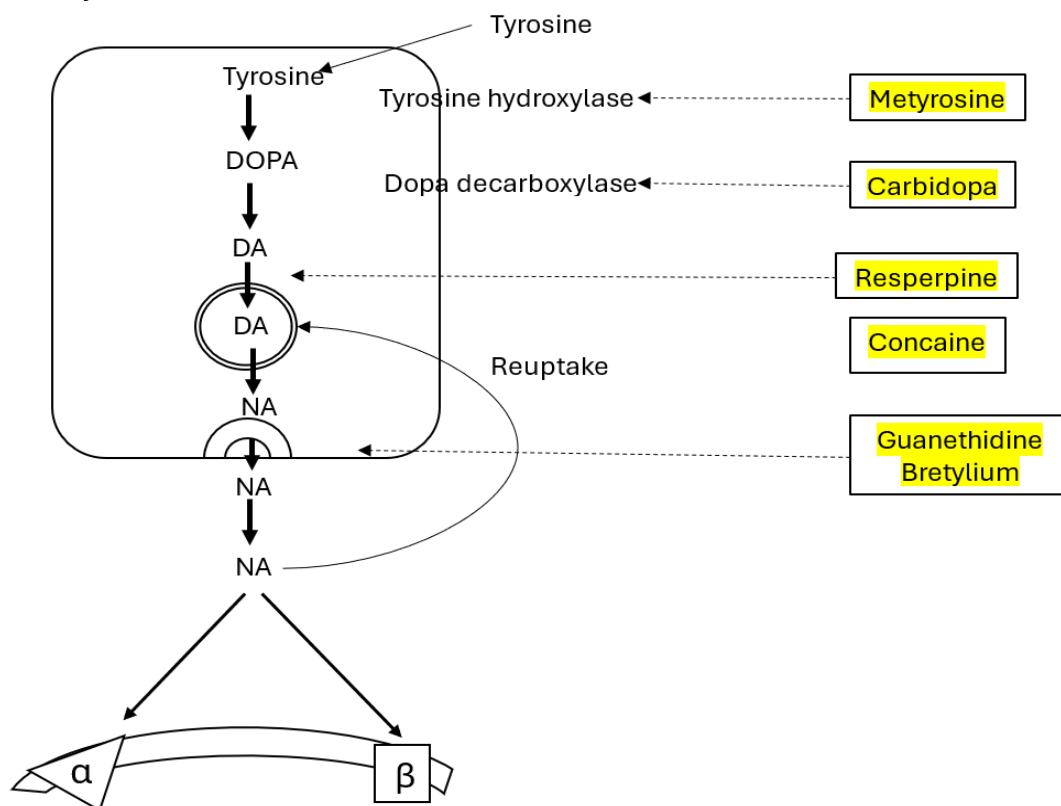
- It is by an active amine pump → NET
- Transports NA by → Na⁺ coupled mechanism.
- Most important for → terminating postjunctional action of NA
- Blocked by → Cocaine

2. Vesicular uptake

- It is by amine pump → vesicular monoamine transporter (VMAT-2).
- Transports CA from cytoplasm to interior of storage vesicle by □ exchanging with H⁺.
- Important in → maintaining NA content of neuron.
- Blocked by → Reserpine

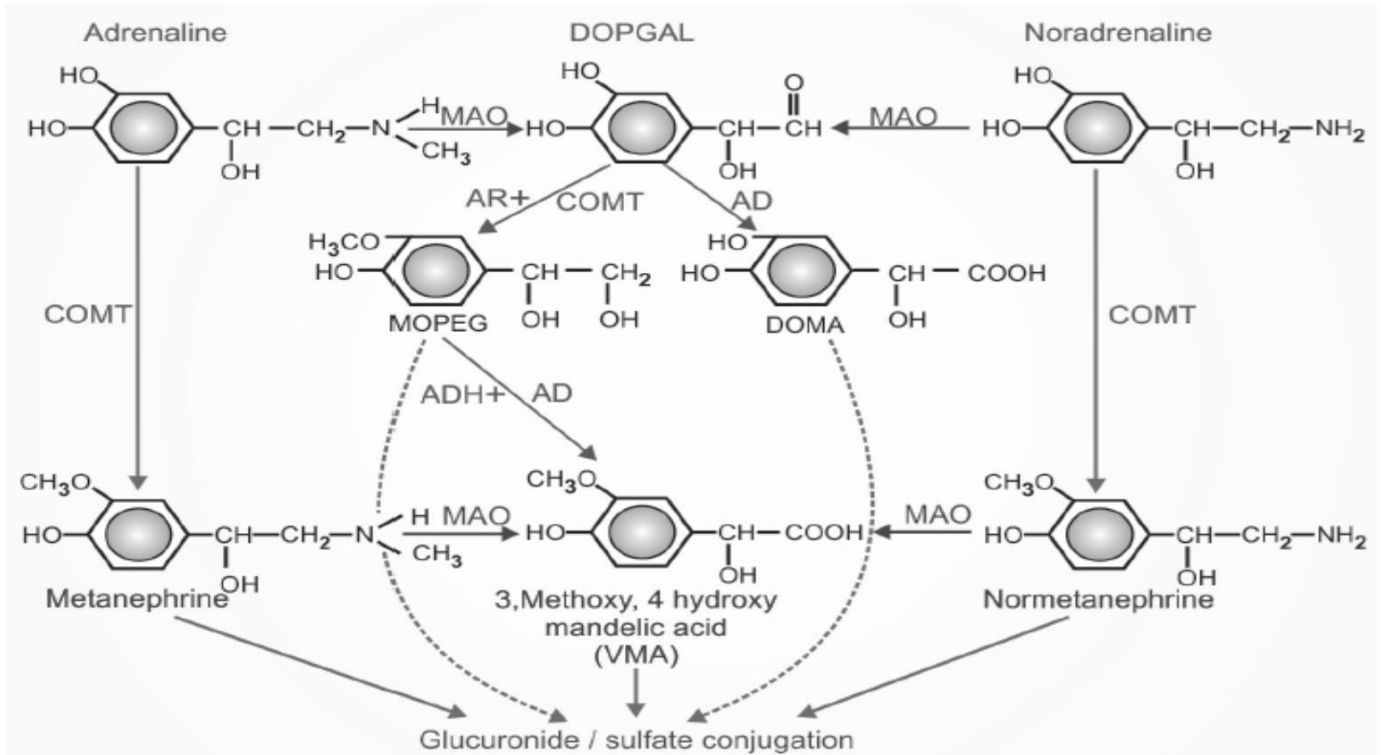
3. Extraneuronal uptake (uptake-2)

- Carried out by extraneuronal amine transporter (ENT) and organic cation transposes (OCT)
- Blocked by → Corticosterone



Metabolism of catecholamines

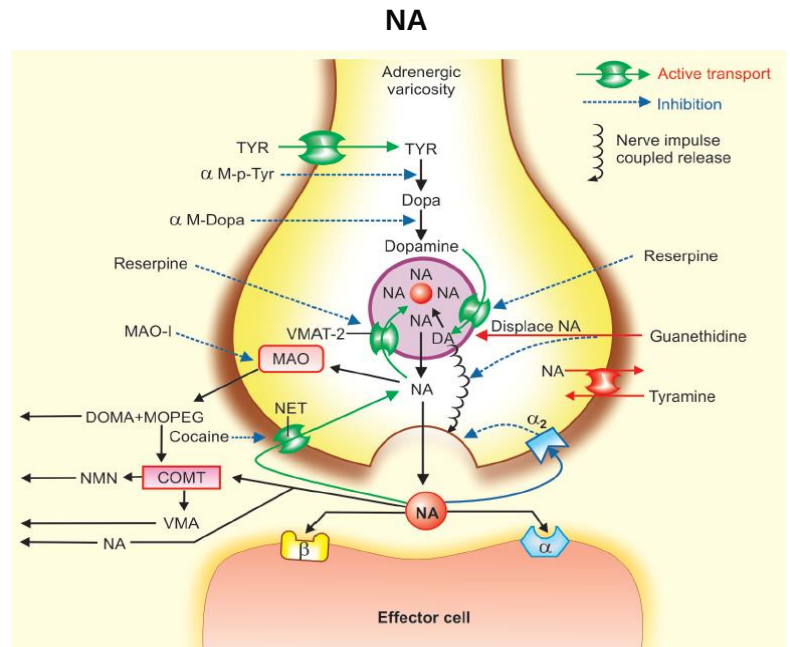
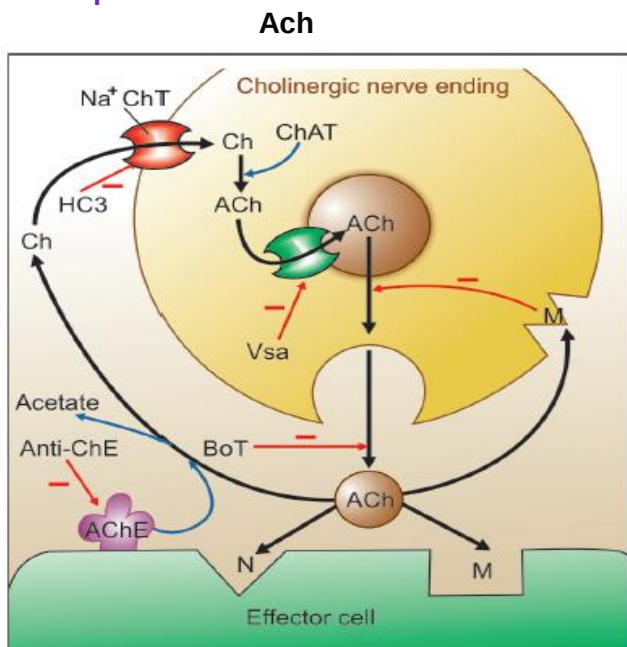
- Part of NA leaking out from vesicles into cytoplasm as well as that taken up by axonal transport is first attacked by MAO
- That NA which diffuses into circulation is first acted upon by catechol-o-methyl transferase (COMT) in liver and other tissues.
- In both cases, the alternative enzyme can subsequently act to produce vanillylmandelic acid (VMA) → major metabolite excreted in urine



Remember

- Metabolism does not play an important role in terminating action of neuronally released (endogenous) CAs.
- It is axonal reuptake that is responsible for terminating the action of endogenous CAs

Compare



Adrenergic Receptors

- α Receptors
- β Receptors

Receptor	Site of action	Effect
α_1	Vascular smooth muscle Genitourinary smooth muscle Intestinal smooth muscle Sphincters Liver Iris Male sex organ	Contraction Contraction Relaxation Constriction Glycogenolysis and gluconeogenesis Contraction of dilator pupillae (mydriasis) Ejaculation
α_2	Presynaptic terminals (at autonomic nerve endings) Platelets Pancreatic β cells Nerves Vascular smooth muscles	Inhibition of release of neurotransmitter Inhibition of insulin secretion Aggregation Inhibition of release of NT Contraction
β_1	Heart Juxtaglomerular cells	Force of contraction (inotropic) Rate of contraction (chronotropic) Conduction (dromotropic) ventricular relaxation & filling (lusitropic) Renin secretion
β_2	Smooth muscles of bronchi, blood vessels, Gastrointestinal & Genitourinary tract Skeletal muscles Liver	Relaxation Glycogenolysis Uptake of potassium Tremors Glycogenolysis, gluconeogenesis and potassium uptake
β_3	Adipose tissue	Lipolysis, thermogenesis

	α Actions	β Actions
Blood vessel	Vaso Constriction $\rightarrow \uparrow$ BP (α_1)	Vaso Dilatation $\rightarrow \downarrow$ BP (β_2)
Heart	Little action	Cardiac stimulation (β_1), $\uparrow$ rate, force, velocity
Lungs	_____	Bronchodilatation (β_2)
Eyes	Contraction of Dilator pupillae $\rightarrow$ Mydriasis (α_1), $\downarrow$ aqueous secretion	No effect on iris, slight relaxation of ciliary muscle, $\uparrow$ aqueous secretion
GIT	Intestine - relax, sphincters - contract	Intestine - relax (β_2)
Bladder	Trigone – contract (α_1)	Detrusor –relax (β_2)
Uterus	Contraction (α_1)	Relaxation (β_2)
Pancreas	Inhibit Insulin (α_1) (dominant)	Augmented Insulin (mild) and glucagon secretion (β_2)

Metabolism		Liver- glycogenolysis (β_2) → hyperlactacidaemia Muscle – glycogenolysis (β_2) → hyperlactacidaemia Fat – lipolysis ($\beta_1 + \beta_2 + \beta_3$) → ↑ FFA, calorogenesis
Kidney	_____	Renin release from kidney (β_1)
Male sex or	Ejaculation (α_1)	
Skeletal muscle	NM facilitated, ↑ Ach release	Tremors (β_2)
CNS	_____	Restlessness, apprehension, ADH secretion (β_1)

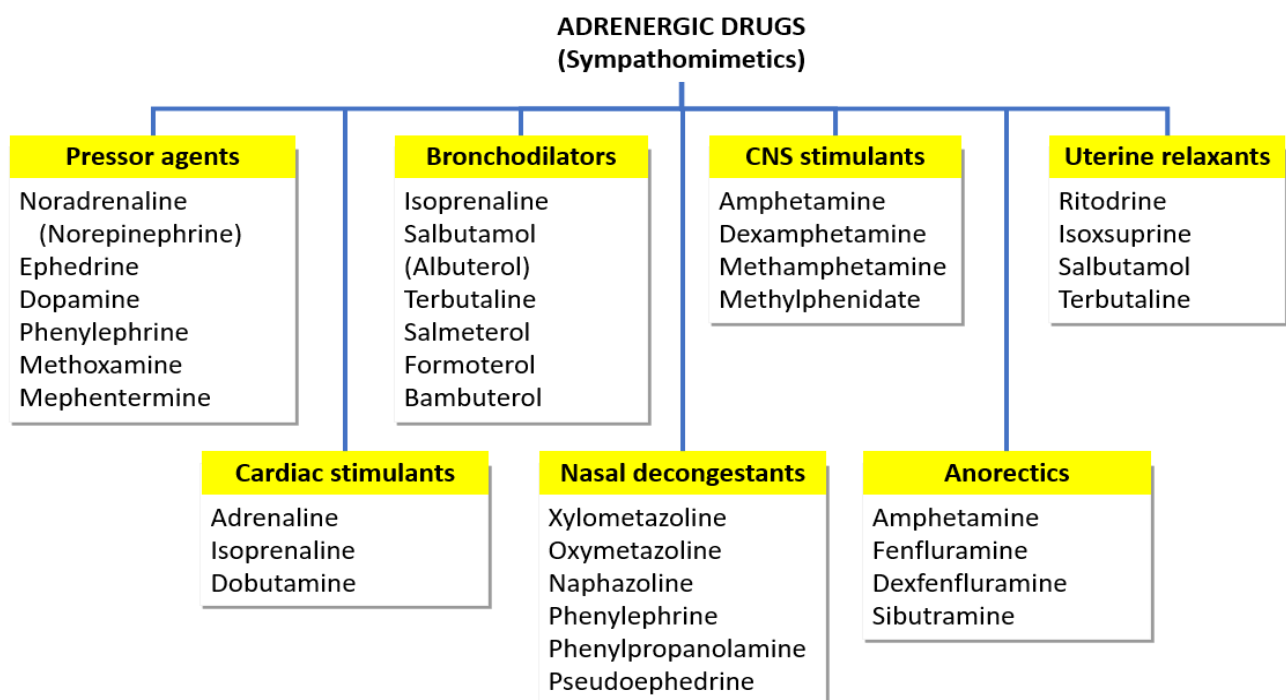
ADRENERGIC DRUGS

	Adrenergic Drugs	AntiaAdrenergic Drugs	
		α Blockers	β Blockers
Definition			
Classification			
MOA			
Pharmacological Actions			
Use			
Contraindication			

Definition

- Adrenergic drugs → mimic action produced by sympathetic nerve stimulation → known as sympathomimetics

Classification



- Some of them are → **α agonist**
- Some of them are → **β agonist**
- Some of them are → **Nonselective (both) agonist**

Remember

- NA: $\alpha_1 + \alpha_2 + \beta_1 + \beta_3$ but no β_2 action
- Iso: $\beta_1 + \beta_2 + \beta_3$ but no α action
- Adr: $\alpha_1 + \alpha_2 + \beta_1 + \beta_2$ and weak β_3 action

MOA

- **Direct sympathomimetics** → Act directly as agonists on α and/or β adrenoceptors
 - Ex. → Adr, NA, isoprenaline (Iso), phenylephrine, methoxamine, xylometazoline, salbutamol
- **Indirect sympathomimetics** → act on adrenergic neurone to release NA, which then acts on adrenoceptors
 - Ex. → Eryamine, amphetamine.
- **Mixed action sympathomimetics** → act directly as well as indirectly
 - Ex. → Ephedrine, dopamine, mephentermine

Pharmacological Actions

1. Blood vessels and BP

- **α_1** → Vasoconstriction
- **β_2** → Vasodilatation
- **Vasoconstriction (α_1 receptors)** → predominate in skin, mucosal, renal and splanchnic blood vessels.
- **Vasodilatation (β_2 receptors)** → predominate in skeletal muscles, liver and coronary blood vessels



$$BP = CO \times PR$$

- **SBP** → determined by cardiac output
- **DBP** → determined by blood vessel status

CRUX

- **α_1** → Vasoconstriction → Increases DBP
- **β_1** → Cardiac Stimulation → Increases SBP
- **β_2** → Vasodilatation → Decreases DBP

Effect on BP

- NA: $\alpha_1 + \alpha_2 + \beta_1 + \beta_3$ but no β_2 action
- Iso: $\beta_1 + \beta_2 + \beta_3$ but no α action
- Adr: $\alpha_1 + \alpha_2 + \beta_1 + \beta_2$ and weak β_3 action

a) NA : $\alpha_1 + \alpha_2 + \beta_1 + \beta_3$ but no β_2 action

- Rise in SBP (β_1 → cardiac stimulation)
- Rise in DBP (α_1 → VC)

- Rise in mean BP
- It does not cause vasodilatation (no β_2 action), peripheral resistance increases consistently due to α action

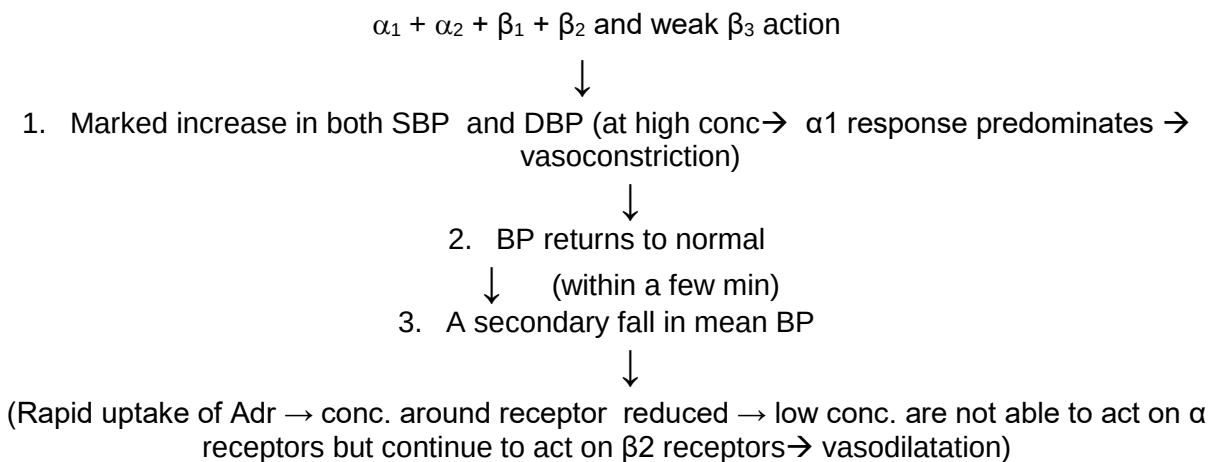
b) Isoprenaline : $\beta_1 + \beta_2 + \beta_3$ but no α action

- Rise in SBP (β_1 —cardiac stimulation)
- Fall in DBP (β_2 — vasodilatation)
- Mean BP generally falls.

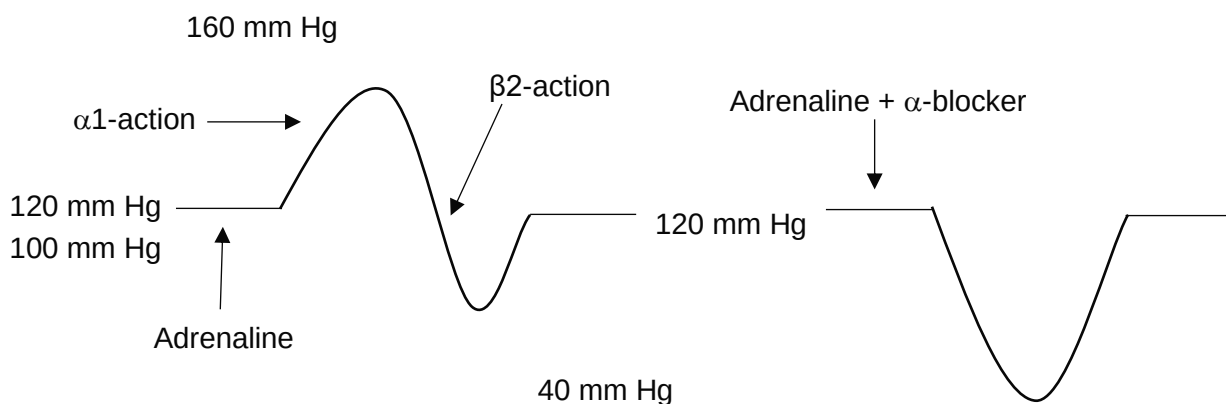
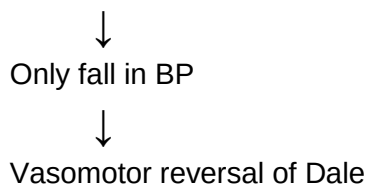
c) Adrenaline : $\alpha_1 + \alpha_2 + \beta_1 + \beta_2$ and weak β_3 action

- At high concentration of adrenaline $\rightarrow$ α_1 response predominates
- At low concentration of adrenaline $\rightarrow$ β_2 response predominates

Adrenaline



Adrenaline after α blocker



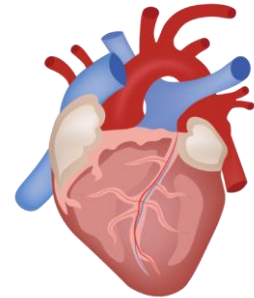
Effect of adrenaline on BP

Vasomotor reversal of Dale

	SBP (β_1)	DBP (β_2 and $\square$)	Heart Rate		
			Direct Action (β_1)	Reflex Action (M_2)	Net effect
A	↑↑	Nil	↑	Nil	↑
NA	↑↑	↑↑	↑	↓↓	↓
Iso	↑↑	↓↓	↑	↑	↑↑

2. Heart

- β_1 → Stimulates heart →
 - **Positive chronotropic** → Increase rate
 - **Positive inotropic** → Increase force of contraction
 - **Positive dromotropic** → Increase conduction



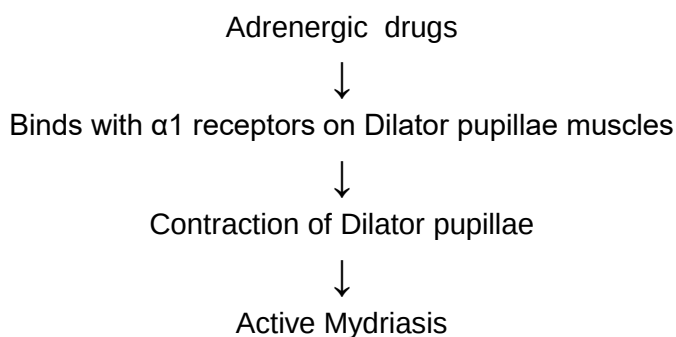
Positive chronotropic
Positive Inotropic
Positive Dromotropic

3. Lungs

- Adr and isoprenaline but not NA → potent bronchodilators (β_2)

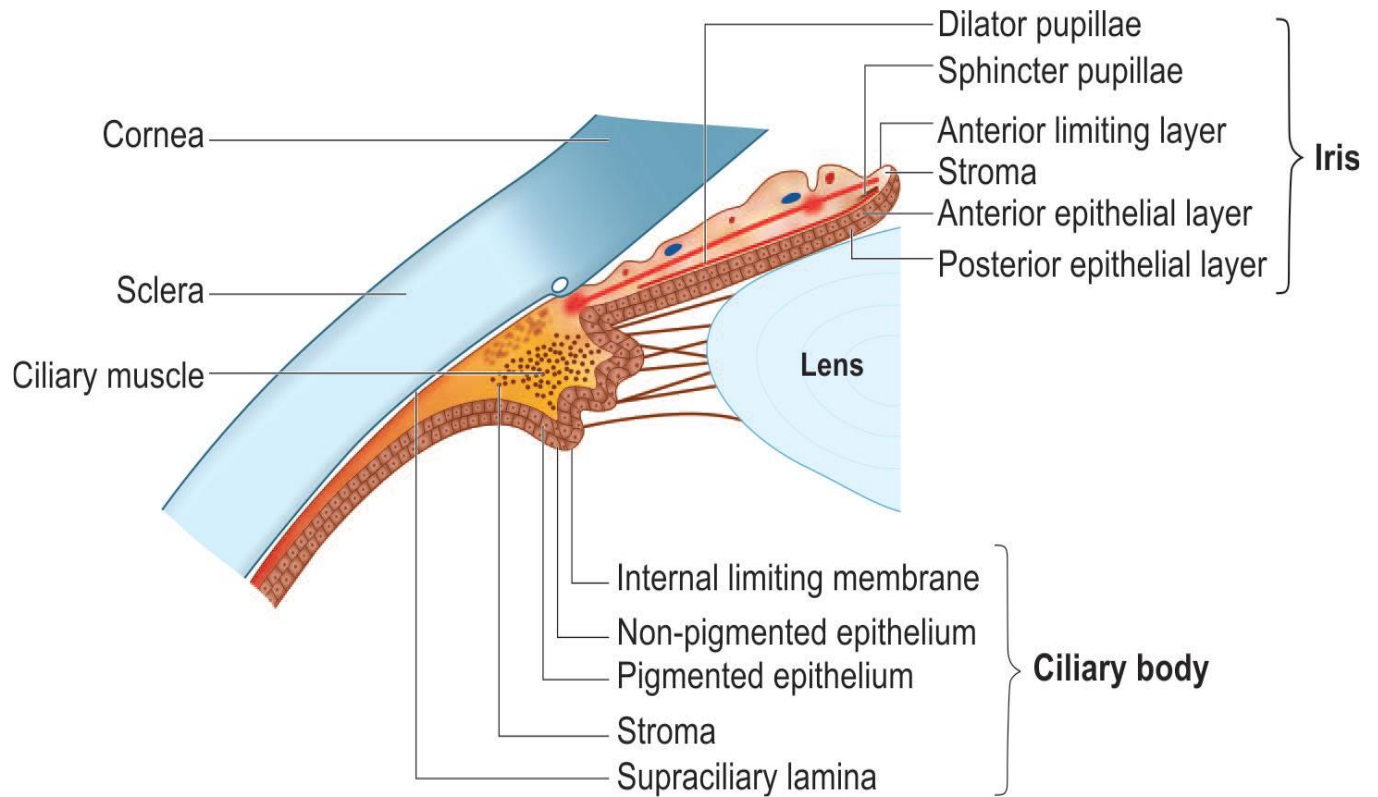


4. Eye



Effect on aqueous humor dynamics

- **α_1 receptor** – Vasoconstriction of ciliary vessels → reduced aqueous formation.
 - **α_2 receptor** – Reduced secretory activity of ciliary epithelium.
 - **β_2 receptor** – Enhanced secretory activity of ciliary epithelium
 - **Augmentation of uveo – scleral outflow.**
- Overall → IOT fall → useful in glaucoma



5. GIT

- Smooth muscle Relaxation (both α and β receptors)
- Sphincters are constricted (α receptors)

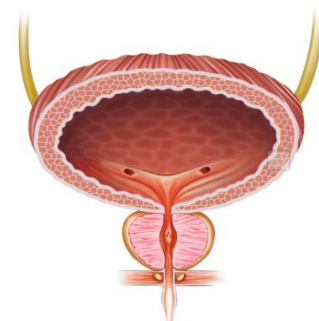
Retention



6. Bladder

- Detrusor is relaxed (β)
- Sphincter is constricted (α)

Retention



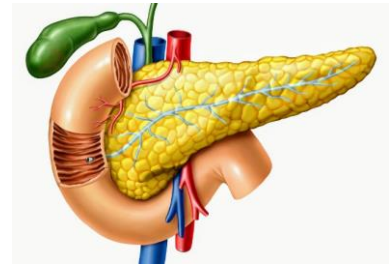
7. Uterus

- Adr $\rightarrow$
 - Contract uterine muscle (α_1)
 - Relax uterine muscle (β_2)
- Overall effect varies with species, hormonal and gestational status.
- Human uterus $\rightarrow$ relaxed by Adr at term of pregnancy, but at other times, its concentrations are enhanced.



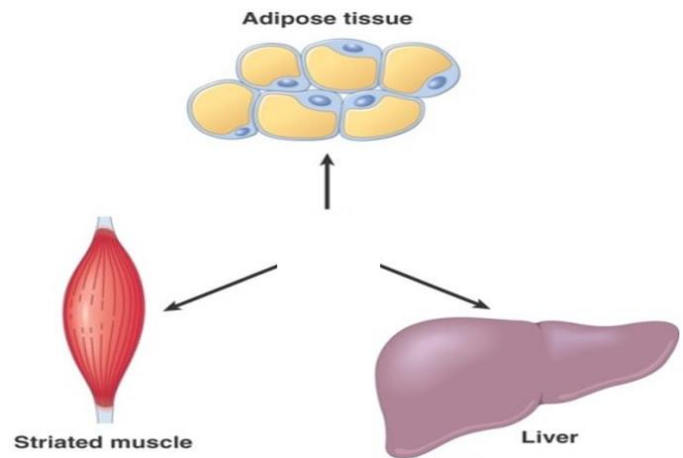
8. Pancreas

- Reduction of Insulin (α_2)
- Augmentation of Glucagon (β_2) secretion.



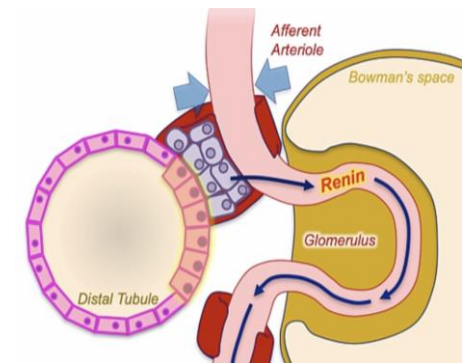
9. Metabolic

- **Liver** → glycogenolysis (β_2) → hyperglycaemia
- **Muscle** → glycogenolysis (β_2) → hyperlactacidaemia
- **Fat** → lipolysis ($\beta_1 + \beta_2 + \beta_3$) → increased blood FFA, Calorigenesis



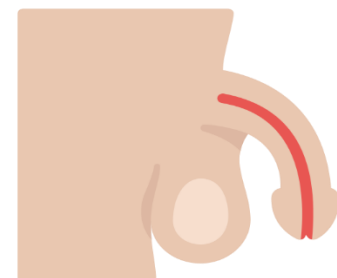
10. Kidney

- Increased renin release (β_1 receptors)



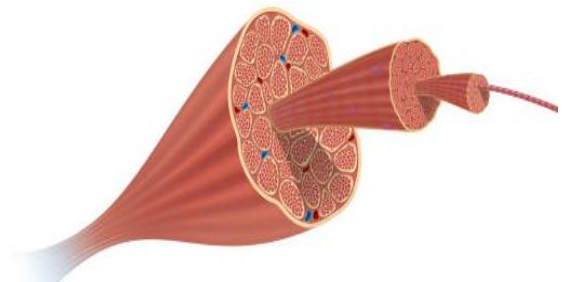
11. Male sex organ

- Ejaculation (α_1)



12. Skeletal muscle

- Tremors (β_2)



13. CNS

- Restlessness, apprehension (β_2)

Uses

1. Pressor Agents (α agonist)
2. Cardiac stimulants (β_1 agonist)
3. Bronchodilators (β_2 agonist)
4. Eye (α agonist)
5. Urinary bladder
6. Uterine relaxant (β_2 agonist)
7. CNS



1. Pressor Agents (α agonist)

Used in →

- Hypotensive states
- Anaphylactic shock
- Along with local anaesthetics
- Control of local bleeding
- Nasal decongestant



a) Hypotensive states

- Shock, spinal anaesthesia, hypotensive drugs
- One of the pressor agents can be used along with volume replacement for neurogenic and haemorrhagic shock

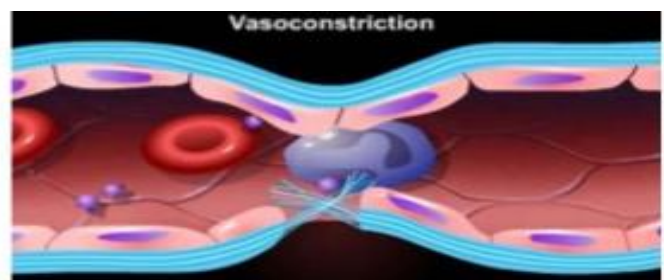
b) Anaphylactic shock

- DOC → Adr 0.5 mg IM
- It raises BP, and also counteracts bronchospasm/ laryngeal edema that may accompany.



c) Along with local anaesthetics

- Adr 1 in 200,000 to 1 in 100,000 for infiltration, nerve block and spinal anaesthesia
 - Duration of anaesthesia is prolonged
 - Systemic toxicity of local anaesthetic is reduced.
 - Local bleeding is minimised



d) Control of local bleeding

From skin and mucous membranes, e.g. epistaxis



Compresses of Adr 1 in 10,000, phenylephrine/ephedrine 1% soaked in cotton



Control arteriolar and capillary bleeding



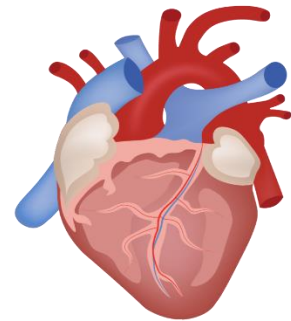
e) Nasal decongestant

In colds, rhinitis, sinusitis, blocked nose
 ↓
 α -agonists is used as nasal drops
 ↓
 Shrinkage of mucosa due to vasoconstriction
 ↓
 Provides relief



2. Cardiac stimulants (β_1 agonist)

- Used in →
 - (a) **Cardiac arrest** → Epinephrine (1:1000 concentration) → DOC in CPR.
 - (b) **Partial or complete A-V block** → Isoprenaline may be used as temporary measure to maintain sufficient ventricular rate.
 - (c) **Congestive heart failure (CHF)**



3. Bronchodilators (β_2 agonist)

Used in → **Asthma**

- Isoprenaline
- Salbutamol
- (Albuterol)
- Terbutaline
- Salmeterol
- Formoterol
- Bambuterol



4. Eye (α agonist)

- Mydriatic (α_1 agonist)** → Phenylephrine → used to facilitate fundus examination



- Reduces IOT (α_2 agonist)** → Apraclonidine, brimonidine → Used in Glaucoma

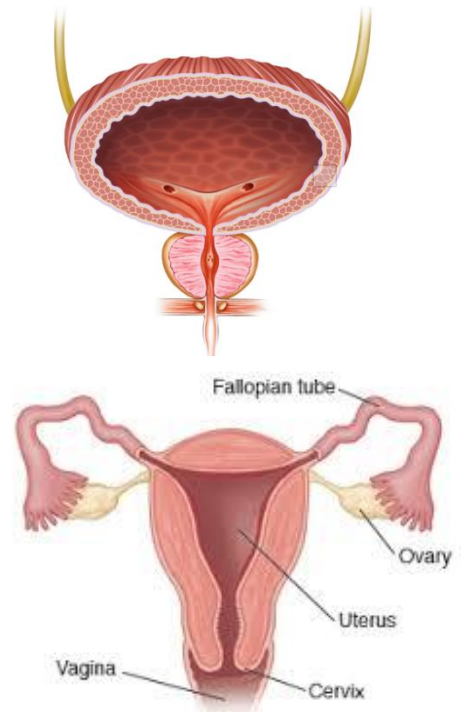


5. Urinary bladder

- Used in →
 - (a) Nocturnal enuresis in children
 - (b) Urinary incontinence
- Amphetamine can be used

6. Uterine relaxant (β_2 agonist)

- Used in →
 - (a) Threatened abortion
 - (b) Dysmenorrhoea
- Isoxsuprine and Ritodrine can be used



7. CNS

- Used in →
 - (a) Attention deficit hyperkinetic disorder (ADHD)
 - (b) Narcolepsy
 - (c) Epilepsy
 - (d) Parkinsonism
 - (e) Obesity → It decreases appetite center (anorectic drugs)



Contraindications

- Marked rise in BP leading to cerebral haemorrhage
- Ventricular tachycardia / fibrillation, angina, myocardial infarction

SUMMARY

Adrenergic drugs

Uses

1. Pressor Agents (α agonist)
2. Cardiac stimulants (β_1 agonist)
3. Bronchodilators (β_2 agonist)
4. Eye (α agonist)
5. Urinary bladder
6. Uterine relaxant (β_2 agonist)
7. CNS

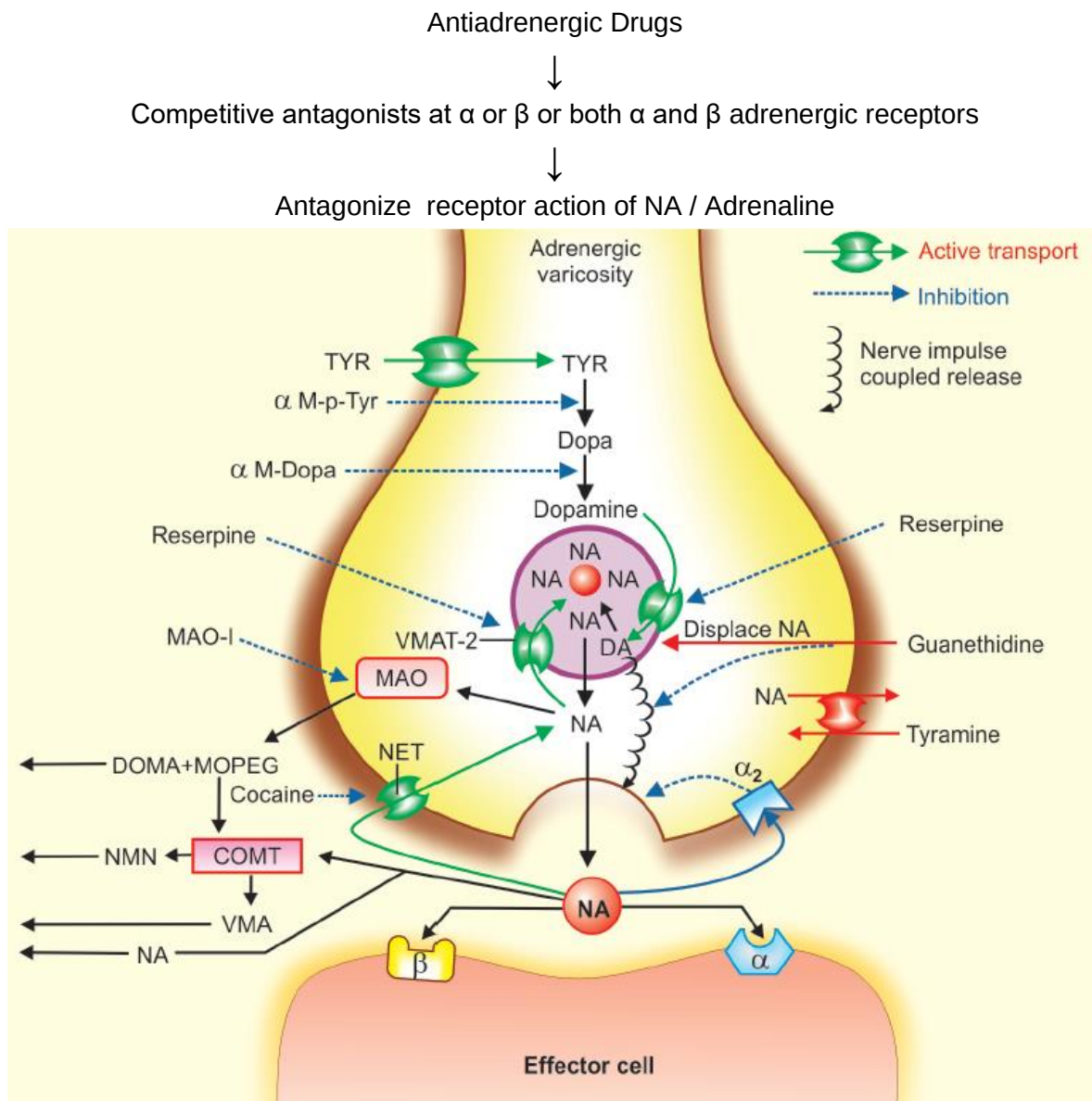
Adverse effects / C/I

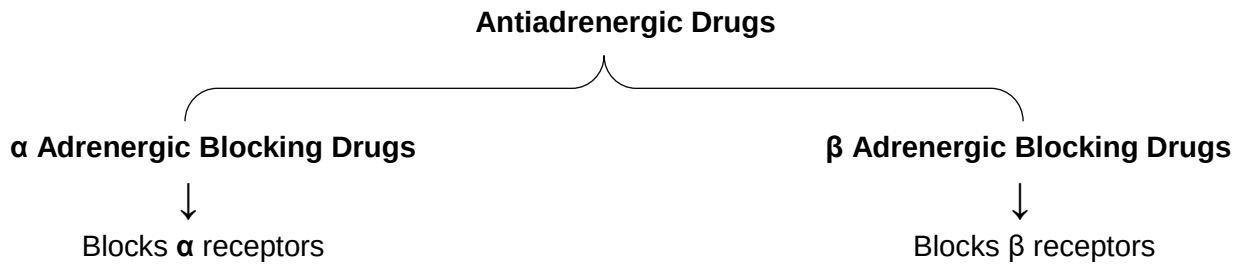
1. Marked rise in BP leading to cerebral haemorrhage
2. Ventricular tachycardia/fibrillation, angina, myocardial infarction

ANTIADRENERGIC DRUGS (ADRENERGIC RECEPTOR ANTAGONISTS)

	Adrenergic Drugs	AntiaAdrenergic Drugs	
		α Blockers	β Blockers
Definition			
Classification			
MOA			
Pharmacological Actions			
Use			
Contraindication			

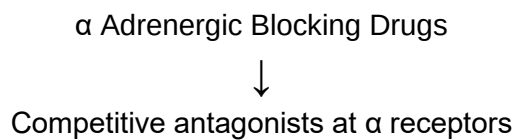
Definition



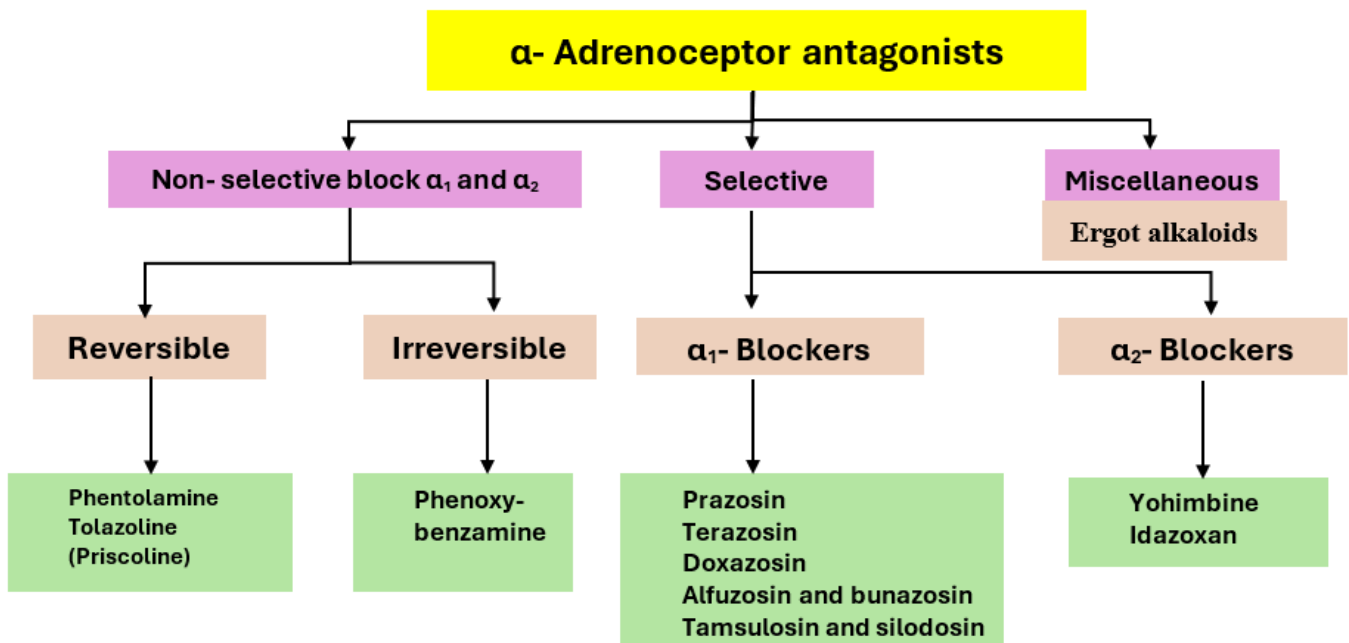


α ADRENERGIC BLOCKING DRUGS

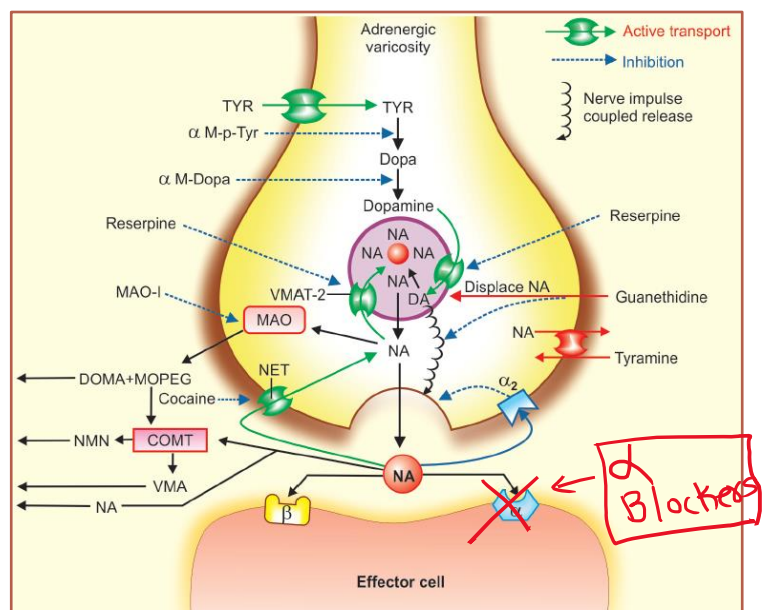
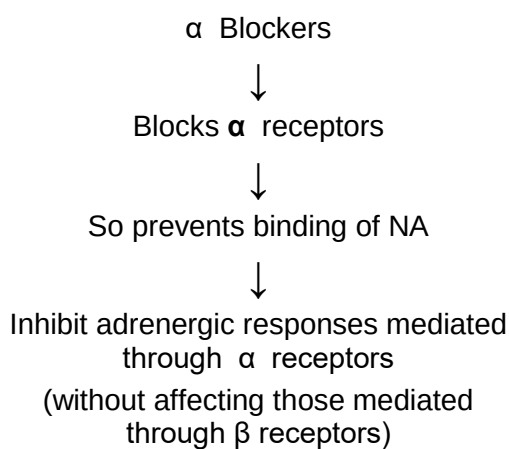
Definition



Classification

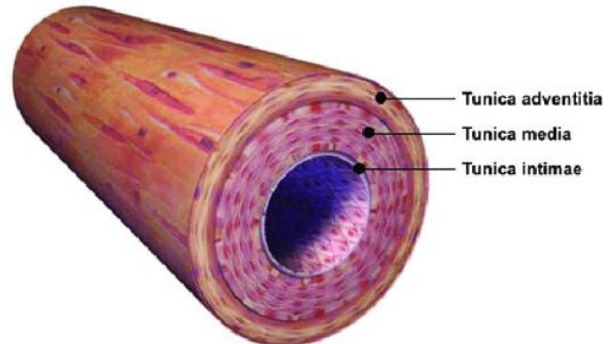
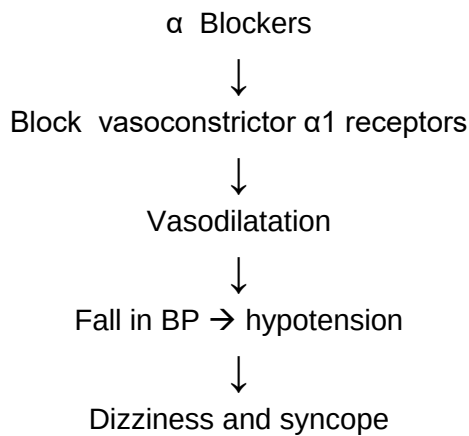


MOA



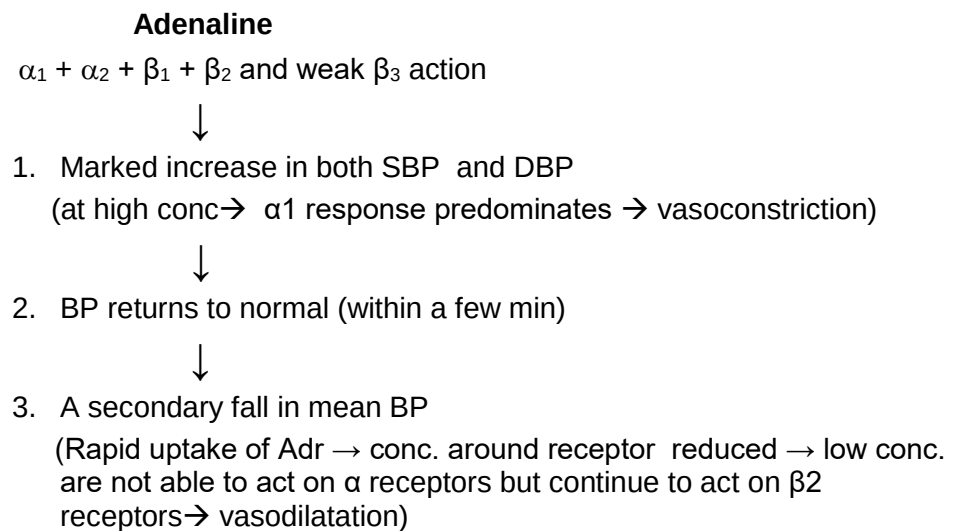
Pharmacological Actions

1. Blood vessels and BP

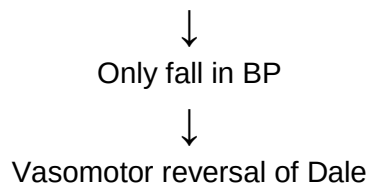


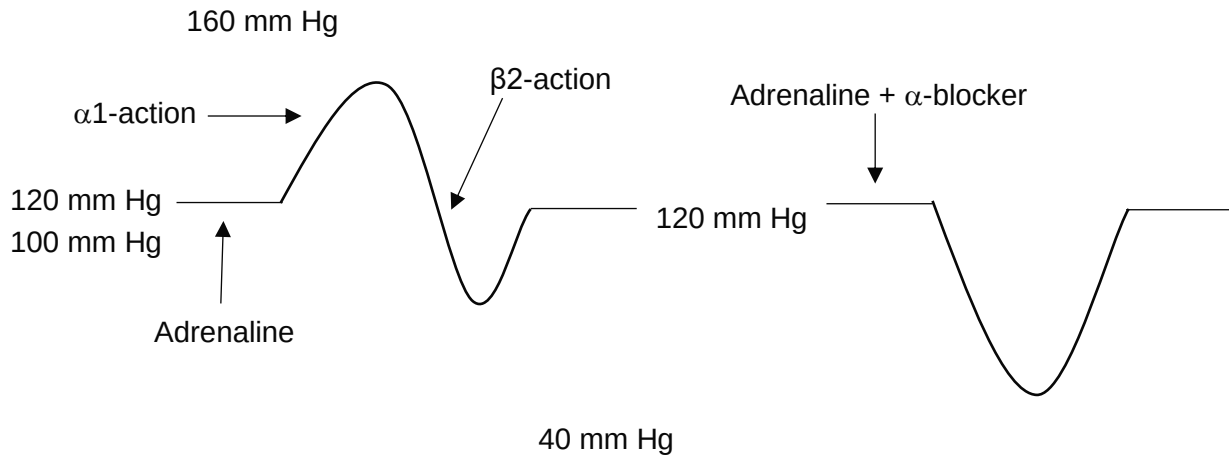
Adrenaline : $\alpha_1 + \alpha_2 + \beta_1 + \beta_2$ and weak β_3 action

- At high concentration of adrenaline → α_1 response predominates
- At low concentration of adrenaline → β_2 response predominates



Adrenaline after α blocker

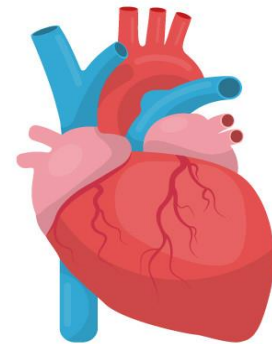
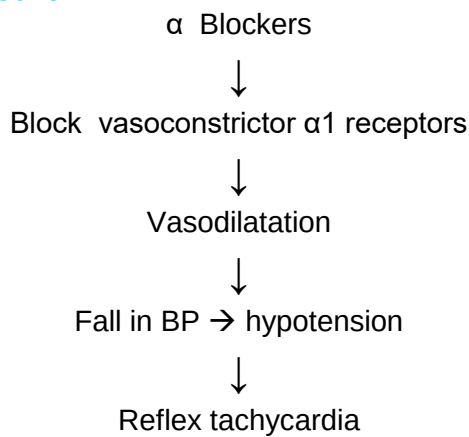




Effect of adrenaline on BP

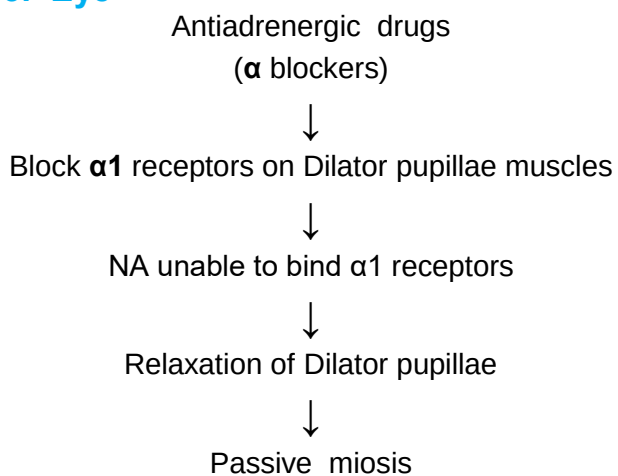
Vasomotor reversal of Dale

2. Heart

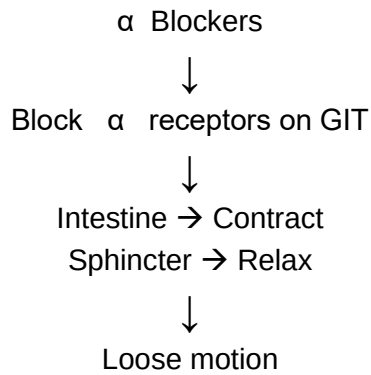


Reflex tachycardia

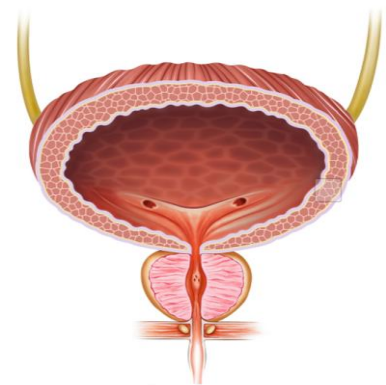
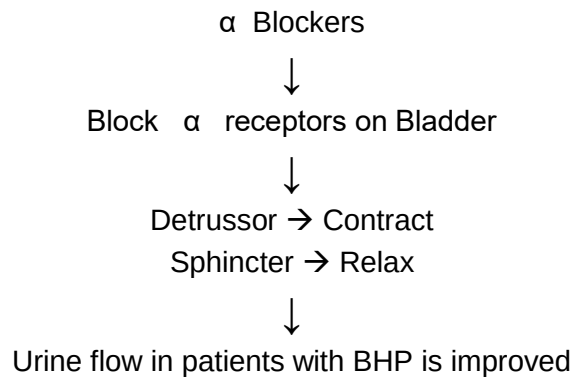
3. Eye



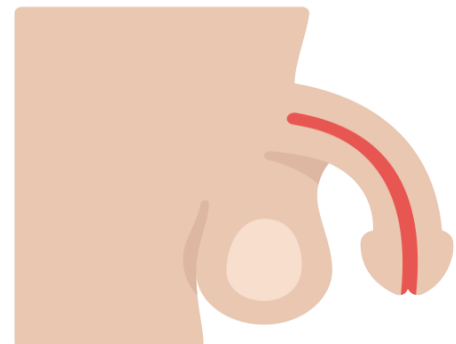
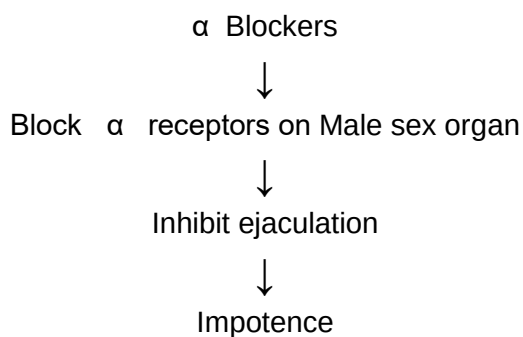
4. GIT



5. Bladder



6. Male sex organ



Uses

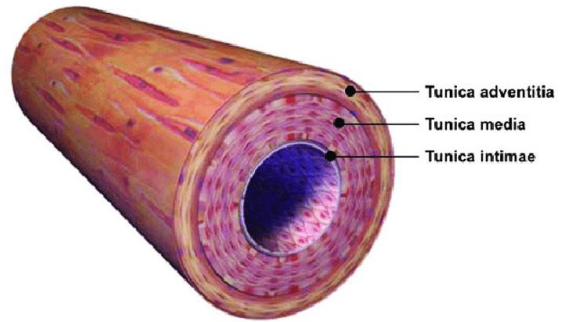
1. Hypertension
2. Pheochromocytoma
3. Secondary shock
4. PVD
5. Congestive heart failure (CHF)
6. Prinzmetal's angina
7. Male impotency due to erectile dysfunction
8. BHP

1. Hypertension

Selective for α_1 receptors (prazosin)

↓
Vasodilatation

↓
Decreases BP



2. Pheochromocytoma

Pheochromocytoma

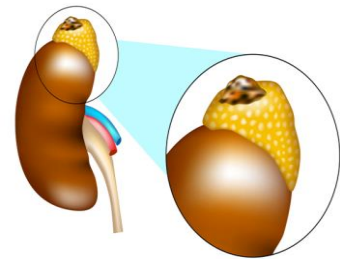
↓
Tumour of adrenal medullary cells

↓
Secrete catecholamine in blood

↓
Excess catecholamine in blood

↓
Intermittent or persistent hypertension

- Diagnosis → Estimation of urinary CA metabolites (VMA, normetanephrine) is diagnostic



Treatment

Inoperable Cases

↓
 α blockers given

↓
Vasodilatation

↓
Decreases BP

- Phenoxybenzamine → DOC
- Prazosin → Alternative

Operable cases

↓
Before and during surgery

↓
 α and β blockers given

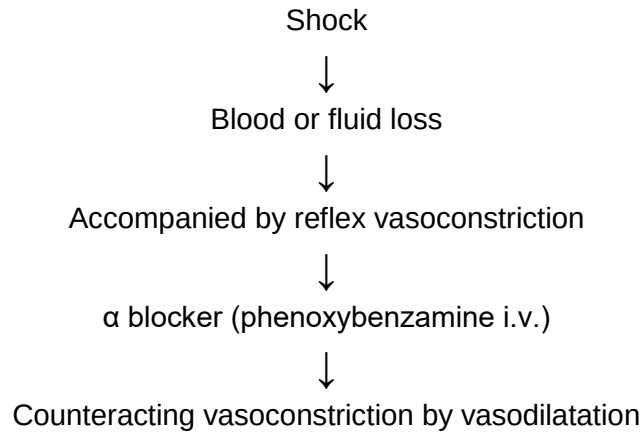
↓
To block α and β receptors

↓

To avoid effects of massive sudden release of catecholamines due to handling of tumour

- Phentolamine → DOC for hypertensive crisis

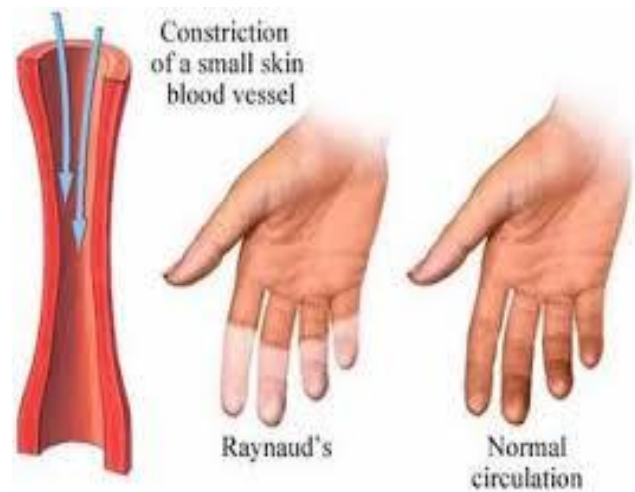
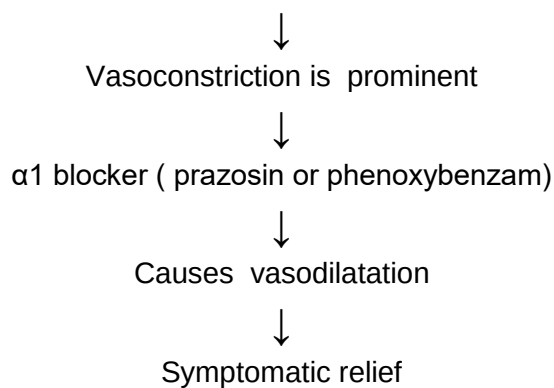
3. Secondary shock



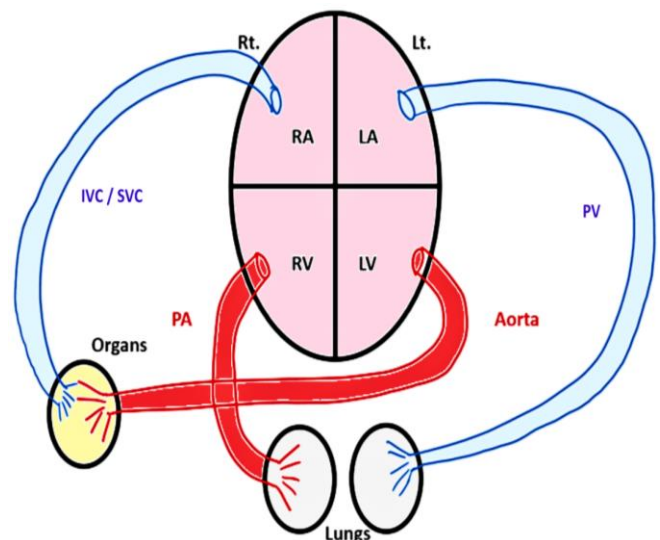
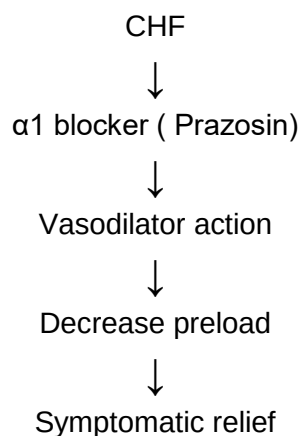
- Volume replacement also given

4. Peripheral vascular diseases

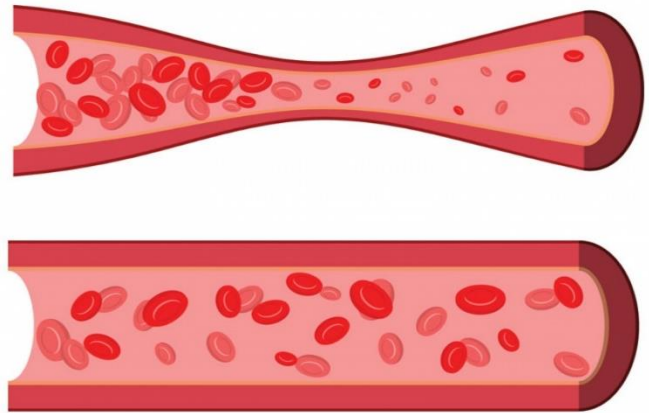
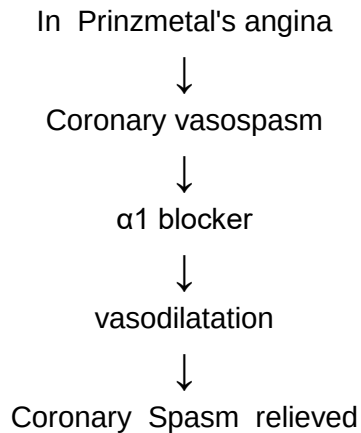
Peripheral vascular diseases
(Raynaud's phenomenon, acrocyanosis)



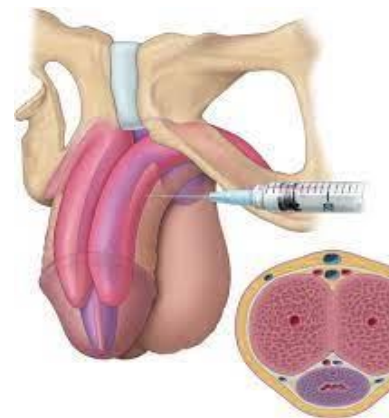
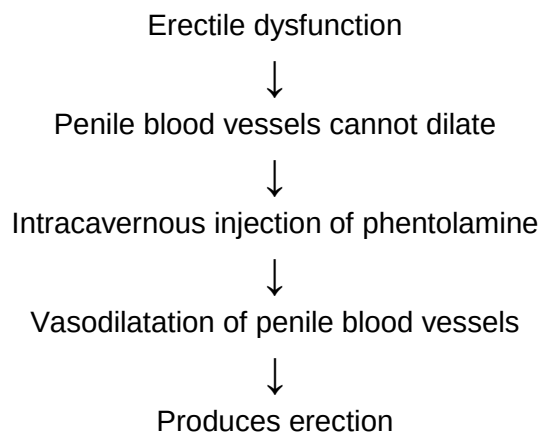
5. Congestive heart failure (CHF)



6. Prinzmetal's angina



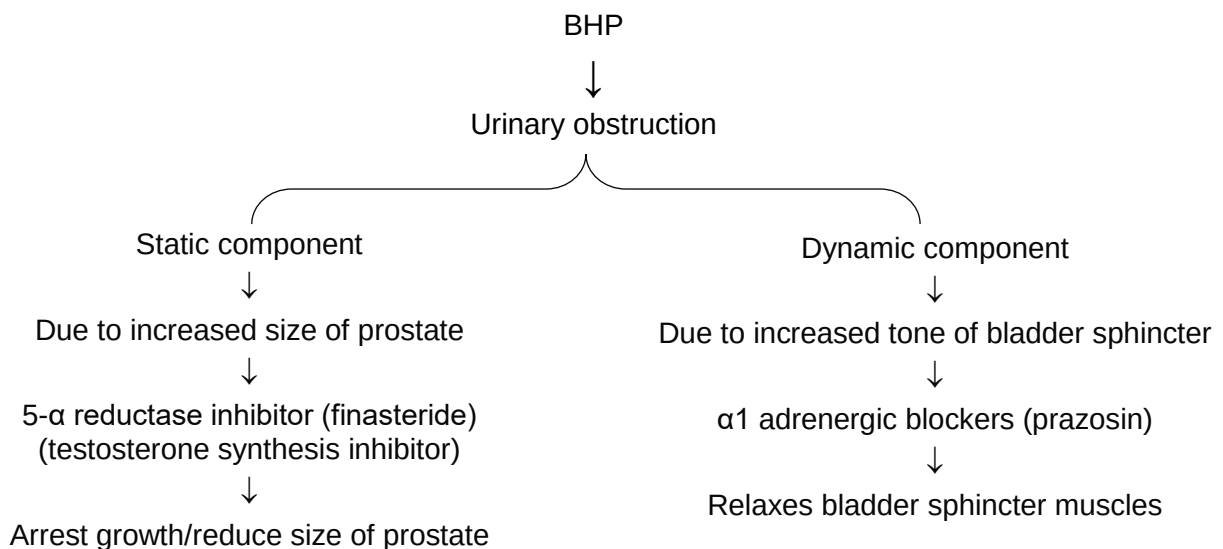
7. Male impotency due to erectile dysfunction



- But there is risk of priapism
- Need for a specialist to give the injection
- Repeated injections can cause penile fibrosis.
- Hence orally effective drug like sildenafil is preferred.



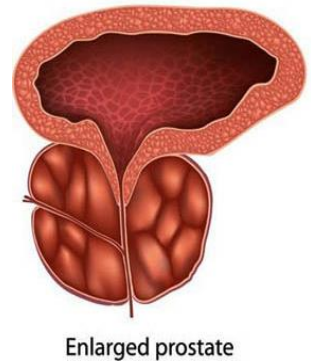
8. Benign hypertrophy of prostate (BHP)



- Tamsulosin and silodosin, ($\alpha 1A$ selective blockers) $\rightarrow$ preferred agents as they do not cause postural hypotension

Adverse effects

1. Postural hypotension $\rightarrow$ seen with first few doses (first dose effect)
2. Nasal blockade
3. Palpitation
4. Loose motions
5. Inhibition of ejaculation and impotence.



Postural hypotension

When a person rises from supine to erect posture



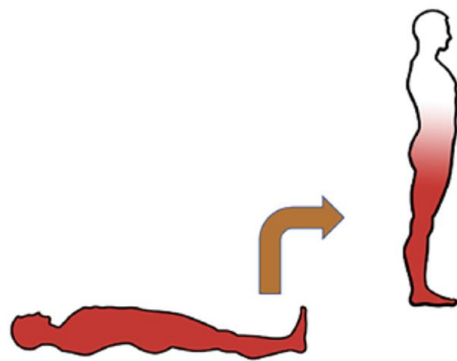
Sympathetic system physiologically activated via Baroreceptors



Causing Vasoconstriction via $\alpha 1$ receptors



BP restored



α Blockers



When a person rises from supine to erect posture



Normal Vasoconstrictive effect of $\alpha 1$ receptors is blocked



Postural hypotension

SUMMARY

α Blockers

Uses

1. Hypertension
2. Pheochromocytoma
3. Secondary shock
4. PVD
5. Congestive heart failure (CHF)
6. Prinzmetal's angina
7. Male impotency due to erectile dysfunction
8. BHP

Adverse effects / C/I

1. Postural hypotension

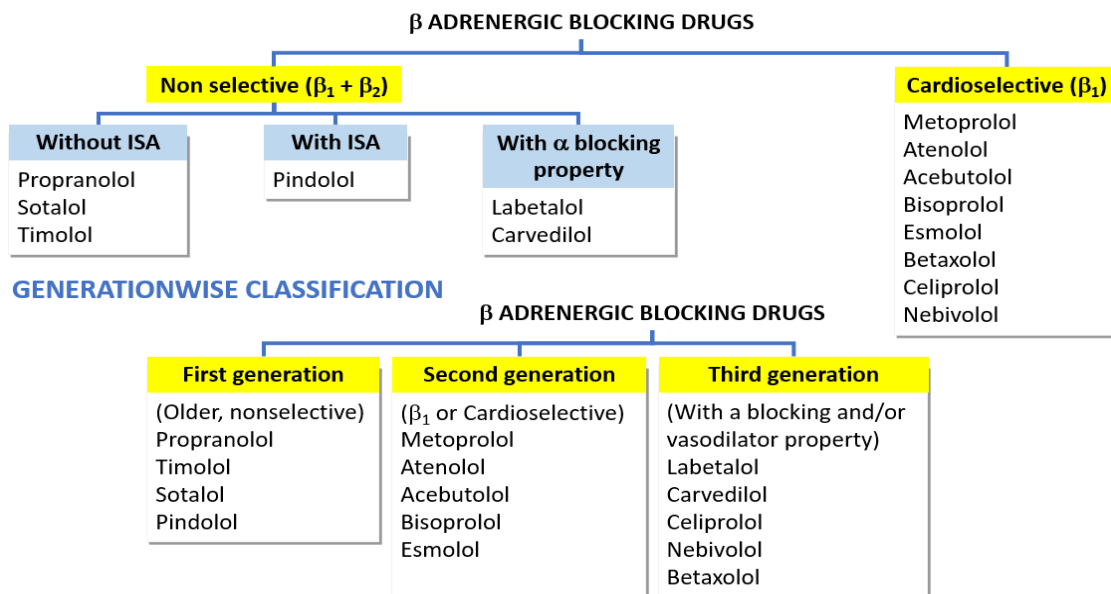
2. Nasal blockade
3. Palpitation
4. Loose motions
5. Inhibition of ejaculation and impotence.

β ADRENERGIC BLOCKING DRUGS

Definition

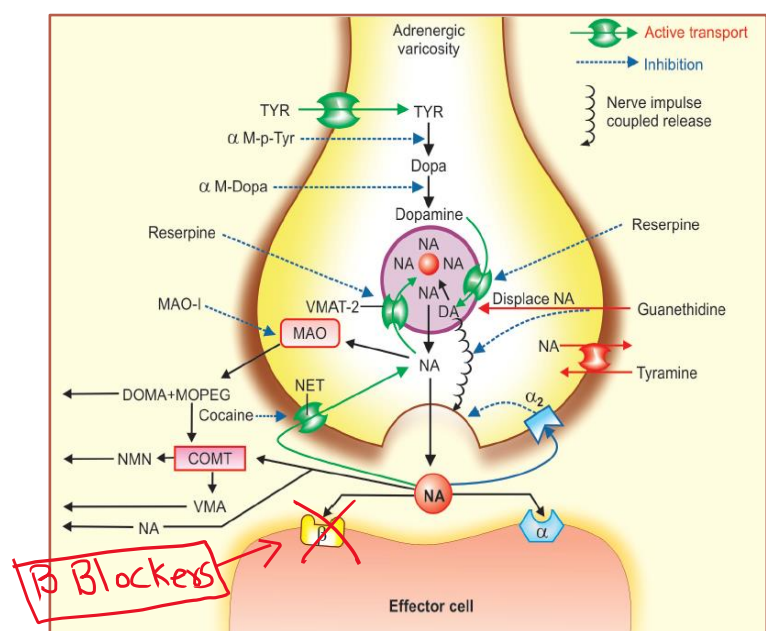
β Adrenergic Blocking Drugs
↓
Competitive antagonists at β receptors

Classification



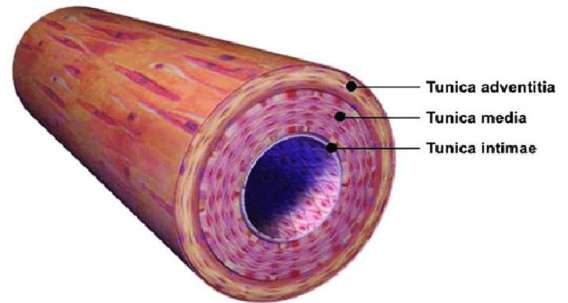
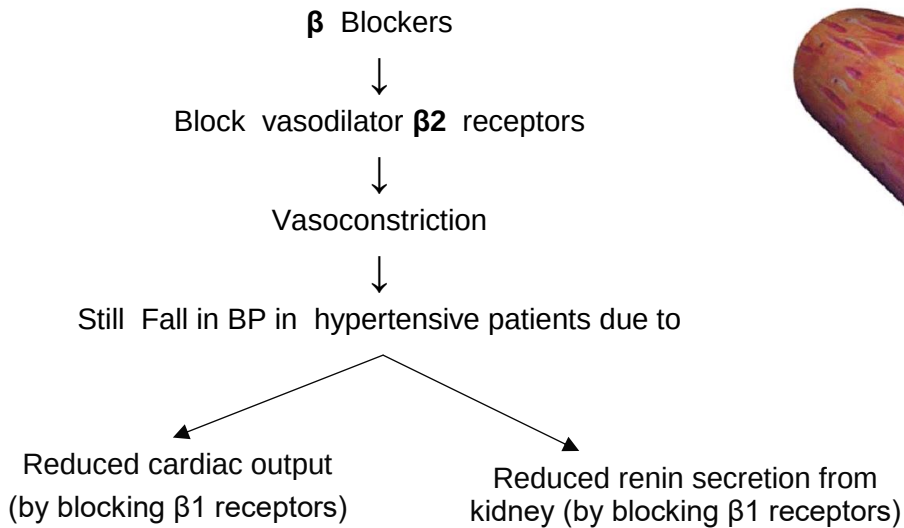
MOA

β Blockers
↓
Blocks β receptors
↓
So prevents binding of NA
↓
Inhibit adrenergic responses mediated through β receptors
(without affecting those mediated through α receptors)

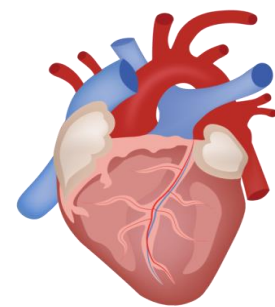
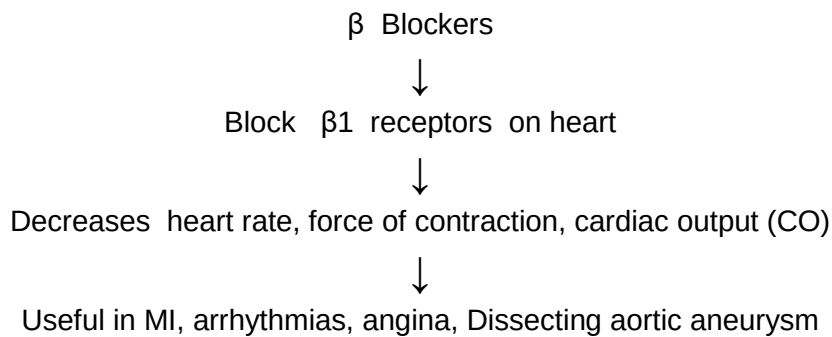


Pharmacological Actions

1. Blood vessels and BP

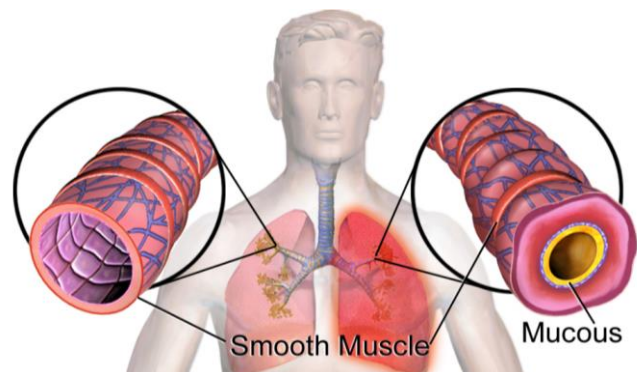
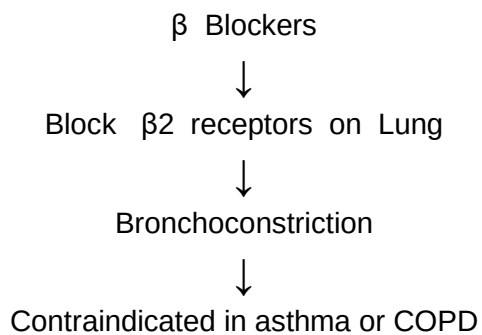


2. Heart

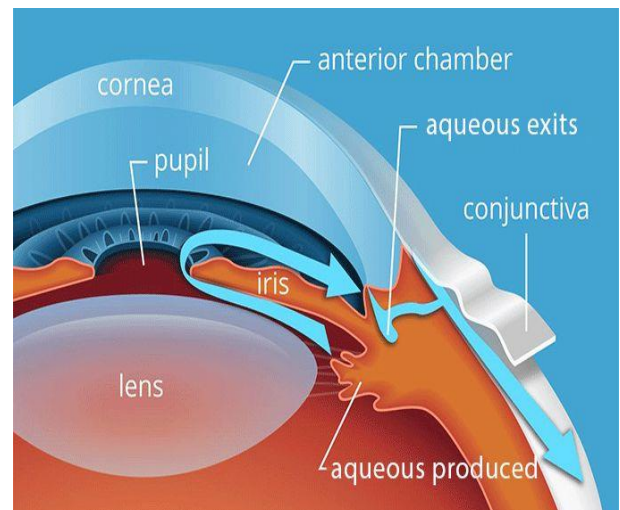
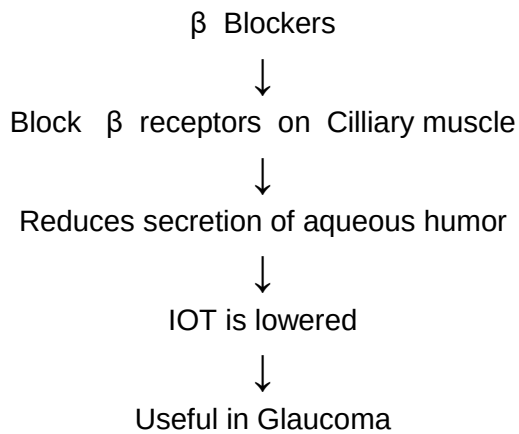


Decreases heart rate,
force of contraction,
Cardiac output

3. Lung

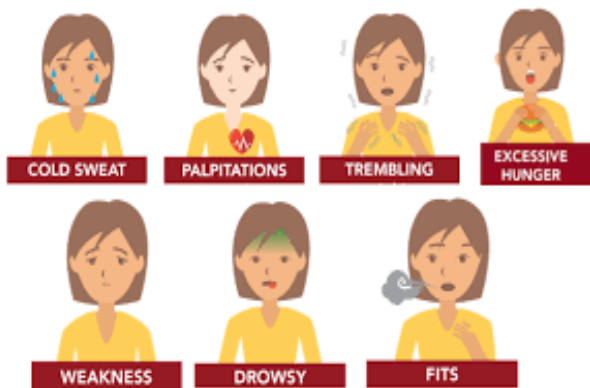


4. Eye

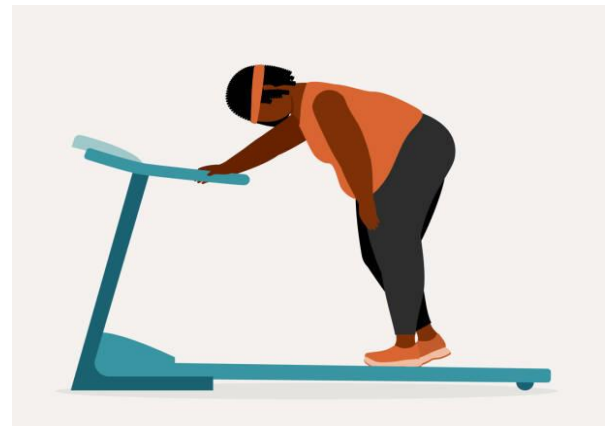


5. Metabolic

- Inhibit glycogenolysis in response to hypoglycemia (which is the compensatory effect of catecholamine).
- So B-blocker delays the recovery from hypoglycemia
- Also masks the symptoms of hypoglycemia like tachycardia and tremors.
- Inhibits lipolysis i.e. release of FFA and thereby enhance LDL and also reduce HDL
- Reduce exercise capacity of muscle



Musk symptoms of hypoglycemia



Reduces Exercise Cupulity

6. CNS

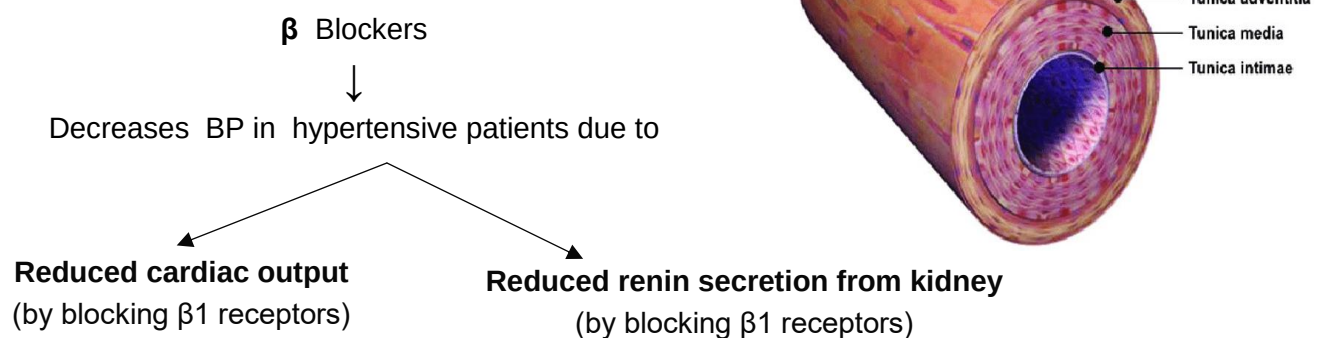
- Propranolol suppresses anxiety



Uses

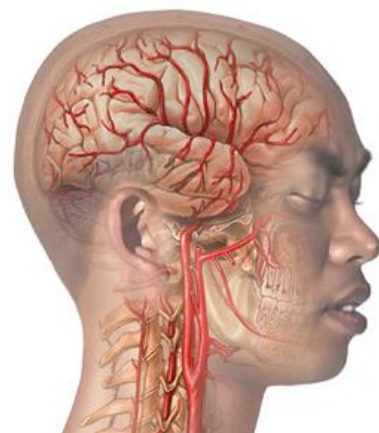
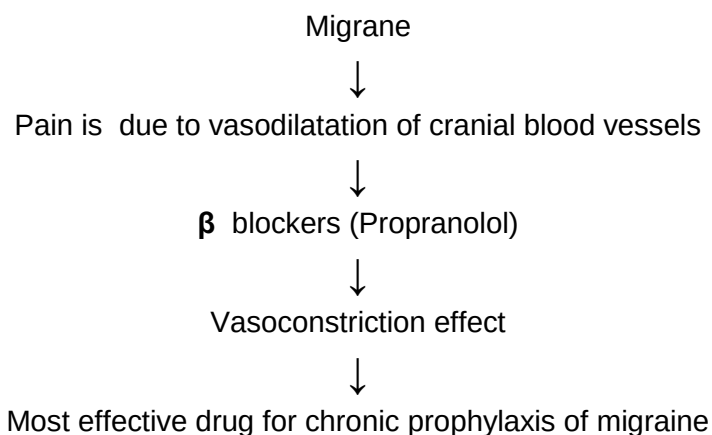
1. Hypertension
2. Migraine
3. Heart → Used for →
 - MI
 - Arrhythmias
 - Angina
 - Dissecting aortic aneurysm
 - CHF
 - Pheochromocytoma
4. Eye → used for → chronic simple (wide angle) glaucoma
5. Essential tremor
6. Anxiety

1. Hypertension



One of the **first choice drugs** because of good patient acceptability and cardioprotective potential

2. Migraine

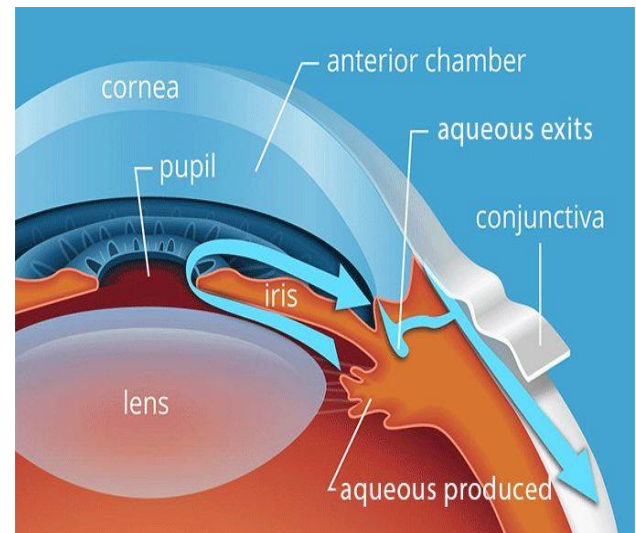
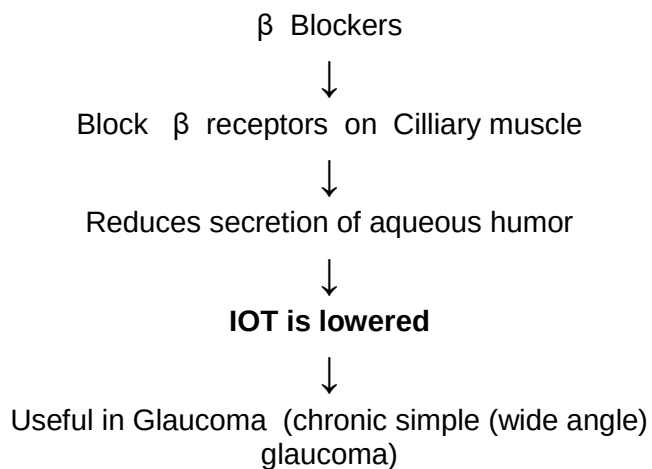


3. Heart

- β blockers** Used in →
1. MI → Cardiac work and oxygen consumption reduced
 2. Arrhythmias → Conduction velocity is reduced and ERP is increased → antiarrhythmic effect.
Also there is membrane-stabilizing effect

3. Angina → Improvement of O₂ supply/demand status
4. Dissecting aortic aneurysm → Reduces cardiac contractile force and aortic pulsation.
5. CHF
6. Pheochromocytoma

4. Glaucoma



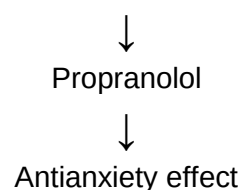
5. Essential tremor

- Nonselective β₁+β₂ blockers are used



6. Anxiety

Conditions which provoke nervousness and panic
(e.g. examination, unaccustomed public appearance)



Adverse Effects

1. Cold hands and feet
2. PVD → Worsens
3. Bradycardia
4. COPD → worsens

5. Carbohydrate tolerance → Impaired
6. Plasma lipid profile → Altered
7. Tiredness and reduced exercise capacity

1. Cold hands and feet

- Due to blockade of vasodilator β_2 receptors



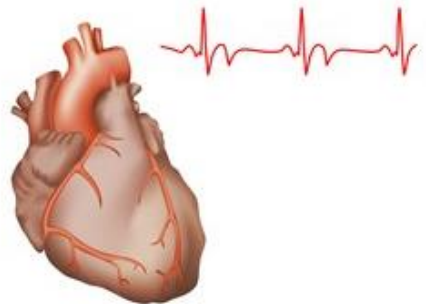
2. PVD

- Worsens
- Due to blockade of vasodilator β_2 receptors



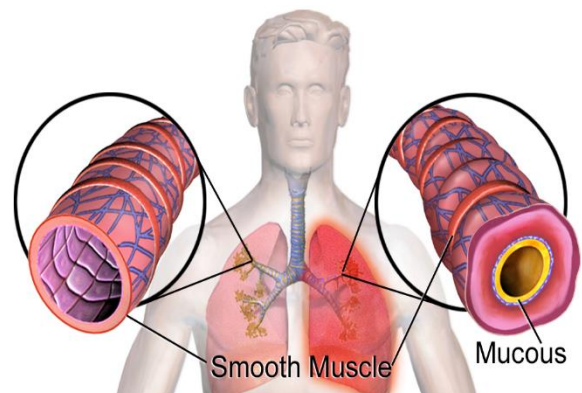
3. Bradycardia

- Contraindicated in partial and complete heart block: arrest may occur



4. COPD

- worsens
- C/I in asthmatics



5. Carbohydrate tolerance

- Impaired → in prediabetics.

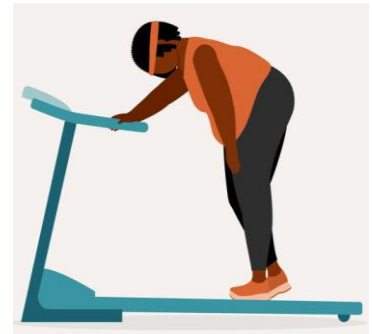


6. Plasma lipid profile is altered

- Total triglycerides and LDL-cholesterol increase, HDL-cholesterol falls → Increases risk of coronary artery disease.

7. Tiredness and reduced exercise capacity

- Due to inhibition of glycogenolysis and lipolysis.



Contraindications

- **A** → Asthma
- **B** → Block (AV)
- **C** → CHF
- **D** → Diabetes

SUMMARY

β Blockers

Uses

1. Hypertension
2. Migraine
3. Heart → Used for →
 - MI
 - Arrhythmias
 - Angina
 - Dissecting aortic aneurysm
 - CHF
 - Pheochromocytoma
4. Eye → used for → chronic simple (wide angle) glaucoma
5. Essential tremor
6. Anxiety

Adverse effects / C/I

1. Cold hands and feet
2. PVD → Worsens
3. Bradycardia
4. COPD → worsens
5. Carbohydrate tolerance → Impaired
6. Plasma lipid profile → Altered
7. Tiredness and reduced exercise capacity

Remember

1. Selective β_1 blockers (cardioselective)
2. B-blockers with membrane stabilizing (Local anaesthetic) action
3. Lipid insoluble β -blockers
4. Beta-blockers with intrinsic sympathomimetic (partial agonist) activity
5. β -blocker with α -blocking activity (Both α + β blocker)

Cardioselective β blockers (Selective β_1 blockers)

New	Nebivolol (Most cardioselective)
Beta	Betaxolol
Blockers	Bisoprolol
Acting	Acebutolol
Exclusively	Esmolol
At	Atenolol
Myo	Metoprolol
Cardium	Cellprolol

Advantages of Selective β_1 blockers (cardioselective)

- (a) Lower propensity to cause bronchoconstriction → Preferred in Asthma.
- (b) Less interference with carbohydrate metabolism → Preferred in DM, however tachycardia in response to hypoglycaemia is blocked
- (c) Less chances of precipitating Raynaud's phenomenon → Preferred in peripheral vascular disease
- (d) No deleterious effect on blood lipid profile → Preferred in hyperlipidemia.
- (e) Less liable to impair exercise capacity

Membrane stabilizing β blockers (Local anaesthetic action)

Possess	Propanolol (maximum)
Membrane stabilizing or	Metoprolol
Local	Labetalol
Anaesthetic	Acebutolol
Property	Pindolol

- Membrane stabilizing (Na^+ channel blocking) activity contributes to antiarrhythmic action.
- These drugs should be avoided in glaucoma due to risk of corneal anaesthesia.

 β -blockers with intrinsic sympathomimetic (partial agonist activity)

Contain	Celiprolol, Oxprenolol
Partial	Pindolol, Penbutolo
Agonistic	Alprenolol
Activity	Acebutolol

- These drugs are partial agonists at β_1 receptors (apart from having β -blocking property).
- These are preferred in patients prone to develop severe bradycardia with β -blockers therapy as they are β_1 agonists (Heart receptor) $\rightarrow$ stimulating action on heart $\rightarrow$ No bradycardia.

Lipid insoluble β -blockers

Not Soluble	Nadolol (longest acting β blocker)
A	Atenolol Acebutolol
B	Betaxolol Bisoprolol
C	Celliprolol

- These agents are excreted in kidney and therefore are contraindicated in renal failure
- Because of lipid insolubility they do not cross BBB (no CNS effects)

β -blocker with α -blocking activity (Both α + β blocker)

1. Carvedilol
2. Niprodilol
3. Labetolol
4. Dilevalol
5. Bucindolol
6. Medroxalol

Remember

- **Nadalol** $\rightarrow$ longest acting β blocker
- **Esmolol** $\rightarrow$ shortest acting β blocker
- **Acebutolol** $\rightarrow$ possesses all activities i.e., cardioselectivity, partial agonist activity, membrane stabilizing activity and lipid insolubility.
- **Sotalol, penbutolol and pindolol** $\rightarrow$ almost 100% bioavailability.
- **Penbutolol** $\rightarrow$ maximum oral absorption
- **Carvedilol** $\rightarrow$ maximum plasma protein binding.
- **Celiprolol** $\rightarrow$ minimum plasma protein binding.



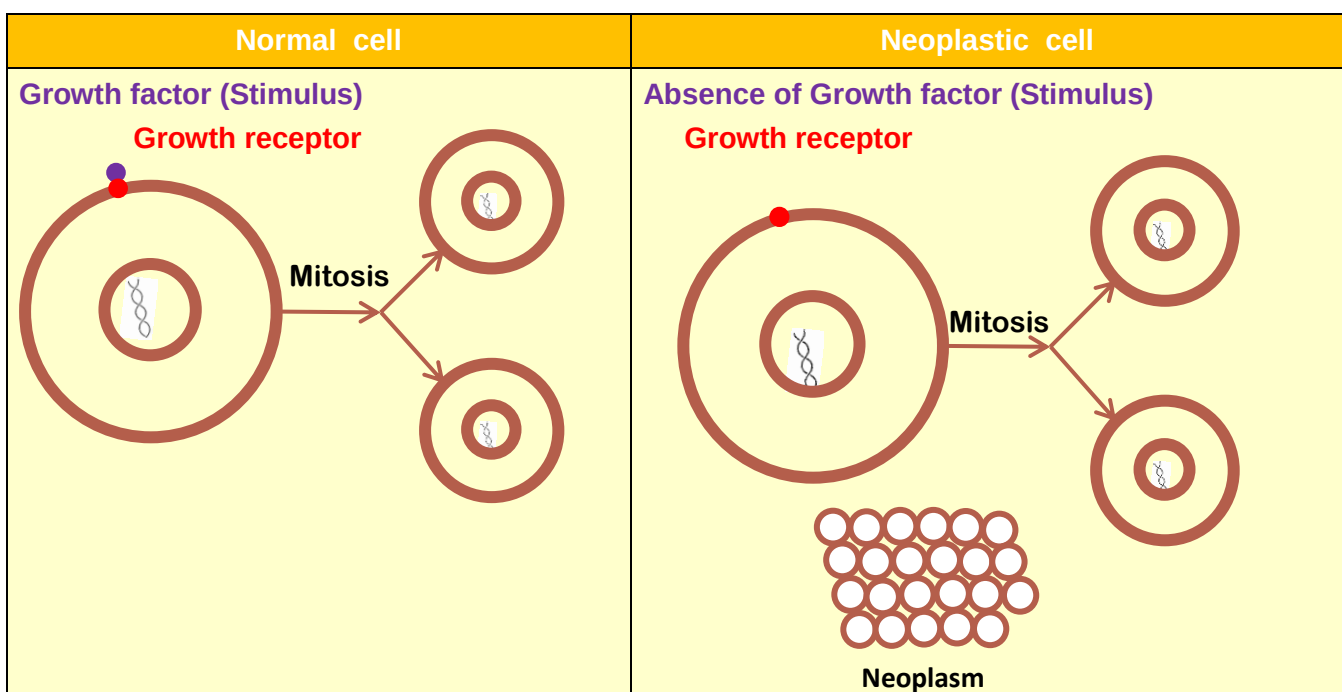
Anticancer Drugs

CHAPTER

3

CANCER

Progressive, Persistent, Purposeless and uncontrolled Proliferation of tissues.

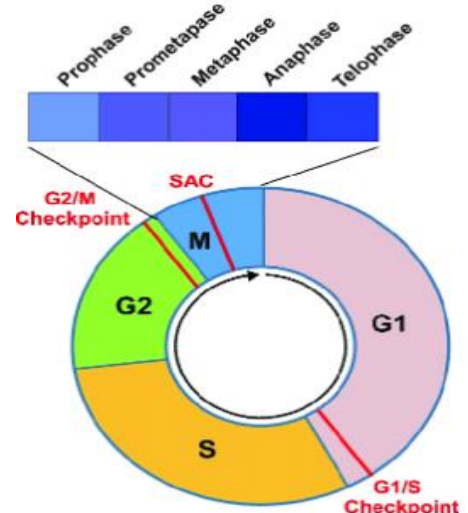


ANTICANCER DRUGS

- Anticancer drugs either kill cancer cells or modify their growth.
- Selectivity is limited → most toxic drugs used in therapy.

Cell cycle

- Both normal and cancerous cells must pass through the following phases of cell cycle
1. **G₁ phase (presynthetic phase):** Synthesis of enzymes and other cellular components needed for DNA synthesis.
 2. **Synthetic phase (S phase):** DNA synthesis takes place.



3. **G₂ phase (premitotic phase):** Synthesis of cellular components for mitosis (proteins and RNA synthesis).
4. **Mitotic phase (M phase):** Mitotic cell division takes place.
5. **G₀ phase (resting phase):** Cells stop dividing temporarily or permanently

Classification of Anticancer Drugs

- Cytotoxic drugs
- Hormonal drugs
- Targeted drugs

Cytotoxic drugs

- A. Alkylating agents
 - (a) Nitrogen mustards
 - (b) Alkyl sulphonate
 - (c) Nitrosoureas
 - (d) Triazene
 - (e) Methyl hydrazine
- B. Platinum-containing compounds
- C. Antimetabolites
 - (a) Folate antagonist
 - (b) Purine antagonists
 - (c) Pyrimidine antagonists
- D. Microtubule damaging agents
 - (a) Vinca alkaloids
 - (b) Taxanes
- E. Topoisomerase inhibitors
- F. Antibiotics
- G. Miscellaneous

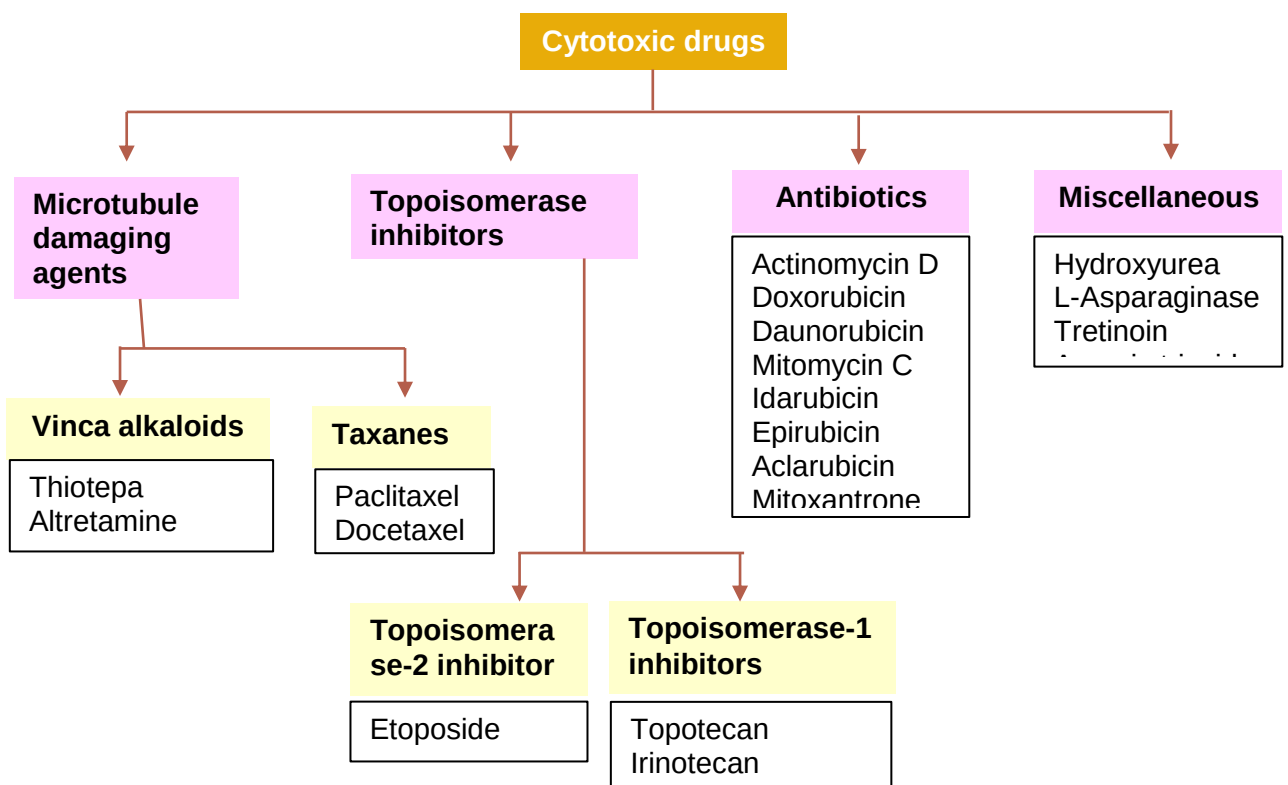
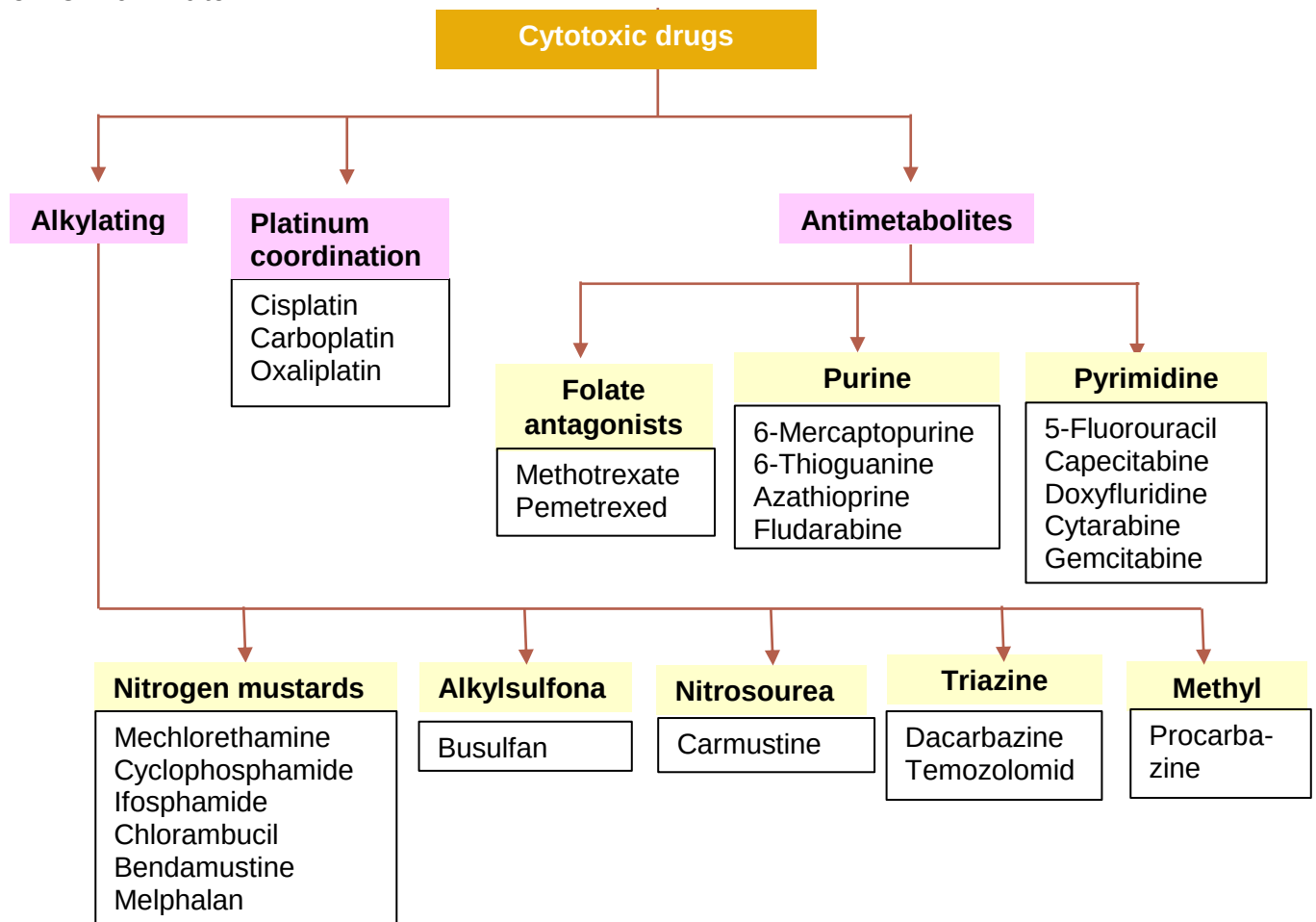
Hormonal drugs

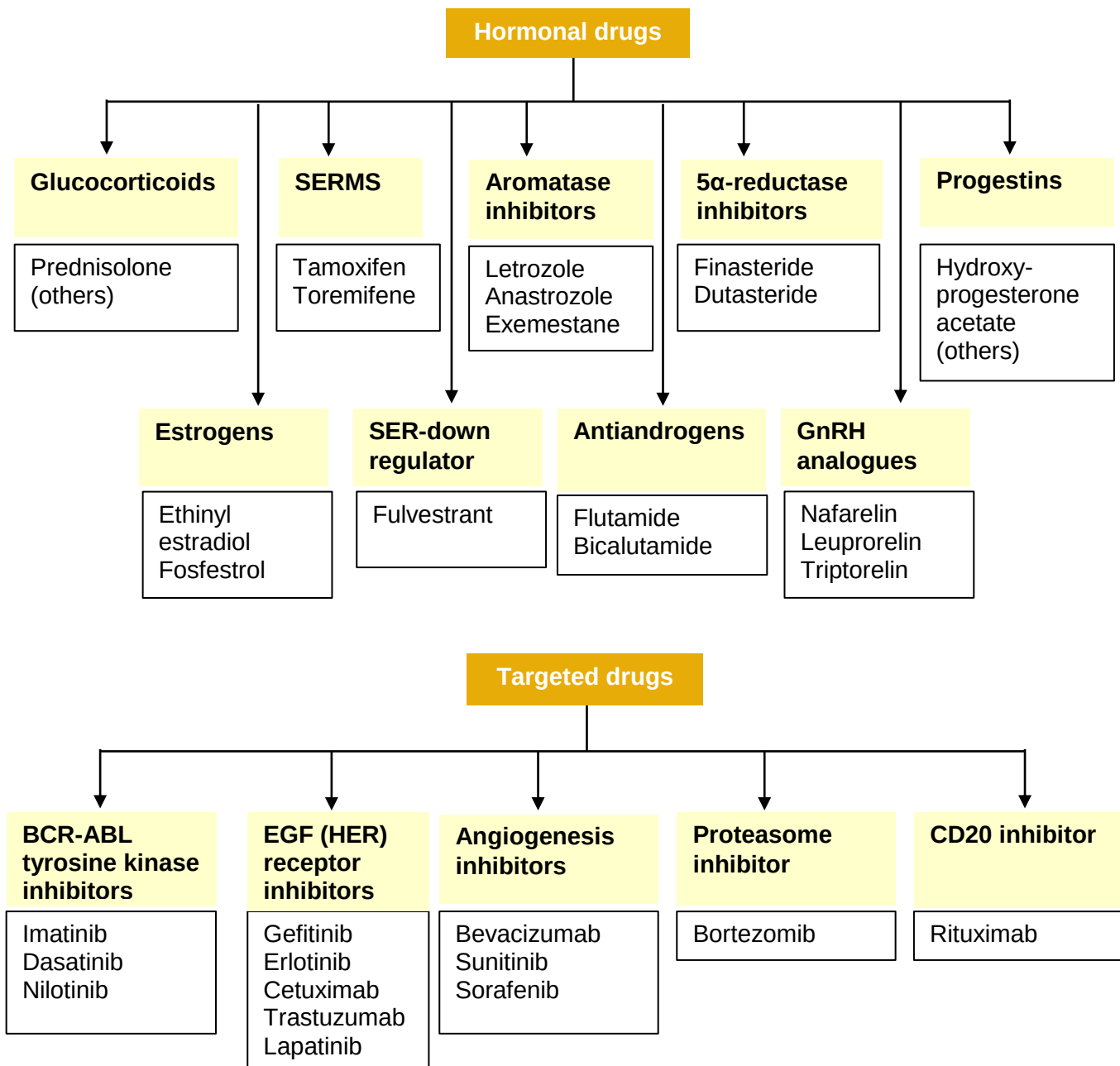
1. Glucocorticoids
2. Oestrogens
3. Selective oestrogen receptor modulators (SERMs)
4. Selective oestrogen receptor downregulators (SERDs)
5. Aromatase inhibitors
6. Antiandrogen
7. 5- α Reductase inhibitor
8. GnRH analogues
9. Progestins

Targeted drugs

1. BCR-ABL tyrosine kinase inhibitors

2. EGF (HER) receptor inhibitors
3. Angiogenesis inhibitors
4. Proteasome inhibitor
5. CD20 inhibitor





Types of Anticancer drugs

1. Cell cycle-specific (CCS)
2. Cell cycle-nonspecific (CCNS)

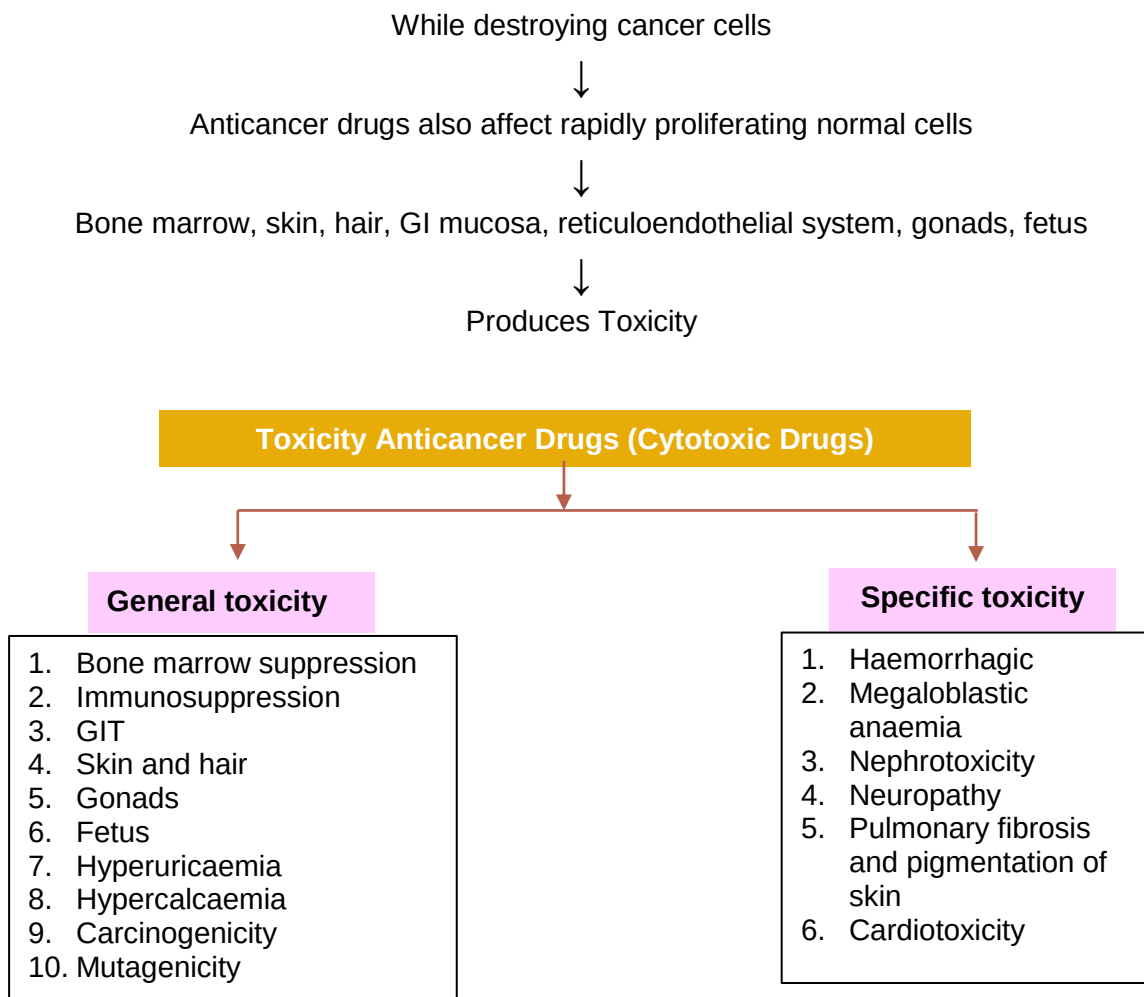
Cell cycle-specific (CCS)

- **CCS drugs act mainly on dividing cells**
 - **Antimetabolites**: Methotrexate, 6-mercaptopurine (6-MP)
 - **Antibiotic**: Bleomycin
 - **Microtubule damaging agents** : Vinblastine, vincristine Paclitaxel
 - **Topoisomerase-2 inhibitor** : Etoposide

Cell cycle-nonspecific (CCNS)

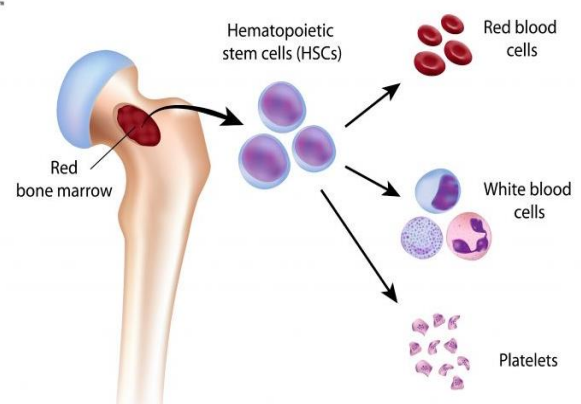
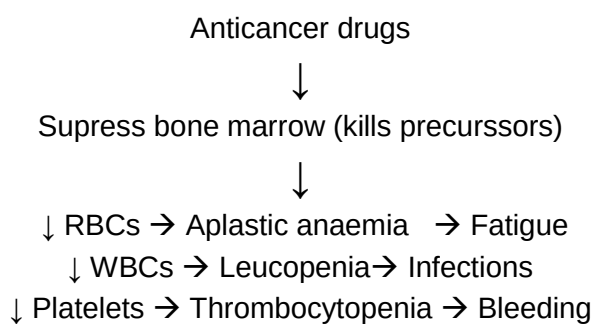
- **CCNS drugs act on dividing as well as resting cells**
 - **Alkylating agents:** Cyclophosphamide, busulphan, mechlorethamine, melphalan
 - **Anticancer antibiotics:** Doxorubicin, daunorubicin, mitomycin, actinomycin D
 - **Platinum coordination complexes :** Cisplatin, carboplatin

TOXICITY ANTICANCER DRUGS (CYTOTOXIC DRUGS)



General toxicity

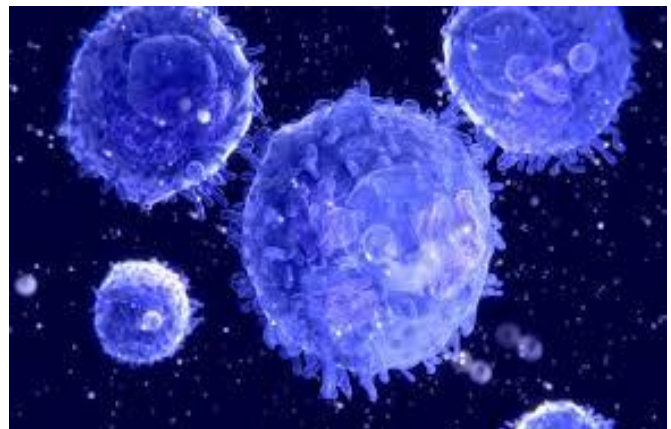
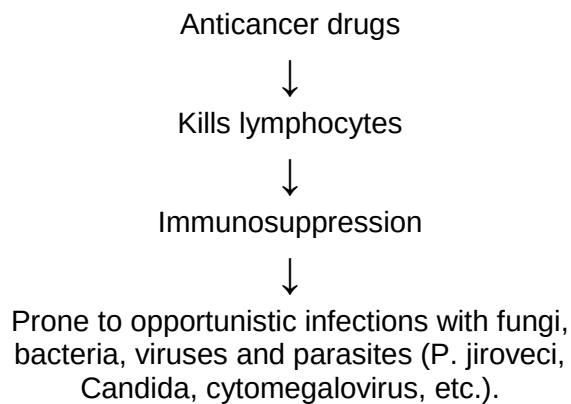
1. Bone marrow suppression



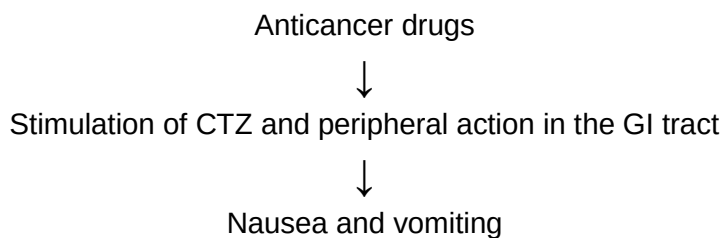
Ameliorated by:

- (i) Platelet transfusion
- (ii) Granulocyte colony-stimulating factor (G-CSF)
- (iii) Erythropoietin
- (iv) Bone marrow transplantation

2. Immunosuppression



3. GIT:



- Cisplatin → most emetogenic potential.



Ameliorated by:

- i. 5-HT₃ antagonists → ondansetron and granisetron,
- ii. Metoclopramide and dexamethasone

Emetogenic potential of cytotoxic drugs

High	Moderate	Mild
Cisplatin	Carboplatin	Bleomycin
Mustine	Cytarabine	Chlorambucil
Cyclophosphamide	Procarbazine	Busulfan
Actinomycin D	Vinblastine	Fluorouracil
Dacarbazine	Doxorubicin	6-Thioguanine
Lomustine	Daunorubicin	Hydroxyurea
	Ifosfamide	Vincristine

	6-Mercapto-	Methotrexate
	Purine	Etoposide
	Paclitaxel	L-Asparaginase

Anticancer drugs
↓
Necrosis of rapidly dividing epithelial cells of gut mucosa
↓
Stomatitis, oral mucositis, diarrhoea, GI bleeding, ulcers



4. Skin and hair

Anticancer drugs
↓
Damage to hair follicles
↓
Alopecia (loss of hair)
↓
Reversible on stoppage of therapy



- Dermatitis and skin rashes too can occur.

5. Gonads

Anticancer drugs
↓
Damage gonadal cells
↓
Oligozoospermia and infertility in males
Amenorrhoea and infertility in females

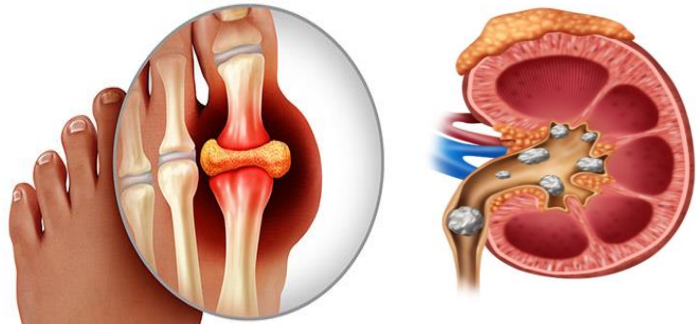
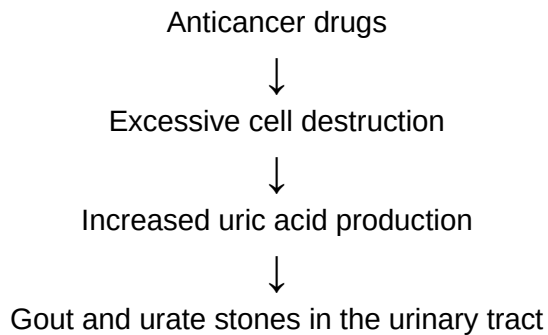


6. Fetus

Anticancer drugs during pregnancy
↓
Damage dividing Fetus
↓
Abortion or teratogenic effects



7. Hyperuricaemia



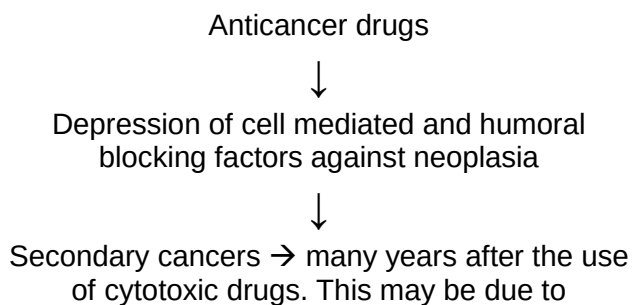
- Prevented by → good hydration, allopurinol and corticosteroids.

8. Hypercalcaemia

- Due to either the malignancy or certain anticancer drugs.
- Treated with** → adequate hydration, bisphosphonates, corticosteroids, etc.



9. Carcinogenicity (secondary malignancy)

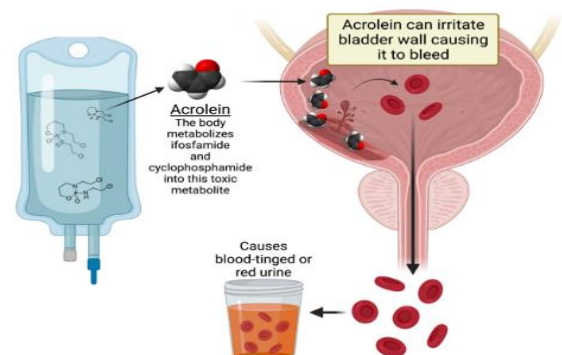


10. Mutagenicity

Specific toxicity

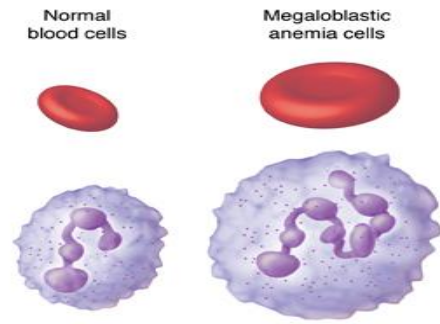
1. Haemorrhagic cystitis

- With Cyclophosphamide
- Ameliorated by** → administering mesna systemically and acetylcysteine locally.



2. Megaloblastic anaemia

- With Methotrexate
- **Ameliorated by** → folinic acid/ leucovorin/citrovorum factor.



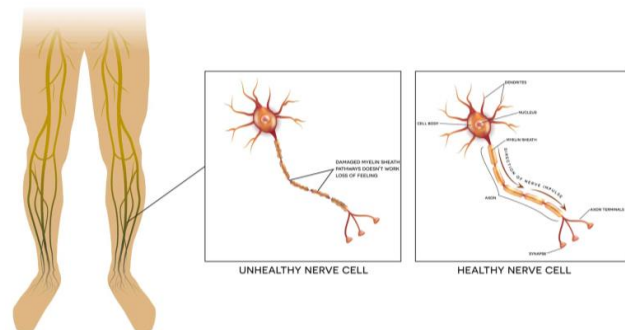
3. Nephrotoxicity

- With Cisplatin
- **Ameliorated by** → Saline infusion and mannitol



4. Neuropathy

- With Vincristine and Paclitaxel



5. Pulmonary fibrosis and pigmentation of

- With busulphan and bleomycin



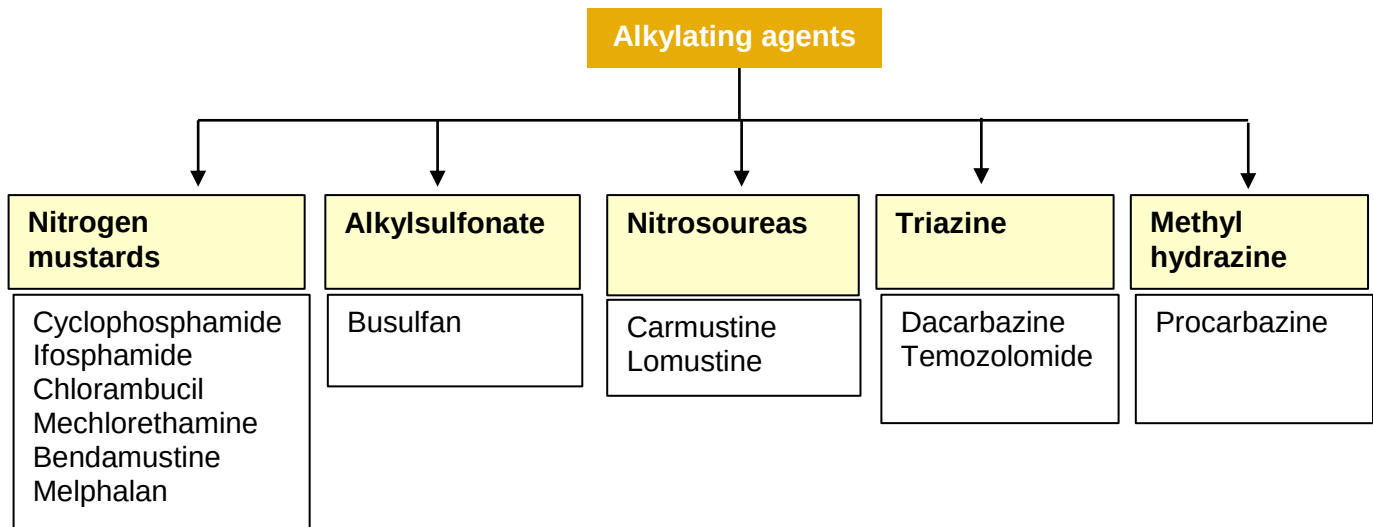
6. Cardiotoxicity

- With Doxorubicin and Daunorubicin.
- **Ameliorated by** → □ Iron chelating agent, dexrazoxane



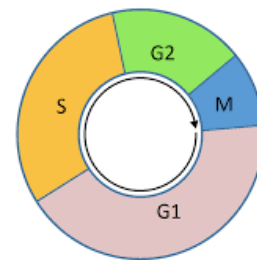
CYTOTOXIC DRUGS

A. ALKYLATING AGENTS

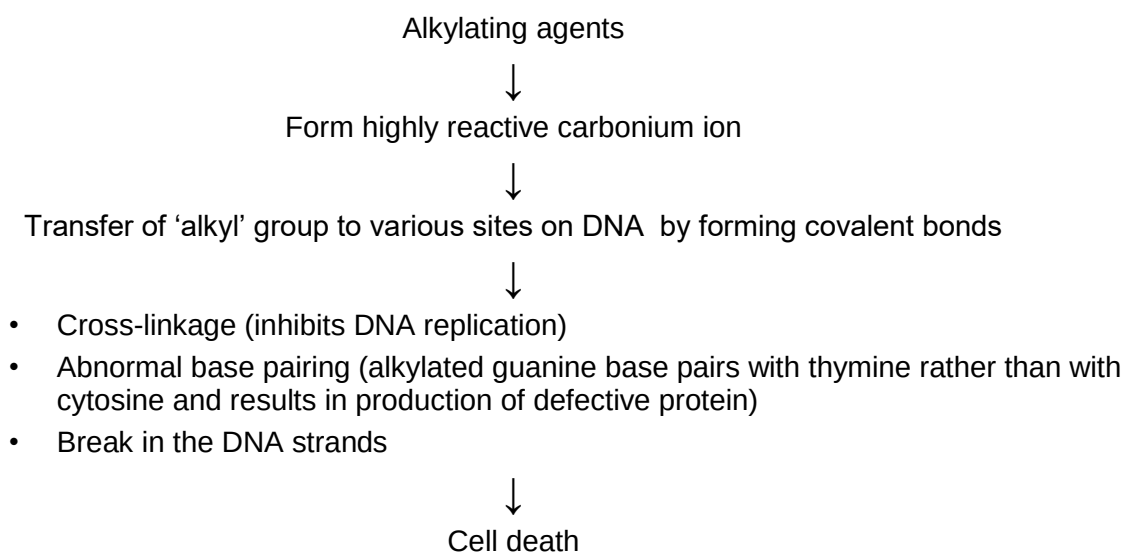


MOA

- CCNS drugs

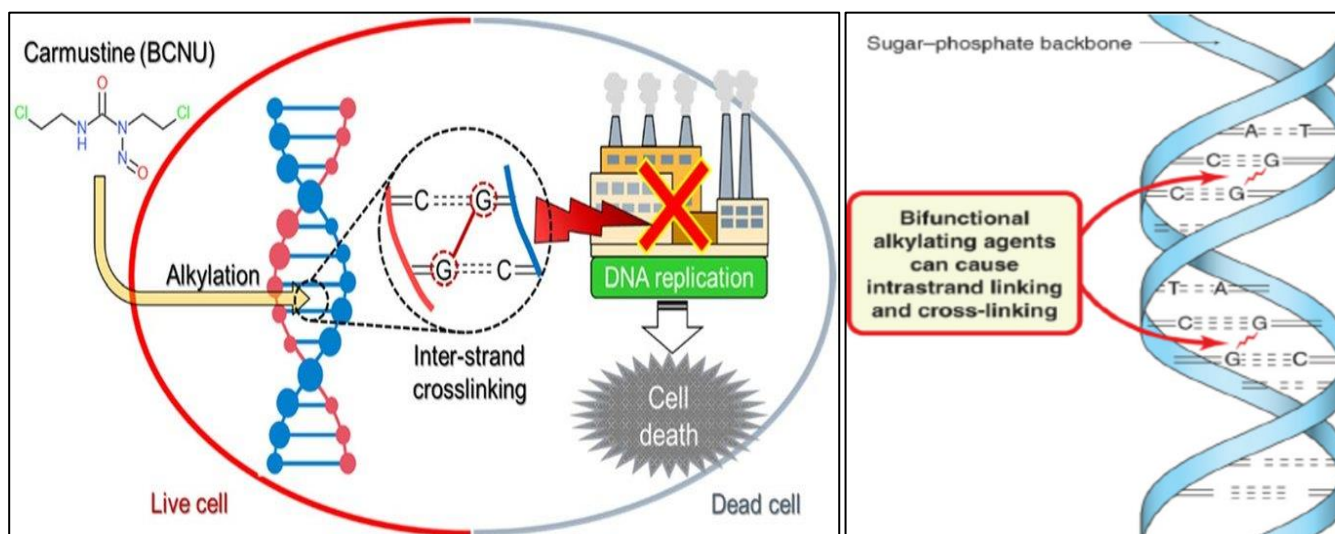


1. On DNA



2. Bind to proteins and damage them

3. Radiomimetic effect



Alkylating agents					
MOA					
Nitrogen mustards					
	Cyclophosphamide	Ifosphamide	Chlorambucil	Mechlorethamine	Melphalan
General features					
Uses					
Adveese effects					

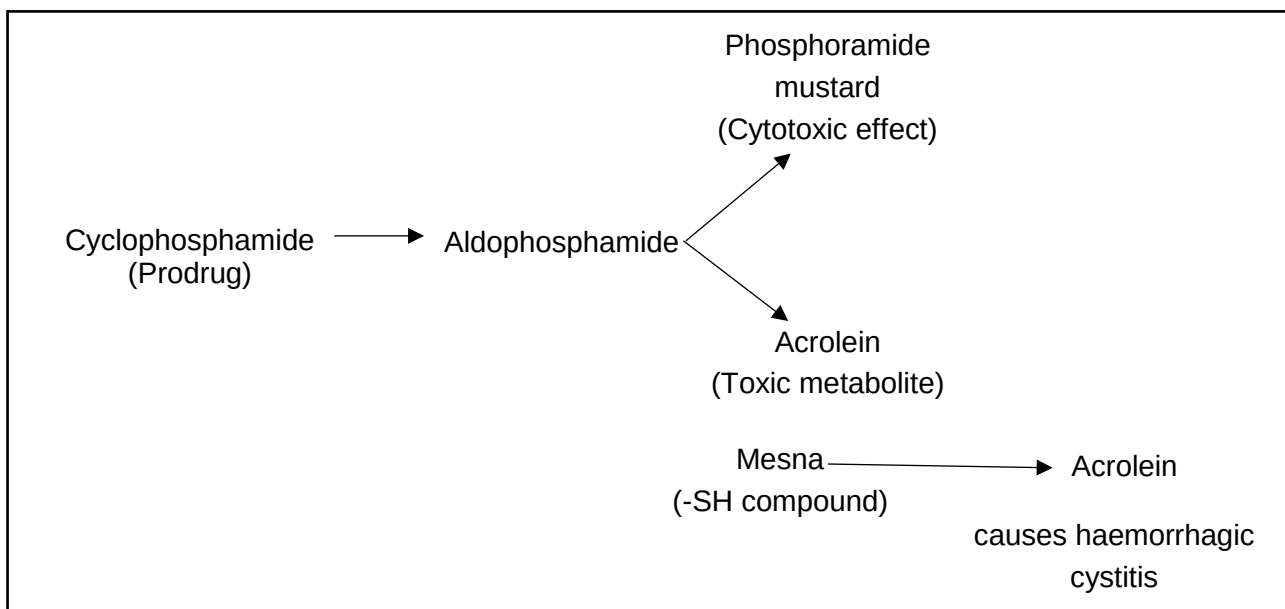
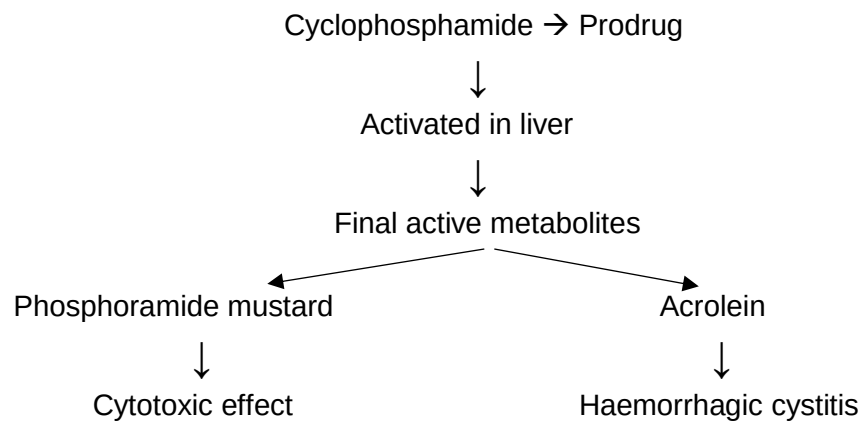
Alkylating agents				
MOA				
	Alkylsulfonate	Nitrosoureas	Triazine	Methyl hydrazine
	Busulfan	Carmustine Lomustine	Dacarbazine Temozolomide	Procarbazine
General features				
Uses				
Adveese effects				

I. Nitrogen Mustards

- Cyclophosphamide
- Ifosfamide
- Chlorambucil
- Mechlorethamine
- Melphalan

a) Cyclophosphamide

Orally or intravenously

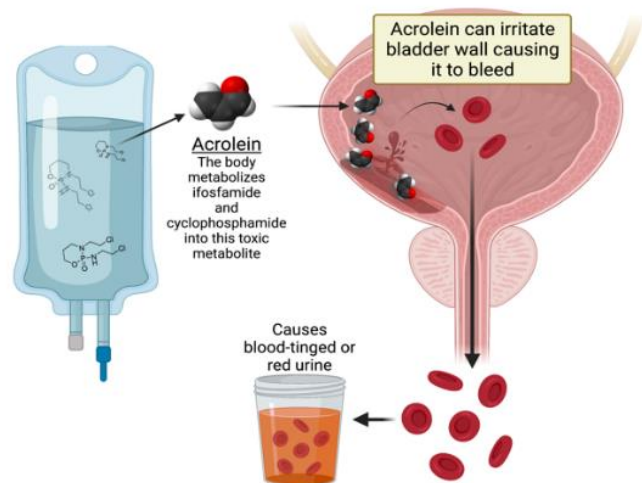


Uses

1. Lymphomas
2. CLL
3. Breast cancer
4. Rheumatoid arthritis, nephrotic syndrome and to prevent as well as to treat graft rejection during organ transplantation. (powerful immunosuppressant effect)

Adverse Effects

1. General toxicity
2. Severe haemorrhagic cystitis →
 - Dysuria (irritation of bladder mucosa)



- Reduced by reduced by adequate hydration and coadministration of i.v. mesna (2-mercaptoethane sulphonate) → binds and inactivates acrolein → prevents haemorrhagic cystitis.

b) Ifosfamide

- Congener of cyclophosphamide
- Administered intravenously
- **Uses** → Testicular cancer and sarcomas.

c) Chlorambucil

- Given orally
- Slow-acting nitrogen mustard.
- Main action is on lymphoid series and it produces marked lympholytic effect.
- **Uses** → standard treatment for CLL.

d) Mechlorethamine

- First nitrogen mustard
- Highly reactive and local vesicant.
- Because of marked acute effects → it is no longer used systemically
- **Uses** → Occasionally used by topical application on cutaneous T cell lymphoma.

e) Melphalan

- **Uses** → multiple myeloma

II. Alkylsulphonate

Busulphan

- Depresses bone marrow with selective action on myeloid series.
- **Use** → CML
- **Adverse effect** →
 1. Pigmentation of the skin
 2. Interstitial pulmonary fibrosis



III. Nitrosoureas

Carmustine and Lomustine

- Highly lipid soluble drugs → reach high concentration in the CSF.
- **Uses** → Brain tumours

IV. Triazine

a) Dacarbazine

- **Use** →
 - Hodgkin's disease
 - Malignant melanoma

b) Temozolomide

- Orally active triazine methylating agent
- Use → DOC → glioma and other malignant brain tumours

V. Methyl hydrazine

Procarbazine

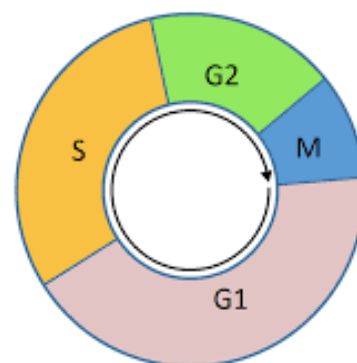
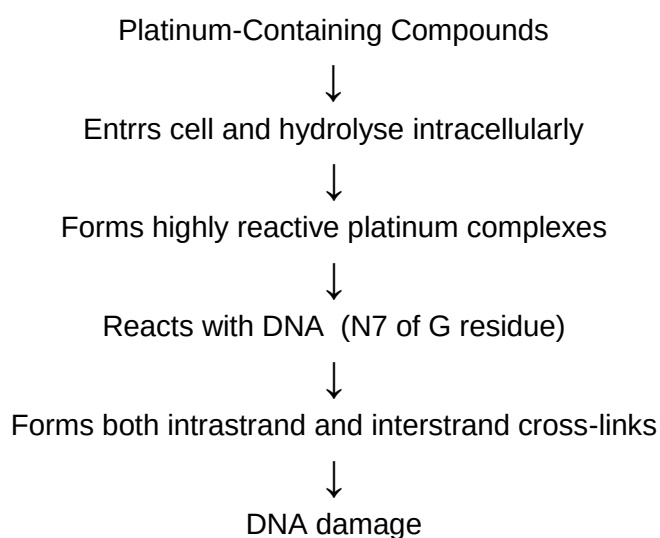
-
- **Use** → component of MOPP regimen for Hodgkin disease.

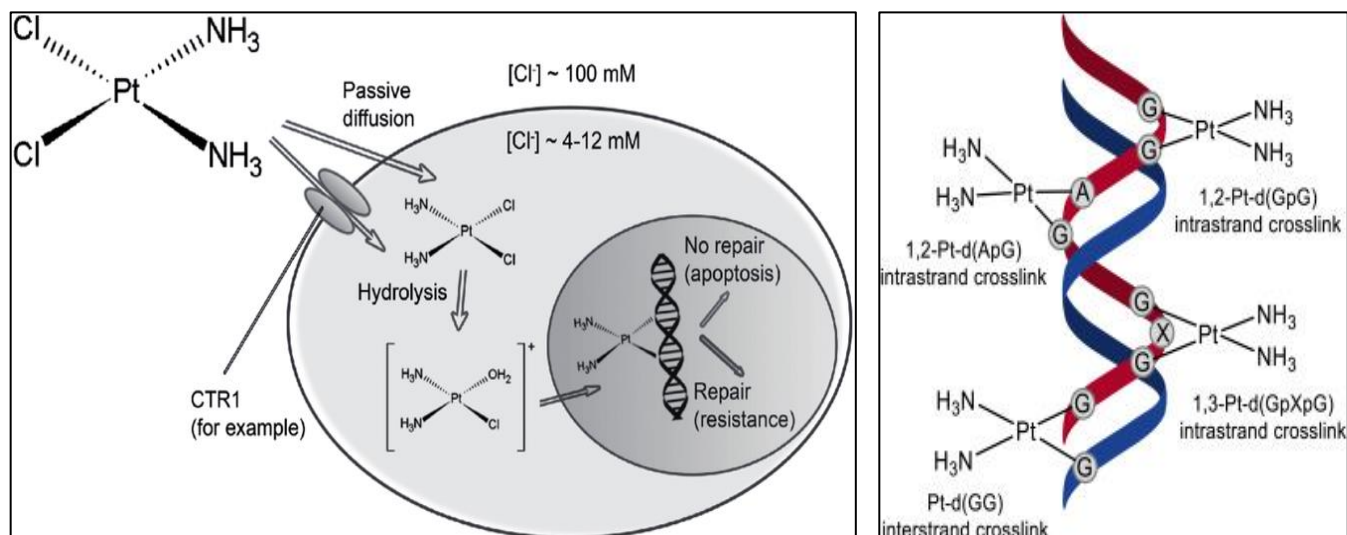
B. PLATINUM COORDINATION COMPLEXES

- Cisplatin
- Carboplatin
- Oxaliplatin

MOA

- CCNS drug
- Acts on both dividing and resting cells.





Platinum coordination complexes			
MOA			
	Cisplatin	Carboplatin	Oxaliplatin
General features			
Uses			
Adverse effects			

I. Cisplatin

- Heavy-metal complex with a highly effective antineoplastic activity.
- Administered intravenously.
- Highly bound to plasma proteins and gets concentrated in → kidney, liver, intestine and testes.
- Poorly penetrates BBB

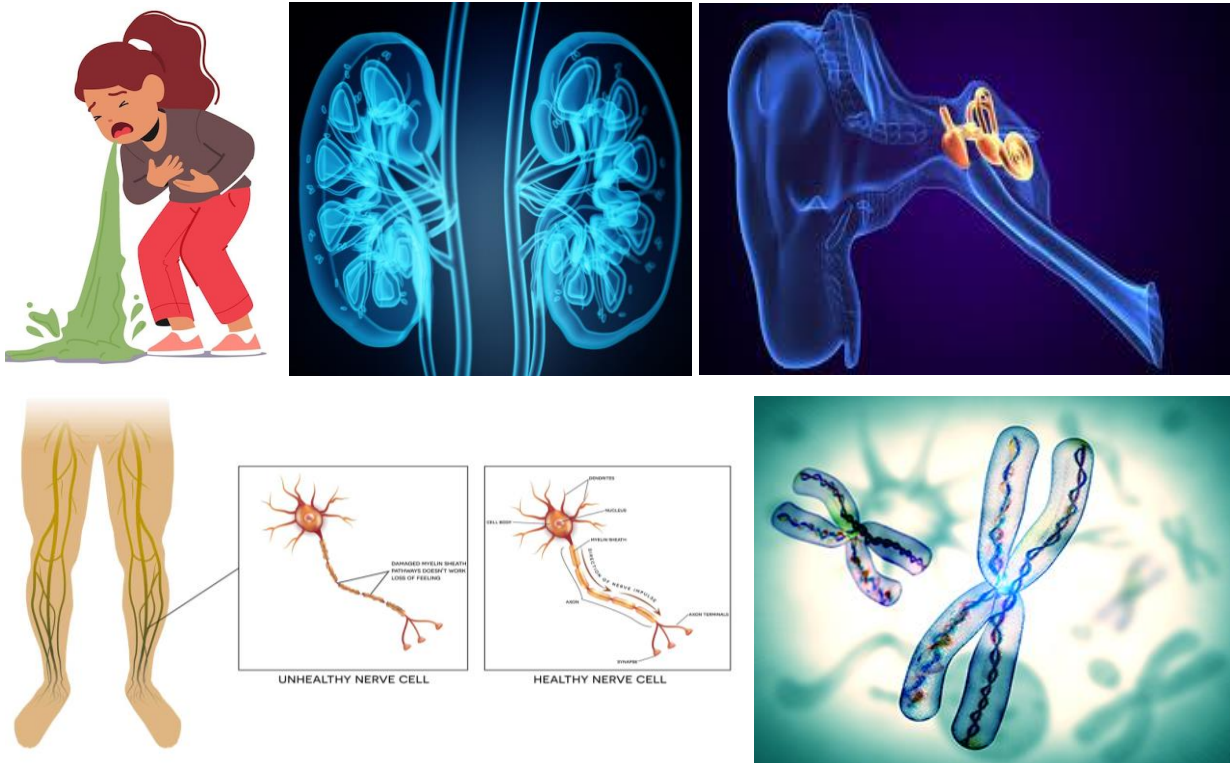
Uses

- Testicular cancer
- Ovarian cancer
- Endometrial cancer
- Bladder cancer
- Lung cancer
- Oesophageal cancer

Adverse Effects

1. Most emetogenic anticancer drug → controlled by 5-HT₃ antagonists, such as ondansetron or granisetron.
2. Nephrotoxicity → Minimized by proper hydration
3. Neuropathy → with higher doses.
4. Ototoxicity with hearing loss → with repeated doses
5. Electrolyte disturbances → Hypokalaemia, hypocalcaemia and hypomagnesaemia

6. Mutagenic, teratogenic and carcinogenic properties



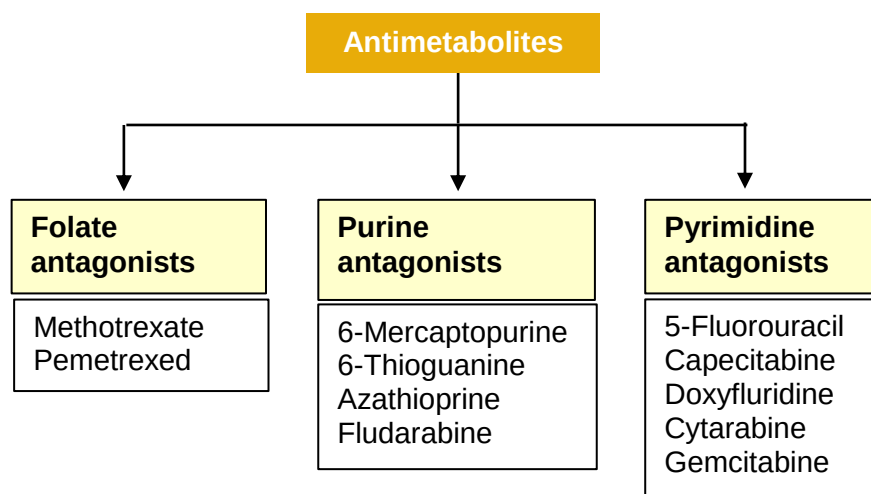
II. Carboplatin

- Better tolerated than cisplatin
- Less nausea, ototoxicity and nephrotoxicity than cisplatin.

III. Oxaliplatin

- Adverse effect → Peripheral neuropathy

C. ANTIMETABOLITES

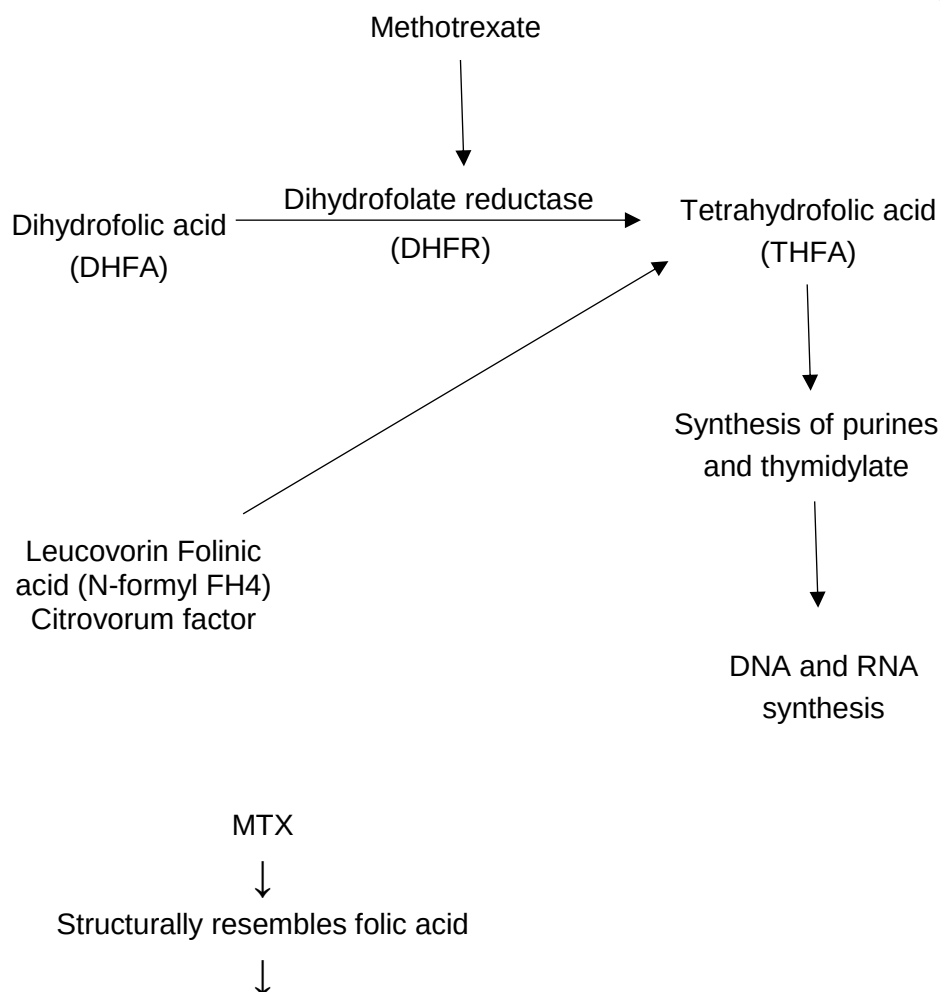


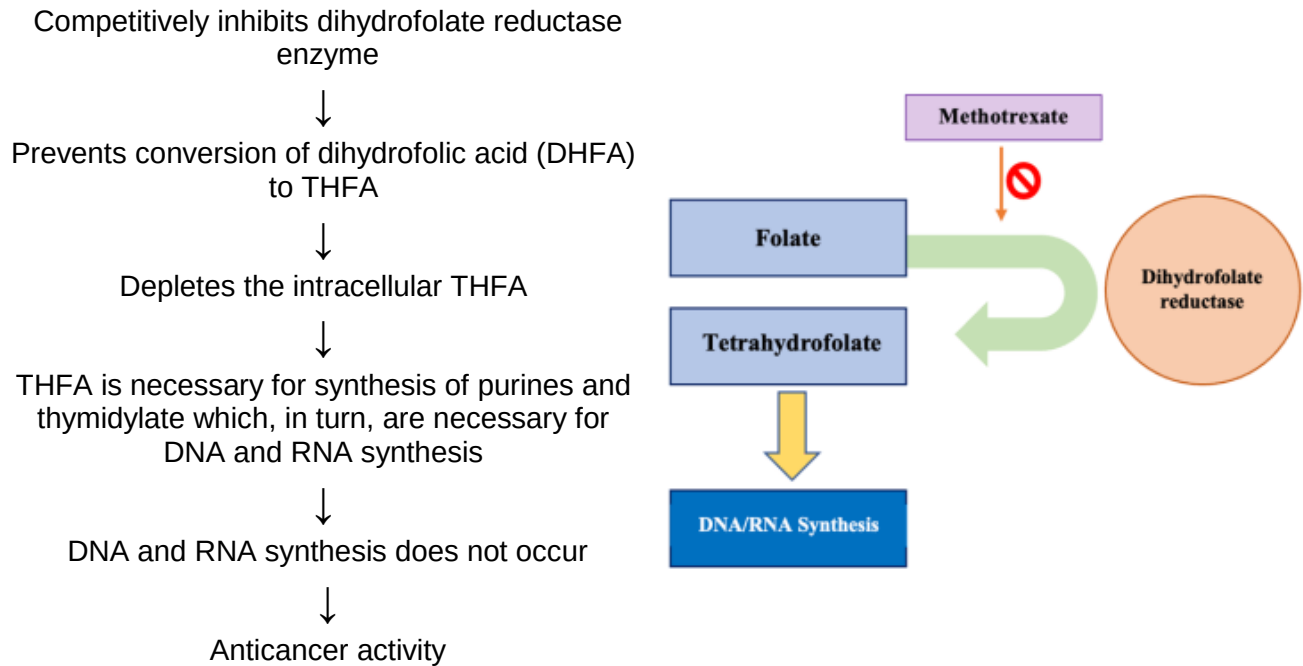
Antimetabolites			
	Folate antagonists	Purine antagonists	Pyrimidine antagonists
	Methotrexate Pemetrexed	6-Mercaptopurine 6- Thioguanine	5-Fluorouracil Capecitabine
General features			
Uses			
Adveese effects			

I. Folate antagonists

MOA

- CCS drug
- Acts during S phase of the cell cycle





a) Methotrexate (MTX)

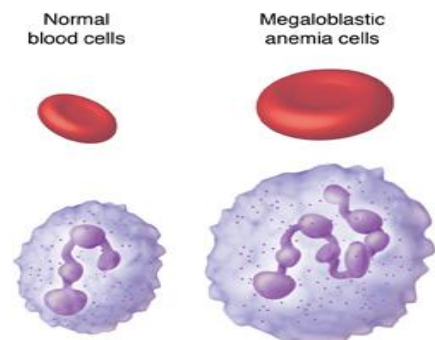
- Absorbed after oral administration, can also be given i.m., i.v. or intrathecally.
- Bound to plasma proteins
- Poorly crosses the BBB
- Has antineoplastic, immunosuppressant and anti-inflammatory effects.

Uses

1. DOC → Choriocarcinoma
2. Acute leukaemias
3. Burkitt lymphoma
4. Breast cancer
5. Rheumatoid arthritis → Low-dose MTX 7.5–25 mg once weekly → prevents joint erosion
6. Psoriasis
7. Inflammatory bowel disease
8. Organ transplantation

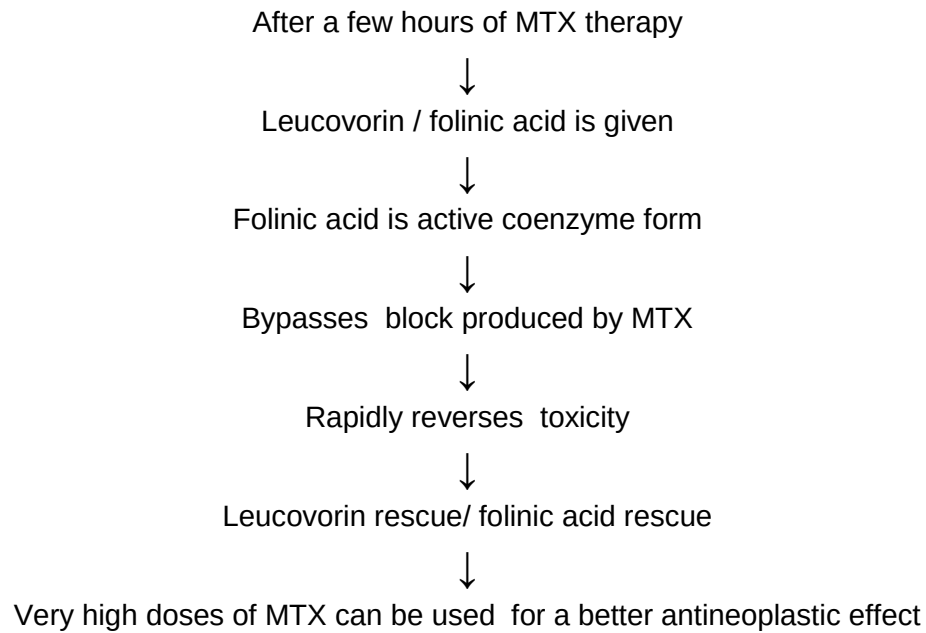
Adverse Effects

1. General toxicity
2. Megaloblastic anaemia
3. Pancytopenia
4. Hepatic fibrosis



Folinic Acid Rescue/Leucovorin Rescue

- To reduce toxic effects of MTX on normal cells



Drug Interactions

- Salicylates/sulphonamides/tetracyclines & MTX → Displace MTX bound to plasma proteins and increase its free form in plasma leading to its toxicity.
- NSAIDs and sulphonamides potentiate MTX toxicity by interfering with its excretion.

b) Pemetrexed

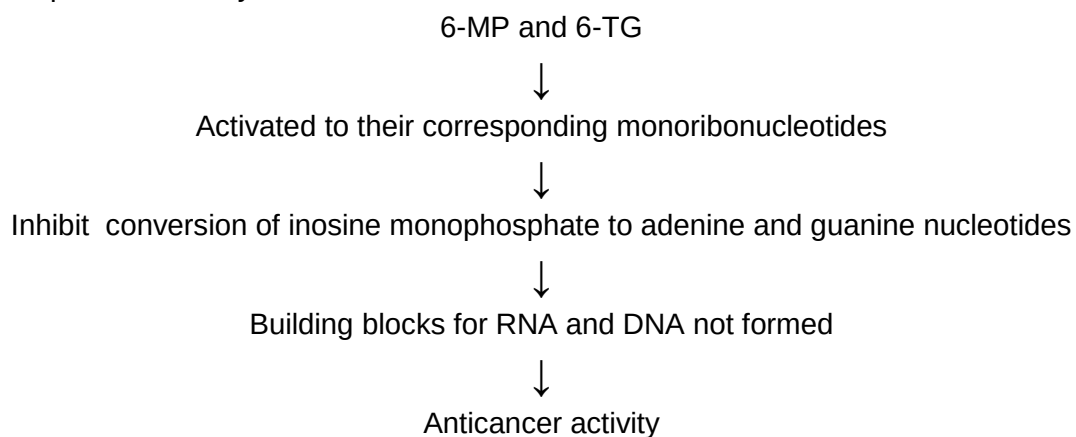
- Affects thymidylate synthase more than dihydrofolate reductase
- Adverse effect → Hand-foot syndrome



II. Purine Antagonists

MOA

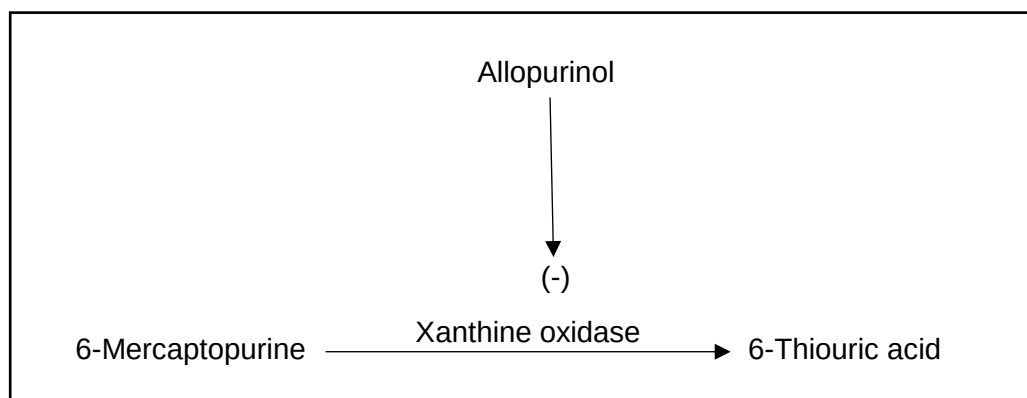
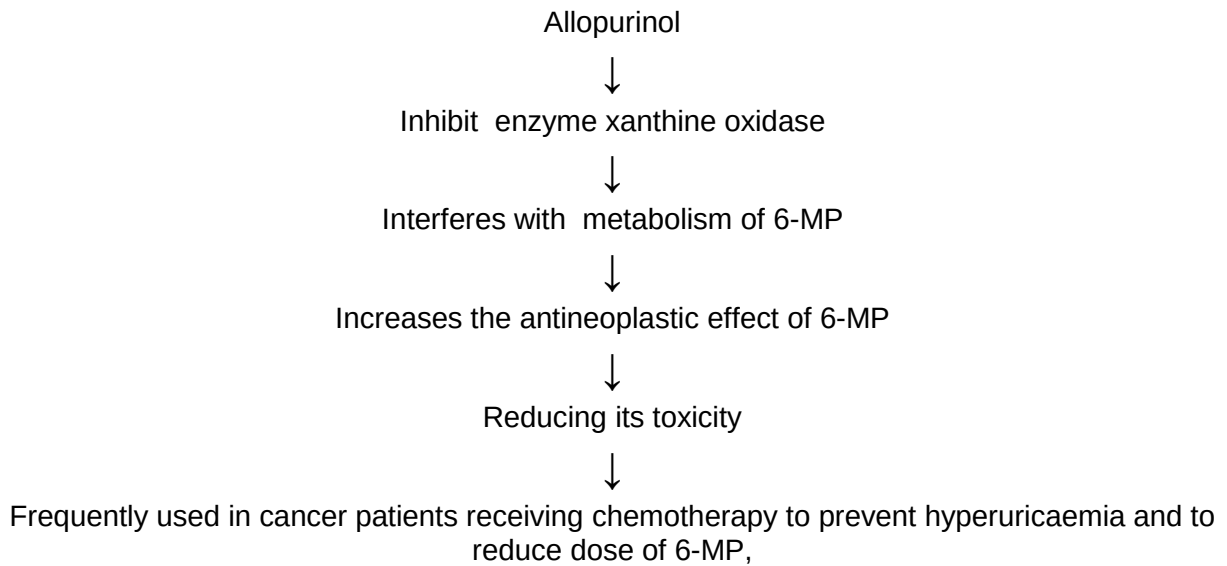
- CCS drugs
- Act in S phase of cell cycle.



6-MP

- Administered orally
- poor penetration through BBB.

- Has immunosuppressant action
- Metabolized by xanthine oxidase and its metabolite is excreted in urine.

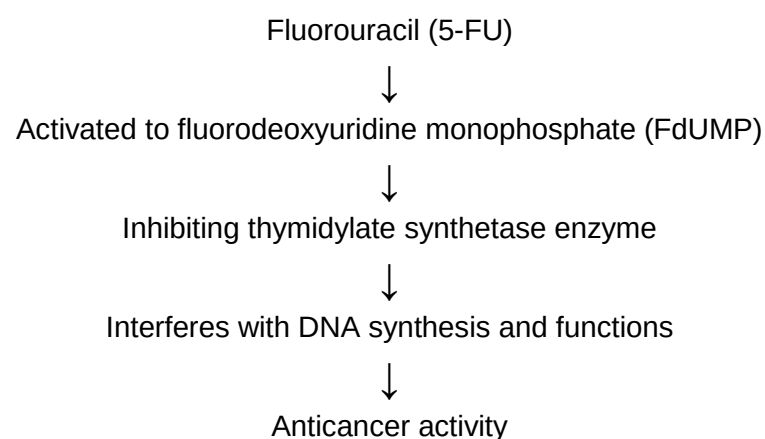


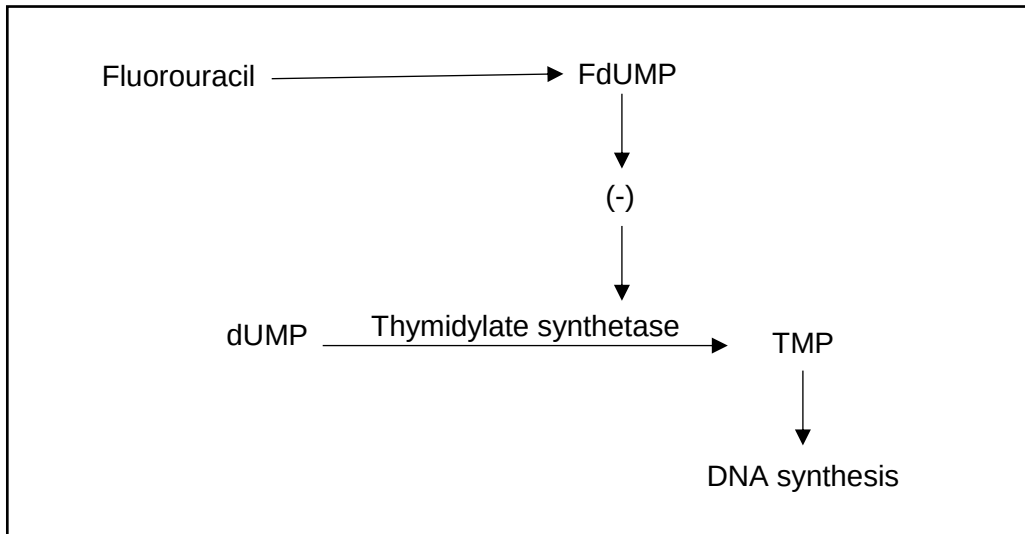
Uses → ALL

Adverse effect → Bone marrow depression

III. Pyrimidine Antagonists

MOA





a) Fluorouracil (5-FU)

Uses →

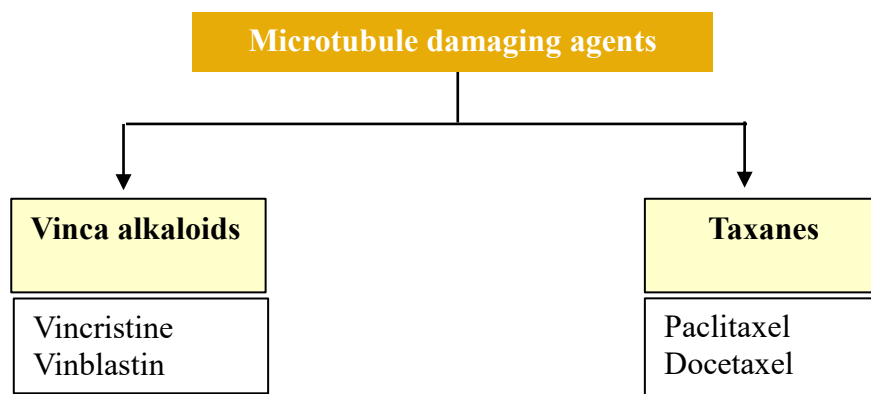
1. Colorectal carcinomas
2. Upper GIT carcinomas
3. Breast carcinomas
4. Ovarian carcinomas

b) Capecitabine

- Prodrug of 5-FU.
- **Uses** →
 - Metastatic breast
 - Colorectal cancer
- **Adverse effect** → Hand-foot syndrome



D. MICROTUBULE DAMAGING AGENTS

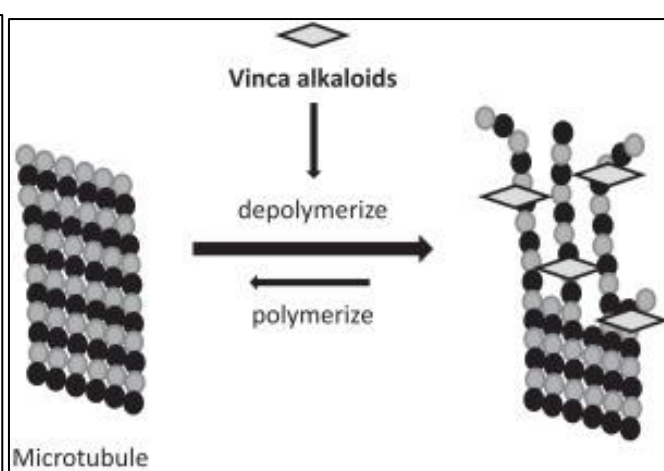
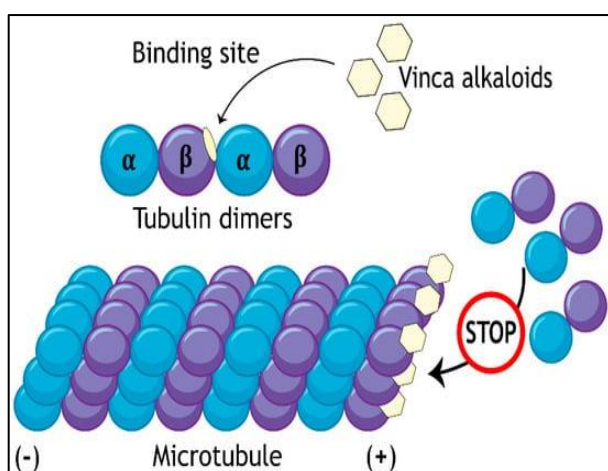
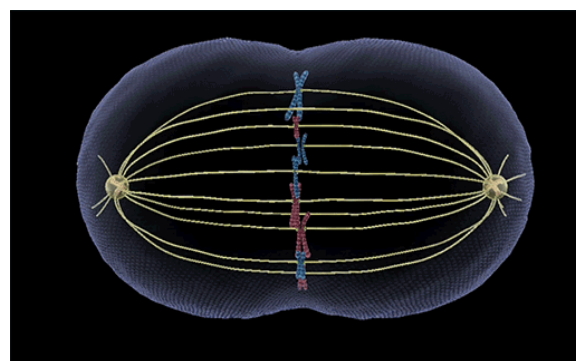
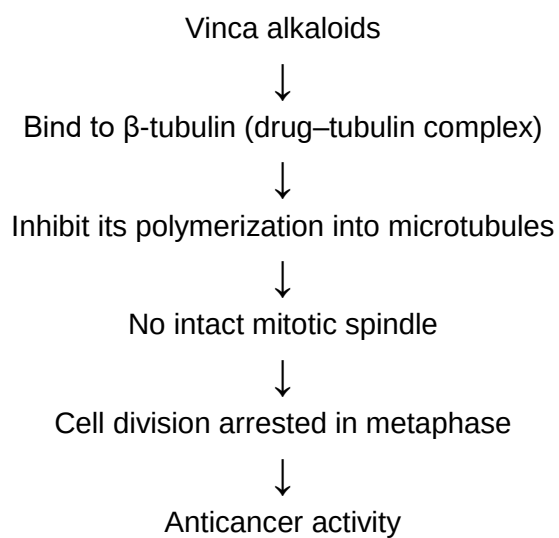
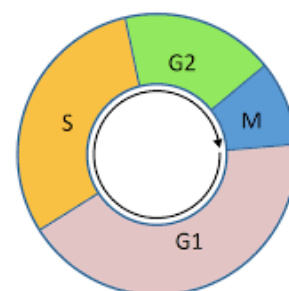


Microtubule damaging agents			
	Vinca alkaloids	Taxanes	
	Vincristine	Vinblastin	Paclitaxel
General features			
Uses			
Adveese effects			

I. Vinca alkaloids

MOA

- CCS agents
- Act during M phase of cell cycle



Vincristine and Vinblastine

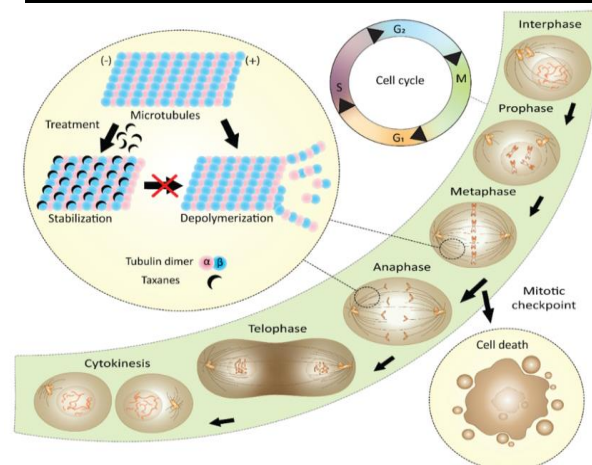
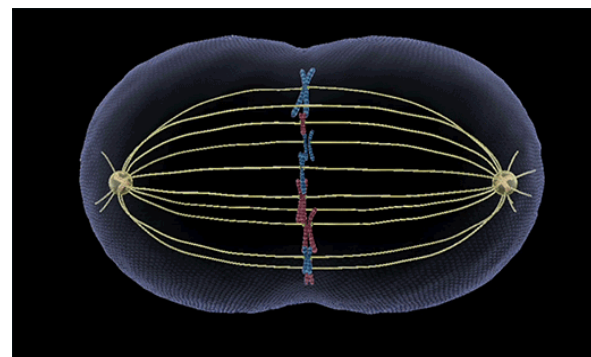
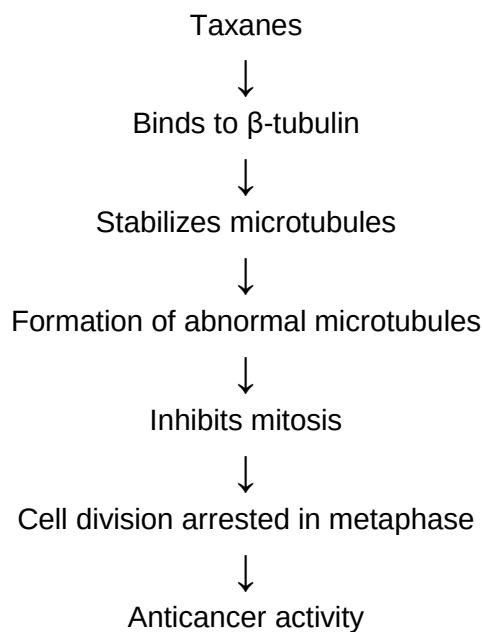
- Derived from the periwinkle plant.

Vinblastine	Vincristine
Uses: - Hodgkin disease - Testicular tumours	Uses: - Childhood leukaemias - Childhood tumours – Wilms tumour, neuroblastoma - Hodgkin disease
Toxicity: Bone marrow suppression, anorexia, nausea, vomiting and diarrhoea	Toxicity: Peripheral neuritis with paraesthesia, constipation Vincristine has minimal myelosuppressive action



II. Taxanes

MOA



Paclitaxel

- Derived from the bark of the western yew tree
- Docetaxel is a newer taxane
- Administered by i.v. infusion

Uses

- Advanced breast
- Ovarian



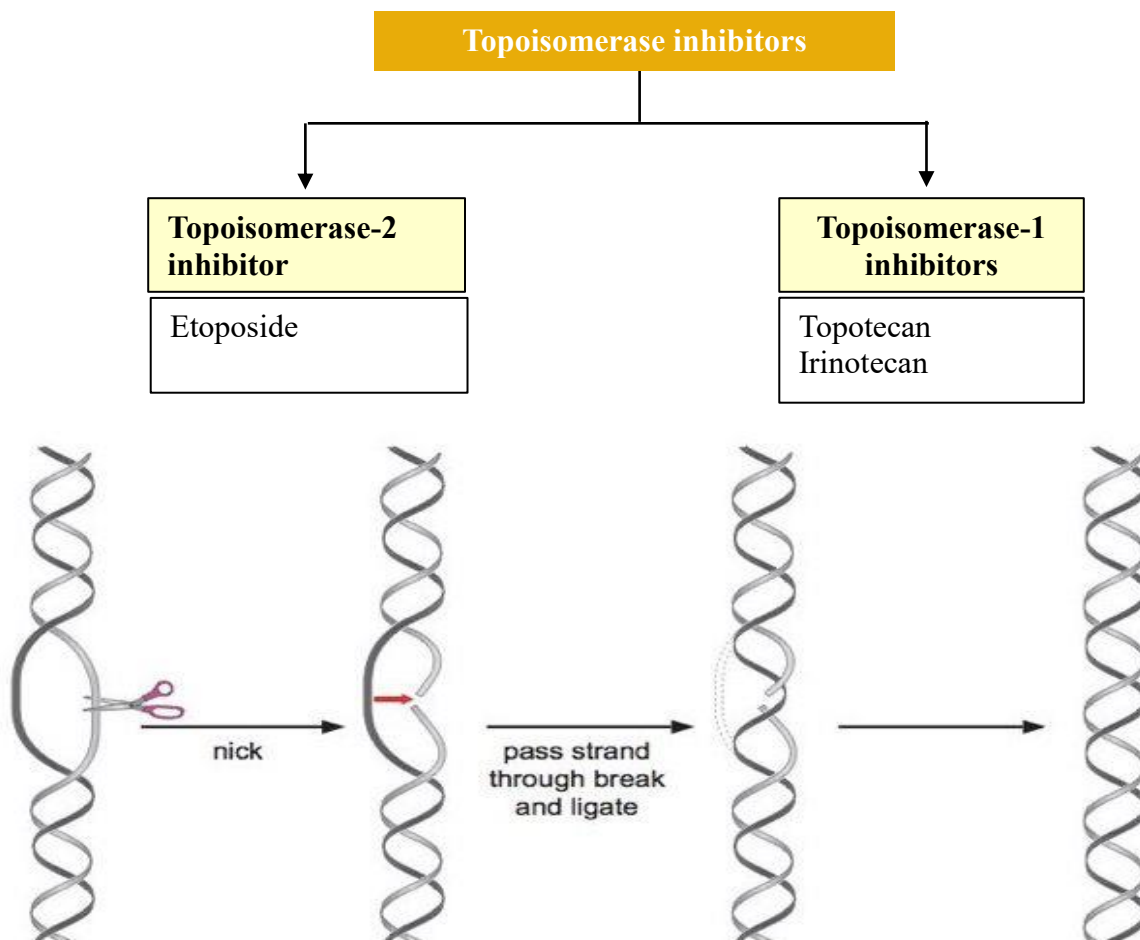
- Lung
- Oesophageal
- Bladder cancer

Adverse effects

- Bone marrow suppression
- Peripheral neuropathy
- Myalgia
- Hypersensitivity reactions

E. TOPOISOMERASE INHIBITORS

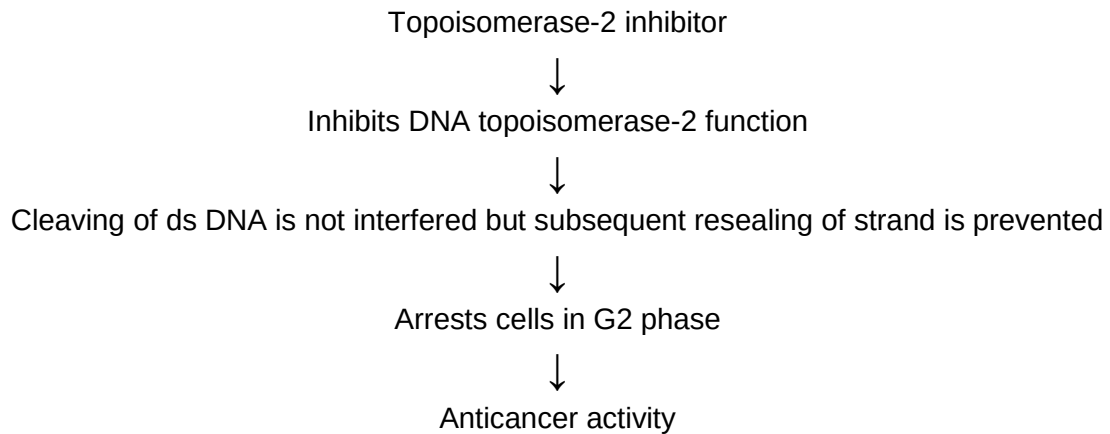
H. Topoisomerase-2 inhibitor



Topoisomerase inhibitor		
	Topoisomerase-2 inhibitor	Topoisomerase-1 inhibitor
	Etoposide	Topotecan Irinotecan
General features		
Uses		
Adverse effects		

I. Topoisomerase-2 inhibitor

MOA



Etoposide

- Semisynthetic derivative of podophyllotoxin, a plant glycoside.
- Not a mitotic inhibitor
- Arrests cells in the G2 phase

Uses

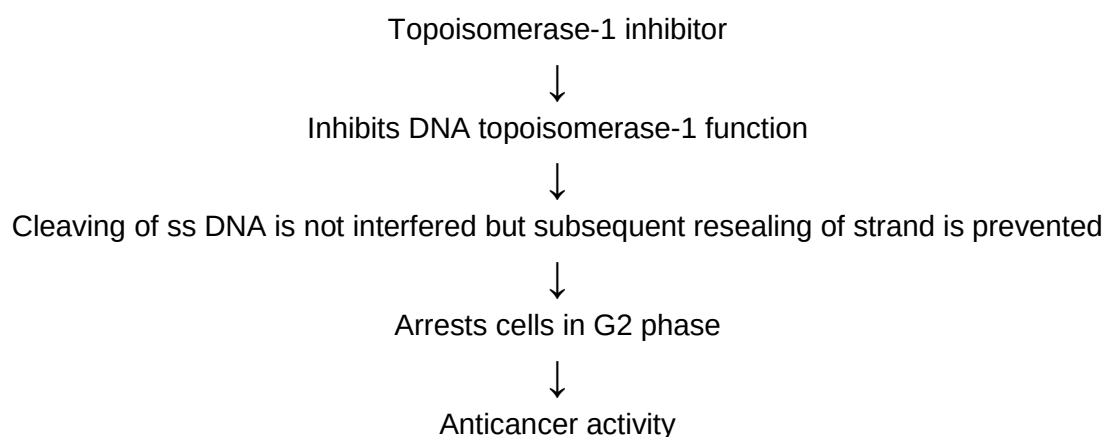
- Testicular tumours
- Lung cancer
- Hodgkin's
- Bladder carcinoma
- Stomach carcinoma

Adverse effects

- Bone marrow depression
- GI toxicity → Vomiting anorexia and diarrhoea.
- Hepatotoxicity → at high doses.

II. Topoisomerase-1 inhibitor

MOA



Topotecan

Uses

1. Metastatic carcinoma of ovary and small cell lung cancer after primary chemotherapy has failed
2. Colorectal cancer

Adverse effects

1. Bone marrow depression,
2. GI toxicity → Vomiting anorexia and diarrhoea.

F. ANTIBIOTICS

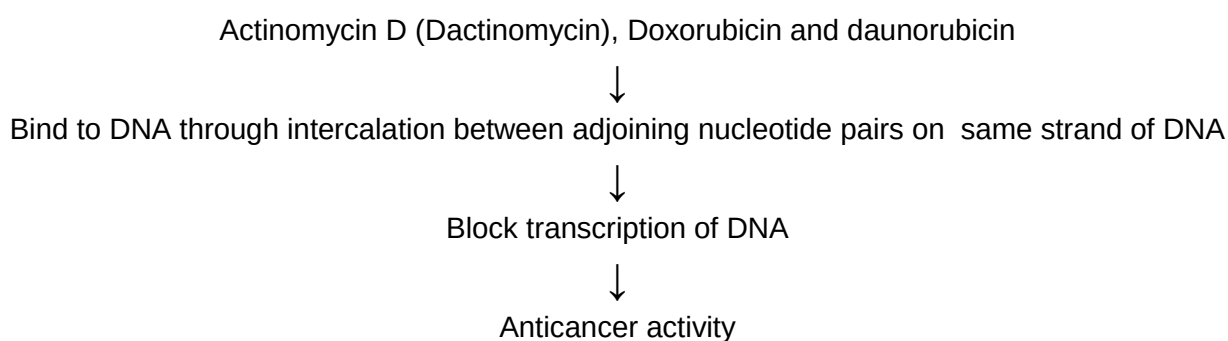
• Antibiotics

- Actinomycin D
- Doxorubicin
- Daunorubicin
- Mitomycin C
- Bleomycins
- Idarubicin
- Epirubicin
- Aclarubicin
- Mitoxantrone

- These are products obtained from microorganisms and have prominent antitumour activity.
- Practically all of them intercalate between DNA strands and interfere with its template function.

Antibiotics			
	Actinomycin D Doxorubicin Daunorubicin	Bleomycins	Mitomycin C
General features			
Uses			
Adveese effects			

I. Actinomycin D (Dactinomycin), Doxorubicin and daunorubicin



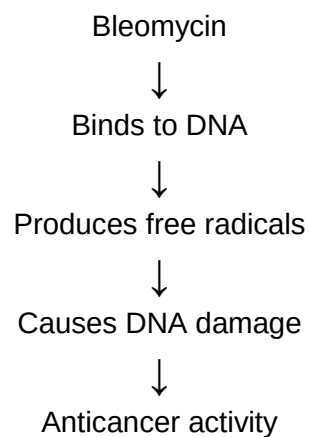
Uses

- Actinomycin D → Wilms tumour, Ewing sarcoma and choriocarcinoma.
- Daunorubicin → Acute leukaemias
- Doxorubicin → solid tumours.

Adverse effects

- Bone marrow suppression, GI disturbances and cardiomyopathy with CCF, hypotension or arrhythmias.

II. Bleomycin



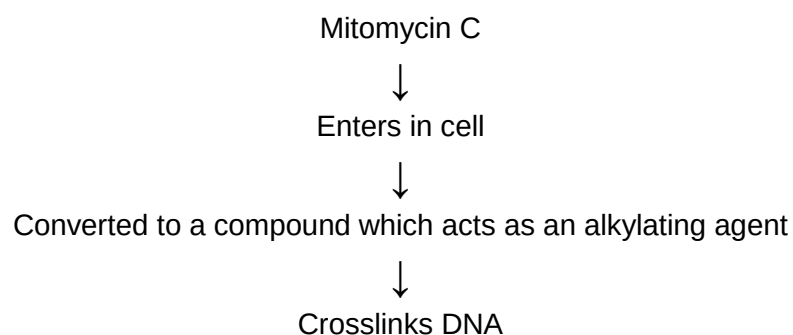
Uses

- Testicular tumours
- Ovarian tumours
- Hodgkin lymphoma (ABVD regimen)

Adverse effects

- Hyperpigmentation of skin
- Pulmonary fibrosis.

III. Mitomycin C



- Also generates free radicals which damage DNA

Uses

- GI tumours
- Cervix cancer
- Bladder cancer

Adverse effects

- Bone marrow suppression
- GI side effects
- Nephrotoxicity

TARGETED DRUGS FOR CANCER

Drug	Use	Adverse effects
Tyrosine kinase inhibitor • Imatinib: (–) Tyr kinase of chronic myeloid leukaemia (CML) cells	CML	Vomiting, abdominal pain
Angiogenesis inhibitor • Bevacizumab (VEGF inhibitor): binds to VEGF and blocks its binding to receptor • Sorafenib (VEGF inhibitor)	• Renal cell cancer • Lung cancer • Breast cancer Hepatocellular carcinoma	Hypertension, thromboembolism, bleeding Anorexia, hypertension
Epidermal growth factor receptor inhibitor • Gefitinib: (–) cellular growth and proloiferation	Non-small cell lung cancer	Rash, diarrhoea
Proteasome inhibitor • Bortezomib: Binds proteasome ↓ (–) proteolytic activity ↓ (–) cell proliferation (+) apoptosis	Multiple myeloma	Peripheral neuropathy
Monoclonal antibodies • Rituximab: Binds to antigen on surface of B lymphocytes and B cell lymphoma	B cell lymphoma	Infusion reaction

HORMONES AND HORMONE ANTAGONISTS

1. **Glucocorticoids:** Because of their marked lympholytic action, they are used in acute leukaemias and lymphomas. Apart from this effect, glucocorticoids:
 - (a) Have anti-inflammatory effect, decrease oedema associated with the tumour
 - (b) Produce feeling of well-being
 - (c) Suppress hypersensitivity reaction due to certain anticancer drugs
 - (d) Control hypercalcaemia
 - (e) Increase the antiemetic effect of ondansetron/granisetron/ metoclopramideBecause of the above effects, glucocorticoids are useful in the treatment of various cancers.
2. **Oestrogens:** The oestrogens are physiological antagonists of androgens. Hence, they are used to antagonize the effects of androgens in androgen-dependent prostatic tumours. Fosfestrol is a prodrug which is activated to stilboestrol in prostatic tissue. It achieves high concentration in prostatic tissue, therefore is preferred in carcinoma of prostate.
3. **Tamoxifen:** This is an antioestrogen mainly used in the palliative treatment of hormone-dependent breast carcinoma.
4. **Progestins:** The progestins are useful in endometrial carcinoma.
5. **Antiandrogens:** Flutamide is a nonsteroidal agent that blocks the action of androgen at the receptor level.
6. **Finasteride:** This blocks the conversion of testosterone to dihydrotestosterone by inhibiting 5 α -reductase. Both flutamide and finasteride are useful for the palliative treatment of advanced carcinoma of prostate. Finasteride is also effective in BPH.
7. **Aromatase inhibitors:** They are used in hormone-dependent breast cancer in postmenopausal women
8. **GnRH agonists:** The pulsatile administration of these agents (buserelin, goserelin, leuprolide, etc.) produces a rise in follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Continuous administration, however, suppresses the pituitary gonadotropins by downregulating GnRH receptors. These agents produce palliative effects in advanced prostatic and breast cancers.

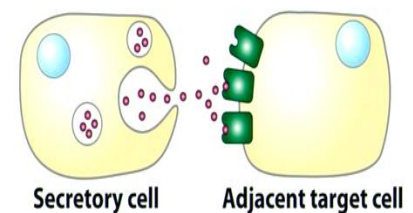
Autacoids and Related Drugs

CHAPTER 4

AUTACOID

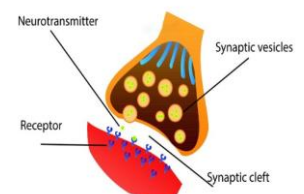
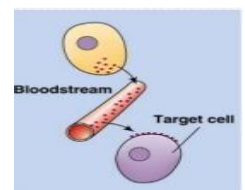
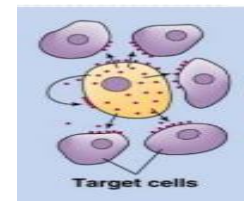
Introduction

- Auto = self, akos = remedy or medicinal agent.
- Chemical substances synthesized at the site of requirement → as if body is administering its own drug
- Diverse substances produced by a wide variety of cells in body
- Have intense biological activity
- Act locally at the site of synthesis and release.

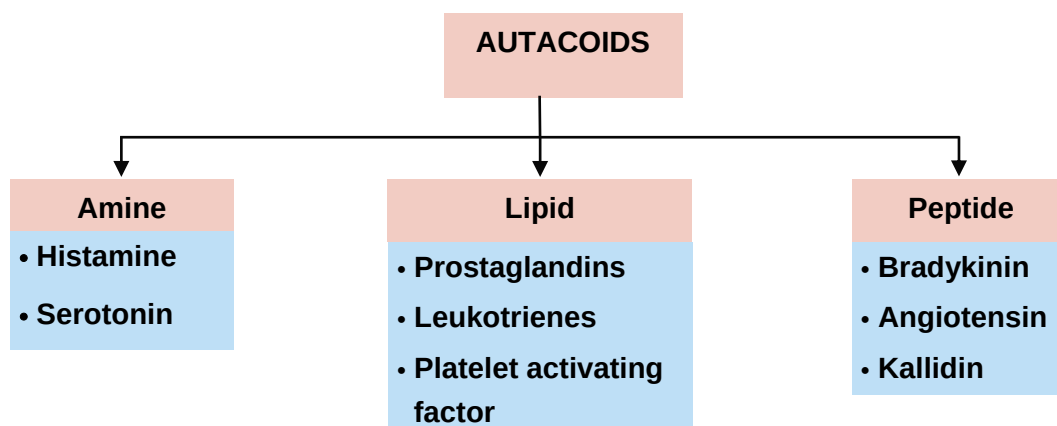


Autacoids Vs Hormones Vs Neurotransmitters

- **Autacoids**
 - act on same site or cells from where they are secreted
- **Hormones**
 - secreted directly into blood stream and acts at distant organ or tissues.
- **Neurotransmitters**
 - released by neurons and act rapidly for a brief period on adjacent neuron or target cell.



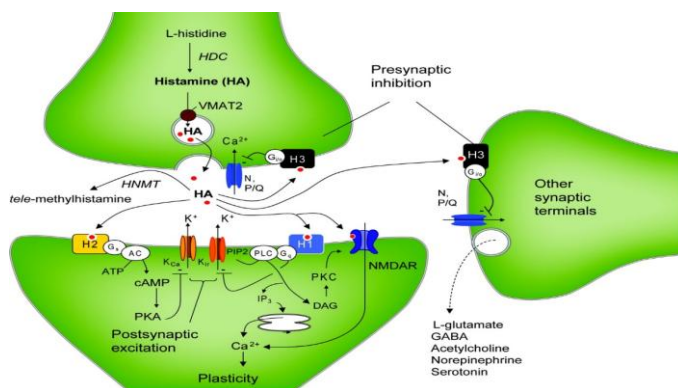
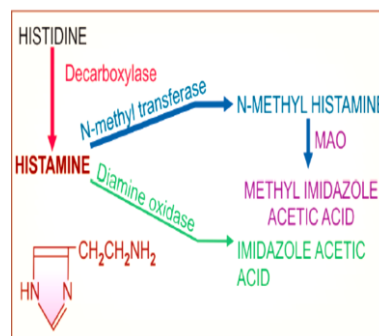
Classification



HISTAMINE

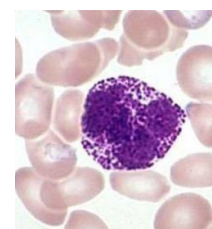
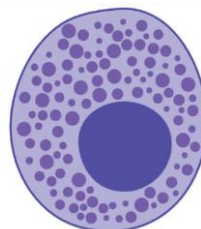
Synthesis and degradation

- Chemically**
 - β imidazoline derivative
- Formed by**
 - decarboxylation of amino acid histidine in presence of histidine decarboxylase
- Degraded by**
 - oxidation and methylation



Major site of storage

1. Mast cells / basophiles
2. Mucosal layer of GIT
3. Cells of epidermis
4. Neurons in CNS
5. Regenerating or rapidly growing tissues.



Histamine Receptors

- 4 types of histaminergic receptors
- All of them are G protein coupled receptors

H1	H2	H3
Smooth muscle (intestine, airway, uterus) → contraction	Gastric glands → acid secretion	Brain (presynaptically) ↓ histamine release → sedation
Blood vessels • Endothelium: Release of NO, PGI₂ → vasodilatation • Smooth muscle of larger vessel → vasoconstriction • Widening of gap → ↑ capillary permeability	Blood vessels (smooth muscle) → Vasodilatation	Lung, spleen, skin, gastric mucosa → ↓ histamine release
Afferent nerve endings → stimulation	Heart → - Atria: +ive chronotropy - Ventricles: +ive inotropy	
Ganglionic cell → stimulation	Brain → transmitter	
Adrenal medulla → release of CAs		
Brain → transmitter		
Allergy		

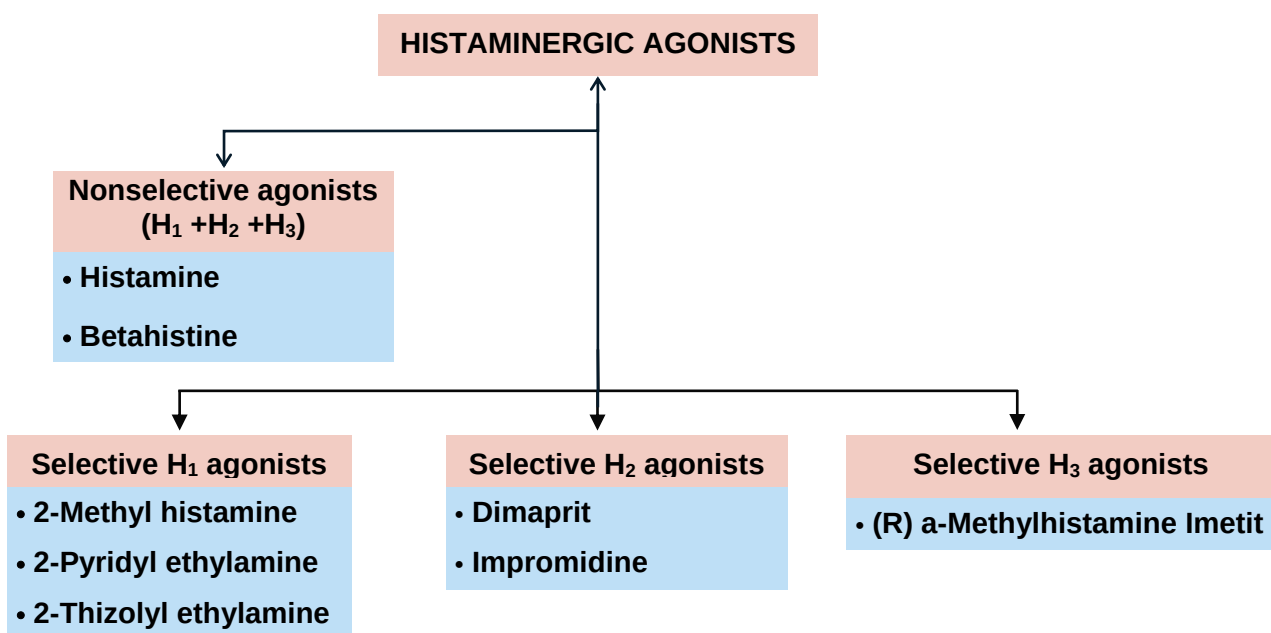
HISTAMINE AGONIST

	Histamine agonist	Histamine antagonist
Definition		
Classification		
MOA		
Pharmacological Actions		
Use		
Adverse effects		
Contraindication		

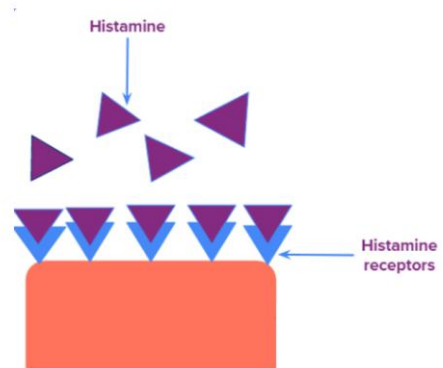
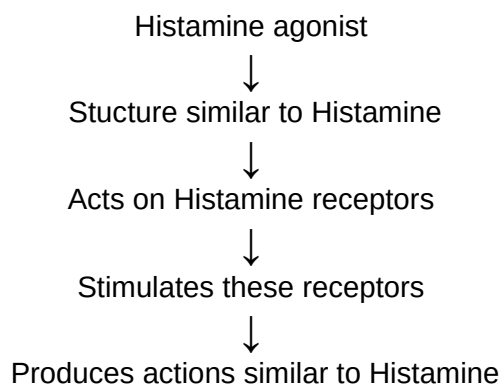
Definition

- Drug that activates histamine receptors

Classification



MOA



Pharmacological Actions

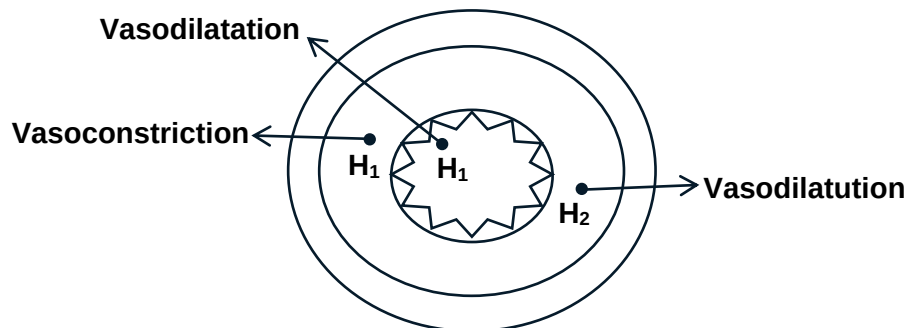
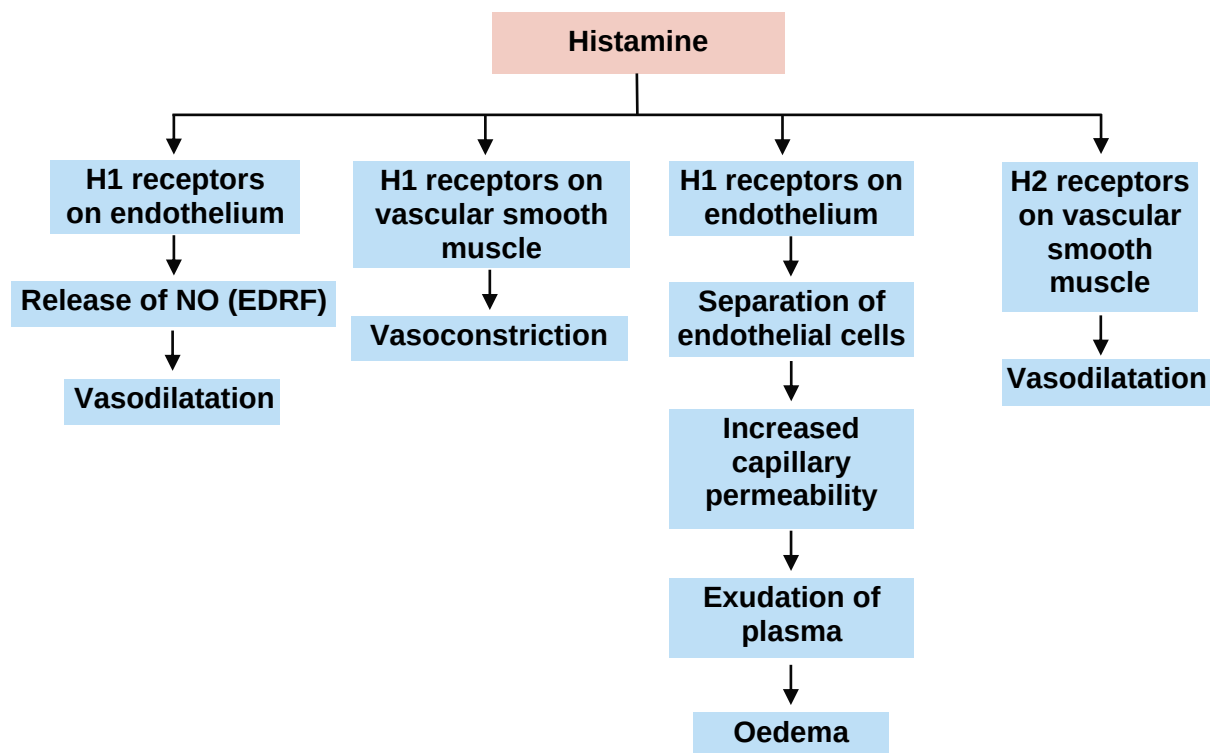
1. Smooth muscles (H₁)

- Contraction
 - **Lung** → Bronchoconstriction → C/I in asthma
 - **GIT** → contractions → Abdominal cramps and colic

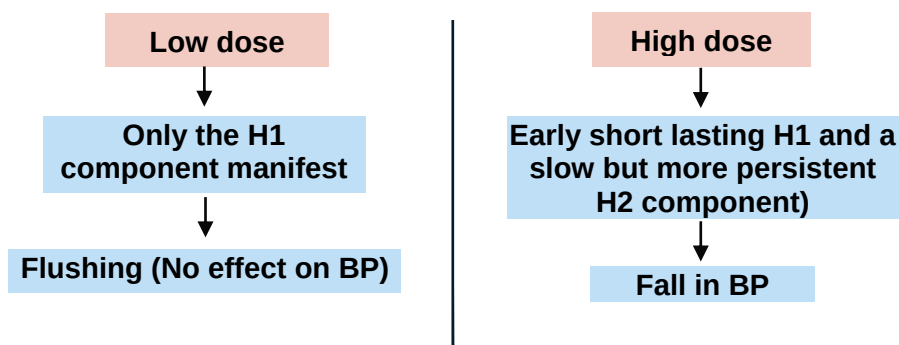
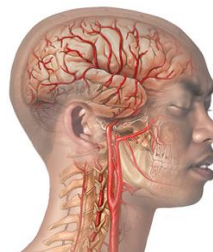


2. Blood Vessels (H1 and H2)

- Vasoconstriction of large blood vessels (arteries and veins)
- Vasodilatation of small blood vessels (capillaries)

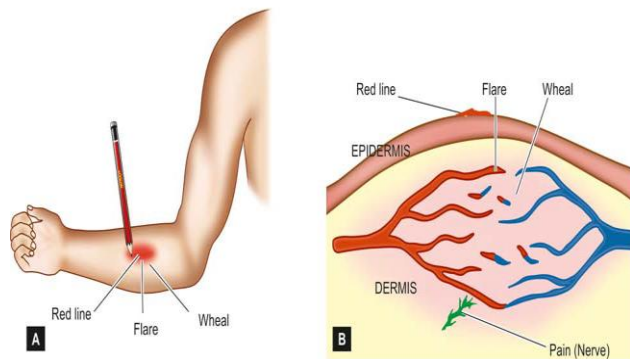


- Dilatation of cranial vessels causes → pulsatile headache



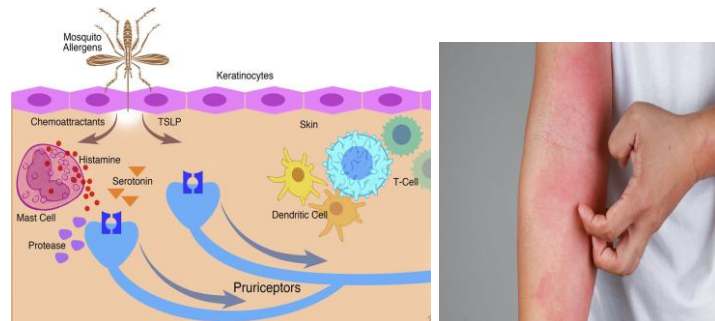
ID administration → Triple response

- Intra-dermal administration leads to a typical triad of phenomenon → 'triple response'.
 - **Red spot** → capillary dilatation
 - **Flare** → due to arteriolar dilatation
 - **Wheal** → due to enhanced permeability



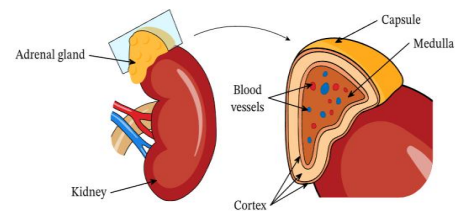
3. Afferent nerves endings (H1)

- Stimulation → Irritation, Pain and Itching.



4. Autonomic ganglia and adrenal medulla (H1)

Stimulation
↓
Release of Adr occurs
↓
Secondary rise in BP



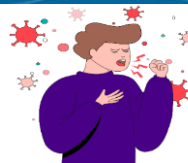
5. Brain (H1 and H2)

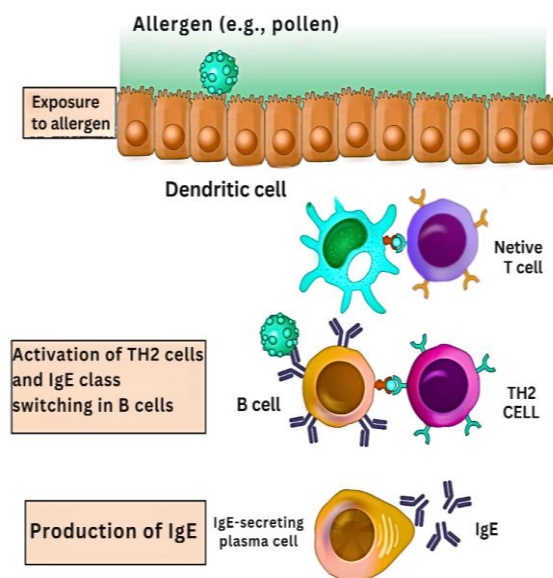
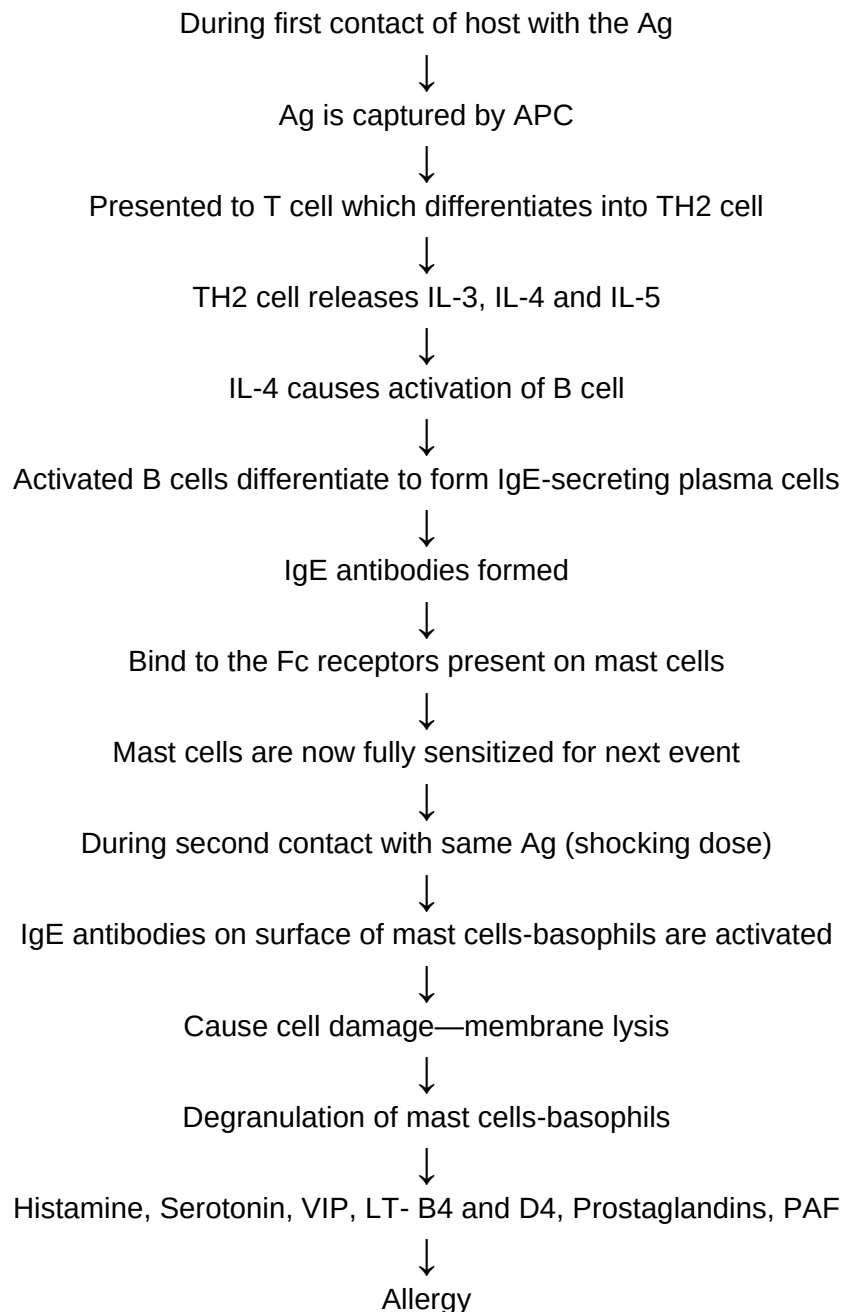
Histamine
↓
Stimulates RAS in brain through
H1 receptors
↓
Wakefulness
Suppression of appetite

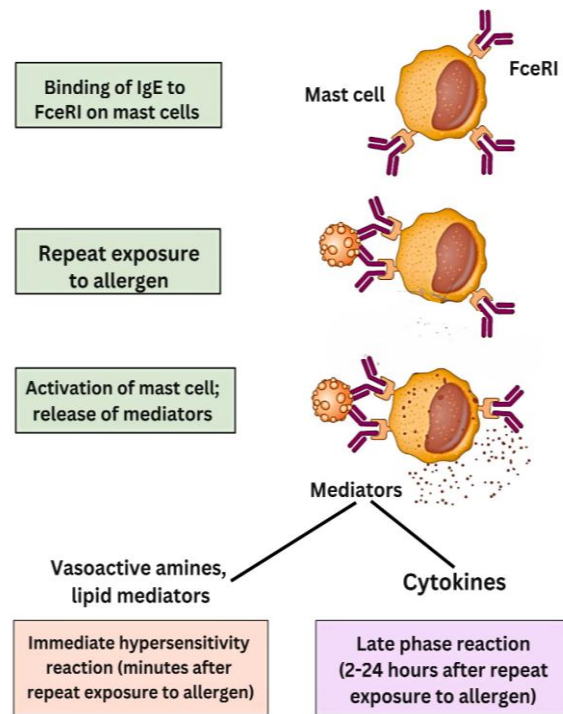


6. Allergy

- Type I Hypersensitivity reactions



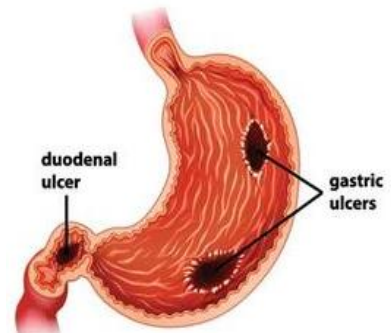
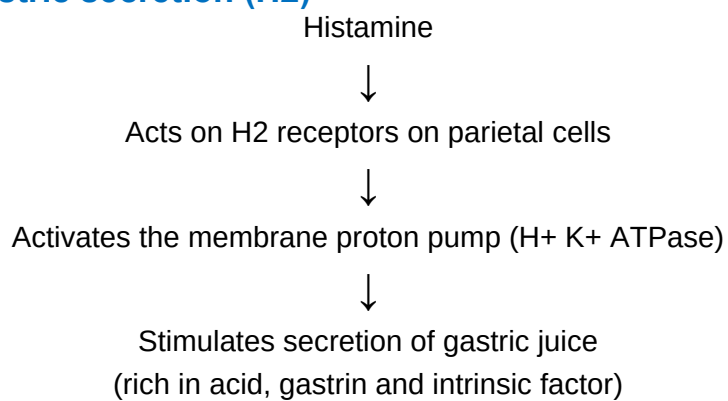




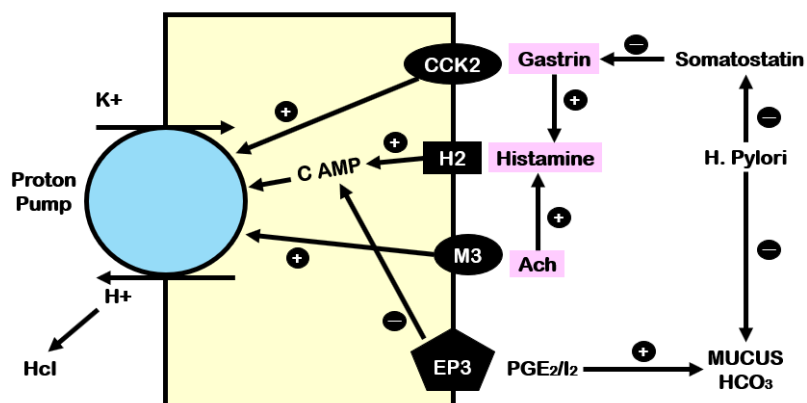
Effects of granules

1. Increased vascular permeability
2. Smooth muscle contraction
3. Early vasoconstriction followed by vasodilatation
4. Shock

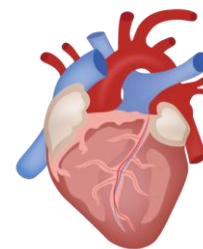
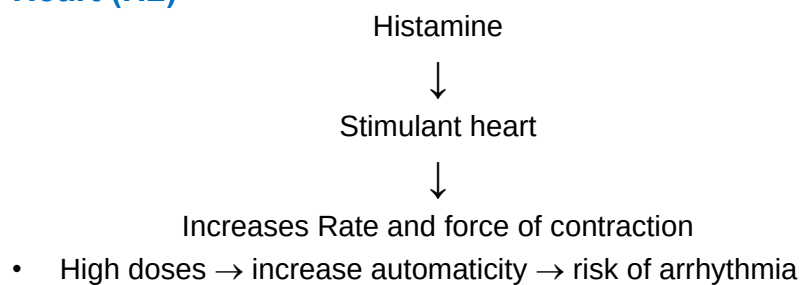
7. Gastric secretion (H₂)



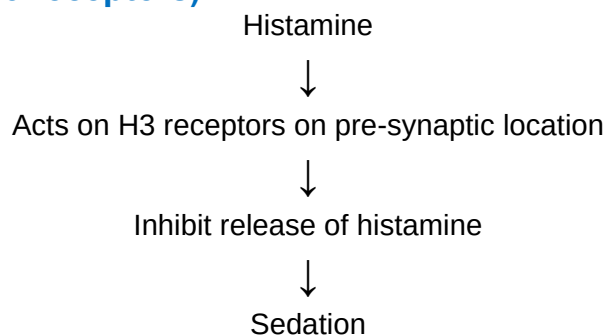
- C/I in peptic ulcer



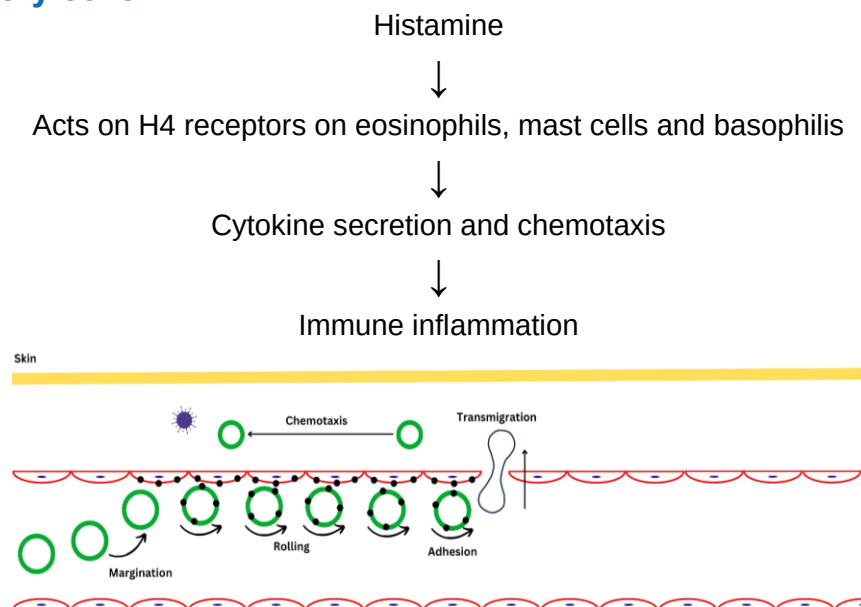
8. Heart (H2)



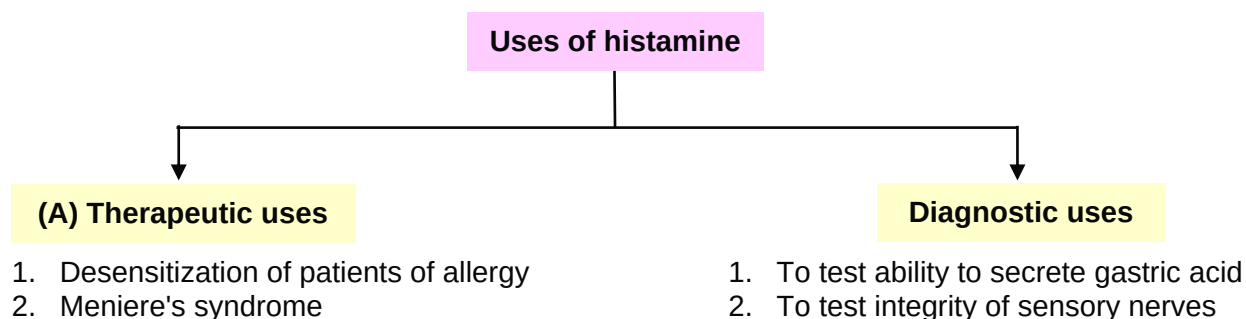
9. Brain (H3 receptors)



10. Inflammatory cells



Autonomic Nervous System (ANS)



A. Allergy

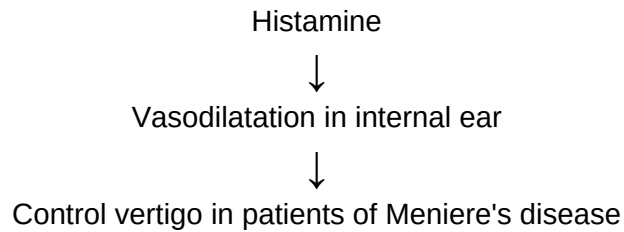
- Betahistine (H1 Selective histamine analogue)

1. Desensitization of patients of allergy

- Also known as → Hyposensitisation, allergy vaccination or specific immunotherapy (SIT).
- Involves targeted training to help immune system get used to the allergen



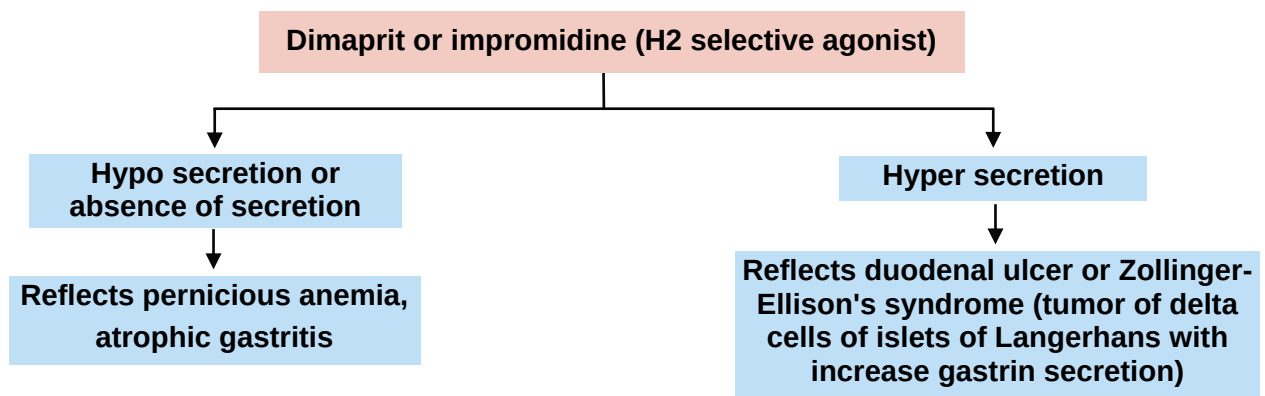
2. Meniere's syndrome (nerve deafness, vertigo and tinnitus)



B. Allergy

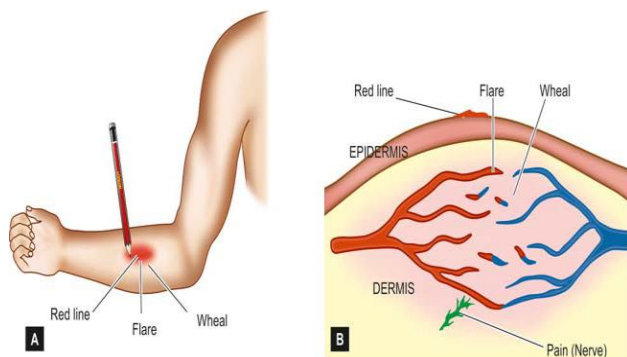
1. To test ability to secrete gastric acid

2.



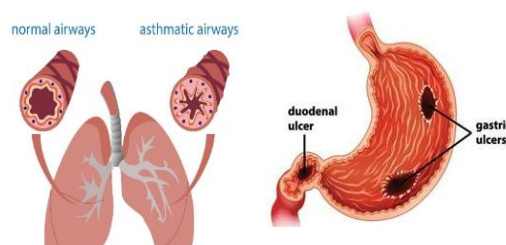
To test integrity of sensory nerves

- Absence of flare on intra-dermal injection indicates the damage to sensory nerves.



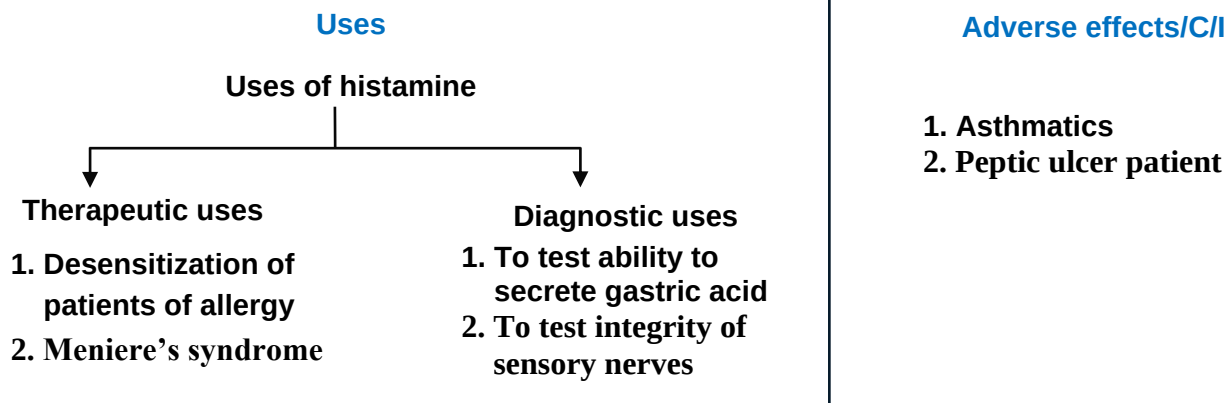
Contraindications

- Asthmatics
- Peptic ulcer patient



SUMMARY

Histamine agonist

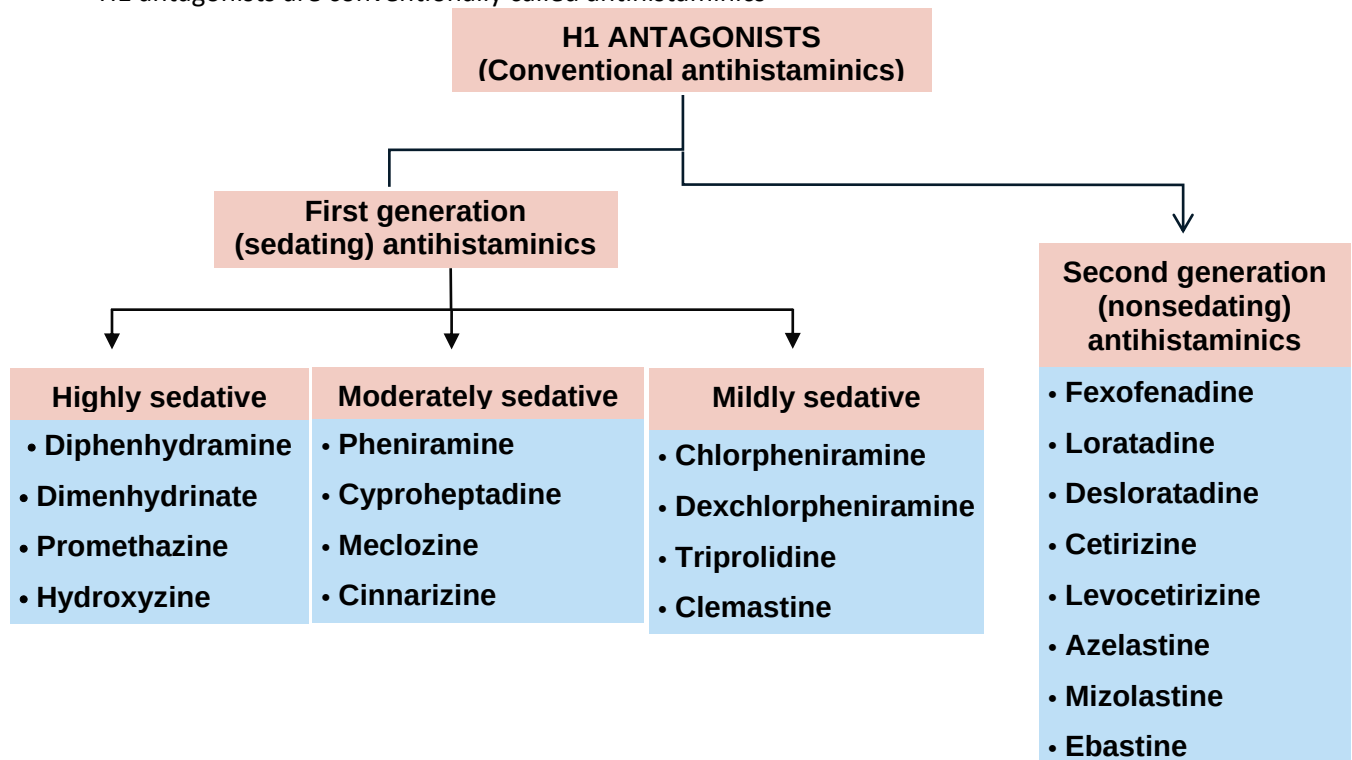


HISTAMINE ANTAGONIST / ANTIHISTAMINICS

	Histamine agonist	Histamine antagonist
Definition		
Classification		
MOA		
Pharmacological Actions		
Use		
Adverse effects		
Contraindication		

Definition

- H1 antagonists are conventionally called antihistaminics



1. Sedative antihistamines (first generations)

First generations Antihistaminics

↓
Cross BBB

↓
Sedation (major side effect)

- In addition to antihistamine effect they also exhibit antimuscarinic / anticholinergic effect.



2. Non Sedative antihistamines (second generations)

Second generations Antihistaminics

↓
Ionized at physiological pH and highly binding to plasma proteins

↓
Do not cross BBB

↓
Free from sedative effect

- Binds to Specific histamine H1 receptor → without any significant anticholinergic effect
- Additional antiallergic mechanisms apart from histamine blockade → inhibit late phase allergic reaction by acting on leukotrienes or by anti platelet activating factor (PAF) effect.



First generations Antihistaminics	Second generations Antihistaminics
Cross BBB	Do not cross BBB
Sedation	Minimal/no sedation
Anticholinergic effects	No anticholinergic effects
Show Antiemetic effect	Lack Antiemetic effect
Relatively Cheap	Relatively Expensive

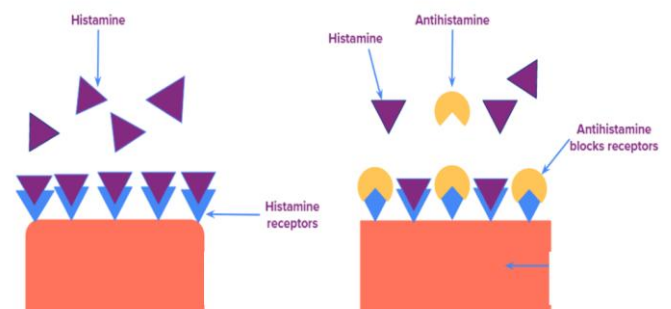
MOA of Thiazide

Competitive antagonist at H1 receptors

↓
Blocks H1 receptors

↓
So prevents binding of Histamine to H1 Receptors

↓
Inhibits Histamine effects at H1



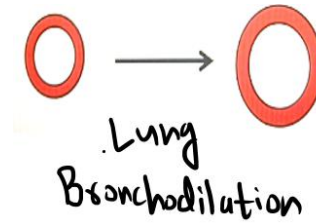
Thiazides

- (A) Antihistaminic effect
- (B) Antimuscarinic effect

A. Antihistaminic effect

1. Smooth muscles

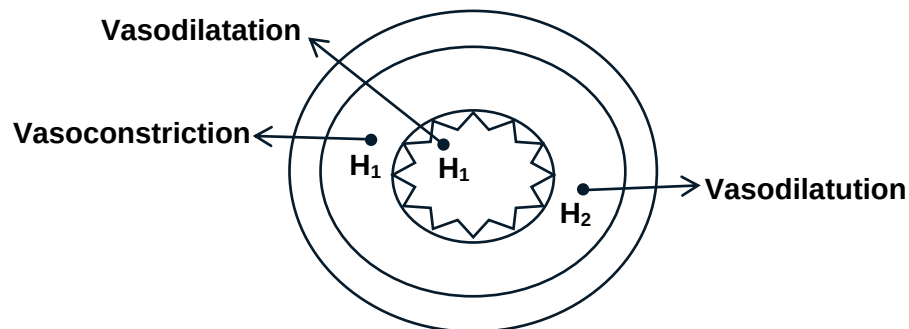
- Bronchoconstriction is blocked → Bronchodilatation
- Contraction of intestinal and other smooth muscle is blocked → Relaxation



GIT
Relaxation

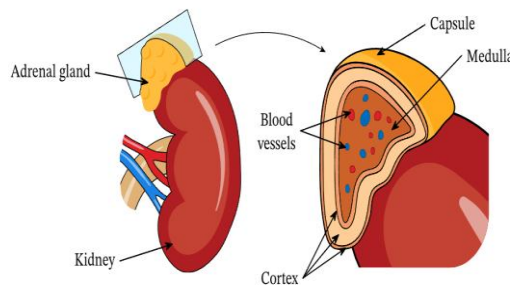
2. Blood vessels

- Fall in BP produced by low doses of histamine is blocked, but additional H₂ antagonists are required for complete blockade of that caused by higher doses.
- Triple response is blocked



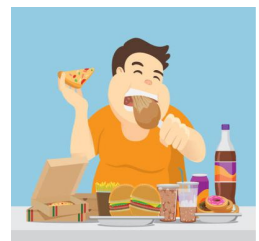
3. Adrenal medulla

- Release of Adr from adrenal medulla in response to histamine is abolished.



4. Brain

- Sedation (most common side effect)
- Depression
- Appetite stimulating effect → cyproheptadine is used



5. Antiallergic action

- Many manifestations of immediate hypersensitivity (type I reactions) are suppressed.



B. Antimuscarinic effect

1. Glands

- Decreased secretions → Dryness of mouth



2. Eye

- Blurring of vision

3. Urinary bladder

- Dysuria

4. CNS

- Anti motion sickness (central antagonism of acetylcholine)
- Reduce tremor, rigidity → Useful in parkinsonism
- Antitussive effect



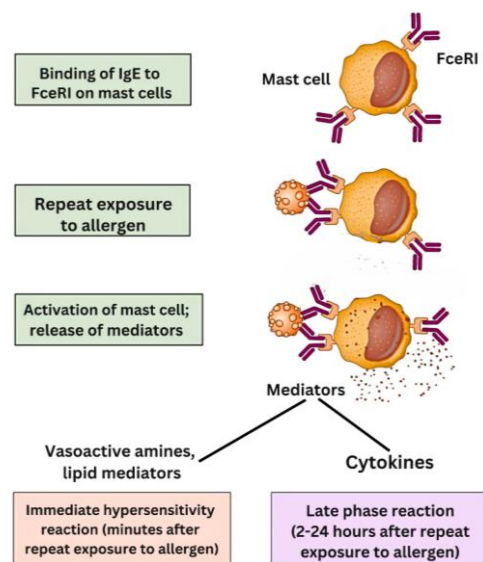
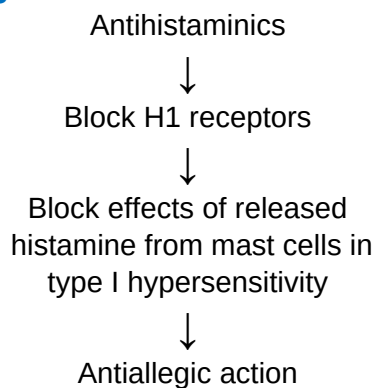
High	Low	Minimal/Absent
Promethazine Diphenhydramine Dimenhydrinate Pheniramine	Chlorpheniramine Hydroxyzine Triprolidine Cyproheptadine	Fexofenadine Astemizole Loratadine Cetirizine Mizolastine

Uses

- **H1 Antagonist** →
 1. Allergic disorders
 2. Pruritides
 3. As sedative, hypnotic, anxiolytic
 4. Appetite stimulating effect
 5. Motion sickness
 6. Common cold
 7. Cough
 8. Preanaesthetic medication
 9. Parkinsonism
- **H2 Antagonist** → peptic ulcer / dyspepsia
- **H3 Antagonist** → Narcolepsy
- **H4 Antagonist** → Allergy

USES OF H1 ANTAGONIST

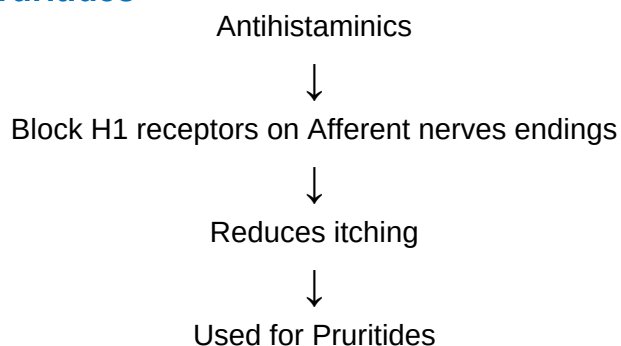
1. Allergic disorders



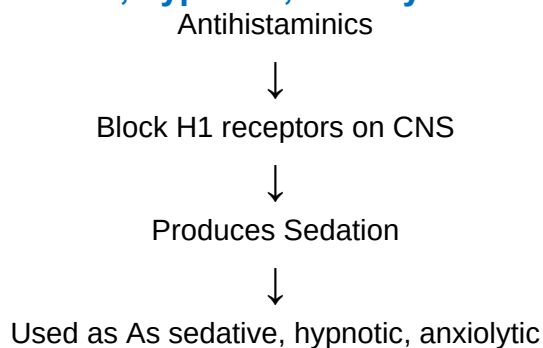
- Afford symptomatic relief →
 - Immediate type of allergies, e.g. itching, urticaria, seasonal hay fever, allergic conjunctivitis
 - Type I hypersensitivity reactions to drugs
 - Insect bite and ivy poisoning
- Benefits are less marked in → perennial vasomotor rhinitis, atopic dermatitis, chronic urticarias
- Ineffective in asthma → because Leukotrienes (C4, D4) and PAF are more important mediators than histamine.
- Laryngeal angioedema and anaphylactic shock → They have a secondary place to Adr. Because their action is slow
- So Adr alone is life-saving in laryngeal angioedema and anaphylactic shock



2. Pruritides



3. As sedative, hypnotic, anxiolytic

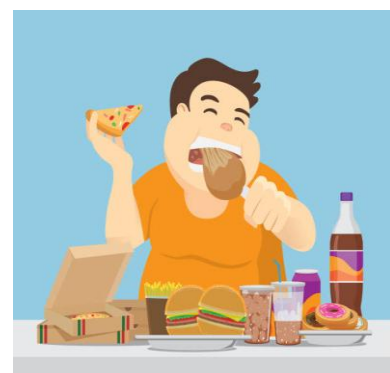


4. Appetite stimulating effect

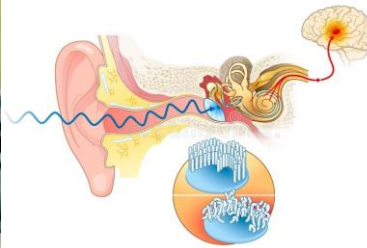
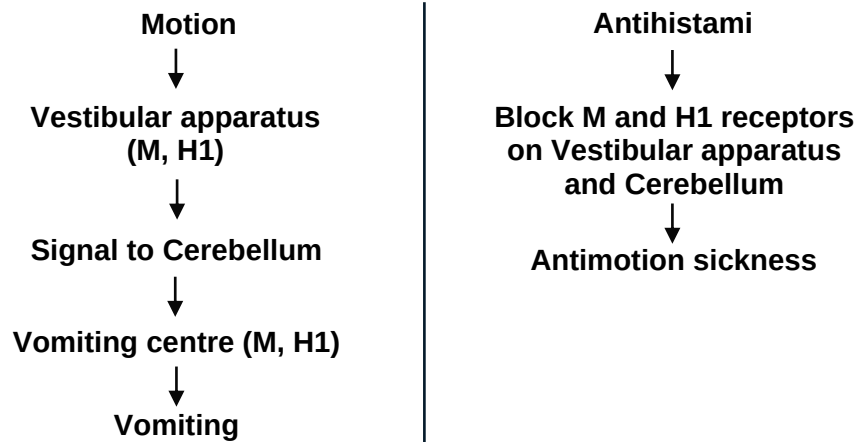
- ```

graph TD
 A[Antihistaminics] --> B[Block H1 receptors on CNS]
 B --> C[Stimulates appetite]
 C --> D[Used for Appetite stimulation]

```
- Cyproheptidine → used in underweight children.

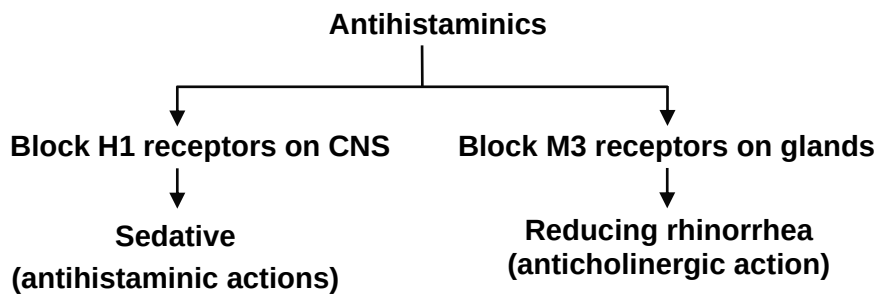


## 5. Motion sickness

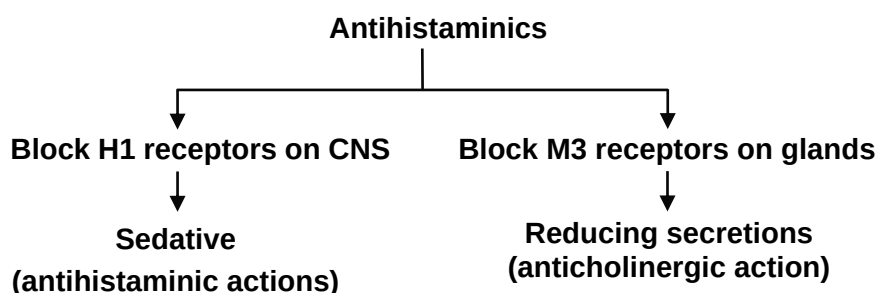


- Promethazine, diphenhydramine, dimenhydrinate and cyclizine → prophylactic value in milder types of motion sickness → should be taken one hour before starting journey.
- Promethazine → also be used in morning sickness, drug induced and postoperative vomiting, radiation sickness.

## 6. Common cold

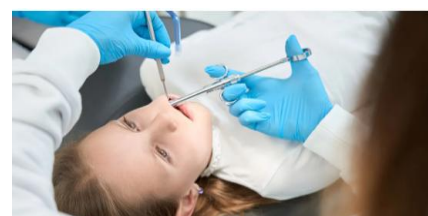
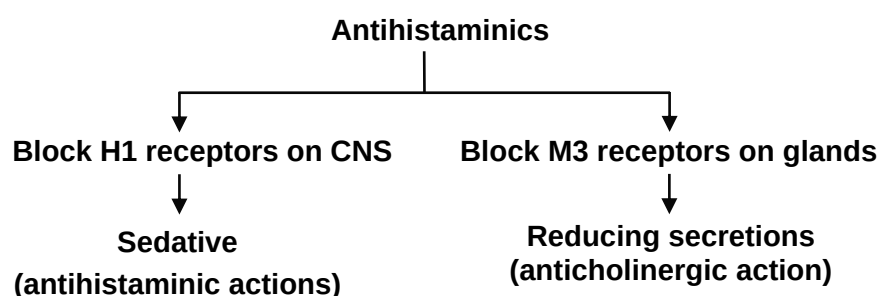


## 7. Cough



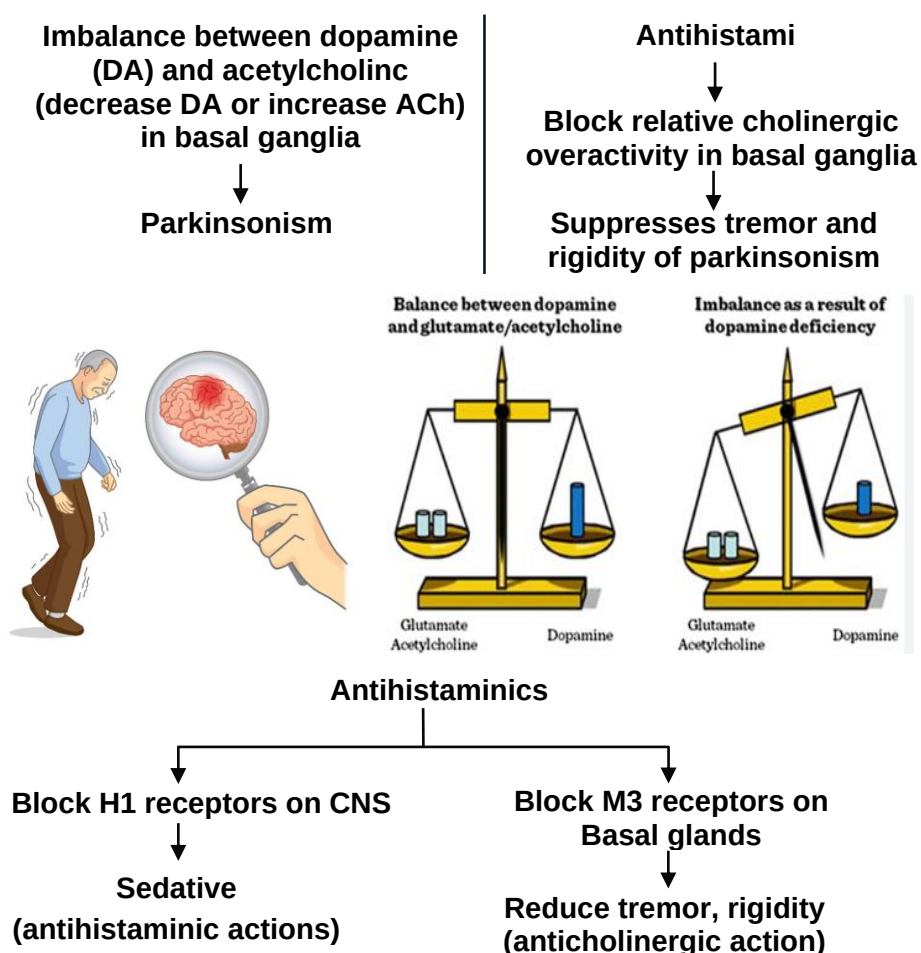
- Chlorpheniramine, Diphenhydramine and Promethazine has been used

## 8. Preanaesthetic medication



- Promethazine has been used

## 9. Parkinsonism



- Promethazine has been used

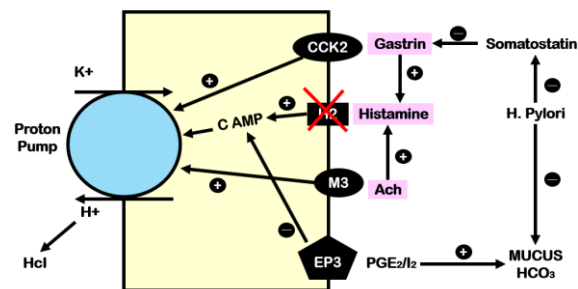
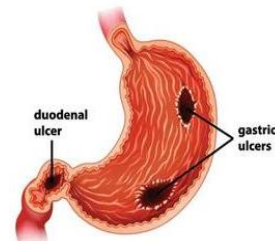
### Remember

| Based on H <sub>1</sub> blocking action                                                                                                                                                                          | Based on anticholinergic properties                                                                                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ol style="list-style-type: none"> <li>Allergic conditions like itching, urticaria, hay fever etc.</li> <li>Insect bite, ivy poisoning and to prevent the adverse effects due to histamine releasers.</li> </ol> | <b>Possess</b> - Parkinsonism<br><b>Anti</b> - Acute muscular dystonia<br><b>Cholinergic</b> - Common cold<br><b>Properties</b> - Prophylaxis motion sickness |

## USES OF H2 ANTAGONIST

### Peptic ulcer / dyspepsia

H2 antagonist  
 ↓  
 Blocks H2 receptors on parietal cells  
 ↓  
 Decreases gastric secretion  
 ↓  
 Used in treatment of peptic ulcer / dyspepsia



## USES OF H3 ANTAGONIST

### Narcolepsy

H3 antagonist  
 ↓  
 Blocks H3 receptors (pre-synaptic in location) which Inhibit release of histamine → Sedation  
 ↓  
 Increase histamine  
 ↓  
 Wakefulness  
 ↓  
 Used for Narcolepsy



- Pitolisant (tiprolisant) (H3 antagonist) → approved for Narcolepsy

## USES OF H4 ANTAGONIST

### Allergy

H4 antagonists  
 ↓  
 Blocks H4 receptors on eosinophils, mast cells and basophils  
 ↓  
 Antiallergic action  
 ↓  
 Used for allergic conditions like allergic rhinitis and asthma



- Pitolisant (tiprolisant) (H3 antagonist) → approved for Narcolepsy



## Adverse effects

1. Sedation
2. Anticholinergic effects

### 1. Sedation

- Most common side effect
- Depression of CNS → ranging from → Drowsiness to deep sleep.
- Dizziness, incoordination, and heaviness.
- Patients should be cautioned not to operate motor vehicles or machinery requiring constant attention
- Alcohol synergises in producing these effects



### 2. Anticholinergic effects

- Second most common side effect
  - Dryness of mouth
  - Blurring of vision
  - Dysuria



| Receptor       | Agonist                                   | Antagonist                                    |
|----------------|-------------------------------------------|-----------------------------------------------|
| H <sub>1</sub> | 2 methyl histamine                        | Diphenhydramine, Mepyramine, chlorpheniramine |
| H <sub>2</sub> | 4 methyl histamine, Impromidine, Dimaprit | Ranitidine                                    |
| H <sub>3</sub> | α methyl histamine                        | Thioperamide,                                 |
| H <sub>4</sub> | Clobenpropit                              | Thioperamide                                  |

### Terfenadine

- Fastest acting antihistaminic drug.
- Possesses arrhythmogenic property → In overdose, it blocks cardiac delayed rectifier K<sup>+</sup> channels and may result in polymorphic ventricular tachycardia (torsades de' pointes) manifested as prolongation of QTc interval.
- Terfenadine is metabolized to an active metabolite "fexofenadine" (available as a separate drug) that lacks K<sup>+</sup> channel blocking property
- Due to this toxicity, terfenadine has been withdrawn

### Astemizole

- Slowest and longest acting agent
- Possesses arrhythmogenic property similar to terfenadine.

### Acrivastine

- Acrivastine is the shortest acting antihistaminic.

### Loratidine

- Another long acting second generation antihistaminics
- Metabolized to desloratidine (available as a separate drug).

### Cetirizine

- Cetirizine is an active metabolite of a first generation antihistaminic drug, hydroxyzine
- All second generation antihistaminics are metabolized to active products except cetirizine and mizolastine.
- In addition to H<sub>1</sub>-blocking effect it can also inhibit the release of histamine.
- Some persons acquire sedative effects with cetirizine.
- Levocetirizine is l-isomer of cetirizine that is more potent and less sedative

### Azelastine



- Azelastine possesses maximum topical activity
- can be given by nasal spray for allergic rhinitis

### Olopatadine

- Olopatadine is a recently approved topical H1 antihistaminic used as nasal spray for seasonal allergic rhinitis.

### Alcaftadine

- Alcaftadine is approved as ophthalmic solution for allergic conjunctivitis.

## SUMMARY

### Antihistaminics

#### Uses

##### H1 Antagonist →

1. Allergic
2. Pruritides
3. As sedative, hypnotic, anxiolytic
4. Appetite stimulating effect
5. Motion sickness
6. Common cold
7. Cough
8. Preanaesthetic medication
9. Parkinsonism

H2 Antagonist → peptic ulcer/dyspepsia

H3 Antagonist → Narcolepsy

H4 Antagonist → Allergy

#### Adverse effects/C/I

1. Sedation
2. Anticholinergic effects

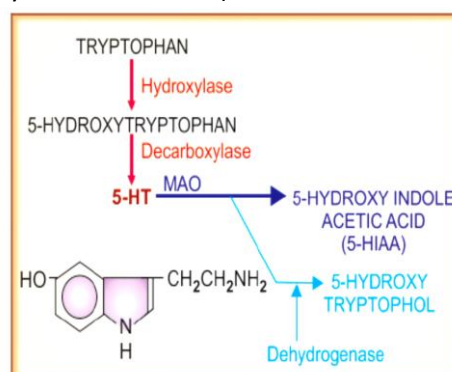
## 5 HYDROXYTRYPTAMINE (5 HT) OR SEROTONIN

### Introduction

- Higher concentrations of 5 HT are found in GIT, platelets and CNS
  - 90% → in intestines
  - 10% → in platelets and brain.

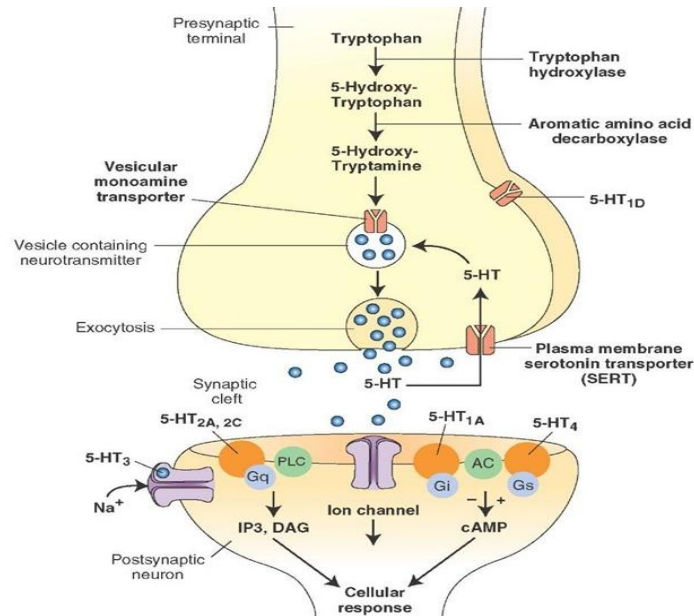
### Synthesis and degradation

- Synthesized from → tryptophan which converts to 5 hydroxy- tryptophan and then to 5 HT.
- Metabolized to → 5 HIAA (Hydroxy indol acetic acid) and melatonin.



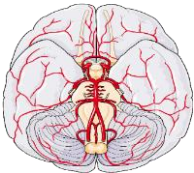
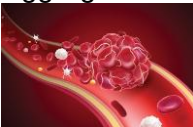
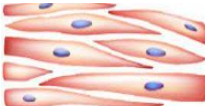
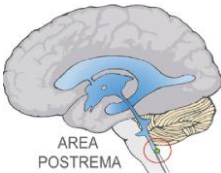
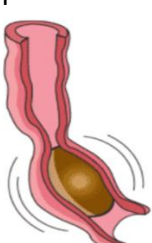
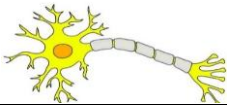
Termination of action of 5-HT

↓  
Occurs via reuptake at membrane of serotonergic nerve endings (Like NA)  
↓  
Axonal uptake → by a Na<sup>+</sup> dependent carrier - amine pump serotonin transporter (SERT) → Inhibited by SSRIs and TCAs  
↓  
Vesicular uptake → by vesicular monoamine transporter (VMAT-2) → Inhibited by reserpine



## Serotonergic (5- HT) Receptors

- 4 families → 5-HT<sub>1</sub>, 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4-7</sub>
- 14 receptor subtypes have so far been recognized
  - All 5-HT receptors (except 5-HT<sub>3</sub>) → G protein coupled receptors
  - 5-HT<sub>3</sub> → ligand gated cation (Na<sup>+</sup>, K<sup>+</sup>) channel

| 5 HT <sub>1A</sub>                                                                  | 5 HT <sub>1D/1B</sub>                                                               | 5 HT <sub>2A/C</sub>                                                                                                                                                                                                 | 5 HT <sub>3</sub>                                                                     | 5 HT <sub>4</sub>                                                                     |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| <b>Brain</b> →<br>Mood Behavior                                                     | <b>Cranial blood vessels</b> → VC                                                   | <b>Platelets</b> →<br>Aggregation                                                                                                                                                                                    | <b>Area postrema</b> →<br>Emesis                                                      | <b>GIT</b> → Stimulate<br>→ peristalsis                                               |
|  |  | <br><b>Smooth muscles</b><br>→ Contraction<br> |  |  |
|                                                                                     |                                                                                     | <b>CNS</b> → Neuronal excitability<br>                                                                                            |                                                                                       |                                                                                       |

## 5HT AGONIST

|                                | 5HT agonist | 5HT agonist |
|--------------------------------|-------------|-------------|
| <b>Definition</b>              |             |             |
| <b>Classification</b>          |             |             |
| <b>MOA</b>                     |             |             |
| <b>Pharmacological Actions</b> |             |             |
| <b>Use</b>                     |             |             |
| <b>Adverse effects</b>         |             |             |
| <b>Contraindication</b>        |             |             |

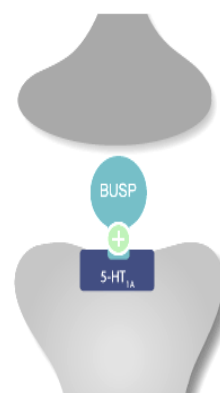
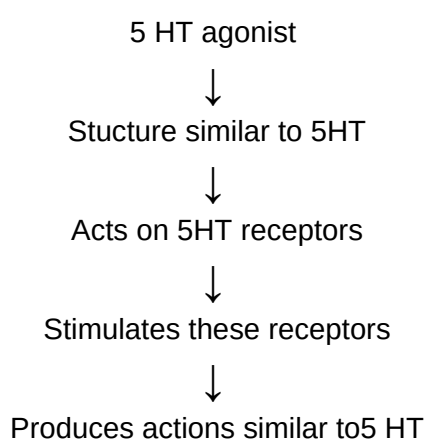
### Definition

- Drug that activates 5 HT receptors

### Classification

- **5HT<sub>1A</sub> agonist** → Fluid retention and hyponatraemia may develop.
- **5-HT<sub>1D/1B</sub> agonist** → Sumatriptan, Rizatriptan, Naratriptan, Zolmitriptan
- **5-HT<sub>4</sub> agonists** → Cisapride, Itopride, renzapride and tegaserod

### MOA



### Pharmacological Actions

- 5HT<sub>1A</sub> → Brain**
  - Neurotransmitter
  - Precursor of melatonin in pineal gland
  - Neuroendocrine function
- 5-HT<sub>1D/1B</sub> → Cranial blood vessels**
  - Migraine
- 5-HT<sub>2A/C</sub> → Platelets, Smooth muscle, CNS neurons**
  - Haemostasis
  - Raynaud's phenomenon
  - Prinzmetal angina
  - Preeclamptic rise in BP
  - Peristalsis

**4. 5HT<sub>3</sub> → Area postrema**

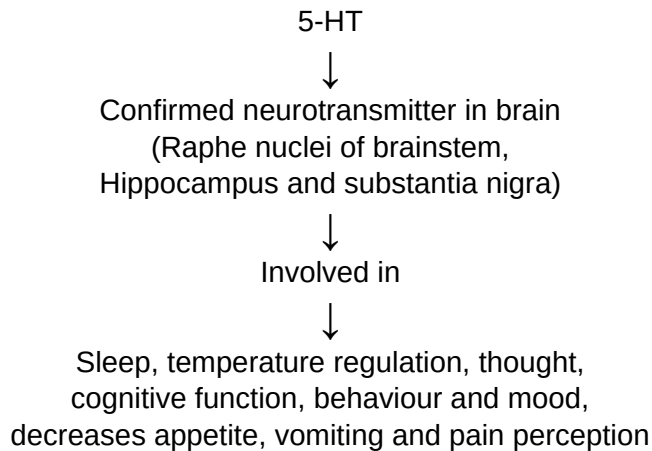
- a. Nausea and vomiting

**5. 5HT<sub>4</sub> → GIT**

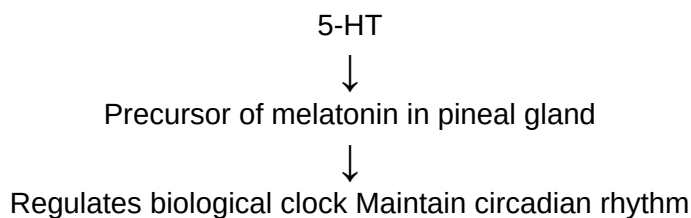
- a. Increased peristalsis

**5 HT<sub>1A</sub> → BRAIN**

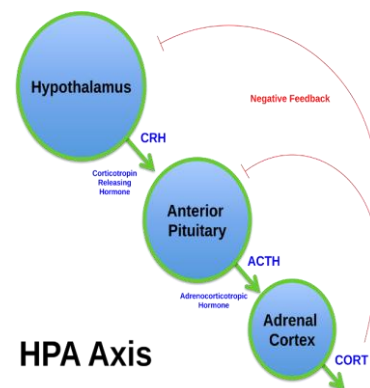
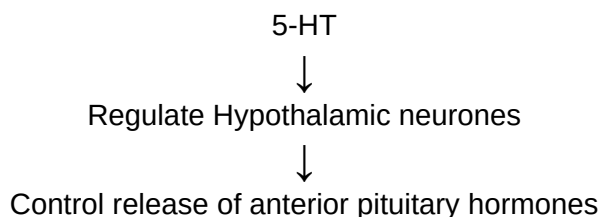
**a) Neurotransmitter (5HT<sub>1A</sub>)**



**b) Precursor of melatonin in pineal gland (5HT<sub>1A</sub>)**



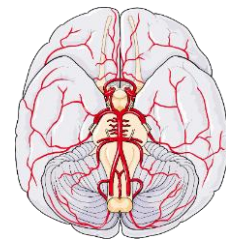
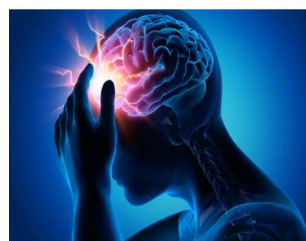
**c) Neuroendocrine function (5HT<sub>1A</sub>)**

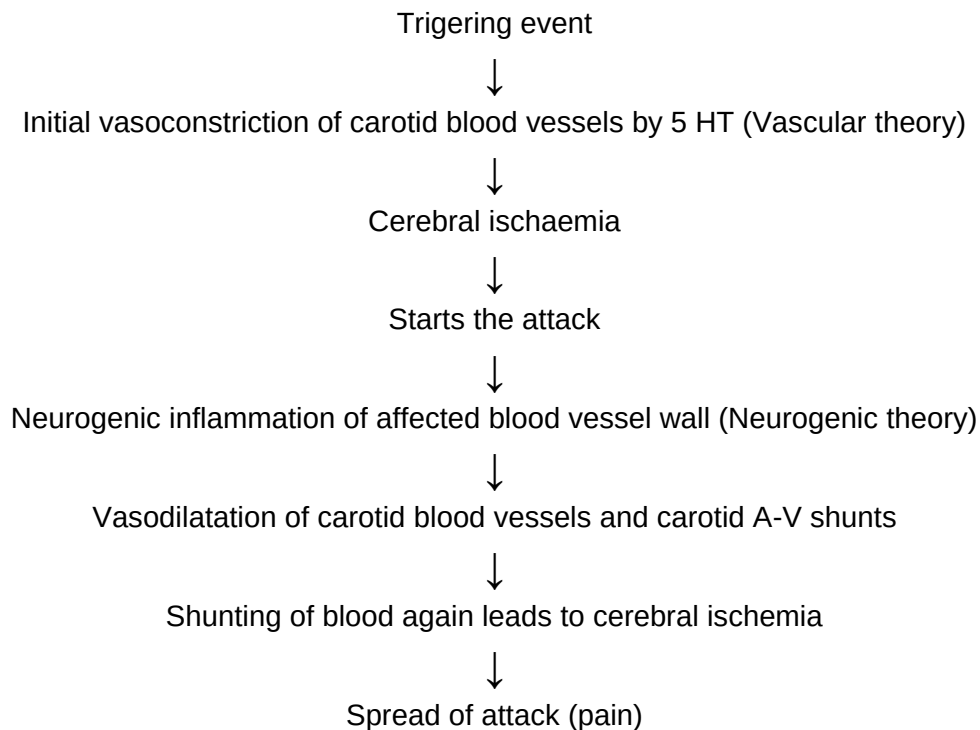


**5-HT<sub>1D/1B</sub> → CRANIAL BLOOD VESSELS**

**Migraine (5-HT<sub>1D/1B</sub>)**

- 5-HT is said to initiate the vasoconstrictor phase of migraine and to participate in neurogenic inflammation of the affected blood vessels.





## Remember

### Vasoconstriction of carotid blood

↓

Responsible for start of attack

↓

So 5-HT antagonist (Methysergide and cyproheptidine) ie. vasodilator is used for prophylaxis for migraine

### Vasodilatation of carotid blood

↓

Responsible for spread of attack (clinical)

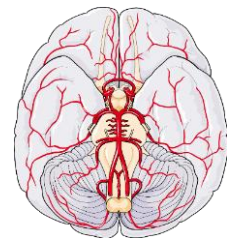
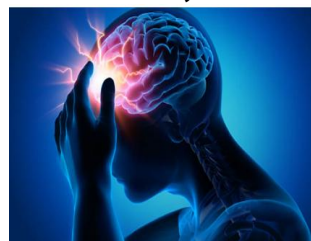
↓

So 5-HT agonist (Sumatriptan) ie. vasoconstrictor is used for prophylaxis for migraine

## 5-HT<sub>2A/C</sub> → PLATELETS, SMOOTH MUSCLE, CNS NEURONS

### a) Haemostasis (5-HT<sub>2A/C</sub>)

- Primary haemostasis occurs in 3 steps →
  - Platelet adhesion
  - Platelet granule release
  - Platelet aggregation
- Platelets release 5-HT during aggregation at site of injury to blood vessel.
- Acting in concert with collagen, this 5-HT accelerates platelet aggregation and clot formation.

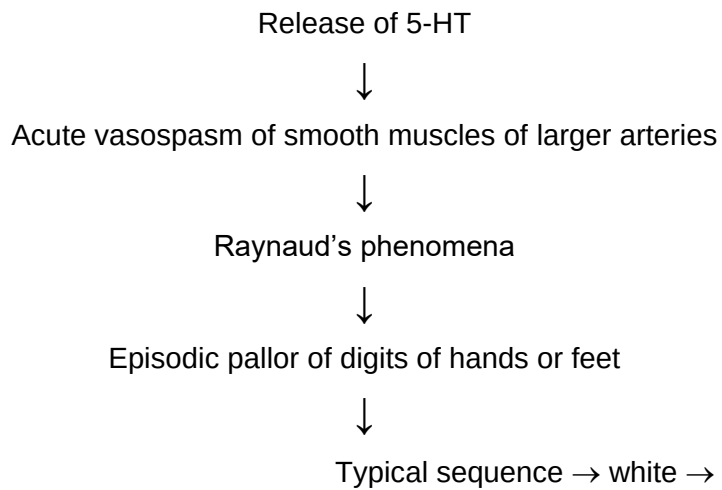


### Platelet granule release

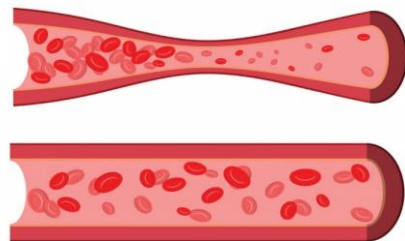
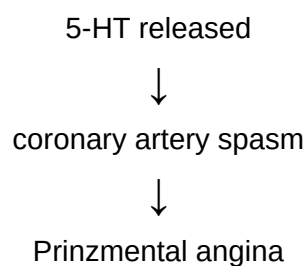
3 types of granules from their cytoplasm:

- Dense granules → Contain ADP, Ca, serotonin and epinephrine.
- $\alpha$ -granules → Contain fibrinogen, fibronectin, factor V & VIII, PDGF, TGF-B and platelet factor 4.
- Lysosomal vesicle

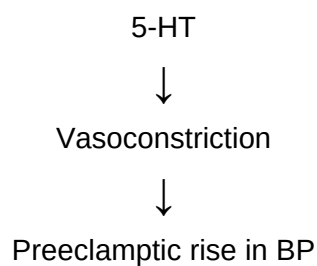
## b) Raynaud's phenomenon (5-HT<sub>2A/C</sub>)



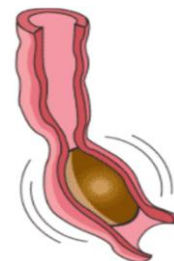
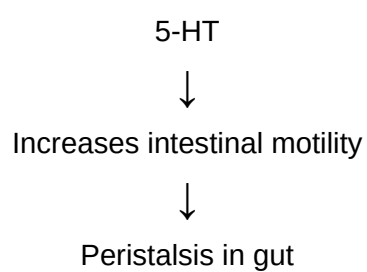
## c) Prinzmetal angina (5-HT<sub>2A/C</sub>)



## d) Preeclamptic rise in BP (5-HT<sub>2A/C</sub>)



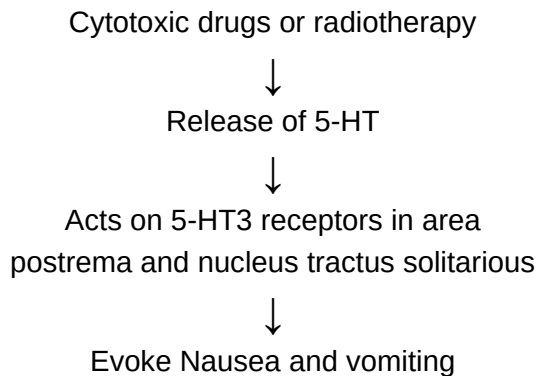
## e) Peristalsis(5-HT<sub>2A/C</sub>)





## 5HT<sub>3</sub> → AREA POSTREMA

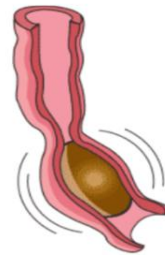
### Nausea and vomiting (5HT<sub>3</sub>)



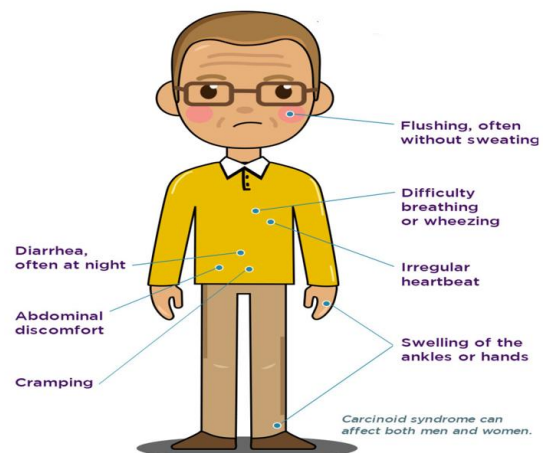
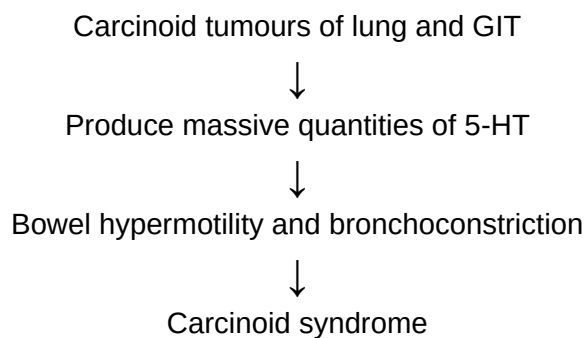
## 5HT<sub>4</sub> → GIT

### Increased peristalsis (5HT<sub>4</sub>)

- GIT → Increased peristalsis



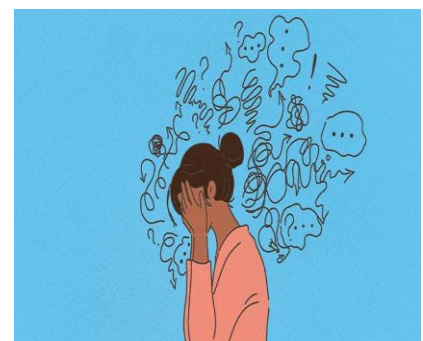
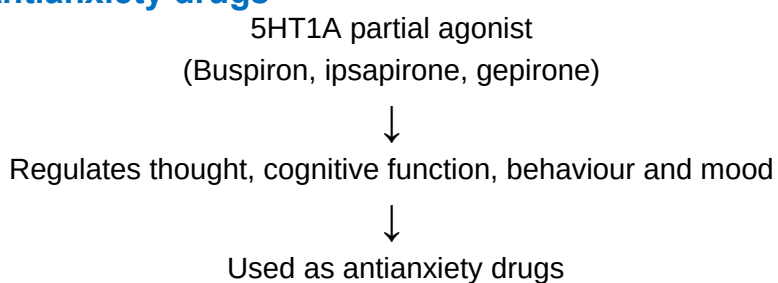
## CARCINOID SYNDROME



### Uses

1. Antianxiety drugs
2. Acute migraine attacks
3. GERD and hypomotility GI disorders

### 1. Antianxiety drugs



## 2. Acute migraine attacks

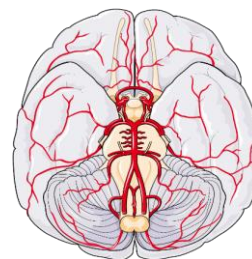
Selective 5-HT<sub>1D/1B</sub> agonists  
(Sumatriptane)



Constrict cerebral blood vessels



DOC for acute migraine attacks



## 3. GERD and hypomotility GI disorders

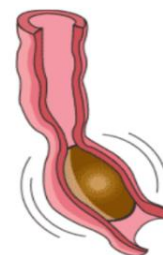
Selective 5-HT<sub>4</sub> agonists  
(Cisapride, renzapride and tegaserod)



Increases gastrointestinal motility  
(Prokinetic action)



Used in GERD and hypomotility GI disorders



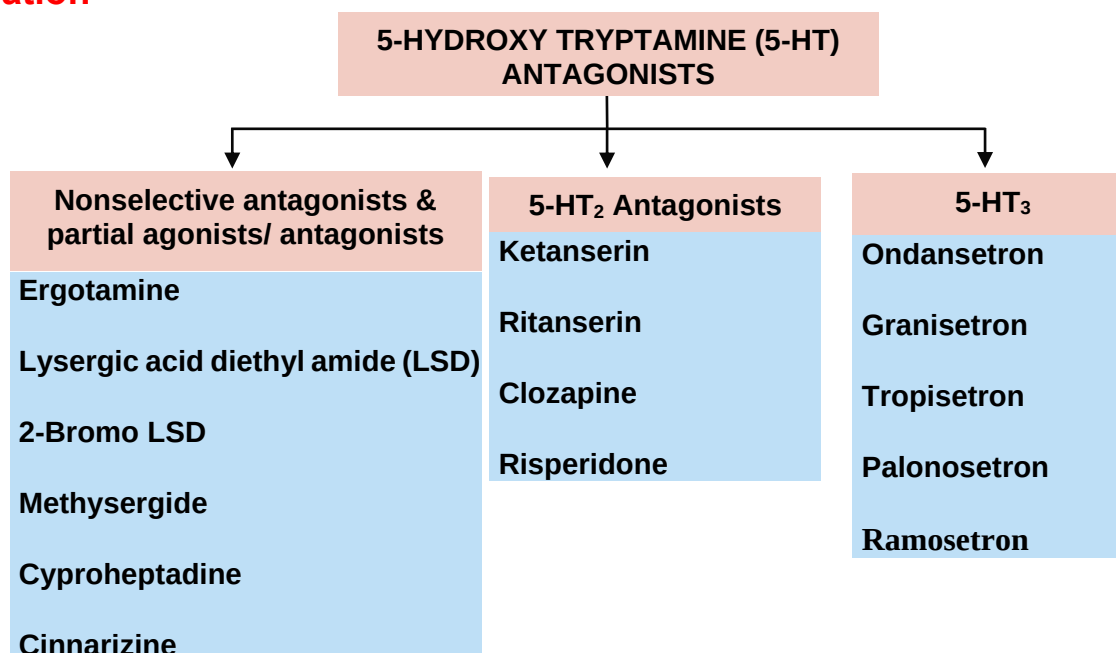
## 5HT ANTAGONIST

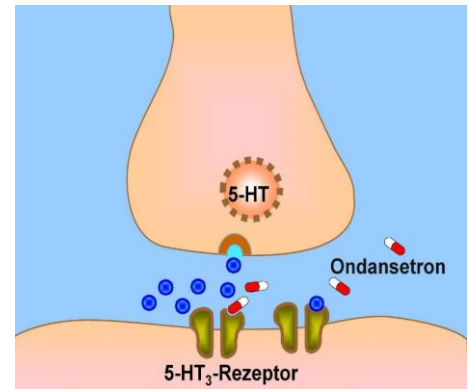
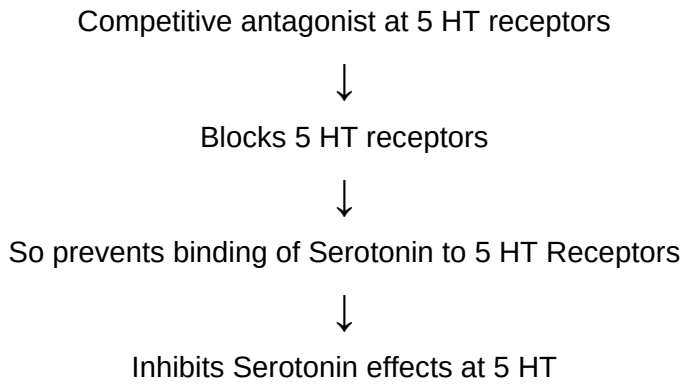
|                         | 5HT agonist | 5HT agonist |
|-------------------------|-------------|-------------|
| Definition              |             |             |
| Classification          |             |             |
| MOA                     |             |             |
| Pharmacological Actions |             |             |
| Use                     |             |             |
| Adverse effects         |             |             |
| Contraindication        |             |             |

### Definition

- 5 HT antagonists are drugs that block 5 HT receptors

### Classification

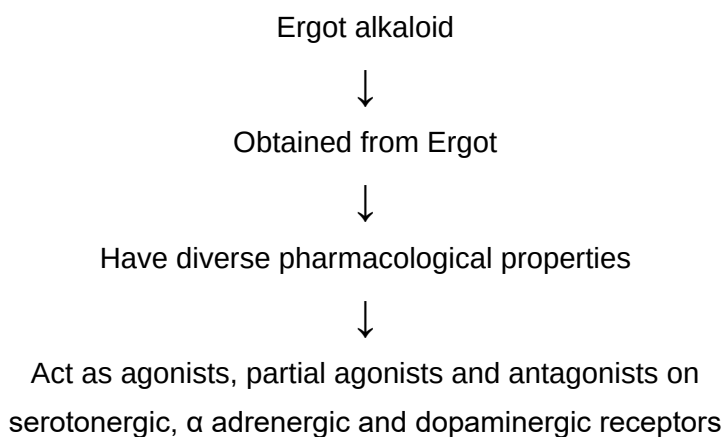


**MOA****Pharmacological Actions, Uses, Adverse effects**

- Ergot Alkaloids
- Cyproheptadine
- Methysergide
- Ketanserin
- Ondansetron

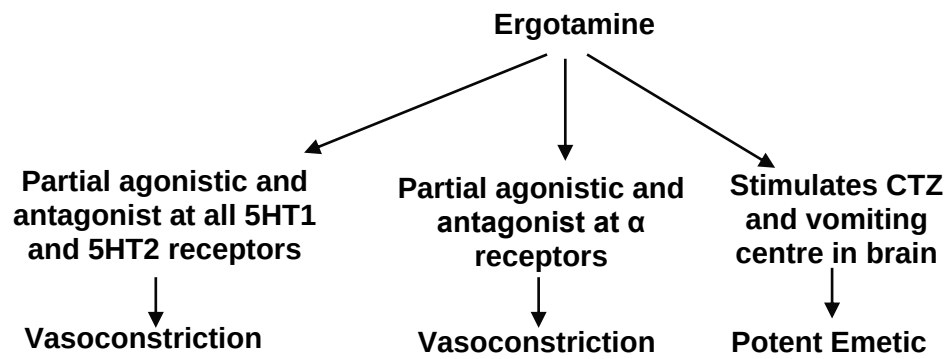
**ERGOT ALKALOIDS**

- Ergot is a fungus *Claviceps purpurea* which grows on rye, millet and some other grains.



- **Natural ergot alkaloids** → derivatives of lysergic acid.
  - (a) Ergometrine : oxytocic
  - (b) Ergotamine, Ergotamine : Partial agonistic and antagonistic at 5HT,  $\alpha$  and dopaminergic receptors
- **Semisynthetic derivatives**
  - Dihydroergotamine (DHE), Dihydroergotamine : antagonistic at  $\alpha$  receptors
    - (a) 2-Bromo- $\alpha$ -ergocryptine (Bromocriptine): dopaminergic D2 agonist
    - (b) Methysergide: anti 5-HT

## Ergotamine



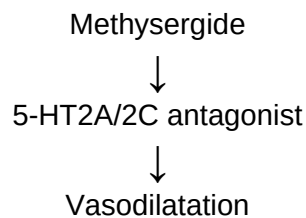
- **Use** → Treatment of acute attack of migraine.

- **Adverse effects**

1. Nausea, vomiting
2. Coronary and other vascular spasm, chest pain (due to coronary vasoconstriction). so contraindicated in coronary artery disease and ischaemic heart disease, peripheral vascular disease, hypertension, pregnancy
3. Dry gangrene of hand and feet

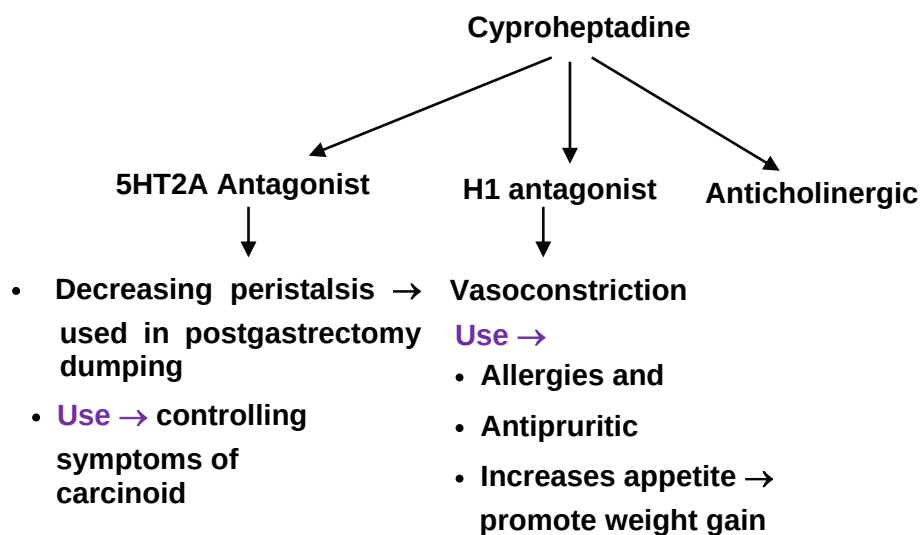


## METHYSERGIDE



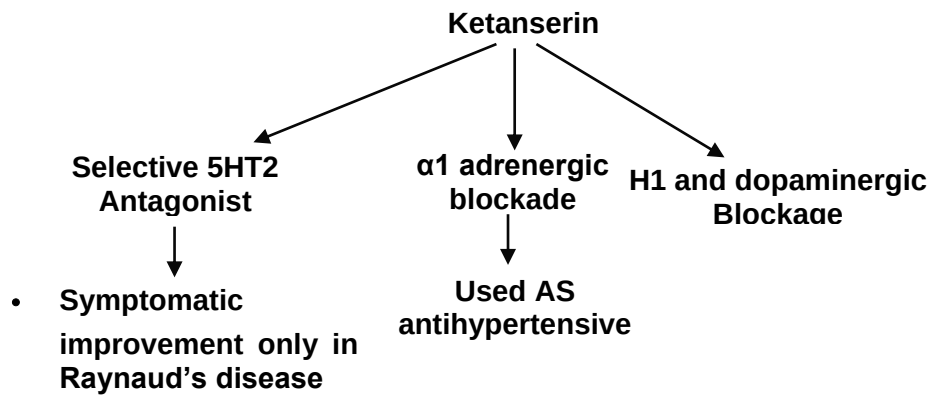
- **Use** → migraine prophylaxis, carcinoid syndrome.
- **Adverse effect** → Abdominal, pulmonary and endocardial fibrosis → Withdrawn

## CYPROHEPTADINE

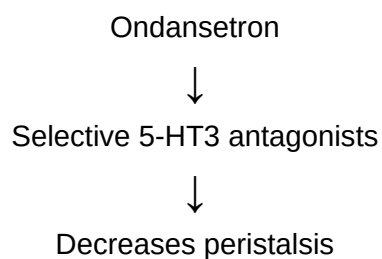


- **Adverse effects** →

1. Dry mouth
2. Drowsiness
3. Confusion



## ONDANSETRON



- **Use** → In Controlling nausea and vomiting following administration of highly emetic anticancer drugs and radiotherapy.

## MIGRAINE

### Introduction

- **Migraine** → vascular, throbbing headache that is recurring and paroxysmal in nature.
- **Laterality** → Usually unilateral but may be bilateral
- **Associated with** → nausea, vomiting and dizziness and disturbances of vision
- Complete freedom in between the attack



### Types

2 Types →

1. **Migraine with aura (classical migraine)** → Headache is preceded by visual or other neurological symptoms
2. **Migraine without aura (common migraine)**

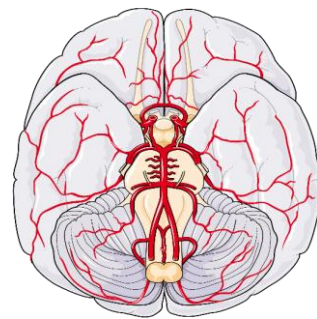
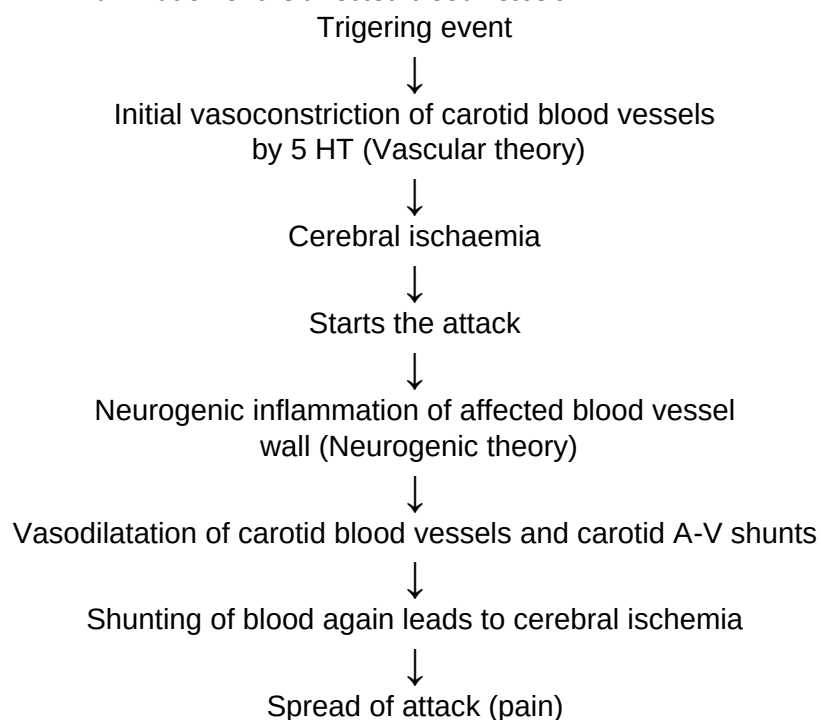
## Factors that may precipitate an attack of migraine

1. Psychological stress → depression, anger
2. Hormonal changes → menstruation, oral contraceptives
3. Glaring light
4. Missing meals
5. Excessive or reduced sleep
6. Weather changes
7. Food and beverages like chocolate, ripened cheese, vinegar, pork, alcohol, onions, citreous fruits, banana, excessive caffeine, and chicken liver.
8. Drugs like reserpine, aminophylline, hydralazine and vasodilators.

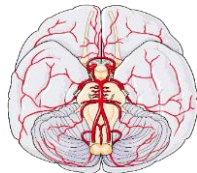
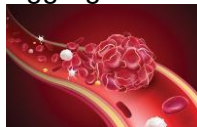
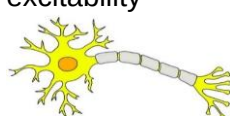
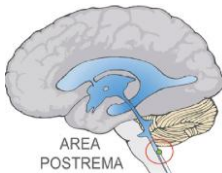
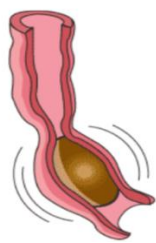


## Pathophysiology

- 5-HT is said to initiate the vasoconstrictor phase of migraine and to participate in neurogenic inflammation of the affected blood vessels.





| 5 HT <sub>1A</sub>                                                                                                   | 5 HT <sub>1D/1B</sub>                                                                                                  | 5 HT <sub>2A/C</sub>                                                                                                                                                                                                                                                                                                                                                             | 5 HT <sub>3</sub>                                                                                                      | 5 HT <sub>4</sub>                                                                                                              |
|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| <b>Brain</b> →<br>Mood Behavior<br> | <b>Cranial blood vessels</b> → VC<br> | <b>Platelets</b> →<br>Aggregation<br><br><b>Smooth muscles</b><br>→ Contraction<br><br><b>CNS</b> → Neuronal excitability<br> | <b>Area postrema</b><br>→ Emesis<br> | <b>GIT</b> → Stimulate<br>→ peristalsis<br> |

### Remember

Vasoconstriction of carotid blood



Responsible for start of attack



So 5-HT antagonist (Methysergide and cyproheptidine) ie. vasodilator is used for prophylaxis for migraine

Vasodilatation of carotid blood



Responsible for spread of attack (clinical)



So 5-HT agonist (Sumatriptan) ie. vasoconstrictor is used for prophylaxis for migraine

### Clinical classification of Migraine

#### • Mild migraine

- Fewer than one attack per month
- Throbbing but tolerable headache
- Lasting upto 8 hours
- Does not incapacitate the individual



#### • Moderate migraine

- One or more attacks occur per month
- Throbbing headache is more intense
- Lasts for 6–24 hours, nausea/vomiting and other features are more prominent
- Patient is functionally impaired.

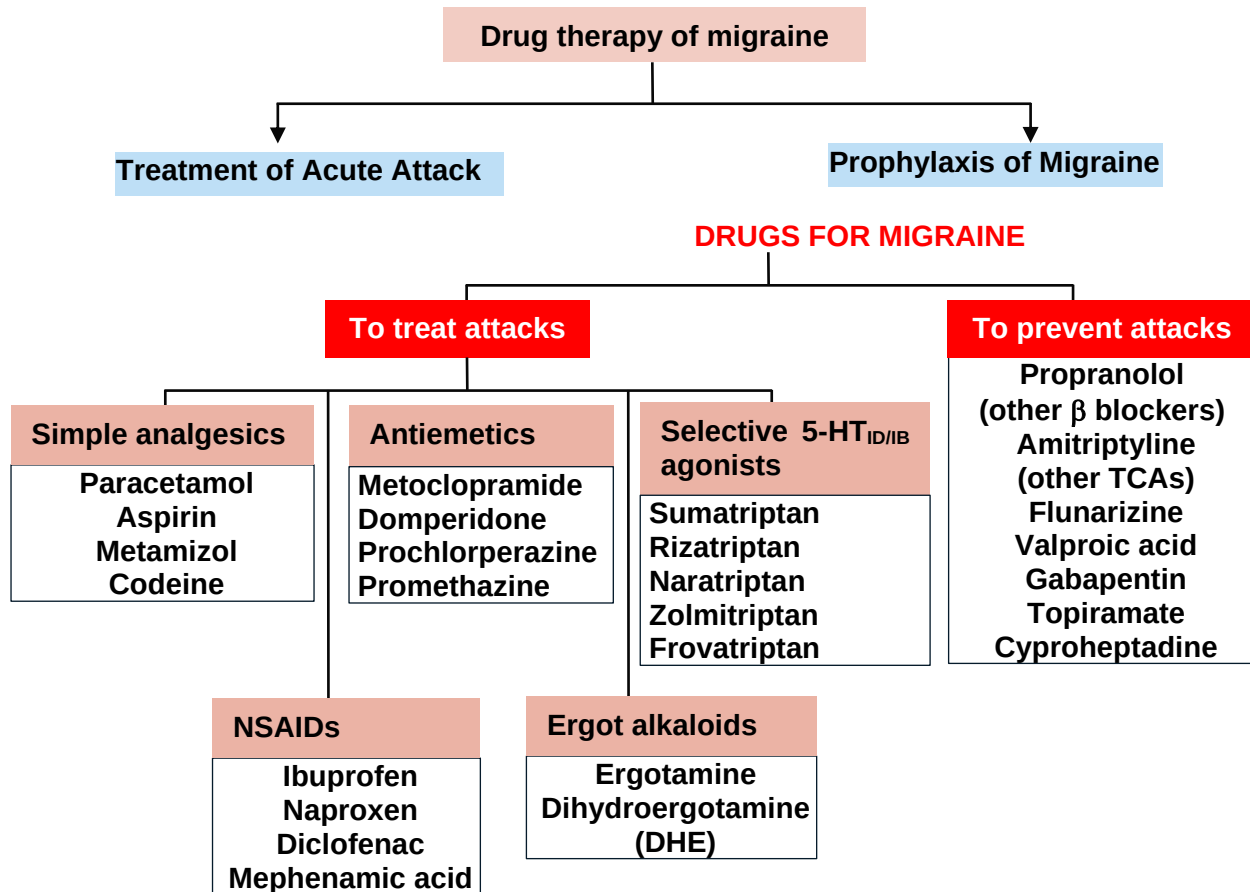


#### • Severe migraine

- 2–3 or more attacks per month
- Severe throbbing headache
- Lasting 12–48 hours, often accompanied by vertigo, vomiting and other symptoms;
- Grossly incapacitated during the attack.



## DRUG THERAPY OF MIGRAINE



## TREATMENT OF ACUTE ATTACK

| Severity        | Drug therapy                                                                                                                                                                                                                                                                                          |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Mild</b>     | 1. Simple analgesics<br>2. NSAIDs or their combinations<br>3. Antiemetic                                                                                                                                                                                                                              |
| <b>Moderate</b> | 1. NSAIDs combinations<br>2. Triptan/Ergot alkaloids<br>3. Antiemetic                                                                                                                                                                                                                                 |
| <b>Severe</b>   | 1. Triptan/Ergot alkaloid (+ antiemetic)<br><br>+ Prophylaxis <ul style="list-style-type: none"> <li>• Propranolol/other B blockers</li> <li>• Amitriptyline/other tricyclic antidepressants</li> <li>• Flunarizine/other Ca<sup>2+</sup> channel blockers</li> <li>• Valproate/topiramate</li> </ul> |

### A) Mild migraine

1. Simple analgesics
2. Nonsteroidal antiinflammatory drugs (NSAIDs)
3. Antiemetics

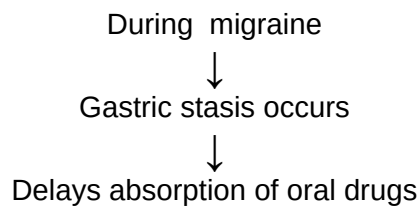
## 1. Simple analgesics

- Paracetamol (0.5– 1 g)
- Aspirin (300–600 mg)
  - Taken at first indication of an attack and repeated 4–6 hourly abort and suppress most mild attacks.

## 2. Nonsteroidal antiinflammatory drugs (NSAIDs)

- Ibuprofen (400–800 mg 8 hourly),
- Naproxen (500 mg followed by 250 mg 8 hourly),
- Diclofenac (50 mg 8 hourly),
- Mephenamic acid (500 mg 8 hourly),
- Indomethacin (50 mg 6–8 hourly)
  - Either alone or combined with paracetamol/codeine/ diazepam

## 3. Antiemetics

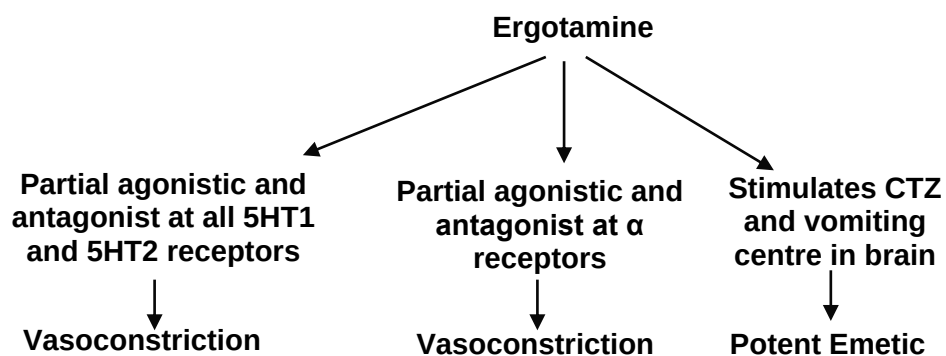


- Metoclopramide (10 mg oral/i.m.)
- Domperidone (10–20 mg oral)
- Prochlorperazine (10–25 mg oral/i.m.)
- Diphenhydramine or promethazine exert sedative as well as antiemetic action.

## B) Mild migraine

1. NSAIDs
2. Specific antimigraine drug, i.e. a triptan or an ergot preparation.
3. Antiemetics

## Ergotamine



## Pharmacokinetics

- Given early in attack, relief is often dramatic and lower doses suffice,
- But when pain has become severe—larger doses are needed and control may be achieved only after few hours.
- Route → Oral/sublingual route is preferred,
- Dose → 1 mg is given at half hour intervals till relief is obtained or a total of 6 mg is given.
- Erratic oral absorption → Caffeine 100 mg taken with ergotamine enhances its absorption from oral and rectal routes and adds to cranial vasoconstricting action
- **Use** → Treatment of acute attack of migraine.

### Adverse effects

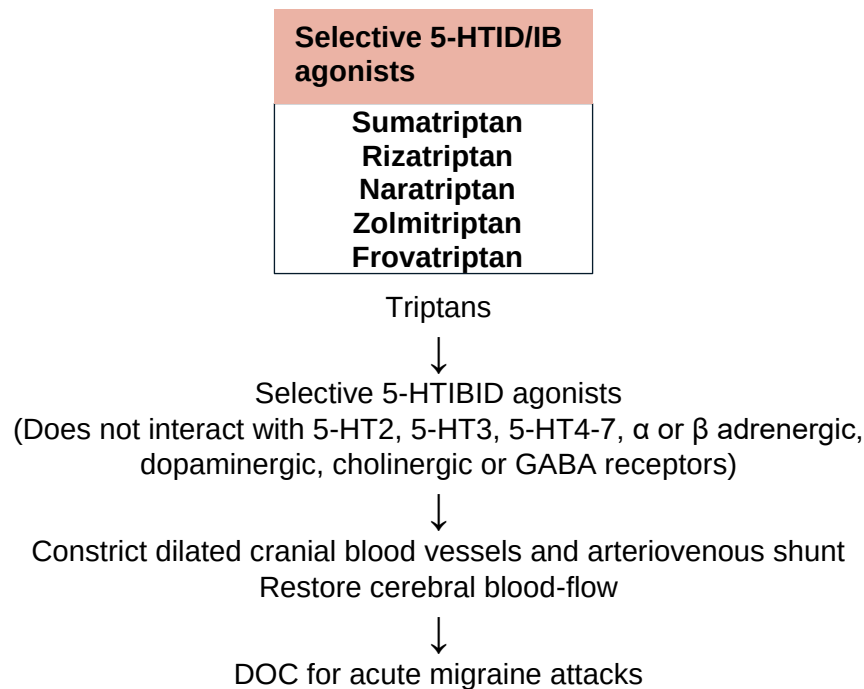
1. Nausea, vomiting
2. Coronary and other vascular spasm, chest pain (due to coronary vasoconstriction) .so contraindicated in coronary artery disease and ischaemic heart disease, peripheral vascular disease, hypertension, pregnancy
3. Dry gangrene of hand and feet



### Contraindications

- Ischaemic heart disease
- Coronary artery disease
- Hypertension
  - Because of erratic oral absorption, frequent side effects, especially nausea and vomiting, and availability of triptans → ergot preparations are rarely used now (except for considerations of cost or when triptans fail)

### Triptans



### Pharmacokinetics

- All triptans are taken by oral routes (tablets).
- Sumatriptan and Zolmitriptan can also be used by nasal route
- Sumatriptan is also used as suppository and subcutaneous injection.
- Sumatriptan is absorbed rapidly and completely after s.c. injection.
- Oral bioavailability averages only 15%.
- Elimination  $t_{1/2}$  is ~2 hours.

### Use

- Acute attack of migraine

**Adverse effects**

- Tightness in head and chest,
- Feeling of heat and other paresthesias in limbs,
- Dizziness, weakness
- Bradycardia,
- Coronary vasospasm and risk of myocardial infarction

**Contraindications**

- Ischaemic heart disease
- Coronary artery disease
- Hypertension

**Triptans**

- **Sumatriptan** → shortest acting triptan
- **Provatriptan** → longest acting triptan
- **Rizatriptan** → fastest acting triptan
- **Provatriptan** → slowest acting triptan
- **Naratriptan** → most potent Sumatriptan is least potent
- **Almotriptan** → maximum oral bioavailability
- **Sumatriptan** → minimum oral bioavailability

|                  | Loop Diuretics | Thiazides | Carbonic Anhydrase Inhibitor | Potassium Sparing Diuretics | Osmotic Diuretics |
|------------------|----------------|-----------|------------------------------|-----------------------------|-------------------|
| Introduction     |                |           |                              |                             |                   |
| Drugs            |                |           |                              |                             |                   |
| Site of action   |                |           |                              |                             |                   |
| MOA              |                |           |                              |                             |                   |
| Pharmacokinetics |                |           |                              |                             |                   |
| Uses             |                |           |                              |                             |                   |
| Adverse effect   |                |           |                              |                             |                   |

**Remember**

- Sumatriptan and ergotamine should not be administered within 24 hours of each other

**C) Mild migraine**

- Analgesics/NSAIDs do not afford adequate relief
- DOC → Specific antimigraine drug, i.e. a triptan or an ergot preparation.

**PROPHYLAXIS OF MIGRAINE**

- Regular medication to reduce the frequency and/or severity of attacks is recommended for moderate-to-severe migraine when 2–3 or more attacks occur per month.
1. **B-blockers:** Pure blocker without intrinsic activity such as propranolol that prevents catecholamine induced vasodilatation in brain vessels.
  2. **Calcium channel blocker:** Flunarizine, which is claimed to improve cerebral blood flow and thereby improve oxygenation
  3. **Tricyclic antidepressants:** amitriptyline → antimigraine effect is independent of antidepressant property
  4. **Anticonvulsants:** Valproic acid and gabapentin → prophylactic effect in migraine.
  5. **5-HT antagonists:** prophylactic effect of methysergide and cyproheptadine is less impressive than  $\beta$  blockers. They are seldom used now for migraine.

## Remember

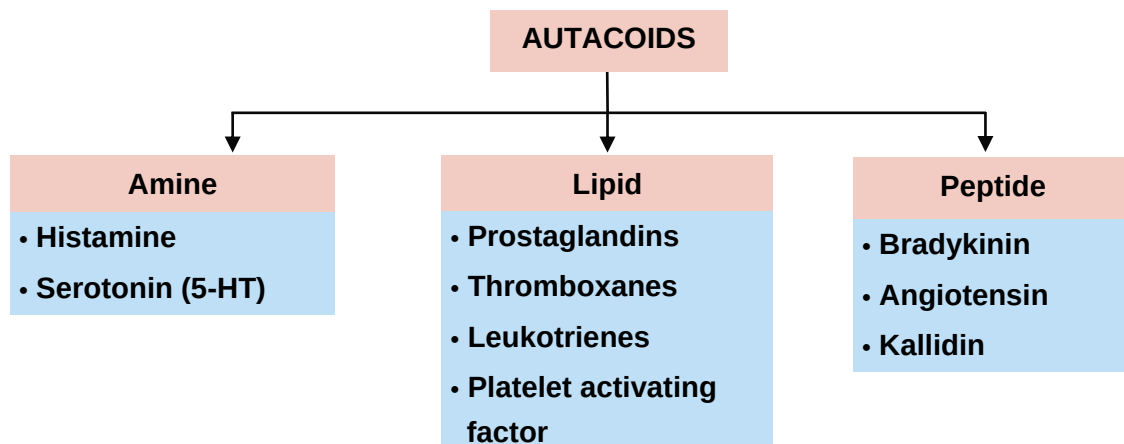
- **Sumatriptan** → DOC for aborting acute attack of migraine.
- **β-blocker (Propranolol)** → DOC for prophylaxis of migraine attack.

# PROSTAGLANDINS (PGs), THROMBOXANES (TXs) LEUKOTRIENES (LTs)

|                         | PGs, TXs, LTs | NSAIDS |
|-------------------------|---------------|--------|
| Introduction            |               |        |
| Classification          |               |        |
| MOA                     |               |        |
| Pharmacological Actions |               |        |
| Use                     |               |        |
| Adverse effects         |               |        |
| Contraindication        |               |        |

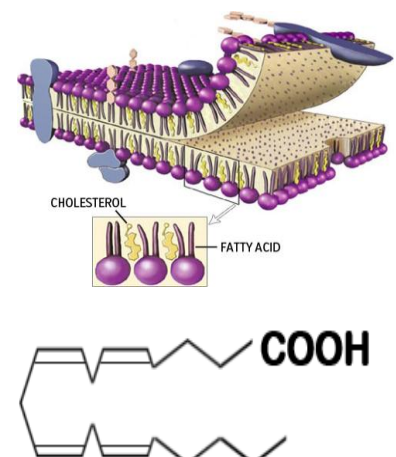
## Introduction

- Lipid derived autacoids

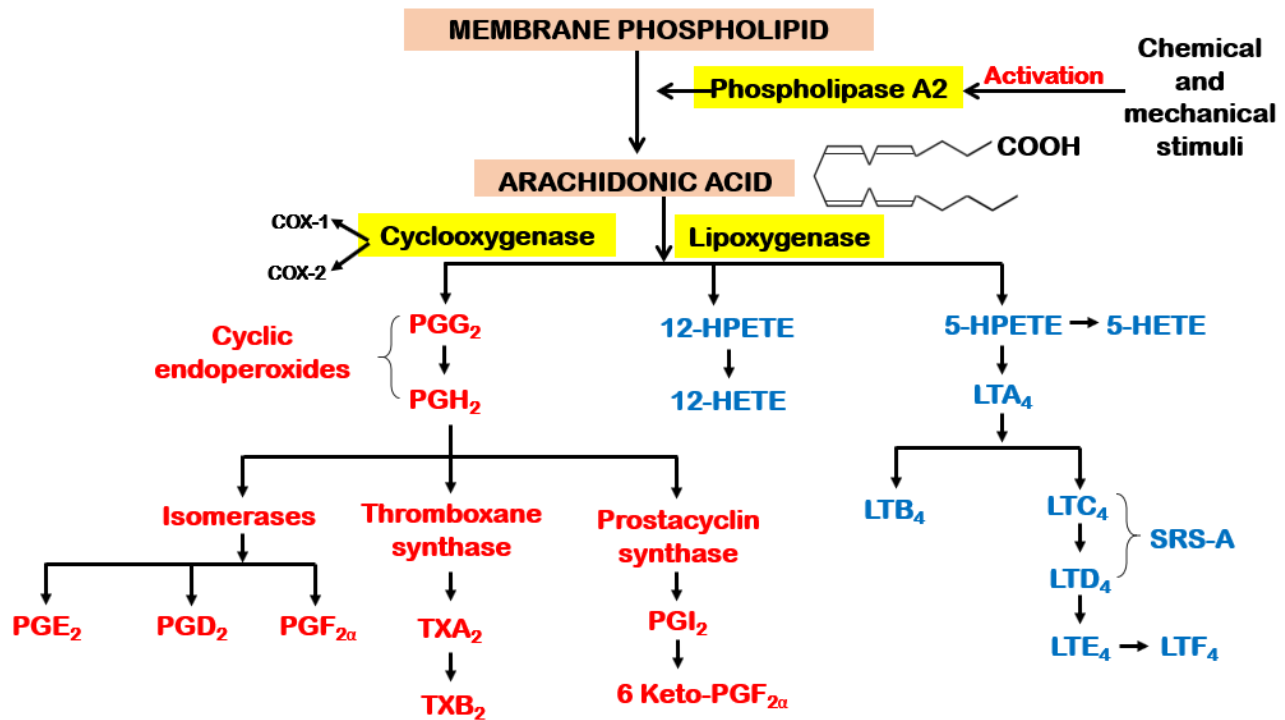


## Introduction

PGs, TXs, LTs  
↓  
Biologically active derivatives of 20 carbon atom  
polyunsaturated essential fatty acids (PUFA)  
released from cell membrane phospholipids  
↓  
Arachidonic acid  
(5,8,11,14 eicosa tetraenoic acid)

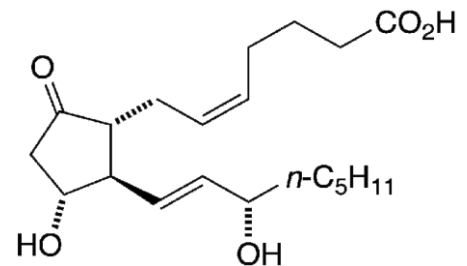






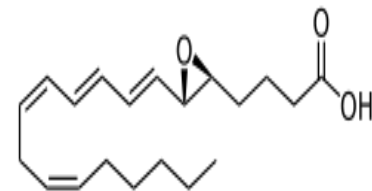
## 1. Cyclooxygenase (COX) pathway

- Produces ring structure compounds → PGs, TXs
- 2 of the 4 double bonds of arachidonic acid get saturated in process of cyclization, leaving 2 double bonds in side chain
- PGs and TX of biological importance → PGE<sub>2</sub>, PGF<sub>2α</sub>, PGI<sub>2</sub>, TXA<sub>2</sub>.



## 2. Lipoxygenase (LOX)

- Produces open chain compounds → LTs
- No cyclization or reduction of double bonds occurs
- LTs of biological importance → LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>



## COX isoforms

COX exist in 2 isoforms →

### 1. COX-1 →

- Constitutive enzyme
- Normally present in Cell
- Active in basal state
- Products of COX-1 → participate in physiological (house keeping) functions

### 2. COX-2 →

- Inducible enzyme
- Normally present in insignificant amounts
- Inducible by cytokines, growth factors and other stimuli during inflammatory response.
- Products of COX-2 → participate in Inflammation

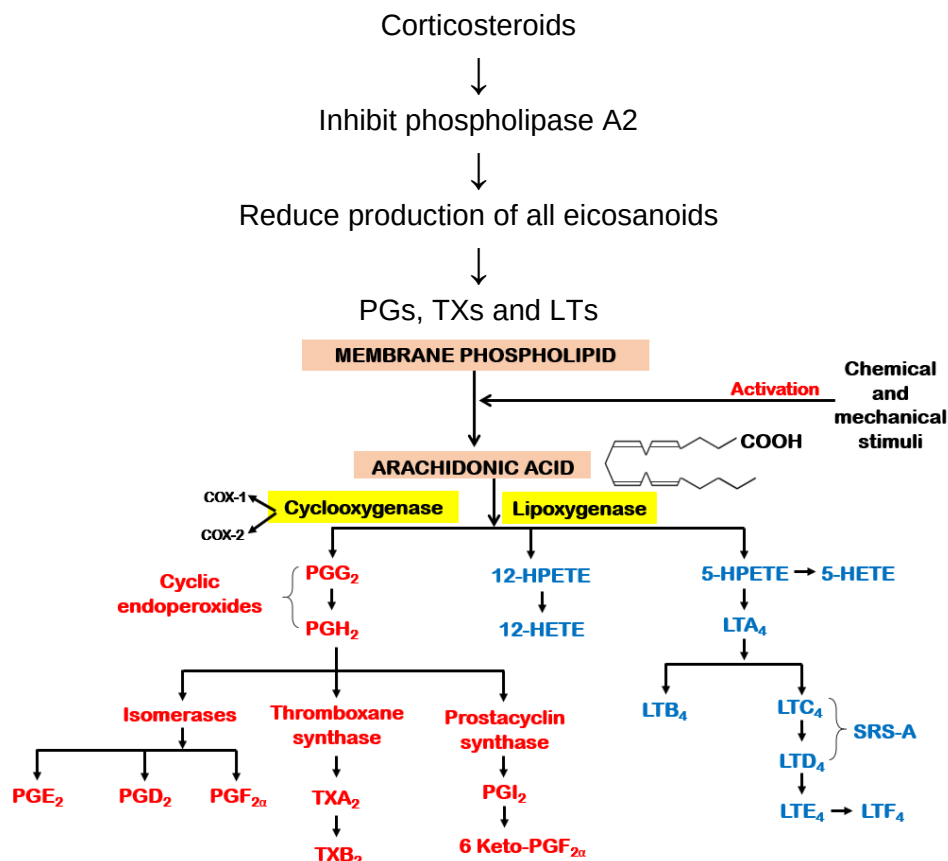
## Remember

- There are no preformed stores of PGs and LTs.
- They are synthesized locally
- Rate of synthesis is governed by rate of release of arachidonic acid from membrane lipids in response to appropriate stimuli.
- There are many series of PGs and thromboxanes (TXs) designated → A, B, C....I → depending on the ring structure and the substituents on it.
- Each series has members with subscript 1, 2, 3 → indicating number of double bonds in the side chains
- All tissues have COX → can form PGG<sub>2</sub> and PGH<sub>2</sub> which are unstable compounds.
- PGE<sub>2</sub> and PGF<sub>2α</sub> → primary prostaglandins
- Name based on separation procedure:
  - PGE partitioned into Ether
  - PGF into phosphate [Fosfat in Swedish] buffer
- PGs A, B and C are not found in the body → they are artifacts formed during extraction procedures.

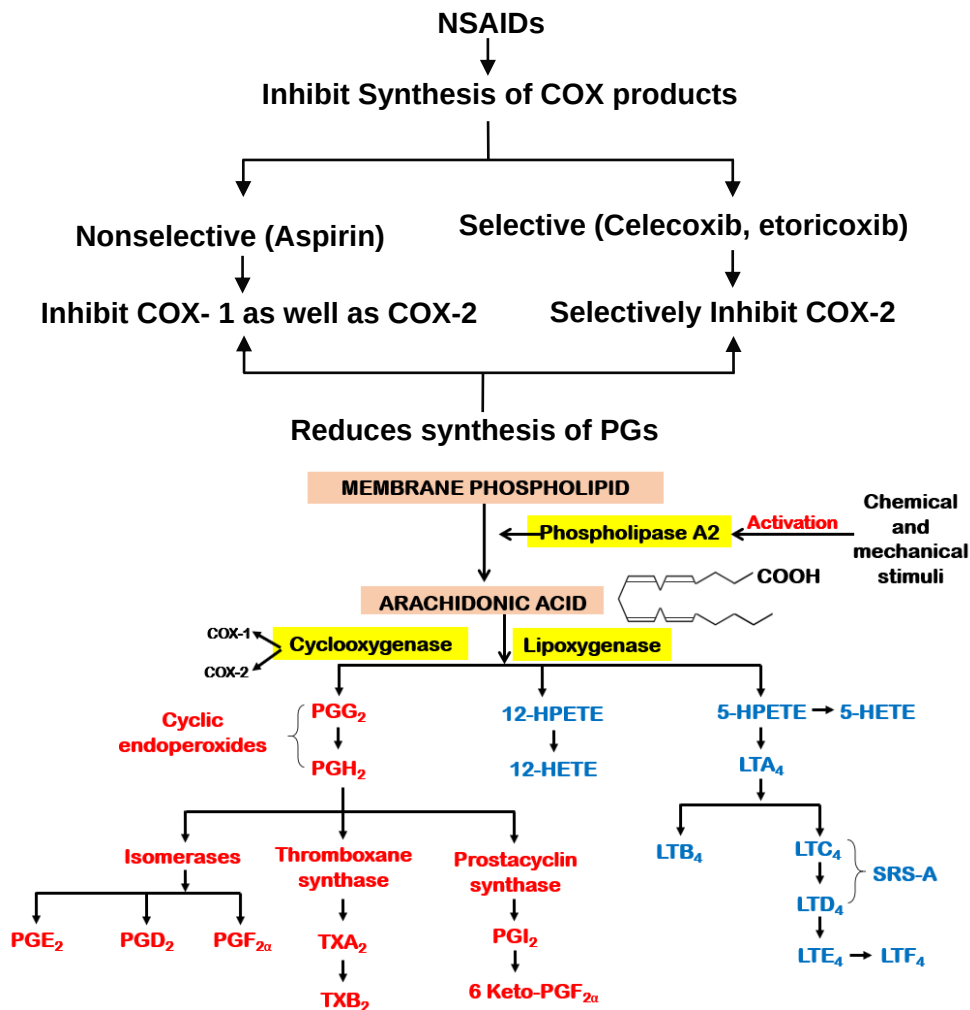
## INHIBITION OF SYNTHESIS

1. Corticosteroids
2. Nonsteroidal antiinflammatory drugs (NSAIDs)
3. Zileuton
4. Zafirlukast, montelukast, iralukast
5. Dazoxiben and piroxicam
6. Daltroban and sulotroban
7. Ridogrel

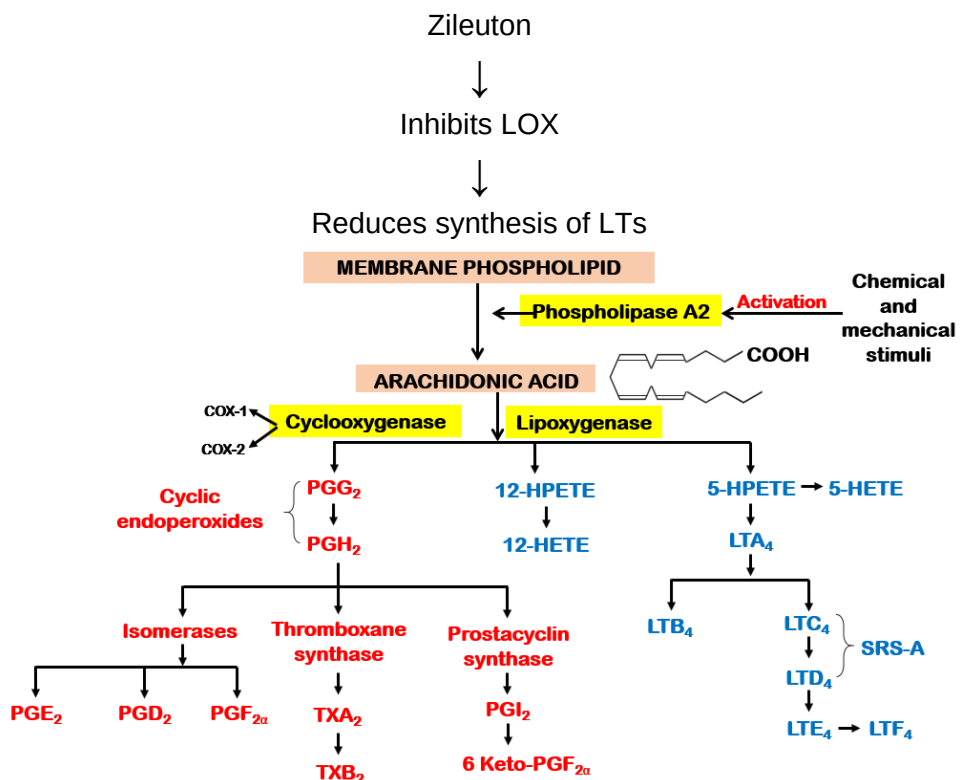
### 1. Corticosteroids



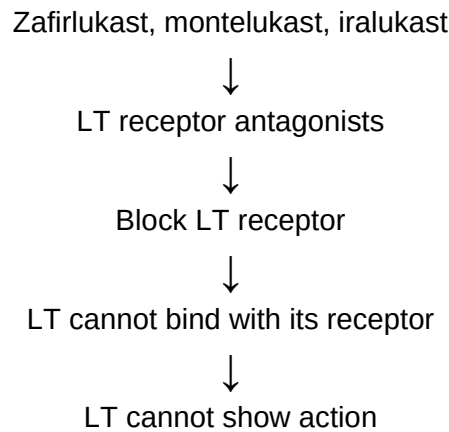
## 2. NSAIDs



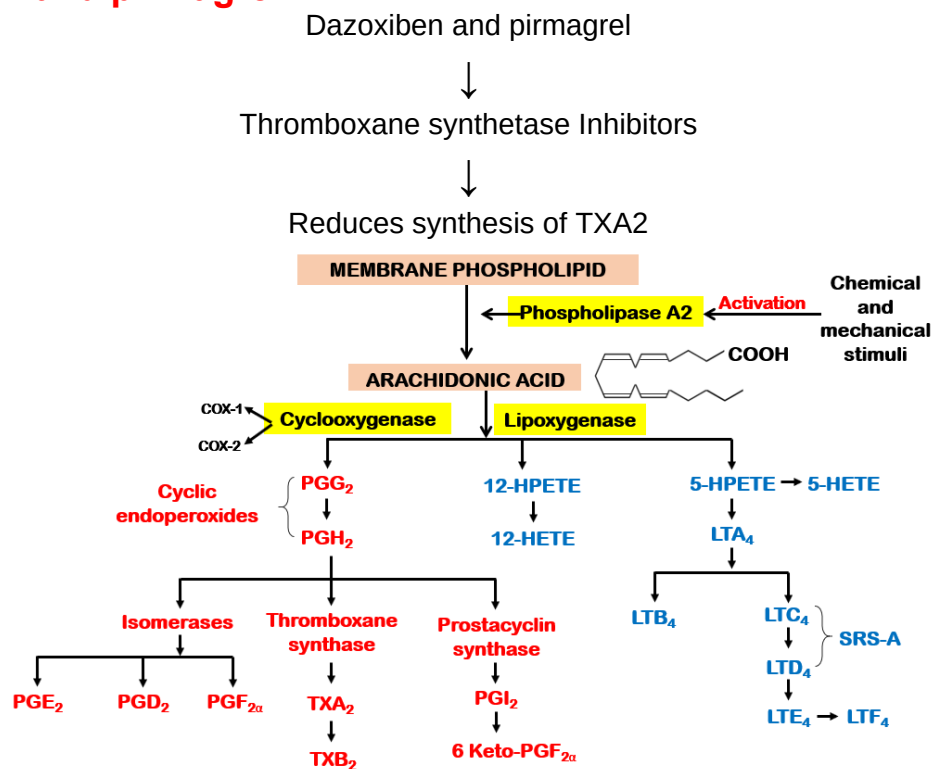
## 3. Zileuton



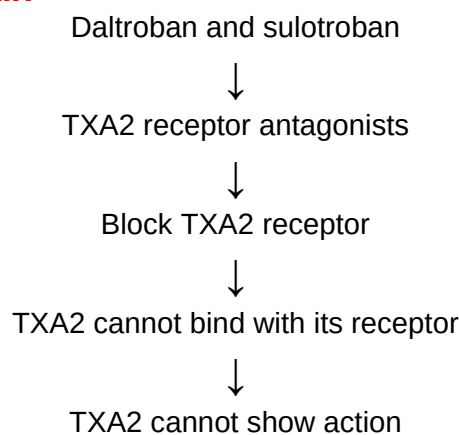
#### 4. Zafirlukast, montelukast, iralukast



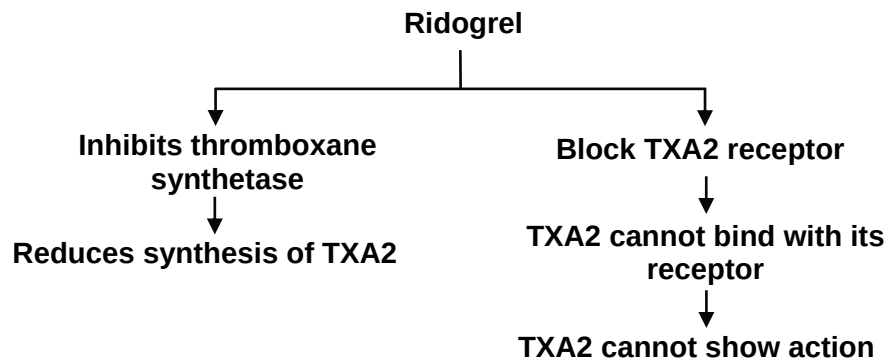
#### 5. Dazoxiben and pirmagrel



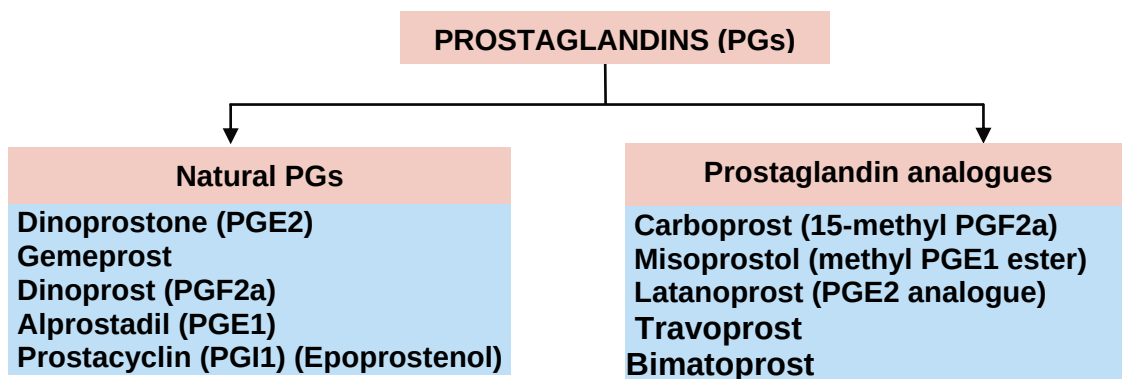
#### 6. Daltroban and sultraban



## 7. Ridogrel



## Classification



## Pharmacological Actions

### Prostaglandins (PGs) and Thromboxane A<sub>2</sub>

1. Blood vessels
2. Heart
3. Platelets
4. Uterus
5. Bronchi
6. Stomach
7. Kidney
8. CNS
9. Afferent nerves
10. Eye
11. Inflammatory

### Leukotrienes (LTs)

1. Blood Vessels
2. Afferent nerves
3. Smooth muscles
4. Inflammation

## PROSTAGLANDINS (PGS) AND THROMBOXANE A<sub>2</sub>

| Organ              | Prostaglandin E <sub>2</sub> (PGE <sub>2</sub> )           | Prostaglandin F <sub>2α</sub> (PGF <sub>2α</sub> )      | Prostacyclin I <sub>2</sub> (PGI <sub>2</sub> ) | Thromboxane A <sub>2</sub> (TXA <sub>2</sub> ) |
|--------------------|------------------------------------------------------------|---------------------------------------------------------|-------------------------------------------------|------------------------------------------------|
| 1. Blood vessels   | Vasodilatation, ↓ BP                                       | Larger veins constrict, little effect on BP             | Vasodilatation (marked), ↓↓ BP                  | Vasoconstriction                               |
| 2. Heart           | Weak inotropic, reflex cardiac stimulation                 | Weak inotropic                                          | -                                               | -                                              |
| 3. Platelets       | Variable effect                                            | -                                                       | Antiaggregatory                                 | Aggregation                                    |
| 4. Uterus          | Contraction (in vivo), softening of cervix                 | Contraction (in vivo and in vitro), softening of cervix | -                                               | -                                              |
| 5. Bronchi         | Dilatation                                                 | Constriction                                            | Dilatation (mild)                               | Constriction                                   |
| 6. Stomach         | ↓ acid secretion, ↑ mucus production                       | -                                                       | ↓ acid secretion, mucosal vasodilatation        | -                                              |
| 7. Kidney          | Natriuresis, ↓ Cl reabsorption, inhibit ADH, renin release | -                                                       | Natriuresis, vasodilatation, renin release      | Vasoconstriction                               |
| 8. CNS             | Pyrogenic                                                  |                                                         |                                                 |                                                |
| 9. Afferent nerves | Sensitize to noxious stimuli → tenderness                  | -                                                       | Same as PGE <sub>2</sub>                        | -                                              |
| 10. Eye            |                                                            | ↑ uveoscleral & trabecular outflow → Lowers IOT         | -                                               | -                                              |
| 11. Inflammation   |                                                            | -                                                       | -                                               | -                                              |

### 1. Simple analgesics

PGs (generated mainly by COX-2)

↓  
Vasodilatation  
Exudation at site of inflammation

**PGE<sub>2</sub>**

↓  
Continuously produced locally in ductus arteriosus by COX-2 during foetal

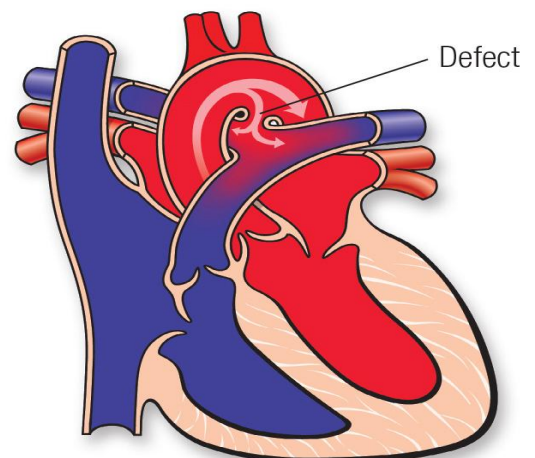
↓  
Vasodilatation

↓  
Keeps ductus arteriosus patent

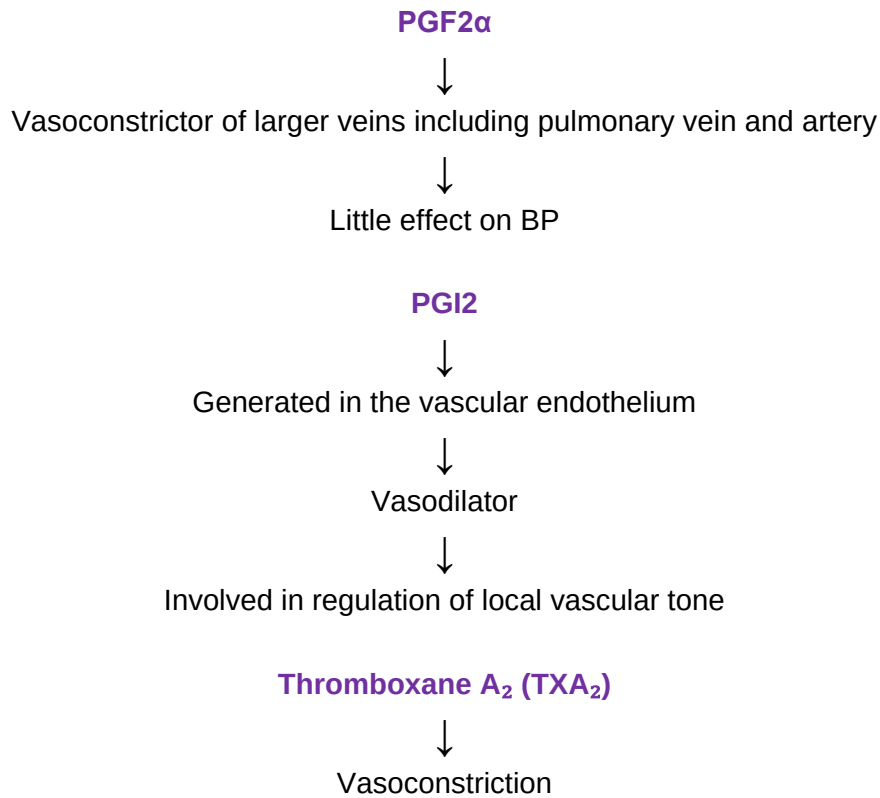
↓  
At birth its synthesis stops

↓  
Closure of ductus arteriosus occurs

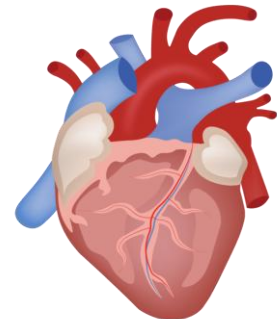
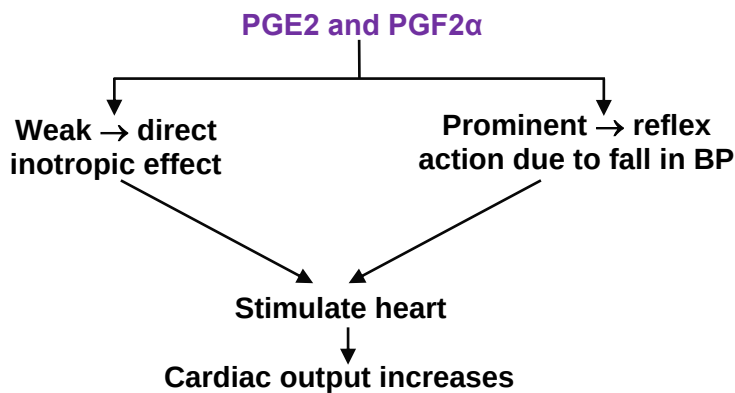
- **Aspirin and indomethacin** → induce closure when it fails to occur spontaneously.



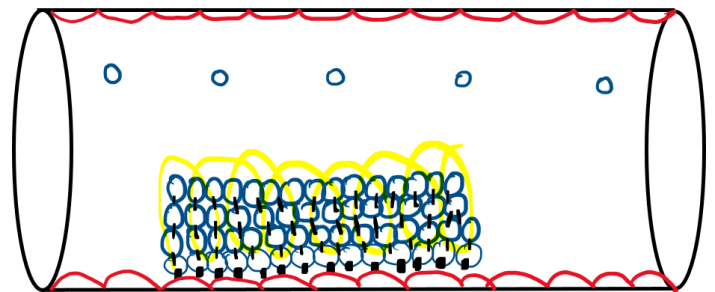
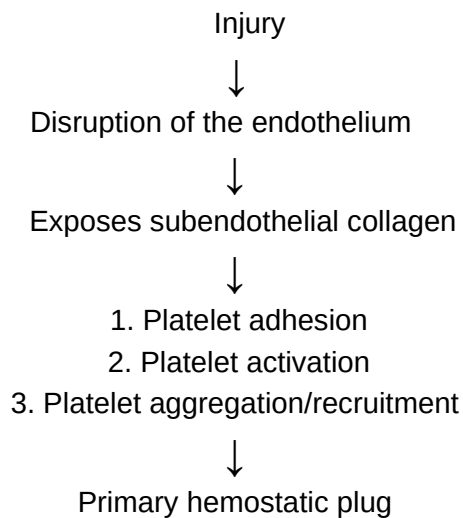




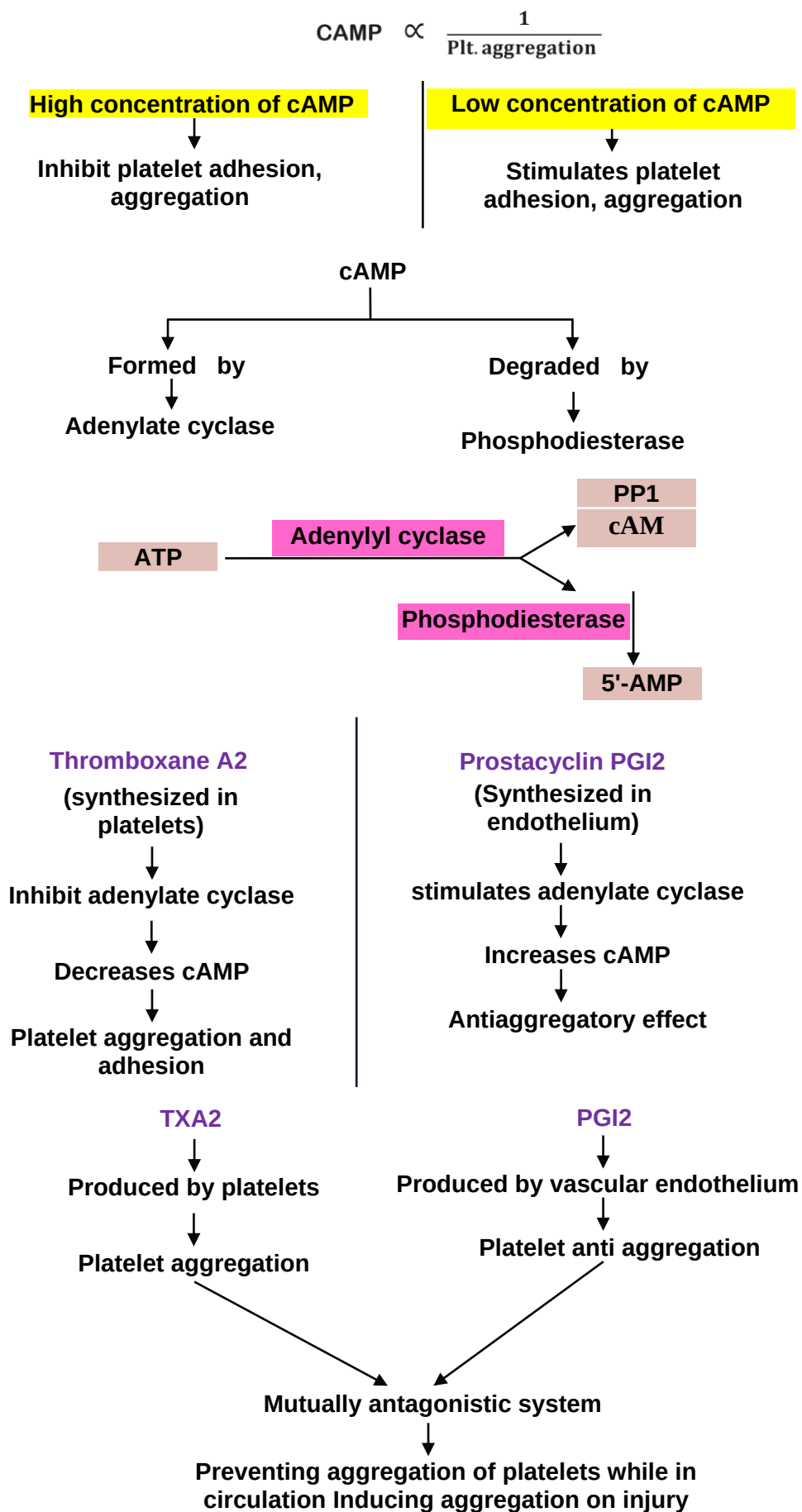
## 2. Heart

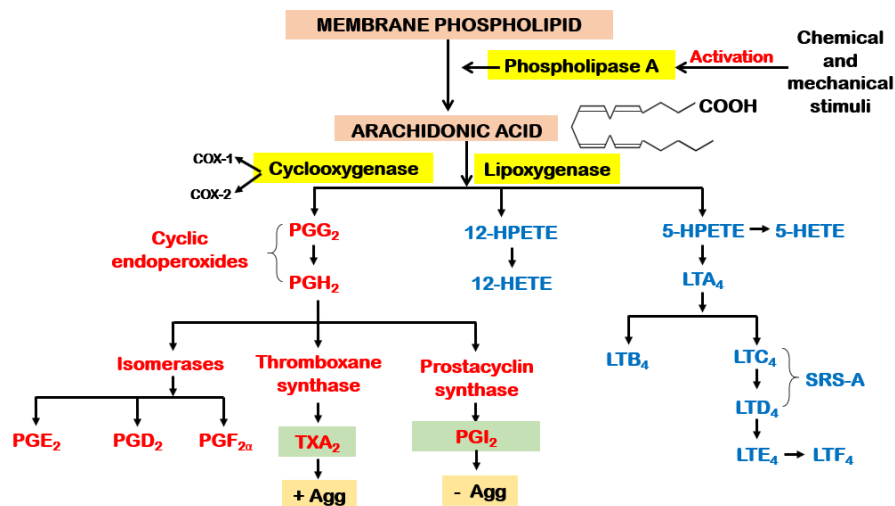


## 3. Platelets

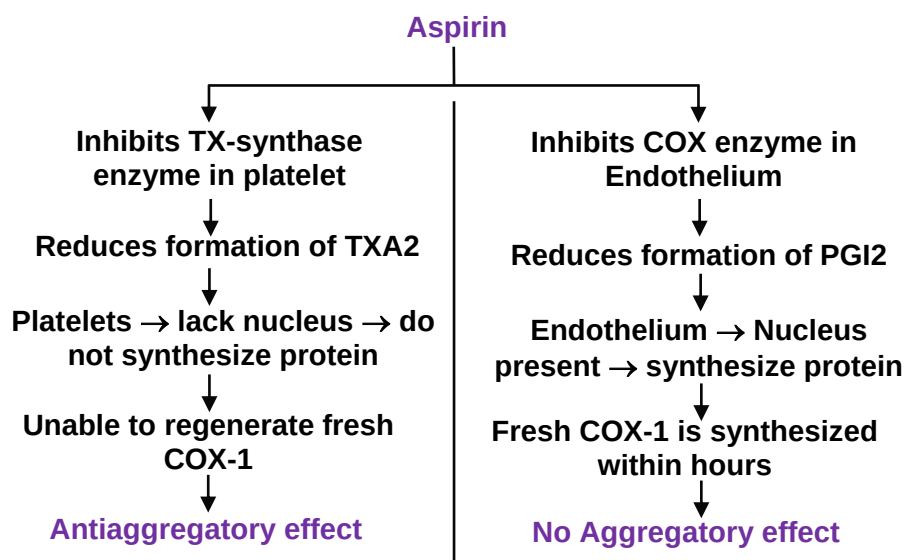


## Platelet mechanism

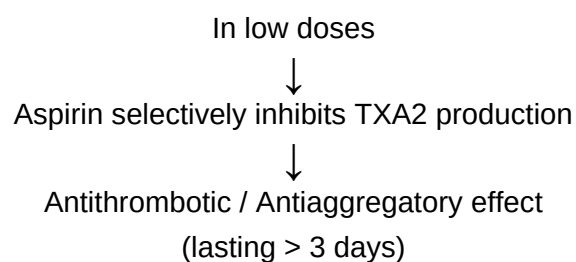




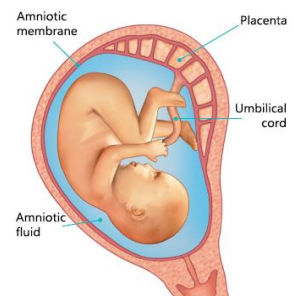
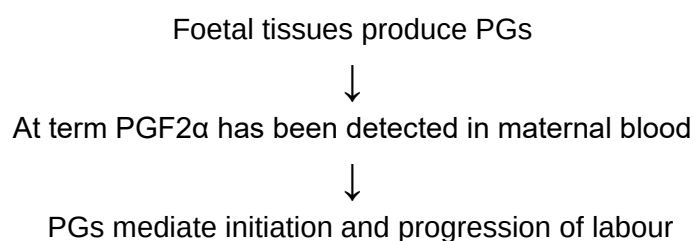
## What does Aspirin do?



## Summary

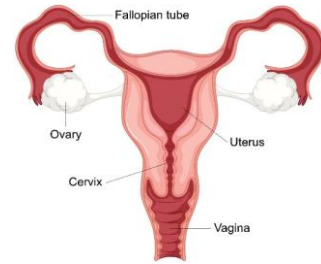
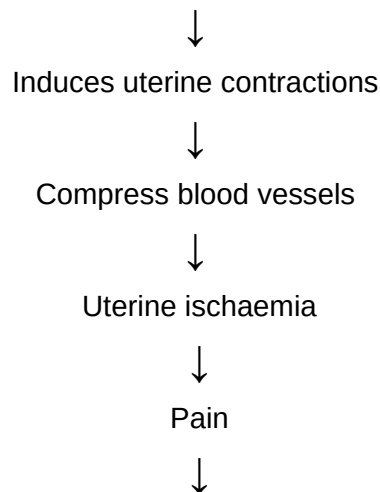


## 4. Uterus



- **Aspirin and indomethacin** → induce closure when it fails to occur spontaneously.

Increased PG synthesis by endometrium during menstruation

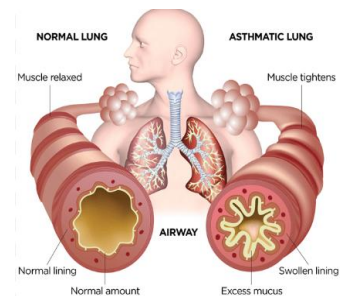


Dysmenorrhoea

- **Aspirin** → highly effective in relieving dysmenorrhoea

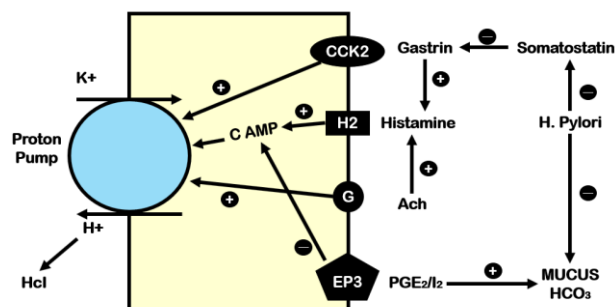
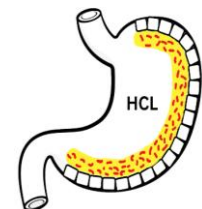
## 5. Hypertension

- **Constrictor PGs** →  $\text{PGF}_2\alpha$ ,  $\text{TXA}_2$  and  $\text{LTs}$
- **Dilator PGs** →  $\text{PGE}_2$ ,  $\text{PGI}_2$
- **Aspirin** → induce asthma → by diverting arachidonic acid to produce excess  $\text{LTC}_4$  and  $\text{D}_4$ .



## 6. Stomach

- PGs are Antiulcerogenic
- **Prostaglandin E2** →
  - Inhibits secretion of gastric acid
  - Enhances mucus secretion to provide a protection to GI mucosa.
  - Improving gastric mucosal blood flow
- **Aspirin** → causes peptic ulcer

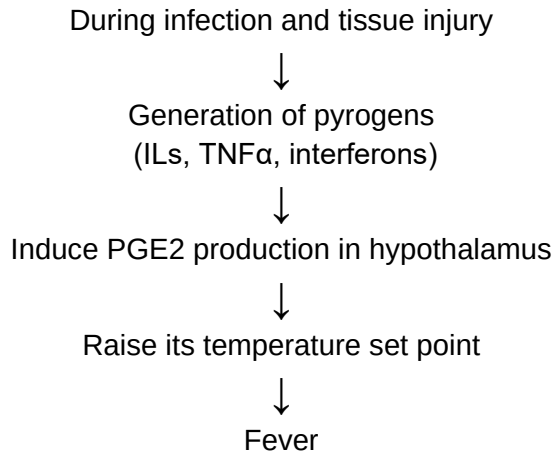


## 7. Kidney

- **PGE2 and PGI2** →
  - Intrarenal regulators of blood flow
  - Tubular reabsorption of Na in kidney → Natriuresis
- **NSAIDs** → tend to retain salt and water.

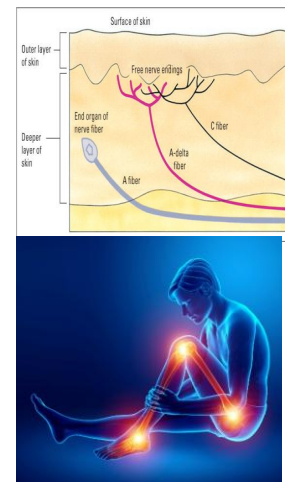
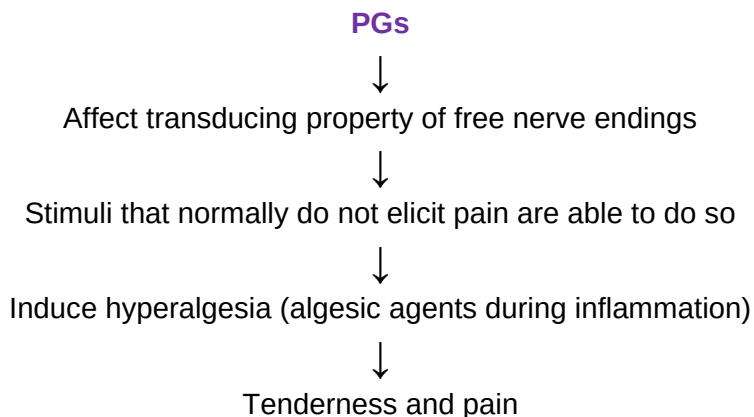


## 8. CNS



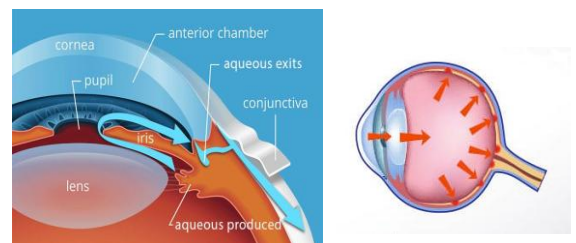
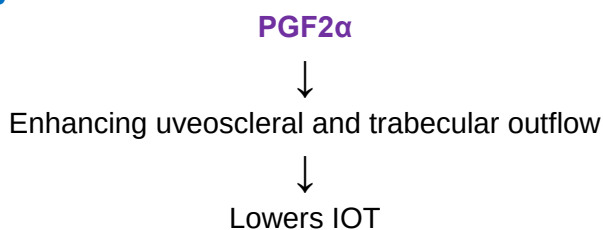
- **Aspirin** → Antipyretic

## 9. Afferent nerves



- **NSAIDs** → Inhibition of PG synthesis → Analgesic

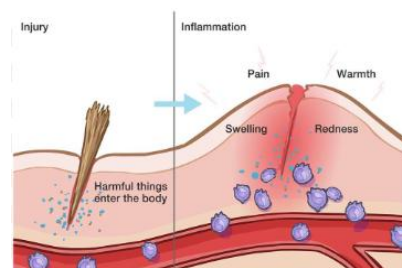
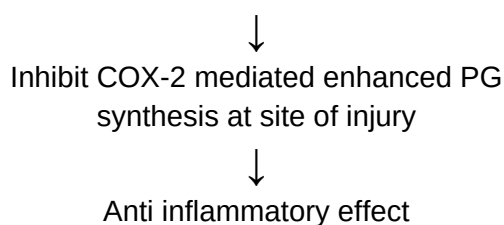
## 10. Eye



- **Latanoprost ( $\text{PGF}_2\alpha$  analogue)** → first line drugs in wide angle glaucoma

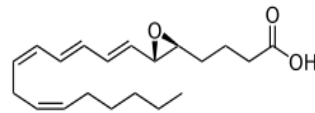
## 11. Inflammation

- **PGs** → one of the mediators of inflammation
- **COX 2 products** → produced during inflammation  
**NSAIDs (Specially COX-2 inhibitors)**

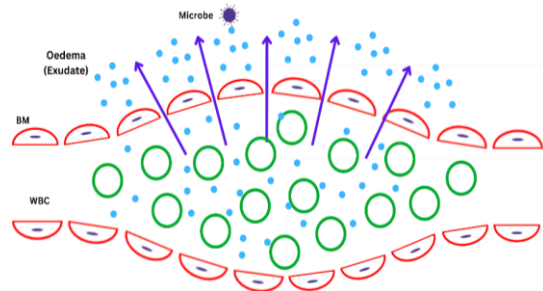
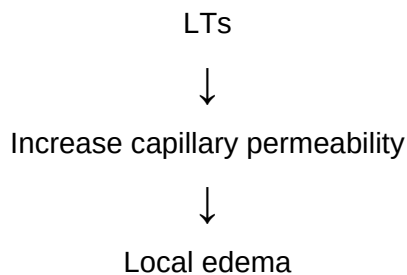


# LEUKOTRIENES (LTS)

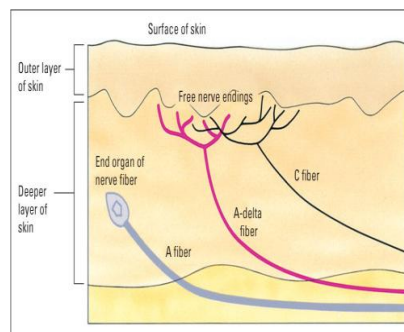
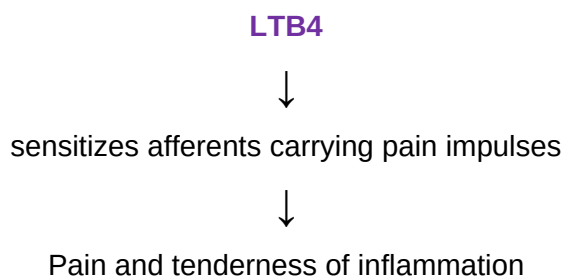
- Leukotrienes →
  - Isolated for the first time from leukocytes → leuko
  - Have 3 conjugated double bonds → triene



## 1. Blood Vessels

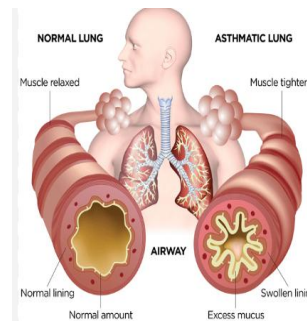


## 2. Afferent nerves



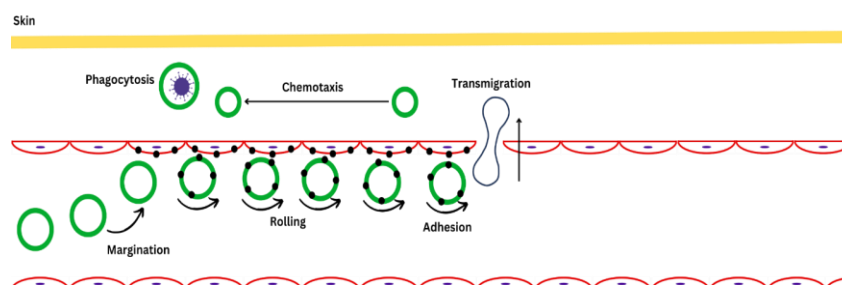
## 3. Smooth muscles

- LTC<sub>4</sub> and D<sub>4</sub> → contract smooth muscles →
  - Bronchoconstrictors → important mediators of human allergic asthma
  - Spastic contraction of GIT → abdominal colics during systemic anaphylaxis



## 4. Inflammation

- LTC<sub>4</sub> → highly chemotactic for neutrophils and monocytes





## Uses

1. To maintain patency of ductus arteriosus Congenital heart disease
2. Primary pulmonary hypertension
3. Impotence due to erectile dysfunction
4. To avoid platelet damage
5. Abortion
6. Induction/augmentation of labour
7. Postpartum haemorrhage (PPH)
8. Cervical priming (ripening)
9. Peptic ulcer
10. Glaucoma

### 1. To maintain patency of ductus arteriosus in Congenital heart disease

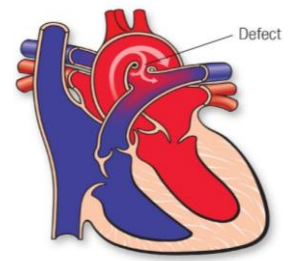
In neonates with Congenital heart disease

↓  
**PGE1 (Alprostadil) and PGI2(epoprostenal)**

↓  
Vasodilatation of ductus arteriosus

↓  
Maintain patency of ductus arteriosus till surgery is undertaken

- **Prostaglandin synthesis inhibitors (indomethacin)** → given to close PDA

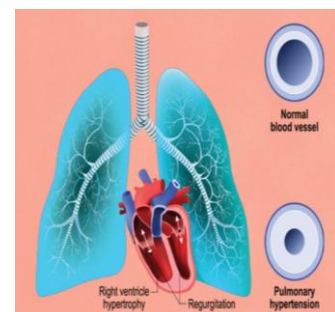


### 2. Primary pulmonary hypertension

**Epoprostenal (PGI2) and treprostinil (longer acting PGI2)**

↓  
Vasodilatation of pulmonary capillaries

↓  
Used in primary pulmonary hypertension



### 3. Impotence due to erectile dysfunction

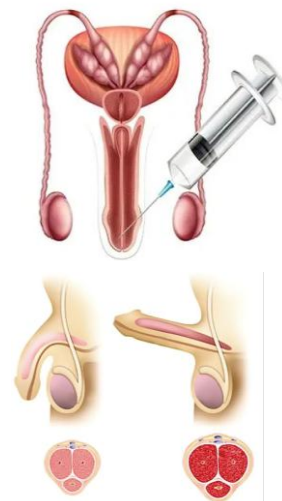
**Alprostadil (PGE1)**

↓  
Injected into penis

↓  
Vasodilatation of blood vessels of Penis

↓  
Increased blood flow fills the cavernosal spaces within penis

↓  
Erection lasting 1–2 hours



- **Oral sildenafil/ tadalafil** → now preferred for erectile dysfunction.

#### 4. To avoid platelet damage

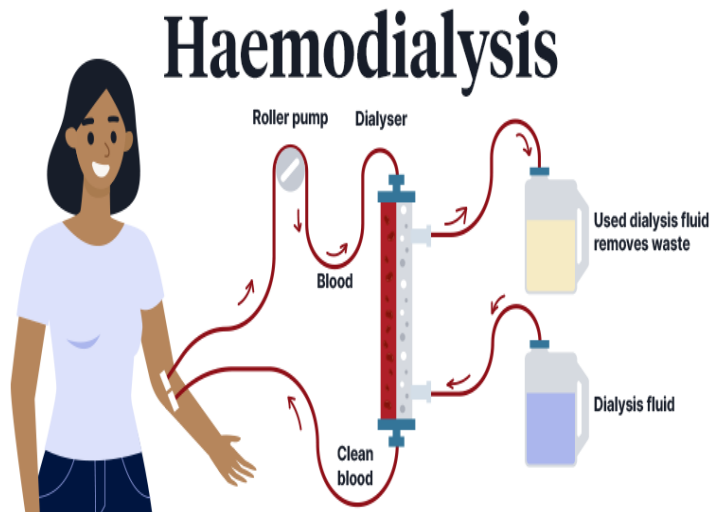
##### PGI<sub>2</sub> (Epoprostenol)

↓  
Stimulates adenylate cyclase

↓  
Increases cAMP

↓  
Antiaggregatory effect

↓  
Used to prevent platelet aggregation during  
haemodialysis or cardiopulmonary bypass



#### 5. Abortion

##### Misoprostol 400 µg (PGE<sub>1</sub>)

↓  
Causes uterine contraction

↓  
Used in Medical termination of  
pregnancy of upto 7 weeks



#### 6. Induction/ Augmentation of labour

- **Oxytocin** → preferred

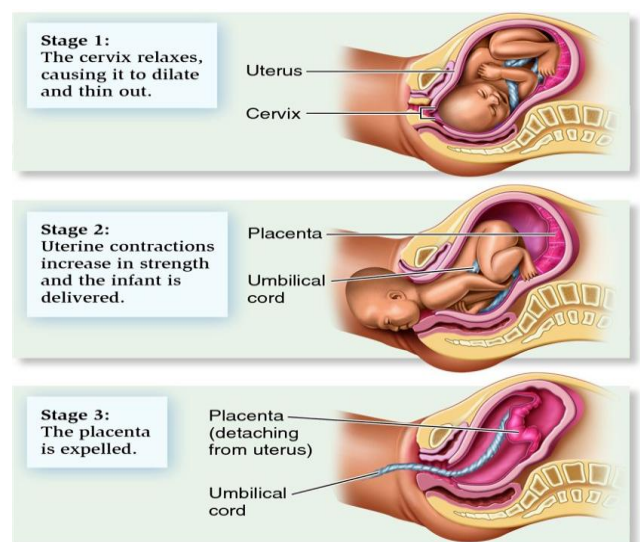
##### Dinoprostone (PGE<sub>2</sub>) or intra-amniotic

##### Carboprost (PGF<sub>2a</sub>)

↓  
Used in place of oxytocin in renal failure patients  
(because PGs do not cause fluid retention that is  
possible with oxytocin)

↓  
Causes uterine contraction

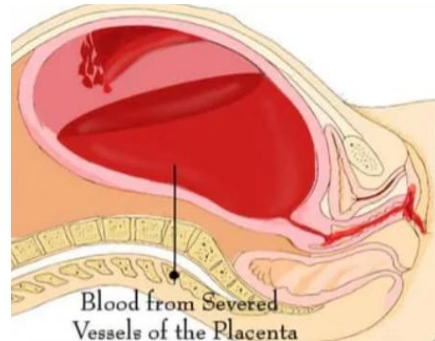
↓  
Induction/augmentation of labour



## 7. Postpartum haemorrhage (PPH)

- **Ergometrine and oxytocin** → preferred  
**Carboprost (15-methyl PGF<sub>2</sub>α)**

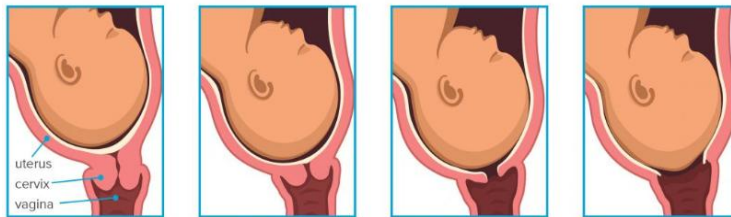
↓  
Alternative drug especially in patients  
unresponsive to Ergometrine and oxytocin  
↓  
Causes uterine contraction  
↓  
Control of PPH due to uterine atony



## 8. Cervical priming (ripening)

**PGE<sub>2</sub> (Dinoprostone)**

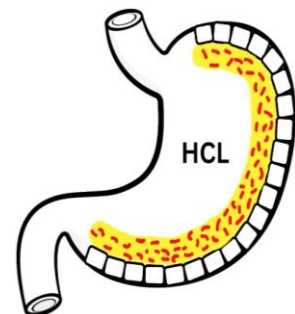
↓  
Applied intravaginally or in cervical canal  
↓  
Make cervix soft and compliant  
↓  
Cervical priming (ripening)



## 9. Peptic ulcer

**PGE<sub>1</sub> (misoprostol)**

↓  
Inhibits secretion of gastric acid Enhances mucus secretion to provide  
protection to GI mucosa Improving gastric mucosal blood flow  
↓  
Used for healing peptic ulcer  
Especially in patients who need continued NSAID therapy

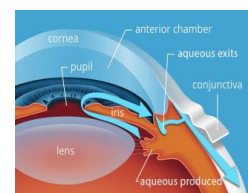


a

## 10. Glaucoma

**Topical PGF<sub>2</sub>α analogues (Latanoprost, travoprost, bimatoprost, Unoprostone)**

↓  
Enhancing uveoscleral and trabecular outflow  
↓  
Lowers IOT  
↓  
First choice drugs in wide angle glaucoma



## Adverse effects

1. Fall in BP
2. Flushing
3. Tachycardia
4. Uterine cramps
5. Fever, malaise, Shivering

## SUMMARY

### Prostaglandins (PGS), Thromboxanes (TXS) Leukotrienes (LTS)

#### Uses

1. To maintain patency of ductus arteriosus Congenital heart disease
2. Primary pulmonary hypertension
3. Impotence due to erectile dysfunction
4. To avoid platelet damage
5. Abortion
6. Induction/augmentation of labour
7. Postpartum haemorrhage (PPH)
8. Cervical priming (ripening)
9. Peptic ulcer
10. Glaucoma

#### Adverse effects

1. Fall in BP
2. Flushing
3. Tachycardia
4. Uterine cramps
5. Watery diarrhoea
6. Fever, malaise, Shivering

## NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS) AND ANTIPYRETIC-ANALGESICS

|                         | PGs, TXs, LTs | NSAIDS |
|-------------------------|---------------|--------|
| Introduction            |               |        |
| Classification          |               |        |
| MOA                     |               |        |
| Pharmacological Actions |               |        |
| Use                     |               |        |
| Adverse effects         |               |        |
| Contraindication        |               |        |

## Introduction

- All drugs grouped in this class have →

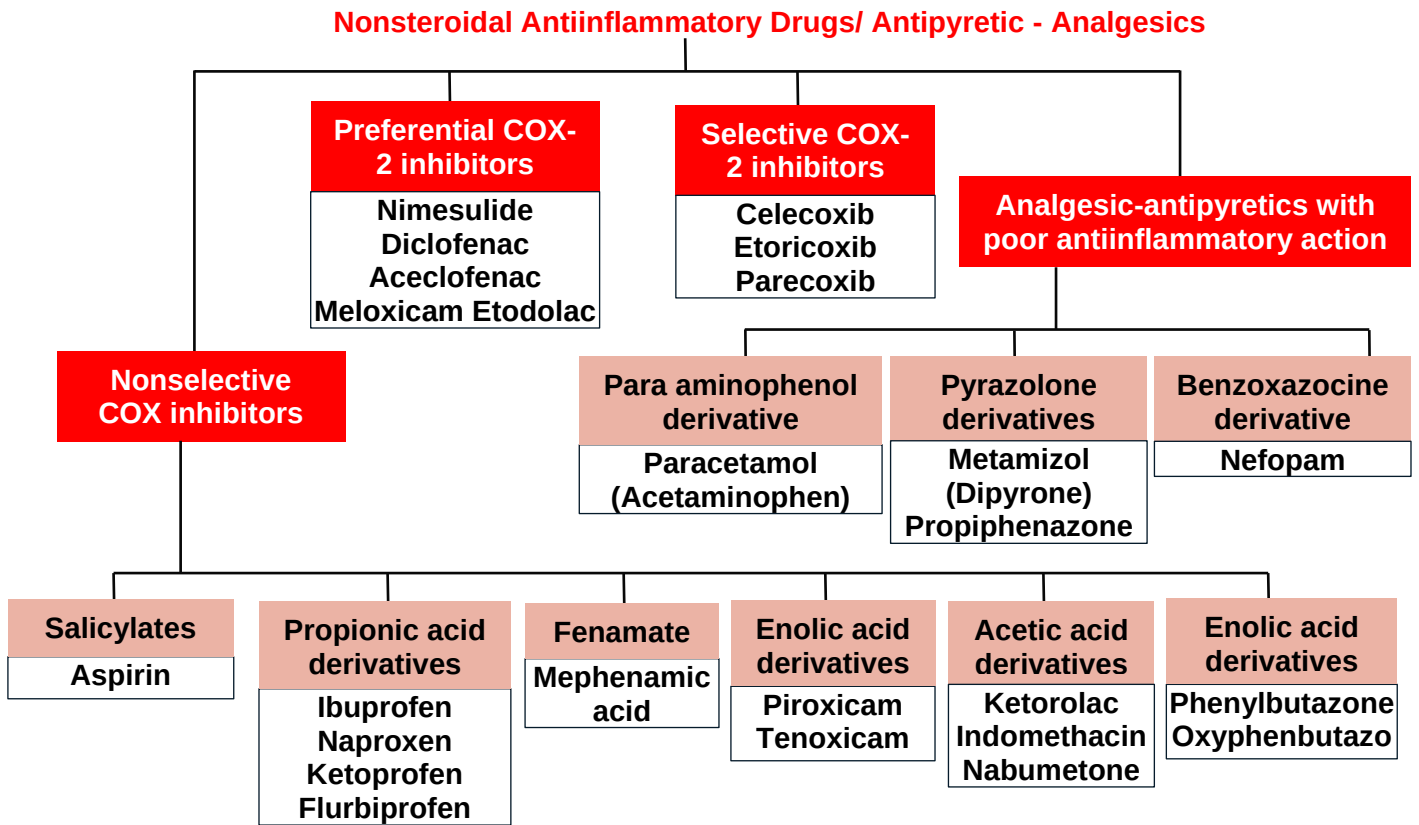
### 1. Antiinflammatory

2. **Analgesic** → Act primarily on peripheral pain mechanisms and also in CNS to raise pain threshold.

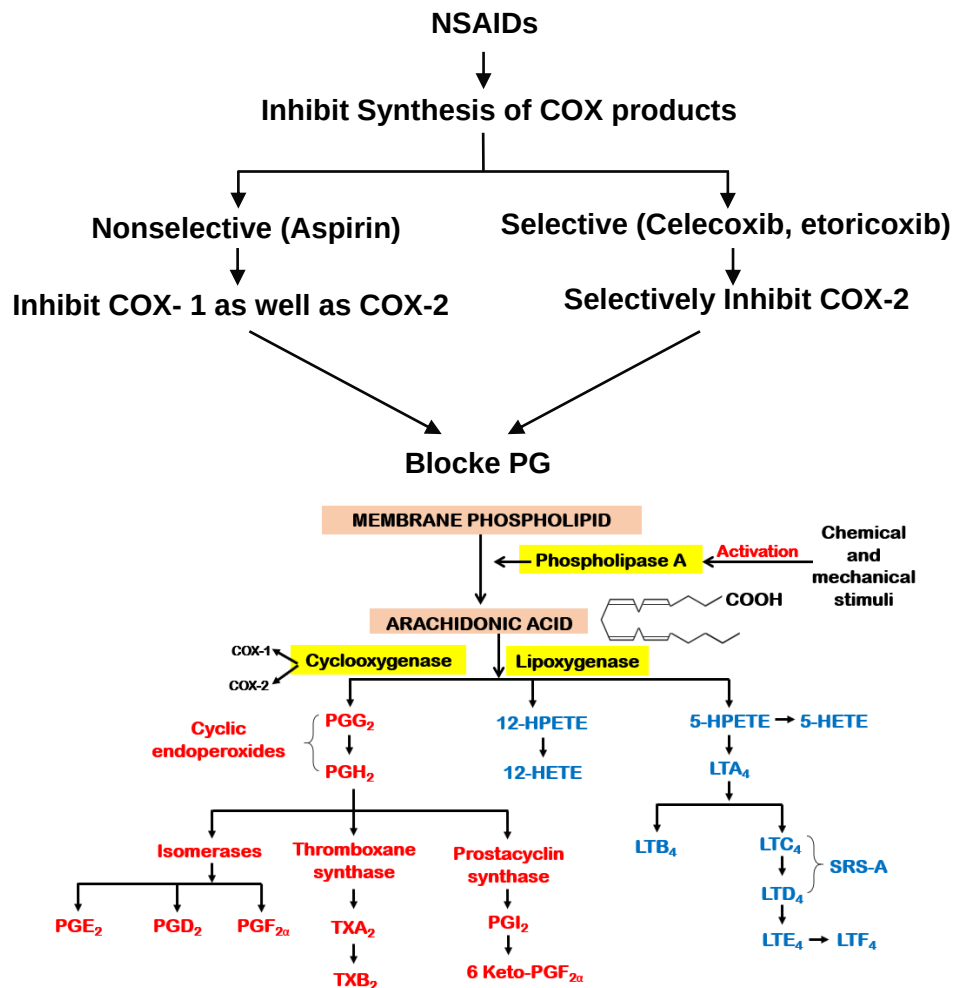
### 3. Antipyretic

- Over-the-counter drugs
- Also called → nonnarcotic, nonopioid or aspirin like analgesics

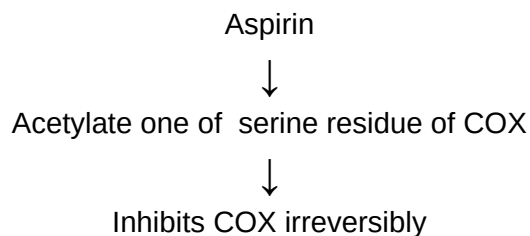
## Classification



## MOA

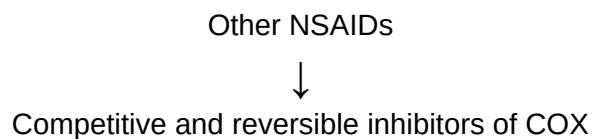


## 1. Aspirin



- Return of COX activity depends on → synthesis of fresh enzyme.

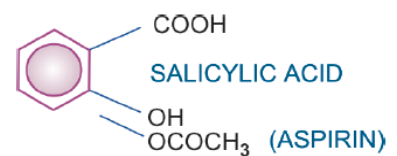
## 2. Aspirin



- Return of activity depends on → dissociation from the enzyme which is governed by → pharmacokinetic characteristics of the compound.

### Aspirin (prototype)

- Aspirin is acetylsalicylic acid
- It is rapidly converted in the body to salicylic acid which is responsible for most of the actions.



## Pharmacological Actions

- Anti inflammatory
- Analgesia
- Antipyresis
- Platelets
- Uterus
- Stomach
- Kidney

| Organ            | Prostaglandin E <sub>2</sub> (PGE <sub>2</sub> ) | Prostaglandin F <sub>2α</sub> (PGF <sub>2α</sub> )      | Prostacyclin I <sub>2</sub> (PGI <sub>2</sub> ) | Thromboxane A <sub>2</sub> (TXA <sub>2</sub> ) |
|------------------|--------------------------------------------------|---------------------------------------------------------|-------------------------------------------------|------------------------------------------------|
| 1. Blood vessels | Vasodilatation, ↓ BP                             | Larger veins constrict, little effect on BP             | Vasodilatation (marked), ↓↓ BP                  | Vasoconstriction                               |
| 2. Heart         | Weak inotropic, reflex cardiac stimulation       | Weak inotropic                                          | -                                               | -                                              |
| 3. Platelets     | Variable effect                                  | -                                                       | Antiaggregatory                                 | Aggregation                                    |
| 4. Uterus        | Contraction (in vivo), softening of cervix       | Contraction (in vivo and in vitro), softening of cervix | -                                               | -                                              |
| 5. Bronchi       | Dilatation                                       | Constriction                                            | Dilatation (mild)                               | Constriction                                   |
| 6. Stomach       | ↓ acid secretion, ↑ mucus production             | -                                                       | ↓ acid secretion, mucosal vasodilatation        | -                                              |

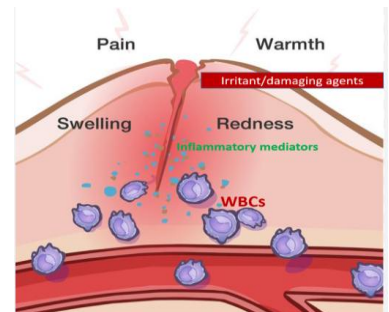


|                    |                                                            |                                                    |                                            |                  |
|--------------------|------------------------------------------------------------|----------------------------------------------------|--------------------------------------------|------------------|
| 7. Kidney          | Natriuresis, ↓ Cl reabsorption, inhibit ADH, renin release | -                                                  | Natriuresis, vasodilatation, renin release | Vasoconstriction |
| 8. CNS             | Pyrogenic                                                  |                                                    |                                            |                  |
| 9. Afferent nerves | Sensitize to noxious stimuli → tenderness                  | -                                                  | Same as PGE <sub>2</sub>                   | -                |
| 10. Eye            |                                                            | ↑ uveoscleral & trabecular outflow<br>→ Lowers IOT | -                                          | -                |
| 11. Inflammation   |                                                            | -                                                  | -                                          | -                |

## 1. Anti inflammatory

**COX 2 products**  
↓  
**Produced During inflammation**  
↓  
**Causes inflammation**

**Aspirin**  
↓  
**Inhibit of COX-2 mediated enhanced PG synthesis at the site of injury**  
↓  
**Anti inflammatory effect**



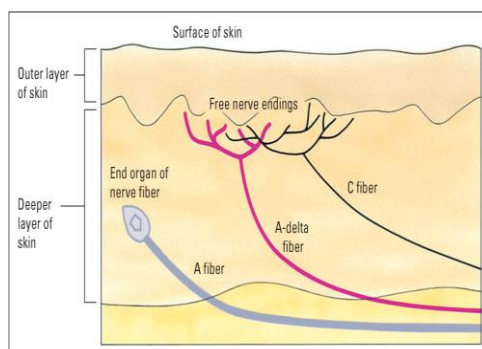
## Remember

- PGs → only one of the mediators of inflammation;
- Inhibition of COX does not depress production of other mediators like LTs, PAF, cytokines, etc.
- So there are → many targets for antiinflammatory action

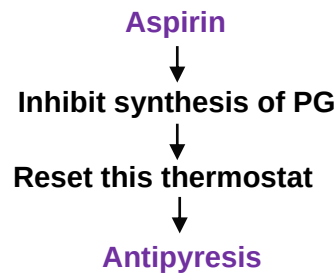
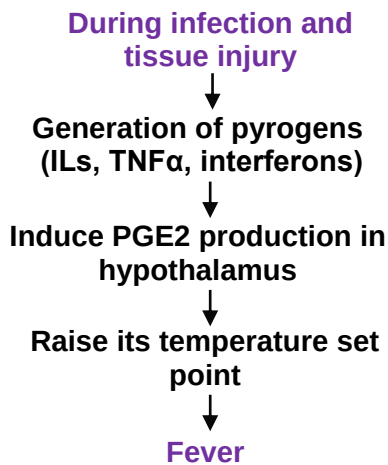
## 2. Analgesia

**PGs**  
↓  
**Affect transducing property of free nerve endings**  
↓  
**Stimuli that normally do not elicit pain are able to do so**  
↓  
**Induce hyperalgesia (algesic agents during inflammation)**  
↓  
**Tenderness and pain**

**Aspirin**  
↓  
**Inhibition of PG synthesis**  
↓  
**Locally** → **Peripheral component**  
↓  
**Spinal dorsal horn neurones and brain** → **Central component**  
↓  
**Analgesic**



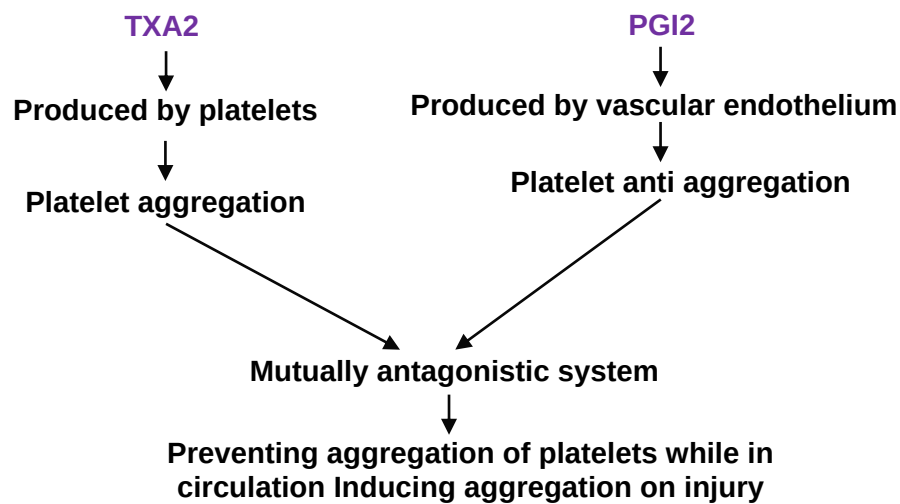
### 3. Antipyresis



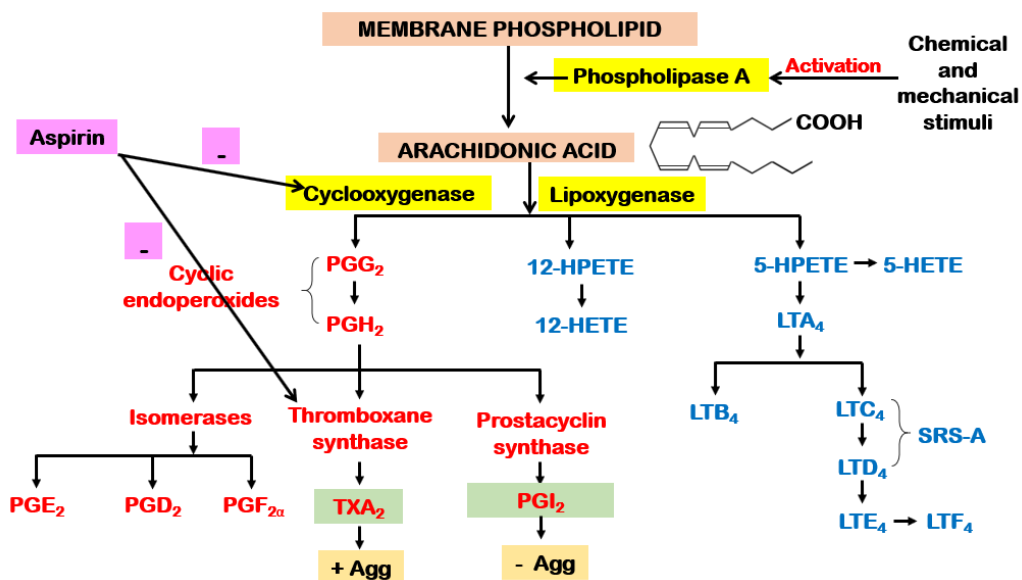
- Normal body temperature is not affected and so there's no hypothermia

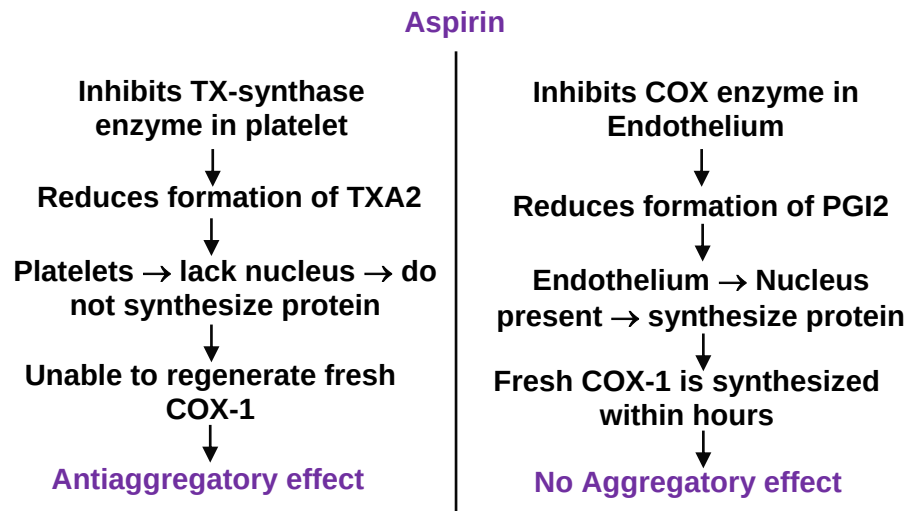


### 4. Platelets

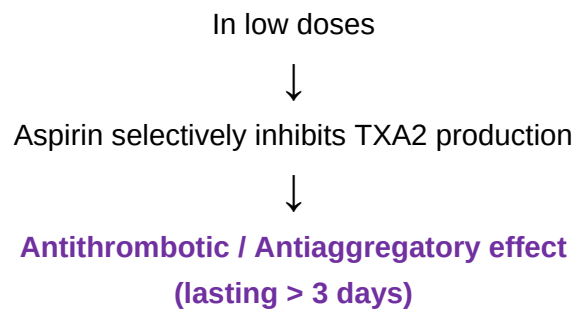


### What does Aspirin do???

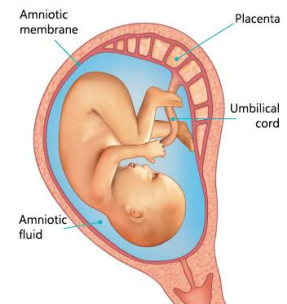
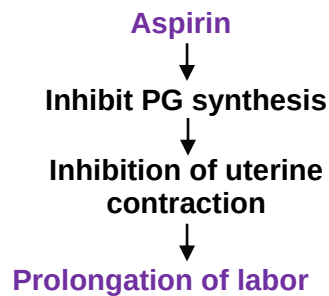
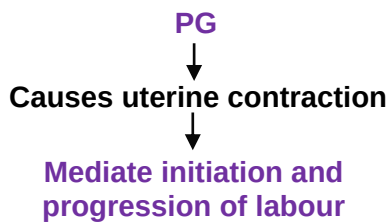




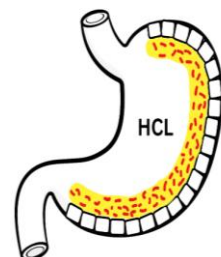
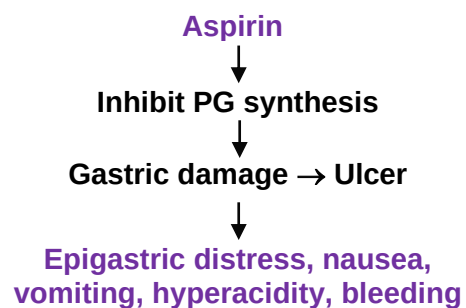
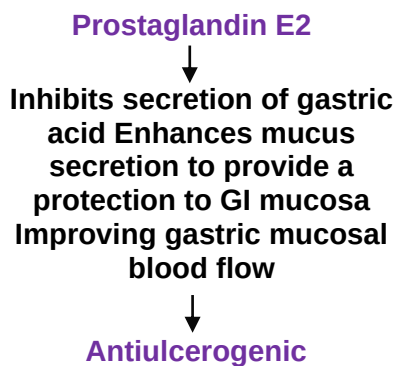
## Summary



## 5. Uterus



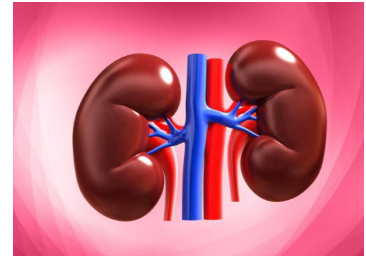
## 6. Stomach



## 7. Kidney

**Renal PGs**  
↓  
In chronic renal disease  
↓  
**Maintenance of circulation  
at time of crisis in**

**Aspirin**  
↓  
Inhibit of renal PG synthesis  
↓  
Decrease renal blood flow in  
patients with compromised  
blood circulation  
↓  
**Precipitation of acute renal  
failure in chronic renal disease**



## Acid-base and electrolyte balance

**Low dose Aspirin**  
↓  
Respiratory center stimulation  
↓  
Increases rate and depth of  
respiration  
↓  
Washing out of more CO<sub>2</sub>  
↓  
Respiratory alkalosis  
↓  
To compensate it → HCO<sub>3</sub>  
excreted in urine  
↓  
**Compensated alkalosis**

**High dose Aspirin**  
↓  
Respiratory depression  
↓  
CO<sub>2</sub> retention  
↓  
Respiratory acidosis  
↓  
To this are added dissociated  
salicylic + metabolically derived  
sulfuric and phosphoric acid  
which are retained due to  
depression of renal function  
↓  
**Uncompensated metabolic acidosis**

## Urate excretion

- Aspirin → Dose-related effect is seen →
  - > 2 g/day → urate retention
  - 2–5 g/day → variable effects
  - > 5 g/day → increased urate excretion
- Aspirin is not suitable for use in chronic gout.

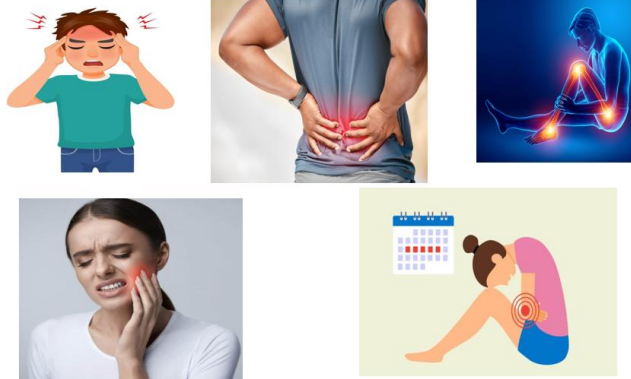


## Uses

- As analgesic
- As antipyretic
- As Anti-inflammatory
- Postmyocardial infarction and poststroke patients
- Pregnancy-induced hypertension and pre-eclampsia
- Patent ductus arteriosus
- Familial colonic polyposis
- Prevention of colon cancer

## 1. As analgesic

- Headache (including mild migraine)
- Backache
- Myalgia
- Joint pain
- Pulled muscle
- Toothache
- Neuralgias
- Dysmenorrhoea



## • Rheumatoid arthritis

- Produces relief of pain, swelling and morning stiffness,
- But progress of the disease process is not affected.

## • Osteoarthritis

- Affords symptomatic relief only
- Used on 'as and when required' basis,
- Paracetamol is the first choice analgesic for most cases.

## 2. As antipyretic

- **Aspirin** → effective in fever of any origin
- **Paracetamol** → safer, generally preferred.

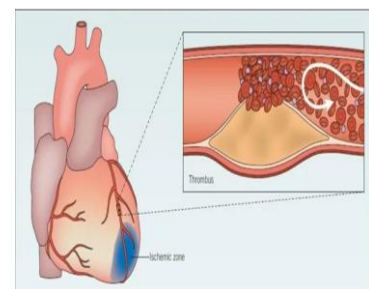
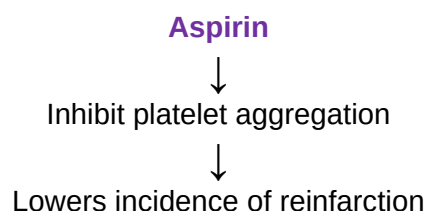


## 3. As Anti-inflammatory

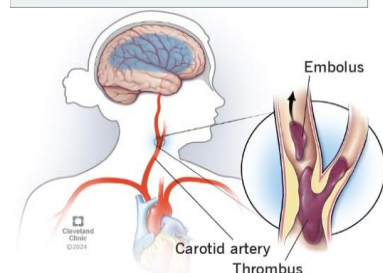
- **Acute rheumatic fever** →
  - DOC → Aspirin
  - In a dose of 4–5 g or 75–100 mg/kg/day → marked symptomatic relief in 1–3 days.
  - Maintenance doses (50 mg/ kg/day) → continued for 2–3 weeks or till signs of active disease (raised ESR) persist.
  - Withdrawal should be gradual over the next 2 weeks



## 4. Postmyocardial infarction and poststroke patients



- **At low doses** → TXA2 synthesis in platelets is inhibited
- **At high doses** → reverse beneficial effects by concurrently inhibiting PGI2 synthesis in vessel wall.
- Large studies have demonstrated that → Aspirin 60–100 mg/day reduces incidence of myocardial infarction (MI)
- It is now routinely prescribed to post-infarct patients.



## 5. Pregnancy-induced hypertension and pre-eclampsia

- Imbalance between TXA2 and PGI2 is believed to be involved

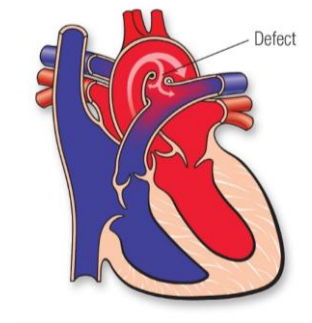
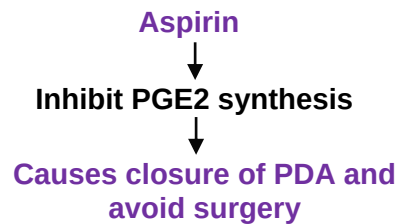
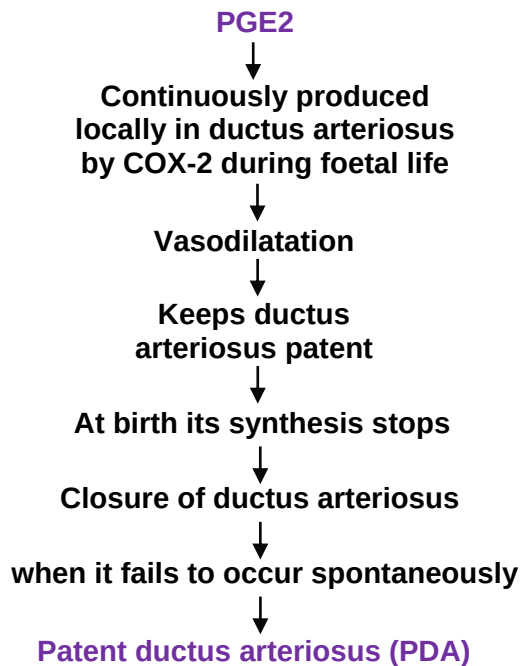
Low dose Aspirin (80–100 mg/day)

Selectively suppressing TXA2 production

Benefits in Pregnancy-induced hypertension and pre-eclampsia



## 6. Patent ductus arteriosus



## 7. Familial colonic polyposis

**Aspirin and other NSAIDs**

↓

Suppress polyp formation

↓

Afford symptomatic relief

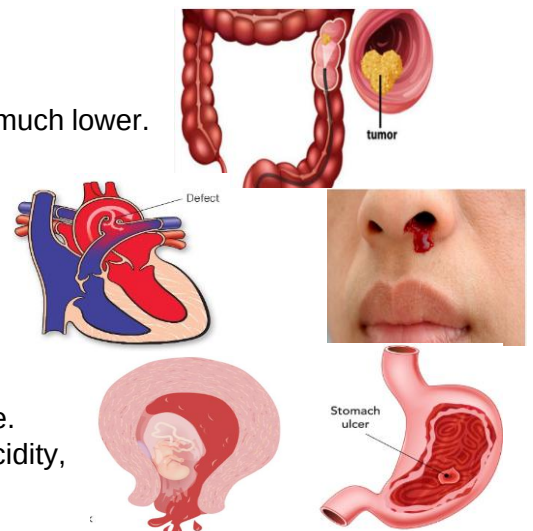


## 8. Prevention of colon cancer

- Incidence of colon cancer among regular aspirin users → much lower.
- Colonic tumours express large quantities of COX-2.

### Adverse effects

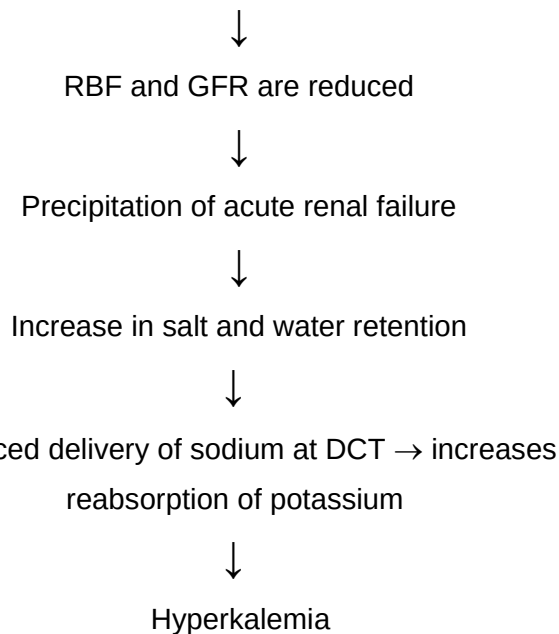
- Blood vessels** → Premature closure of PDA
- Platelet** → Excessive bleeding
- Uterus** →
  - Prolongation of labor → since PG responsible for uterine contraction are reduced.
  - Increased risk of anti partum and post partum hemorrhage.
- Stomach** → Epigastric distress, nausea, vomiting, hyperacidity, peptic ulceration and bleeding.





## 5. Kidney →

- With normal kidney there's little effect  
CCF, cirrhosis, chronic renal disease, and hypovolemia

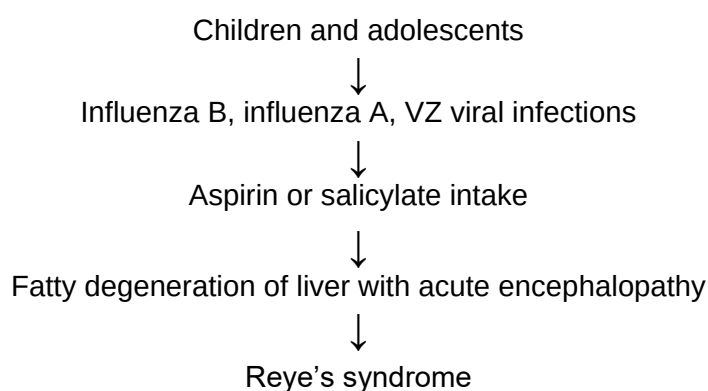


- With high doses or long term use → risk of renal papillary necrosis and chronic interstitial nephritis  
→ Analgesic nephropathy

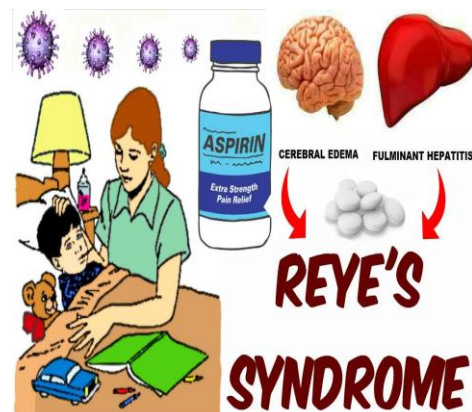
## 6. Salicylism → mild chronic intake lead to salicylism →

- Headache
- Dizziness
- Ringing in ears (Earliest)
- Decreased hearing
- Decreased vision
- Confusion
- Sweating, thirst
- Hyperventilation
- Nausea and vomiting

## 7. Reye's syndrome →



- Cause is unknown



## Acute salicylate poisoning

- More common in children.
- Fatal dose in adults → 15–30 g
- Serious toxicity is seen at serum salicylate levels → > 50 mg/dl.



## Clinical features

1. Vomiting
2. Dehydration
3. Electrolyte imbalance
4. Acidotic breathing
5. Petechial haemorrhages
6. Hyperpyrexia
7. Restlessness, delirium, Hallucinations,
8. Convulsions
9. Coma and death due to respiratory failure + cardiovascular collapse.

## Treatment of Toxicity

- Emesis, gastric lavage, activated charcoal.
- Sponging with water or alcohol if there's hyperpyrexia.
- I/v fluids for dehydration.
- Bicarbonate for acidosis and also to increase urinary excretion of salicylate.
- Forced diuresis with furosemide, to increase excretion.
- Dialysis
- Blood transfusion or vitamin K, if there's excessive bleeding.

## Contraindications to Aspirin

### Mnemonic → CHAMPIONS KG

1. **C** - Children with viral fevers (Reye's syndrome risk)
2. **H** - Hypersensitivity reactions
3. **A** - Asthma (Bronchial)
4. **M** - Marginal fertility in males (↓ PG in seminal fluid)
5. **P** - Peptic ulcer
6. **I** - Insufficiency of kidneys (Renal insufficiency)
7. **O** - Organism-induced hemorrhagic fevers (like Dengue)
8. **N** - Nasal polyps
9. **S** - Suspected pregnancy
10. **K** - K-deficiency or Hemophilia
11. **G** - Gout (Acute)

## Remember

- **Paracetamol (acetaminophen)** → has no anti-inflammatory activity and Nimesulide and nefopam do not act by decreasing PG synthesis
- **Aspirin** → only irreversible inhibitor of COX enzyme
- **Aspirin** → contraindicated in children (<12 yrs old) due to increased risk of Reye's syndrome.

- **Sulindac and nabumetone** → prodrugs.
- **Piroxicam and tenoxicam** → longest acting NSAIDs due to enterohepatic cycling.
- **Indomethacin** → inhibits PLPA, and possesses immuno-suppressive properties apart from its COX inhibitory action. It causes more GI upset than other NSAIDs. It is implicated in causing headache (analgesic causing pain) and sedation. Treatment with indomethacin, combined with potassium repletion and spironolactone is associated with improvement in the symptoms and biochemical derangements of Bartter's syndrome.
- **Propionic acid derivatives include ibuprofen, ketoprofen and flurbiprofen** → Ketoprofen possesses additional lysosomal stabilizing action and flurbiprofen can be used topically as eye drops. Ibuprofen has been cleared for paediatric patients.
- **Naproxen and oxaprozin** → long acting drugs that also inhibit leucocyte migration.
- **Mefenamic acid** → possesses PG receptor antagonistic and PLPA, inhibitory activity. It is very useful in dysmenorrhoea.
- **Phenacetin (prodrug of paracetamol)** → implicated in causing analgesic nephropathy
- **Ketorolac** → only NSAID that can be used i.v apart from paracetamol. It is also available as eye drops. Course longer than 5 days is not recommended.
- **Apazone** → possess potent uricosuric activity. It is indicated in conditions, in which other NSAIDs have failed.

## SUMMARY

### NSAIDS

#### Uses

1. As analgesic
2. As antipyretic
3. As Anti-inflammatory
4. Postmyocardial infarction and poststroke patients
5. Pregnancy-induced hypertension and pre-eclampsia
6. Patent ductus arteriosus
7. Familial colonic polyposis
8. Prevention of colon cancer

#### Adverse effects

1. Blood vessels
2. Platelet
3. Uterus
4. Stomach
5. Kidney
6. Salicylism
7. Reye's syndrome

#### Contraindications CHAMPIONS KG

1. **C** – Children with viral fevers (Reye's syndrome risk)
2. **H** – Hypersensitivity reactions
3. **A** – Asthma (Bronchial)
4. **M** – Marginal fertility in males (↓ PG in seminal fluid)
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11. **G** – Gout (Acute)

## COX-2 INHIBITORS

### Introduction

- COX-2 is an inducible enzyme
- It leads to inflammatory and other pathological changes

### Drugs

1. Celecoxib
2. Etoricoxib
3. Parecoxib
4. Valdecoxib
5. Lumitracoxib
6. Rofecoxib

## Remember

- COX-2 generated PGs may also play a role in inflammation
- So COX-2 inhibitors may not have as broad range of efficacy as traditional NSAIDs.

| Action                                    | COX-1/COX-2 inhibitors | COX-2 inhibitors |
|-------------------------------------------|------------------------|------------------|
| 1. Analgesic                              | +                      | +                |
| 2. Antipyretic                            | +                      | +                |
| 3. Antiinflammatory                       | +                      | +                |
| 4. Antiplatelet aggregatory               | +                      | -                |
| 5. Gastric mucosal damage                 | +                      | -                |
| 6. Renal salt/water retention             | +                      | +                |
| 7. Delay/prolongation of labour           | +                      | +                |
| 8. Ductus arteriosus closure              | +                      | ?                |
| 9. Aspirin sensitive asthma precipitation | +                      | -                |

## Important properties of COX-2 inhibitors

### 1. Increased cardiovascular risk & stroke

COX-2 inhibitors reduce endothelial PGI<sub>2</sub> production  
without affecting platelet TX-A<sub>2</sub> synthesis



Prothrombic effect  
(in contrast to non-selective inhibitor  
which are anti-aggregatory)



Increased cardiovascular risk & stroke

- Rofecoxib and valdecoxib → withdrawn for increasing cardiovascular risk
- Lumiracoxib marketed only in Europe has been suspended due to hepatotoxicity
- Currently 3 selective COX-2 inhibitors (also called coxibs) → Celecoxib, Etoricoxib and Parecoxib are available in India.

### 2. Juxtaglomerular COX-2 is constitutive (at all other site it is inducible)

- So renal toxicity is similar to nonselective COX inhibitors, i.e., Salt & water retention, pedal edema, rise in BP, and precipitation of CHF.
- COX-2 in brain is also constitutive

## Remember

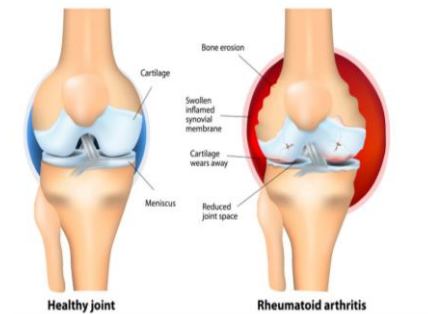
- **Rofecoxib and valdecoxib** → withdrawn due to increased incidences of MI and thrombotic disorders.
- **Etoricoxib** → longest acting coxib.
- **Parecoxib** → prodrug of valdecoxib that can be administered parenterally.

## ANTIRHEUMATOID DRUGS

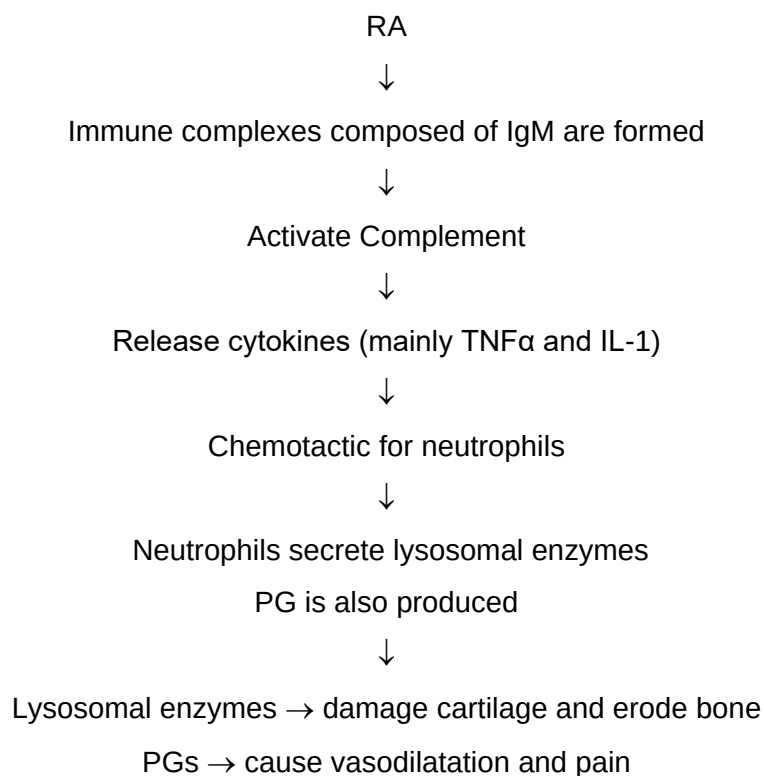
### RHEUMATOID ARTHRITIS (RA)

#### Introduction

- Autoimmune disease in which there is →
  - Joint inflammation
  - Synovial proliferation
  - Destruction of articular cartilage.

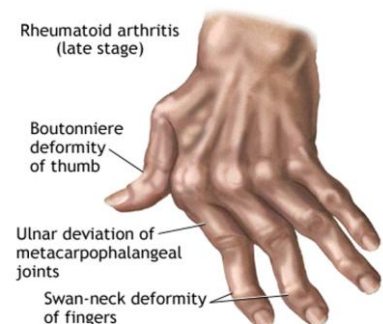


#### Pathogenesis



#### Clinical features

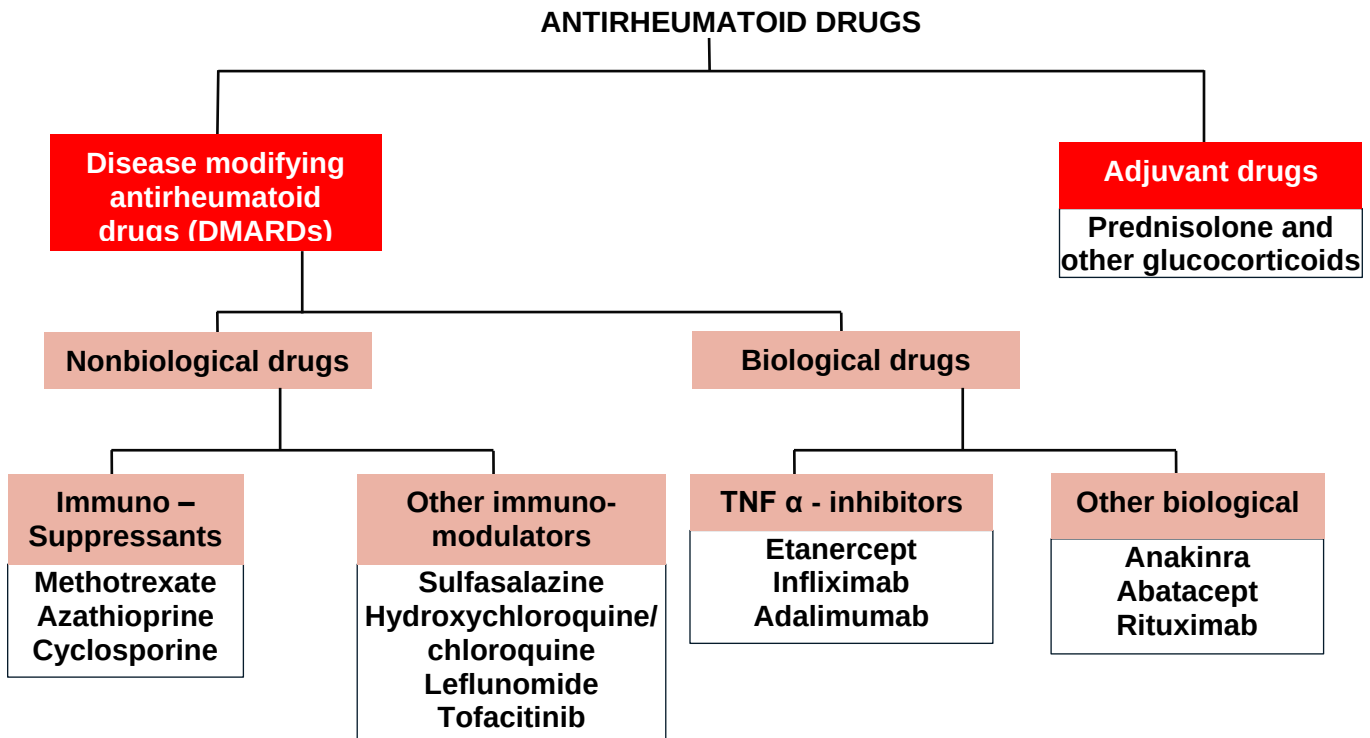
- RA is a chronic progressive, crippling disorder
- Waxing and waning course
- Multiple small joints of hands and feet → preferentially affected
- Deformities are produced as disease progresses.
- NSAIDs → first line drugs which afford symptomatic relief in pain, swelling, morning stiffness, immobility, but do not arrest the disease process.



#### Clinical features

- **Ameliorate** → pain, swelling and joint stiffness
- **Prevent** → articular cartilage damage and bony erosions
- **Preserve** → joint function and prevent deformity.

## Classification



## DISEASE MODIFYING ANTI RHEUMATIC DRUGS (DMARDS) OR SLOW ACTING ANTI RHEUMATIC DRUGS (SAARDS)

- Drugs which (except corticosteroids) →
  - Suppress rheumatoid process
  - Bring about a remission
  - Retard disease progression
  - Do not have nonspecific anti inflammatory or analgesic action.
- Onset of benefit with DMARDs takes a few months of regular treatment
- Relapses occur at least a few months after cessation of therapy.



## Current recommendation

- Current recommendation → to add DMARDs as soon as the diagnosis of RA is confirmed.
- More than one DMARD may be used concurrently
- All DMARDs tend to lose effectiveness with time → So Advanced cases may require 2 or 3 drugs together





|                  | Nonbiological drugs |               |                                    |             | Biological agents       |
|------------------|---------------------|---------------|------------------------------------|-------------|-------------------------|
|                  | Methotrexate        | Sulfasalazine | Hydroxychloroquine/<br>Chloroquine | Tofacitinib | TNF $\alpha$ inhibitors |
| Introduction     |                     |               |                                    |             |                         |
| MOA              |                     |               |                                    |             |                         |
| Pharmacokinetics |                     |               |                                    |             |                         |
| Interactions     |                     |               |                                    |             |                         |
| Use in RA        |                     |               |                                    |             |                         |
| Adverse effects  |                     |               |                                    |             |                         |

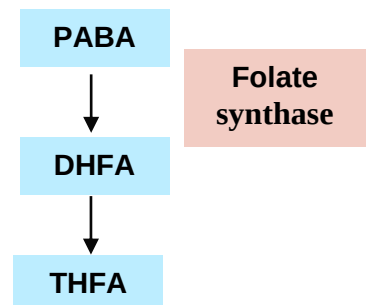
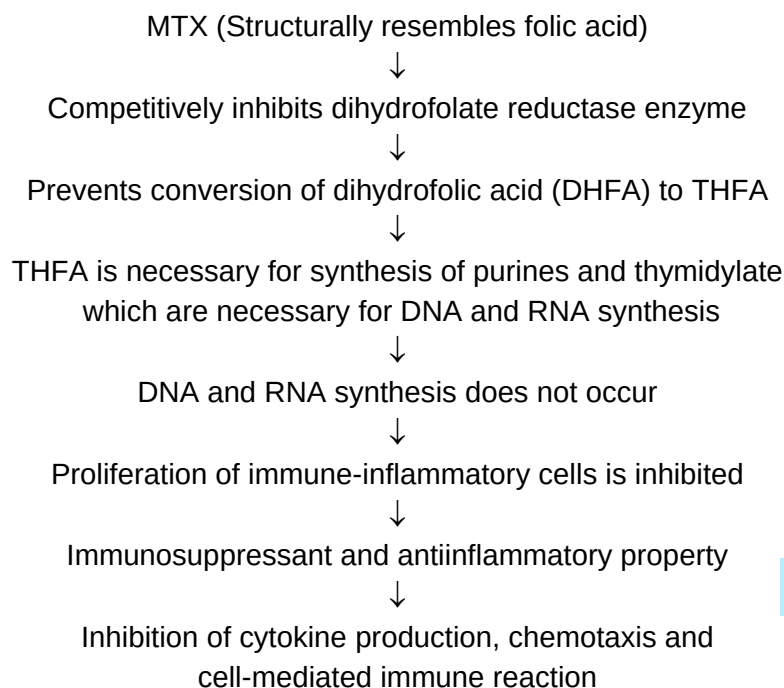
## NONBIOLOGICAL DRUGS

### Methotrexate

#### Introduction

- DMARD of first choice

#### Introduction



#### Pharmacokinetics

- Oral bioavailability of Mtx is variable and affected by food.
- Its excretion is hindered in renal disease → therefore, not recommended for such patients.



#### Interactions

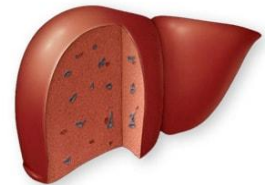
- Probenecid and aspirin** → increase Mtx levels and toxicity.
- Trimethoprim** → add to inhibition of dihydrofolate reductase and depress bone marrow.

## Use in RA

- Mtx is now the DMARD of first choice and the standard treatment for most patients, including cases of juvenile RA.
- Induction of oral low-dose (7.5–15 mg) weekly Mtx regimen
- Onset of symptom relief is relatively rapid (3–6 weeks) → Mtx is preferred for initial treatment.
- Response is more predictable and sustained over long-term.
- Combination regimens of 2 or 3 DMARDs mostly include Mtx.

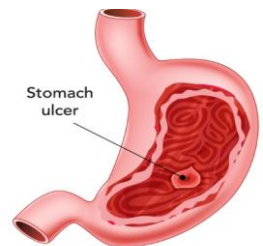
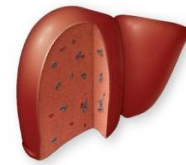
## Adverse effects

1. Oral ulceration
2. GIT upset
3. Dose dependent progressive liver damage leading to cirrhosis occurs in some patients



## Contraindication

1. Pregnancy
2. Breast-feeding
3. Liver disease
4. Peptic ulcer



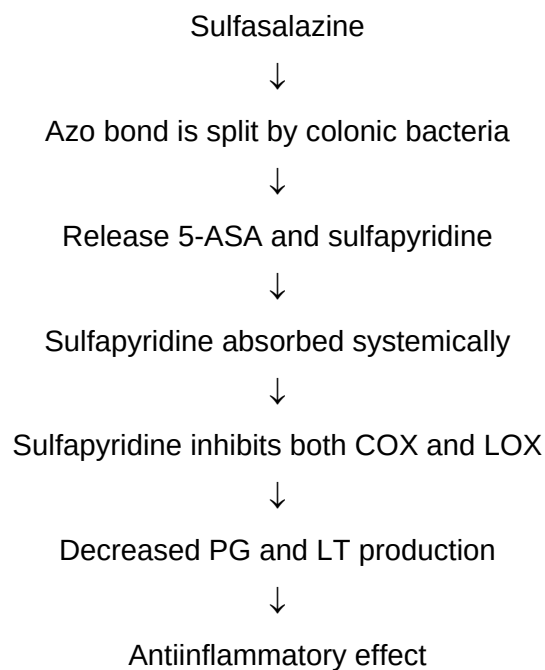
## Sulfasalazine

### Introduction

- It is a compound of 5-aminosalicylic acid (5-ASA) with sulfapyridine linked through an azo bond.



### MOA



## Use in RA

- Efficacy of sulfasalazine in RA is modest
- Used as a second line drug for milder cases or is combined with Mtx.
- Dose: 1–3 g/day in 2–3 divided doses.

## Adverse effects

1. Neutropenia / thrombocytopenia
2. Hepatitis

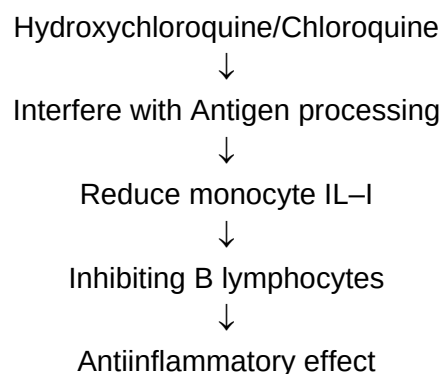
## Hydroxychloroquine / Chloroquine

### Introduction

- These are antimalarial drugs found to induce remission in up to 50% of patients with RA
- Take 3–6 months.
- **Advantage** → relatively low toxicity
- **Disadvantage** →
  - Efficacy is also low
  - Bony erosions are not prevented.

### MOA

- Not known clearly

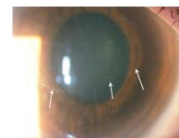


## Use in RA

- **Indications** →
  - Milder nonerosive disease, especially when only one or a few joints are involved
  - Combined with Mtx/sulfasalazine.
- **Dose** → Hydroxychloroquine 400 mg/day for 4–6 weeks, followed by 200 mg/day for maintenance.

## Adverse effects

1. Retinal damage
2. Corneal opacity
3. Graying of hair
4. Irritable bowel syndrome
5. Myopathy
6. Neuropathy
7. Rashes

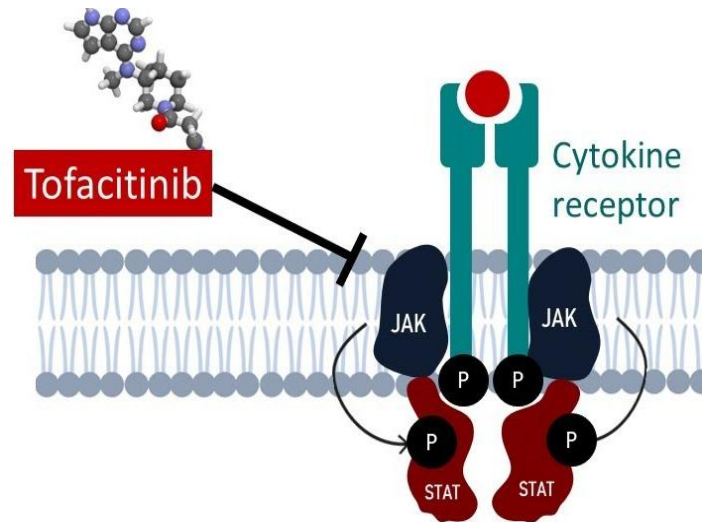
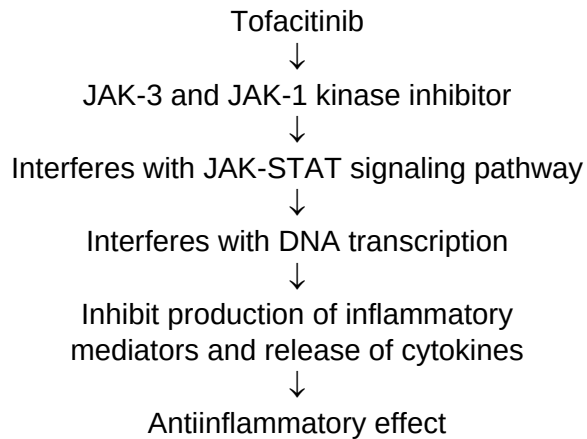


## Tofacitinib

### Introduction

- New synthetic drug

### MOA

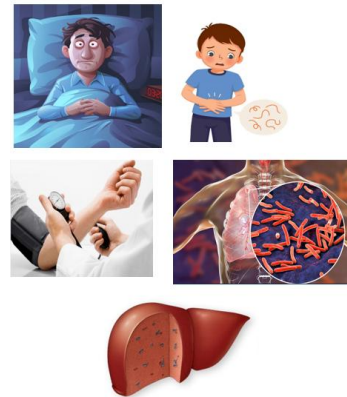


### Use in RA

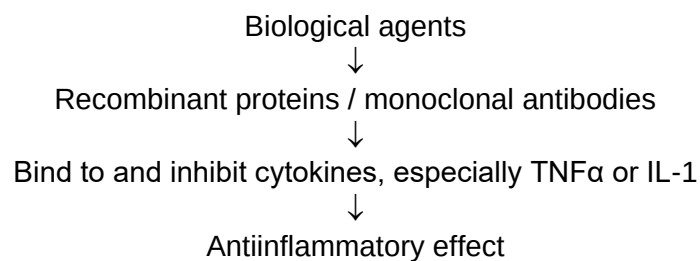
- Approved for severe cases of RA that are not responding to Mtx.
- Tofacitinib can be used alone or concurrently with Mtx, but should not be combined with azathioprine, cyclosporine or biological DMARDs.
- Dose: 5 mg BD

### Adverse effects

1. Insomnia
2. Diarrhoea
3. Hypertension
4. Anaemia
5. Susceptibility to respiratory infections
6. Flaring of tuberculosis
7. Liver damage



## BIOLOGICAL AGENTS



- Produce prominent adverse effects
- Expensive
- Used only as reserve drugs for severe refractory disease.

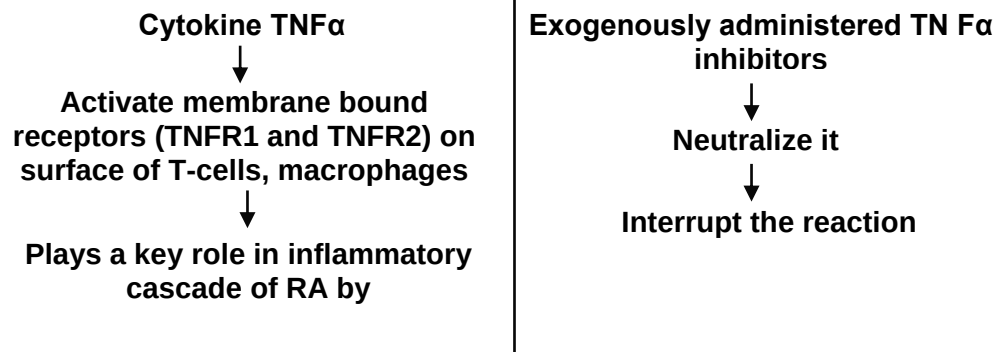
## TNFα Inhibitors

### Introduction

#### Advantages →

- Quicker response than nonbiologic DMARDs has been obtained.
- Inflammatory changes in joint regress
- New erosions are slowed.

## MOA



## Use in RA

- Added to Mtx when response to the latter is not adequate or in rapidly progressing cases.

## Adverse effects

- Susceptibility to opportunistic infections (tuberculosis and pneumocystis pneumonia) is increased → because TNF $\alpha$  plays important role in combating bacterial infection, especially granulomatous infections.



## Types

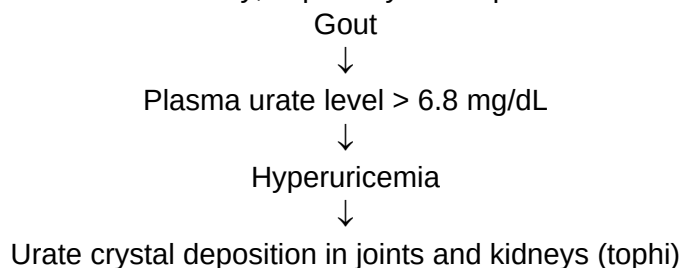
- **Etanercept**
  - Recombinant fusion protein of TNF-receptor with Fc portion of human IgG1
  - Administered by s.c. injection 50 mg weekly.
- **Infliximab**
  - Chimeral monoclonal antibody which binds and neutralizes TNF $\alpha$
  - 3–5 mg/kg is infused i.v. every 4–8 weeks.
- **Adalimumab**
  - Recombinant human monoclonal anti- TNF antibody
  - Administered s.c. 40 mg every 2 weeks.

# ANTIGOUT DRUGS

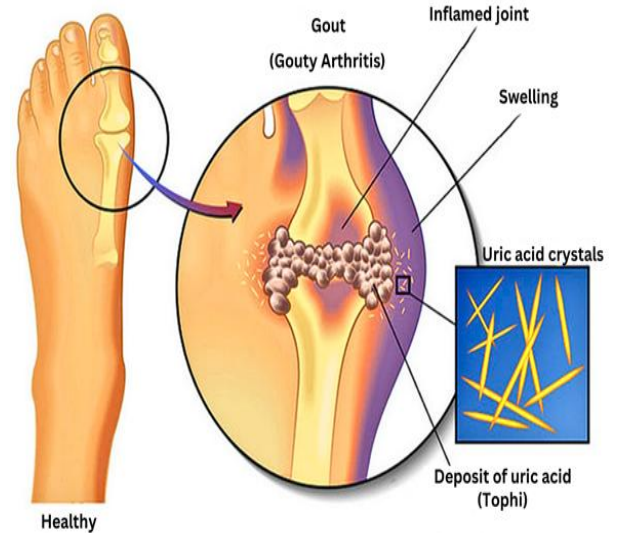
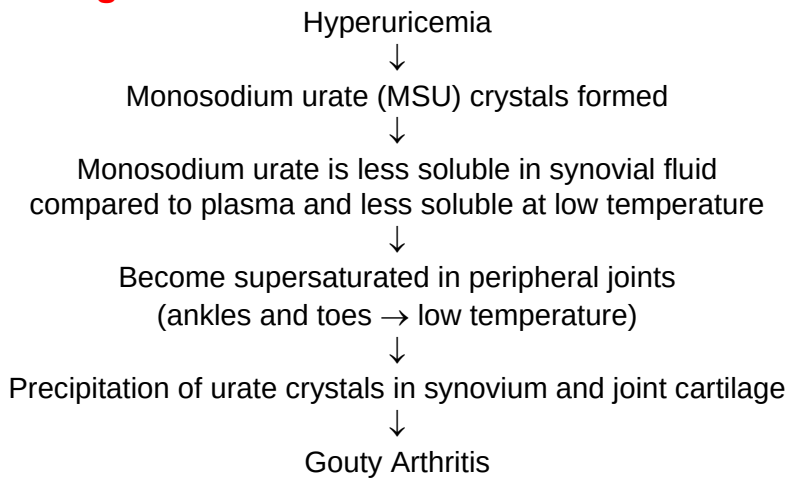
## GOUT

### Introduction

- Gout is a heterogeneous group of diseases characterized by hyperuricemia
- Normal plasma urate → 2–6 mg/dl
- Uric acid →
  - Product of purine metabolism
  - Low water solubility, especially at low pH.



## Pathogenesis

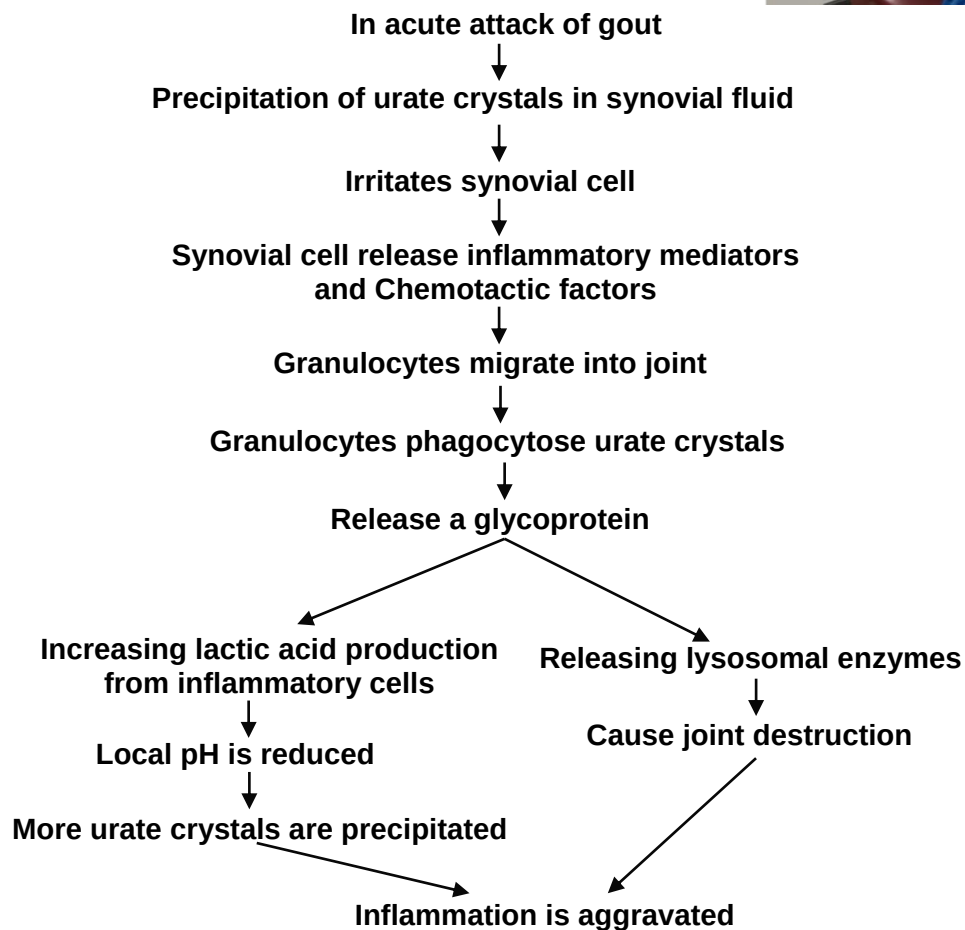


## Gouty Arthritis

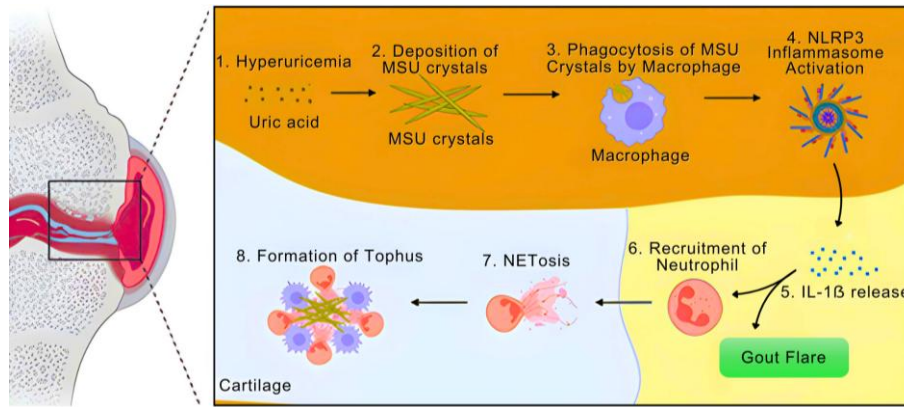
1. Acute gouty arthritis
2. Chronic Gout

### 1. Acute gouty arthritis

- Sudden onset of severe inflammation in a small joint
- Commonest is metatarso-phalangeal joint of great toe due to precipitation of urate crystals in the joint space.
- Joint becomes red, swollen and extremely painful





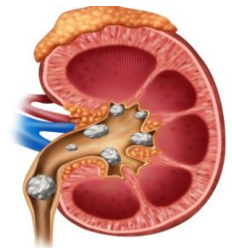


### Treatment →

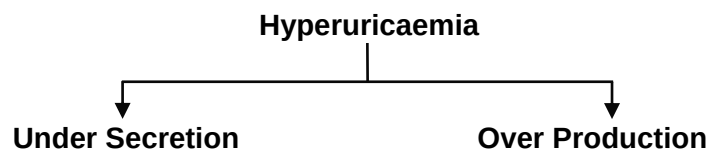
- Requires immediate treatment with strong antiinflammatory drugs, without attempting to lower blood urate level.
- When the attack subsides → urate lowering therapy is instituted
- Antiinflammatory cover is continued for several weeks.

## 2. Chronic Gout

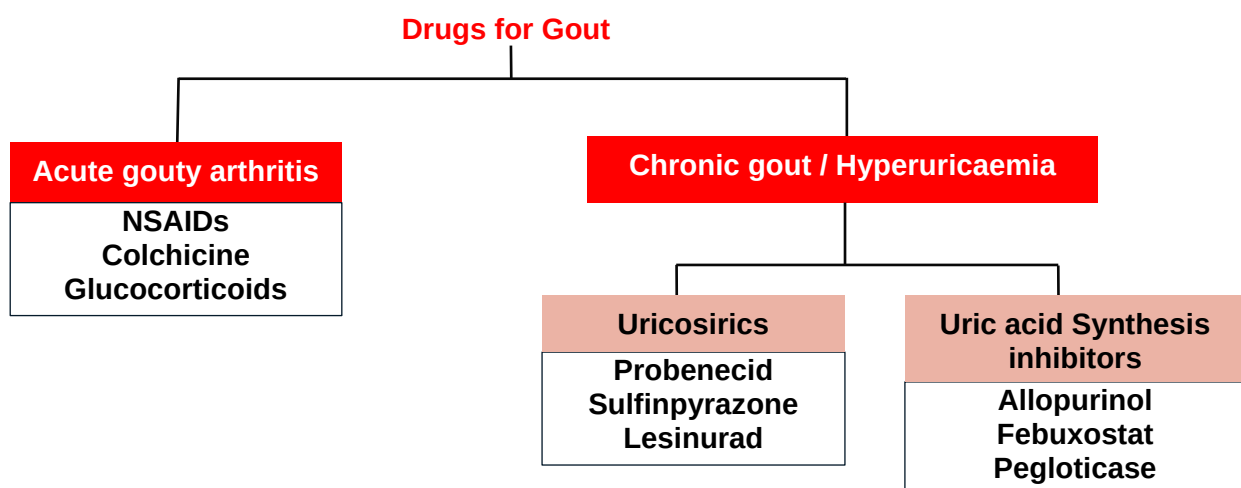
- When pain and stiffness persist in a joint between attacks → gout has become chronic.
- **Hyperuricaemia** → In majority of patients, hyperuricaemia is due to undersecretion of uric acid, while in few it is due to over production.
- **Tophi** → chalk-like stones under skin in pinna, eyelids, nose, around joints and other places
- **Urate stones** → in kidney



### MOA



### Classification



|                   | Acute gouty arthritis |            |                 |             | Chronic Gout                   |
|-------------------|-----------------------|------------|-----------------|-------------|--------------------------------|
|                   | NSAIDs                | Colchicine | Glucocorticoids | Uricosirics | Uric acid Synthesis inhibitors |
| Introduction      |                       |            |                 |             |                                |
| Drugs             |                       |            |                 |             |                                |
| MOA               |                       |            |                 |             |                                |
| Pharmaco kinetics |                       |            |                 |             |                                |
| Interactions      |                       |            |                 |             |                                |
| Uses              |                       |            |                 |             |                                |
| Adverse effects   |                       |            |                 |             |                                |

## DRUGS FOR ACUTE GOUTY ARTHRITIS

1. NSAIDs
2. Colchicine
3. Glucocorticoids

### 1. NSAIDs

#### Introduction

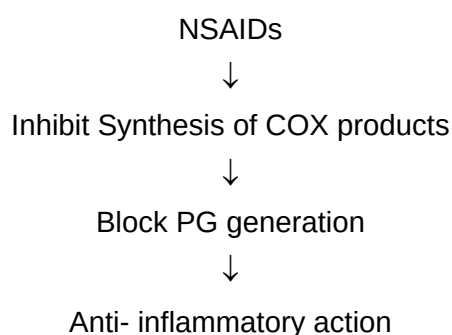
- Their strong Anti-inflammatory (not uricosuric) action is responsible for benefit in Gout

#### Drugs

One of strong antiinflammatory drugs →

- Naproxen
- Piroxicam
- Diclofenac
- Indomethacin
- Etoricoxib

#### MOA



- Naproxen and piroxicam → specifically inhibit chemotactic migration of leucocytes into inflamed joint.

## Use in Gout

- Given in relatively high and quickly repeated doses.
- Effective in terminating the attack, but may take 12–24 hours
- Complete resolution takes 5–10 days.
- Response is slower than with colchicine
- Generally better tolerated.
- Majority of patients prefer NSAIDs over colchicine.
- After the attack is over → NSAIDs should be continued at lower doses for 3–4 weeks and drugs to control Hyperuricaemia take effect.

## Adverse effects

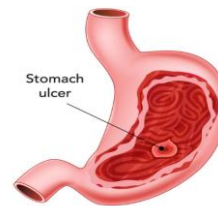
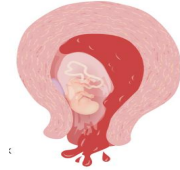
1. **Platelet** → Excessive bleeding

2. **Uterus** →

- Prolongation of labor → since PG responsible for uterine contraction are reduced.
- Increased risk of anti partum and post partum hemorrhage.

3. **Stomach** → Epigastric distress, nausea, vomiting, hyperacidity, peptic ulceration and bleeding.

4. **Kidney** → Electrolyte imbalance



## 2. Colchicine

### Introduction

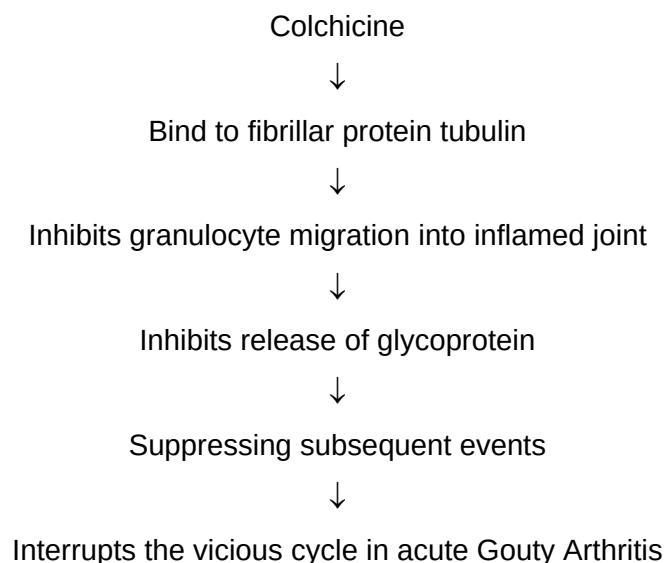
- It is an alkaloid obtained from *Colchicum autumnale* which has been used in gout since 1763.



### MOA

#### • Colchicine →

- Neither analgesic nor anti-inflammatory
- Does not inhibit the synthesis or promote the excretion of uric acid.
- Specifically suppresses gouty inflammation.



## Other actions

- (a) **Antimitotic** → causes metaphase arrest by binding to microtubules of mitotic spindle.
- (b) **Increases gut motility** → through neural mechanisms.

## Pharmacokinetics

- Rapidly absorbed orally
- Partly metabolized in liver
- Excreted in bile → Enterohepatic circulation
- Ultimate disposal occurs in urine and faeces over many days.

## Interactions

- **Inhibitors of CYP3A4** → retard colchicine metabolism and enhance its toxicity.

## Use in Gout

- Colchicine → fastest acting drug to control an acute attack of gout
  - 0.5 mg 1–3 hourly with a total of 4 doses in a day
  - Maximum 6.0 mg in a course spread over 3–4 days.
- Control of attack is usually achieved in 6–12 hours
- Complete resolution may take 3–5 days.
- Response is dramatic
- Because of higher toxicity → it is a second line option to NSAIDs.

## Adverse effects

1. Accumulation of the drug in intestine and inhibition of mitosis in its rapid turnover mucosa →
  - Nausea, vomiting
  - Watery or bloody diarrhoea
  - Abdominal cramps
  - Intestinal bleeding
2. Kidney damage
3. CNS depression
4. Death is due to muscular paralysis and respiratory failure.



## 3. Glucocorticoids

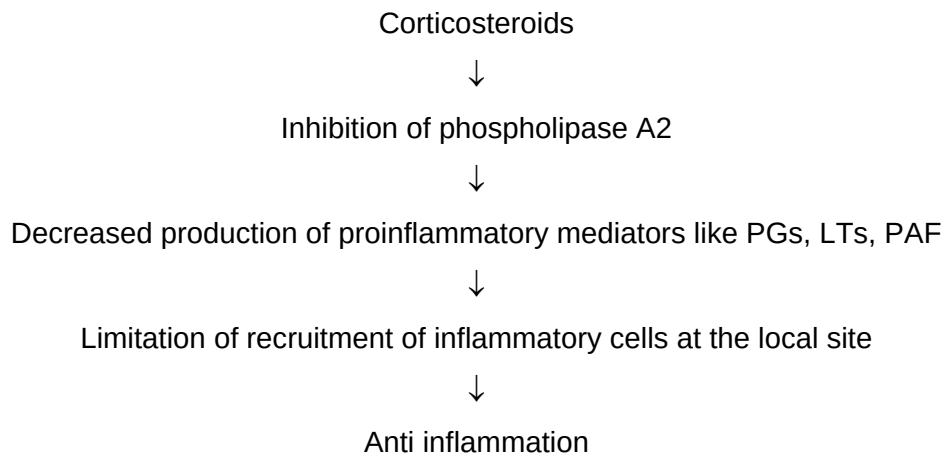
### Introduction

- Highly effective and produce nearly as rapid a response as colchicine
- Reserved for patients with renal failure, history of peptic ulcer bleed in whom NSAIDs are contraindicated or for cases not responding to or not tolerating NSAIDs.

## Drugs

- Triamcinolone acetonide

## MOA



## Use in Gout

- **Indications** →
  - When only one or few joints are involved
  - In those not tolerating NSAIDs/colchicine.
- Intraarticular injection of a soluble steroid (e.g. triamcinolone acetonide 10 mg in small finger/toe joints, 30 mg in wrist) → suppresses symptoms of acute gout.
- Crystalline preparations should not be used.



## Adverse effects

### CORTICOSTEROIDS

1. Cushing's habitus
2. Osteoporosis
3. Reduced growth
4. Thin skin
5. Immunosuppression
6. Cataracts
7. Oedema
8. Suppressed HPA axis
9. Teratogenic
10. Emotional/mood disturbances
11. Rise in blood pressure
12. Obesity (truncal)
13. Increased hair grow
14. Diabetes
15. Striae

# DRUGS FOR CHRONIC GOUT

1. Uricosirics
2. Uric acid Synthesis inhibitors

## 1. Uricosirics

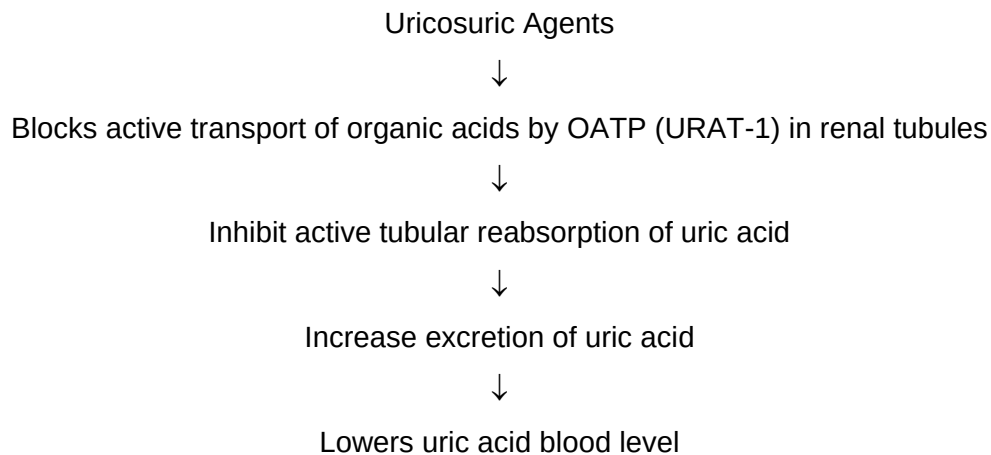
### Introduction

- Rapid acting but poorly tolerated.
- Neither analgesic nor antiinflammatory.

### Drugs

- Probenecid (Prototype)
- Sulfipyrazone
- Lesinurad

### MOA



### Pharmacokinetics

- **Probenecid** →
  - Absorbed orally
  - 90% plasma protein bound
  - Partly conjugated in liver and excreted by the kidney

### Introduction

1. Probenecid inhibits the urinary excretion of penicillins, cephalosporins, sulfonamides, Mtx and indomethacin.
2. It inhibits biliary excretion of rifampicin.
3. Probenecid inhibits tubular secretion of nitrofurantoin which may not attain antibacterial concentration in urine.
4. Aspirin blocks uricosuric action of probenecid.



## Uses

### 1. Chronic gout and hyperuricaemia

- Probenecid is a second line/adjuvant drug to allopurinol.
- It gradually depletes urate pool in body → lowers blood urate level.
- Arthritis, tophi and other lesions may take months to resolve.
- Colchicine/NSAID cover is advised during the initial 1–2 months to avoid precipitation of acute gout.
- Probenecid are ineffective in the presence of renal insufficiency → should be used only when creatinine clearance is > 50 ml/min or serum creatinine is < 2 mg/dl.
- Plenty of fluids should be given with probenecid to avoid urate crystallization in urinary tract.

**2. To prolong penicillin or ampicillin action** → by enhancing and sustaining their blood levels, e.g. in gonorrhoea, SAbE.

**3. CMV retinitis in AIDS patients** → Probenecid is given along with cidofovir in AIDS patients to prevent its nephrotoxicity.

## Adverse effects

**1. Dyspepsia** → most common side effect → used cautiously in peptic ulcer patients.

**2. Rashes**



## Other Uricosuric Agents

### • Sulfapyrazone

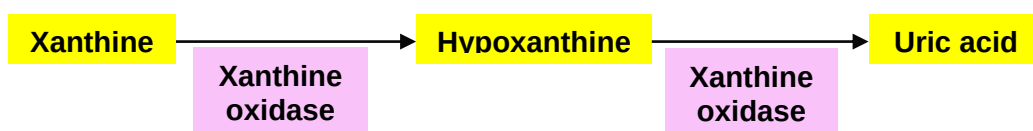
- Though equally efficacious as probenecid, sulfapyrazone has gone into disuse because of more gastric irritation
- Inhibits platelet aggregation

### • Lesinurad

- New uricosuric drug, approved recently by US-FDA as a treatment option for hyperuricaemia, either alone or in combination with a xanthine oxidase inhibitor.

## 1. Uric acid Synthesis inhibitors

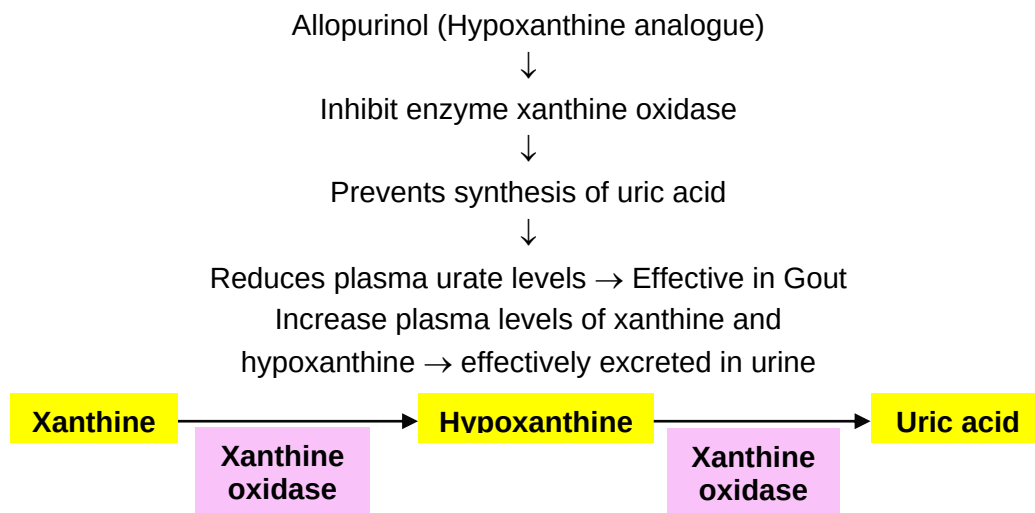
### Introduction



## Drugs

- Allopurinol (Prototype)
- Febuxostat
- Pegloticase

## MOA



## Pharmacokinetics

- **Allopurinol** →
  - About 80% of orally administered allopurinol is absorbed.
  - It is not bound to plasma proteins
  - Metabolized largely to Alloxanthine (oxypurine)
    - Allopurinol itself → short-acting ( $t_{1/2}$  2 hrs) → competitive inhibitor of xanthine oxidase
    - Its major metabolite Alloxanthine (oxypurine) → long-acting ( $t_{1/2}$  24 hrs) → noncompetitive inhibitor

## Interactions

1. Allopurinol inhibits the degradation of 6-mercaptopurine and azathioprine → their doses should be reduced to 1/3rd
2. Probenecid given with allopurinol has complex interaction → while probenecid shortens  $t_{1/2}$  of alloxanthine, allopurinol prolongs  $t_{1/2}$  of probenecid.
3. Allopurinol can potentiate warfarin and theophylline → by inhibiting their metabolism.

## Uses

### 1. Chronic gout

- Allopurinol is first choice drug in chronic gout.
- More severe cases with tophi or nephropathy also respond well.
- Tophi disappear gradually
- Nephropathy is halted and reversed.

### 2. Secondary hyperuricaemia → due to cancer chemotherapy/radiation/ thiazides or other drug

## Adverse Effects

1. **Hypersensitivity** → Skin rashes, itching, erythema, headache, fever and rarely Stevens–Johnson syndrome
2. **GIT** → Nausea, vomiting, diarrhoea and occasionally hepatotoxicity may

## Contraindications

1. Hypersensitive patients
2. Pregnancy
3. Lactation

## Other Uric acid Synthesis inhibitors

### Febuxostat

- **MOA** →
  - Newer nonpurine xanthine oxidase inhibitor
  - Same as that of Allopurinol
  - Equally or more effective than allopurinol in lowering blood uric acid level
- **Indication** → Alternative drug to allopurinol
- **Adverse effect** →
  - Hypersensitivity reactions are rare
  - Most important adverse effect is liver damage

### Pegloticase

- **MOA** → Recombinant uricase → an enzyme which oxidizes uric acid to highly soluble allantoin → that is easily excreted by kidney.
- **Indication** → only in rare cases of refractory symptomatic gout.
- **Adverse effect** → Immunogenic → carries high risk of infusion reactions and anaphylaxis.



# Drugs affecting Blood and Blood formation

## CHAPTER 5

### CONTENT

- Drugs Affecting Coagulation
- Hypolipidaemic Drugs

### DRUGS AFFECTING COAGULATION

#### Introduction

- Circulating blood contains 3 main types of mature blood cells—
- 1. **RBCs** (erythrocytes)
- 2. **WBCs** (leucocytes)
- 3. **Platelets** (thrombocytes)

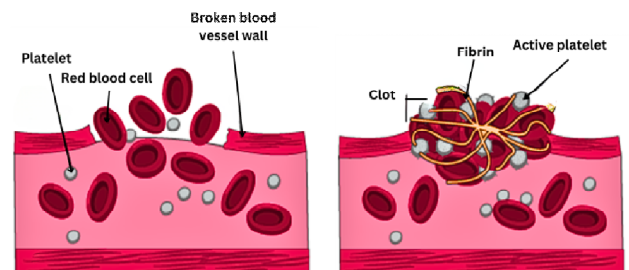


#### Function of platelets

- Main functions of platelets → Haemostasis

### HEMOSTASIS

- Physiological process → bleeding is stopped after injury → protecting integrity of vascular system after tissue injury.

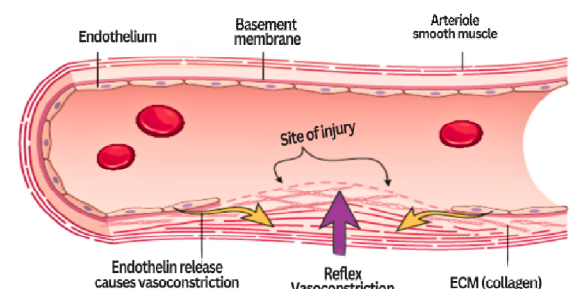


#### Steps

1. Arteriolar vasoconstriction
2. Primary hemostasis
3. Secondary hemostasis
4. Clot stabilization and resorption

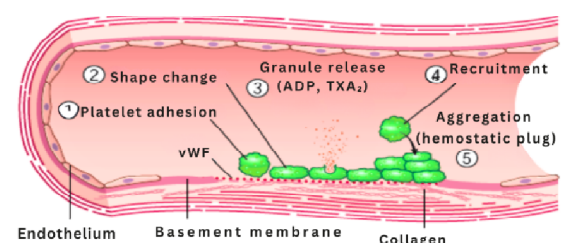
#### 1. Arteriolar vasoconstriction

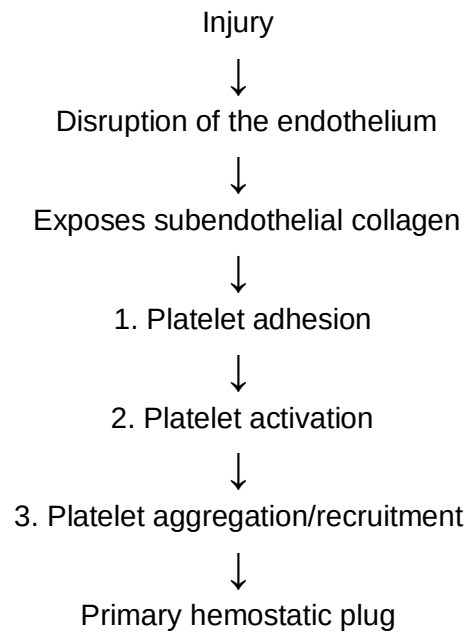
- Occurs immediately and is transient



#### 2. Primary hemostasis

- Formation of the platelet plug





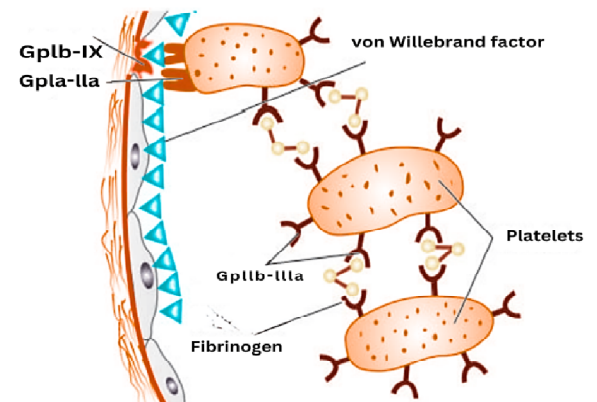
1. **Platelet adhesion** → Platelets adhere to collagen in sub endothelium due to presence of receptor (Gp) Ia-IIa and Gp Ib-IX

- vWF forms a bridge between collagen of endothelium and platelet

2. **Platelet activation** → 2 types of granules

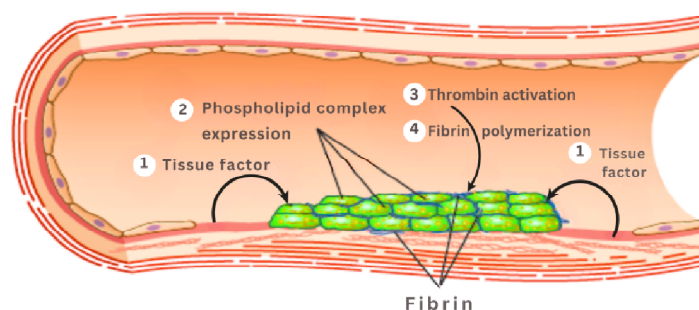
- Alpha -granules
- Dense granules

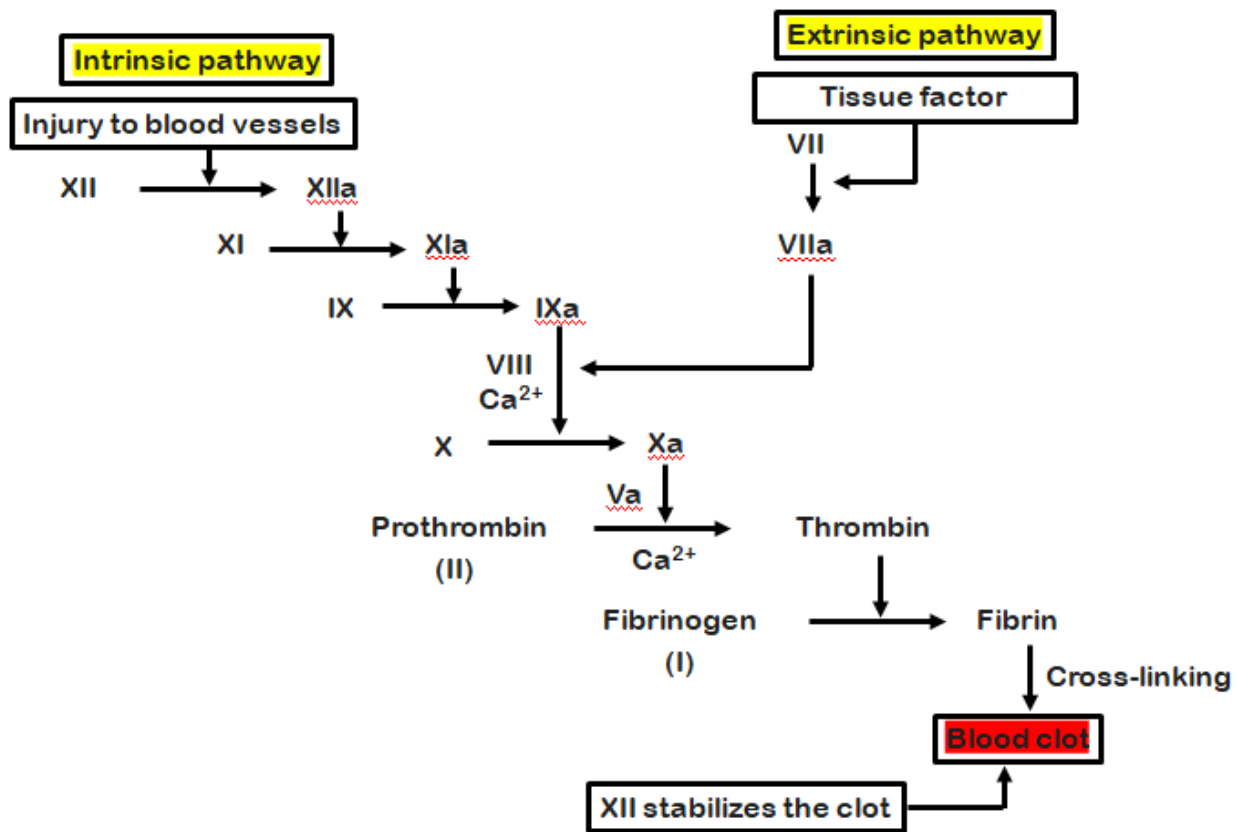
3. **Platelet aggregation** → Adherence of platelets to one another due to presence of receptor Gp IIb-IIIa



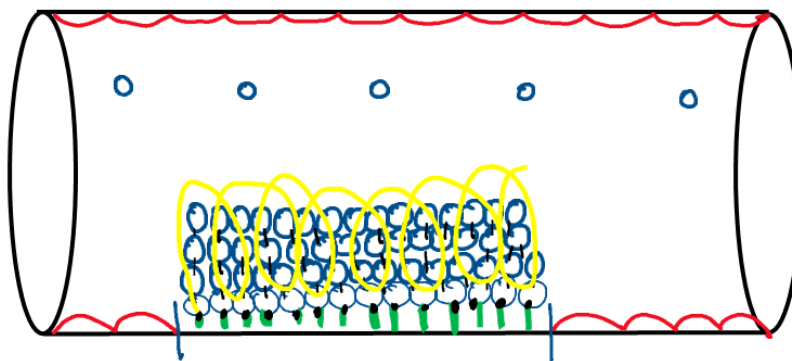
### 3. Secondary hemostasis

- Deposition of fibrin





Injury  
↓  
Tissue factor binds and activates factor VII or factor XII  
↓  
A cascade starts (Intrinsic, extrinsic, common)  
↓  
Fibrinogen into insoluble fibrin  
↓  
Fibrin meshwork is formed  
↓  
Secondary hemostasis



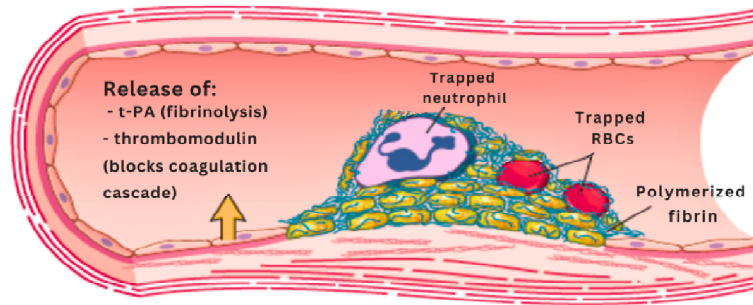


## Remember

- **Primary clot** → Platelet
- **Secondary clot** → Coagulation factors (I to XII)

## 4. Clot stabilization and resorption

Counterregulatory mechanisms ( tissue plasminogen activator, t-PA, thrombomodulin) → Clot resorption



## COMMONLY USED TESTS FOR COAGULATION DISORDERS

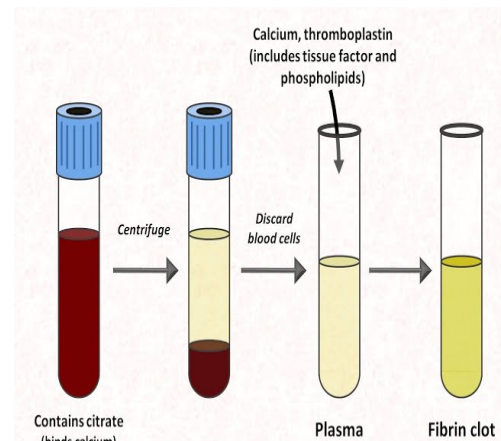
1. Bleeding time (BT)
2. Prothrombin time (PT)
3. Activated partial thromboplastin time (APTT)
4. Thrombin time (TT)

### 1. Bleeding time (BT)

- Prolongation generally indicates the defect in platelet number or function

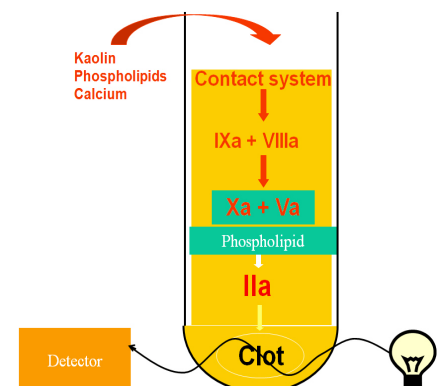
### 2. Prothrombin time (PT)

- This test assesses the extrinsic and common coagulation pathways.
- The clotting of plasma after addition of an exogenous source of tissue thromboplastin (e.g., brain extract) and  $\text{Ca}^{2+}$  ions is measured in seconds.
- A prolonged PT can result from deficiency or dysfunction of → factor V, factor VII, factor X, prothrombin, or fibrinogen.



### 3. Activated partial thromboplastin time (aPTT)

- This test assesses the intrinsic and common clotting pathways.
- The clotting of plasma after addition of kaolin, cephalin, and  $\text{Ca}^{2+}$  ions is measured in seconds.
- Kaolin activates the contact dependent factor XII, and cephalin substitutes for platelet phospholipids.
- Prolongation of the PTT can be due to deficiency or dysfunction of → factors V, VIII, IX, X, XI, or XII, prothrombin, or fibrinogen



## 4. Thrombin time

- It tests the conversion of fibrinogen to fibrin
- It is elevated to fibrinogen deficiency.

### Remember

- **Normal BT:** 2-9 minutes
- **Normal aPTT:** 28-35 seconds
- **Normal PT:** 11-13 seconds
- **Normal TT:** 15-20 seconds
- In common coagulation pathway defect both PT and aPTT are elevated

|                | Defect in Extrinsic pathway | Defect in Intrinsic pathway | Defect in Common pathway |
|----------------|-----------------------------|-----------------------------|--------------------------|
| <b>Factors</b> |                             |                             |                          |
| <b>PT</b>      |                             |                             |                          |
| <b>aPTT</b>    |                             |                             |                          |

## NATURAL ANTICOAGULANT

1. Antithrombin III
  2. Protein C
  3. Protein S
  4. Antithromboplastin
  5. Fibrinolysin system (Plasminogen)
- Tend to oppose coagulation and lyse formed clot

Coagulants = Anticoagulants



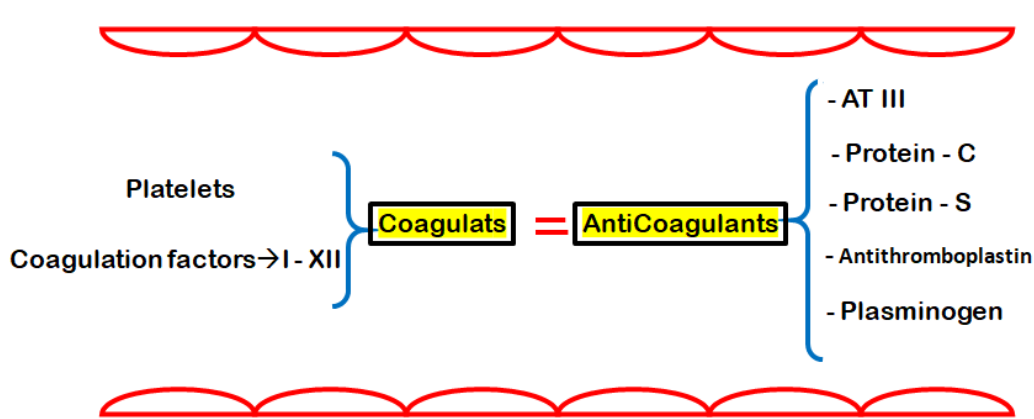
A balance system operates



Maintain blood in a fluid state while in circulation

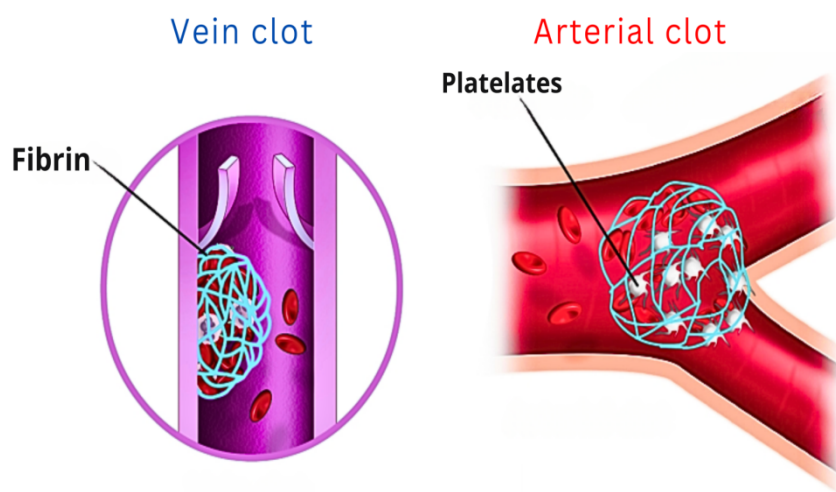


Allows rapid haemostasis following injury



## THROMBOSIS

- Thrombosis is formation of a blood clot (solid mass) in unruptured CVS from constituents of flowing blood → obstructs flow of blood

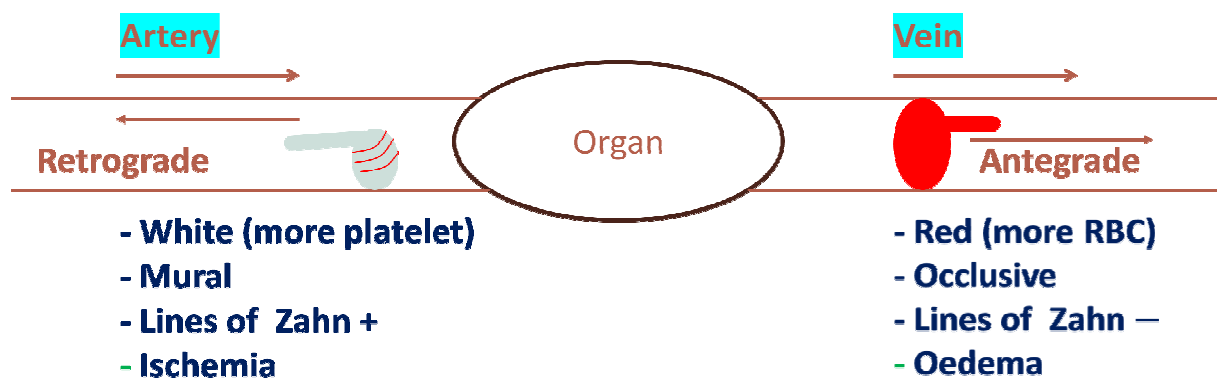


### Remember

- Haemostasis** → occurs after injury to CVS and is useful as it stops escape of blood and plasma
- Thrombosis** → occurs in unruptured CVS (without injury) and has harmful effects of ischemia

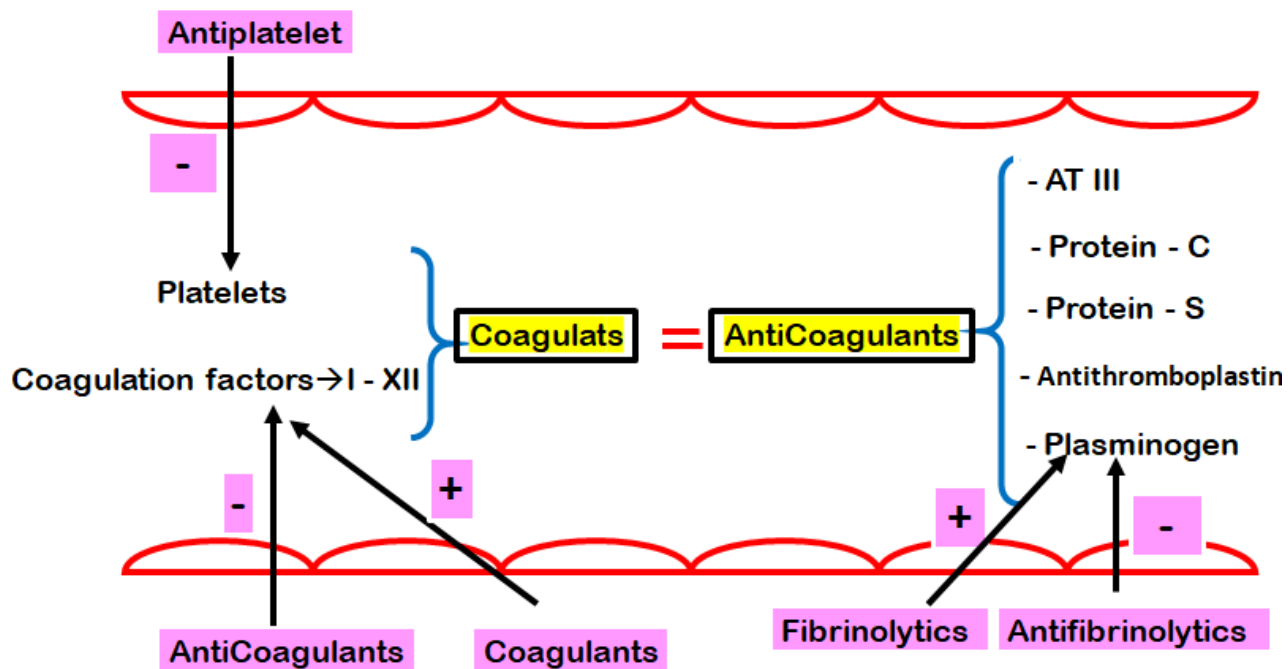
### Types of thrombus

- Arterial thrombus (Platelet thrombus)
- Venous thrombus (Fibrin thrombus)



## DRUGS AFFECTING COAGULATION SYSTEM

- Coagulants
- Anticoagulants
- Antiplatelets
- Fibrinolytics
- Antifibrinolytics

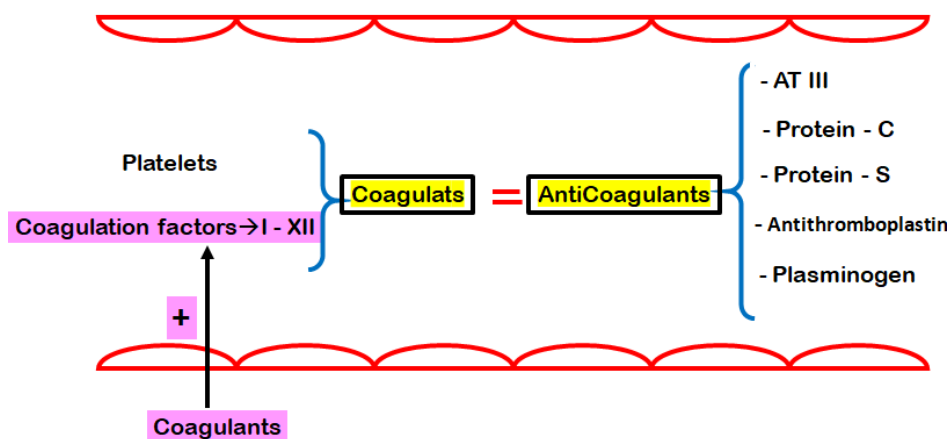


|                 | Coagulants | Anticoagulants | Antiplatelets | Fibrinolytics | Antifibrinolytics |
|-----------------|------------|----------------|---------------|---------------|-------------------|
| Introduction    |            |                |               |               |                   |
| Classification  |            |                |               |               |                   |
| MOA             |            |                |               |               |                   |
| Use             |            |                |               |               |                   |
| Adverse effects |            |                |               |               |                   |

## COAGULANTS

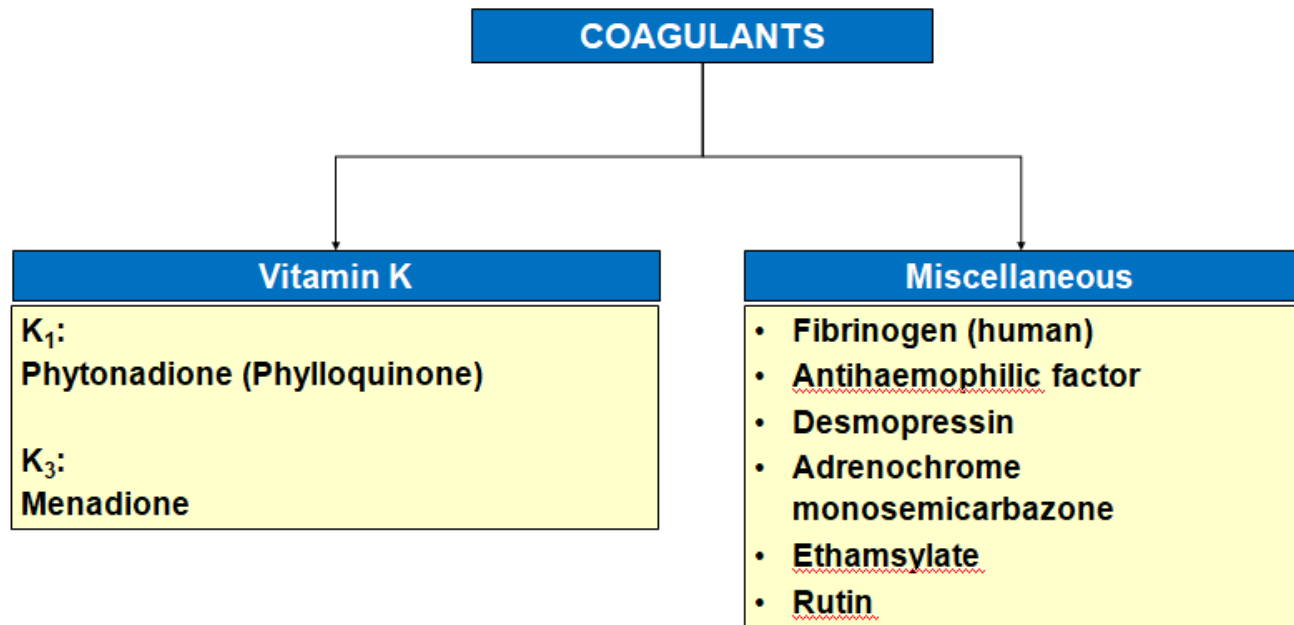
### Introduction

- **Coagulants** → substances which promote coagulation
- **Indication** → in haemorrhagic states



## Classification

1. Fresh whole blood or plasma → provide all the factors needed for coagulation and are the best therapy for deficiency of any clotting factor and they act immediately
2. Vitamin K
3. Miscellaneous



---

## VITAMIN K

---

### Introduction

- Fat soluble vitamin.
- Major coagulant of human body
- Required for → synthesis of clotting factors
- Half life of vit K → 72 hours

### Types

3 types →

1. **K1** (from plants) - Phytonadione
2. **K2** (Produced by bacteria) - Menaquinones
3. **K3** (Synthetic) - Menadione

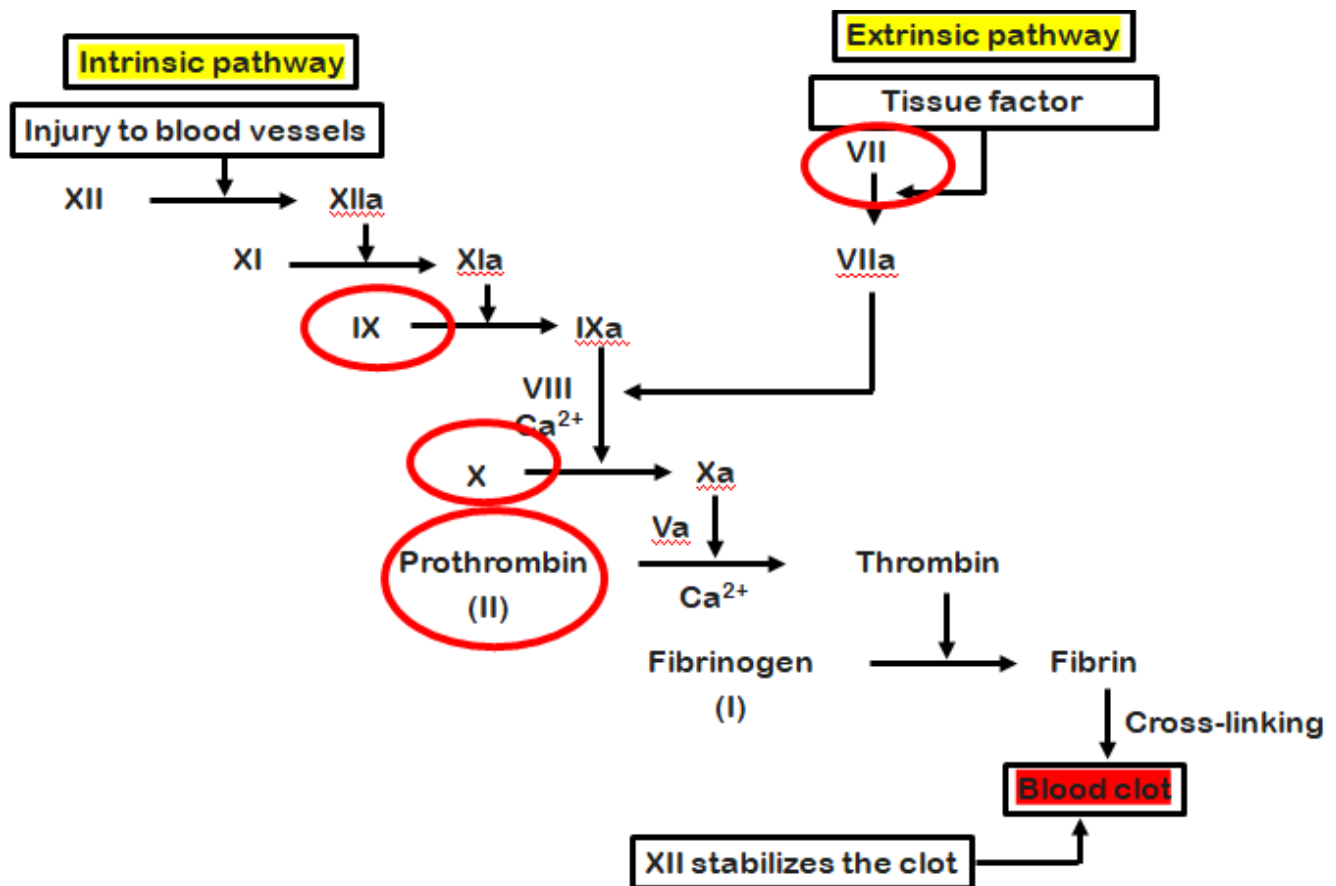
### Absorption

- Fat-soluble forms of vit K are absorbed from the intestine via lymph and require bile salts for absorption
- Water-soluble forms are absorbed directly into portal blood.

## MOA

Vit K acts as a cofactor at a late stage in synthesis of coagulation factors by liver →

1. Prothrombin (factor II)
2. Factor VII
3. Factor IX
4. Factor X
5. Protein C & Protein S



Factor II, Factor VII, IX and X , Protein 'C & Protein S' contains glutamate residues in their structures



Vitamin K cause gamma carboxylation of their glutamate residues

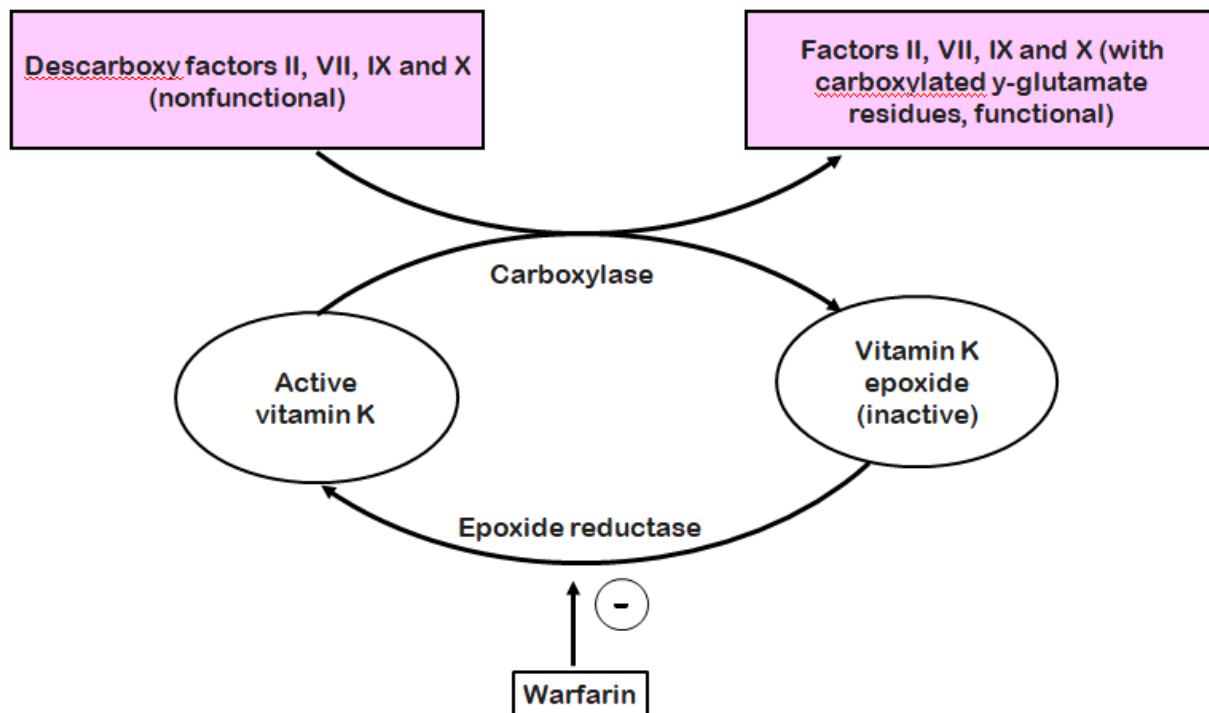


Confers capacity to bind Ca<sup>2+</sup> and to get bound to phospholipids surfaces



Activation of factor II , VII, IX and X , protein 'C & Protein S'





- During this reaction Vitamin K active form ( hydroquinone) gets converted into inactive form ( epoxide)
- Vitamin K epoxide again gets converted into Vitamin K hydroquinone by enzyme Vitamine K epoxide reductase

## Uses

- Phytonadione (K1) → preparation of choice because it acts most rapidly.
  1. Deficiency states
  2. Liver disease
  3. Haemorrhagic disease of newborn
  4. Overdose of oral anticoagulants

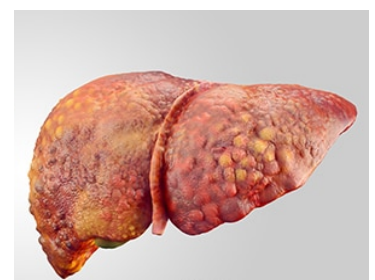


### 1. Deficiency states

- Dietary deficiency
- Prolonged antimicrobial therapy
- Obstructive jaundice
- Malabsorption syndrome.



### 2. Liver disease



### 3. Haemorrhagic disease of newborn

- All newborns have low levels of prothrombin and other clotting factors
- Defect is exaggerated in premature infant
- HDN can be prevented and treated with Vit K. 1 mg. IM injection of Vit. K is given prophylactically at time of delivery.



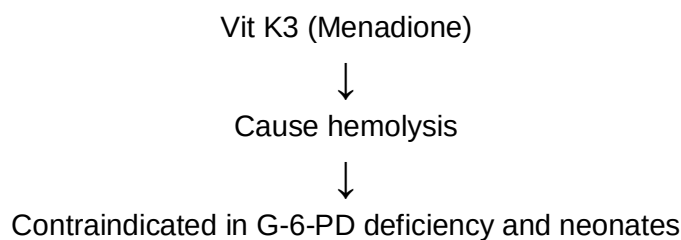
### 4. Overdose of oral anticoagulants

- Oral anticoagulant interfere with synthesis of Vit K dependent clotting factor
- So Vit K can be used to reverse the effect.

### Adverse effects

1. Hemolysis
2. Kernicterus

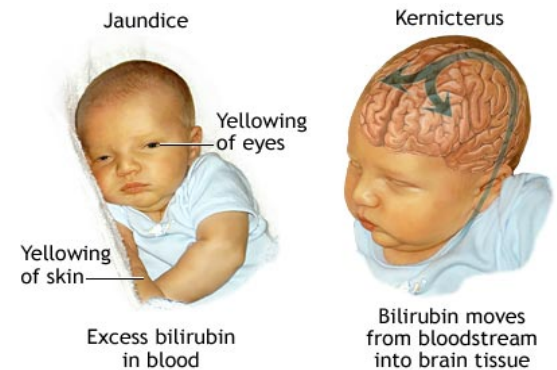
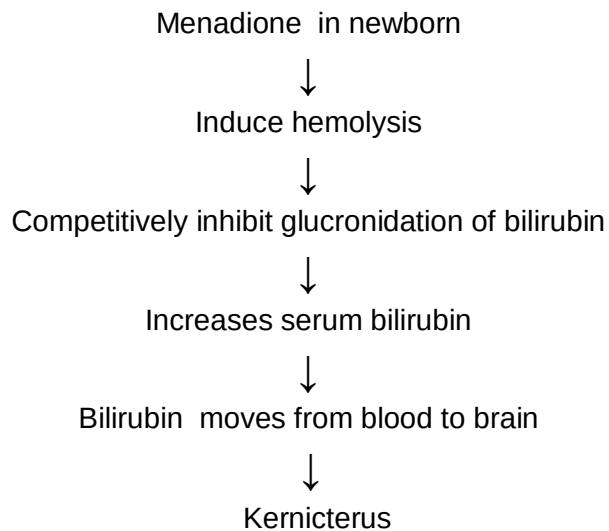
#### 1. Hemolysis



| Normal person                                            | Person with G6PD deficiency                                  |
|----------------------------------------------------------|--------------------------------------------------------------|
| ↓                                                        | ↓                                                            |
| Oxidant stress                                           | Oxidant stress                                               |
| ↓                                                        | ↓                                                            |
| G6PD present                                             | NADPH is not generated in HMP shunt                          |
| ↓                                                        | ↓                                                            |
| NADPH is generated in HMP shunt                          | Oxidized glutathione is not converted to Reduced glutathione |
| ↓                                                        | ↓                                                            |
| Oxidized glutathione is converted to Reduced glutathione | RBCs are not protected from oxidant injury                   |
| ↓                                                        | ↓                                                            |

|                                                                                               |                                                  |
|-----------------------------------------------------------------------------------------------|--------------------------------------------------|
| <p>Reduced glutathione protects RBCs<br/>From oxidant injury</p> <p>↓</p> <p>No hemolysis</p> | <p>Intravascular and extravascular hamolysis</p> |
|-----------------------------------------------------------------------------------------------|--------------------------------------------------|

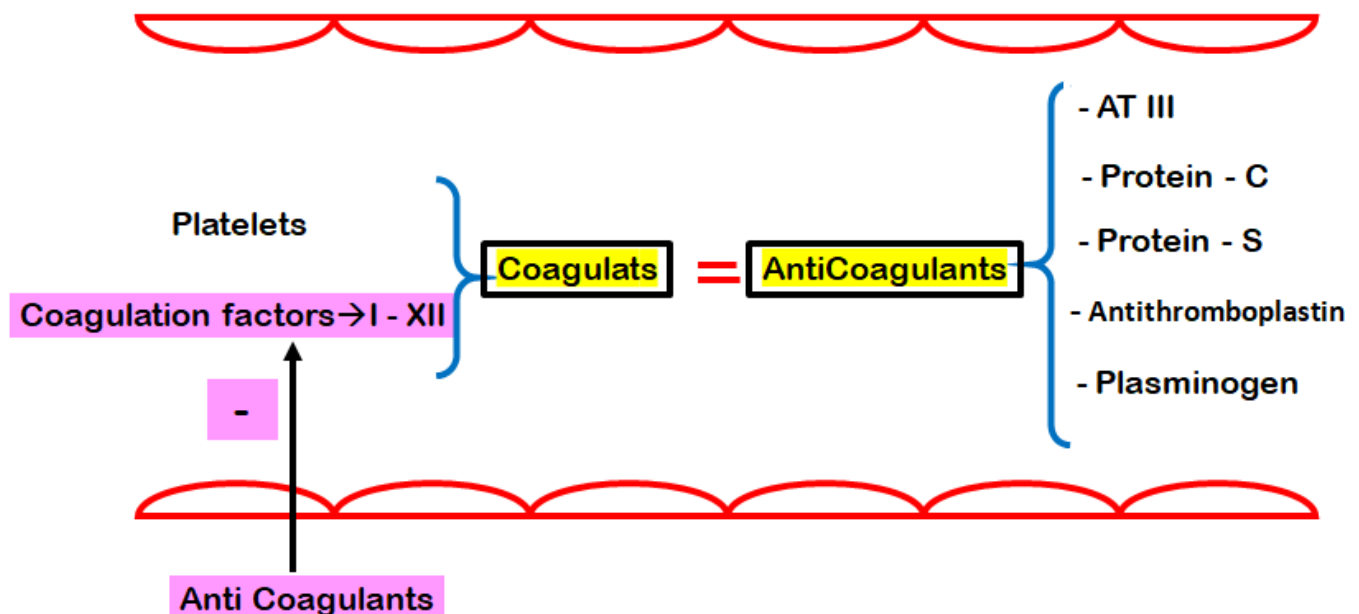
## 2. Kernicterus



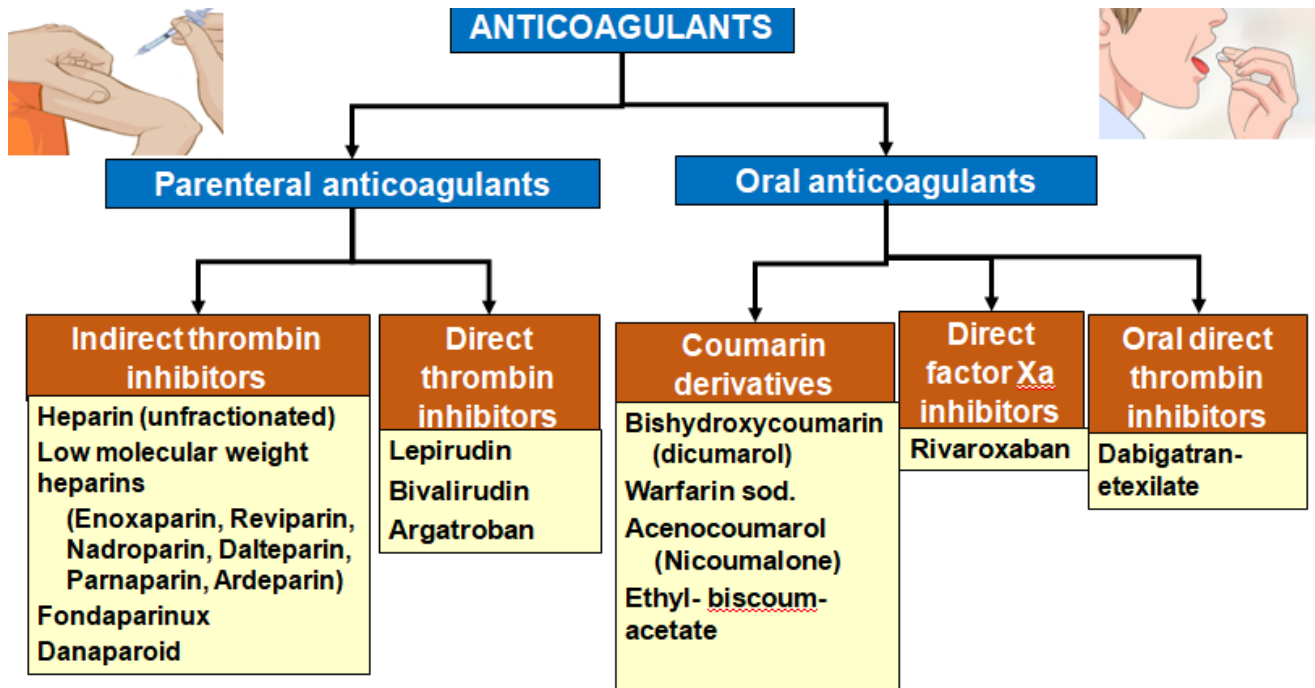
## ANTICOAGULANTS

### Introduction

- Anticoagulants → Drugs used to reduce coagulability of blood



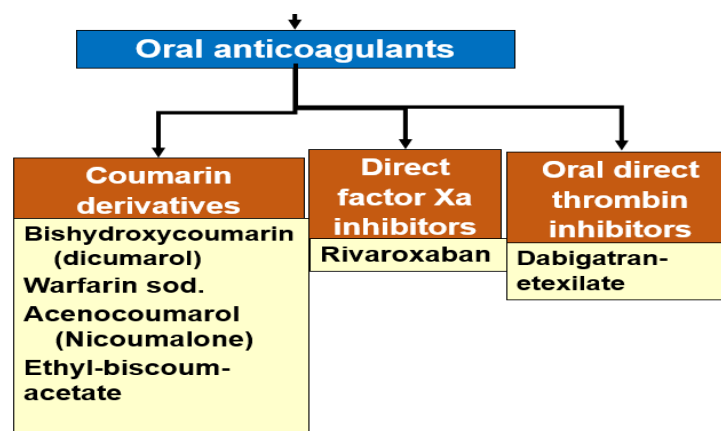
## Classification



## ORAL ANTICOAGULANTS



## Classification



| Oral Anticoagulants            |                      |                             |                                |
|--------------------------------|----------------------|-----------------------------|--------------------------------|
|                                | Coumarin derivatives | Direct Factor Xa Inhibitors | Oral Direct Thrombin Inhibitor |
| Drugs                          |                      |                             |                                |
| MOA                            |                      |                             |                                |
| Dose regulation and Monitoring |                      |                             |                                |
| Advantages                     |                      |                             |                                |
| Use                            |                      |                             |                                |
| Adverse effects                |                      |                             |                                |
| Contraindications              |                      |                             |                                |
| Interactions                   |                      |                             |                                |

## COUMARIN DERIVATIVES

### Drugs

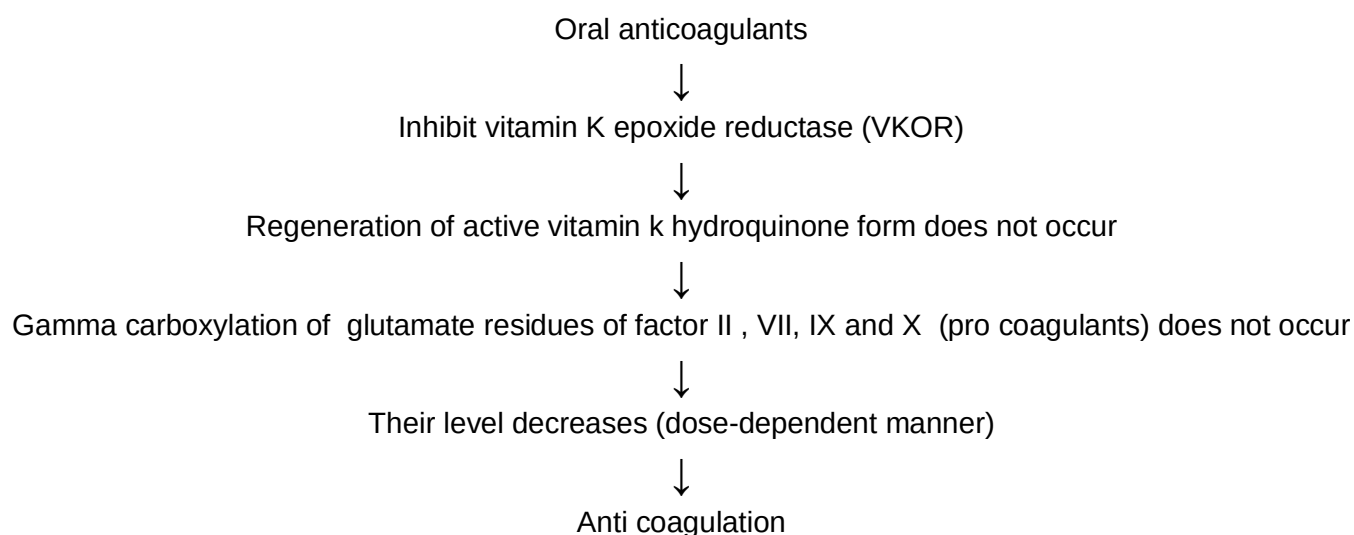
- Coumarin derivatives → Bishydroxycoumarin (dicumarol)
- Warfarin sod.
- Acenocoumarol (Nicoumalone)
- Ethyl-biscoum-acetate

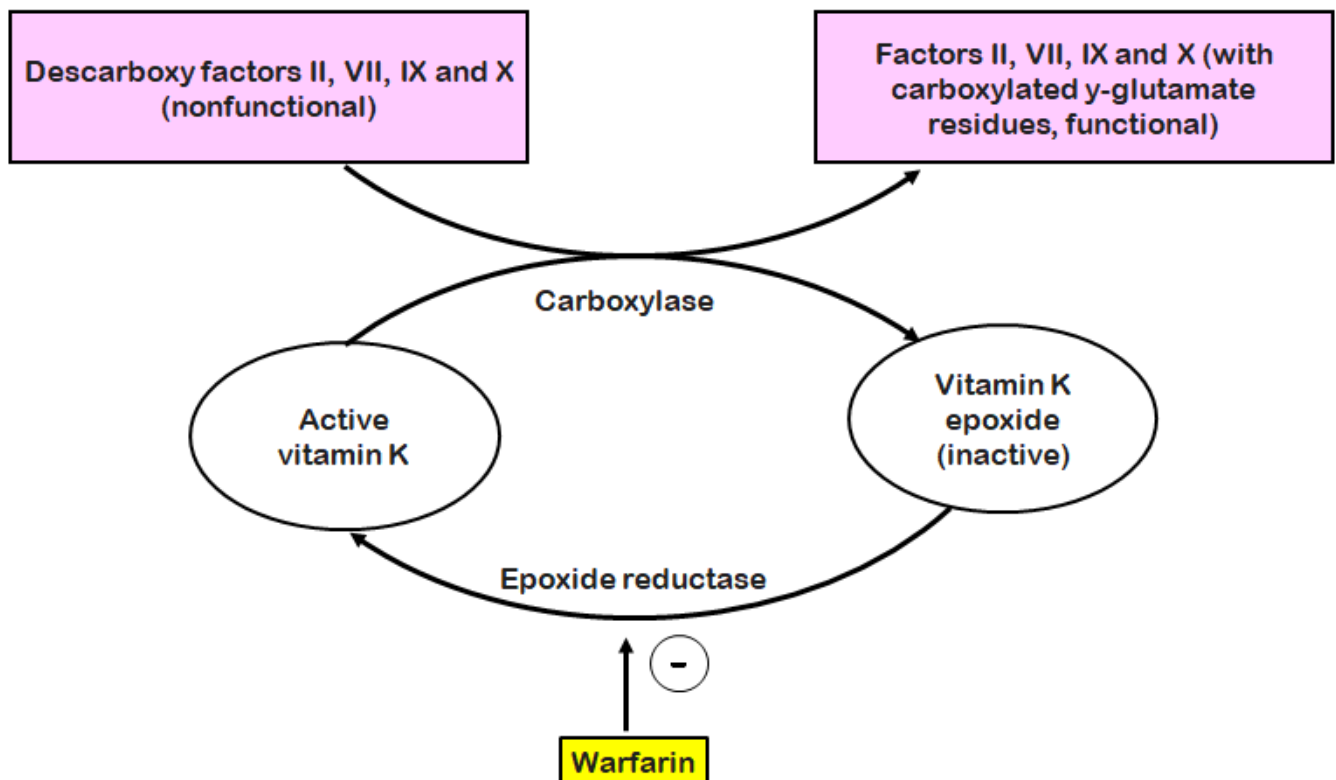
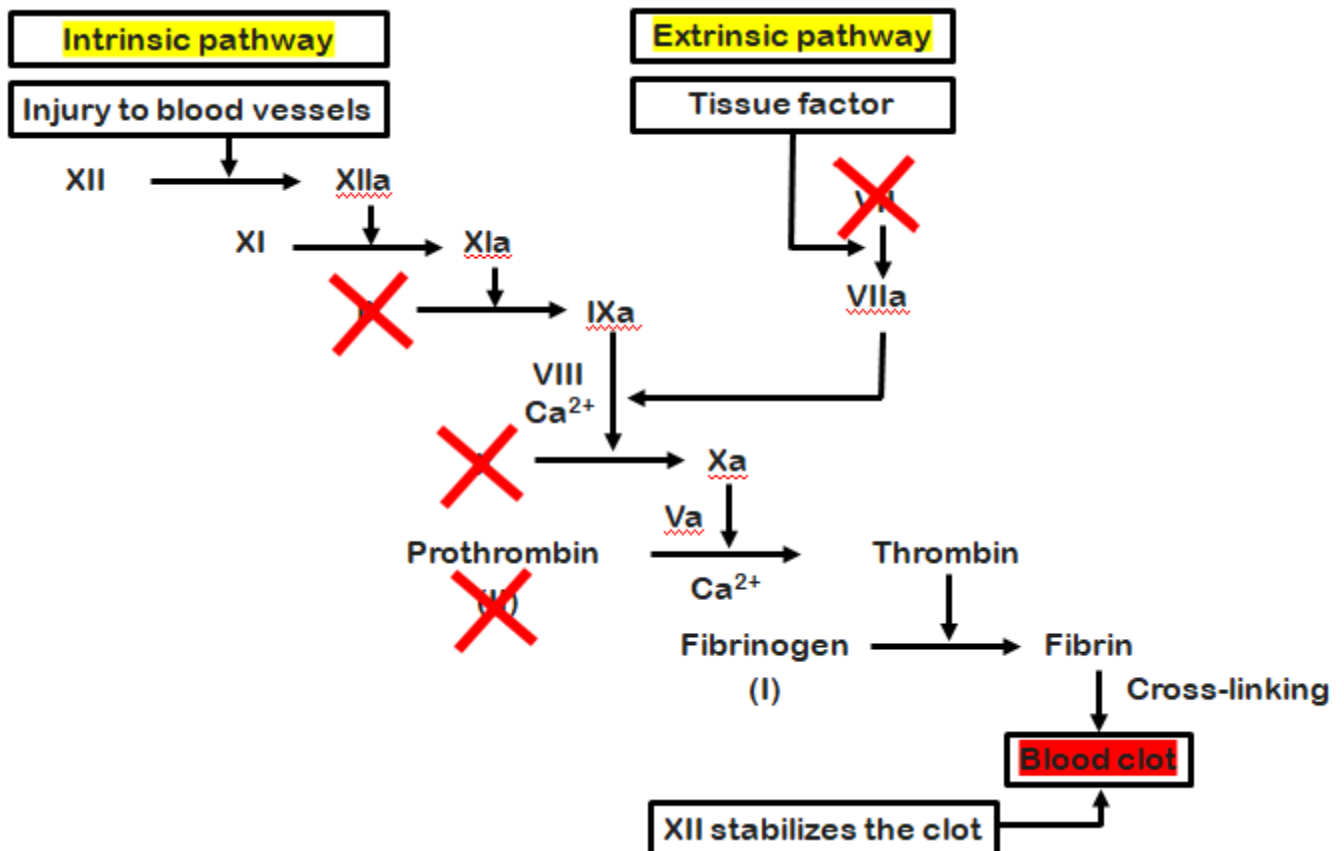
### Remember

- **Warfarin** → prototype oral anticoagulant.
- **Bishydroxycoumarin (Dicumarol)** → longest acting oral anticoagulant
- **Ethylbiscoumacetate** → shortest acting anticoagulant.

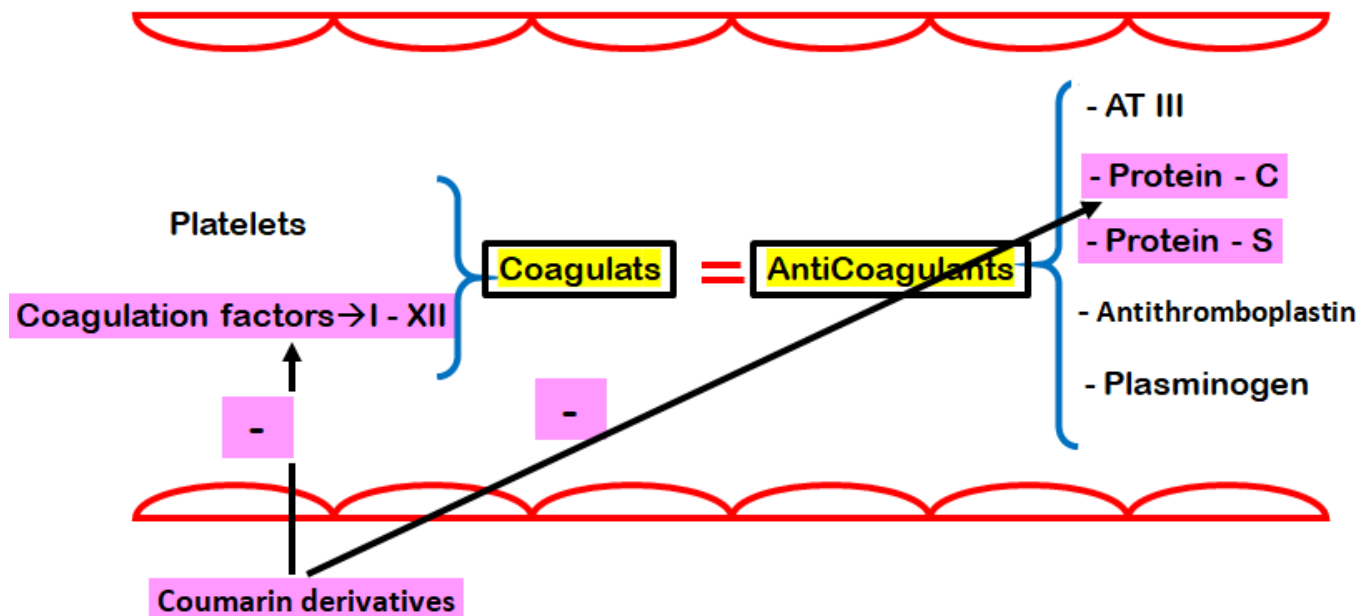
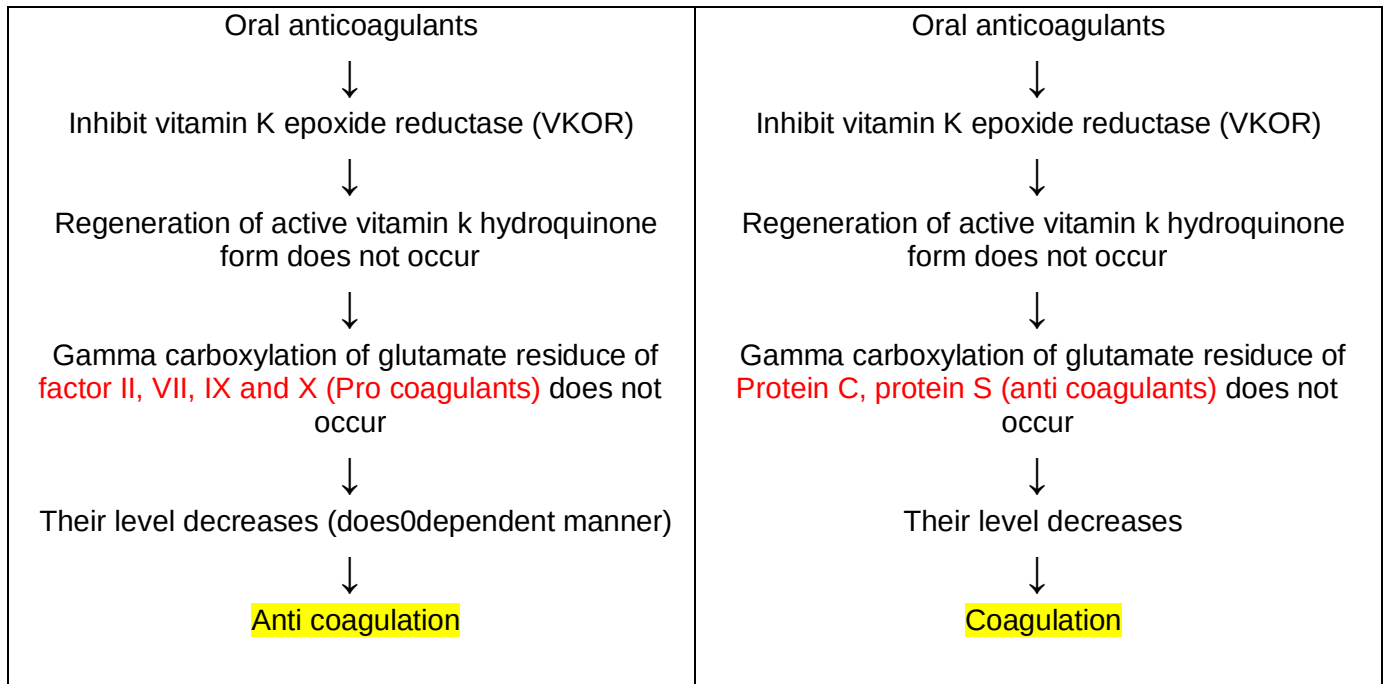
### MOA

- They act indirectly by interfering with synthesis of vit K dependent clotting factors in liver.



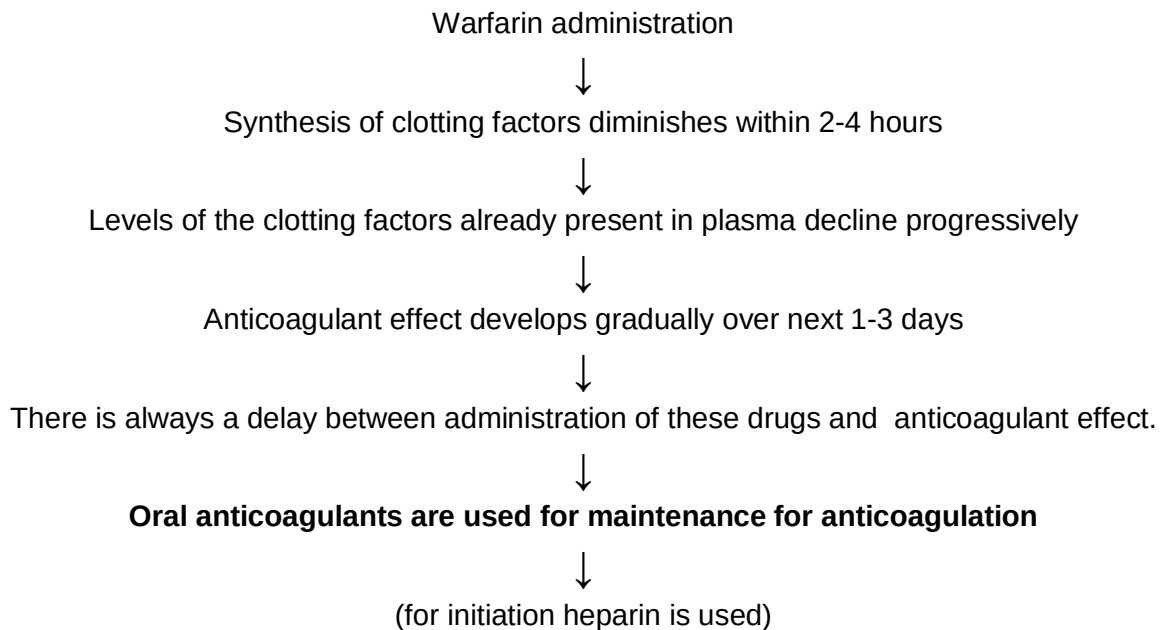
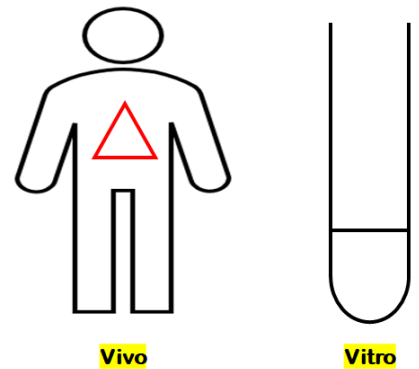
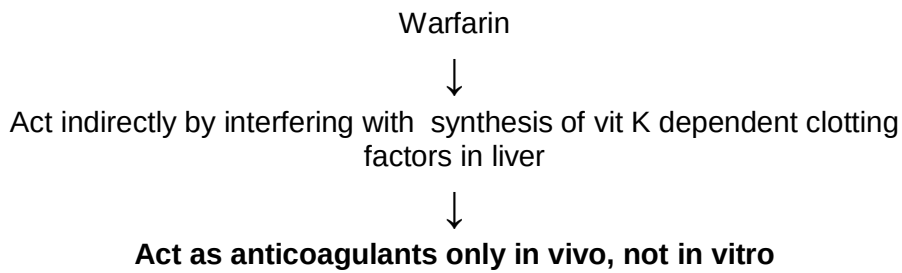


## Remember



- Anti coagulants (Protein C and Protein S) have a shorter t<sub>1/2</sub> than procoagulant factors (II, VII, IX & X)
- Anti coagulants (Protein C and Protein S) more rapid decline in concentration
  - **Transient hypercoagulable state is achieved**
  - Initiate anticoagulation with heparin until effect of warfarin is well established.





### Sequence of level fall

- Factor VII has shortest plasma  $t_{1/2}$  (6 hrs), its level falls first when warfarin is given
- Factor VII (6 hrs) > factor IX (24 hrs) > factor X (40 hrs) > Factor II (60 hrs)

### Dose regulation and Monitoring

1. Prothrombin time
2. INR

#### 1. Prothrombin time

- Dose of oral anticoagulant must be individualised by repeated measurement of prothrombin time (because they selectively inhibit extrinsic pathway)
- Aim → to achieve a therapeutic effect without unduly increasing chances of bleeding

#### 2. INR

- Optimum ratio of PT during treatment with oral anticoagulant to normal value (of testing laboratory)

$$INR = \left\{ \frac{PT_{pt}}{PT_{ref}} \right\}^{ISI}$$

| Recommended INR for various indication of oral anticoagulants                | INR   |
|------------------------------------------------------------------------------|-------|
| 1. Prophylaxis of deep vein thrombosis and similar indications               | 2-2.5 |
| 2. Treatment of deep vein thrombosis, pulmonary embolism, TIAS, hip surgery  | 2-3   |
| 3. Recurrent thromboembolism, arterial disease (MI), prosthetic heart valves | 3-3.5 |

## Uses

- Heparin is utilized for rapid and shortlived Action → Initiation therapy
  - Oral anticoagulants → maintenance therapy.
    - Generally, the two are started together
    - Heparin is discontinued after 4–7 days when warfarin has taken effect.
1. Deep vein thrombosis (DVT) and pulmonary embolism (PE)
  2. Prophylaxis of Deep vein thrombosis (DVT) and pulmonary embolism (PE)
  3. Myocardial infarction (MI)
  4. Unstable angina
  5. Atrial fibrillation (AF)
  6. Vascular surgery, prosthetic heart valves, retinal vessel thrombosis, extracorporeal circulation, haemodialysis
  7. DIC

## Adverse effects

1. Bleeding
2. Alopecia
3. Dermatitis and skin necrosis

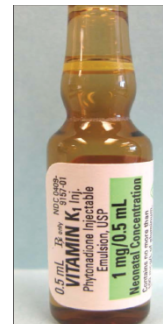
### 1. Bleeding

- Bleeding as a result of extension of desired pharmacological action
- Bleeding is more likely if therapy is not properly monitored or when INR exceeds 4
- Ecchymosis, epistaxis, hematuria, bleeding in GIT
- Intracranial or other internal haemorrhages may be fatal.



## Treatment of bleeding due to oral anticoagulants

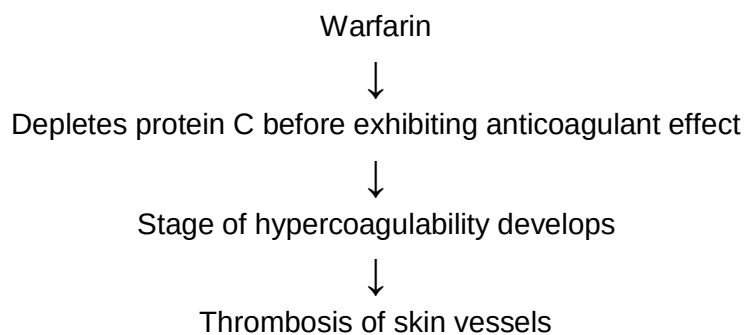
- Withhold anticoagulant.
- Give fresh blood transfusion or fresh frozen plasma → this supplies clotting factors and replenishes lost blood.
- Give vit K1



## 2. Alopecia



## 3. Dermatitis and skin necrosis



## Contraindications

1. Bleeding disorders
2. History of heparin induced thrombocytopenia.
3. Severe hypertension (risk of cerebral haemorrhage), threatened abortion, piles, g.i. ulcers (risk of aggravated bleeding).
4. Subacute bacterial endocarditis (risk of embolism)
5. Chronic alcoholics, cirrhosis, renal failure.
6. Aspirin and other antiplatelet drugs should be used very cautiously during heparin therapy.

• **Pregnancy** →

- Given in early pregnancy → Foetal warfarin syndrome → hypoplasia of nose, eye socket, hand bones, and growth retardation.
- Given later in pregnancy → CNS defects, foetal haemorrhage, foetal death



## Interactions

- a) Enhanced anticoagulant action
- b) Reduced anticoagulant action

### A) Enhanced anticoagulant action

1. Enzyme inhibitors → inhibit warfarin metabolism.
2. Long acting sulfonamides, indomethacin, phenytoin and probenecid: displace warfarin from plasma protein binding.
3. Broad-spectrum antibiotics: inhibit gut flora and reduce vit K production.
4. Aspirin:
  - Inhibits platelet aggregation and causes g.i. bleeding—this may be hazardous in anticoagulated patients.
  - High doses of salicylates have synergistic hypoprothrombinemic action and also displace warfarin from protein binding site.

### B) Reduced anticoagulant action

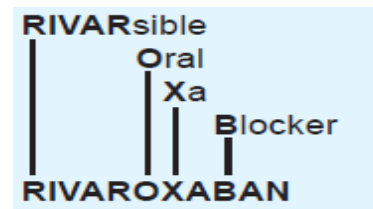
1. Enzyme inducers induce metabolism of oral anticoagulant
2. Oral contraceptives: increase blood levels of clotting factors.

|                            | WARFARIN                               | HEPARIN                                |
|----------------------------|----------------------------------------|----------------------------------------|
| 1. Chemistry               | Coumarin derivative                    | Mucopolysaccharide                     |
| 2. Source                  | Synthetic                              | Hog lung, pig intestine                |
| 3. Route of admin.         | Oral                                   | Parenteral (i.v., s.c.)                |
| 4. Onset of action         | delayed (1-3 days)                     | Immediate                              |
| 5. Duration of action      | 3-6 days                               | 4-6 hrs                                |
| 6. Activity                | In vivo only                           | In vitro and in vivo                   |
| 7. Mechanism               | Inhibits synthesis of clotting factors | Blocks action of factor X and thrombin |
| 8. Antagonist              | Vit K                                  | Protamine sulphate                     |
| 9. Variability in response | Marked                                 | little                                 |
| 10. Lab. control           | Prothrombin time/INR (essential)       | aPTT/clothing time (desirable)         |
| 11. Drug interactions      | Many and significant                   | Few and not significant                |
| 12. Use                    | For maintainance                       | to initiate therapy                    |

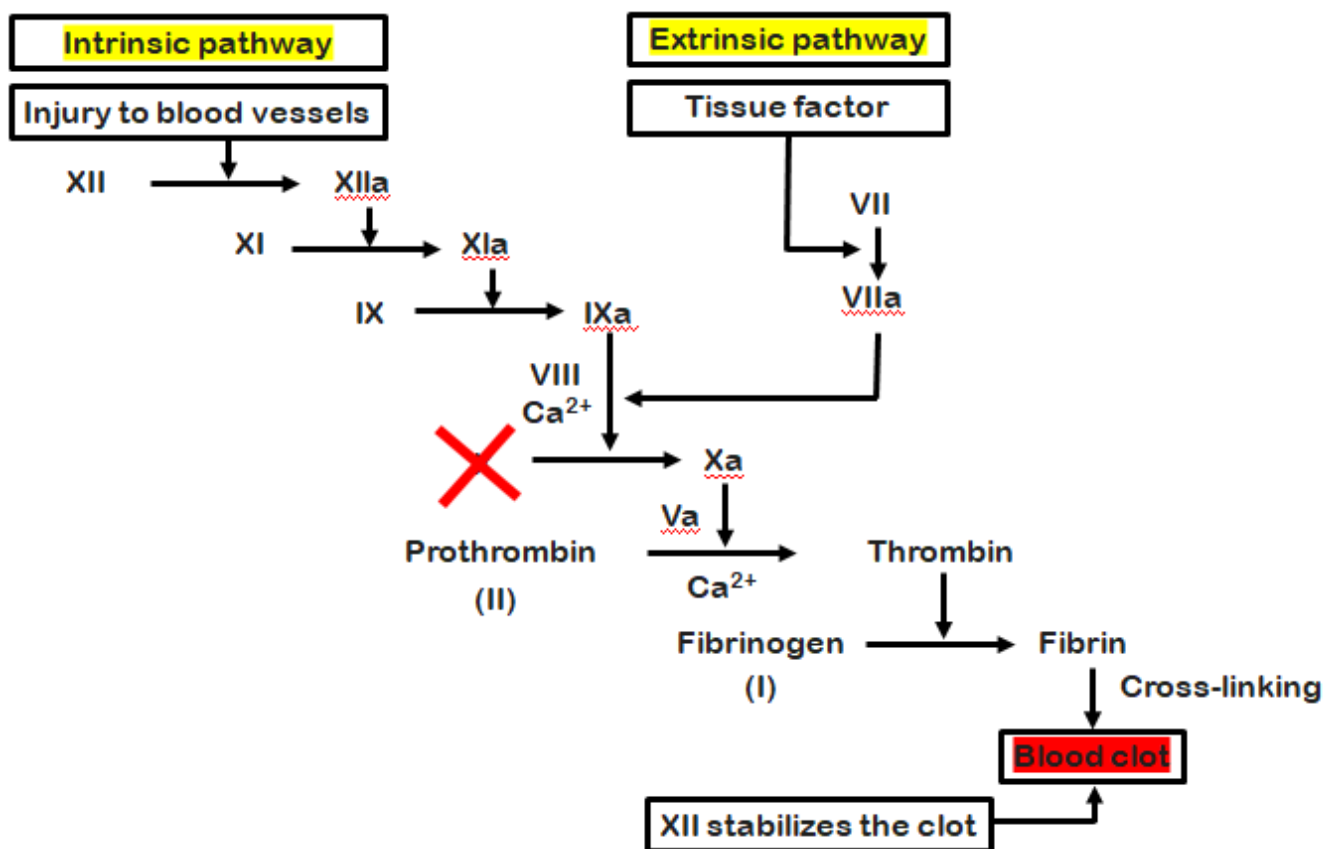
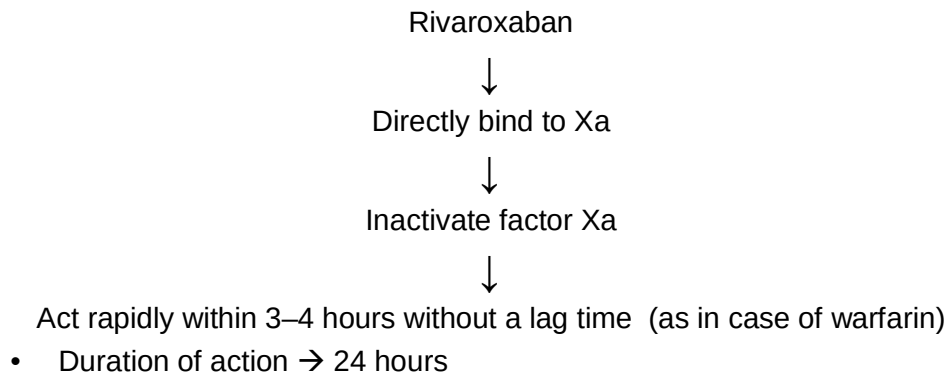
# DIRECT FACTOR XA INHIBITORS

## Drugs

- Rivaroxaban



## MOA



## Advantages

- Act rapidly without a lag time (It directly bind to and inactivate factor Xa, instead of inhibiting its synthesis)
- No laboratory monitoring of PT or APTT is required
- Efficacy has been found similar to a regimen of LMW heparin followed by warfarin.

## Uses

- For prophylaxis and treatment of DVT



## Adverse effects

1. Bleeding
2. Nausea
3. Hypotension
4. Tachycardia
5. Edema

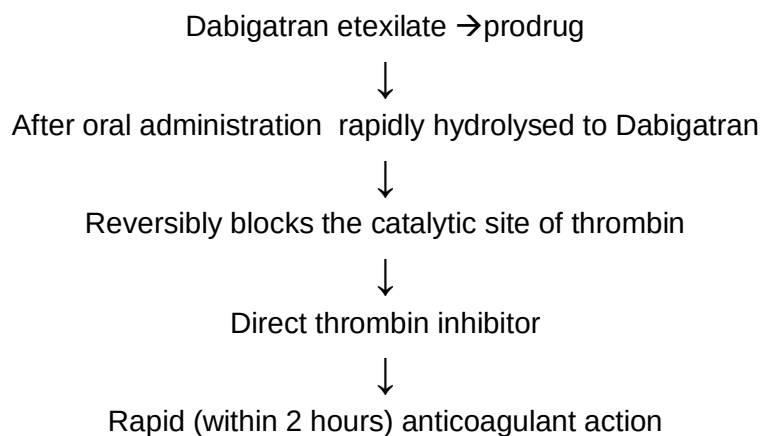


## ORAL DIRECT THROMBIN INHIBITOR

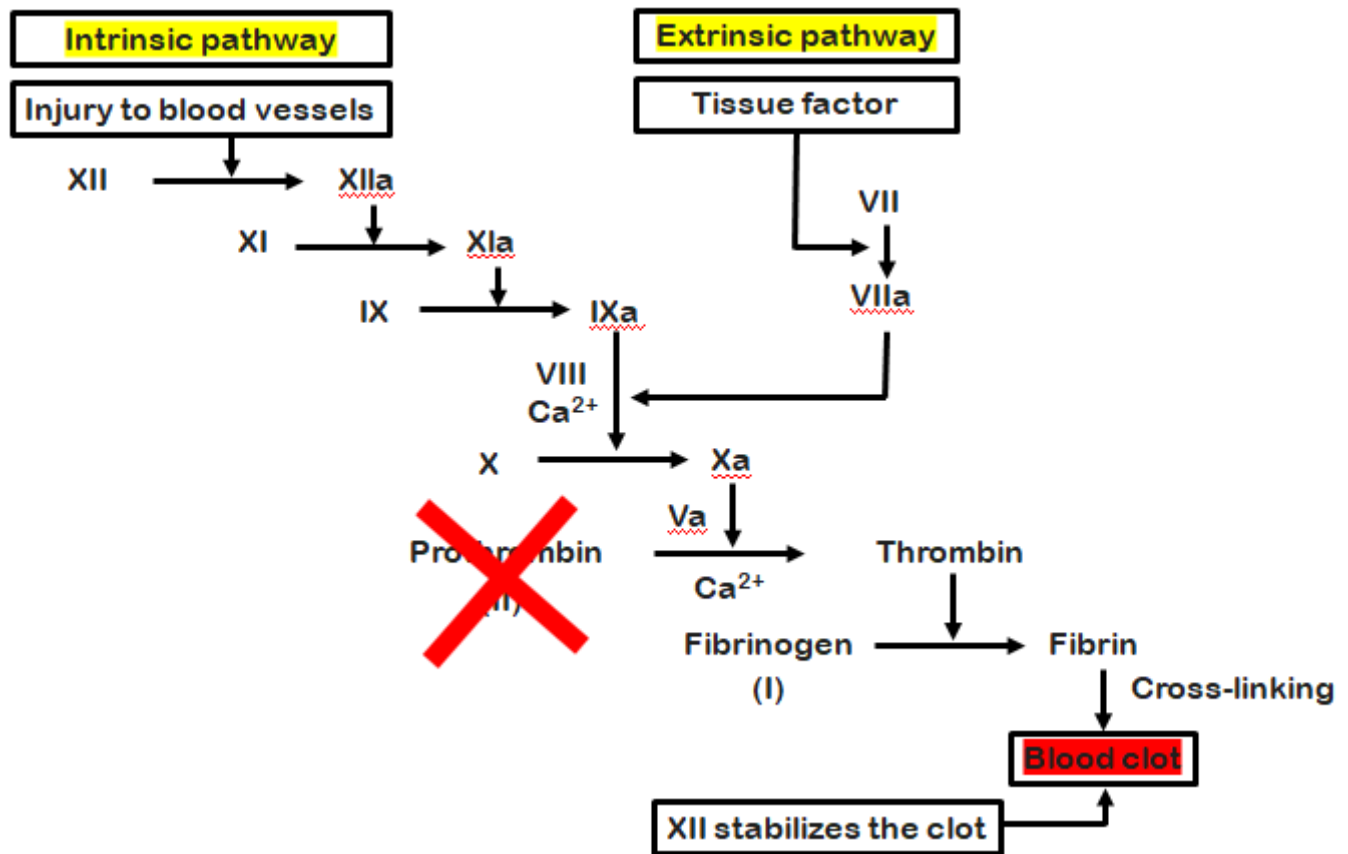
### Drugs

- Dabigatran etexilate

### MOA



- Duration of action → 24 hours.



## Advantages

1. Act rapidly without a lag time (It directly inactivate thrombin, instead of inhibiting its synthesis)
2. No laboratory monitoring of PT is required

## Uses

- For prophylaxis and treatment of DVT



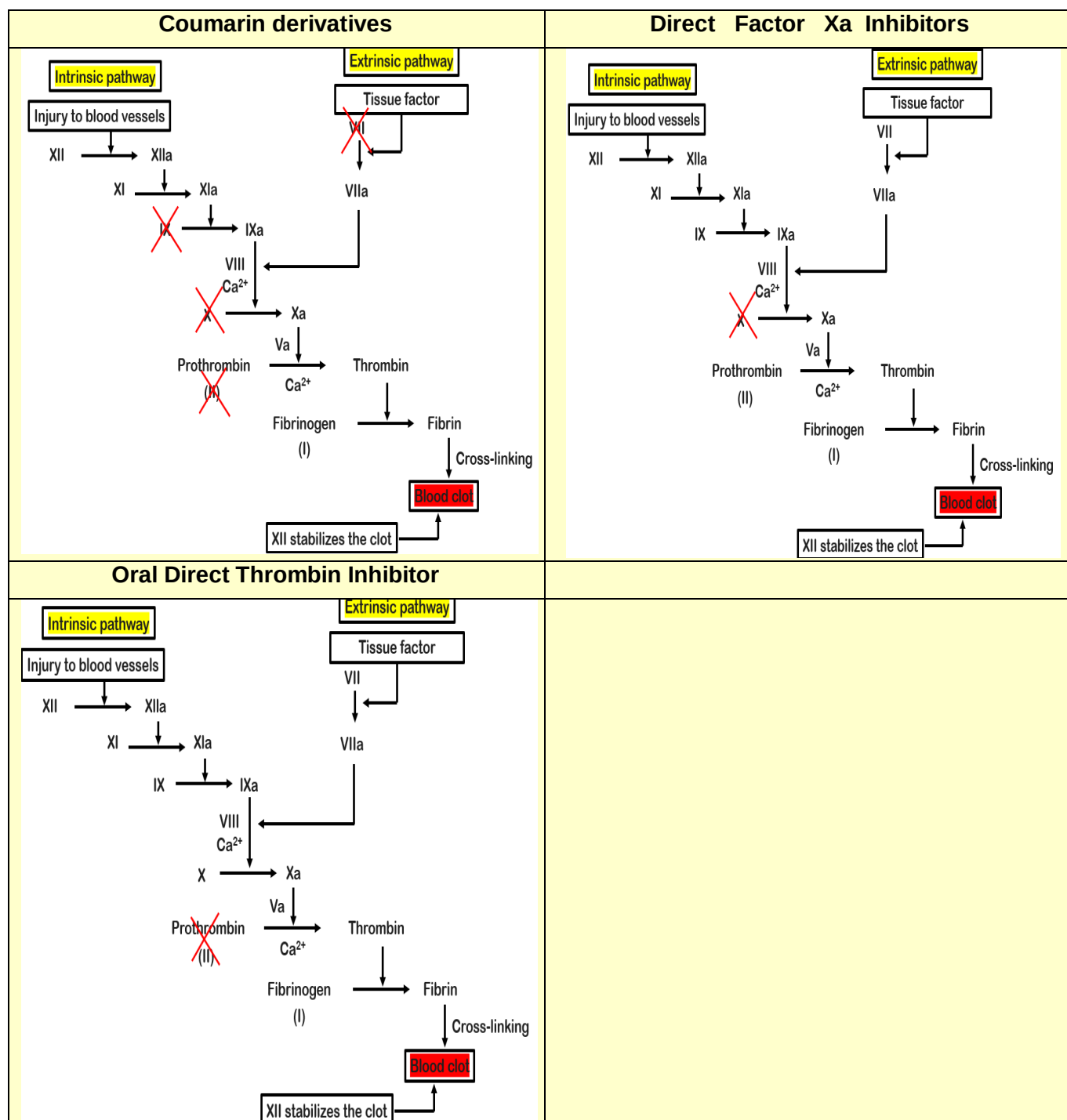
## Adverse effects

1. Bleeding
2. Hepatobiliary disorders





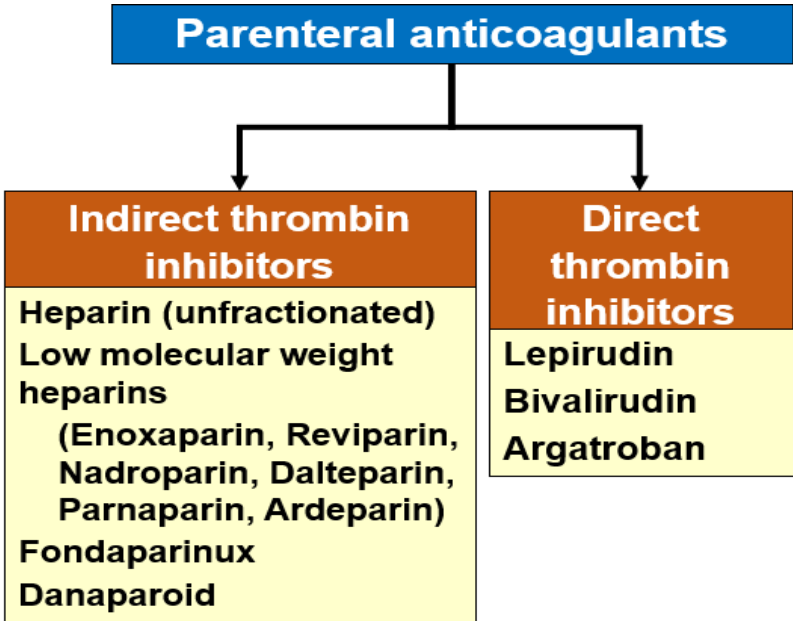
## SUMMARY



# PARENTERAL ANTICOAGULANTS



## Classification



| Parenteral Anticoagulants      |                                            |                                     |
|--------------------------------|--------------------------------------------|-------------------------------------|
|                                | Indirect thrombin inhibitors               | Direct thrombin inhibitors          |
|                                | Heparin LMWH<br>Fondaparinux<br>Danaparoid | Lepirudin Bivalirudin<br>Argatroban |
| MOA                            |                                            |                                     |
| Dose regulation and Monitoring |                                            |                                     |
| Advantages                     |                                            |                                     |
| Use                            |                                            |                                     |
| Adverse effects                |                                            |                                     |
| Contraindications              |                                            |                                     |
| Interactions                   |                                            |                                     |

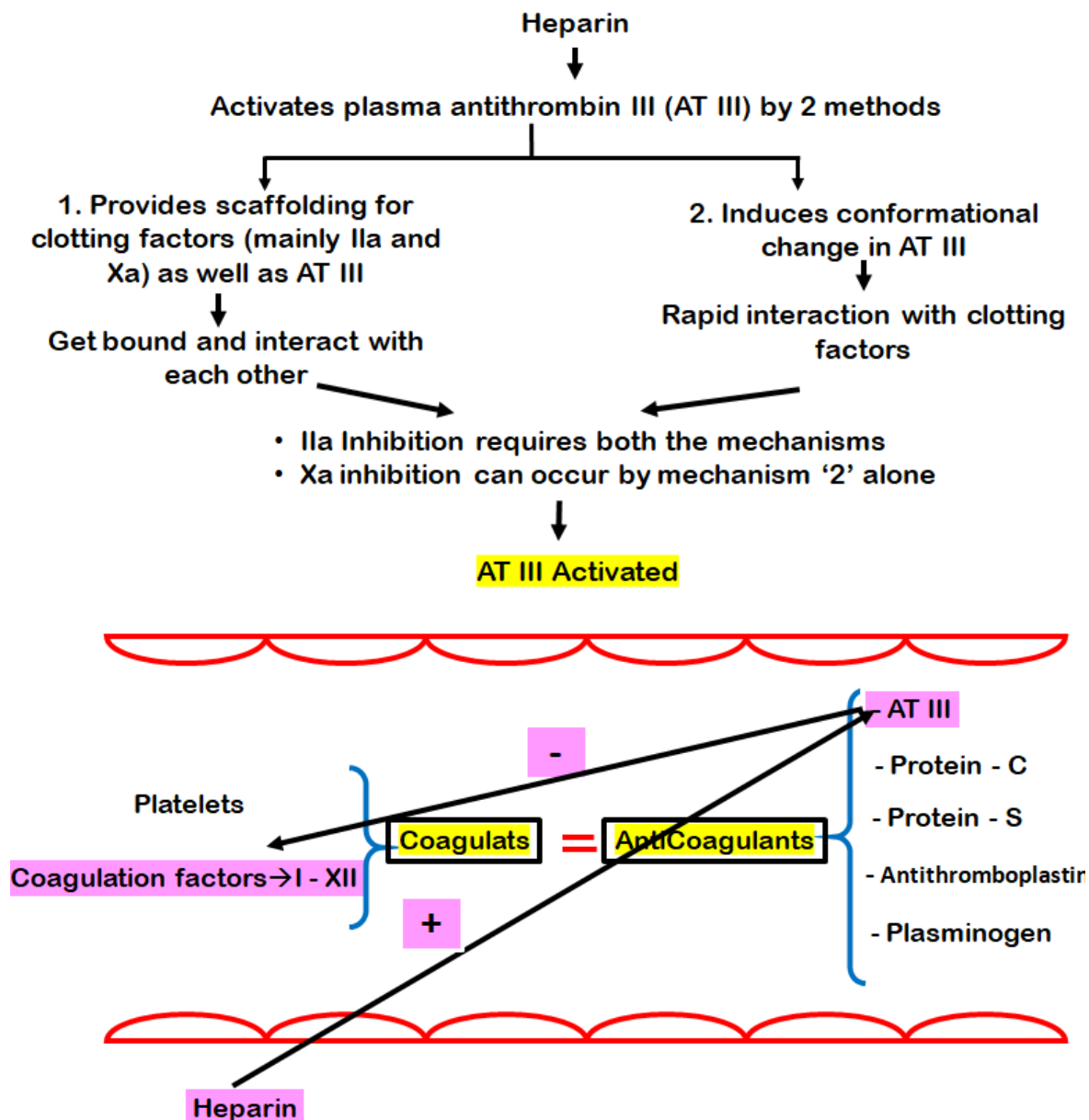
# HEPARIN

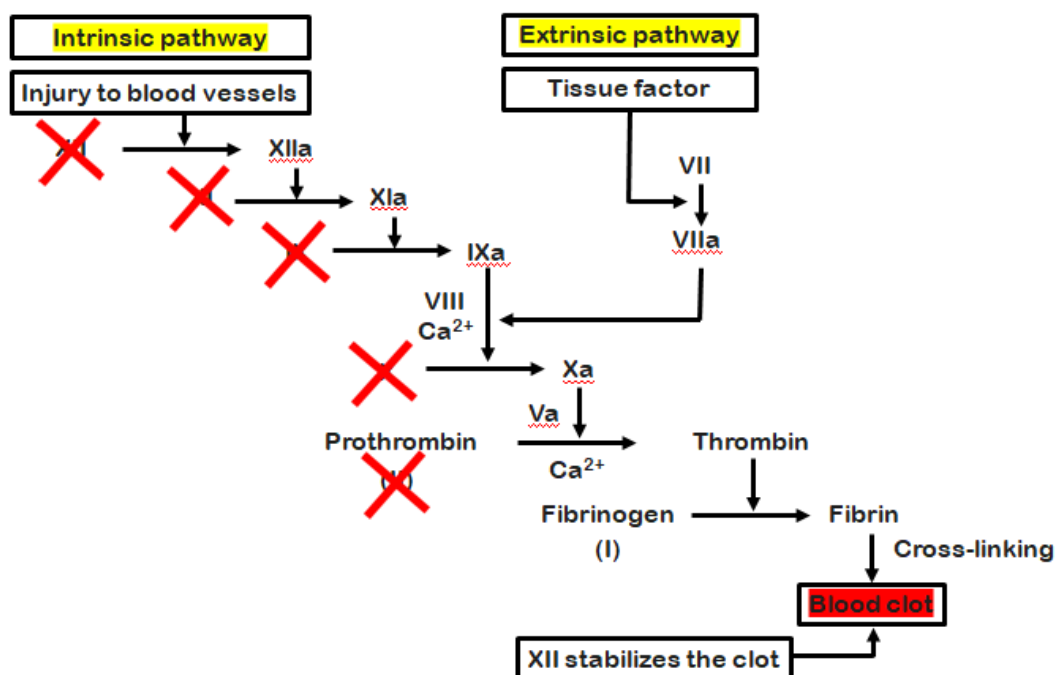
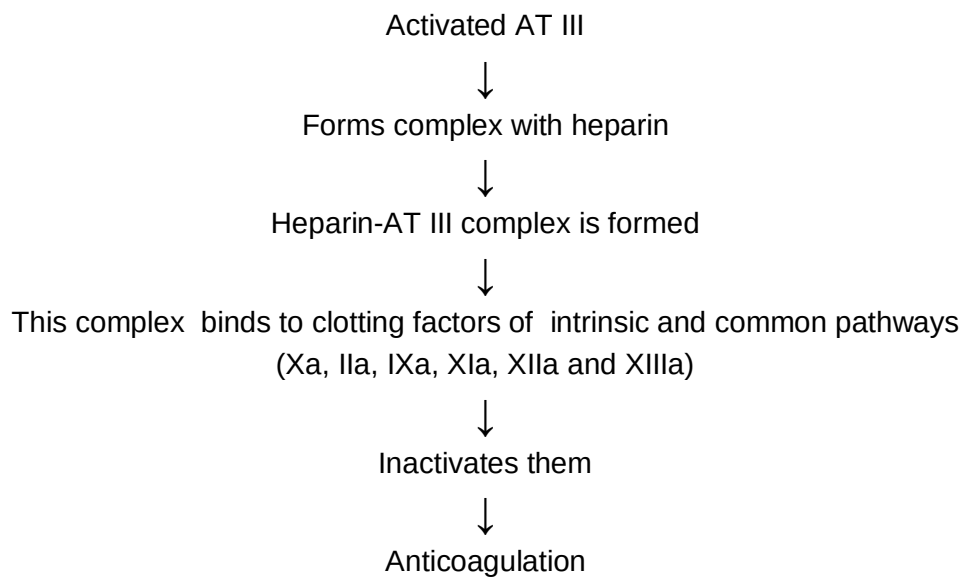
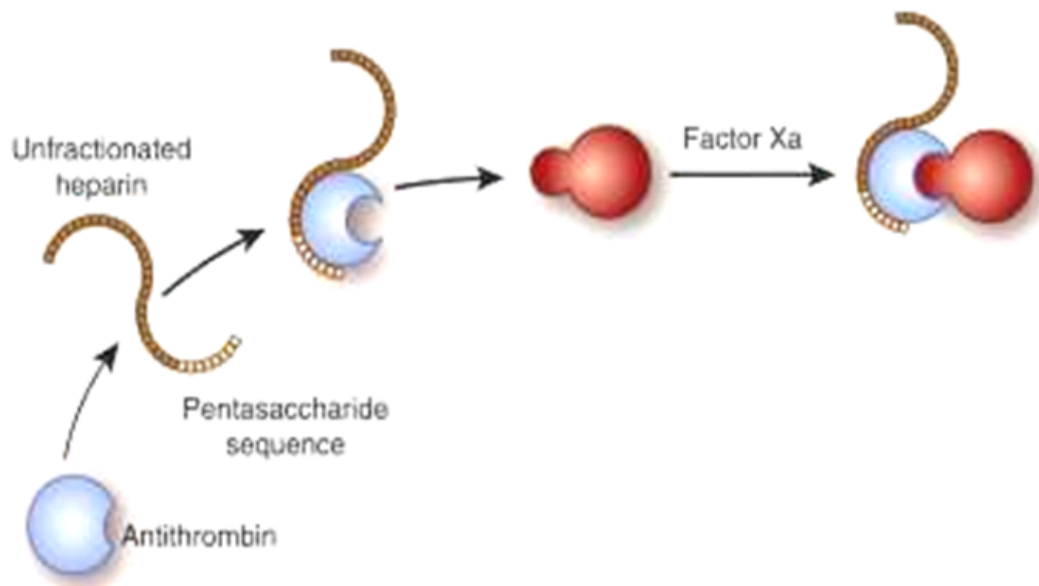
## Introduction

- Heparin → Prototype
- Heparin is a polymer of two sulfated disaccharide units:
  - D-glucosamine-L-iduronic acid
  - D-glucosamine-D-glucuronic acid
- Heparin carries strong electronegative charges
- It is the strongest organic acid present in body.
- It occurs in mast cells
- Commercially it is produced from ox lung and pig intestinal mucosa.

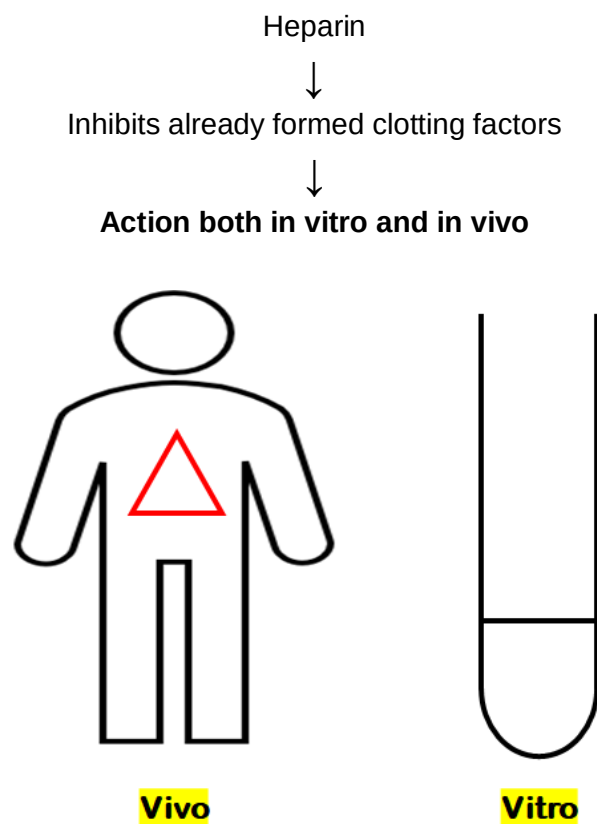
## MOA

- It acts indirectly by activating plasma antithrombin III (AT III)

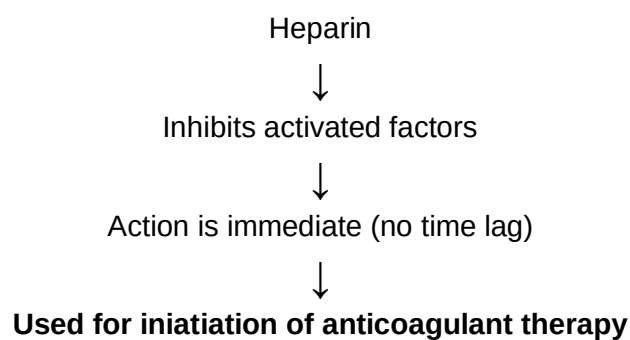




## Remember



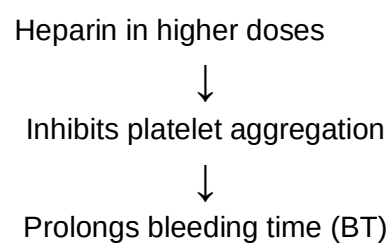
- **Heparin** → action both in vitro and in vivo → because it inhibits already formed clotting factors
- **Oral anticoagulants** → action only in vivo activity → because it inhibits the synthesis of new clotting factors in liver



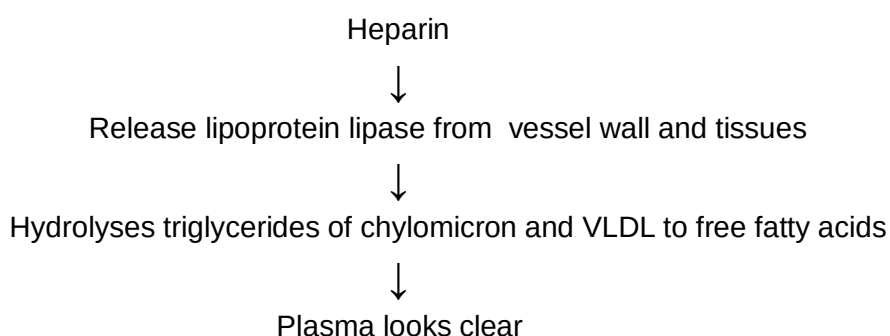
## Other Actions

- Antiplatelet action
- Lipaemia clearing

### 1. Antiplatelet action



## 2. Lipaemia clearing



### Pharmacokinetics

- Heparin is a large, highly ionized molecule → not absorbed orally.
- Heparin is given by sc or iv routes
- IM route is contraindicated - hematoma may occur.



### Dose regulation and Monitoring

- Effect of heparin is monitored by aPTT because at low doses it selectively inhibits intrinsic system.
- aPTT is kept at 50–80 sec. or 1.5–2.5 times the patient's pretreatment value.

### Remember

| Low concentrations of heparin                    | High concentrations of heparin                     |
|--------------------------------------------------|----------------------------------------------------|
| ↓                                                | ↓                                                  |
| Interfere selectively with intrinsic pathway     | Interfere with intrinsic as well as common pathway |
| ↓                                                | ↓                                                  |
| Prolong aPTT without significantly prolonging PT | Prolong both aPTT and PT                           |

### Uses

- Heparin is utilized for rapid and shortlived Action → Initiation therapy
- Oral anticoagulants → maintenance therapy.
  - Generally, the two are started together
  - Heparin is discontinued after 4–7 days when warfarin has taken effect.

1. Deep vein thrombosis (DVT) and pulmonary embolism (PE)
2. Prophylaxis of Deep vein thrombosis (DVT) and pulmonary embolism (PE)
3. Myocardial infarction (MI)
4. Unstable angina
5. Atrial fibrillation (AF)
6. Vascular surgery, prosthetic heart valves, retinal vessel thrombosis, extracorporeal circulation, haemodialysis
7. DIC

## Adverse Effects

1. Bleeding
2. Thrombocytopenia
3. Transient and reversible alopecia
4. Osteoporosis
5. Hypersensitivity reactions are rare

### 1. Bleeding

- Bleeding due to overdose
- Haematuria is generally first sign.
- **Treatment of Bleeding due to Heparin** → Protamine sulfate (Heparin Antagonist)
  - It is a strongly basic, low molecular weight protein
  - Obtained from sperm of certain fish.
  - Given i.v.
  - It neutralises heparin weight for weight
  - 1 mg of Protamine sulfate is needed for every 100 U of heparin.
  - Whole blood transfusion is needed to replenish loss when bleeding is severe.



### 2. Thrombocytopenia

- Generally it is mild and transient
- Occurs due to aggregation of platelets.
- In some patients antibodies are formed to the heparin-platelet complex and marked depletion of platelets occurs
- Heparin should be discontinued in such cases.

### 3. Transient and reversible alopecia





## 4. Osteoporosis



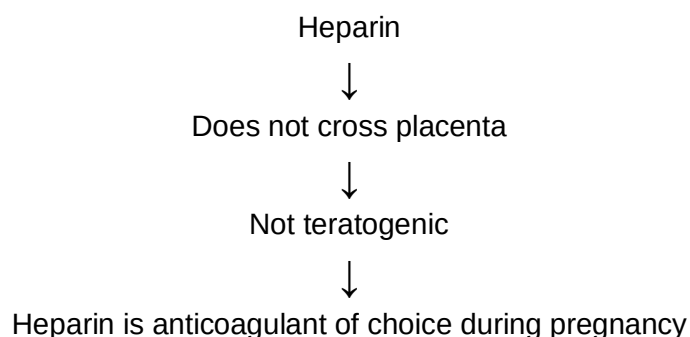
## 5. Hypersensitivity reactions



## Contraindications

1. Bleeding disorders
2. History of heparin induced thrombocytopenia.
3. Severe hypertension (risk of cerebral haemorrhage), threatened abortion, piles, g.i. ulcers (risk of aggravated bleeding).
4. Subacute bacterial endocarditis (risk of embolism)
5. Chronic alcoholics, cirrhosis, renal failure.
6. Aspirin and other antiplatelet drugs should be used very cautiously during heparin therapy.

## Remember



- Pregnant females receiving heparin therapy should be supplemented with calcium to prevent osteoporosis.



|                            | WARFARIN                               | HEPARIN                                |
|----------------------------|----------------------------------------|----------------------------------------|
| 1. Chemistry               | Coumarin derivative                    | Mucopolysaccharide                     |
| 2. Source                  | Synthetic                              | Hog lung, pig intestine                |
| 3. Route of admin.         | Oral                                   | Parenteral (i.v., s.c.)                |
| 4. Onset of action         | delayed (1-3 days)                     | Immediate                              |
| 5. Duration of action      | 3-6 days                               | 4-6 hrs                                |
| 6. Activity                | In vivo only                           | In vitro and in vivo                   |
| 7. Mechanism               | Inhibits synthesis of clotting factors | Blocks action of factor X and thrombin |
| 8. Antagonist              | Vit K                                  | Protamine sulphate                     |
| 9. Variability in response | Marked                                 | little                                 |



## Advantages

1. A lower incidence of bleeding complications compared to UFH
2. Thrombocytopenia is less frequent.
3. Risk of osteoporosis after long term use is much less with LMW heparin compared with UFH.
4. Better subcutaneous bioavailability (70–90%) compared to UFH (20–30%)
5. Longer and more consistent monoexponential  $t_{1/2}$ : (4–6 hours); making possible once daily s.c. administration.
6. Since aPTT is not prolonged, laboratory monitoring is not needed

## Remember

- LMW heparins to be equally efficacious to UFH except during cardiopulmonary bypass surgery, in which high dose UFH is still the preferred anticoagulant, because LMW heparin is less effective in preventing catheter thrombosis

| FEATURE                                   | HEPARIN   | LMWH  |
|-------------------------------------------|-----------|-------|
| Bioavailabillity After S.C Administration | 90%       | 100%  |
| Plasma $t_{1/2}$                          | 4 Hr      | 17 Hr |
| Release Of TFPI                           | Yes       | No    |
| Antidote                                  | Protamine | No    |

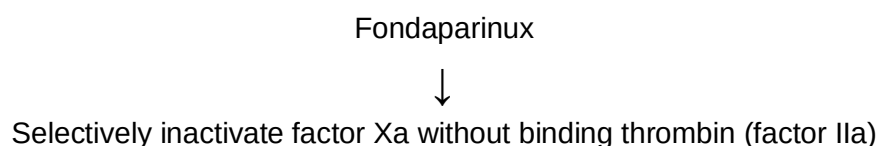
| ADVANTAGE OF LMWH OVER HEPARIN                                    |                                       |
|-------------------------------------------------------------------|---------------------------------------|
| Advantage                                                         | Consequences                          |
| -Better Bioavailability And Longer $T_{1/2}$ After S.C. Injection | Can Be Given S.C. Once Or Twice Daily |
| -Does Independent Clearance                                       | Simplified Clearance                  |
| -Predictable Response                                             | No Need Of Monitoring                 |
| - Lower Risk Of Osteoporosis                                      | Safe For Long Term Use                |

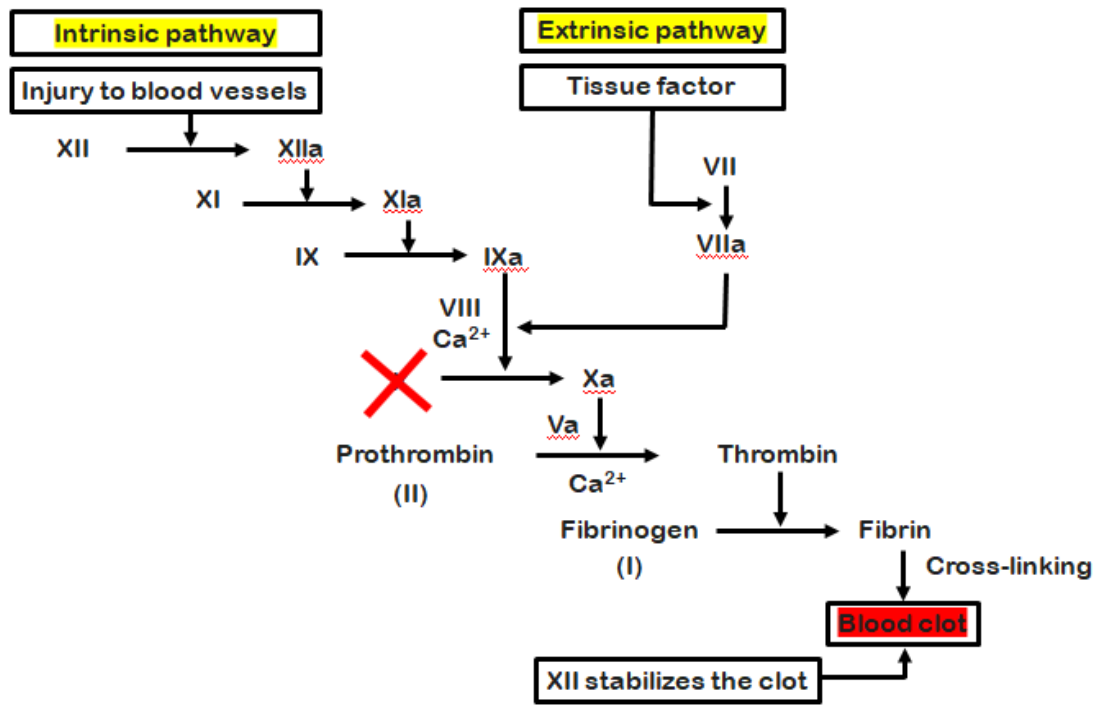
## FONDAPARINUX AND DANAPAROID

### Introduction

- These have propties and action similar to LMW heparins.

### MOA



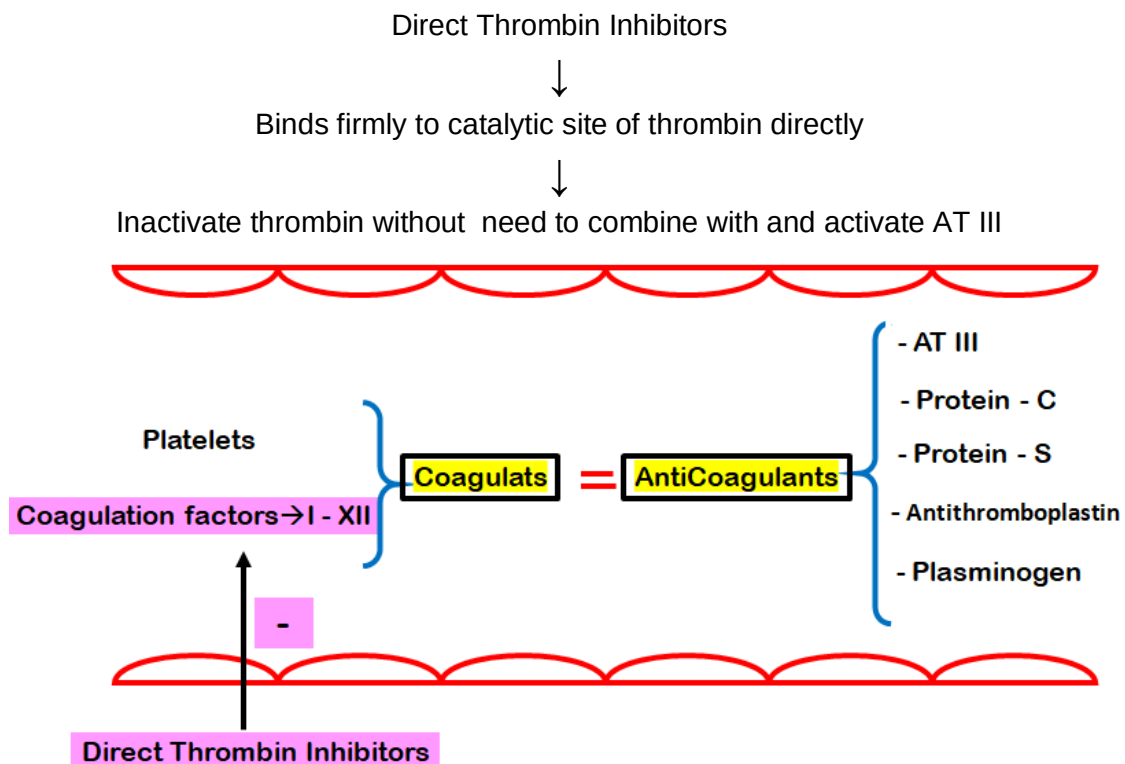


## Advantages

1. The bioavailability of fondaparinux injected s.c. is 100%
2. It is longer acting ( $t_{1/2}$  17 hours)
3. Fondaparinux does not require laboratory monitoring of APTT
4. Fondaparinux is less likely to cause thrombocytopenia compared to even LMW heparins.
5. Risk of osteoporosis after prolonged use is also minimal.

## DIRECT THROMBIN INHIBITORS

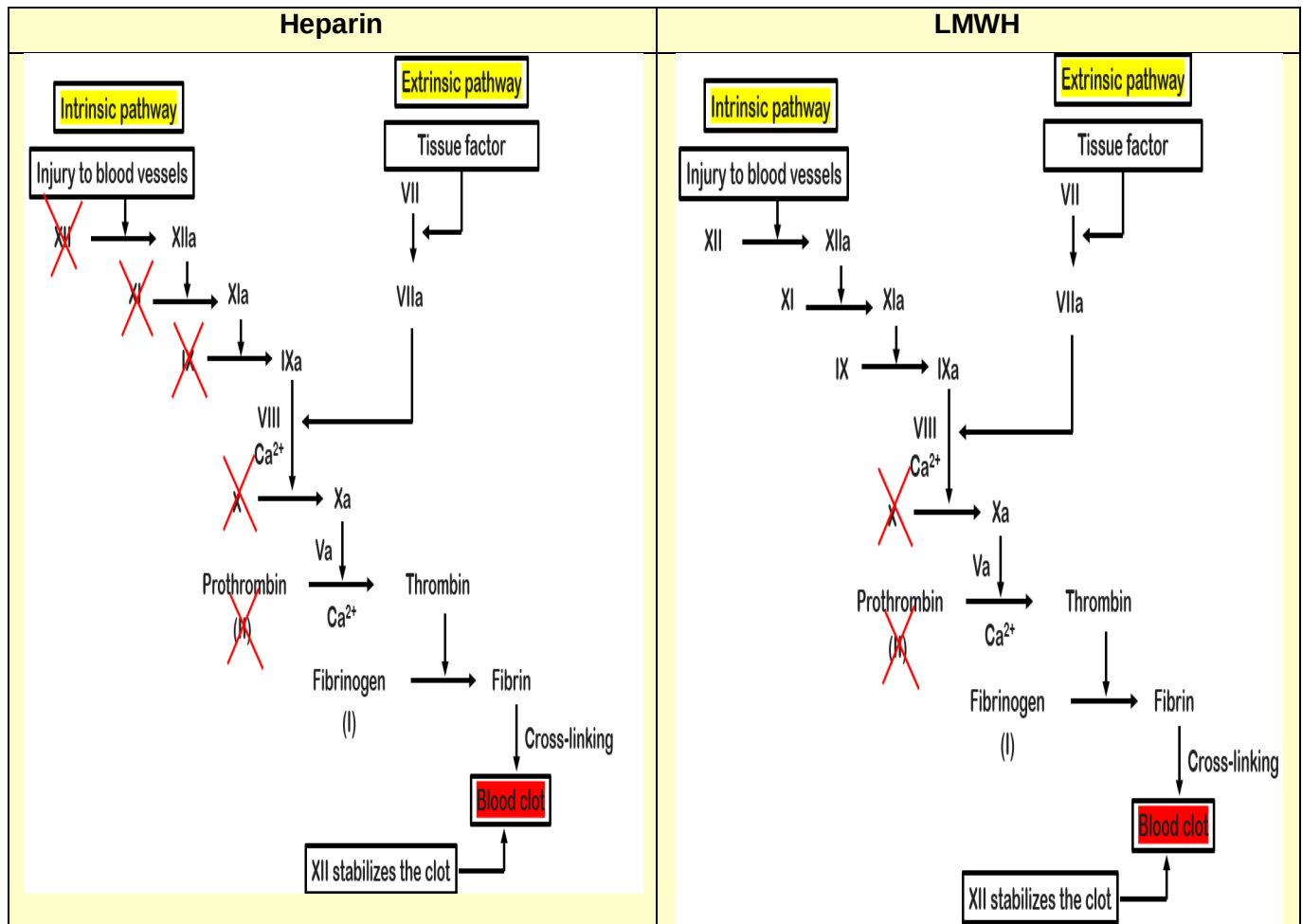
### MOA

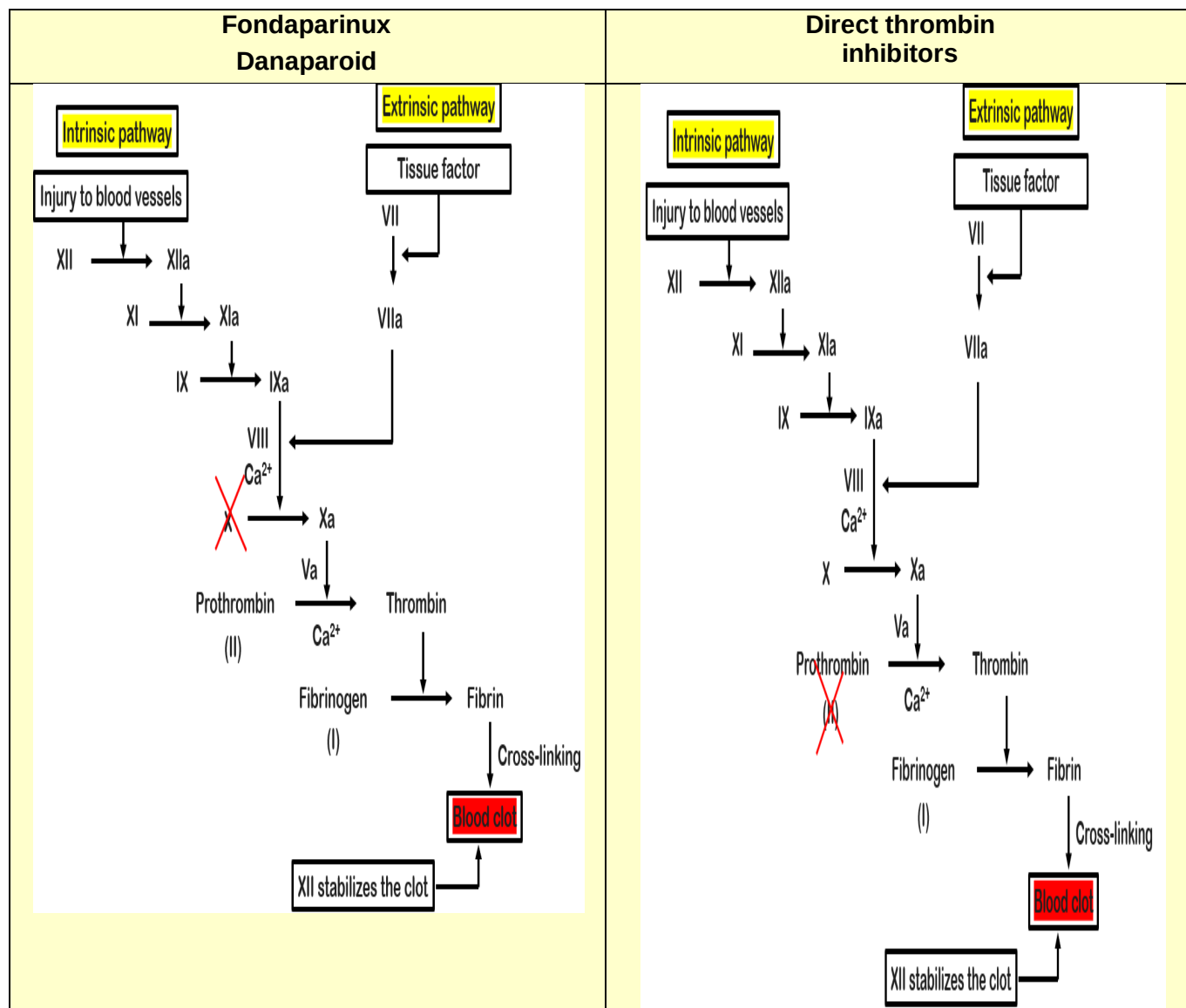


## Use

- It is indicated only in patients who are at risk of heparin induced thrombocytopenia (HIT)

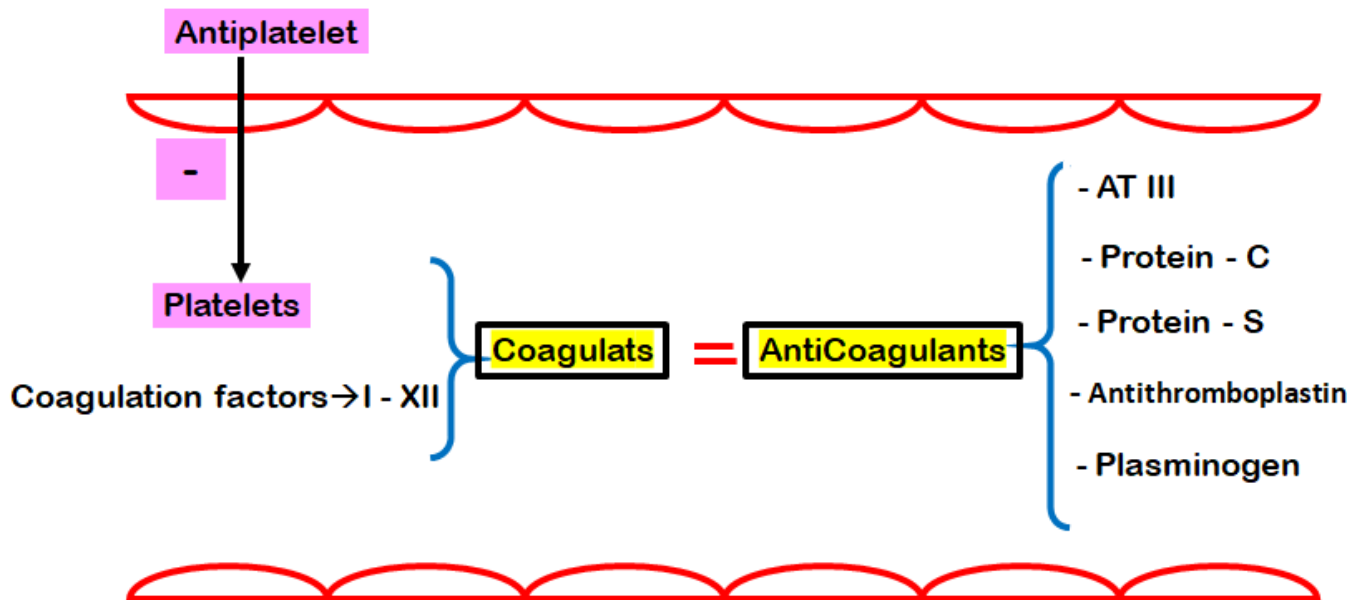
## SUMMARY



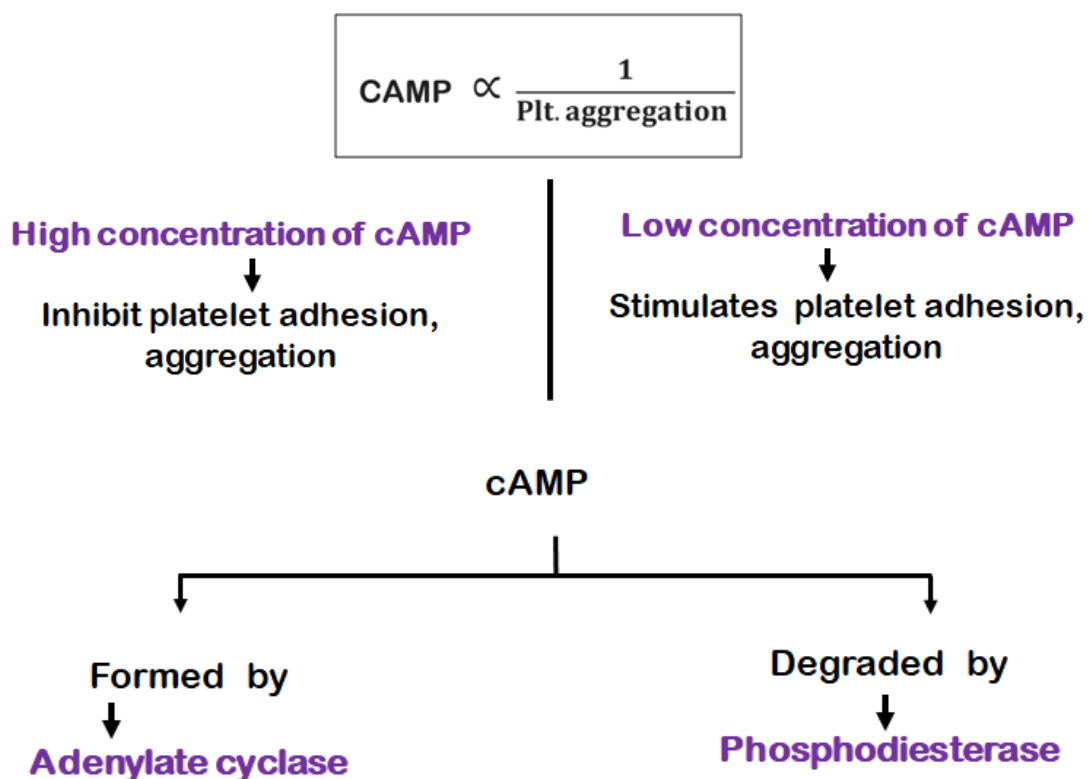


| Anticoagulant                        | Mechanism of action                               | Clotting factors affected                             |
|--------------------------------------|---------------------------------------------------|-------------------------------------------------------|
| Warfarin (oral)                      | Inhibits vitamin K epoxide reductase              | Inhibits synthesis of clotting factors II, VII, IX, X |
| Rivaroxaban (oral)                   | Direct inhibition of Xa                           | xa                                                    |
| Dabigatran (oral)                    | Direct inhibitor of thrombin                      | Direct inhibitor of thrombin                          |
| Heparin (parenteral)                 | Activates AT III and forms heparin-AT III complex | Inactivates Factors IIa, IXa, Xa, XIa, XIIa, XIIIa    |
| LMWH (parenteral)                    | LMWH-AT III complex                               | Inactivates factor Xa                                 |
| Fondaparinux (parenteral)            | Fondaparinux-AT III complex                       | Inactivates factor Xa                                 |
| Bivalirudin, argatroban (parenteral) | Direct inhibitors of Thrombin                     | Thrombin                                              |

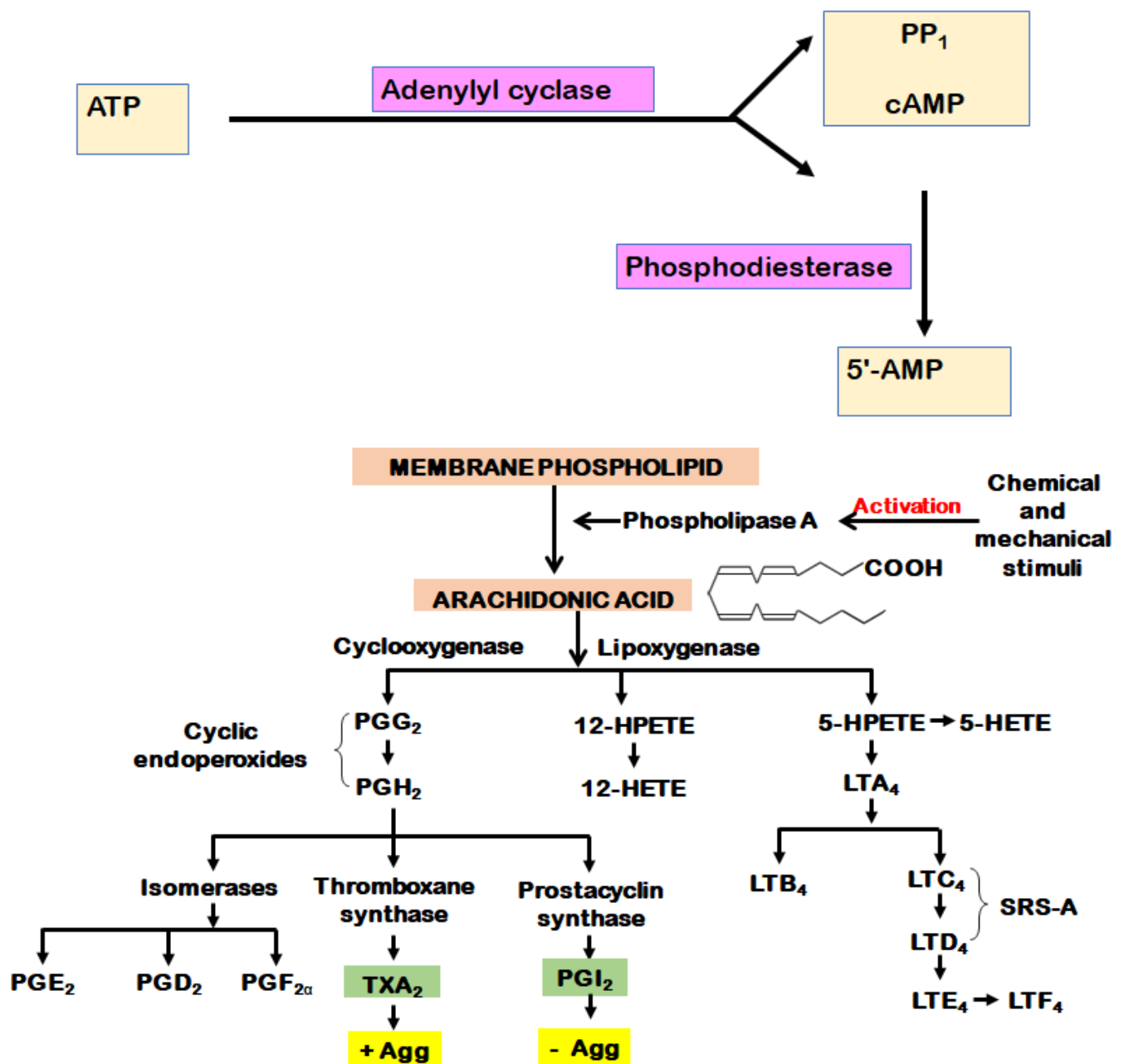
## ANTIPLATELETS



### Platelet mechanism



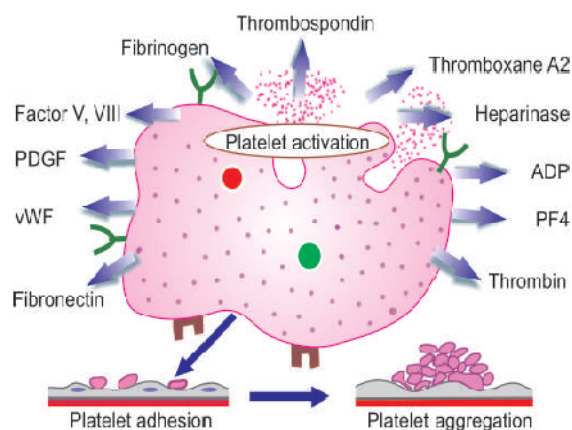
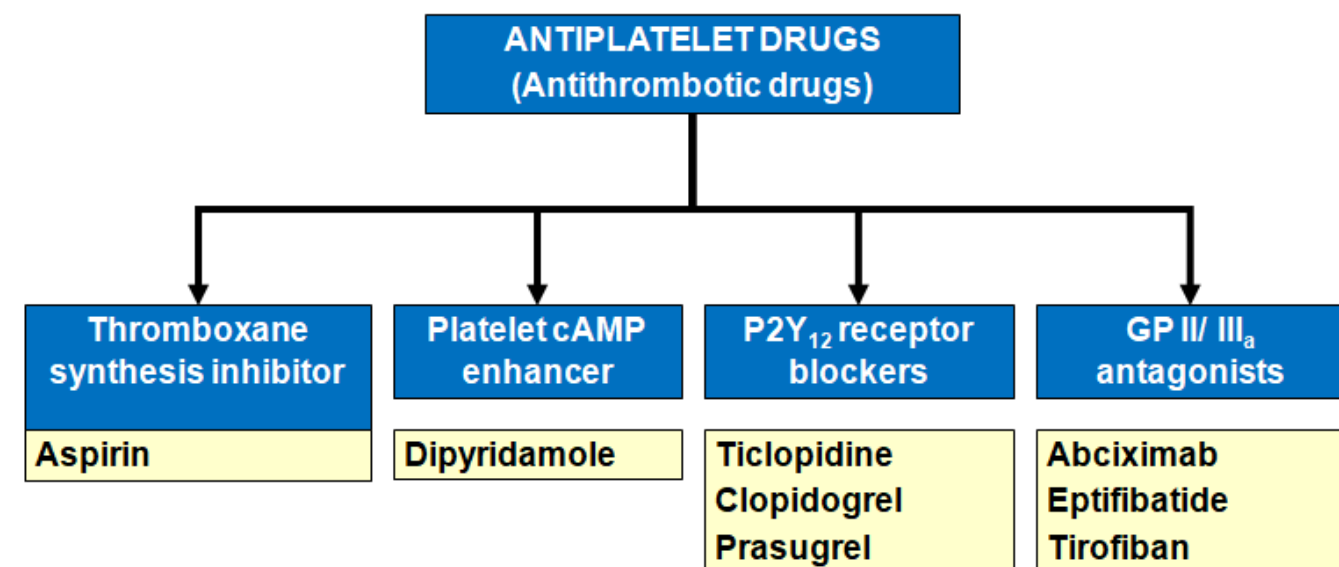




|                                                                                                                                                                                                                      |                                                                                                                                                                                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Thromboxane A<sub>2</sub></b></p> <p>↓</p> <p>(synthesized in platelets)</p> <p>↓</p> <p>Inhibit adenylate cyclase</p> <p>↓</p> <p>Decreases cAMP</p> <p>↓</p> <p><b>Platelet aggregation and adhesion</b></p> | <p><b>Prostacyclin PGI<sub>2</sub></b></p> <p>↓</p> <p>(Synthesized in endothelium)</p> <p>↓</p> <p>stimulates adenylate cyclase</p> <p>↓</p> <p>Increases cAMP</p> <p>↓</p> <p><b>Antiaggregatory effect</b></p> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**Remember**

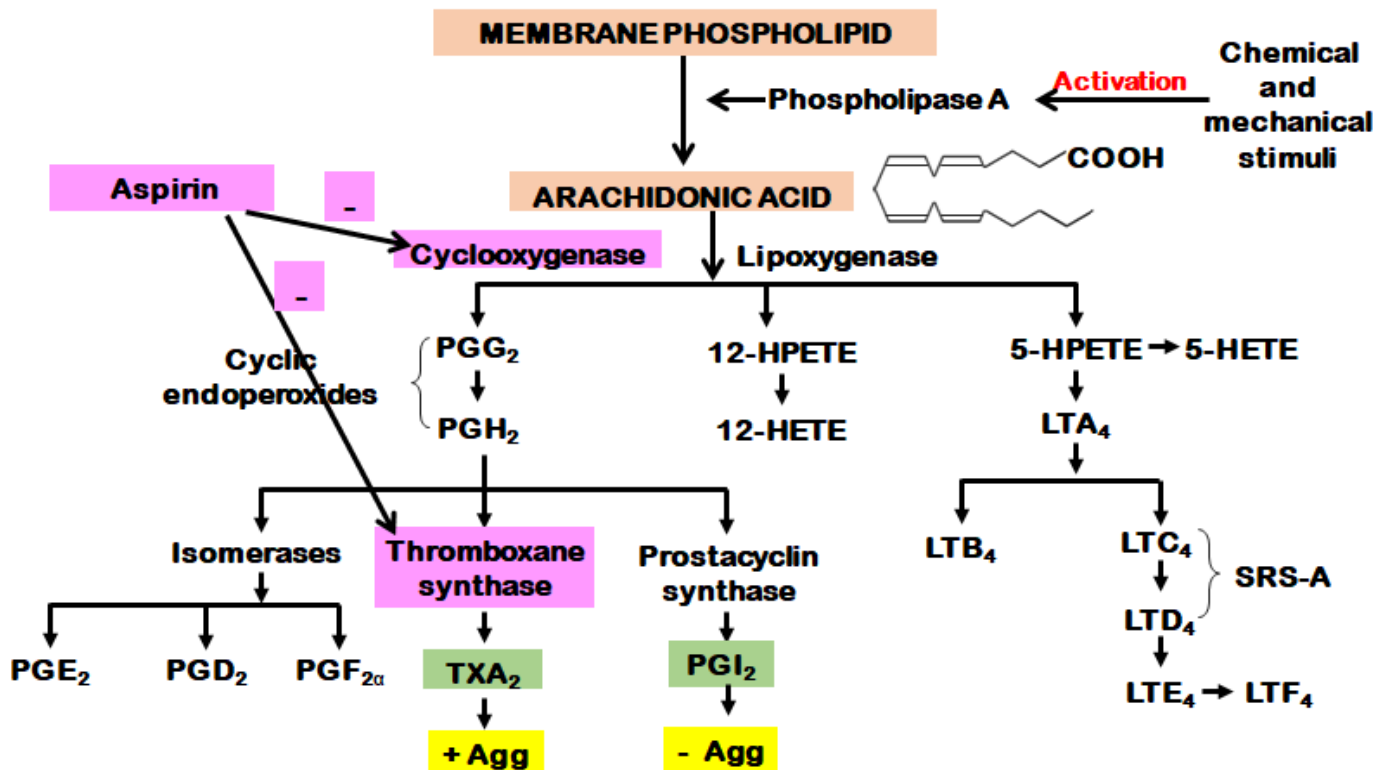
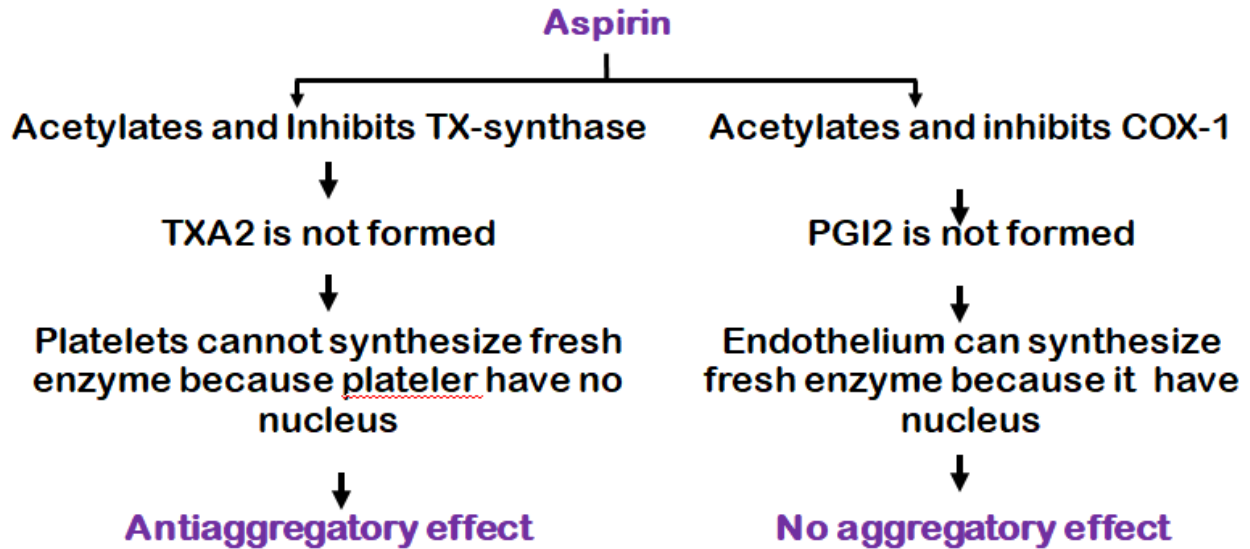
- TXA2 and ADP → proaggregatory
- PGI2 → anti-aggregatory mediators

**ANTIPLATELET DRUGS (ANTITHROMBOTIC DRUGS)****Classification**

|     | Aspirin | Dipyridamole | Ticlopidine<br>Clopidogrel<br>Prasugrel | Abciximab<br>Eptifibatide<br>Tirofiban |
|-----|---------|--------------|-----------------------------------------|----------------------------------------|
| MOA |         |              |                                         |                                        |
| Use |         |              |                                         |                                        |

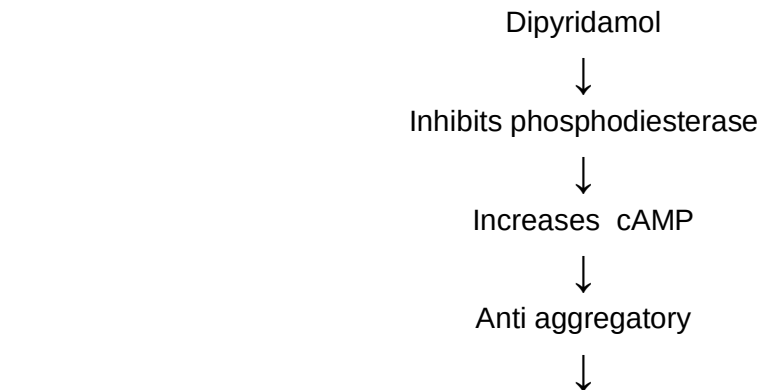
# ASPIRIN

## MOA

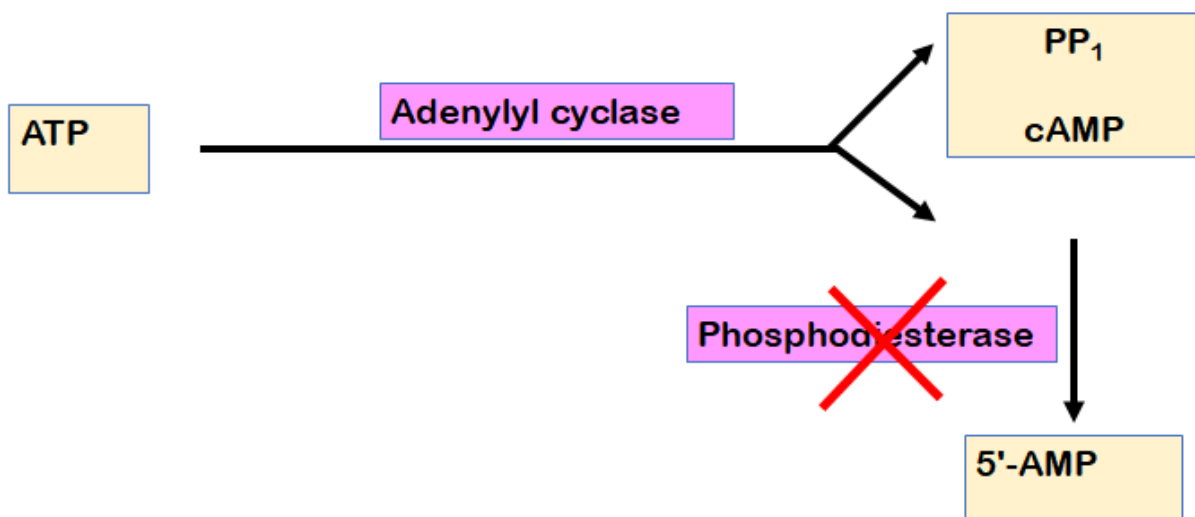
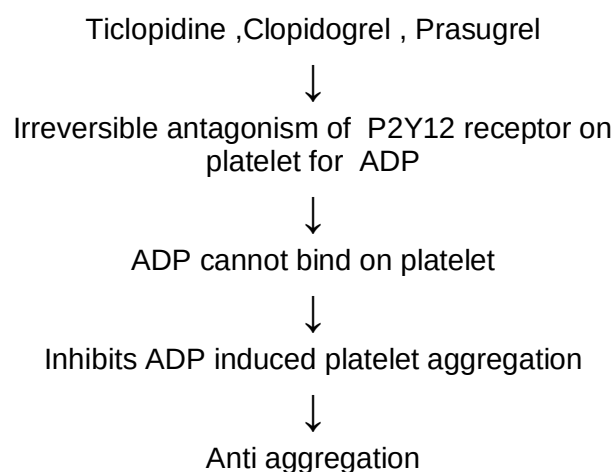
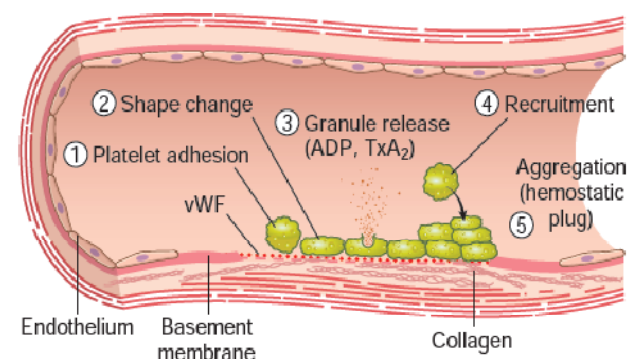


**Remember**

- Although aspirin inhibits both  $\text{Tx A}_2$  and  $\text{PG I}_2$  but effects are only anti aggregatory not aggregatory

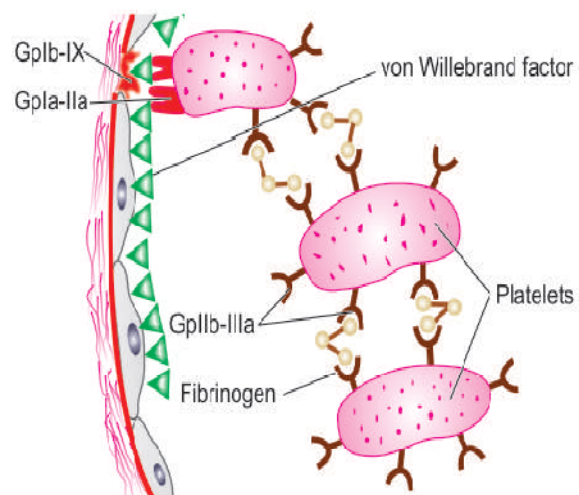
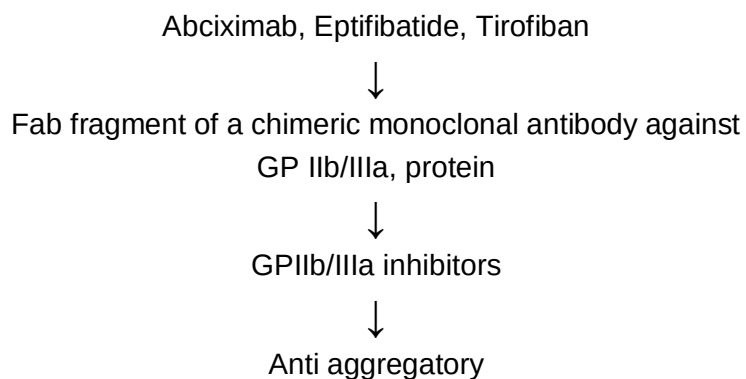
**MOA**

2. It also blocks uptake of adenosine

**TICLOPIDINE, CLOPIDOGREL, PRASUGREL****MOA****B. PRIMARY HEMOSTASIS**

## ABCIXIMAB, EPTIFIBATIDE, TIROFIBAN

### MOA



| Feature                     | Abciximab   | Eptifibatide  | Tirofiban   |
|-----------------------------|-------------|---------------|-------------|
| Specificity For Gp IIb/IIIa | No          | Yes           | Yes         |
| Plasma $t_{1/2}$            | Short (Min) | Long (2.5 hr) | Long (2 hr) |
| Platelets Bound $t_{1/2}$   | Long (Days) | Short (S)     | Short (S)   |
| Renal Clearance             | No          | Yes           | Yes         |

### Uses

1. Coronary artery disease
2. Cerebrovascular disease
3. Prosthetic heart valves and arteriovenous Shunts
4. Venous thromboembolism
5. Peripheral vascular disease

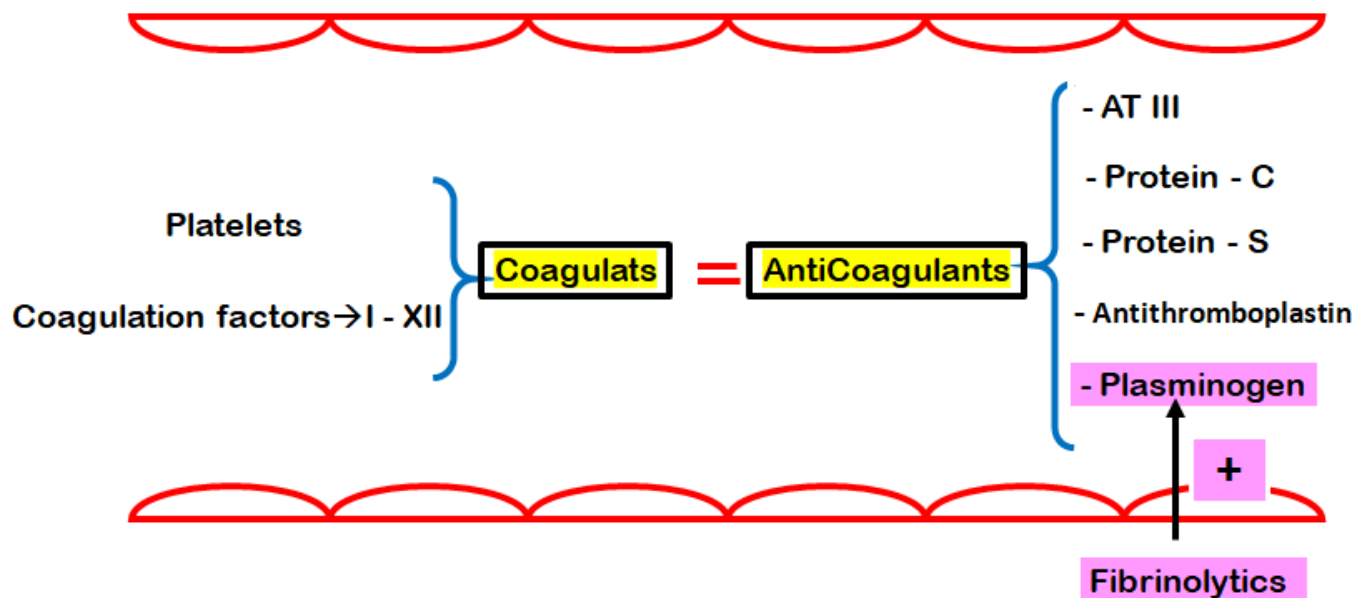
### Remember

- **Arterial thrombus** → mainly made up of platelets → antiplatelet drugs are more effective than anticoagulants.
- **Venous thrombi** → mainly fibrin thrombi → anticoagulants are more effective.

## FIBRINOLYTICS (THROMBOLYTICS)

### Introduction

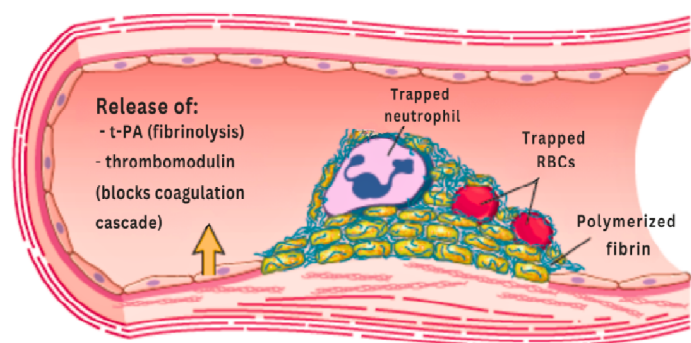
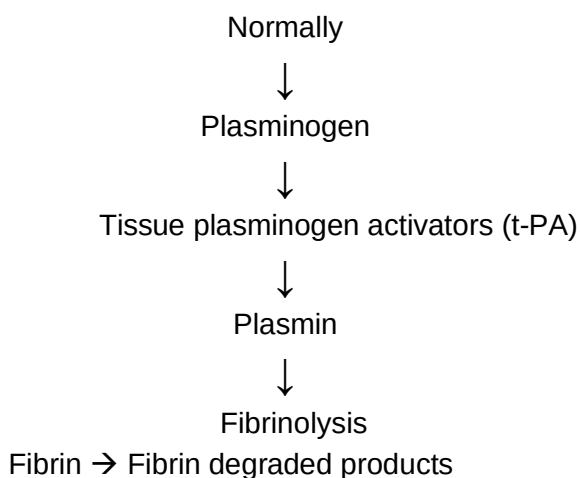
- These are drugs used to lyse thrombi/clot to recanalize occluded blood vessels (mainly coronary artery)
- They are therapeutic rather than prophylactic



### Classification

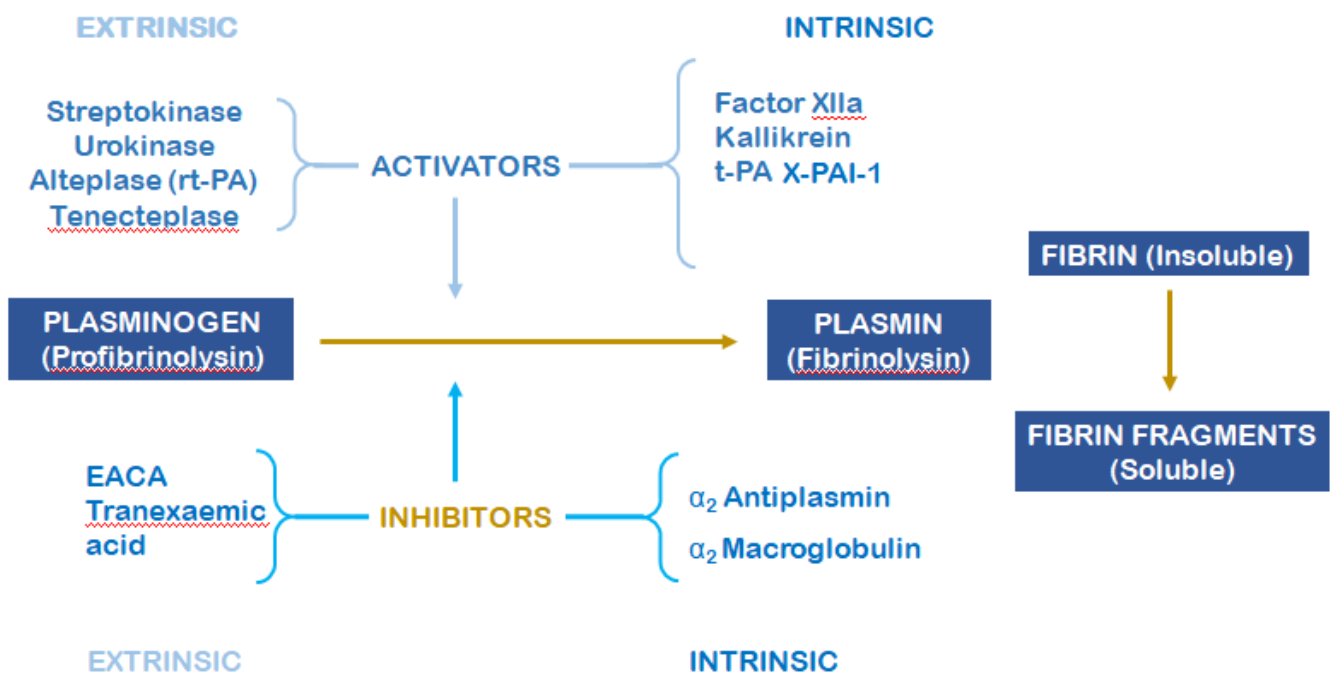
- **Fibrinolytics (Thrombolytics)** →
  - Streptokinase
  - Urokinase
  - Alteplase (rt-PA)
  - Reteplase
  - Tenecteplase

### MOA



- Plasminogen circulates in plasma (free form) as well as remains bound to fibrin.
- t-PA selectively activates fibrin bound plasminogen within thrombus (not the free plasmin)

Fibrinolytics  
↓  
Activating natural fibrinolytic system  
↓  
Venous thrombi are lysed more easily by fibrinolytics than arterial



## STREPTOKINASE

- Streptokinase is obtained from group C  $\beta$ -hemolytic streptococci.
- It is the first fibrinolytic drug to be used clinically
- It activates both circulating and fibrin bound plasminogen.
- Therefore, it depletes circulating fibrinogen and predisposes to bleeding.

### Disadvantages

1. Stk is antigenic—can cause hypersensitivity reactions (anaphylaxis occurs in 1–2% patients)
2. It cannot be used second time due to neutralization by antibodies generated in response to the earlier dose.



## UROKINASE

- It is an enzyme isolated from human urine; but commercially prepared from cultured human kidney cells.
- It is not antigenic.

## ALTEPLASE , RETEPLASE, TENECTEPLASE

- Alteplase , Reteplase, tenecteplase are recombinant t-PA.
- These are non antigenic
- They activate fibrin bound plasminogen only
- Alteplase has very short half life of 5 min

### Uses of fibrinolytics

1. Acute MI (chief indication)
2. DVT
3. Pulmonary embolism
4. Peripheral arterial occlusion
5. Stroke

### Contraindications

1. H/o Intracranial haemorrhage
2. H/o Ischaemic stroke in past 3 months
3. H/o Head injury in past 3 months
4. Intracranial tumour/vascular abnormality/aneurysms
5. Active bleeding/bleeding disorders
6. Peptic ulcer, esophageal varices
7. Any wound or recent fracture or tooth extraction
8. H/o major surgery within 3 weeks
9. Uncontrolled hypertension
10. Pregnancy

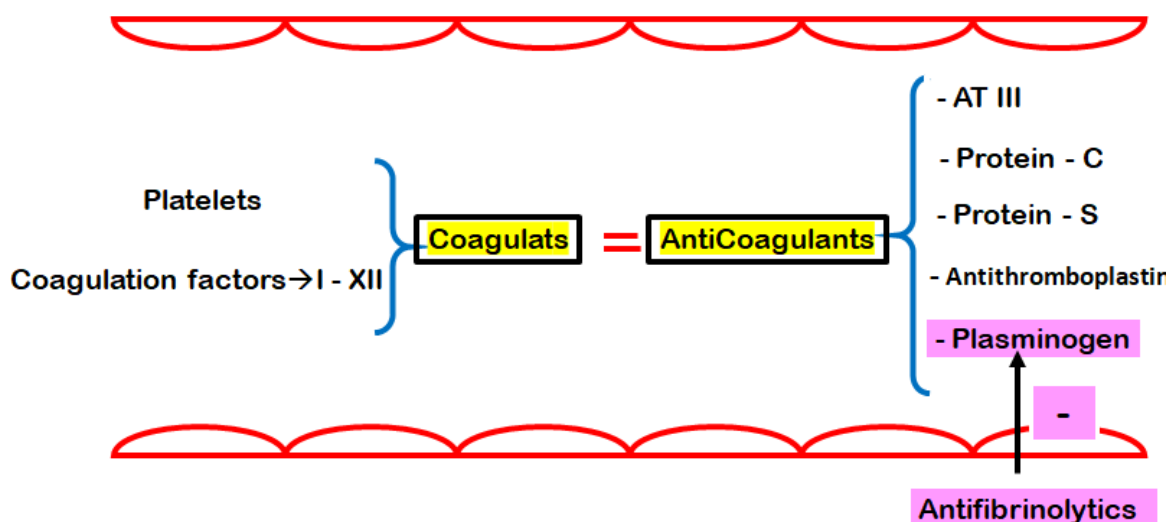
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## ANTIFIBRINOLYTIC DRUGS

---

### Introduction

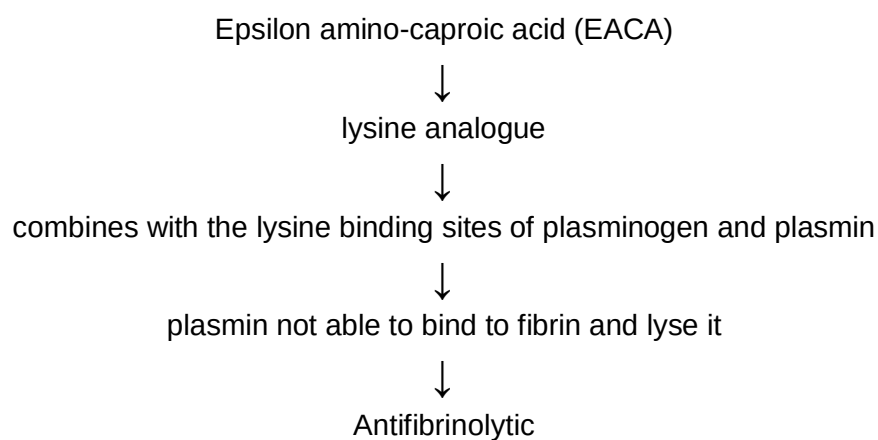
- These are drugs which inhibit plasminogen activation and dissolution of clot
- Used to check fibrinolysis associated bleeding.



## Classification

- **Antifibrinolytics (Antithrombolytics)** →
  - Epsilon amino-caproic acid (EA CA)
  - Tranexamic acid

## MOA



## Uses

1. Overdose of streptokinase/urokinase/alteplase
2. To prevent recurrence of subarachnoid fibrinolysis and GI haemorrhage
3. Certain traumatic and surgical bleeding (prostatectomy, tooth extraction in hemophiliacs)
4. Abruptio placentae, PPH
5. certain cases of menorrhagia.

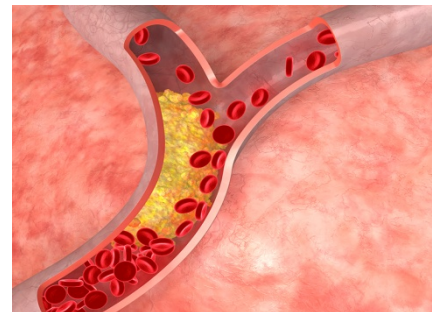
## Adverse effects

1. Nausea
2. Diarrhoea
3. Thromboembolic events
4. Disturbed colour vision
5. Allergic reactions

## HYPOLIPIDAEMIC DRUGS

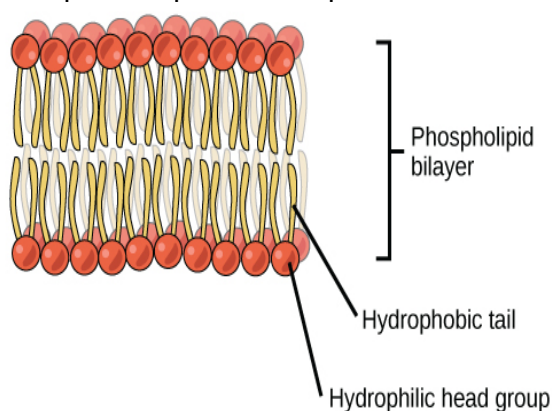
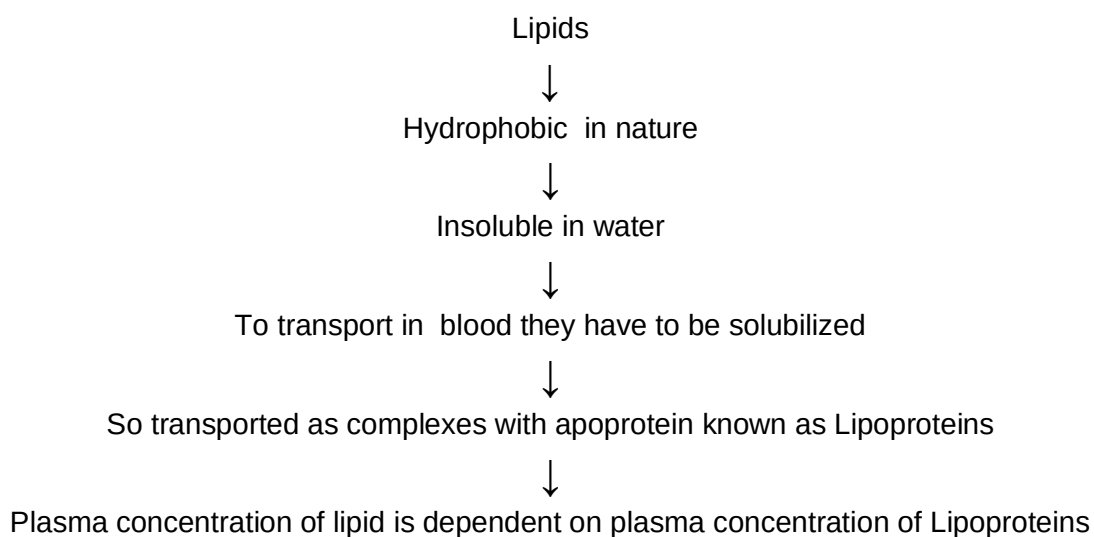
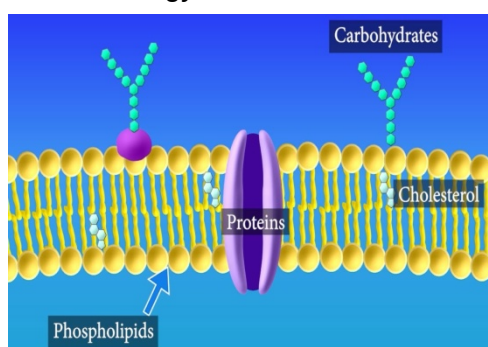
### Introduction

- Hypolipemic drugs are the agents used for the treatment of different types of hyperlipoproteinemias.



### Lipids

- Cholesterol:** Involved in synthesis of cell membrane, steroid hormone and bile acid.
- Triglycerides:** Transfer energy from food to cells.



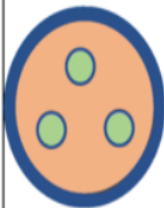
## Structure of lipoproteins

- **Hydrophobic core** → consists of triglycerides (TGs) or cholesteryl esters (CHEs)
- **Outer polar layer** → consists of Phospholipids, free cholesterol (CH) and apoproteins.

## Types of lipoproteins

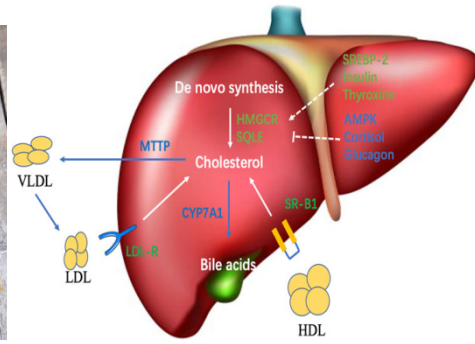
- Lipoproteins have been divided into 6 classes on the basis of their particle size, density and ratio of TG and CHE

| LIPOPROTEIN CLASS | DIAMETER (NM) | LIPID CONTAIN     | SOURCE OF LIPID   | FUNCTION                                   |
|-------------------|---------------|-------------------|-------------------|--------------------------------------------|
| 1. CHY            | 100-500       | TG >> CHE         | Diet              | Dietary TG Transport                       |
| 2. CHY.REM.       | 30-50         | CHE >> TG         | Diet CHY.         | Dietary Ch Transport                       |
| 3. VLDL           | 40-80         | TG >> CHE         | Liver             | Endogenous TG Transport                    |
| 4. IDL            | 30-35         | CHE ≥ TG          | VLDL              | Transport Che & TG To Liver, source Of LDL |
| 5. LDL            | 20-25         | CHE               | IDL               | Transport Ch To Tissues And Liver          |
| 6. HDL            | 5-10          | Phospholipid, Che | Tissue Cell Memb. | Removal Of Ch From Tissues                 |

|                                                                                     | Chylomicron                                                                         | Chylomicron Remnant                                                                 | VLDL                                                                                | IDL                                                                                  | LDL                                                                                   | HDL                                                                                   |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
|  |  |  |  |  |  |  |
| Density                                                                             | <0.93                                                                               | 0.93-1.006                                                                          | 0.93-1.006                                                                          | 1.006-1.019                                                                          | 1.019-1.063                                                                           | 1.063-1.210                                                                           |
| Major Lipids                                                                        | Triglycerides                                                                       | Triglycerides<br>Cholesterol                                                        | Triglycerides                                                                       | Triglycerides<br>Cholesterol                                                         | Cholesterol                                                                           | Cholesterol<br>Phospholipids                                                          |
| Major Apolipoproteins                                                               | ApoB-48, ApoC, ApoE, ApoA-I, ApoA-IV                                                | ApoB-48, ApoE                                                                       | ApoB-100, ApoE, ApoC                                                                | ApoB-100, ApoE, ApoC                                                                 | ApoB-100                                                                              | ApoA-I, ApoA-II, ApoC, ApoE                                                           |

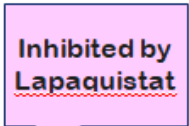
## Sources

- **Cimetidine** → Diet
- **Endogenous** → Synthesised by liver

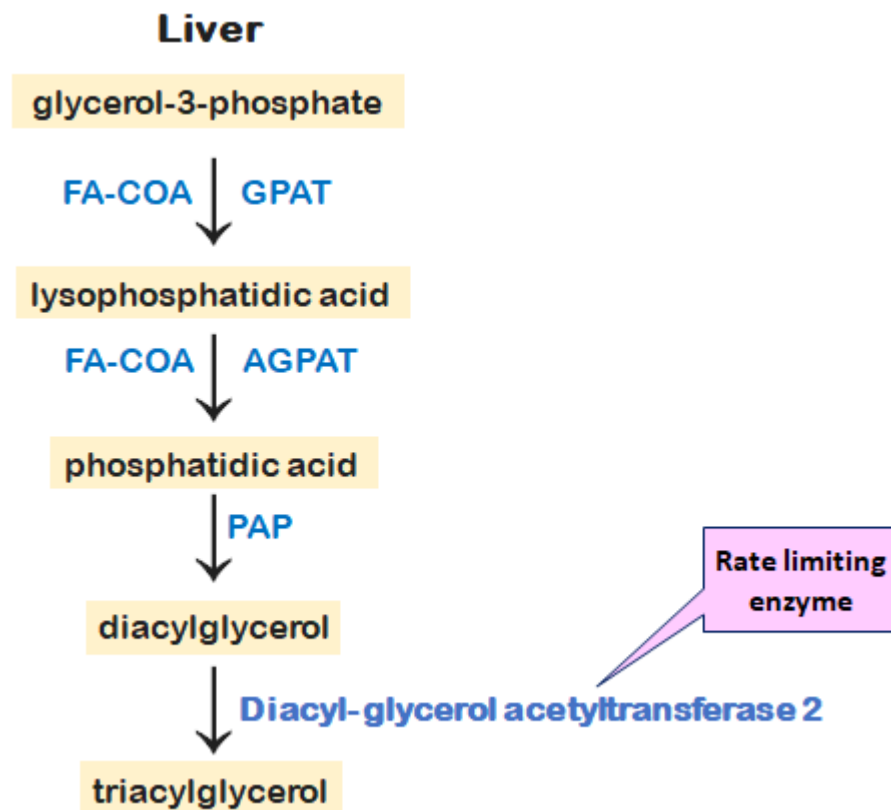


1. Cholestrol
2. Triglycerides

## Cholesterol



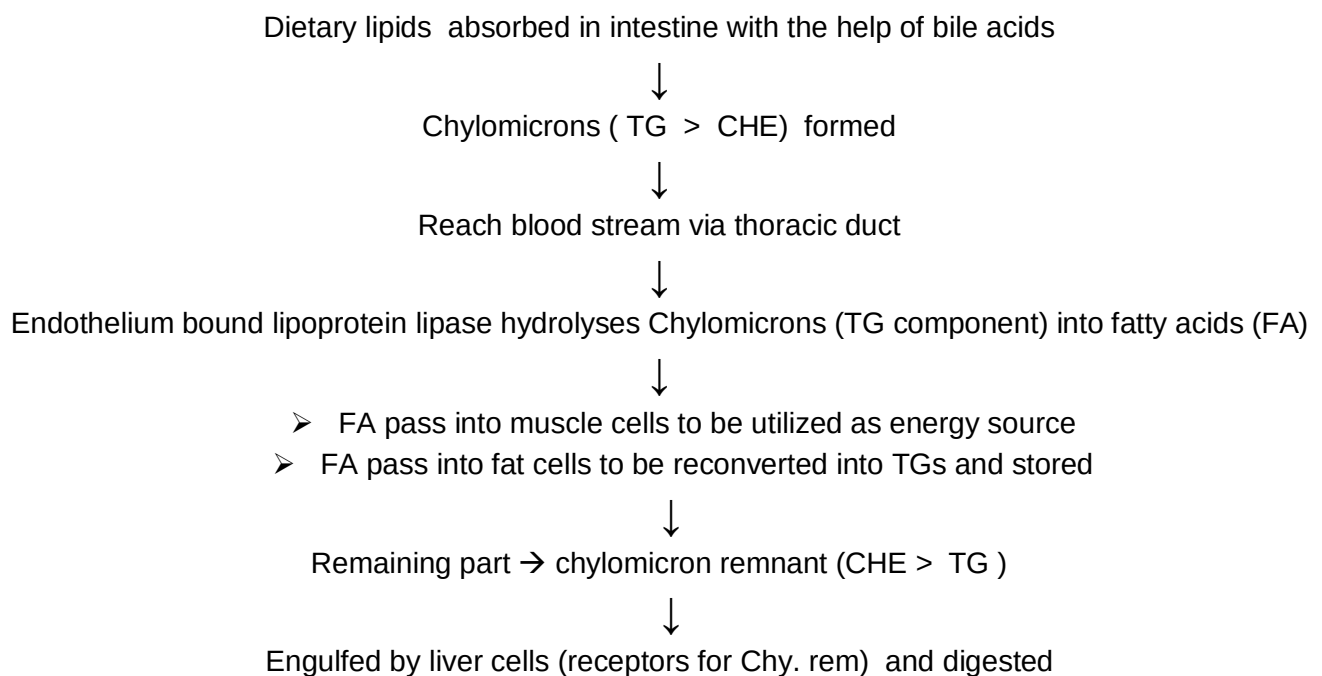
## B. Triglycerides



## Transport

1. Exogenous pathway
2. Endogenous pathway

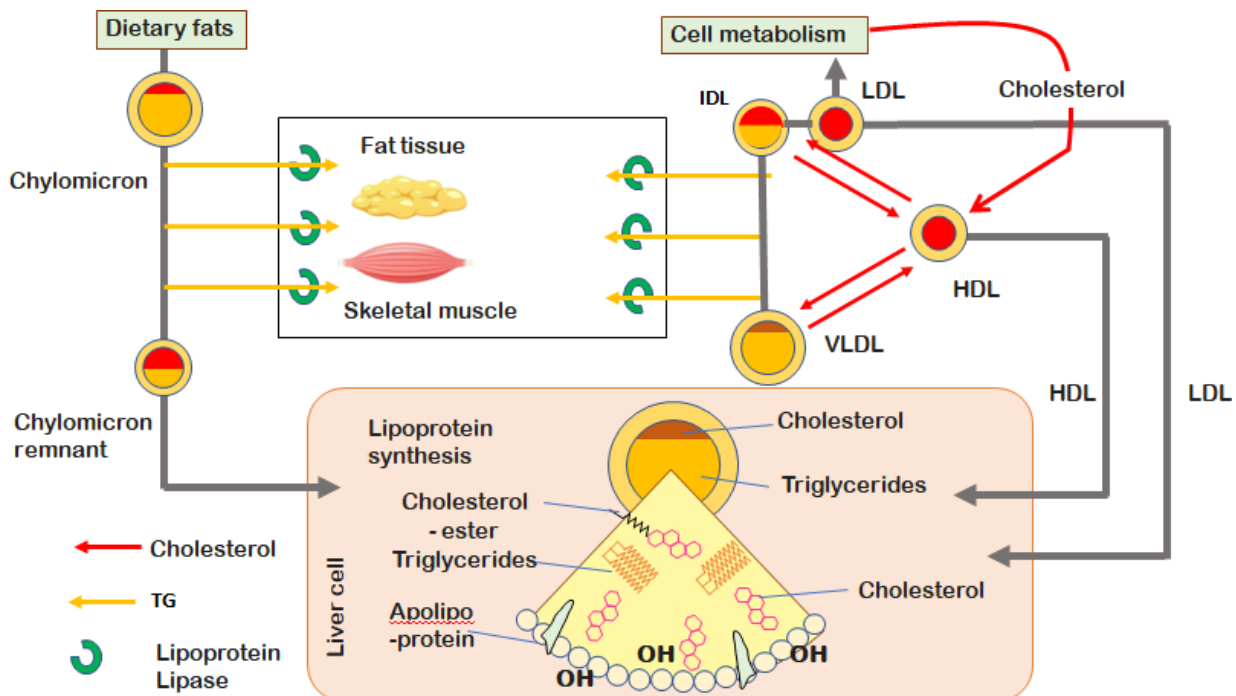
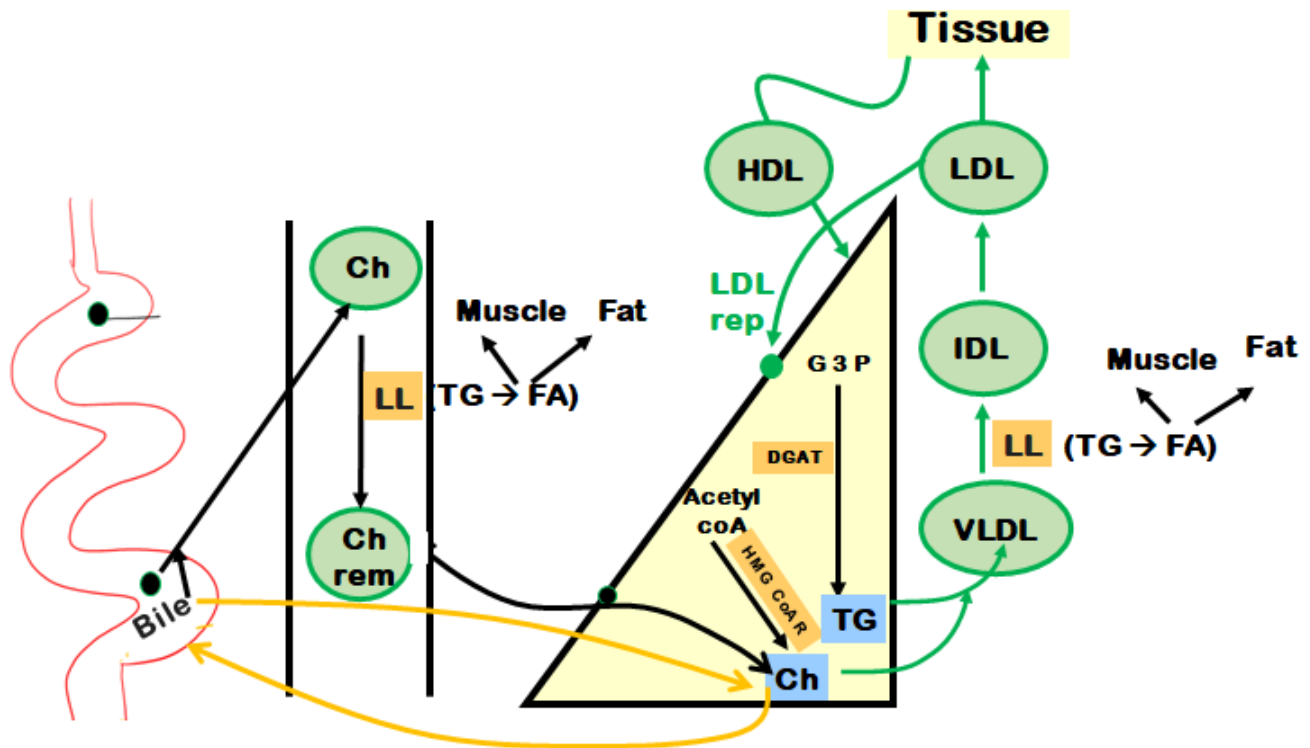
### A. Exogenous pathway



Free CH liberated

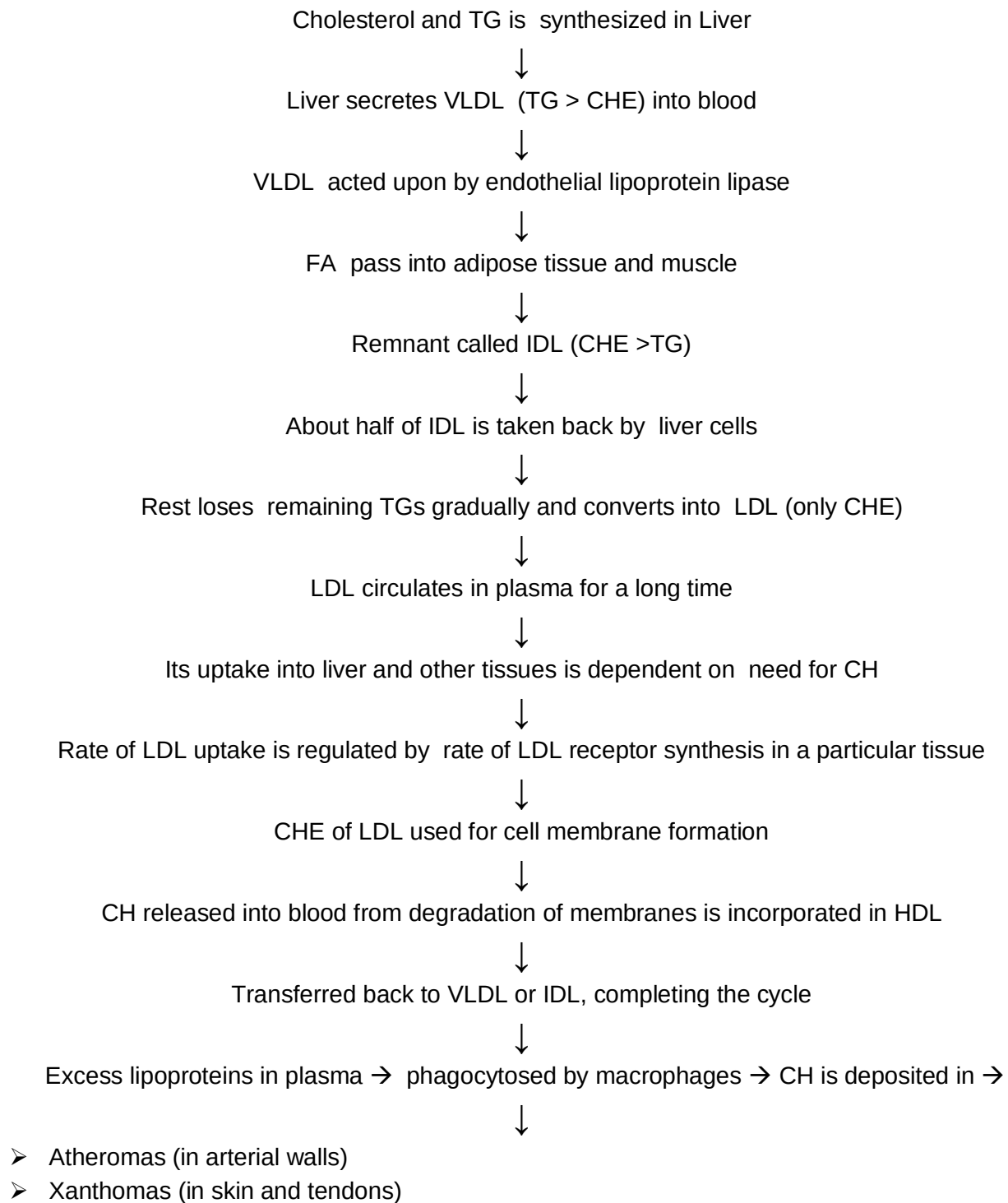


- Stored in liver cells or
- Excreted in bile as bile acids or
- Incorporated into a different lipoprotein and released in blood





## B. Endogenous pathway



### Remember

- VLDL, IDL and LDL → Atherogenic
- HDL → Protective (because HDL facilitates removal of CH from tissues)

## Hyperlipoproteinemia

Plasma concentration of Ch or triglyceride carrying lipoprotein



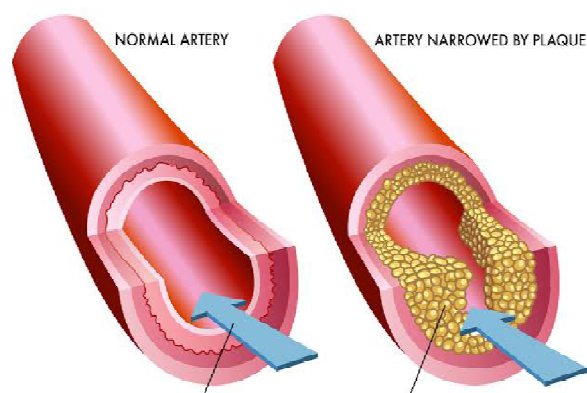
Exceeds beyond a limit



Hyperlipoproteinemia



Increases risk of atherosclerosis and its complications like thrombosis, infarction, and severe pancreatitis



## Types

1. Primary
2. Secondary

### 1. Primary

- Genetic defect leading to increase in cholesterol, triglycerides or both

| Type Disorder                         | Cause | Occurrence  | Elevated plasma lipoprotein | Plasma CH | Lipids TG |
|---------------------------------------|-------|-------------|-----------------------------|-----------|-----------|
| 1. Familial lipoprotein               | G     | Very rare   | Chylomicron                 | ↑↑        | ↑↑↑       |
| 2.(A) familial hypercholesterolaemia  | G     | Less common | LDL                         | ↑↑        | N         |
| 2.(B) polygenic hypercholesterolaemia | MF    | Commonest   | LDL                         | ↑         | N         |
| 3. Familial Dysbetalipoproteinaemia   | G     | Rare        | IDL, Chy. rem.              | ↑         | ↑↑        |
| 4. Hypertriglyceridaemia              | MF,G  | Common      | VLDL                        | N         | ↑↑        |
| 5. Familial combined hyperlipidaemia  | G     | Less common | VLDL, LDL                   | ↑         | ↑         |

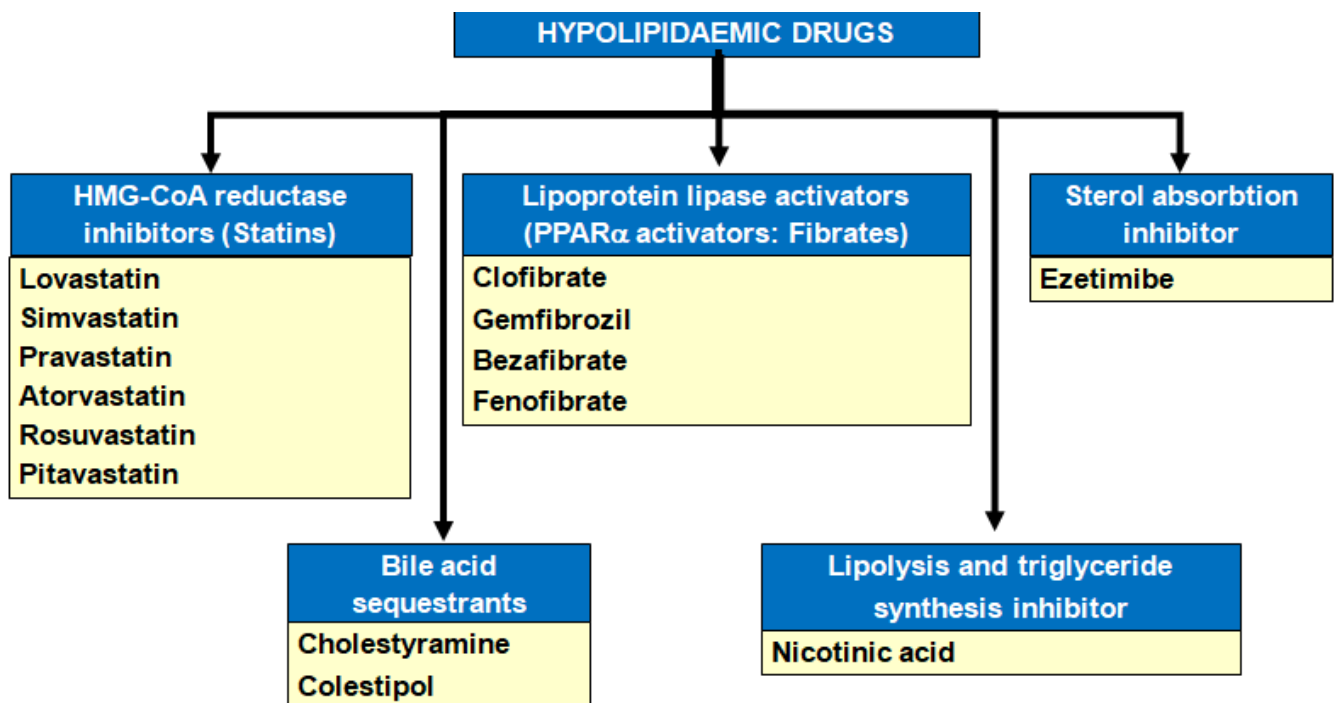
### 2. Secondary

- Diabetes
- Obesity
- Sedentary life styles
- Hypothyroidism
- Alcohol

- Nephrotic syndrome
- Uremia
- Primary Biliary Cirrhosis
- Drugs like oral contraceptive, B blockers, diuretics, isotretionin, protease inhibitors.

## HYPOLIPIDAEMIC DRUGS

### Classification



|                        | HMG-CoA reductase inhibitors (Statins) | Bile acid sequestrants | Lipoprotein lipase activators (PPAR $\alpha$ activators: Fibrates) | Lipolysis and TG synthesis inhibitor | Sterol absorption inhibitor |
|------------------------|----------------------------------------|------------------------|--------------------------------------------------------------------|--------------------------------------|-----------------------------|
| <b>Classification</b>  |                                        |                        |                                                                    |                                      |                             |
| <b>MOA</b>             |                                        |                        |                                                                    |                                      |                             |
| <b>Use</b>             |                                        |                        |                                                                    |                                      |                             |
| <b>Adverse effects</b> |                                        |                        |                                                                    |                                      |                             |

## Color coding

**Statins**

**Bile acid sequestrants**

**Fibrates**

**Nicotinic acid**

**Ezetimibe**

## HMG-COA REDUCTASE INHIBITORS (STATINS)

### Introduction

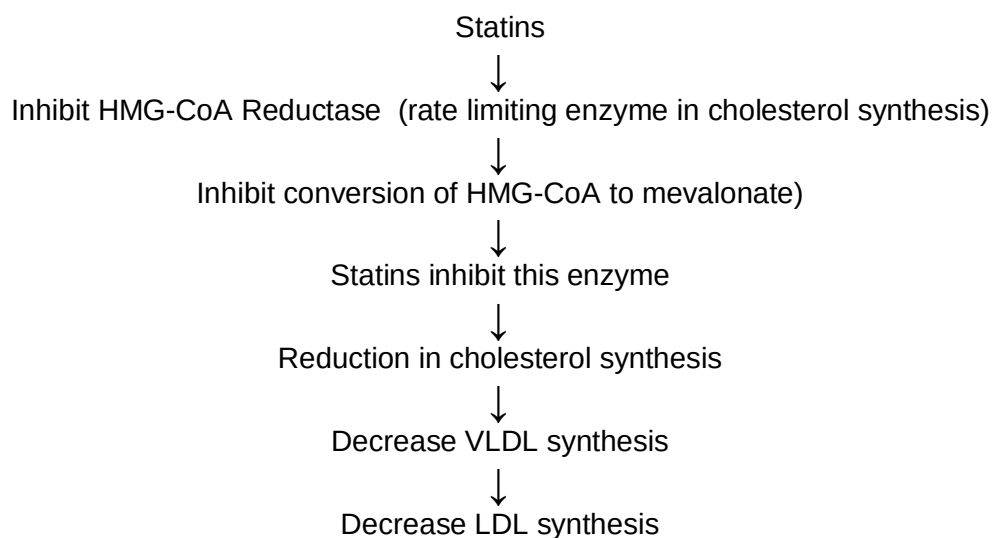
- Most commonly used hypolipidemic drugs.
- Most powerful LDL lowering drugs.
- Most effective and best tolerated hypolipidemic drugs.

### Classification

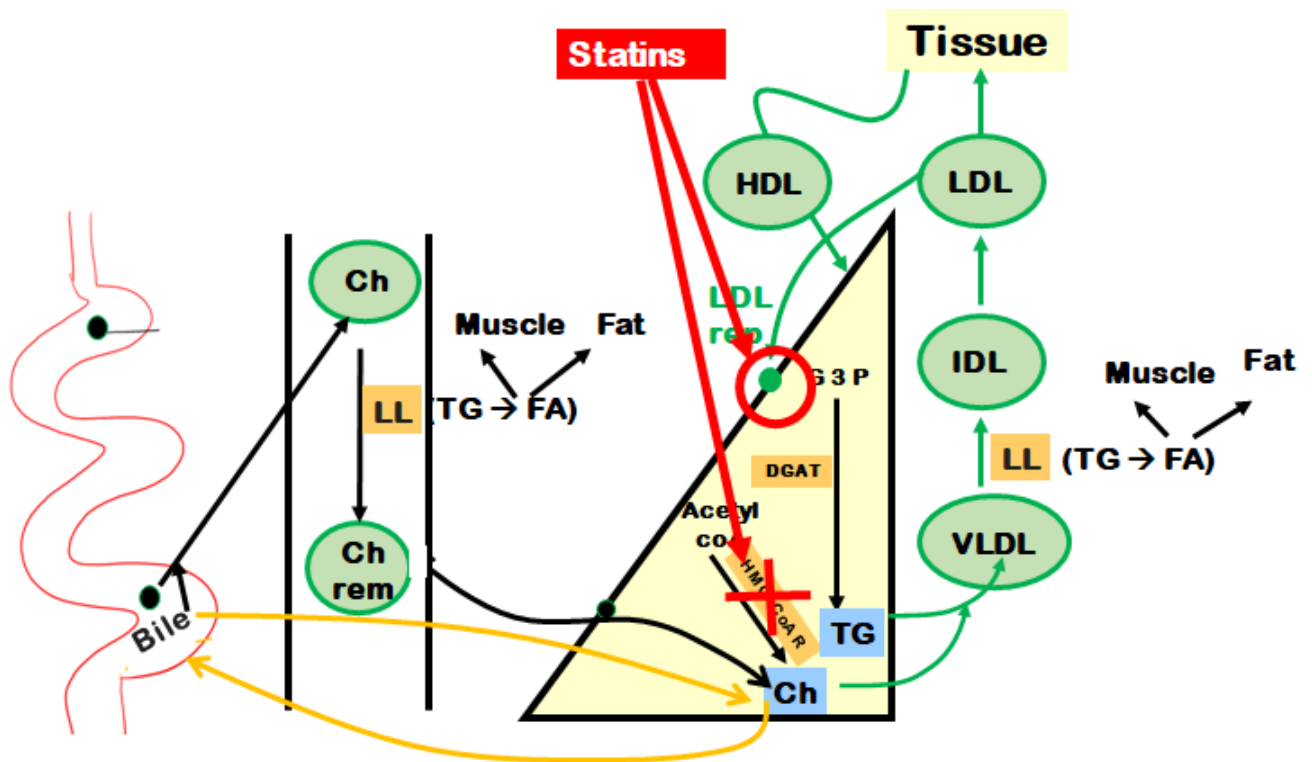
- Lovastatin
- Simvastatin
- Pravastatin
- Atorvastatin
- Rosuvastatin
- Pitavastatin
- Fluvastatin

### MOA

- 3 MOA







## Remember

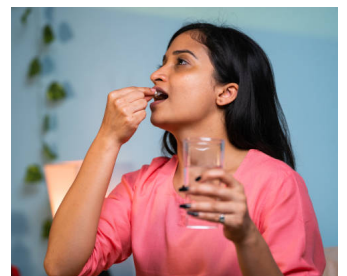
- **Statins** →
  - Decrease LDL
  - Decrease VLDL
  - Decrease triglyceride
  - Increase in HDL

HMG-CoA reductase activity

↓  
Maximum at midnight

↓  
All statins are administered at bed time to obtain maximum effectiveness

- This is not necessary for atorvastatin and rosuvastatin, which have long plasma t<sub>1/2</sub>



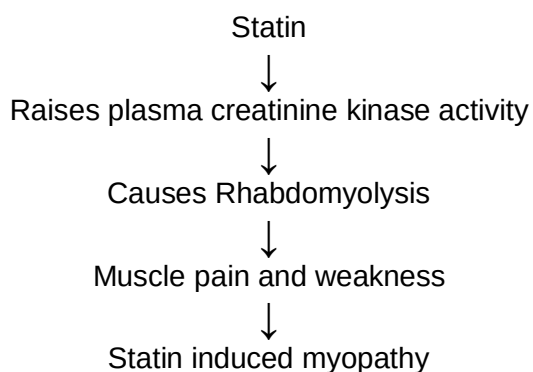
## Uses

- **Statins are first choice drugs for** →
  - Primary hyperlipidemias with raised LDL (Type IIa , IIb, V)
  - Secondary hypercholesterolaemia

## Adverse effect

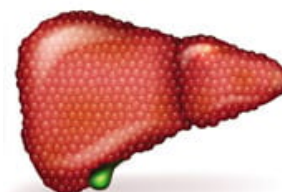
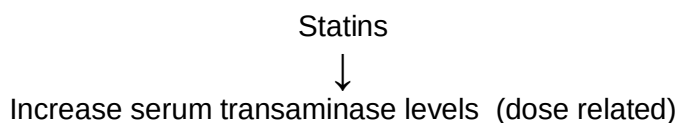
1. Myopathy
2. Hepatotoxicity
3. Gastrointestinal

## 1. Myopathy



- Statin induced myopathy → Increased by →
  - Nicotinic acid
  - Erythromycin
  - Clofibrate
  - Fibrates (maximum with gemfibrozil)
  - Ketoconazole
  - Cyclosporine
  - HIV protease inhibitors
- Among fibrates → fenofibrate appears to be most suitable for combining with statin, because statins metabolism is minimally affected.

## 2. Hepatotoxicity



## 3. Gastrointestinal

- Anorexia
- Nausea
- Vomiting
- Diarrhoea



## Remember

- All statins, except **rosuvastatin** and **pravastatin** are metabolized by CYP3A4.
- All statins are absorbed orally, maximum absorption is for **Fluvastatin**
- Food increases absorption of all statins except **pravastatin**
- **Lovastatin** and **simvastatin** → prodrugs
- **Pravastatin, fluvastatin, atorvastatin and rosuvastatin, Pitavastatin** → administered in active form.
- **Pitavastatin > Rosuvastatin** → most potent
- **Fluvastatin and lovastatin** → least potent
- **Rosuvastatin > atorvastatin** → long acting



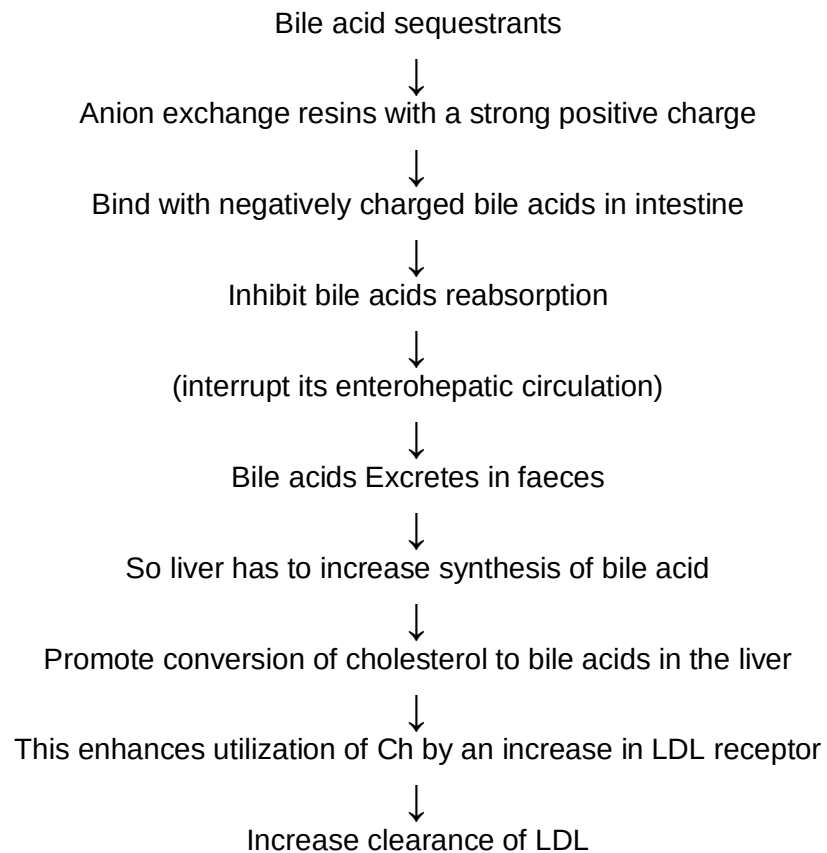
- **Rosuvastatin** → causes greater rise in HDL - cholesterol than other statins.
- **Pravastatin** → minimum drug interactions, minimum food interactions, minimum CNS penetration and minimum risk of myopathy.
- **Pravastatin** → decreases plasma fibrinogen level
- **Atorvastatin** → additional antioxidant property

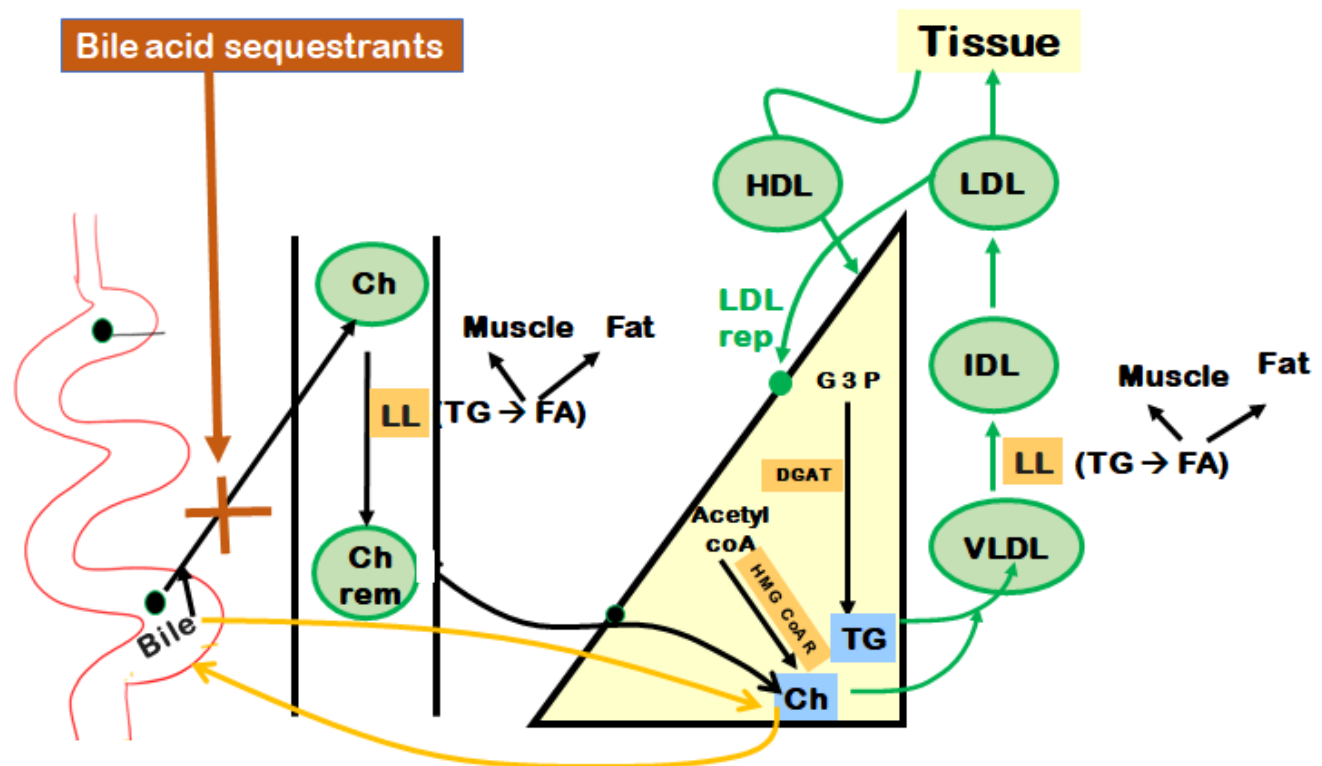
## BILE ACID SEQUESTRANTS

### Classification

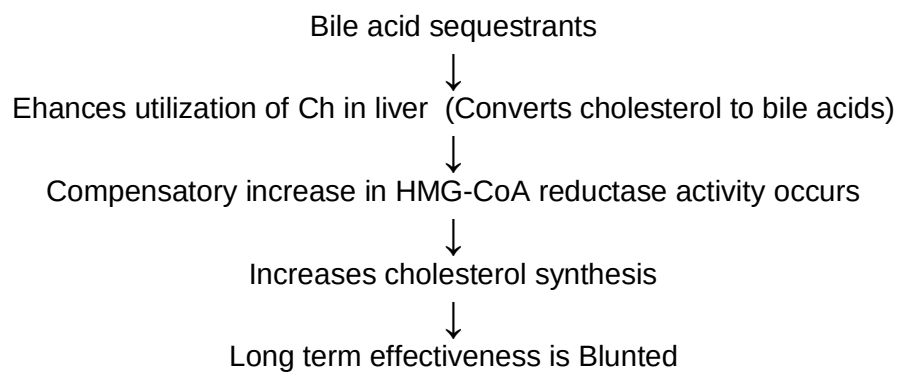
- Cholestyramine
- Colestipol

### MOM





## Remember

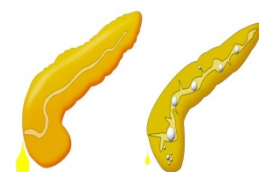


## Uses

- Useful only when LDL-CH is raised (in Type IIa disorder), but not in other types.

## Adverse effects

1. Constipation, bloating, nausea, flatulence
2. Steorrhoea



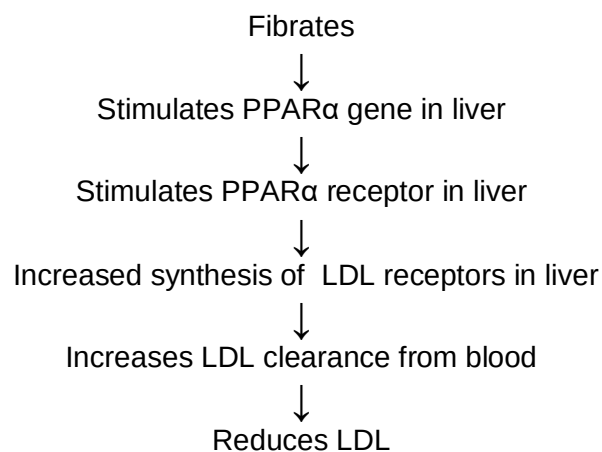
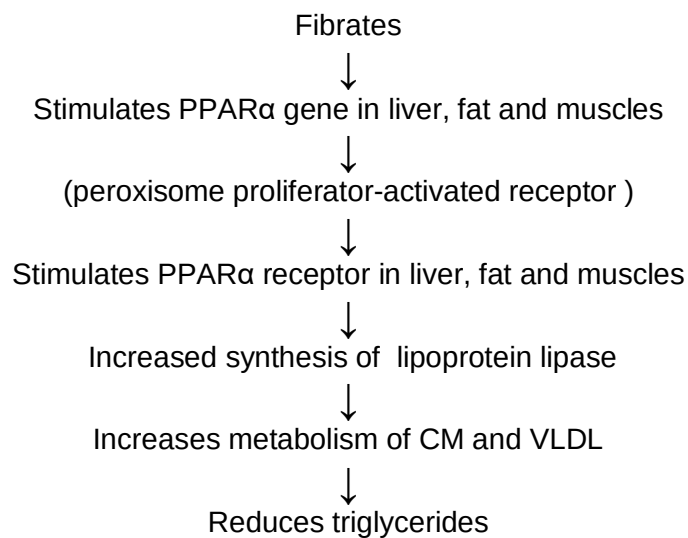
## LIPOPROTEIN LIPASE ACTIVATORS (PPARA ACTIVATORS: FIBRATES)

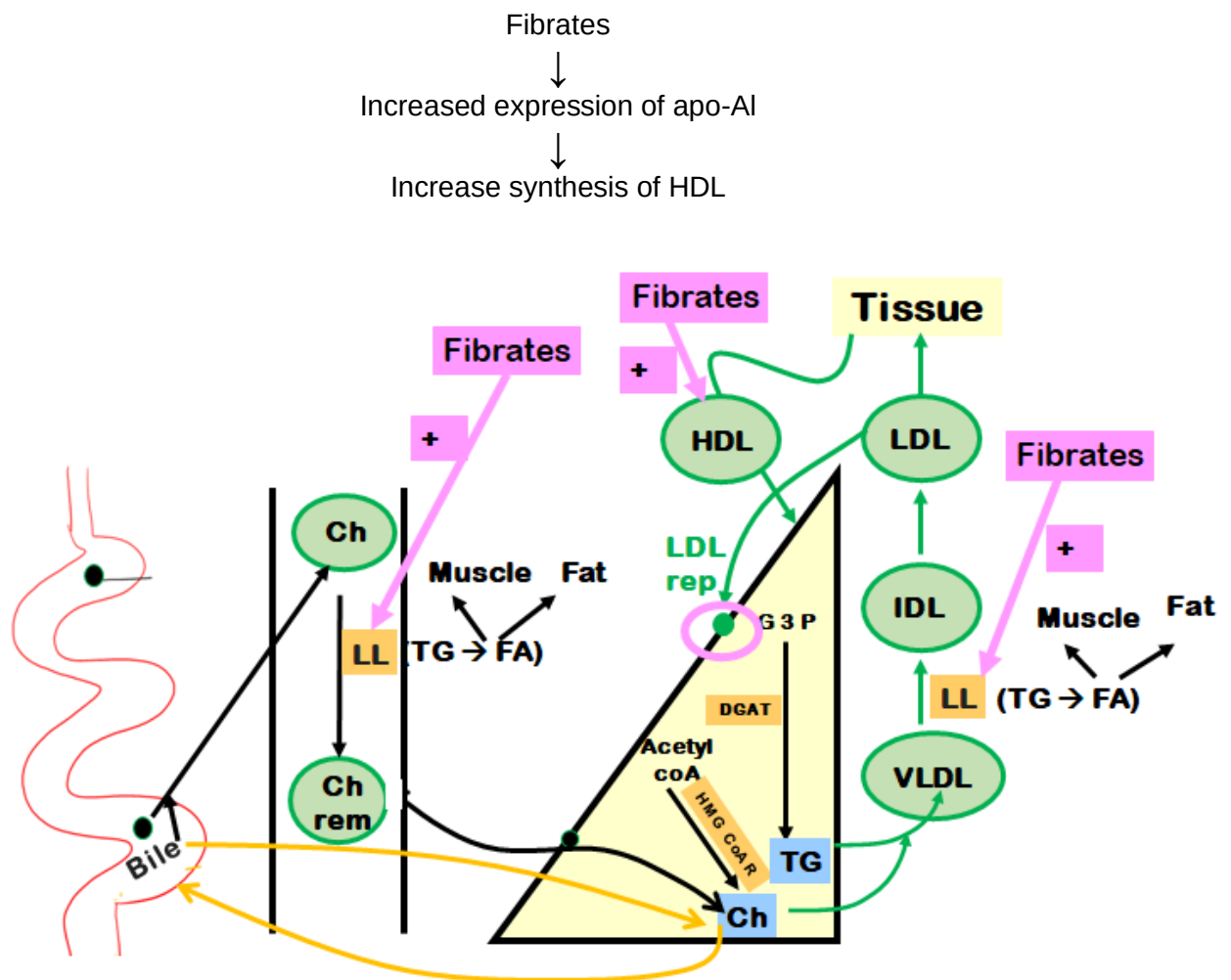
### Classification

- Clofibrate
- Gemfibrozil
- Bezafibrate
- Fenofibrate

### MOA

- 3 MOA





## Uses

- Fibrates are drugs of choice for →
  - Type III hyperlipoproteinaemia
  - Severe hypertriglyceridaemia
 (Statins are DOC in type II & V)

## Adverse effects

- GI symptoms
- Myopathy
- Rashes
- Arrhythmias
- Hypokalemia
- High blood level of aminotrasferases or alkaline phosphatase.



## Remember

- **Fenofibrate** →
  - Longest acting and is a prodrug.
  - Most suitable fibrate for combining with statins, because statin metabolism is minimally affected.
  - Maximum LDL - CH reducing ability amongst fibrates.
  - Uricosuric and can be used with coexisting hyperuricemia.
  - **Gemfibrozil** →
    - Absorption is improved when taken with food
    - Additional actions → promotion of fibrinolysis.
- **Bezafibrate** → decreases fibrinogen and glucose level.

## LIPOLYSIS AND TG SYNTHESIS INHIBITOR

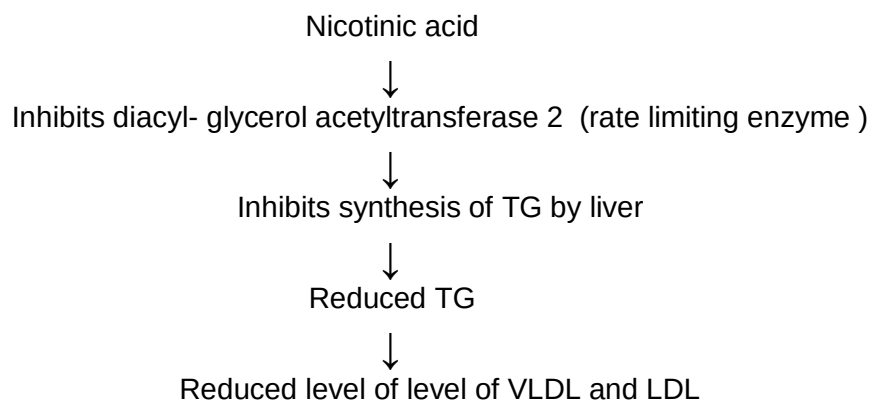
### Classification

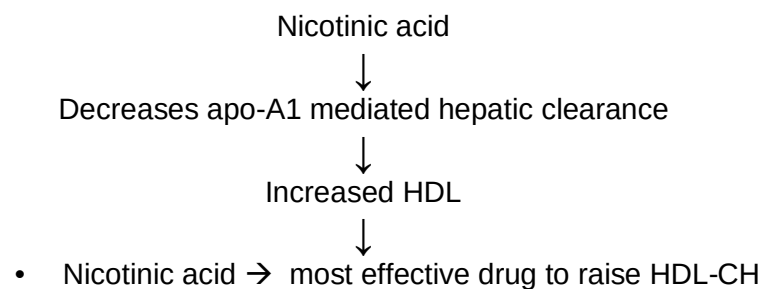
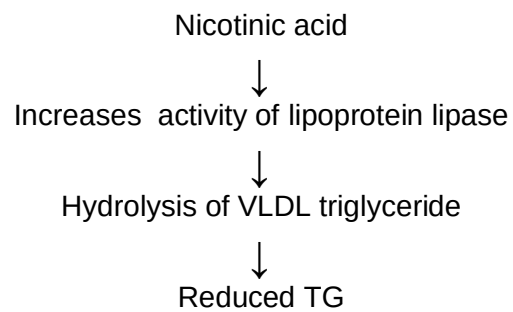
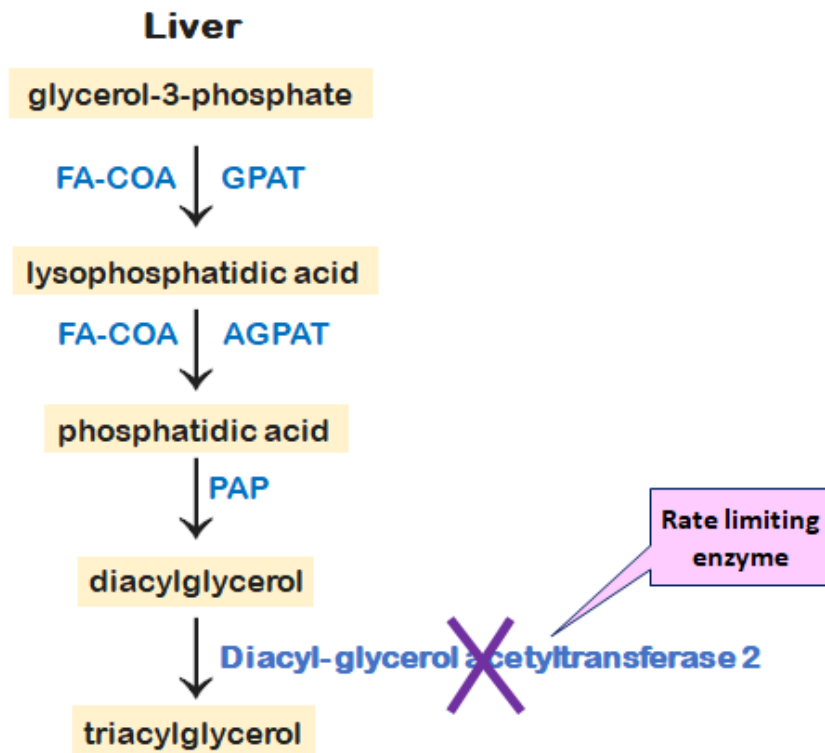
#### Nicotinic acid

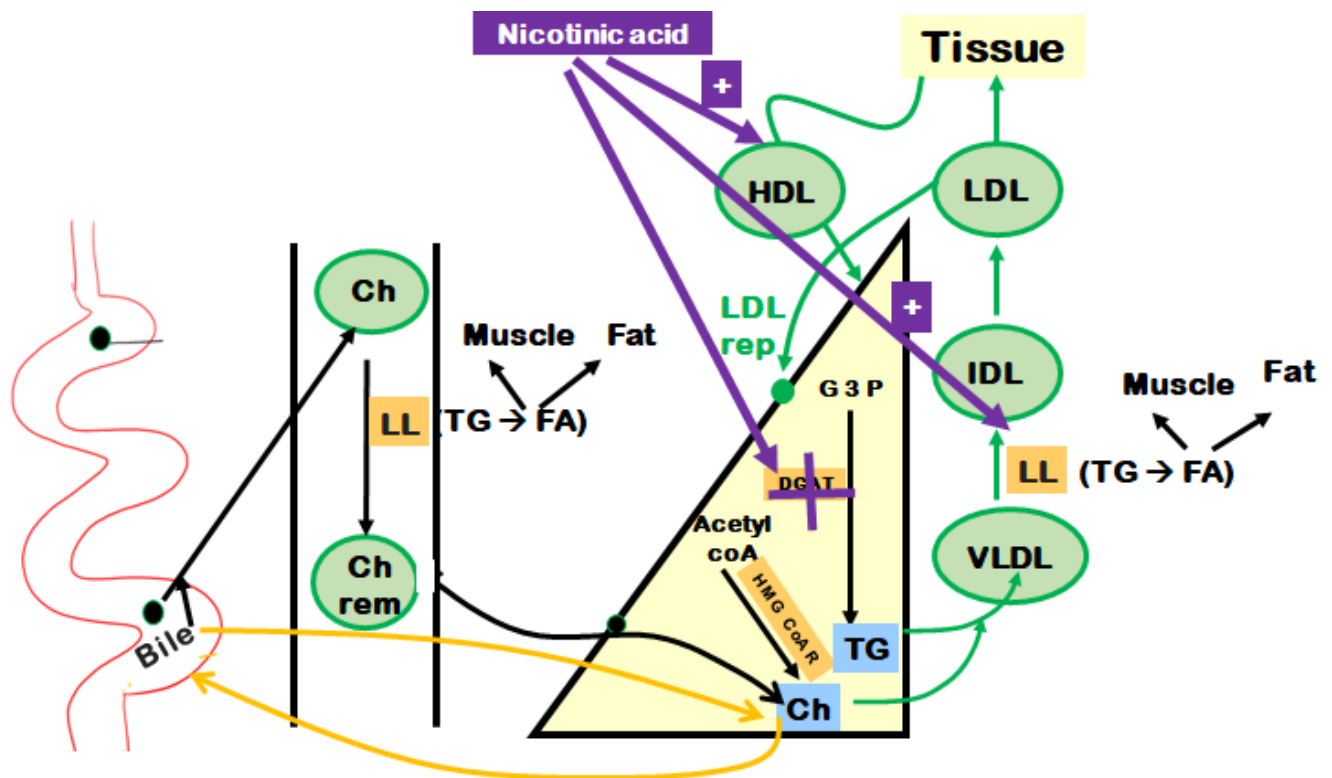
- It is a B group vitamin which in much higher doses reduces plasma lipids
- This action is unrelated to its vitamin activity and not present in nicotinamide

### MOA

- 3 MOA







## Uses

- Used to lower VLDL and raise HDL levels, and as an adjunctive drug to statins/fibrates.
  - Highly efficacious in hypertriglyceridaemia (type III, IV, V)
- Most effective drug in reducing plasma TG levels.
  - Used to control pancreatitis associated with severe hypertriglyceridaemia, mostly in genetic type IV and type V disorders.
- Long-term in post-MI patients → to reduce recurrences of MI and overall mortality.

## Adverse effects

- Skin changes

Nicotinic acid  
 ↓  
 Causes release of PGs  
 ↓  
 Cutaneous vasodilatation  
 ↓  
 Marked flushing, itching (pruritis) and heat  
 ↓  
 can be prevented by pretreatment with aspirin





- 2) Acanthosis nigricans
- 3) Dyspepsia, vomiting and diarrhoea
- 4) Liver dysfunction
- 5) Hyperglycemia
- 6) Hyperuricemia

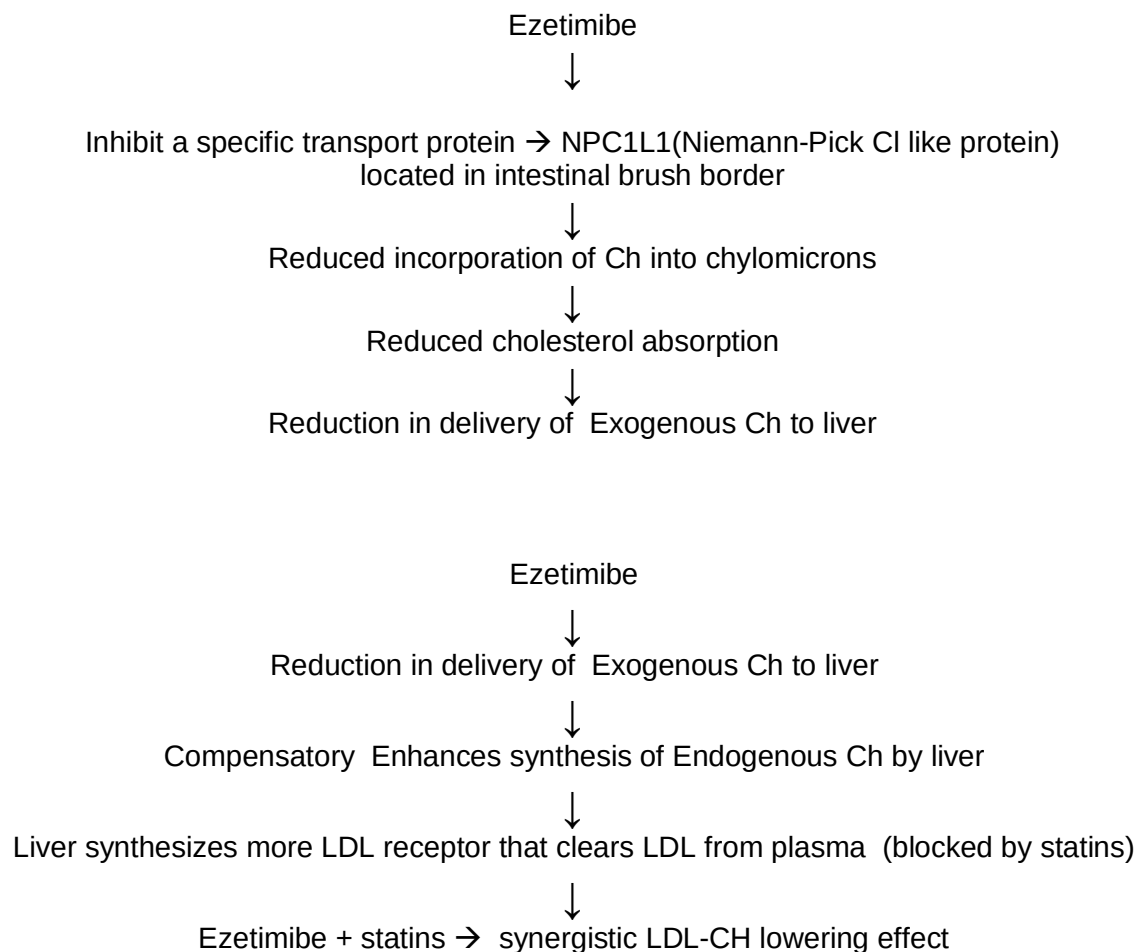
## STEROL ABSORPTION INHIBITOR

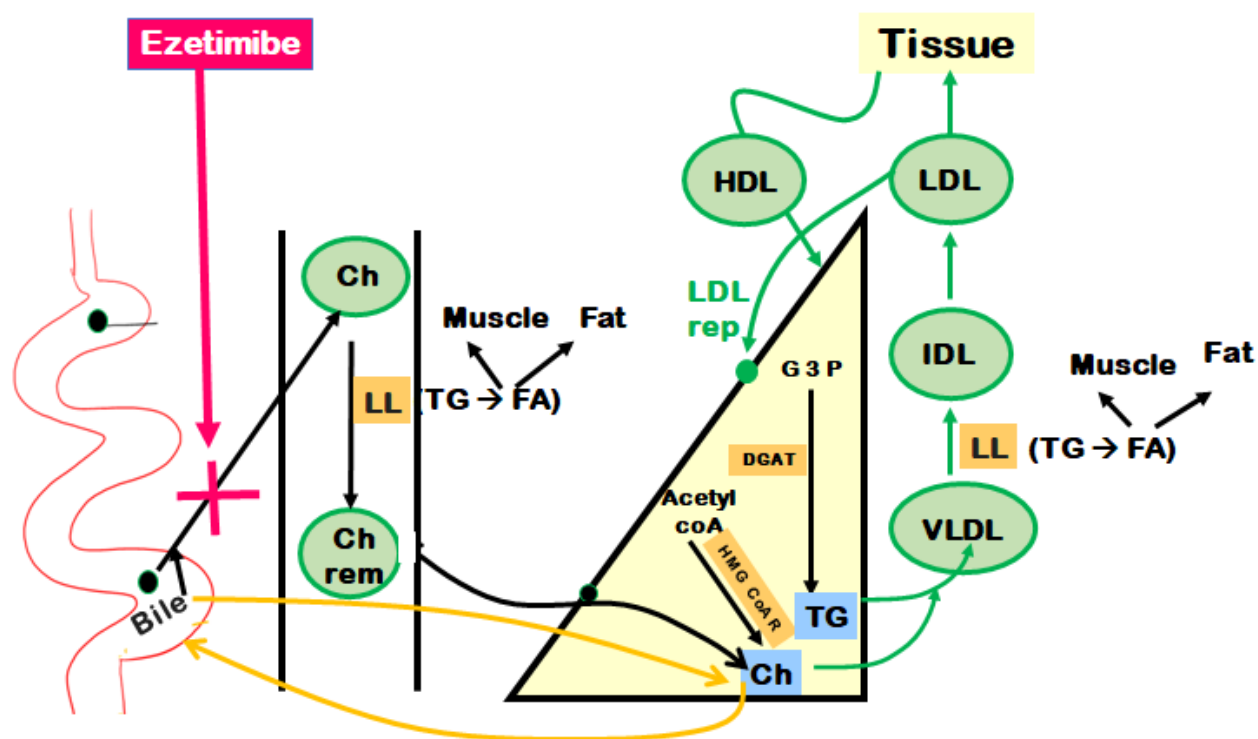
### Classification

- Ezetimibe

### MOA

- 2 MOA





## Uses

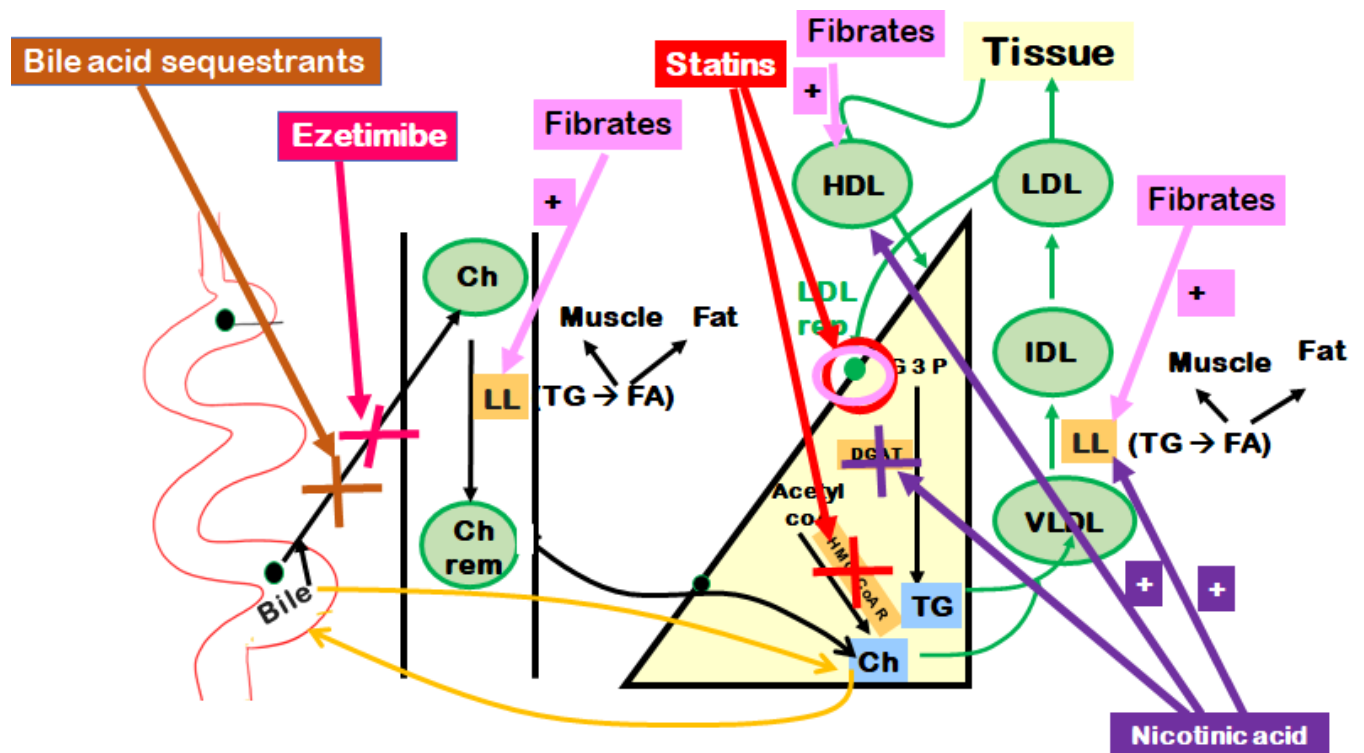
1. To supplement statins without increasing their dose
2. Used alone in mild hypercholesterolaemia when a statin is contraindicated or not tolerated

## Adverse effect

1. Reversible hepatic dysfunction
2. Myositis (Rarely)

## PROTOSUMMARY

| Drug (daily dose)            | Mechanism of action                                                                              | Effect on lipids (%)                                       |
|------------------------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| HMG-CoA reductase inhibitors | ↓ CH synthesis by inhibition of rate limiting HMG-CoA reductase                                  | LDL ↓ 20-55<br>HDL ↑ 5-15<br>TG ↓ 10-35                    |
| Bile acid sequestrants       | ↓ bile acid absorption, ↑ hepatic conversion of CH to bile acids, ↑ LDL receptors on hepatocytes | LDL ↓ 15-30<br>HDL ↑ 3-5<br>TG not affected, may ↑ in some |
| Fibric acid derivatives      | ↑ Activity of lipoprotein lipase, ↓ release of fatty acids from adipose tissue                   | LDL ↓ 5-20<br>HDL ↑ 10-20<br>TG ↓ 20-50                    |
| Nicotinic acid               | ↓ Production of VLDL, ↓ lipolysis in adipocytes                                                  | LDL ↓ 15-25<br>HDL ↑ 1 20-35<br>TG ↓ 20-50                 |





# Cardiovascular drugs

CHAPTER

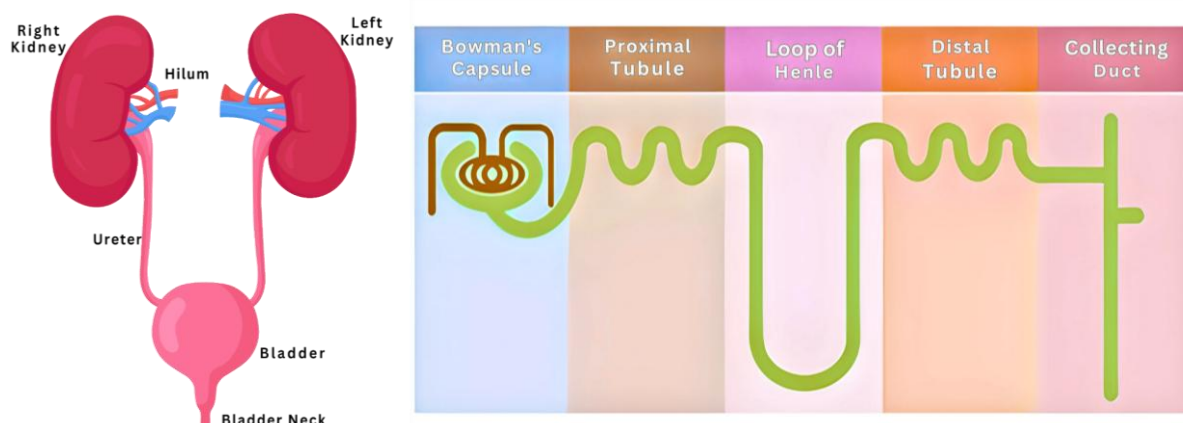
6

## CONTENT

- Drugs Affecting Renin-Angiotensin System (RAS)
- Drugs for Heart Failure
- Antianginal and Other Anti-ischaemic Drugs
- Antihypertensive Drugs
- Antiarrhythmic Drugs

## DRUGS AFFECTING RENIN ANGIOTENSIN SYSTEM (RAS)

### Normal kidney → Anatomy



### Nephron

- Parenchyma is composed of approx one million microstructures called nephrons
- **5 major parts** →
  1. Glomerular capsule (glomerulus and Bowman's capsule)
  2. Proximal convoluted tubule (PCT)
  3. Loop of Henle
  4. Distal convoluted tubule (DCT)
  5. Collecting ducts

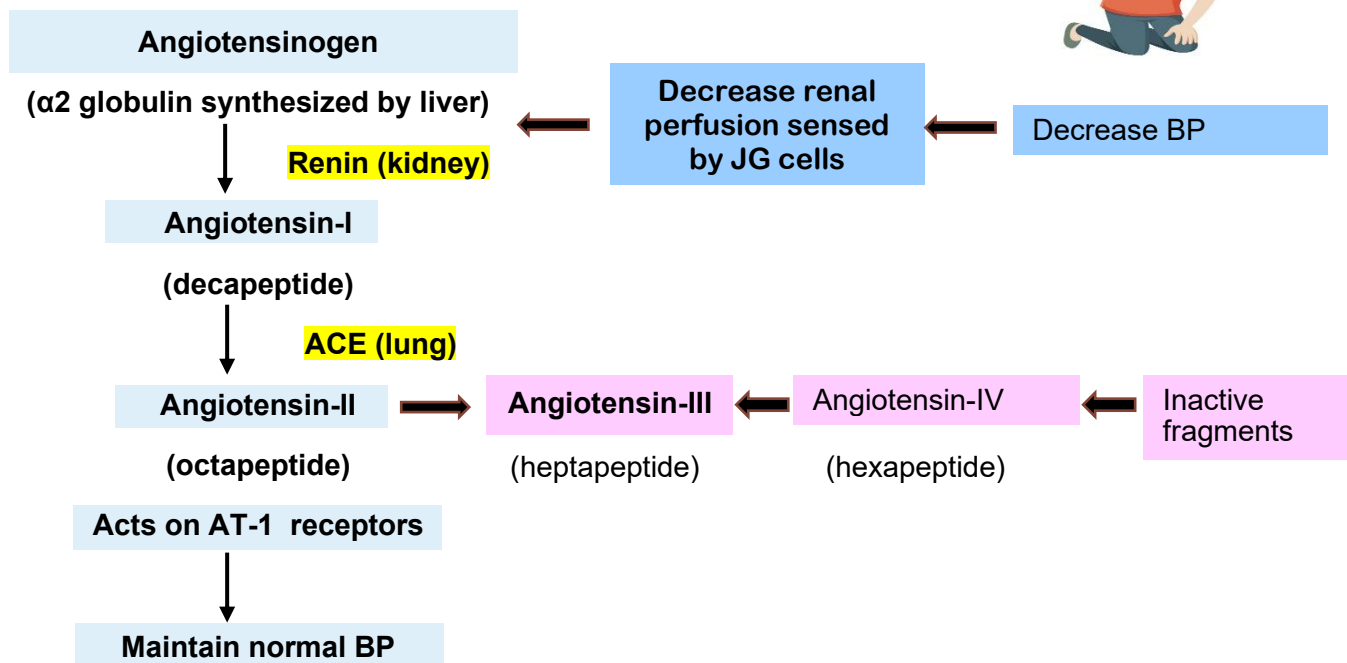
### Glomerulus

- Invagination of blind end of PCT
- Has a capillary tuft fed by afferent arteriole and drained by efferent arteriole



## Renin-Angiotensin System (RAS)

- Renin is a proteolytic enzyme
- It is produced by juxtaglomerular cells of kidney
- It is secreted in response to:
  - Decrease in arterial blood pressure
  - Decrease  $\text{Na}^+$  in macula densa
  - Increased sympathetic nervous activity



## Remember

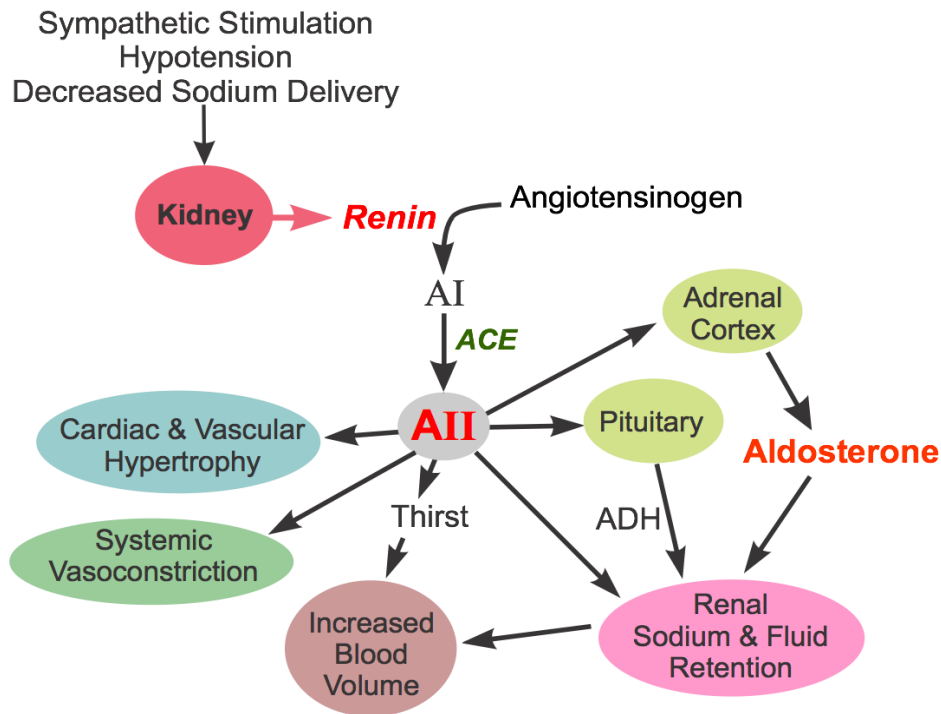
- Plasma  $t_{1/2}$  of renin → 15 min
- Plasma  $t_{1/2}$  of AT-II → 1 min
- Ang I is 100 times less potent than Ang II
- Ang III is 2–10 times less potent than Ang II

## Angiotensin receptors

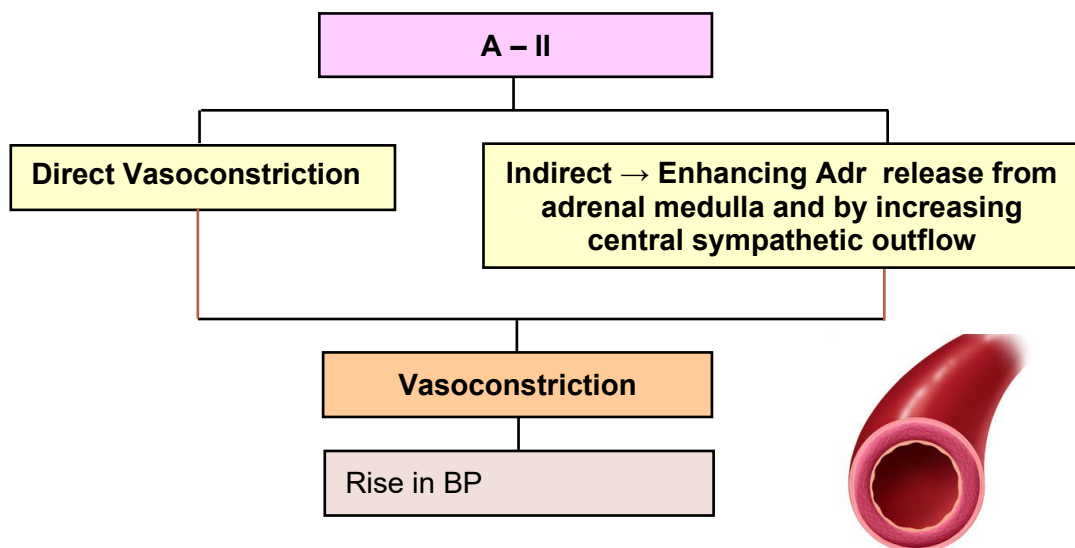
- Two subtypes → AT1 and AT2
- Both subtypes are G-protein coupled receptors.
- All known effects of A-II appear to be mediated by AT 1 receptor

## Actions of Angiotensinogen II

1. Blood vessels
2. Heart
3. Adrenal cortex
4. Kidney
5. CNS
6. Peripheral sympathetic structures

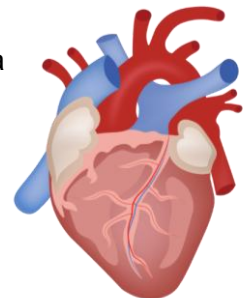


## 1. Blood vessels

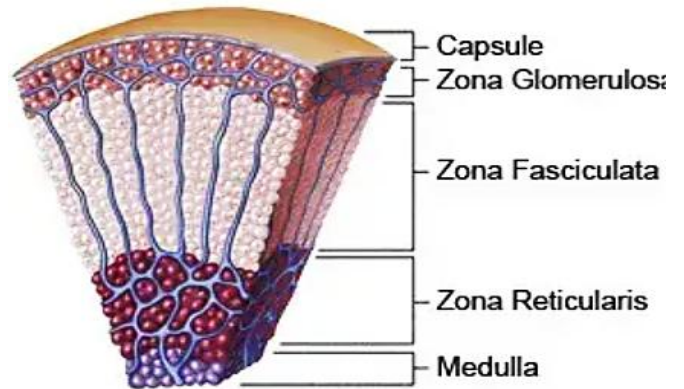
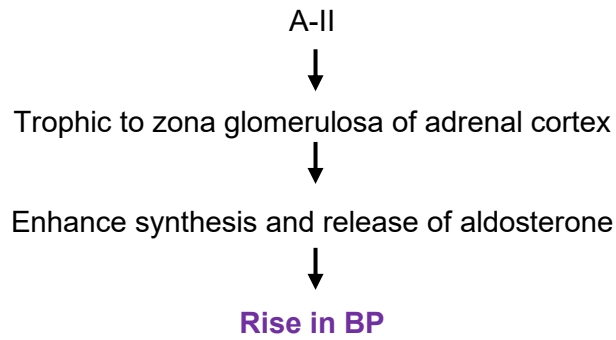


## 2. Heart

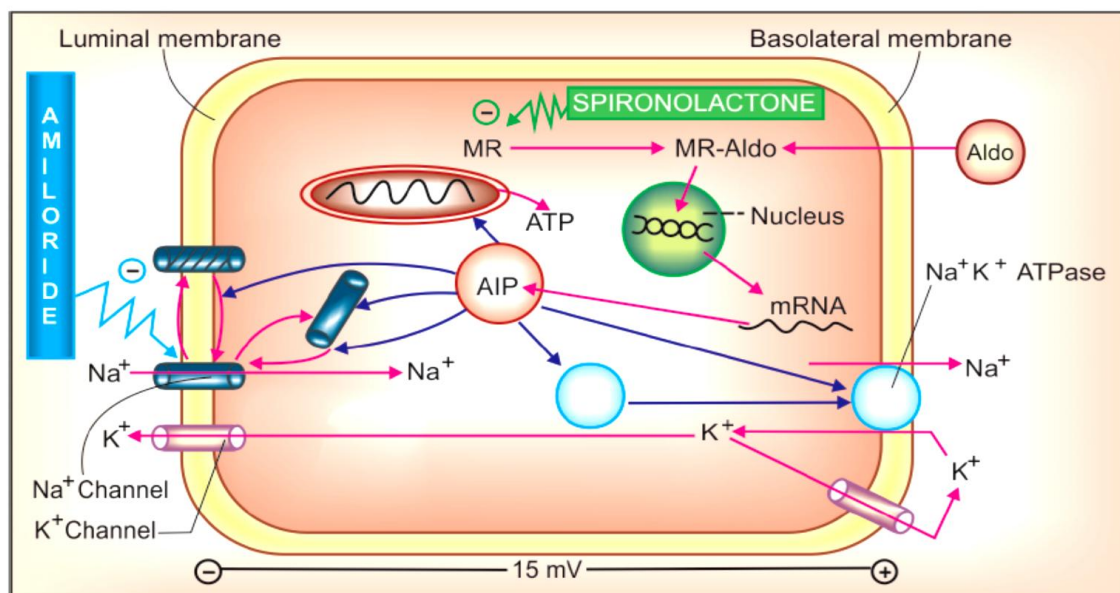
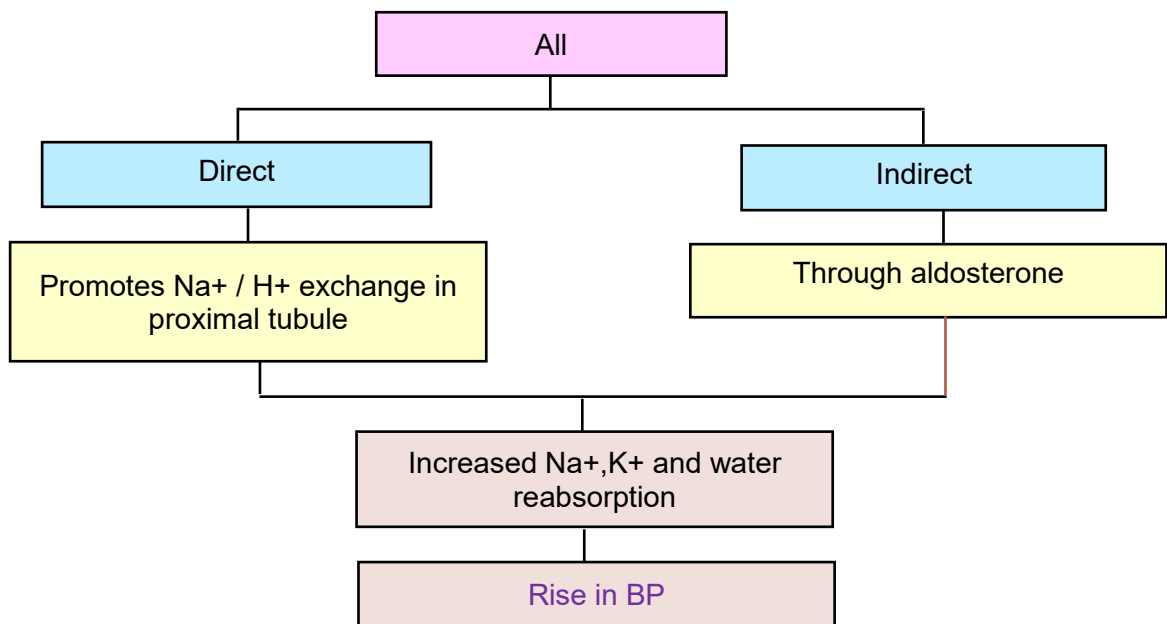
- Increases force of myocardial contraction by promoting  $\text{Ca}^{2+}$  influx.
- Increase heart rate by enhancing sympathetic activity, but reflex bradycardia predominates
- Cardiac output is reduced
- Cardiac work is increased
- On a chronic basis induces hypertrophy in myocardium
- Increases vessel wall intimal thickening
- These changes are important risk factors for cardiovascular morbidity and mortality



### 3. Adrenal cortex

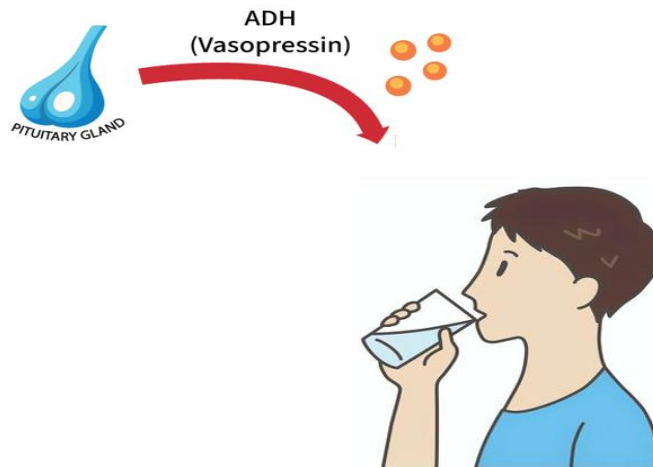
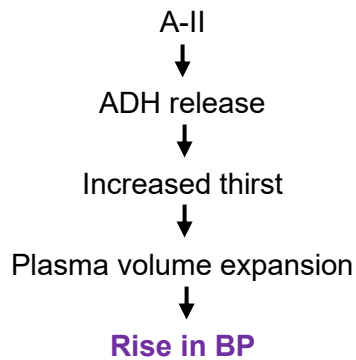


### 4. Kidney

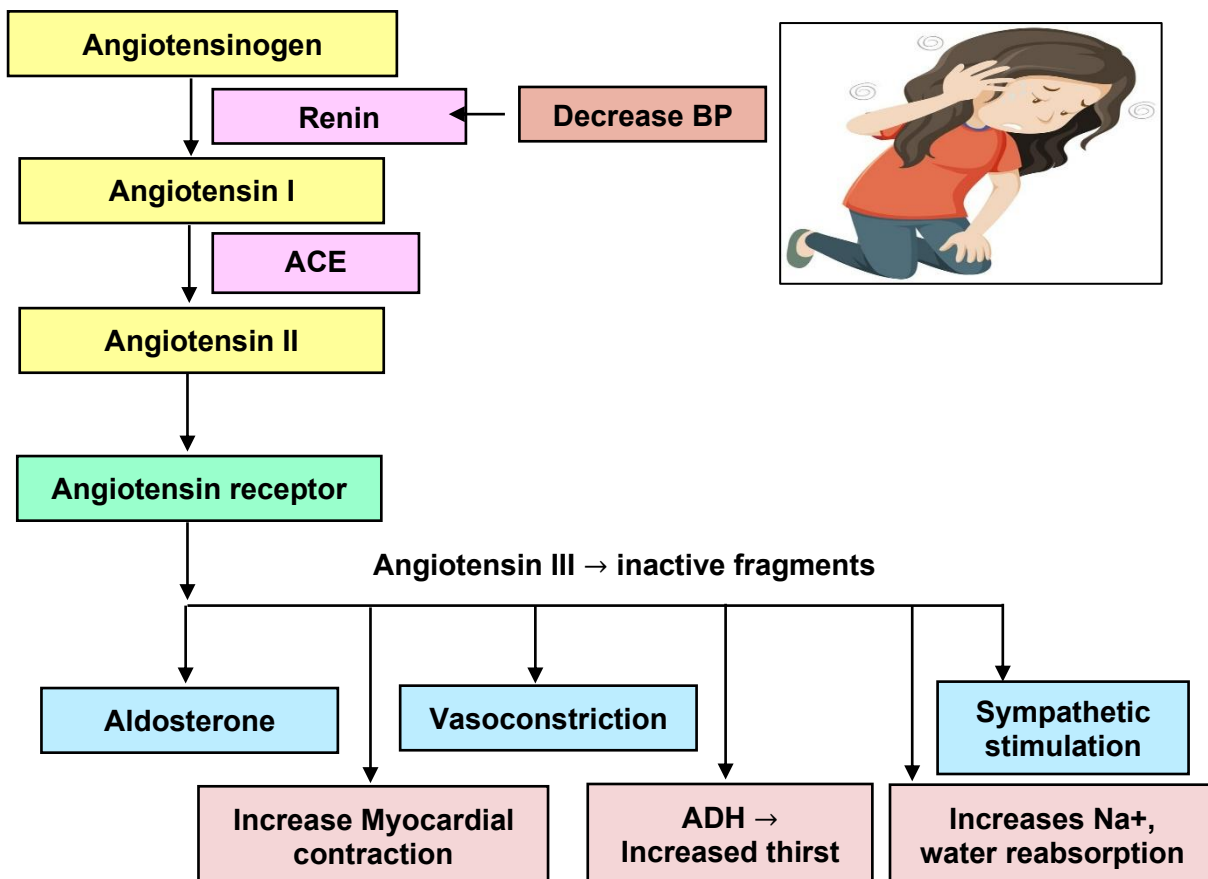




## 5. CNS

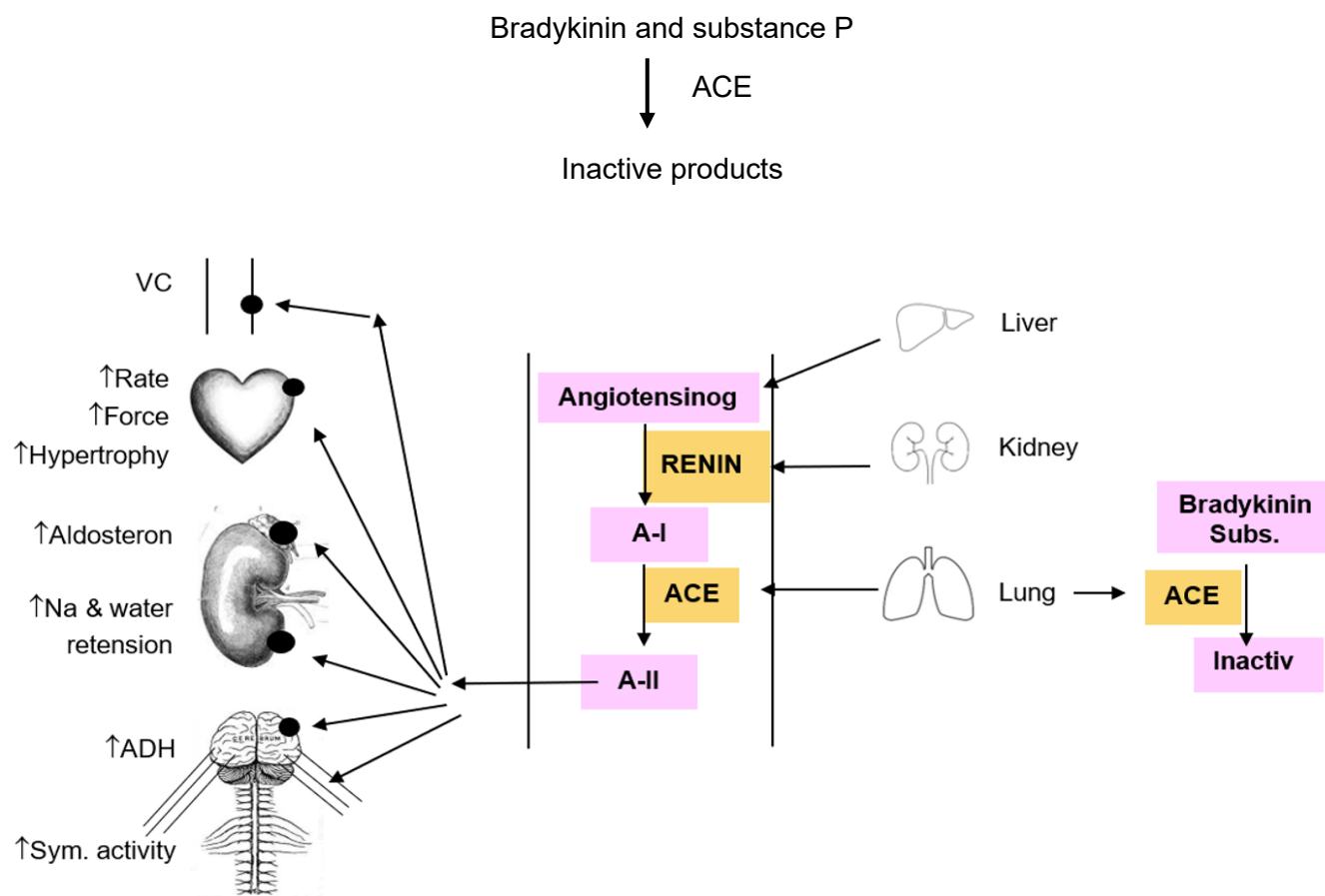


## 6. Peripheral sympathetic structures



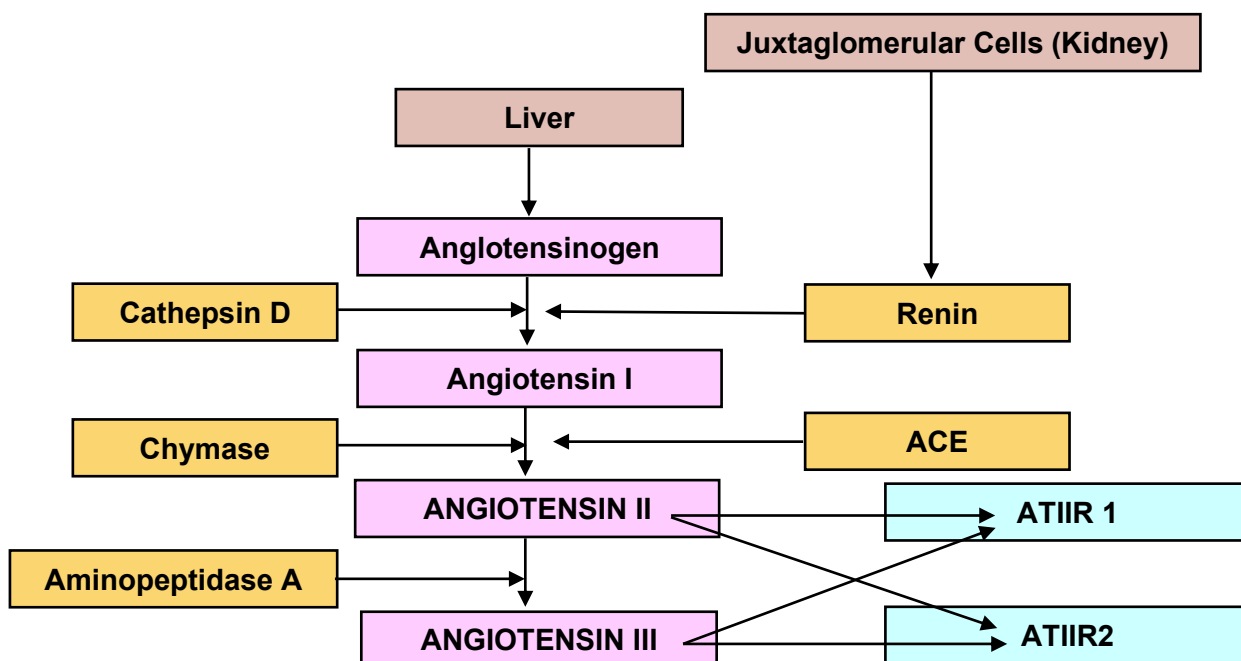
## Other action of ACE enzyme

ACE secreted from lung also convert Kinins (bradykinin) and substance P into inactive products.



## Alternative (ACE-independent) pathway of Ang II production

In addition to primary pathway described above, small quantities of Ang I and Ang II can be produced from angiotensinogen by action of other proteases like cathepsin and Chymase

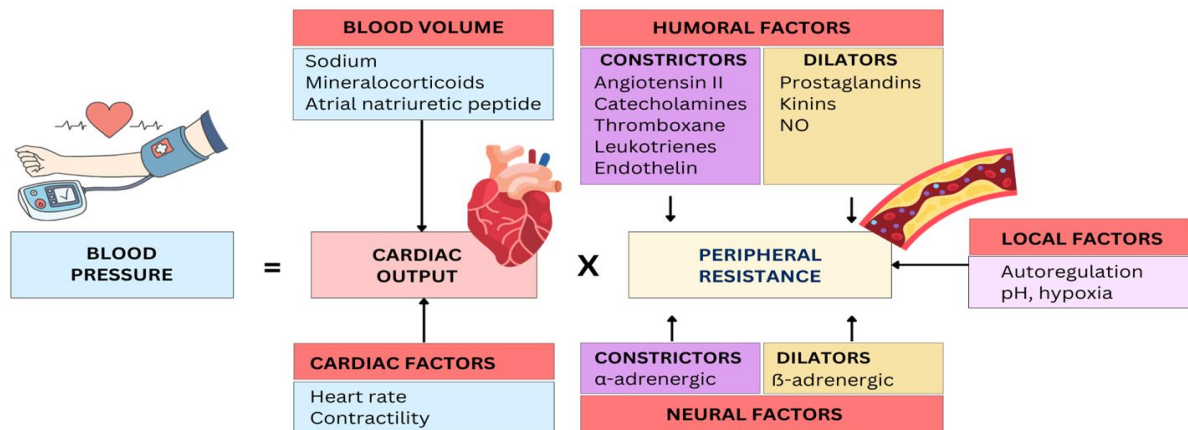


## Hypertension

- Sustained increase in blood pressure
- BP has 2 components → Systolic and Diastolic



## Blood Pressure Regulation

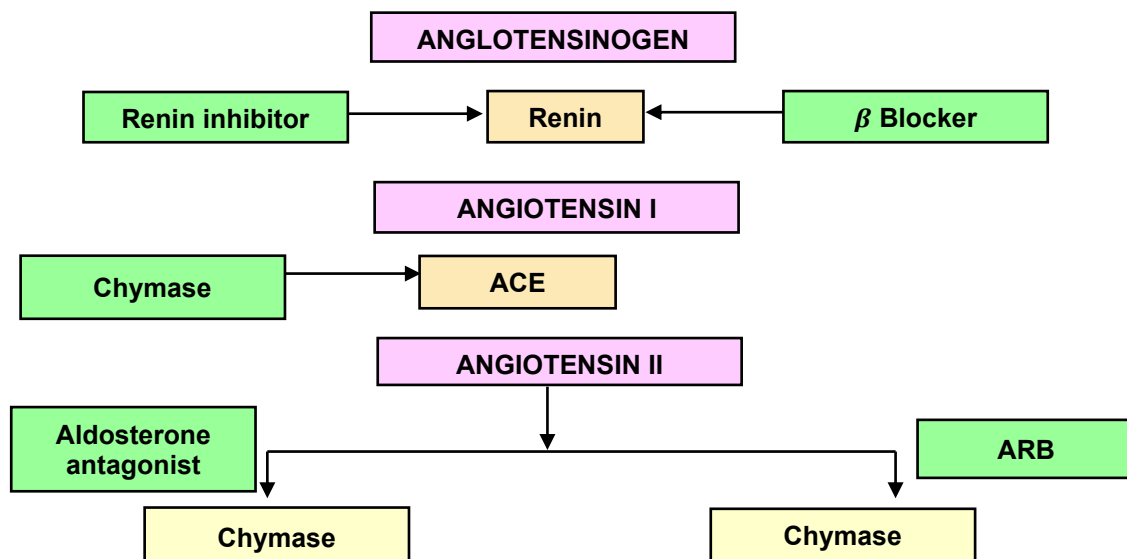


|                 | Systolic<br>mm Hg |     | Diastolic<br>mm Hg |
|-----------------|-------------------|-----|--------------------|
| Normal          | <120              | and | <80                |
| Prehypertension | 120 - 139         | or  | 80-89              |
| Stage I         | 140- 159          | or  | 90-99              |
| Stage II        | ≥160              | or  | ≥100               |

## Types

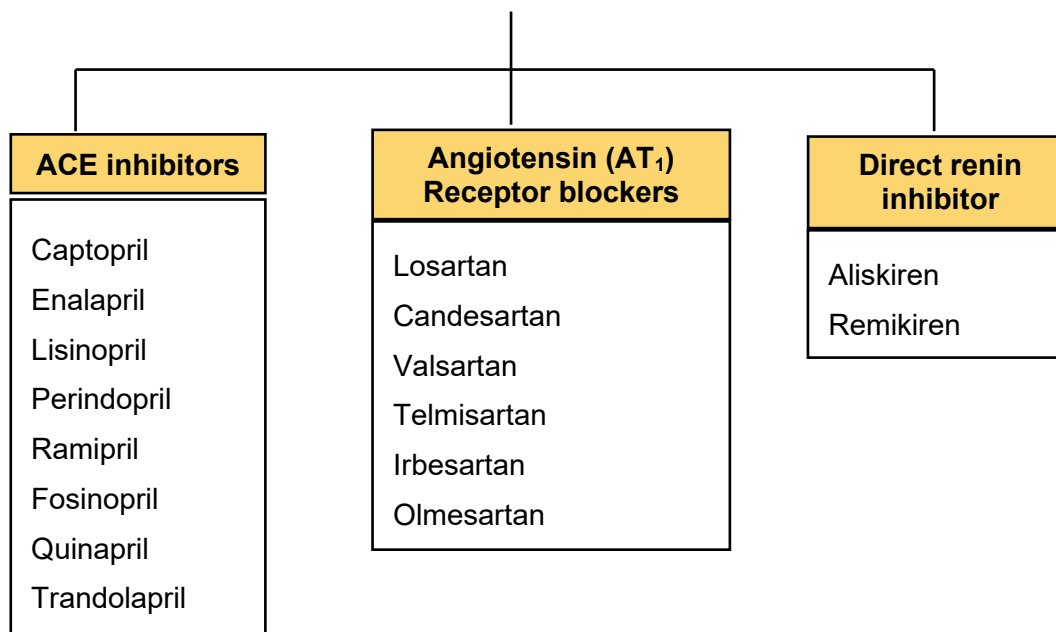
1. **Essential hypertension** → RAS is overactive
2. **Secondary hypertension** → Secondary to other disease processes □ Renal, Endocrine, Cardiovascular, Neurogenic

## INHIBITION OF RAS



1. **Inhibitors to renin release** → B blockers
2. **Inhibitors to renin activity** → Direct renin inhibitors (DRIs)
3. **Prevent generation of the active principle Ang II** → Angiotensin converting enzyme (ACE) inhibitors
4. **Antagonise the action of Ang II on target cells** → Angiotensin receptor blockers (ARB)
5. **Block mineralocorticoid receptors** → Aldosterone antagonists (Spironolactone)

## Drugs Affecting Renin-Angiotensin System



|                          | ACE inhibitors | ARBs | Direct Renin Inhibitors |
|--------------------------|----------------|------|-------------------------|
| <b>Introduction</b>      |                |      |                         |
| <b>Drugs</b>             |                |      |                         |
| <b>MOA</b>               |                |      |                         |
| <b>Uses</b>              |                |      |                         |
| <b>Adverse effect</b>    |                |      |                         |
| <b>Contraindications</b> |                |      |                         |

## ACE INHIBITORS

### Introduction

- Sulfhydryl containing dipeptide
- Abolishes pressor action of Ang II but not that of Ang I
- Does not block AT<sub>1</sub> or AT<sub>2</sub> receptors.

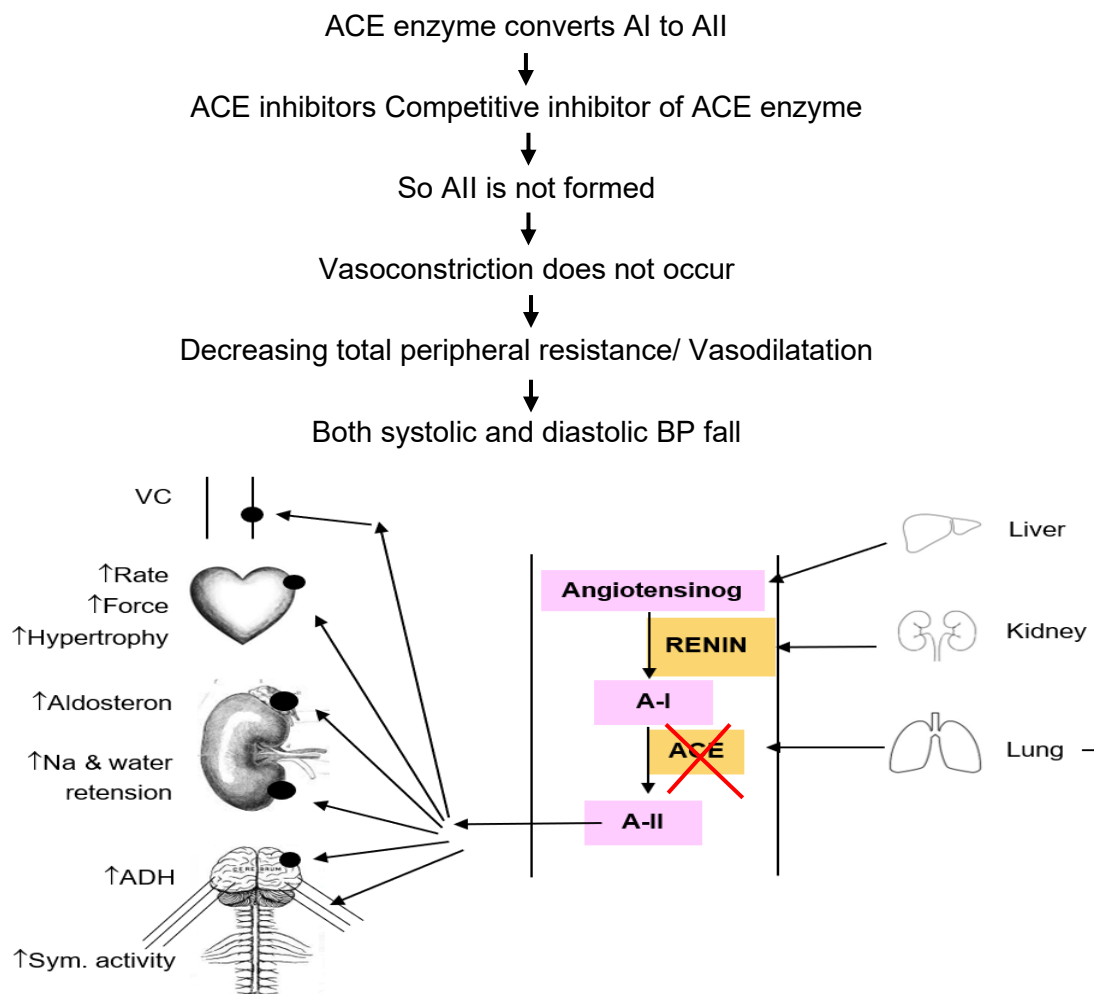
### Drugs

- Captopril (Prototype drug)
- Lisinopril

- Enalapril
- Perindopril
- Ramipril
- Fosinopril
- Quinapril
- Trandolapril

|                                    | Captopril  | Enalapril | Lisinopril | Fosinopril    | Perindopril | Ramipril |
|------------------------------------|------------|-----------|------------|---------------|-------------|----------|
| <b>Chemical nature</b>             | Sulfhydryl | Carboxyl  | Carboxyl   | Phosphinate   | Carboxyl    | Carboxyl |
| <b>Activity status</b>             | Active     | Prodrug   | Active     | Prodrug       | Prodrug     | Prodrug  |
| <b>Bioavailability</b>             | 70%        | 50%       | 25%        | 30%           | 30-50%      | 60%      |
| <b>Time to peak action</b>         | 1 hr       | 4-6 hr    | 6-8 hr     | 3-5 hr        | 6 hr        | 3-6 hr   |
| <b>Elimination t<sub>1/2</sub></b> | 2 hr       | 11 hr     | 12 hr      | 12 hr         | 25-30 hr    | 8-48 hr  |
| <b>Mode of excretion</b>           | Renal      | Renal     | Renal      | Renal/hepatic | Renal       | Renal    |
| <b>Duration of action</b>          | 6-12 hr    | 24 hr     | > 24 hr    | 24 hr         | > 24 hr     | >24 hr   |
| <b>Daily dose (mg)</b>             | 25-150     | 2.5-40    | 5-40       | 10-40         | 2-8         | 1.25-10  |

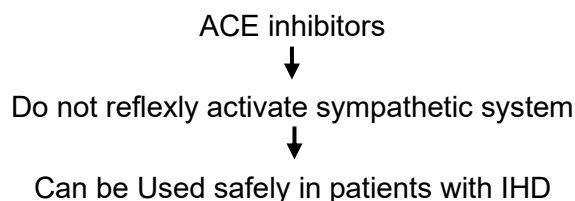
## MOA



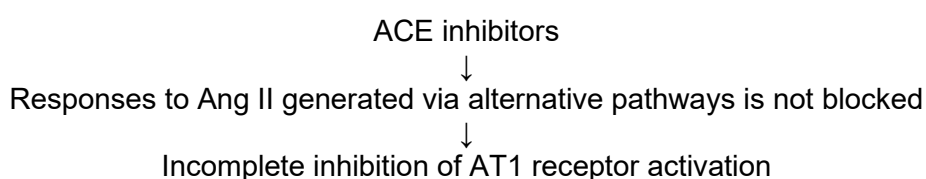
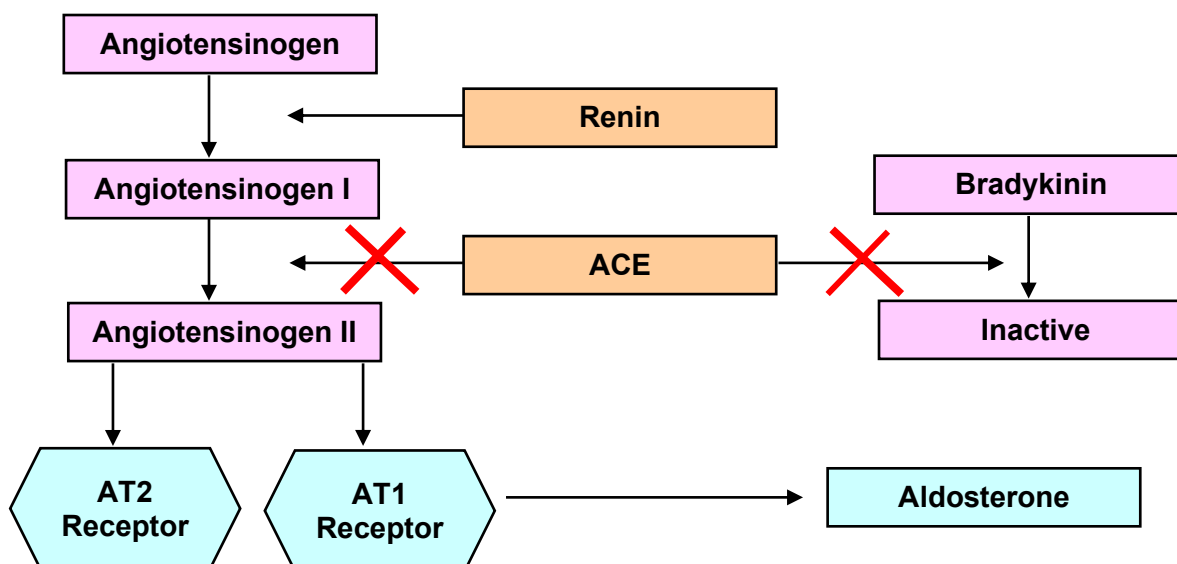
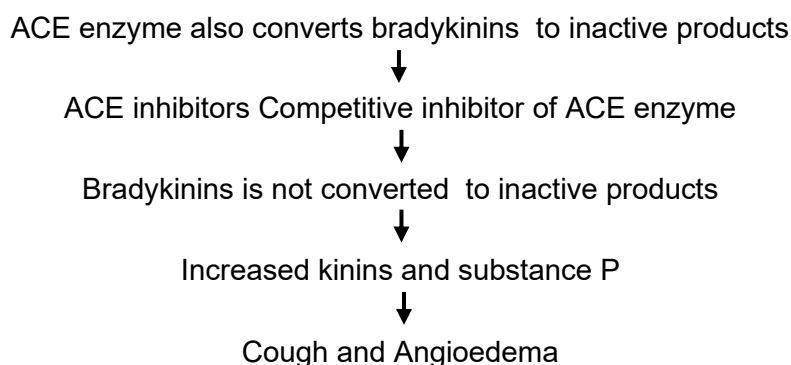
- Levels of plasma renin and A-I are increased as a compensatory measure.
- Plasma aldosterone basal levels are decreases

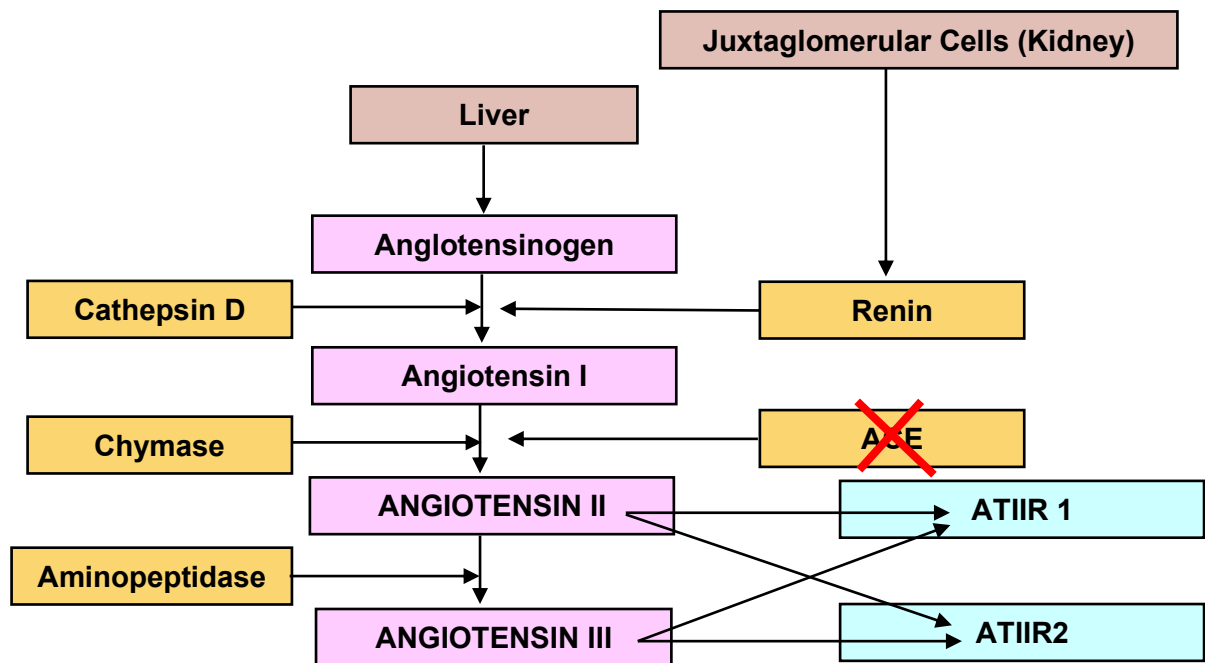
## Remember

1. **Postural hypotension is not problem** → There is little dilatation of capacitance vessels
2. **First dose hypotension occur** → Because of faster action of captopril an initial sharp fall in BP →
3. **ACE inhibitors can be Used safely in patients with IHD**



## 4. ACE inhibitors causes Cough and Angioedema





## Pharmacokinetics

### Captopril →

- Available only orally
- 70% - 75% is absorbed
- Food interferes with its absorption
- Half life: 2 Hrs
- Action stays for 6-12 Hrs

## Interactions

1. **Diuretics** → synergise with the hypotensive action of ACE inhibitors by depleting Na<sup>+</sup> and raising renin levels. In diuretic treated patients, the starting dose of ACE inhibitors should be low.
2. **K<sup>+</sup> supplements /K<sup>+</sup> sparing diuretics** → Hyperkalaemia can occur
3. **Indomethacin (and other NSAIDS)** → decreases the hypotensive action.
4. **Antacids** → reduce bioavailability

## Uses

### Home Care Makes Patients Definitely Strong

- **H**ome → **H**ypertension
- **C**are → **C**HF
- **M**akes → **M**I
- **P**atients → **P**rophylaxis in high cardiovascular risk
- **D**efinitely → **D**iabetic nephropathy
- **S**trong → **S**cleroderma crisis

## 1. Hypertension

- 1st line of Drug



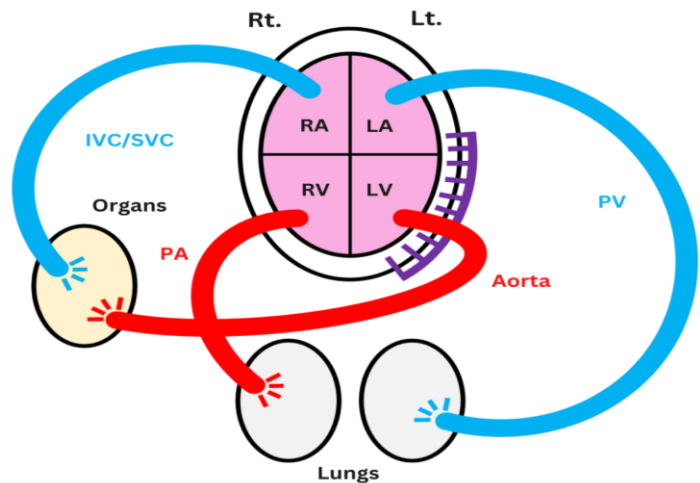
- First line drugs in all grades of hypertension → 50% patients respond to monotherapy with ACE inhibitors and rest to their combination with diuretics or b blockers.
- But angiotensin receptor blockers (ARBs) have now surpassed them in popularity.
- Hypotensive effect of lower doses develops gradually over 2–3 weeks

### Advantages

- No postural hypotension
- No electrolyte imbalance (no fatigue or weakness)
- Safe in asthmatics and diabetics
- Renal perfusion well maintained
- Reverse ventricular hypertrophy and increase in lumen size of vessel
- No hyperuracemia
- No deleterious effect on plasma lipid profile
- No rebound hypertension
- Minimal worsening of quality of life – general wellbeing, sleep and work performance etc.

## 2. CHF

ACE inhibitors in CHF patients  
 ↓  
 Cause both arterial and venodilatation  
 ↓  
 Reduce afterload as well as preload  
 ↓  
 Cardiac output is increased



- Heart rate reduced.
- Cardiac work (heart rate x PR) is reduced
- Exercise capacity of CHF patients is enhanced.
- NYHA functional class of most patients is improved.
- Multicentric trials have shown that ACE inhibitors retard progression and prolong survival of CHF patients of all grades (I to IV).
- Mortality is reduced by ~ 20% in symptomatic CHF patients.
- Unless contraindicated, ACE inhibitors are now advocated as first line drugs in all patients with symptomatic as well as asymptomatic CHF patients

## 3. Myocardial infarction (MI)

- ACE inhibitor administered in MI (within 24 hr of an attack) and continued for 6 weeks → reduces early as well as long-term mortality.
- If there are no contraindications → all MI patients gain from ACE inhibitor therapy although benefit is greatest in hypertension and or diabetes

## 4. Prophylaxis in high cardiovascular risk

- ACE inhibitors are protective in high cardiovascular risk subjects

- Protective effect is exerted both on myocardium as well as blood vessels, and is independent of hypotensive action.

## 5. Diabetic nephropathy

- RAS → accentuate micro- and macrovascular complications in diabetics
- ACE inhibitors inhibit RAS so protect kidney
  - a) ACE inhibitor therapy has been found to prevent end-stage renal disease in type I as well as type II diabetics.
  - b) Albuminuria remains stable
  - c) Require less dialysis and have longer life expectancy
- All patients with diabetic nephropathy, whether hypertensive or normotensive → deserve ACE inhibitor therapy

## 6. Scleroderma crisis

- Marked rise in BP and deterioration of renal function in scleroderma crisis is mediated by A-II
- ACE inhibitors produce dramatic improvement and are life saving in this condition .

## Adverse effects

### CAPTOPRIL

|          |   |                                                         |
|----------|---|---------------------------------------------------------|
| <b>C</b> | - | <b>C</b> ough                                           |
| <b>A</b> | - | <b>A</b> ngioneurotic oedema                            |
| <b>P</b> | - | <b>P</b> roteinuria                                     |
| <b>T</b> | - | <b>T</b> aste disturbance/ Teratogenic in 1st trimester |
| <b>O</b> | - | <b>O</b> ther (fatigue, headache)                       |
| <b>P</b> | - | <b>P</b> otassium increased                             |
| <b>R</b> | - | <b>R</b> enal impairment                                |
| <b>I</b> | - | <b>I</b> tch                                            |
| <b>L</b> | - | <b>L</b> ow BP (1st dose)                               |

## 1. Hypotension

- Risk is more with first dose, if patient is having high renin activity like renal artery stenosis, diuretics and sodium deficiency.
- It may lead to cerebral or myocardial ischemia or decrease renal perfusion.



## 2. Cough

- A persistent, dry cough with wheeze has been reported in about 5- 20% of patients.
- Excess of bradykinin and substance-P are responsible for it.



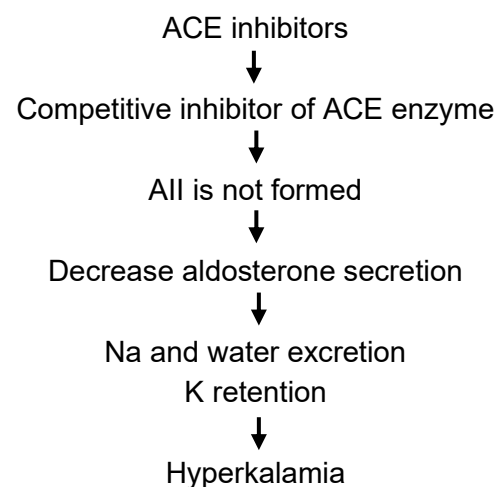
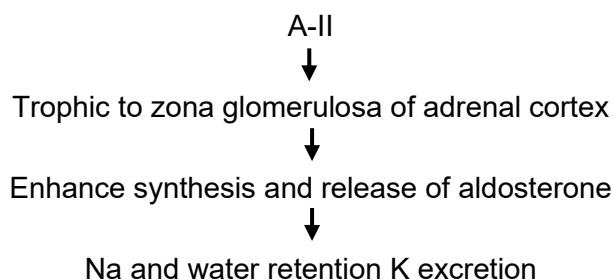
## 3. Angioedema

- Occurs due to bradykinin
- Rapid swelling of nose, throat, mouth, glottis, larynx, lips and tongue.
- It may be life threatening in its severe form.
- Only life saving measure is adrenaline



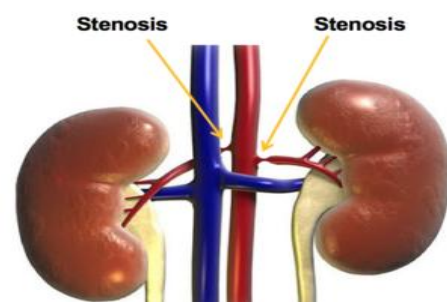
## 4. Hyperkalemia

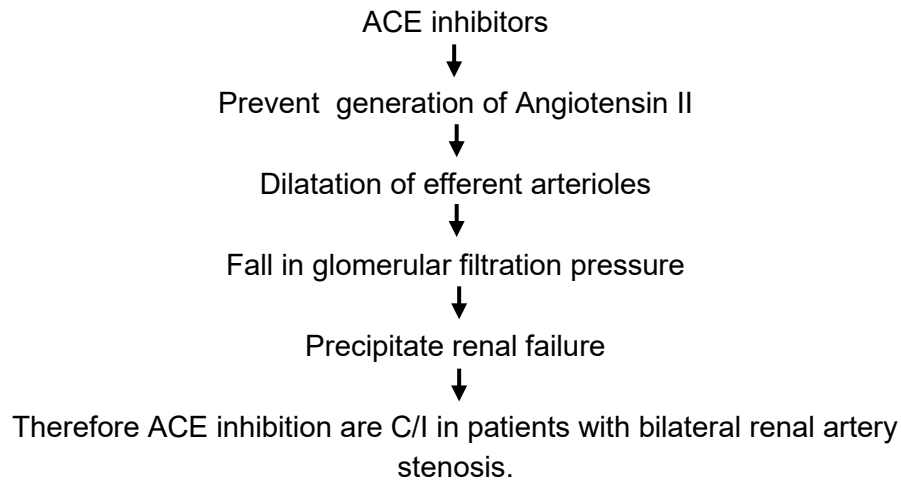
- Since they decrease aldosterone secretion so more retention of potassium.
- Especially the risk is more with other agents, which also increase blood potassium level like Potassium sparing agent
  - a) Potassium supplements
  - b) Beta blockers
  - c) NSAIDs
  - d) Succinyl choline
  - e) Renal insufficiency



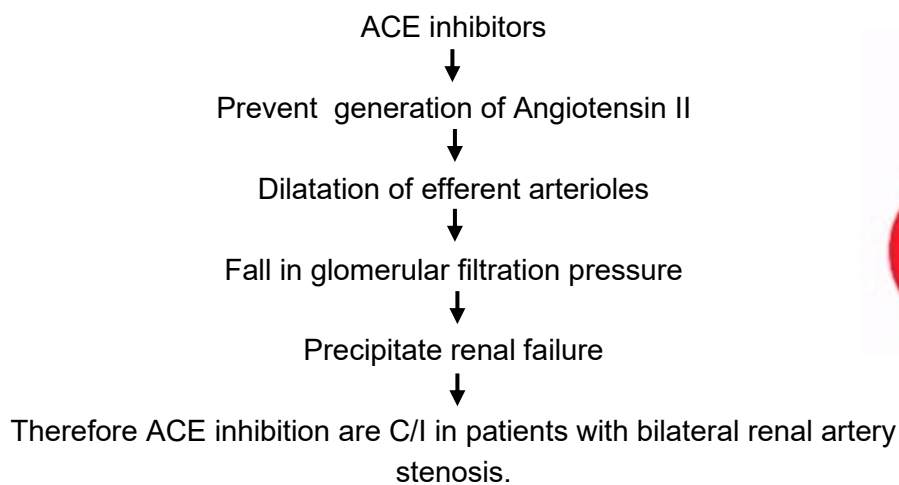
## 5. Acute renal failure

Patients with renal artery stenosis  
 ↓  
 Dependent on efferent arteriolar vasoconstriction for maintenance of glomerular filtration pressure  
 ↓  
 Angiotensin II is responsible for vasoconstriction of efferent arteriole





## 6. Teratogenic



## 7. Itching

- Rashes, urticarial



## 8. Dysgeusia

- Loss or alteration of taste



## Contraindications

### PARK

1. **P**regnancy
2. **A**llergy or hypersensitivity
3. Bilateral **R**enal artery stenosis
4. Hyper**K**alaemia

## Other ACE inhibitors

### Enalapril

- It's a prodrug – converted to enalaprilate

#### Advantages over captopril:

1. Longer half life – OD (5-20 mg OD)
2. Absorption not affected by food
3. Rash and loss of taste are less frequent
4. Longer onset of action
5. Less side effects

### Lisinopril

- Not a prodrug
- Slow oral absorption – less chance of 1st dose phenomenon
- Absorption not affected by food
- Long duration of action – single daily dose
- Doses: available as 1.25, 2.5, 5, 10 and 20 mg tab – start with low dose

### Ramipril

- It's a popular ACEI
- It is also a prodrug with long half life
- Blacks in USA are resistant to Ramipril – addition of diuretics help
- Dose: Start with low dose; 2.5 to 10 mg daily

## Remember

- All ACE inhibitor are prodrugs except → **captopril and lisinopril**
- **Enalapril** → tripeptide ; whereas captopril is dipeptide.
- **Captopril** → shortest and fastest acting ACE inhibitor.
- **Captopril** → maximum bioavailability among ACE inhibitors.
- **Lisinopril** → slowest acting
- Presence of food in stomach reduces bioavailability of → **captopril** (not other ACE inhibitors).
- **Benazepril** → considered safe in renal failure
- **Fosinopril** → unique in being a phosphinate compound that is glucuronide conjugated and eliminated both by liver and kidney (only kidney is the mode of excretion for all other ACE inhibitors after metabolism in the liver).

## ANGIOTENSIN RECEPTOR BLOCKERS (ARB)

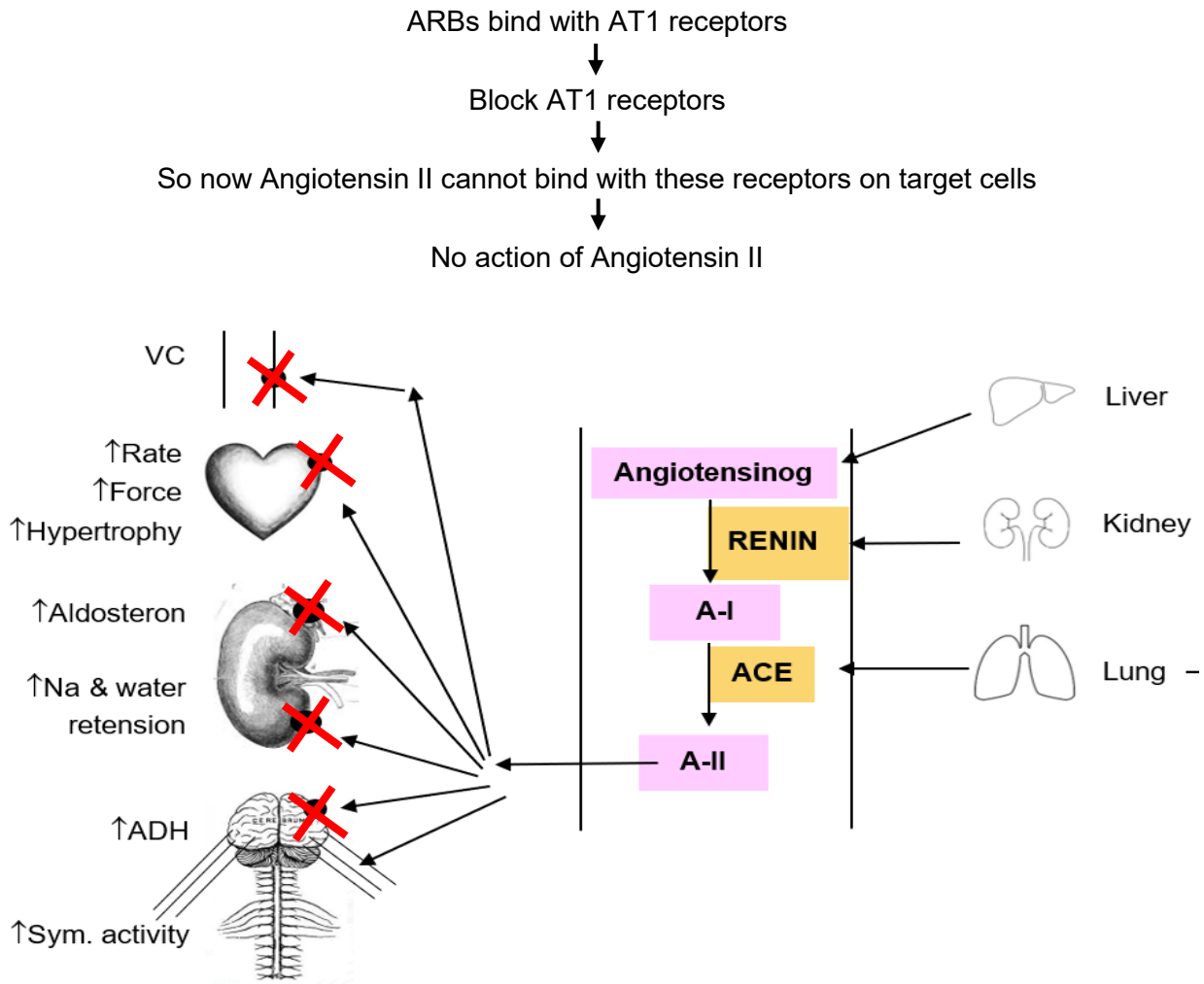
### Introduction

- Several nonpeptide orally active AT1 receptor blockers (ARBs) have been developed as alternatives to ACE inhibitors.

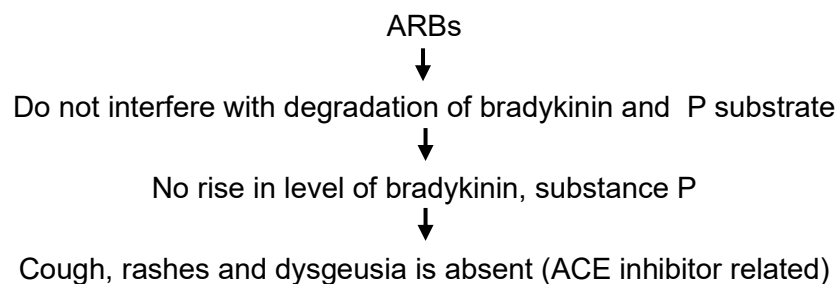
## Drugs

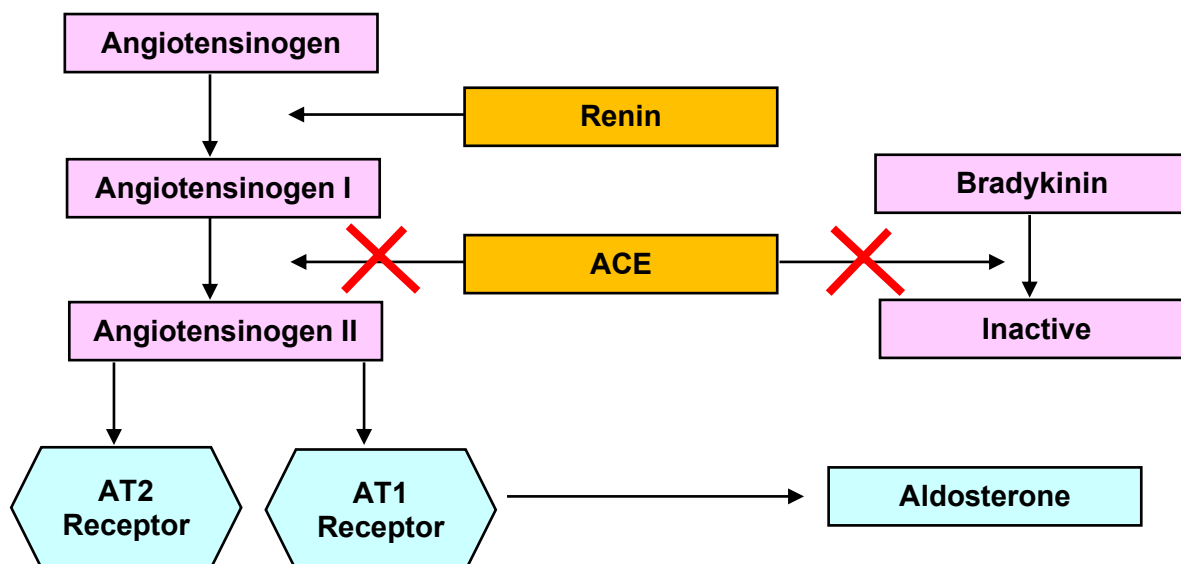
- Losartan (Prototype drug)
- Candesartan
- Valsartan
- Telmisartan
- Irbesartan
- Olmesartan

## MOA



## Differences from ACE inhibitors





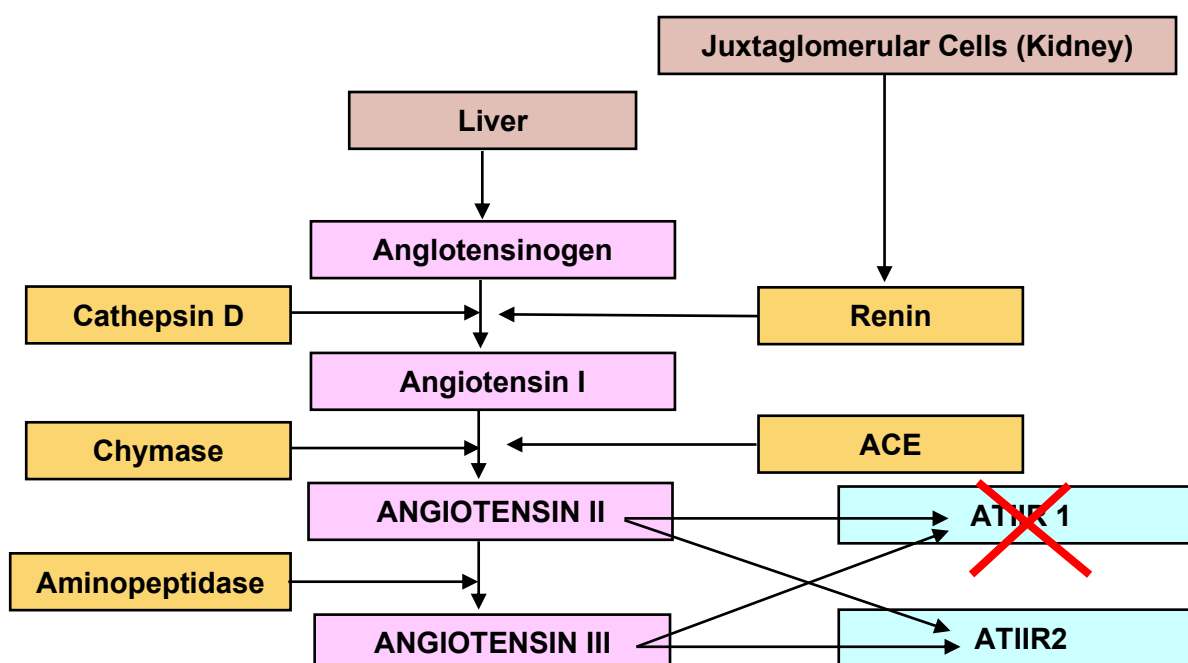
ARBs



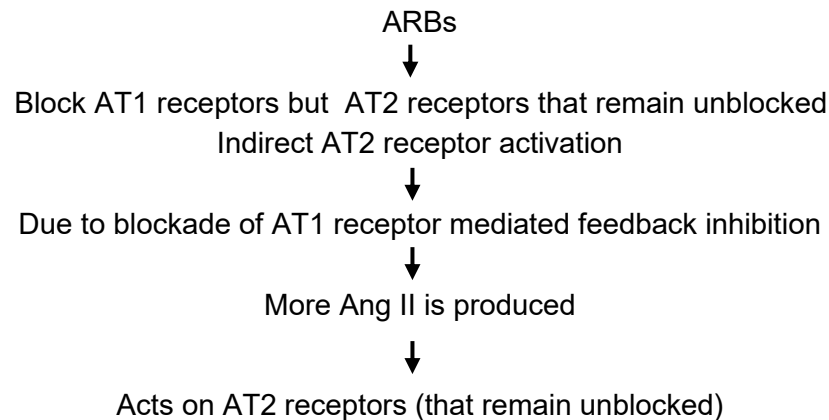
Responses to Ang II generated via alternative pathways is also blocked  
activation (which remain intact with ACE inhibitors)



More complete inhibition of AT1 receptor activation







- ACE inhibitors result in attenuation of both AT1 and AT2 receptor activation.

## Uses

Home Care Makes Patients Definitely Strong

- Home → Hypertension
- Care → CHF
- Makes → MI
- Patients → Prophylaxis in high cardiovascular risk
- Definitely → Diabetic nephropathy
- Strong → Scleroderma crisis

### 1. Hypertension

- Losartan and other ARBs are now first line drugs, comparable in efficacy and desirable features to ACE inhibitors, with advantage of not inducing cough and a lower incidence of angioedema, rashes and dysgeusia.

### 2. CHF

- ARBs afford clear-cut symptomatic relief as well as survival benefit in CHF

### 3. Myocardial infarction

- Long-term survival is comparable to ACE inhibitors.

### 4. Diabetic nephropathy

- ARBs are renoprotective in type 2 diabetes mellitus, independent of BP lowering.
- The magnitude of benefit is comparable to ACE inhibitors, but because of better tolerability profile, many consider ARBs to be the first choice now

## Adverse effects

1. Hypotension
2. Hyperkalemia
3. Teratogenic

## DIRECT RENIN INHIBITORS

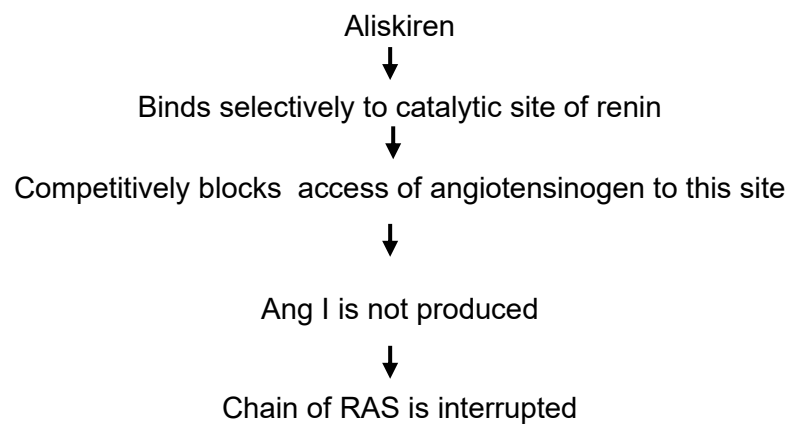
### Introduction

- Direct renin inhibitors (DRIs) are latest class of RAS inhibitory drugs

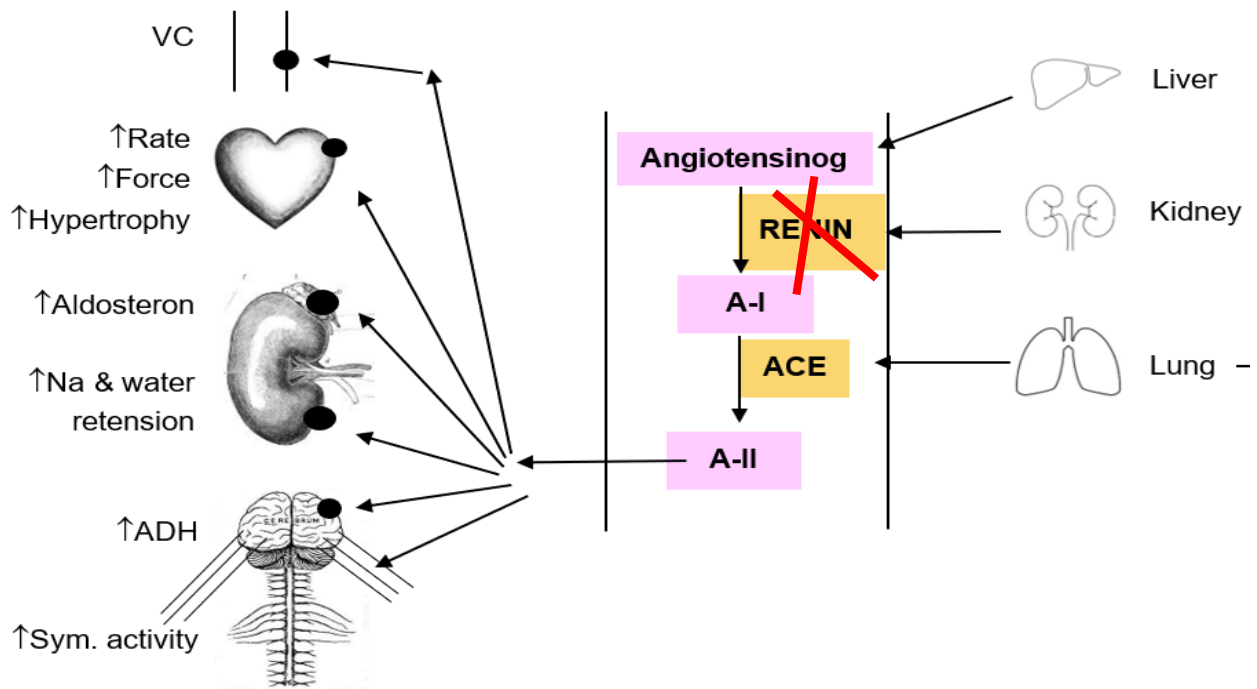
### Drugs

- Aliskiren
- Remikiren

### MOA



- Concentration of renin in plasma is increased by feed back
- Ang I and Ang II levels fall.



## Uses

### 1. Hypertension

- Antihypertensive efficacy of aliskiren is equivalent to that of ACE inhibitors or ARBs.
- Combination of these drugs with aliskiren produces greater fall in BP, at least in the short term.

### 2. CHF

- Aliskiren can reduce hypertensive left ventricular hypertrophy and benefit CHF patients

### 3. Diabetic nephropathy

- Aliskiren is renoprotective in type 2 diabetes mellitus,

## Remember

- At present, aliskiren is recommended as an alternative antihypertensive drug (for those who do not respond/do not tolerate 1st line drugs) and in combination with others for greater BP lowering

## Adverse effects

1. **Mild side effects** → Dyspepsia, abdominal pain, loose motions, headache and dizziness
2. **Acute hypotension**
3. **Hyperkalaemia**

## Contraindication

- Pregnancy

---

## DRUGS FOR HEART FAILURE

---

### Preload

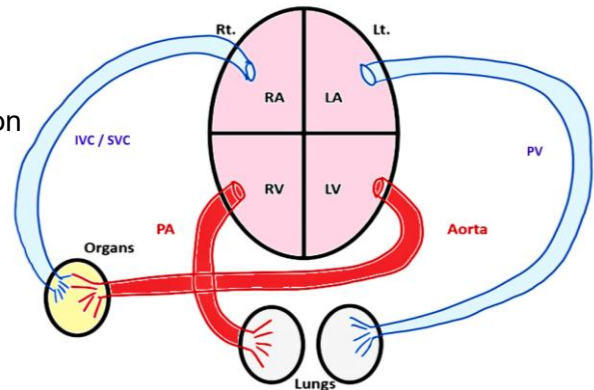
- Preload → End-diastolic pressure when ventricle is filled.
- Preload mainly depends on venous return
- More the venous return, more is the preload.

### Afterload

- Afterload → Pressure in the artery leading from the ventricle
- e.g. afterload of left ventricle is the systolic pressure in aorta.
- Sometimes Afterload is loosely considered to be peripheral resistance in the circulation rather than pressure.
- Afterload (Peripheral resistance) is mainly dependent on arterioles.

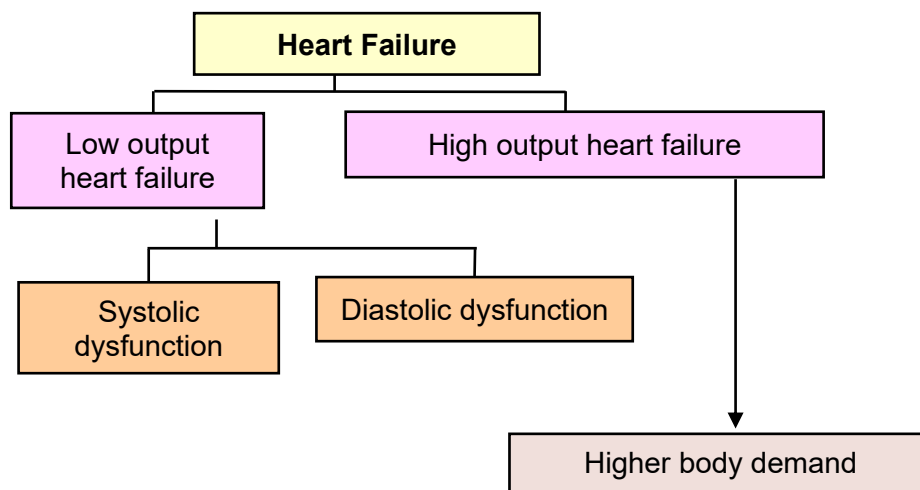
## Functions of heart

To receive deoxygenated blood  
 ↓  
 Then to push it to pulmonary circulation for oxygenation  
 ↓  
 Thereafter recollect oxygenated blood  
 ↓  
 Distribution to whole body



## Heart failure

In Heart failure → Heart fails to perform its function effectively so it is unable to pump blood in proportion to body's demand.



## Causes

1. Systolic dysfunction
2. Diastolic dysfunction
3. Higher body demand

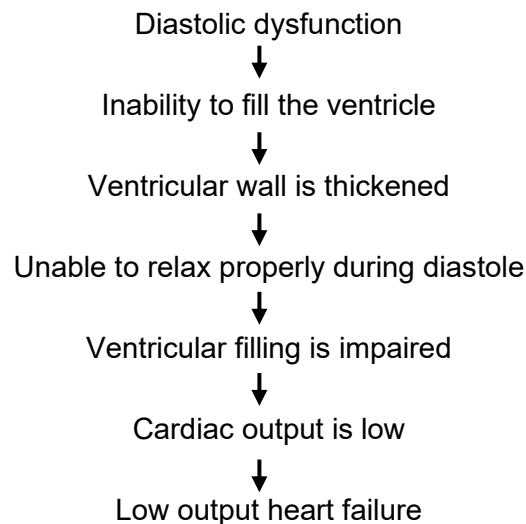
### 1. Systolic dysfunction

Systolic dysfunction  
 ↓  
 Inability to empty the ventricle  
 ↓  
 Ventricles are dilated  
 ↓  
 Unable to develop sufficient wall tension to eject adequate quantity of blood  
 ↓  
 Cardiac output is low  
 ↓  
 Low output heart failure

### Causes

- Reduced myocardial contractility in myocardial infarction.
- Increased preload (volume of blood that fills the ventricle during diastole) → eg. valvular regurgitation
- Increased after load (the resistance against which heart has to pump blood) eg. aortic stenosis and hypertension.
- Heart rate → Too slow or too rapid rate, leads to inadequacy of heart function.

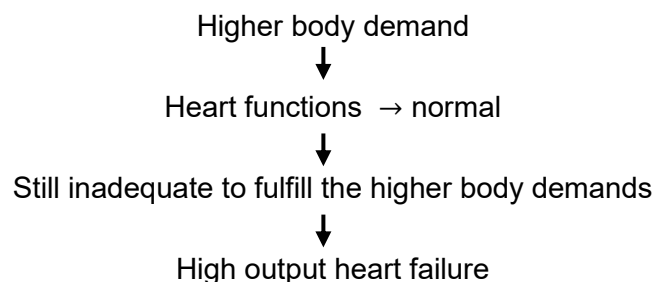
## 2. Diastolic dysfunction



### Causes

- Filling of the ventricle is impaired since the chamber is non-compliant (stiff) due to
  - Excessive hypertrophy from long standing hypertension,
  - Stenotic valvular disease
  - Hypertrophic cardiomyopathy

## 3. Higher body demand

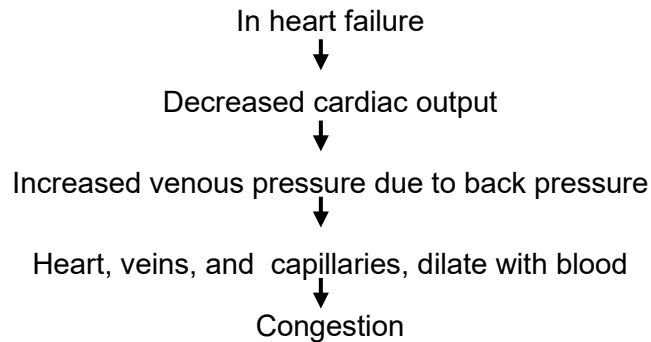


### Causes

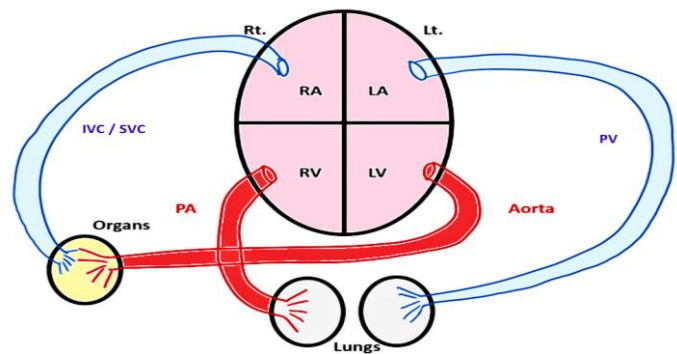
- Thyrotoxicosis
- Beriberi
- Severe anemia
- Paget's disease of bone

## CONGESTIVE HEART FAILURE (CHF)

Heart failure is also known as Congestive heart failure (CHF) because



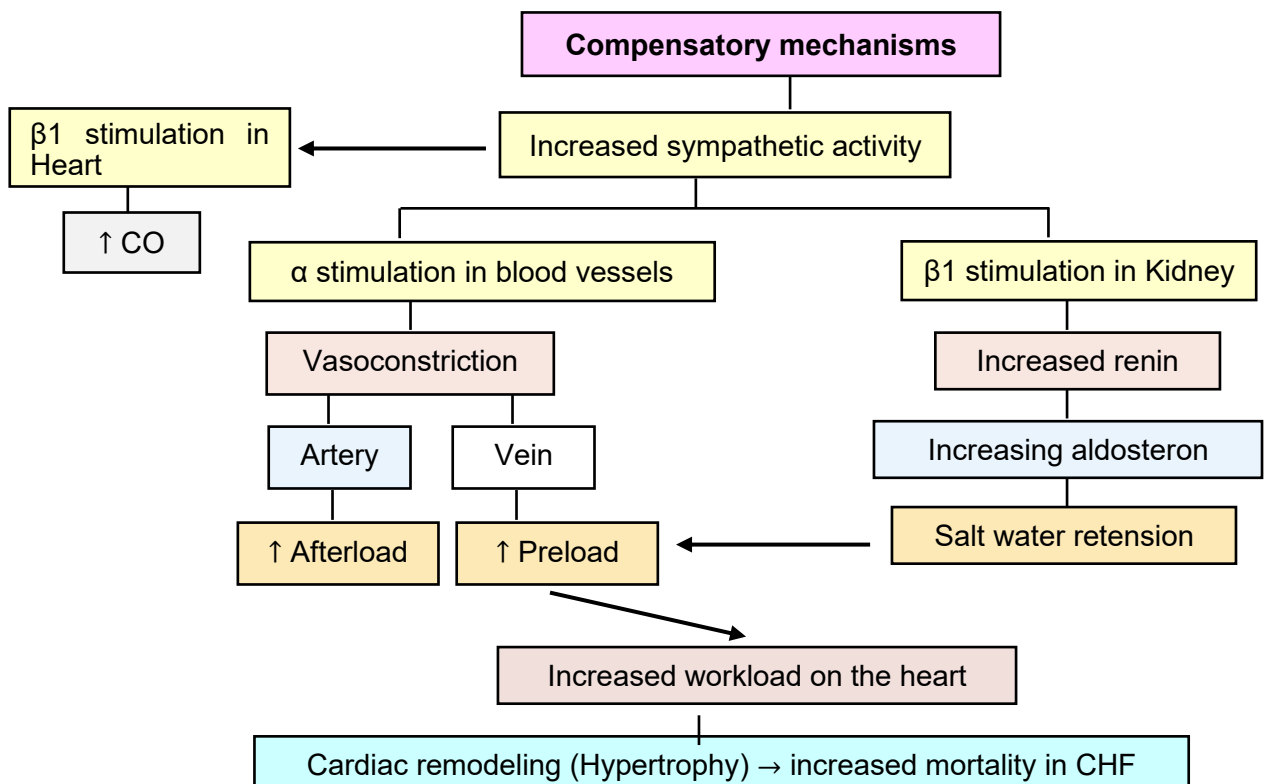
- **LVF** → Pulmonary congestion manifest as dyspnea, orthopnea, cough, basal creps, gallop rhythm, fatigue and increase in heart size.
- **RVF** → Edema, increase in venous pressure, and hepatomegaly.



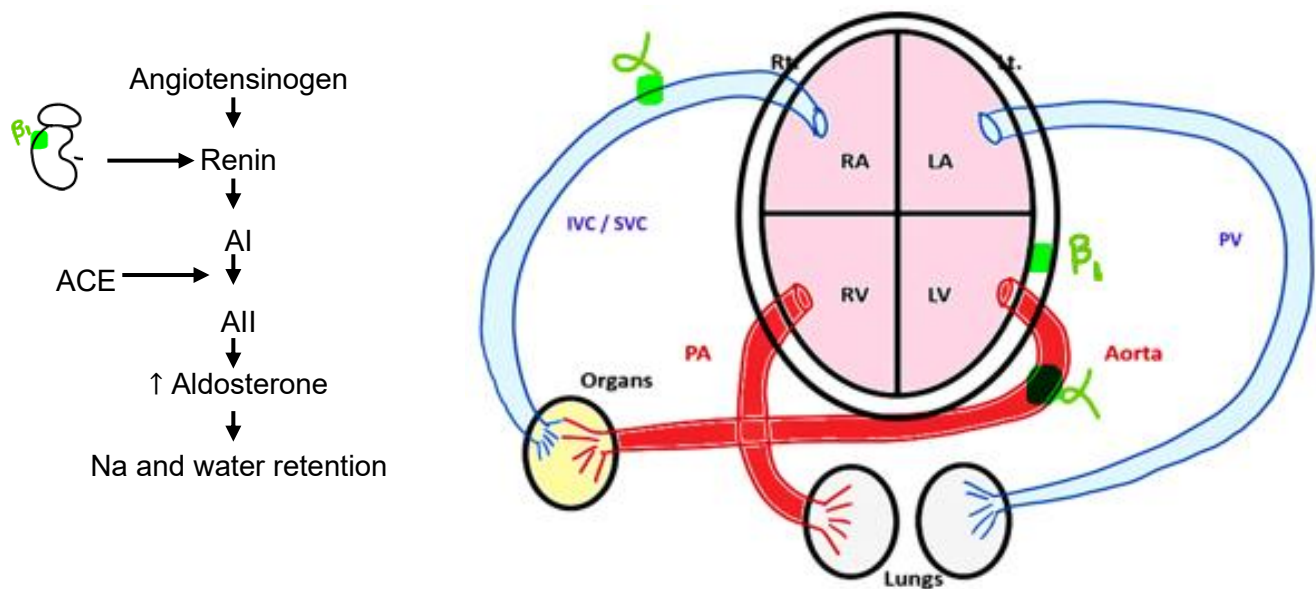
### Compensatory mechanism in failing heart

- Human body also has compensatory mechanisms to maintain the homeostasis.

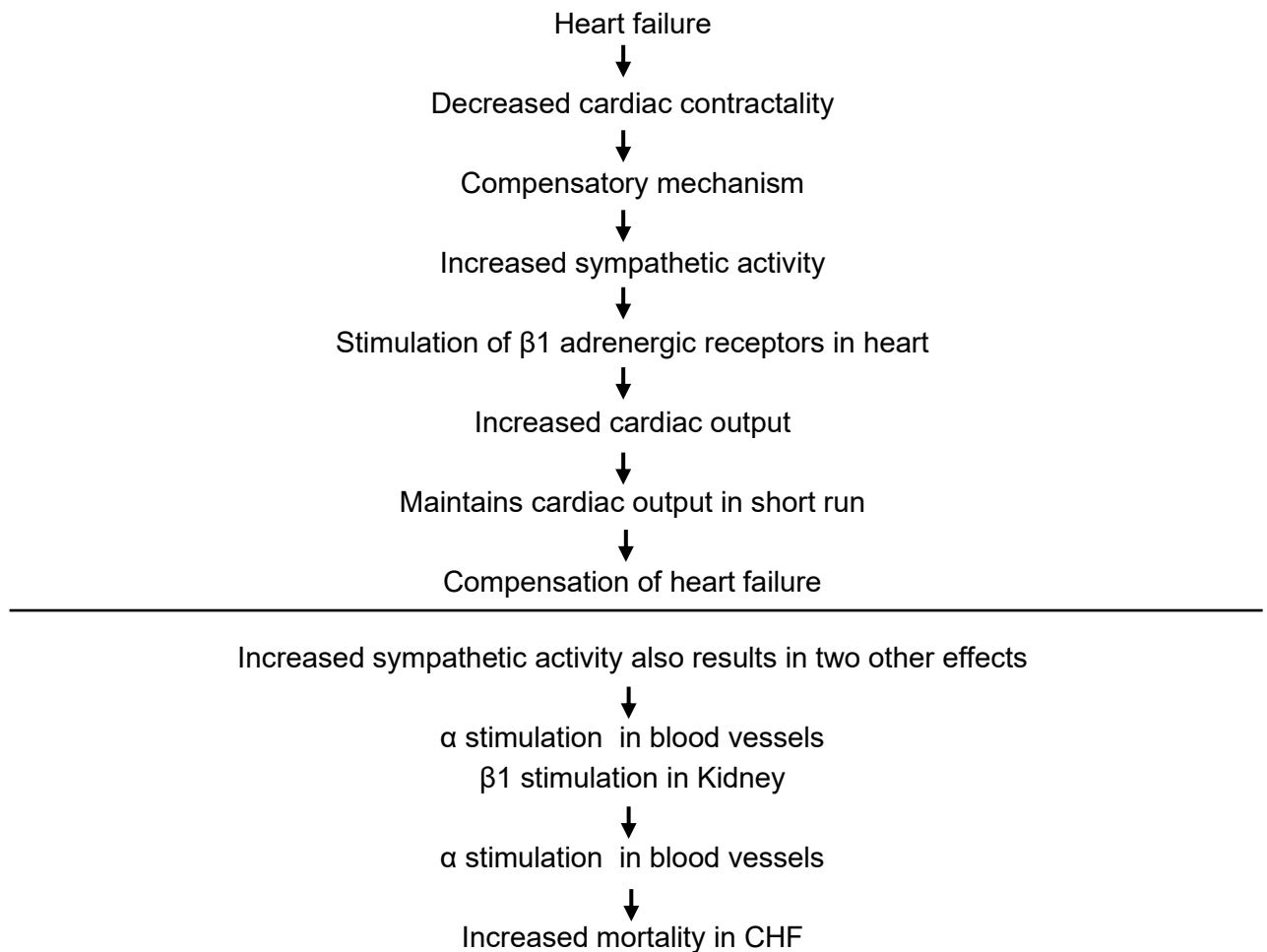
Heart failure → cardiac contractility →



|                        | $\alpha$ Actions                                                                                       | $\beta$ Actions                                                                                                                                                                                                                               |
|------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Blood vessel</b>    | Vaso Constriction $\rightarrow \uparrow$ BP ( $\alpha_1$ )                                             | Vaso Dilatation $\rightarrow \downarrow$ BP ( $\beta_2$ )                                                                                                                                                                                     |
| <b>Heart</b>           | Little action                                                                                          | Cardiac stimulation ( $\beta_1$ ), $\uparrow$ rate, force, velocity                                                                                                                                                                           |
| <b>Lungs</b>           | _____                                                                                                  | Bronchodilatation ( $\beta_2$ )                                                                                                                                                                                                               |
| <b>Eyes</b>            | Contraction of Dilator pupillae $\rightarrow$ Mydriasis ( $\alpha_1$ ), $\downarrow$ aqueous secretion | No effect on iris, slight relaxation of ciliary muscle, $\uparrow$ aqueous secretion                                                                                                                                                          |
| <b>GIT</b>             | Intestine - relax, sphincters - contract                                                               | Intestine - relax ( $\beta_2$ )                                                                                                                                                                                                               |
| <b>Bladder</b>         | Trigone – contract ( $\alpha_1$ )                                                                      | Detrusor –relax ( $\beta_2$ )                                                                                                                                                                                                                 |
| <b>Uterus</b>          | Contraction ( $\alpha_1$ )                                                                             | Relaxation ( $\beta_2$ )                                                                                                                                                                                                                      |
| <b>Pancreas</b>        | Inhibit Insulin ( $\alpha_1$ ) (dominant)                                                              | Augmented Insulin (mild) and glucagon secretion ( $\beta_2$ )                                                                                                                                                                                 |
| <b>Metabolism</b>      |                                                                                                        | Liver- glycogenolysis ( $\beta_2$ ) $\rightarrow$ hyperlactacidaemia<br>Muscle – glycogenolysis ( $\beta_2$ ) $\rightarrow$ hyperlactacidaemia<br>Fat – lipolysis ( $\beta_1 + \beta_2 + \beta_3$ ) $\rightarrow \uparrow$ FFA, calorigenesis |
| <b>Kidney</b>          | _____                                                                                                  | Renin release from kidney ( $\beta_1$ )                                                                                                                                                                                                       |
| <b>Male sex or</b>     | Ejaculation ( $\alpha_1$ )                                                                             |                                                                                                                                                                                                                                               |
| <b>Skeletal muscle</b> | NM facilitated, $\uparrow$ Ach release                                                                 | Tremors ( $\beta_2$ )                                                                                                                                                                                                                         |
| <b>CNS</b>             | _____                                                                                                  | Restlessness, apprehension, ADH secretion ( $\beta_1$ )                                                                                                                                                                                       |







## Types of Heart Failure

- 1) Acute (decompensated) heart failure
- 2) Chronic (compensated or congestive) heart failure (CHF)

### 1. Acute (decompensated) heart failure

- Heart is not able to pump blood efficiently.

#### Main treatment is aimed at

1. Increasing contractility by inotropic agents
2. Decreasing congestive symptoms (with diuretics)

### 2. Chronic (compensated or congestive) heart failure (CHF)

- Compensatory mechanisms tries to maintain homeostasis.
- There is increased sympathetic activity to maintain cardiac output.
- This leads to activation of renin-angiotensin-aldosterone (B1 stimulation causes renin release).
- Activation RAA system results in salt and water retention which is responsible for cardiac remodeling and left ventricular hypertrophy.

#### Main treatment is aimed at

1. Drugs which block the effects of adrenergic system ( $\beta$ -blockers)
2. Drugs which block RAS system (ACE inhibitors\ AT antagonists, aldosterone antagonists, spironolactone) arrest/reverse the disease progression and reduce mortality

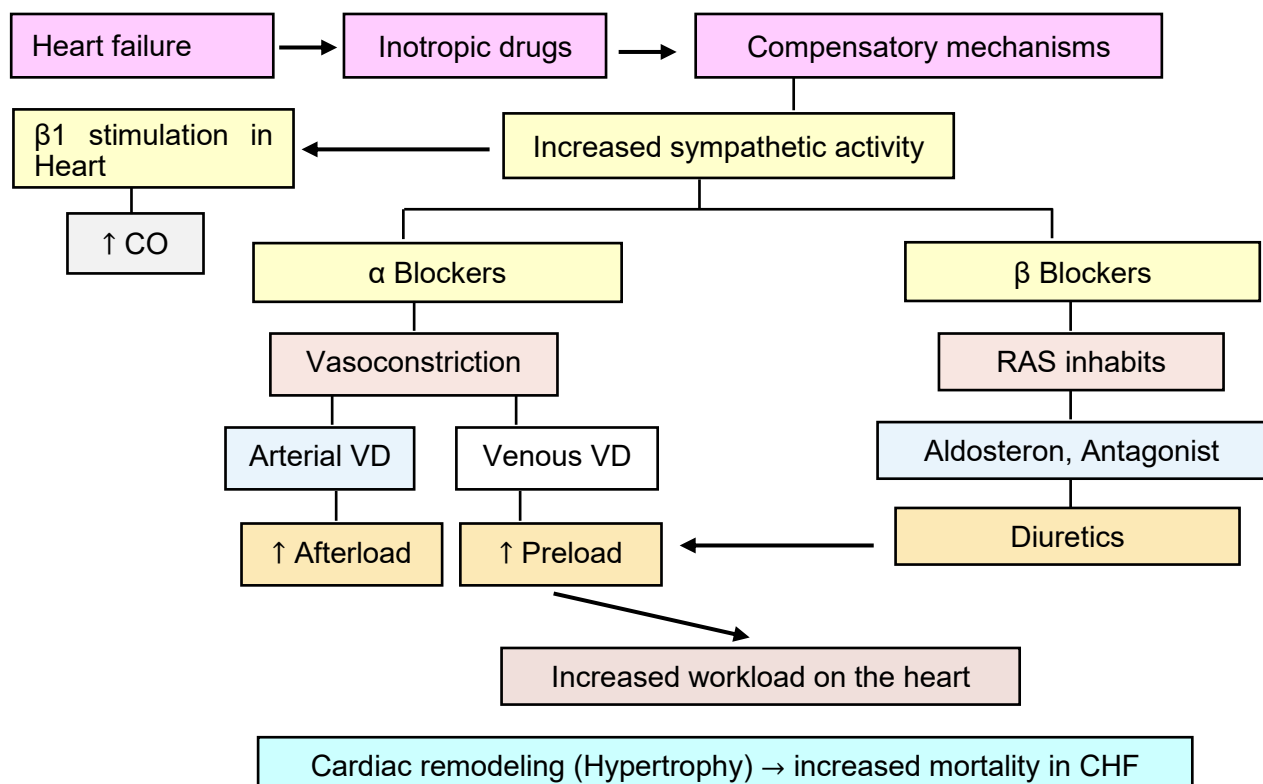
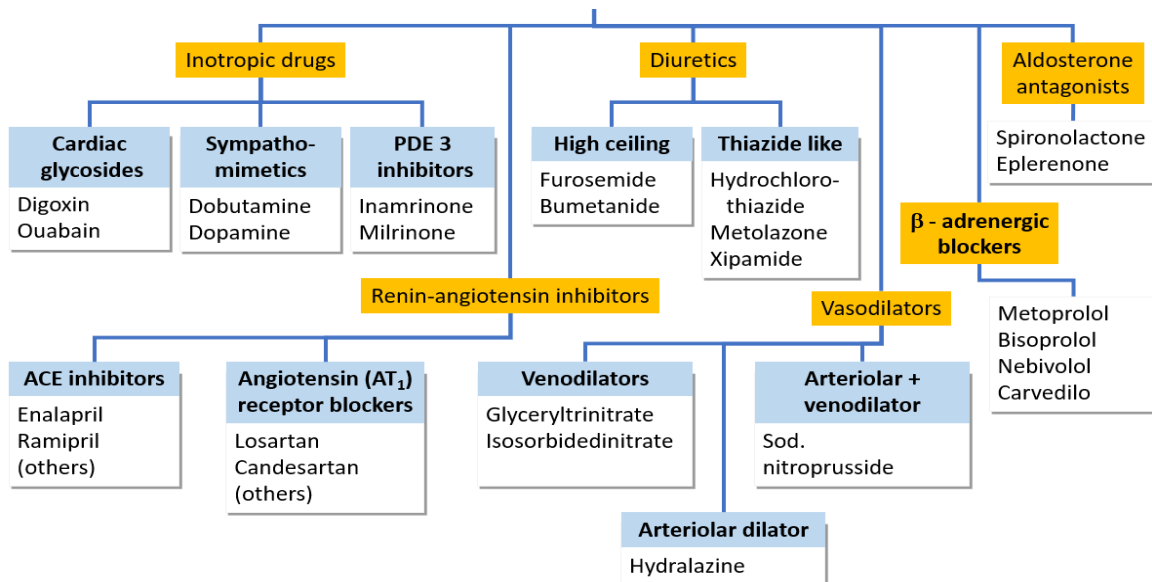
## NYHA Classification

NYHA is New York Heart Association, who has categorized CCF according to its severity-

- **I** → Symptoms with greater than ordinary activity.
- **II** → Limitation of ordinary activity - fatigue, palpitation.
- **III** → Symptoms with limited activity, but relieved at rest.
- **IV** → Symptoms even at rest.

## DRUGS OF CHF

1. Drugs to Improve Contractility of Heart (Inotropic Agents)
2. Drugs to Reduce the Load of Heart (Other drugs)



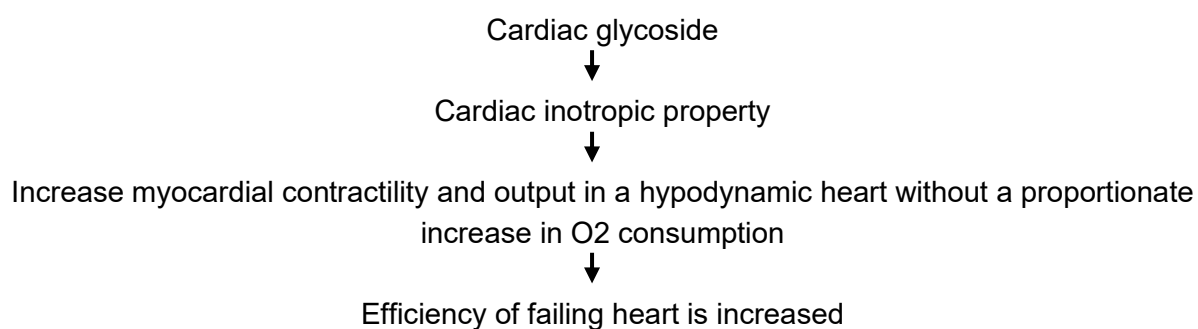
|                | Inotropic drugs | Vasodilators | RAS inhibitors | Diuretics | Aldosteron Antagonist | B Blockers |
|----------------|-----------------|--------------|----------------|-----------|-----------------------|------------|
| Introduction   |                 |              |                |           |                       |            |
| Drugs          |                 |              |                |           |                       |            |
| MOA            |                 |              |                |           |                       |            |
| Uses           |                 |              |                |           |                       |            |
| Adverse effect |                 |              |                |           |                       |            |

## INOTROPIC DRUGS

| Inotropic Agents        |                    |                  |                  |
|-------------------------|--------------------|------------------|------------------|
|                         | Cardiac glycosides | PDE 3 Inhibitors | Sympathomimetics |
| Introduction            |                    |                  |                  |
| Drugs                   |                    |                  |                  |
| MOA                     |                    |                  |                  |
| Pharmacological Actions |                    |                  |                  |
| Uses                    |                    |                  |                  |
| Adverse effect          |                    |                  |                  |
| Contraindications       |                    |                  |                  |

## CARDIAC GLYCOSIDES

### Introduction

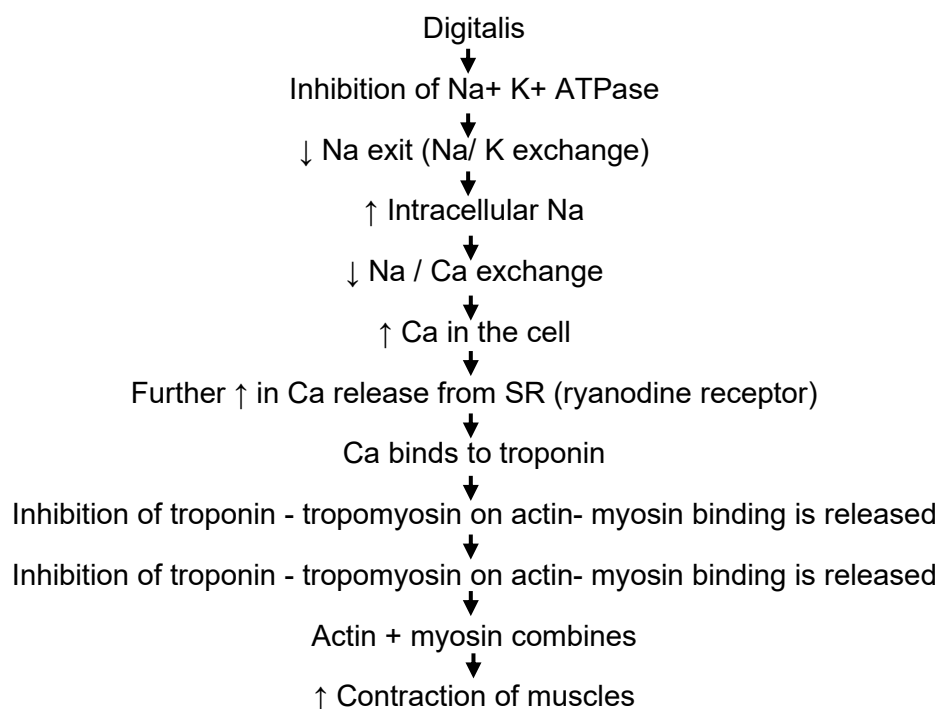
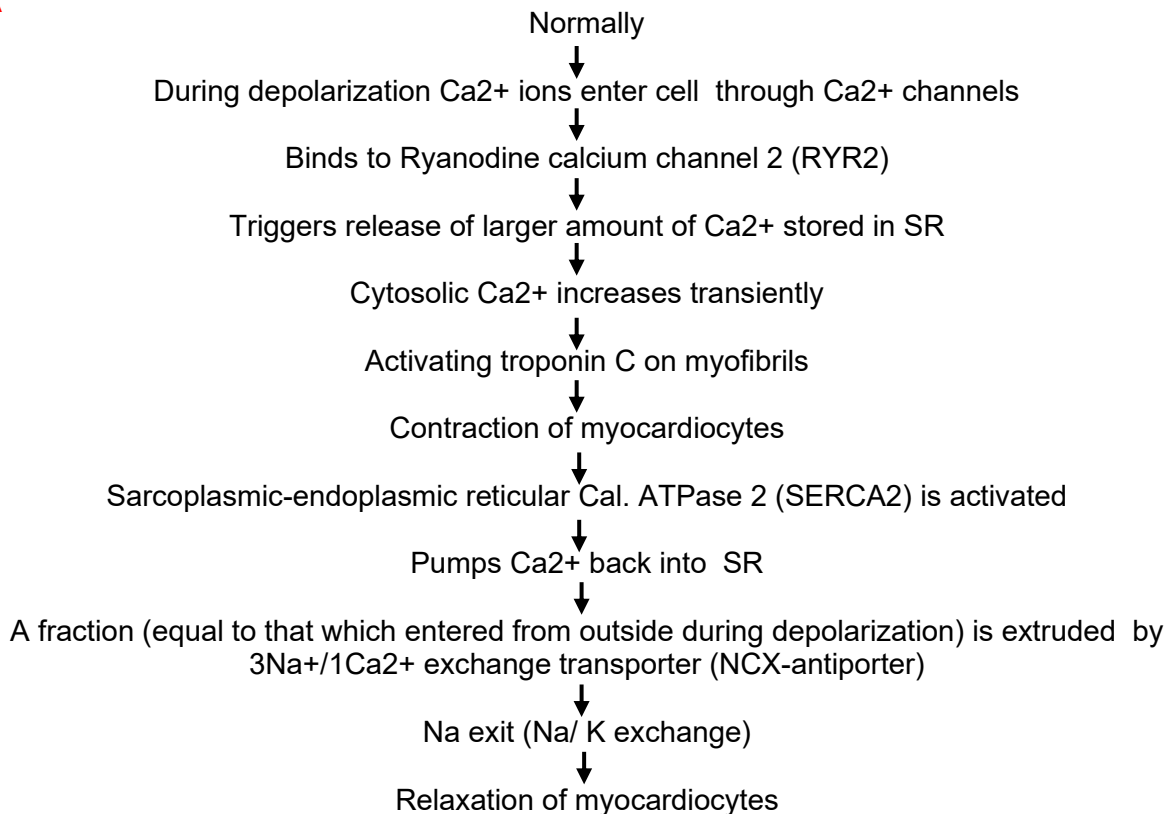


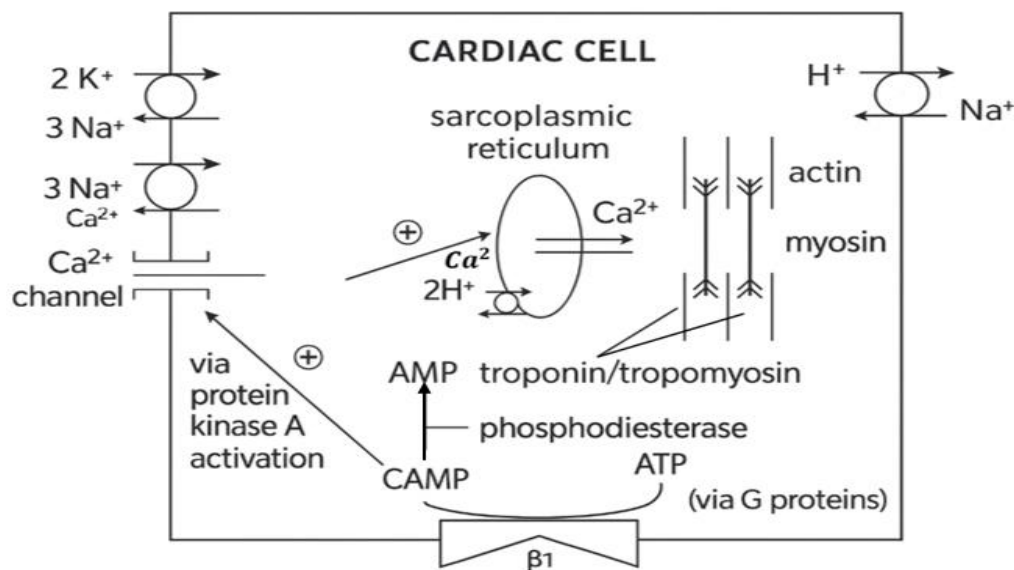
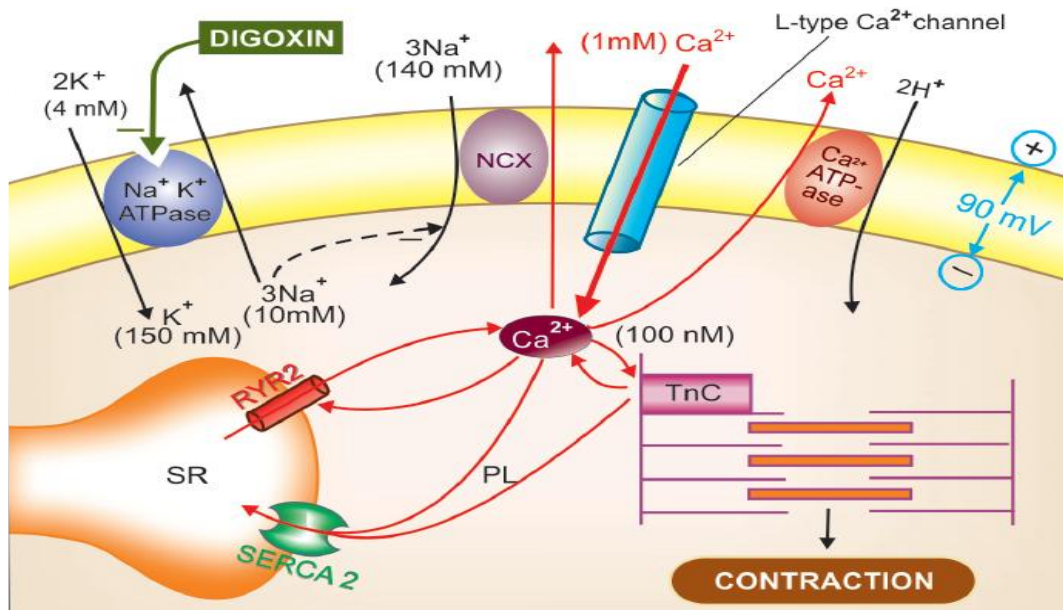
## Drugs

- Drugs of this group are collectively known as Digitalis
- Commonly used compounds are →
  - **Digoxin** → Obtained from *Digitalis lanata*
  - **Digitoxin** → Obtained from *Digitalis purpurea*
- Other cardiac glycosides (digitalis) are→
  - **Oubain , Strophanthin**
- Digoxin→ only cardiac glycoside available widely and used clinically now.



## MOA





## Remember

1. **Delayed action of digitalis** → Binding of cardiac glycosides to  $\text{Na}^+/\text{K}^+$  ATPase is slow and also after binding, intracellular  $\text{Ca}^{++}$  increases gradually
2. **Increase calcium** → synergies with digitalis to enhance toxicity.
3. **Reduced potassium** → Increases digitalis toxicity

Digitalis binds to  $\text{K}^+$  binding site of enzyme  
 ↓  
 Competition occurs between  $\text{K}^+$  and digitalis  
 ↓  
 Reduced potassium increases binding of digitalis  
 ↓  
 Increases digitalis toxicity

## Important points

- **Reduced potassium** → Increases digitalis toxicity
- **Increase calcium** → Increases digitalis toxicity

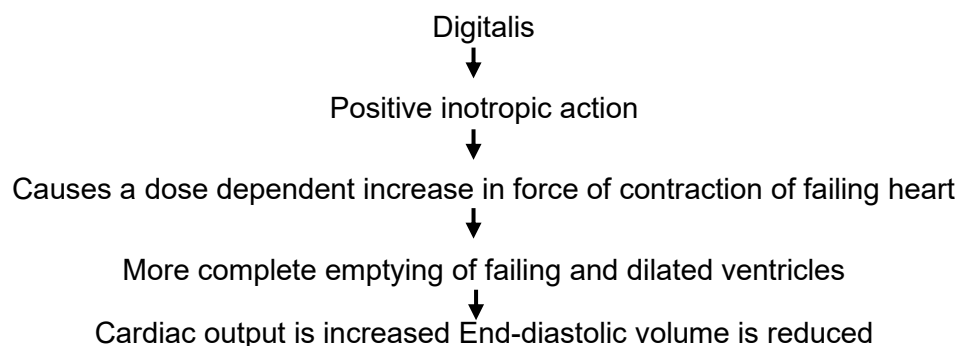
## Pharmacological Actions

1. Heart
2. Blood Vessels
3. Kidney
4. CNS

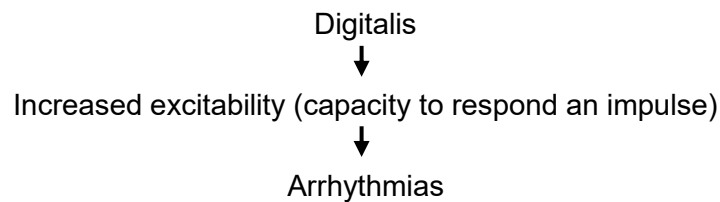
### 1. Heart

- a) Force of contraction
- b) Excitability
- c) Heart Rate
- d) ECG changes produced by digitalis

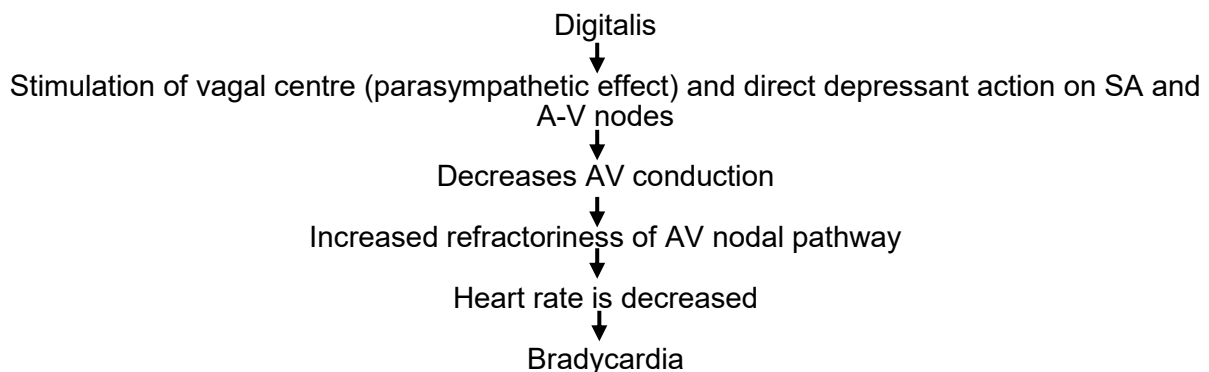
#### a) Force of contraction



#### b) Excitability

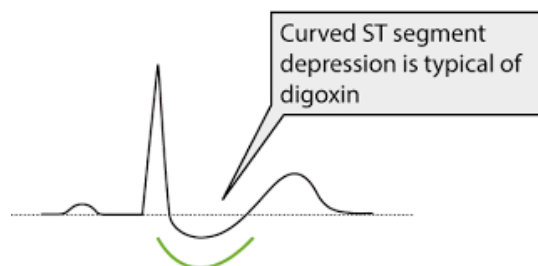


#### c) Heart Rate



### e) ECG changes produced by digitalis

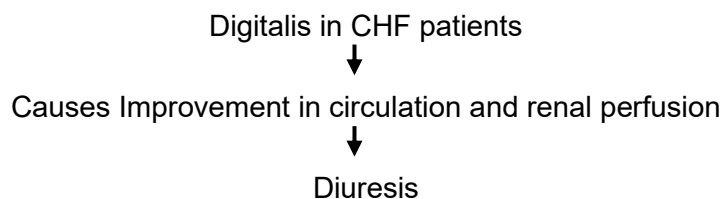
- Increased PR interval
- Decreased QT interval
- Decreased amplitude or inversion of T wave
- ST segment depression



## 2. Blood vessels

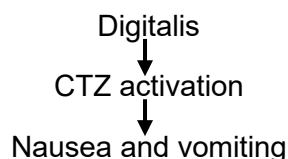
- Digitalis→
  - **Direct effect** → mild vasoconstrictor (increased peripheral resistance)
  - **Indirect effect** → Increases vagal tone → vasodilator (decreased peripheral resistance)
  - **Net** → Decreased peripheral resistance → vasodilator
- No prominent effect on BP (not contraindicated in hypertensives)
- No significant effect on coronary circulation (not contraindicated in coronary insufficiency)

## 3. Kidney



- No diuresis occurs in normal individuals or in patients with edema due to other causes.

## 4. CNS



- Still higher doses produce hyperapnoea, central sympathetic stimulation, mental confusion, disorientation and visual disturbances.

## Pharmacological Actions

| # | Parameter                    | Digitoxin                               | Digoxin                                    |
|---|------------------------------|-----------------------------------------|--------------------------------------------|
| 1 | Source                       | Digitoxin purpurea and <i>D. lanata</i> | <i>Digitalis lanata</i>                    |
| 2 | Oral absorption              | Very good (90–100%)                     | Good (60–80%), I/V also                    |
| 3 | Plasma protein binding       | 95%                                     | 25%                                        |
| 4 | Vd (Volume of distribution)  | 38 L/70 kg                              | 500 L/70 kg                                |
| 5 | Plasma $t_{1/2}$ (half-life) | 5–7 days                                | 40 hrs                                     |
| 6 | Elimination                  | Hepatic metabolism                      | Renal excretion (by glomerular filtration) |
| 7 | Dose adjustment in           | Liver failure                           | Kidney failure                             |



|    |                      |             |                                 |
|----|----------------------|-------------|---------------------------------|
| 8  | Uses                 | Maintenance | Routine treatment and emergency |
| 9  | Target concentration | 10 ng/mL    | 1 ng/mL                         |
| 10 | Toxic concentration  | > 35 ng/mL  | > 2 ng/mL                       |

## Uses

1. **Congestive heart failure** → Inotropic effect
2. **Cardiac arrhythmias** → Bradycardia

## Adverse Effects (Digitalis Toxicity)

- Margin of safety of Digitalis is low → therapeutic index 1.5–3
  1. Extracardiac
  2. Cardiac

### 1. Extracardiac

- Anorexia, nausea, vomiting and abdominal pain → due to gastric irritation and CTZ stimulation (Earliest)
- Fatigue, malaise, headache, mental confusion, restlessness,
- Hyperapnoea
- Disorientation, psychosis and visual disturbances
- Skin rashes
- Gynaecomastia



### 2. Cardiac

- Almost every type of arrhythmia can be produced by digitalis except Mobitz type II heart block and Atrial flutter →
  - (a) For tachyarrhythmias
  - (b) For ventricular arrhythmias
  - (c) For supraventricular arrhythmias
  - (d) For A-V block and bradycardia
- Most common arrhythmia earned by digitalis → ventricular bigeminus
- Most characteristic arrhythmia → non-paroxysmal atrial tachycardia with variable AV block.

## Factors predisposing Digitalis toxicity

| Metabolic           | Drugs      | Diseases                    |
|---------------------|------------|-----------------------------|
| K (Hypokalemia)     | Quinidine  | Partial AV block            |
| Mg (Hypomagnesemia) | Thiazides  | Hypothyroidism              |
| Ca (Hypercalcemia)  | Verapamil  | Myocarditis                 |
|                     | Amiodarone | WPW syndrome                |
|                     |            | Thyrotoxicosis              |
|                     |            | Renal failure (for digoxin) |
|                     |            | Hepatic failure (digitoxin) |

## Treatment of toxicity

- **Digoxins must be stopped**
- **Digoxin antibody** → Purified fab fragments from bovine antidigoxin antisera that binds free glycosides in plasma is the specific antidote that may reverse the effect within one hour, in about 90 % cases.
- **Hemodialysis & Diuretics** → not effective

## Contraindications

|                        |                                                      |
|------------------------|------------------------------------------------------|
| <b>Contraindicated</b> | - <b>C</b> arditis (Myocarditis)                     |
| <b>In</b>              | - <b>I</b> ncreased Ca <sup>2+</sup> (Hypercalcemia) |
| <b>Weak</b>            | - <b>W</b> PW Syndrome                               |
| <b>H</b>               | - <b>H</b> ypokalemia and Hypomagnesemia             |
| <b>E</b>               | - <b>E</b> lderly                                    |
| <b>A</b>               | - <b>A</b> V Block (Partial)                         |
| <b>R</b>               | - <b>R</b> enal failure (Digoxin)                    |
| <b>T</b>               | - <b>T</b> hyroid (hyper or hypothyroidism)          |

## Interactions

- **Diuretics** → cause hypokalemia which increases the risk of digitalis arrhythmias; potassium supplements should be given prophylactically.
- **Calcium** → synergises with digitalis → precipitates toxicity.
- **Quinidine** → reduces binding of digoxin to tissue proteins as well as its renal and biliary clearance by inhibiting efflux transporter P-glycoprotein → plasma concentration of digoxin is doubled → toxicity can occur.
- **Adrenergic drugs** → can induce arrhythmias in digitalized patients; both increase ectopic automaticity.
- **Propranolol, verapamil, diltiazem and disopyramide** → may additively depress A-V conduction
- **Metoclopramide, sucralfate, antacids, neomycin, sulfasalazine** → Reduces Digoxin absorption
- **Atropinic drugs, tricyclic antidepressants** → Increases Digoxin absorption

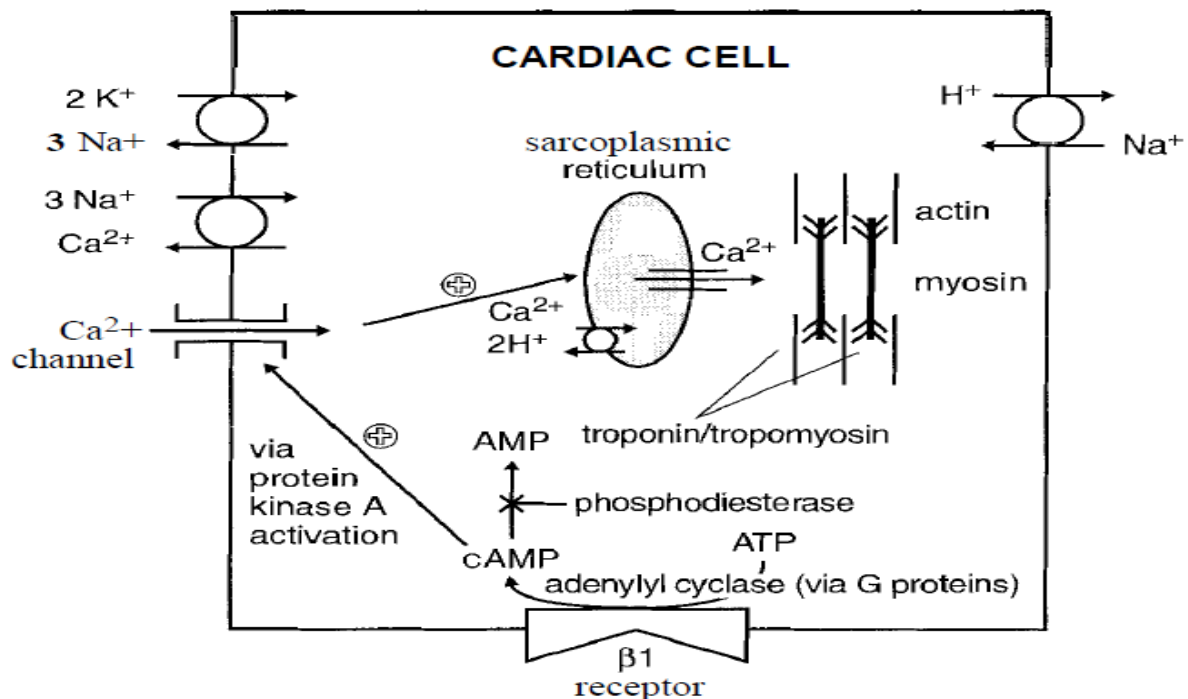
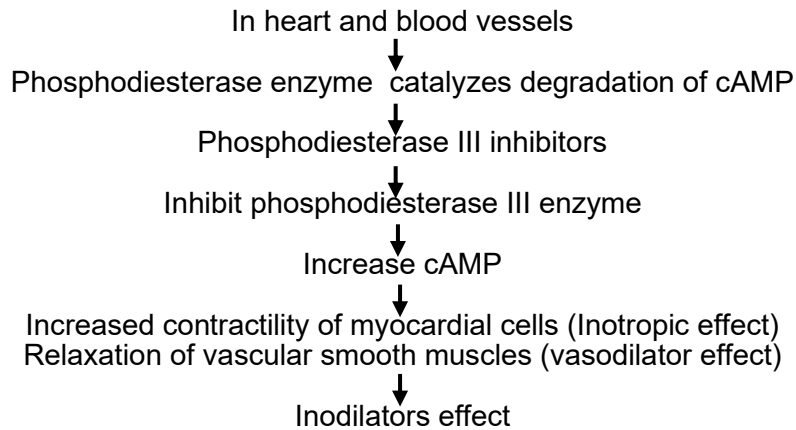
## PDE 3 INHIBITORS

### Drugs

1. Inamrinone (previously called amrinone)
2. Milrinone
3. Vesnarinone

### MOA

- Inodilators because it causes →
- **Positive inotropy of heart** → Increases contractility of heart
- **Vasodilatation of blood vessels** → Both preload and afterload on the heart is reduced.



## Uses

- Indicated only for short-term i.v. use in severe and refractory CHF, as an additional drug to conventional therapy with digitalis, diuretics and vasodilators.

## Adverse effects

- Thrombocytopenia → transient and asymptomatic
- Other → Nausea, diarrhoea, abdominal pain, liver damage, fever and arrhythmias

## Remember

### Milrinone →

- Atleast 10 times more potent than inamrinone
- Thrombocytopenia is not significant
- Milrinone is preferred over amrinone and should be restricted to short-term use only.

## SYMPATHOMIMETICS

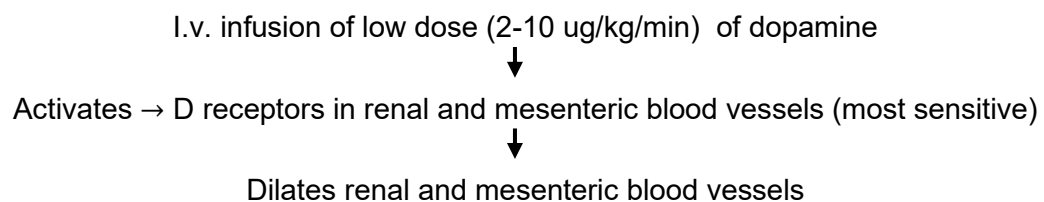
### Drugs

1. Dobutamine
2. Dopamine

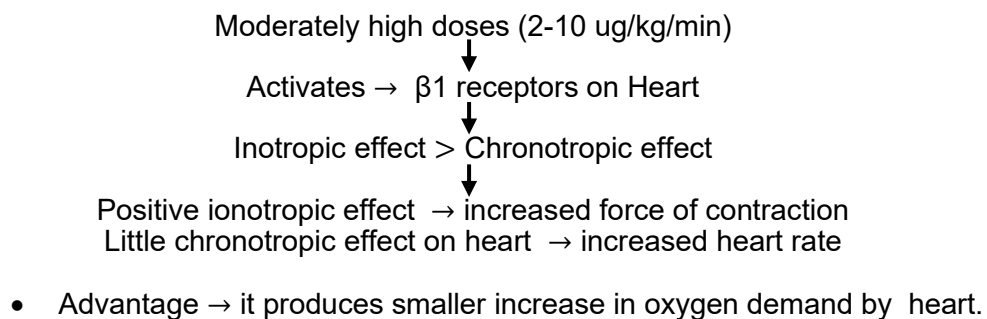
### Dopamine

1. Dopamine (D1 and D2 agonist)
2.  $\alpha$  agonist
3.  $\beta_1$  agonist (not  $\beta_2$  agonist)

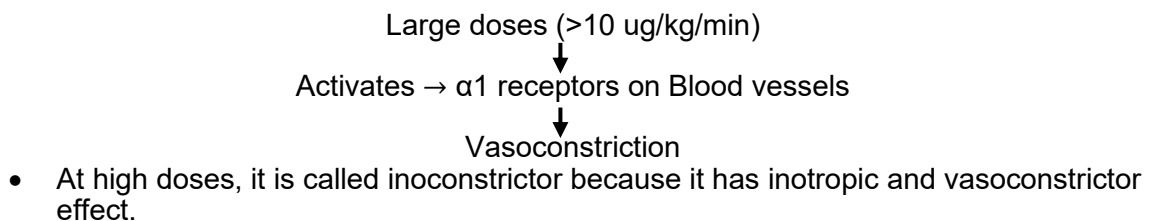
### Low dose (2-10 ug/kg/min)



### Moderate dose (2-10 ug/kg/min)



### High dose (>10 ug/kg/min)



### Uses

1. Cardiogenic or septic shock
  2. Severe CHF
- $T_{1/2}$  of dopamine is 2 minutes

**Remember****Dopamine →**

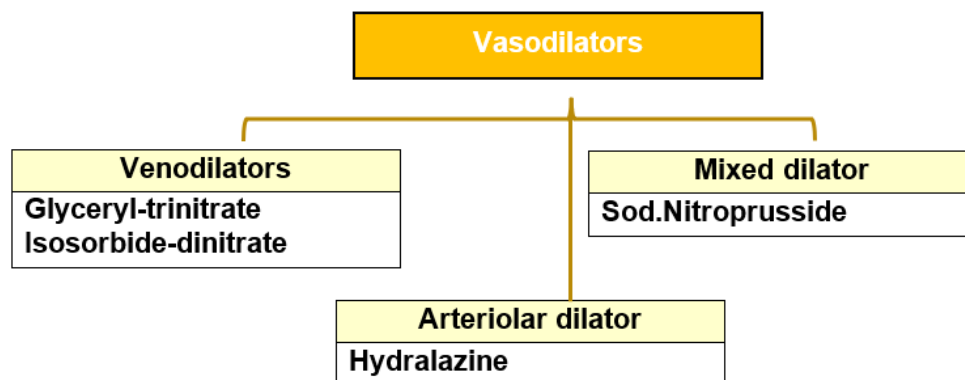
- Low dose → antagonized by Dopamine antagonist (haloperidol)
- Moderate dose → antagonized by  $\beta$ - blockers (propranolol)
- High dose → antagonized by  $\alpha$ -blockers (phentolamine).

**Dobutamine**

- Selective  $\beta_1$  agonist
- An increase in force of cardiac contraction and output, without a significant change in HR., BP and Peripheral resistance
- Half life of dobutamine is 2 minutes
- Duration of action is less than 10 minutes
- Onset of action after 1 -2 minutes.

**Uses**

- Used as an inotropic agent in pump failure accompanying myocardial infarction, cardiac surgery
- Short term management of severe congestive heart failure.

**VASODILATORS****Drugs**

| Vasodilators          |             |                    |               |
|-----------------------|-------------|--------------------|---------------|
|                       | Venodilator | Arteriolar dilator | Mixed dilator |
| <b>Introduction</b>   |             |                    |               |
| <b>Drugs</b>          |             |                    |               |
| <b>MOA</b>            |             |                    |               |
| <b>Uses</b>           |             |                    |               |
| <b>Adverse effect</b> |             |                    |               |

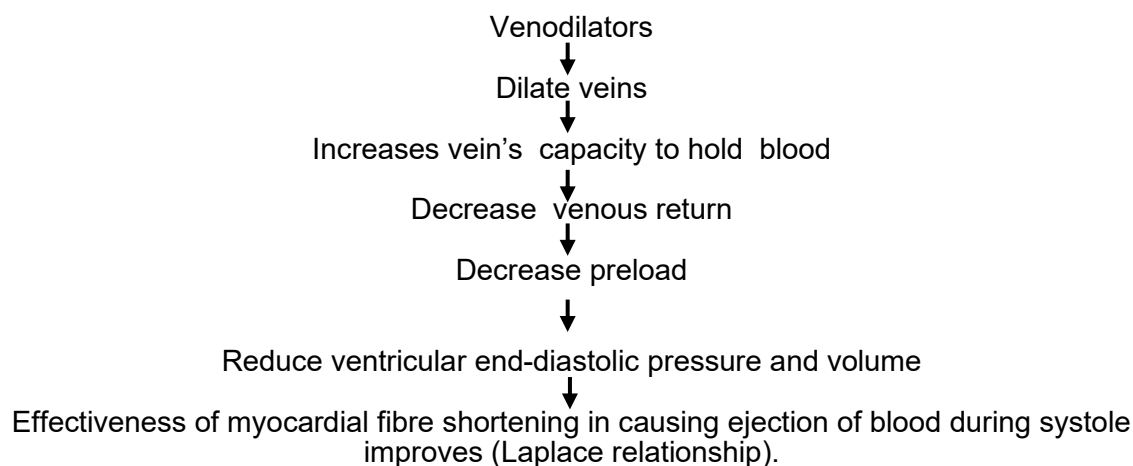
## VENODILATOR

### Introduction

- Nitrates are the prototype

| Venodilators                                                  |
|---------------------------------------------------------------|
| <b>Glyceryl – trinitrate</b><br><b>Isosorbide – dinitrate</b> |

### MOA



### Uses

#### Mnemonic

- A** – Angina Pectoralis
- B** – Biliary colic
- C** – Cyanide Poisoning
- D** – Dil ka Daura (MI)
- E** – Esophagral Spasm
- F** – Failure (Heart Failure)

### Adverse effects

#### Mnemonic

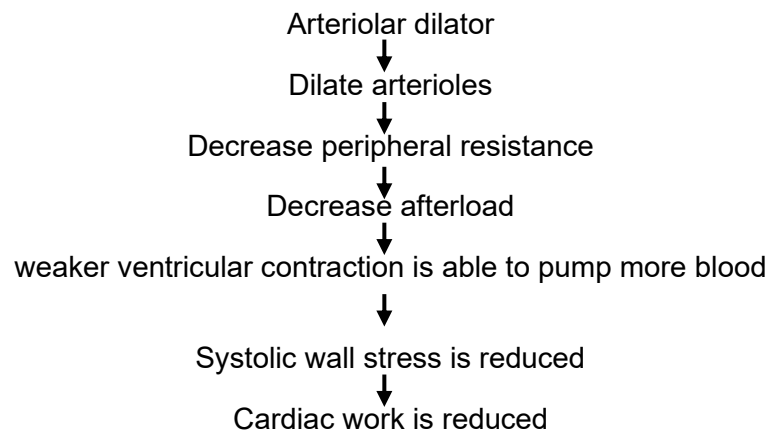
- T** – Tolerance, Throbbing, headache
- D** – Dependence
- S** – Skin Rashes
- R** – Reflex tachycardia
- O** – Orthostatic Hypotension
- M** – Methemoglobinemia

## ARTERIOLAR DILATOR

### Introduction

- Hydralazine is the prototype

## MOA



## Uses

- Effective in forward failure when without a marked increase in CVP

## Adverse effects

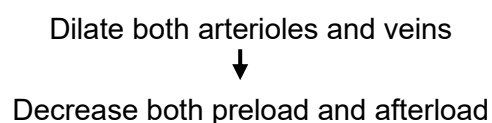
- Marked tachycardia
- Fluid retention

## MIXED DILATOR

### Introduction

- Sod. Nitroprusside is the prototype

## MOA

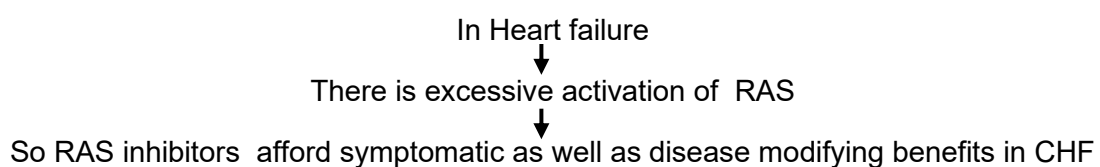


## Uses

- Severely decompensated patients in conjunction with a loop diuretic + i.v. inotropic drug

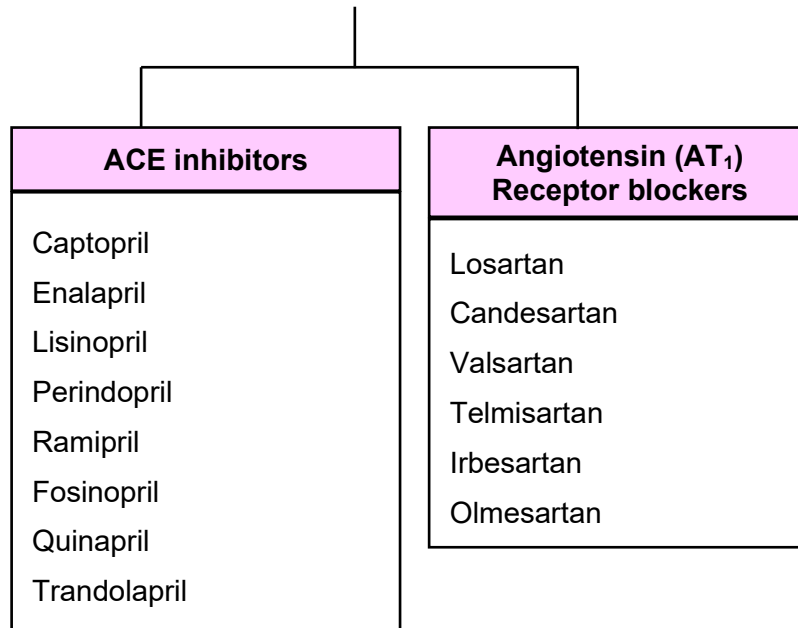
## RAS INHIBITORS

### Introduction





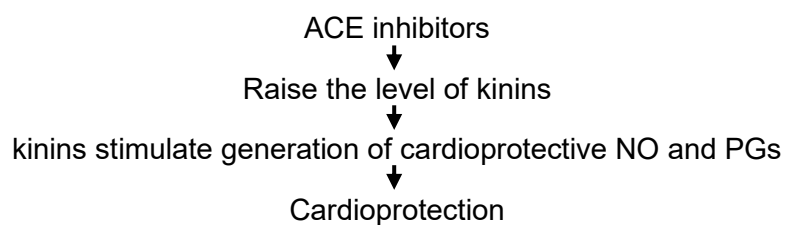
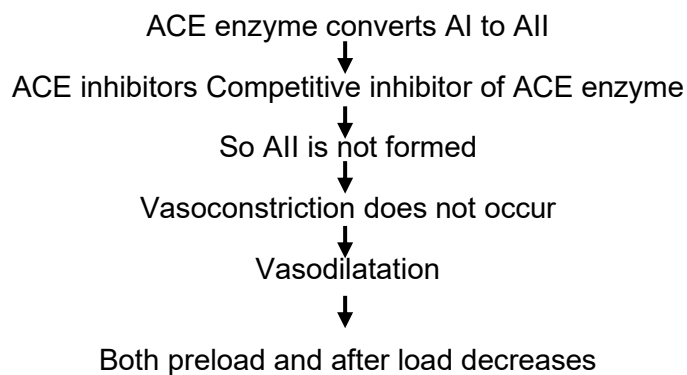
## Drugs

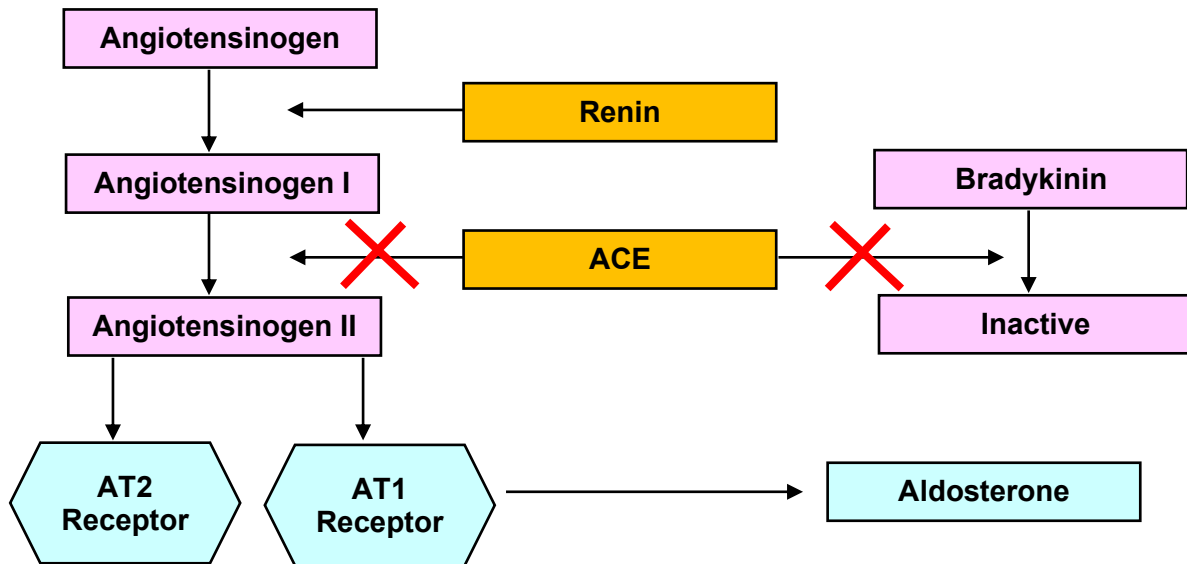


## MOA

- MOA of ACE inhibitors
- MOA of ARBs

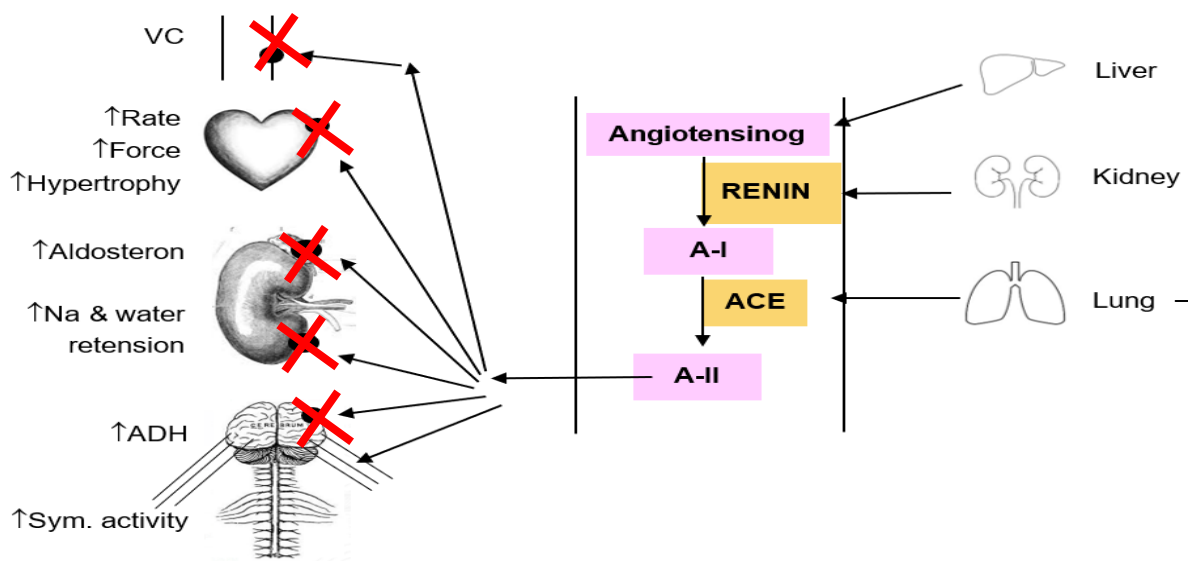
### MOA of ACE inhibitors





## MOA of ARBs

ARBs bind with AT1 receptors  
 ↓  
 Block them  
 ↓  
 So now Angiotensin II cannot bind with these receptors on target cells  
 ↓  
 No action of Angiotensin II



## Uses

- First line drugs for all the grades of CCF unless contraindicated
- Afford symptomatic as well as disease modifying benefits in CHF
- Cause arrest / reversal of disease progression and prolongation of survival in CHF.

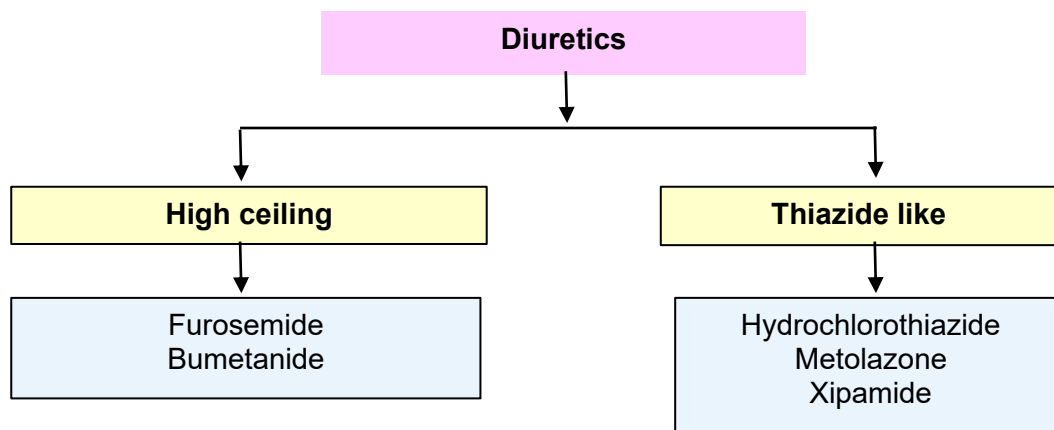
## Adverse effects

**CAPTOPRIL**

- C** - Cough
- A** - Angioneurotic oedema
- P** - Proteinuria
- T** - Taste disturbance/ Teratogenic in 1st trimester
- O** - Other (fatigue, headache)
- P** - Potassium increased
- R** - Renal impairment
- I** - Itch
- L** - Low BP (1st dose)

## DIURETICS

### Drugs



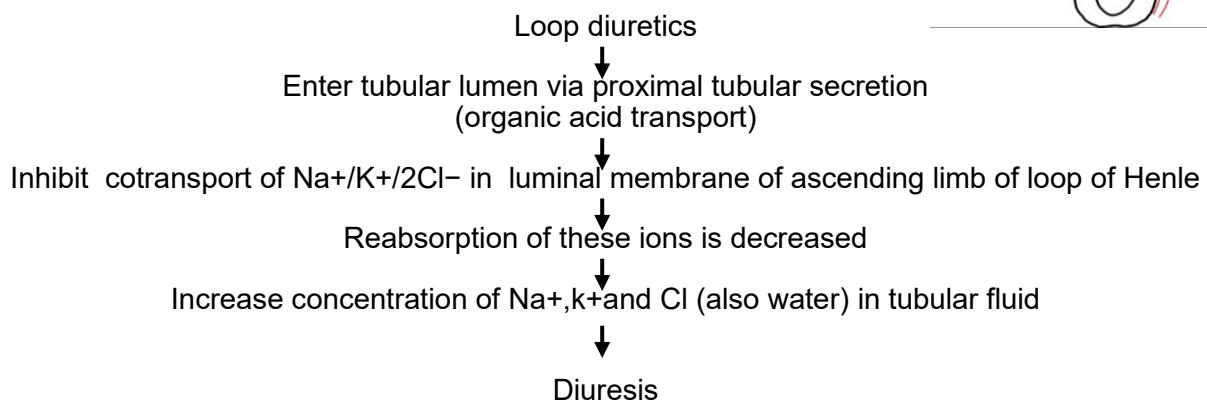
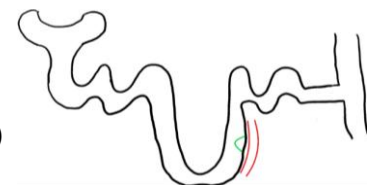
### MOA

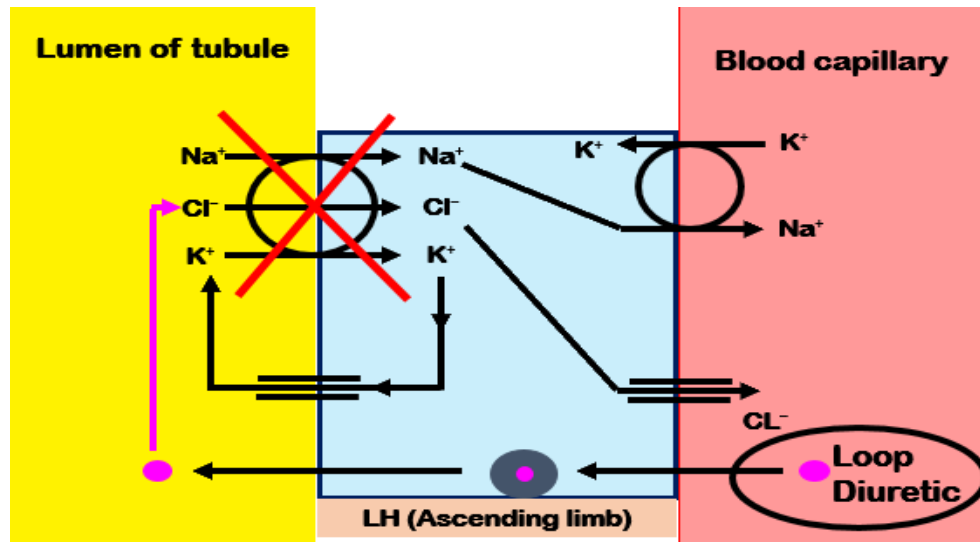
- MOA of High ceiling Diuretics
- MOA of Thiazide Diuretics

### MOA of High ceiling Diuretics

**SITE OF ACTION** → Loop diuretics acts on ascending limb of the loop of Henle

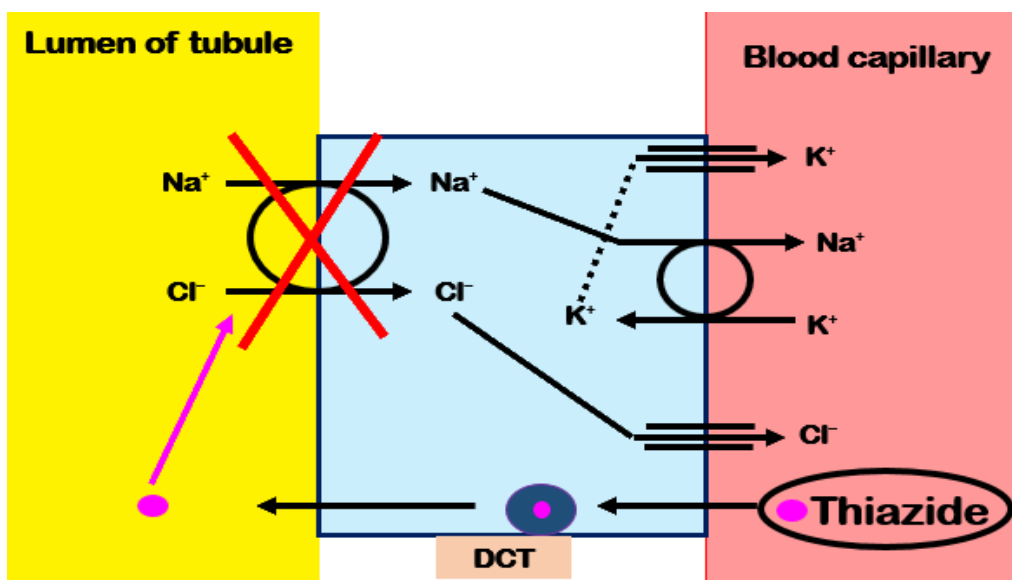
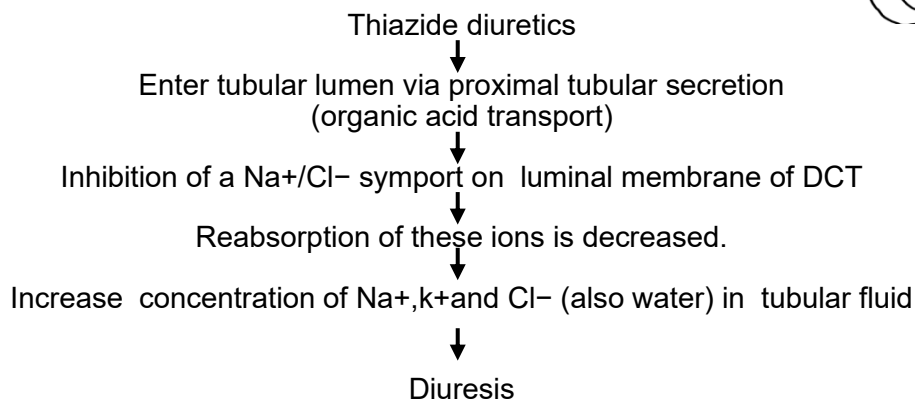
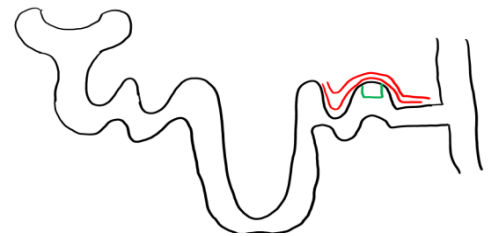
(COLT Pee)

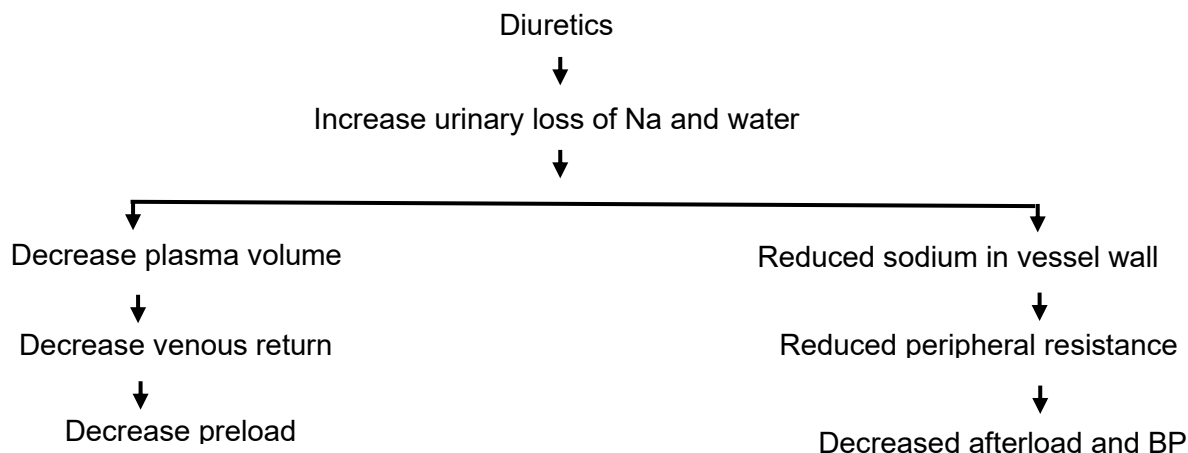




### MOA of High ceiling Diuretics

**SITE OF ACTION** → The thiazide diuretics acts on distal convoluted tubule (DCT)





- **In acute LVF** → Diuretics has beneficial effect because of venodilator effect (not because of diuretic action)
- **In chronic HF** → beneficial effect of Diuretics is due to diuretic action which reduces the fluid overload and congestive symptoms.

## Uses

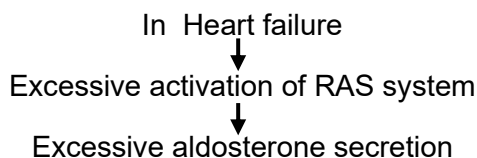
- Almost all cases of symptomatic CHF are treated with a diuretic
- But it is only for symptomatic improvement of congestive symptoms (DOC for CHF is ACE inhibitor).
- Diuretics do not arrest / reverse disease progression and do not decrease mortality in CHF.
  1. **For mild/moderate CCF** → a thiazide diuretic may be used
  2. **For a severe case** → a loop diuretic is the drug of choice

## Adverse effects

1. Diuretics do not arrest / reverse the disease progression and do not decrease mortality in CHF.
2. Cause activation of RAS (if hypovolemia occurs) which has adverse cardiovascular consequences.
3. Hypokalaemia, alkalosis and carbohydrate intolerance

# ALDOSTERON ANTAGONIST

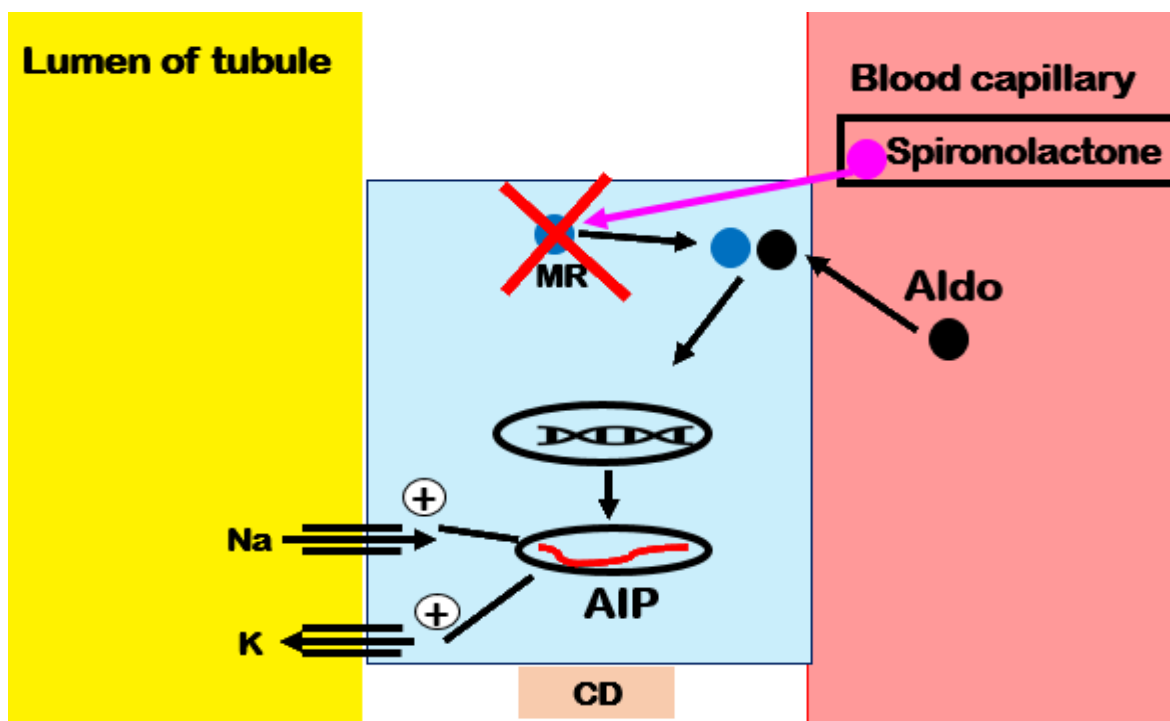
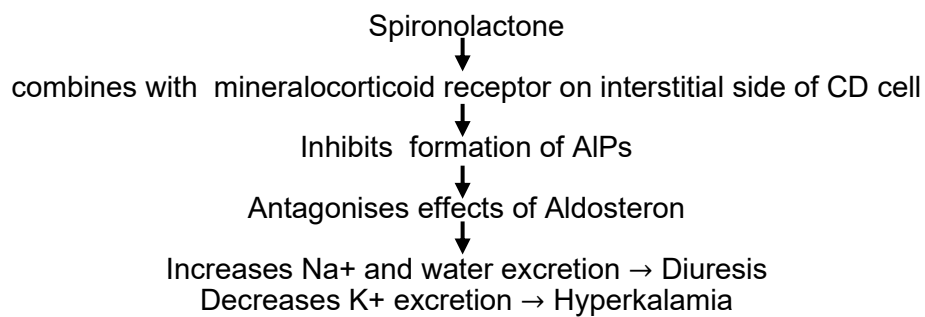
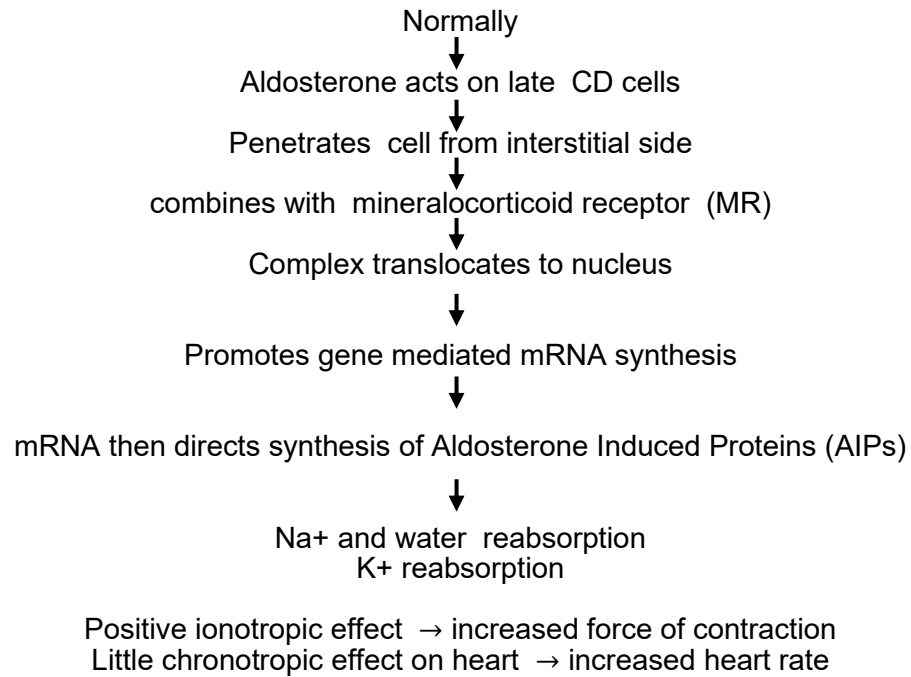
## Introduction



- Aldosterone antagonists abolish the action of aldosterone by combining with mineralocorticoid receptors.

## Drugs

- Spironolactone
- Eplerenone

**MOA**

## Uses

- Indicated as add-on therapy to ACE inhibitors + other drugs in moderate-to-severe CHF.
- Aldosterone antagonists cause reversal of disease progression and decrease mortality
- Only diuretics which decrease mortality in CHF.

## Adverse Effects

### 1. Hyperkalemia risk

- In CRF patients
- Patients taking ACEI (Enalapril) or ARB (Losartan)
- KCl supplement

### 2. Antiandrogen

- Gynaecomastia, Impotence in males
- Hirsutism, menstrual irregularities in female



## B BLOCKERS

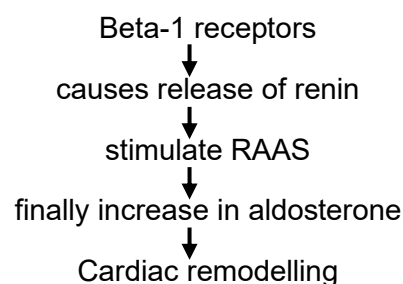
### Drugs

#### $\beta$ -adrenergic blockers

- Metoprolol
- Bisoprolol
- Nebivolol
- Carvedilol

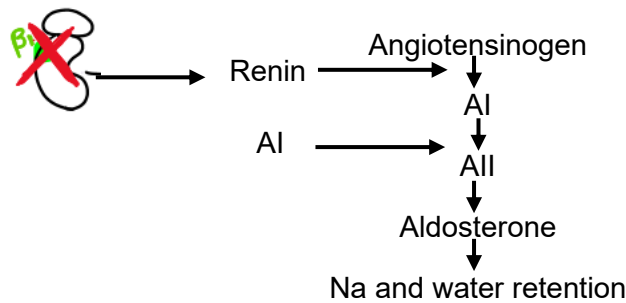
### MOA

- Previously beta blockers were considered to be contra-indicated in CHF due to their negative inotropic action
- But now it has been found that if used carefully, these drugs can increase the longevity of CHF patients.



- Beta blockers antagonize this pathway resulting in reversal of remodelling





## Uses

- Indicated in CCF if ejection fraction is less than 35% (normal is above 60%) NYHA class II or III symptoms.
- Most widely used beta blocker → carvedilol, metoprolol and bisoprolol.
- $\beta$ -blockers cause reversal of disease progression and decrease mortality

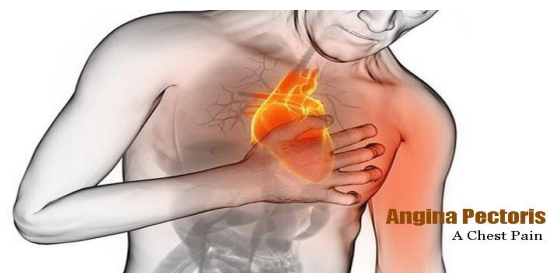
## Contraindications to $\beta$ Blocker in CCF

- Acute heart failure
- NYHA class IV
- Heart failure shortly after myocardial infarction.
- Heart failure with normal ejection fraction

# ANTIANGINAL DRUGS

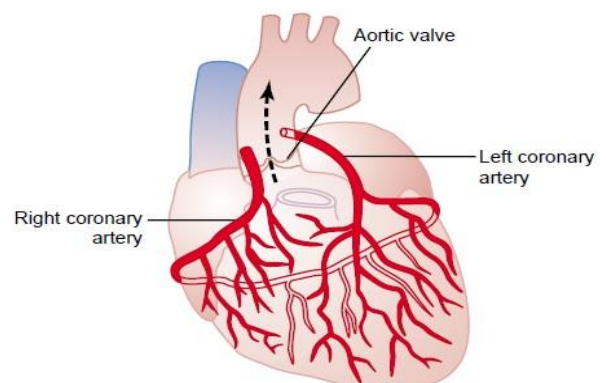
## Introduction

- Antianginal drugs are those that prevent, abort or terminate attacks of Angina pectoris.



## Blood Supply To Heart

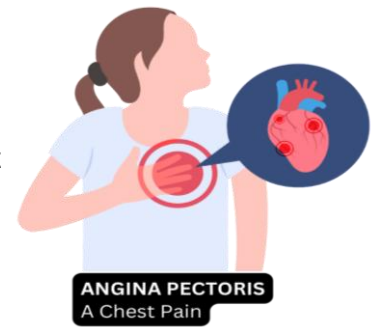
- Coronary arteries are the large conducting arteries that run epicardially and give collateral vessels to endocardial region.
- Blood flow to endocardium occurs mainly during diastole.



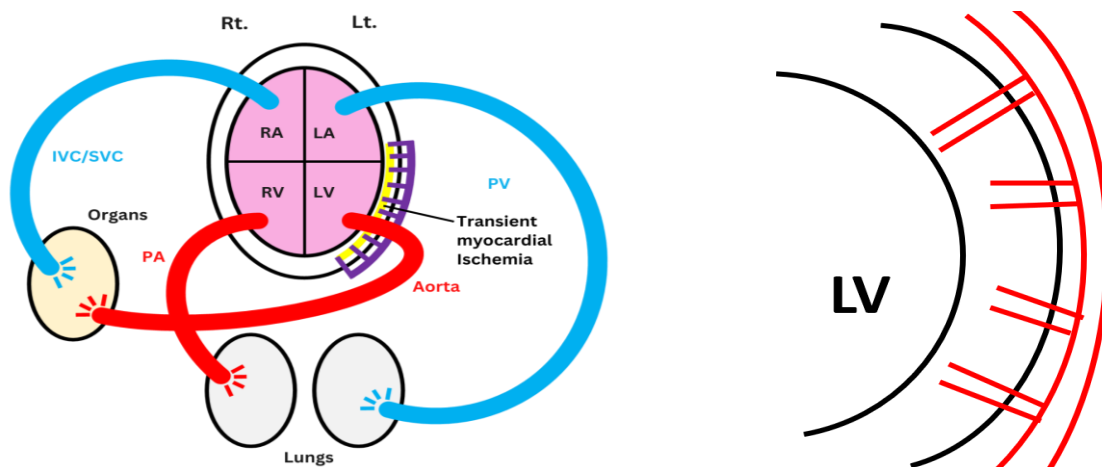
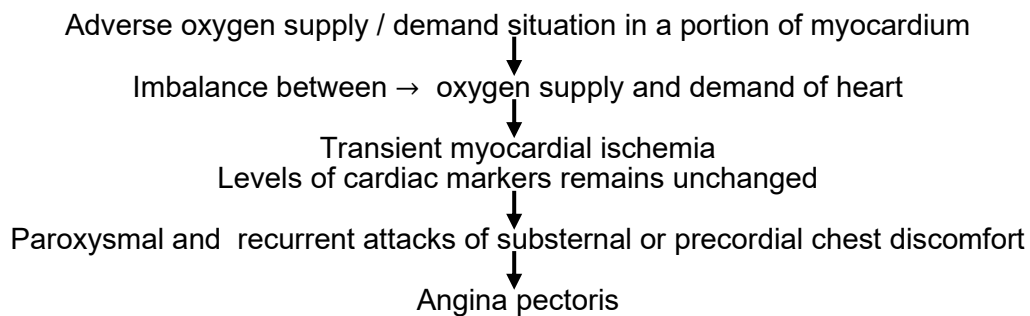
# ANGINA PECTORIS

## Definition

- Paroxysmal and recurrent attacks of substernal or precordial chest discomfort caused by transient myocardial ischemia
- Levels of cardiac markers remains unchanged

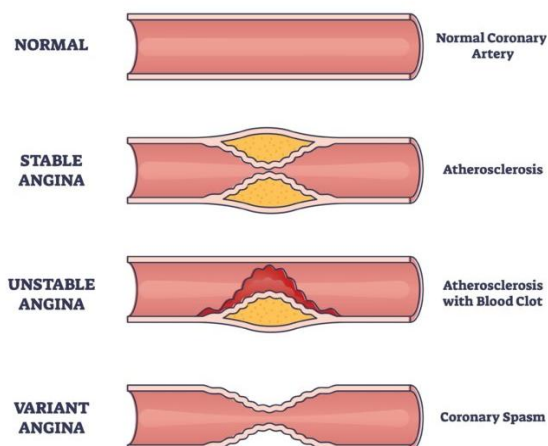


## Pathogenesis



## Types

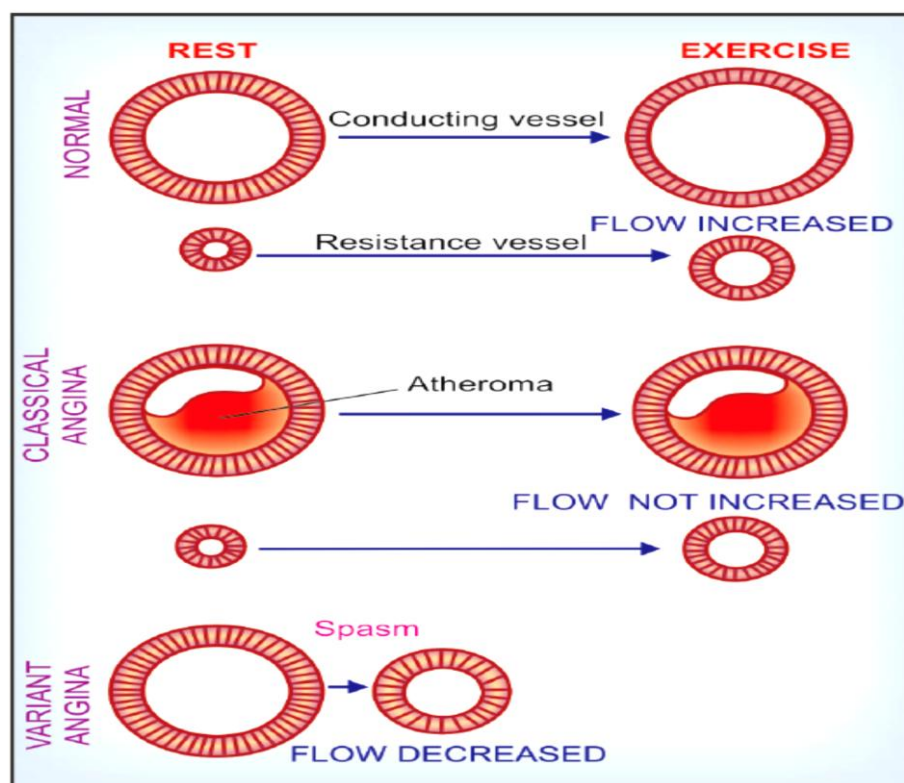
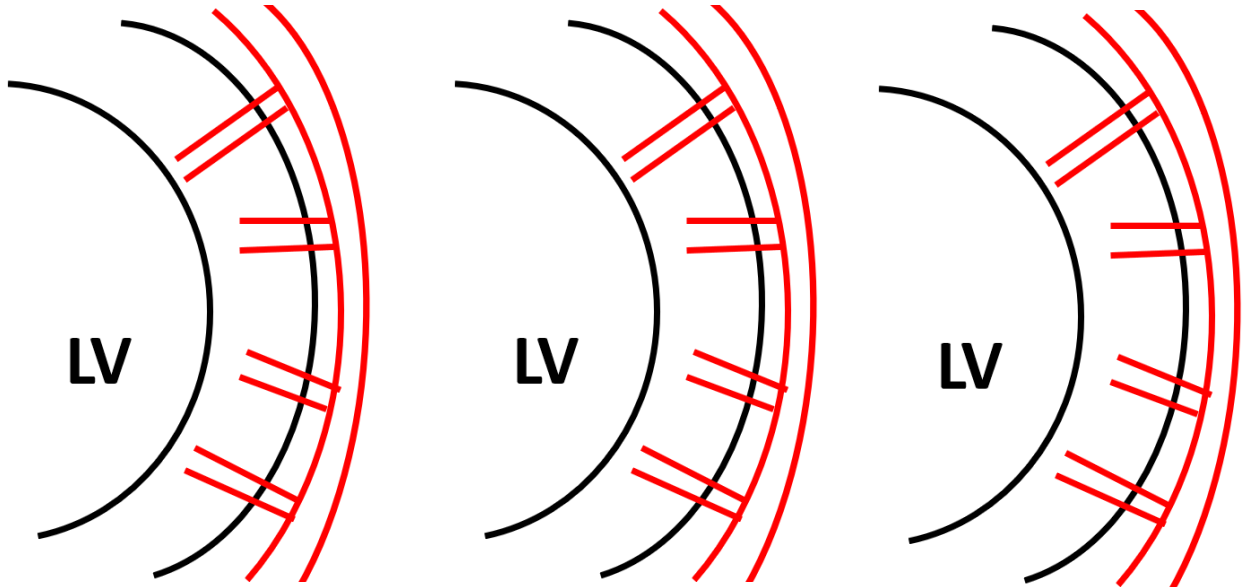
1. Stable or Classical angina
2. Unstable or crescendo angina
3. Prinzmetal's variant angina



Stable or Classical angina

Unstable or crescendo angina

Prinzmetal's variant angina



## Synthesis and storage of ACh

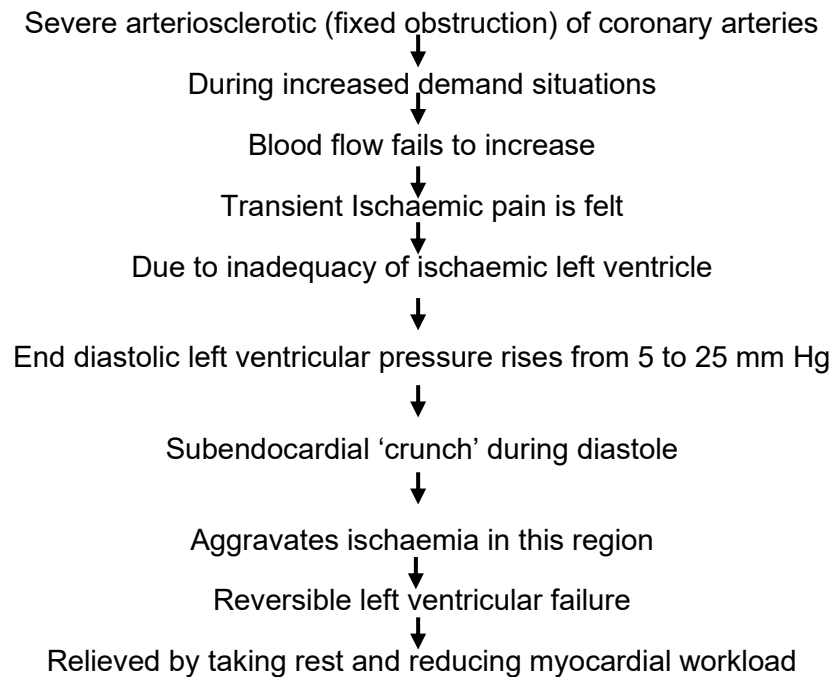
- Predictably
- Provoked (stable angina) by exercise, emotion, eating or coitus



- Attacks are subsided when the increased energy demand is withdrawn



### Pathology



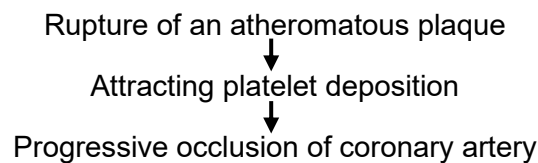
### Treatment aims at

- Drugs that reduce cardiac work (to decrease oxygen consumption) →
  1. Directly by acting on heart
  2. Indirectly by reducing preload hence end diastolic pressure, and afterload).

## 2. Unstable angina

- Rapid increase in duration and severity of attacks

### Pathology



### Treatment aims at

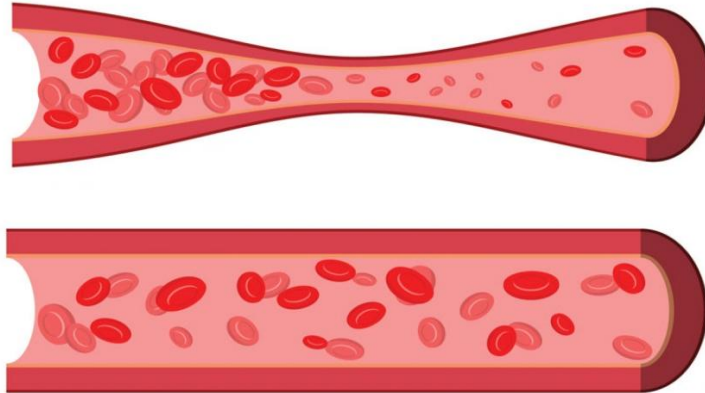
- Antithrombotic drugs such as aspirin reduces risk of M.I.

### 3. Variant/Prinzmetal/Vasospastic angina

- Unpredictable
- Attacks occur at rest or during sleep

#### Pathology

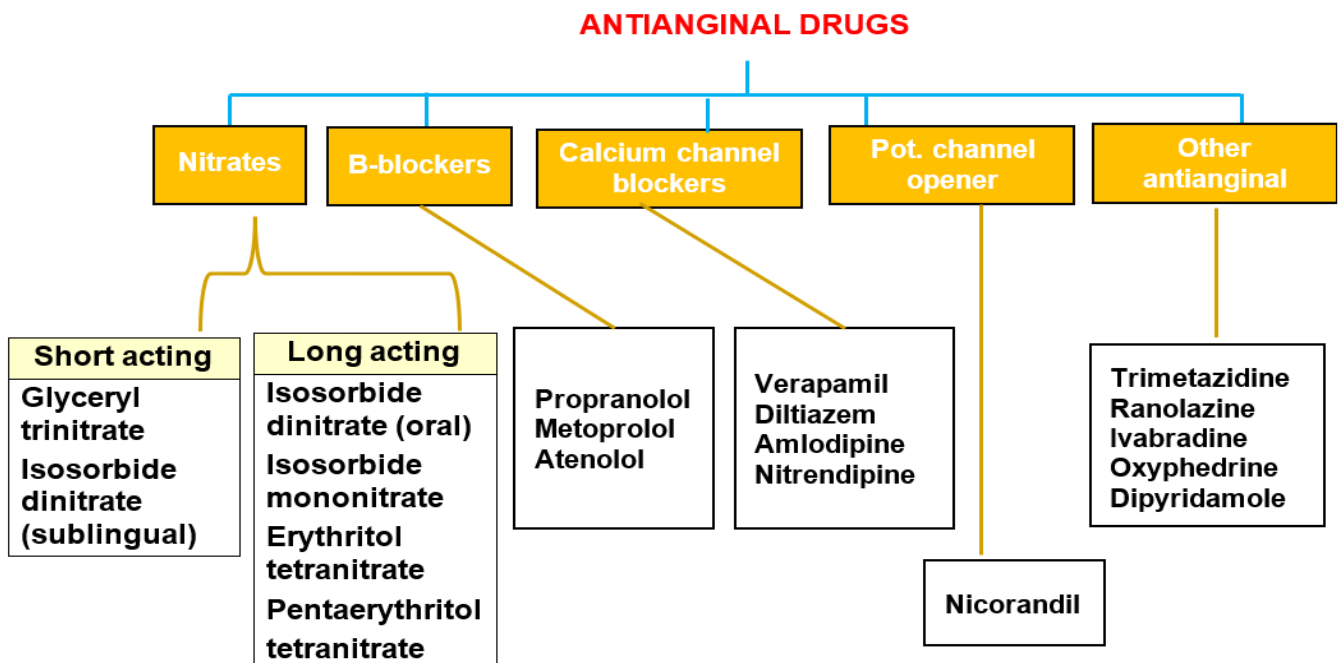
- Recurrent localized coronary vasospasm



#### Treatment aims at

- Drugs are aimed at preventing and relieving the coronary vasospasm

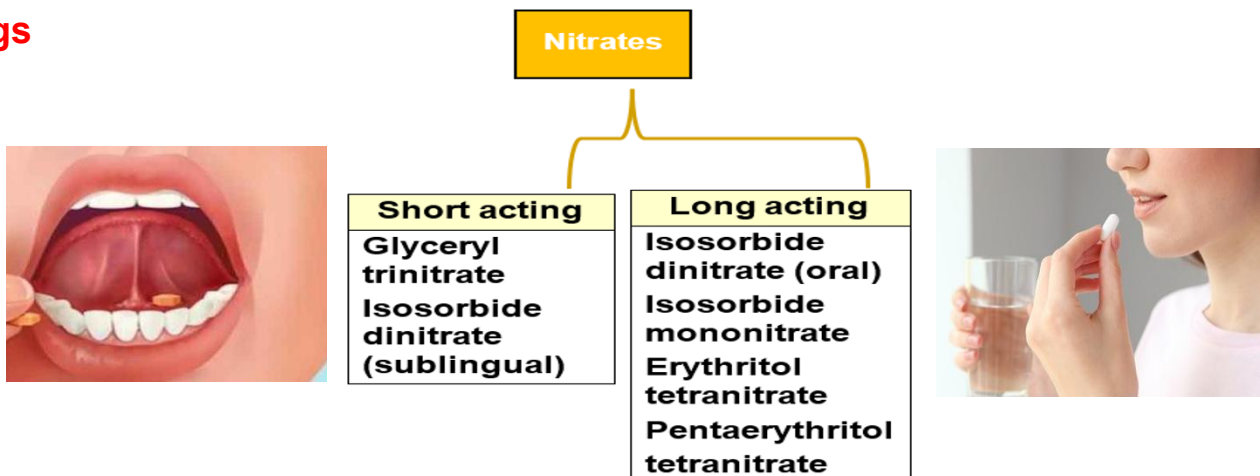
## ANTIANGINAL DRUGS



|                | Nitrates | $\beta$ Blockers | CCBs | Potassium Channel Activators | Dipyridamole | pFOX Inhibitor |
|----------------|----------|------------------|------|------------------------------|--------------|----------------|
| Drugs          |          |                  |      |                              |              |                |
| MOA            |          |                  |      |                              |              |                |
| Uses           |          |                  |      |                              |              |                |
| Adverse effect |          |                  |      |                              |              |                |
| Interactions   |          |                  |      |                              |              |                |

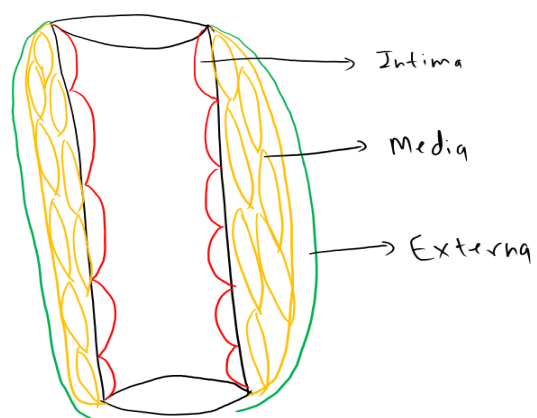
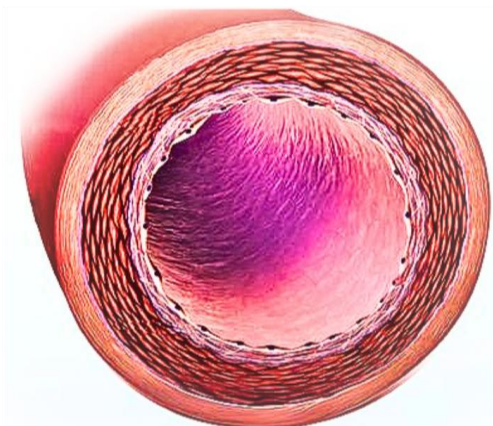
## NITRATES

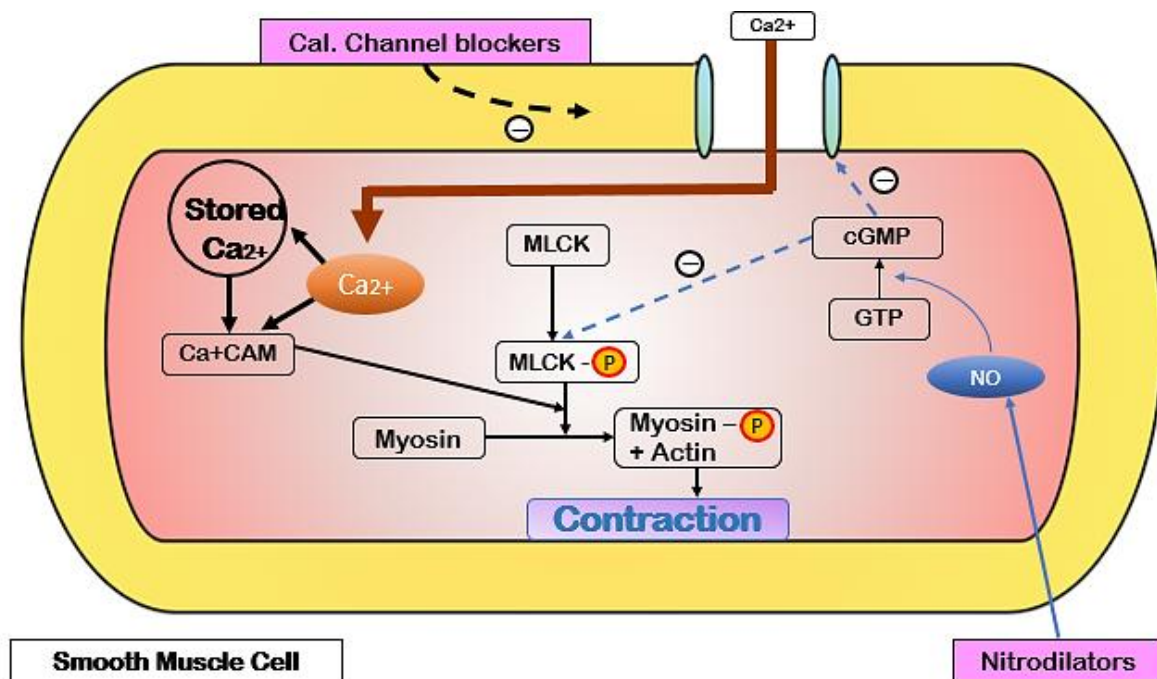
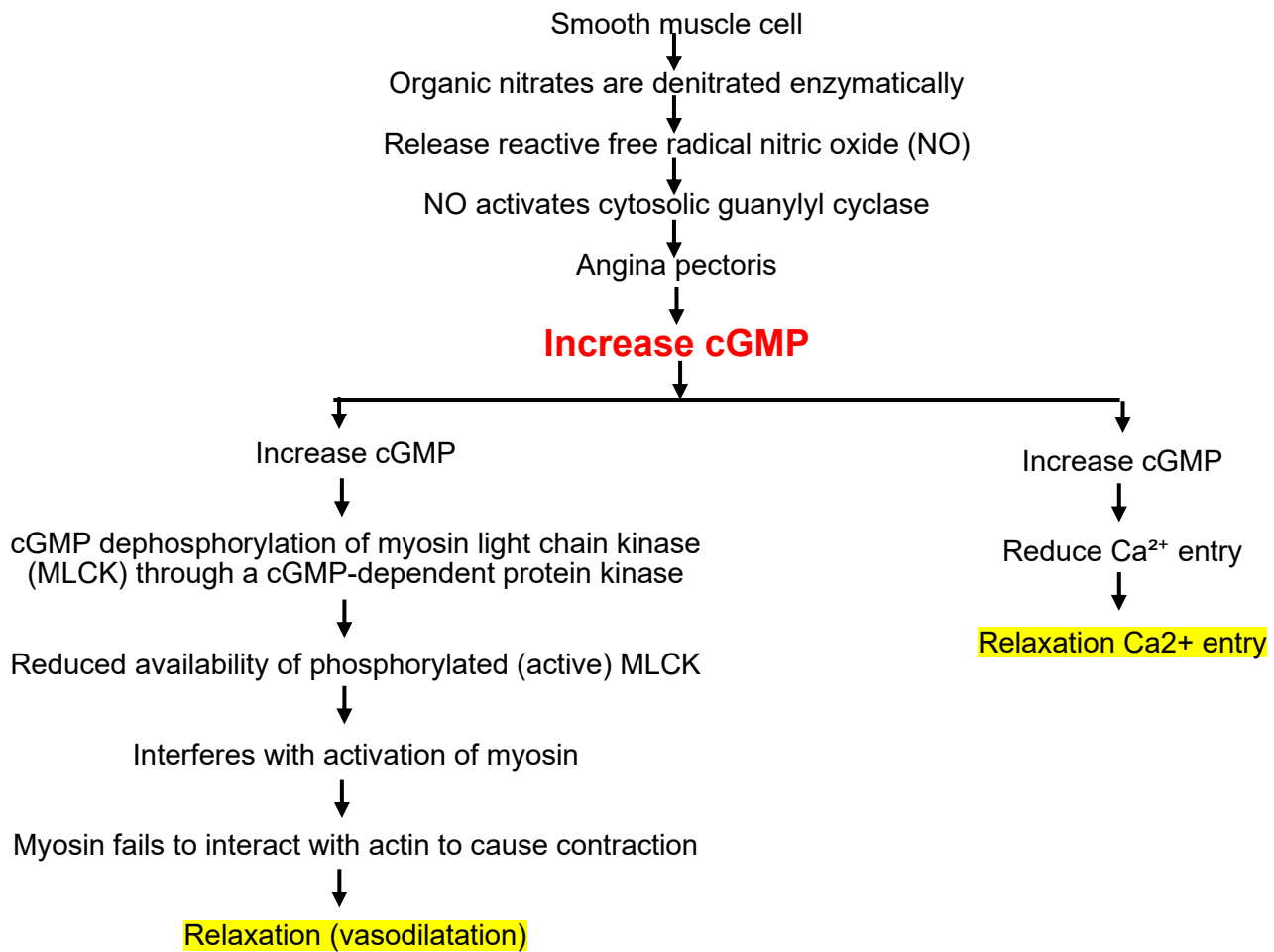
### Drugs



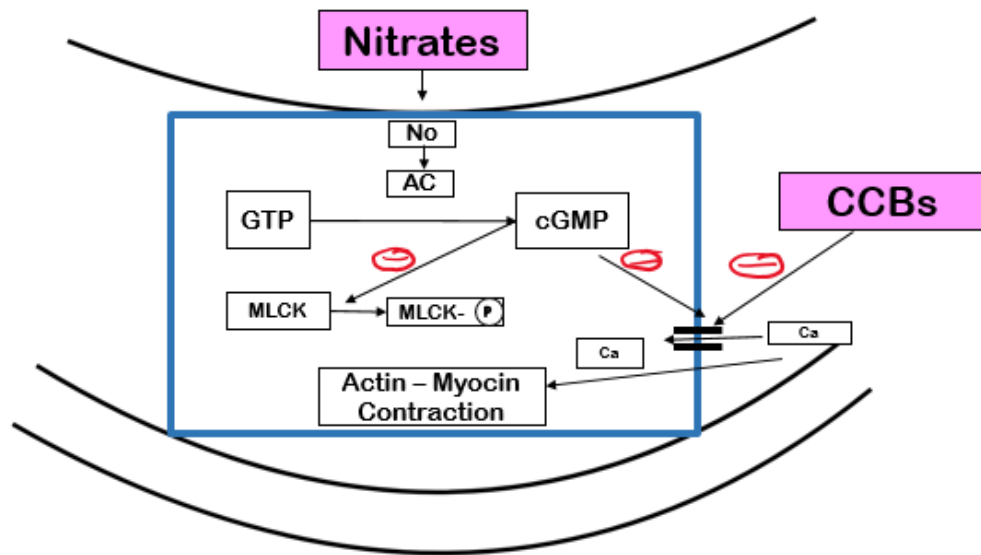
### MOA

- Smooth muscle cells



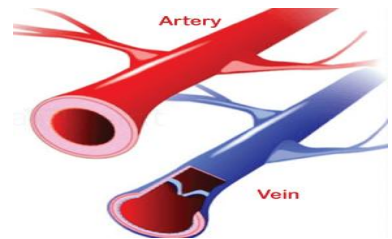






## Remember

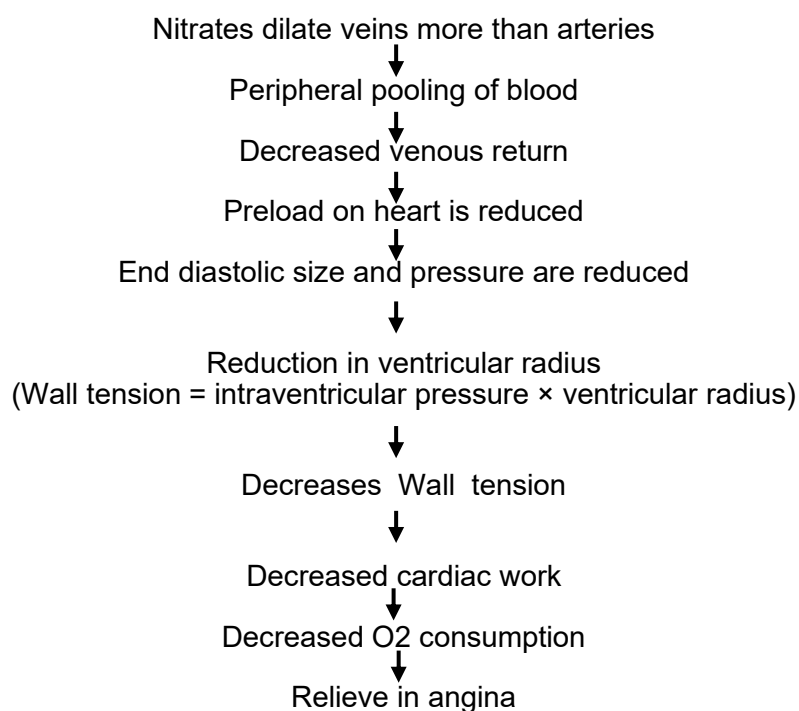
- Nitrates preferentially dilate capacitance vessels, i.e. veins (selective venodilators) because enzyme responsible for release of NO from nitrates is present mainly in veins.
- Other smooth muscles (biliary duct, oesophagus) are also relaxed



## Effects of vasodilatation

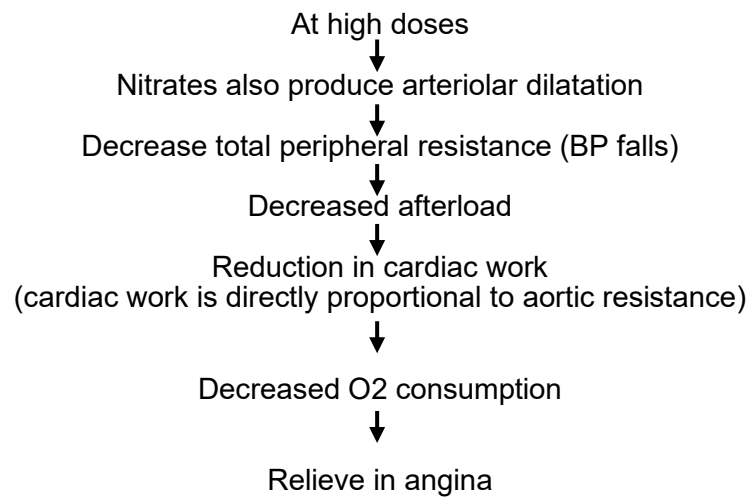
1. Preload reduction
2. Afterload reduction
3. Redistribution of coronary flow

### 1. Preload reduction

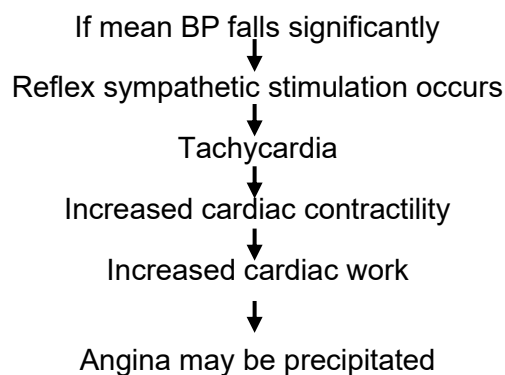


- Cardiac output (c.o.) is reduced
- This is principal action of nitrates benefiting 'Stable' angina

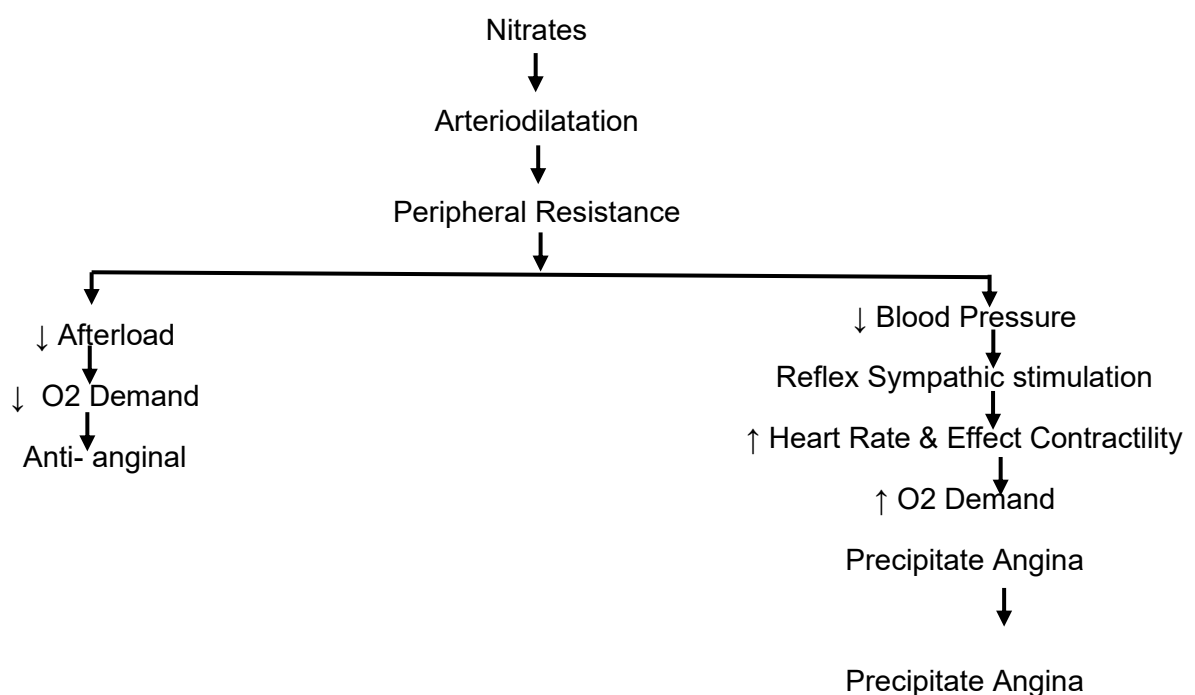
## 2. Afterload reduction



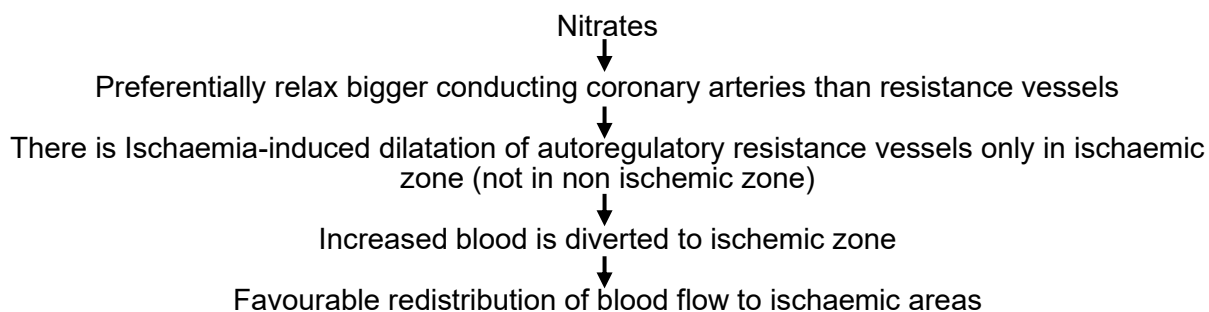
### Remember



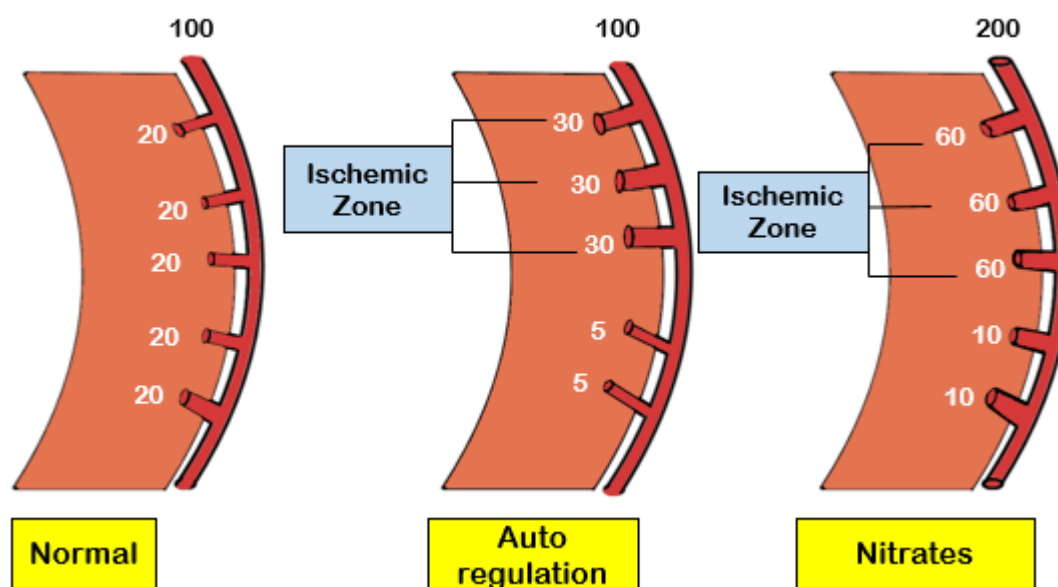
- This can be prevented by lying down and raising the foot end.



### 3. Redistribution of coronary flow



- Principal action of nitrates benefiting 'variant' angina

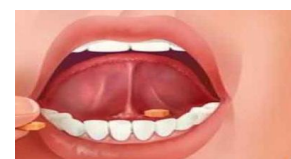


### Remember

- Nitrates have no direct stimulant or depressant action on the heart
  - Nitrates decreases cardiac work by decreasing preload and afterload
  - Nitrates also causes coronary dilatation

### Pharmacokinetics

- Nitroglycerine (glyceryl trinitrate) and isosorbide dinitrate** → used sublingually for aborting acute angina attack
- All other nitrates** → used by oral routes for prophylaxis of angina.



- **All nitrates except isosorbide mononitrate** → undergo extensive first pass metabolism in liver  
→ Thus isosorbide mononitrate is the only nitrate with minimal first pass metabolism.
- **Amyl nitrite** → shortest acting nitrite
- **Pentaerythritol tetranitrate** → longest acting nitrate.

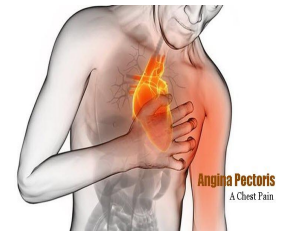
## Uses

### Mnemonic

1. **A** – **A**ngina Pectoralis
2. **B** – **B**iliary colic
3. **C** – **C**yanide Poisoning
4. **D** – **D**il ka Daura (MI)
5. **E** – **E**sophagral Spasm
6. **F** – **F**ailure (Heart Failure)

### 1. Angina pectoris

- Effective in classical as well as variant angina.
- For terminating an attack, sublingual GTN tablet or spray, or isosorbide dinitrate is taken on 'as and when required' basis.

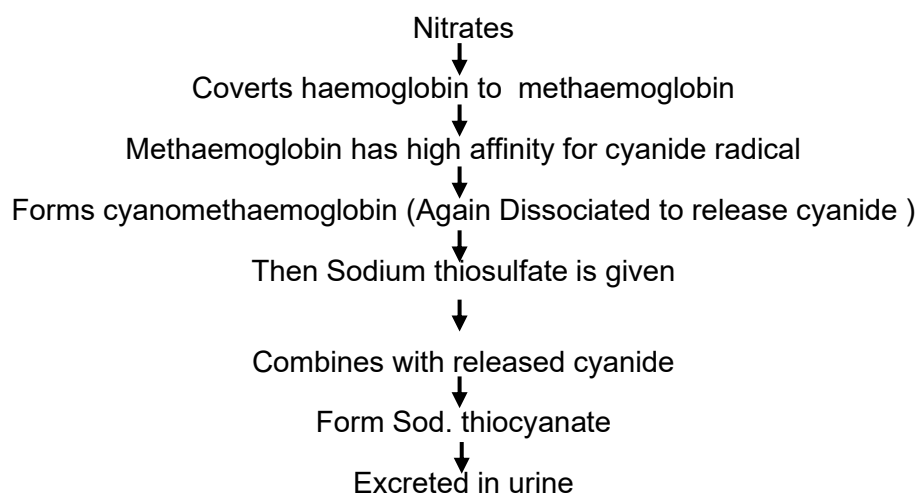


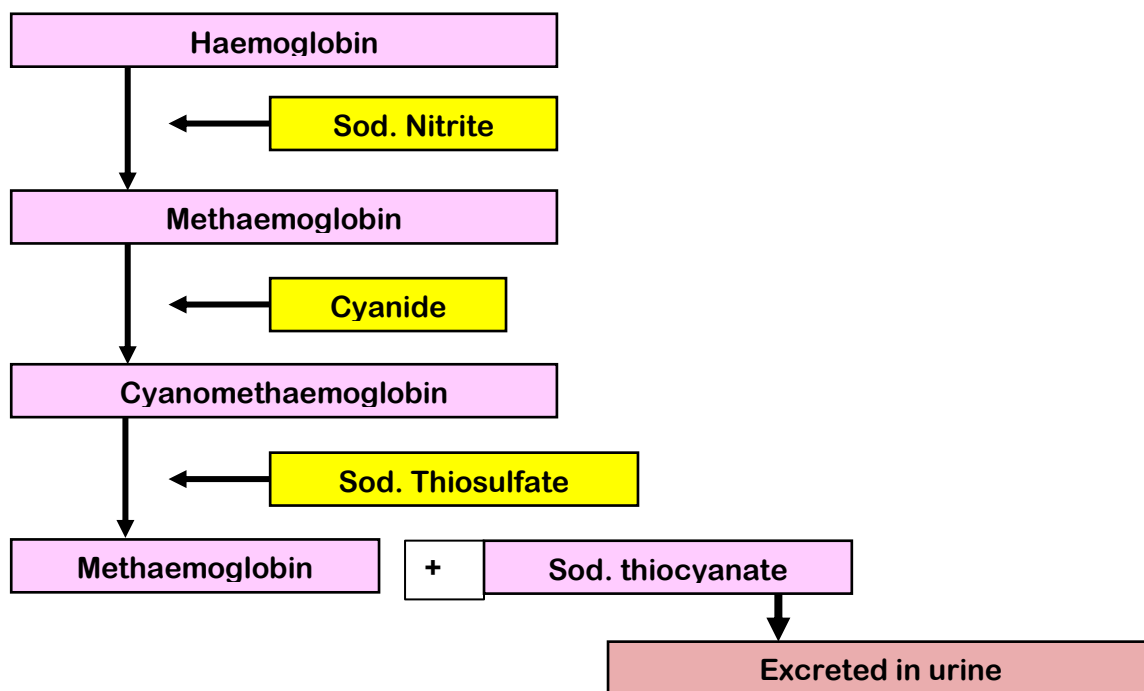
### 2. Biliary colic

- By smooth muscle relaxation



### 3. Cyanide poisoning





#### 4. Myocardial infarction (MI)

- GTN should not be administered if:
  - Systolic BP is < 90 mm Hg
  - Heart rate is < 50 or > 100 beats/min



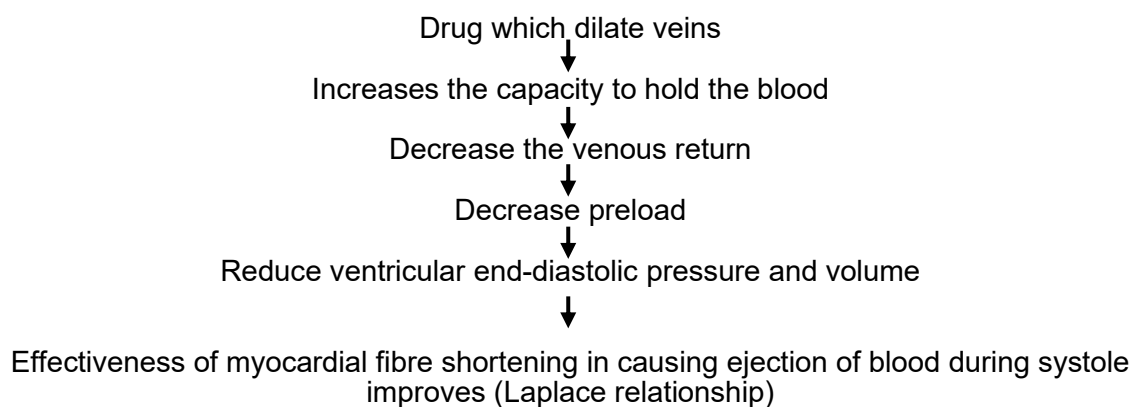
#### 5. Esophageal spasm

- By smooth muscle relaxation



#### 6. CHF

- Venodilator

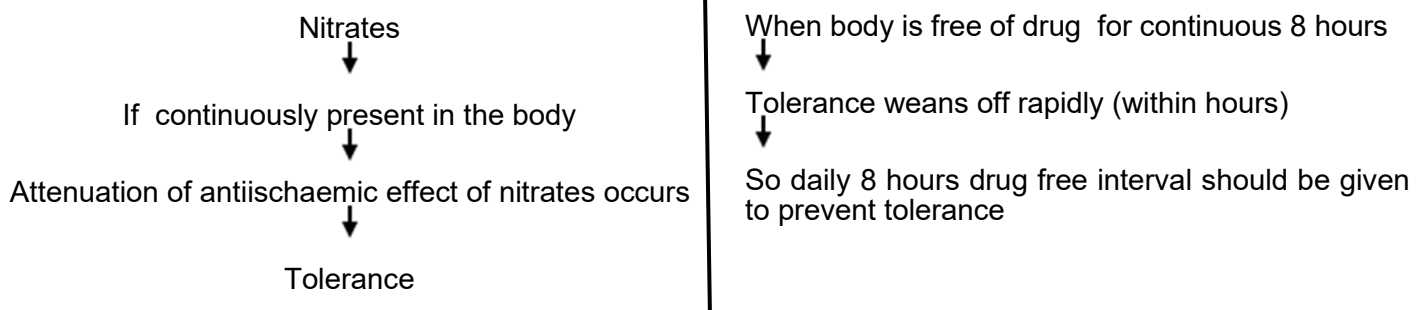


## Adverse effects

### Mnemonic

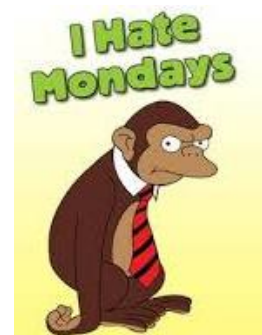
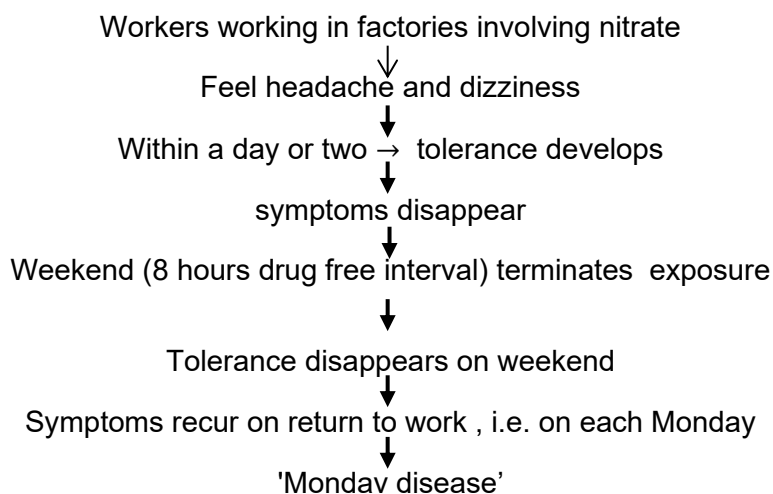
T – Tolerance, Throbbing headache  
 D - Dependence  
 S – Skin Rashes  
 R – Reflex tachycardia  
 O – Orthostatic Hypotension  
 M – Methemoglobinemia

### 1. Tolerance



### Remember

- Tolerance is not seen with sublingual route.
- Molsidomine is an emerging agent in this category to which tolerance does not develop

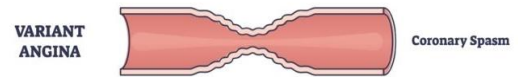


- **Throbbing headache, Fullness in head** → due to vasodilatation



## 2. Dependence

Nitrates  
↓  
Sudden withdrawal after prolonged exposure  
↓  
Spasm of coronary and peripheral blood vessels



## 3. Skin Rashes

- Common with pentaerythritol tetranitrate



## 4. Reflex tachycardia

Nitrates  
↓  
causes vasodilatation  
↓  
Reflex tachycardia  
↓  
Reflex tachycardia

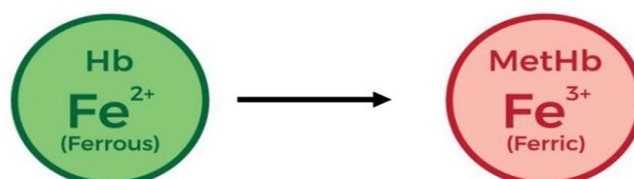
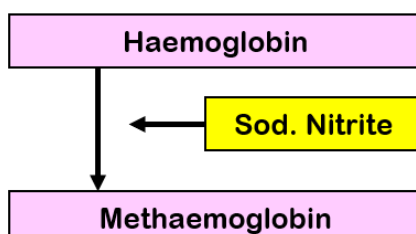


## 5. Orthostatic Hypotension

Nitrates  
↓  
causes vasodilatation  
↓  
Orthostatic Hypotension

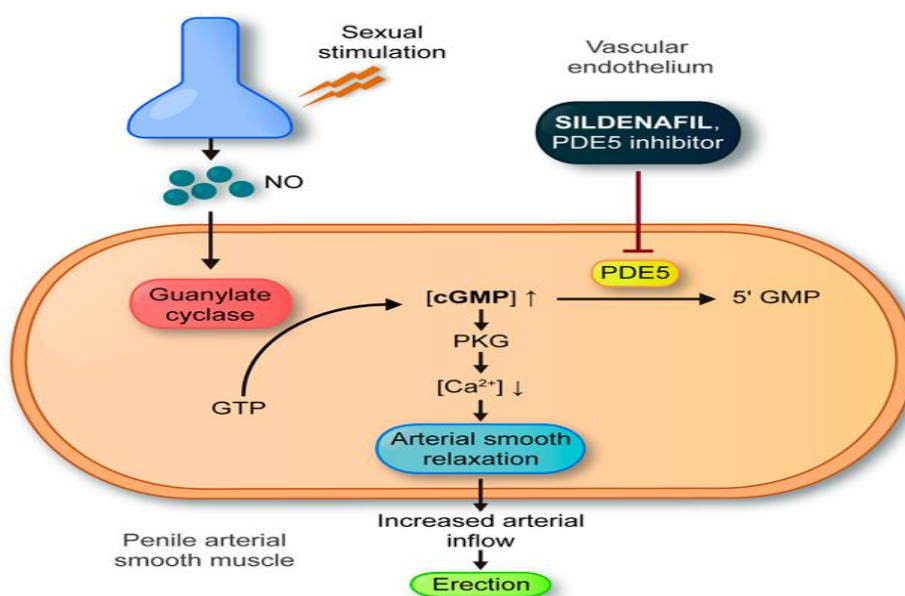
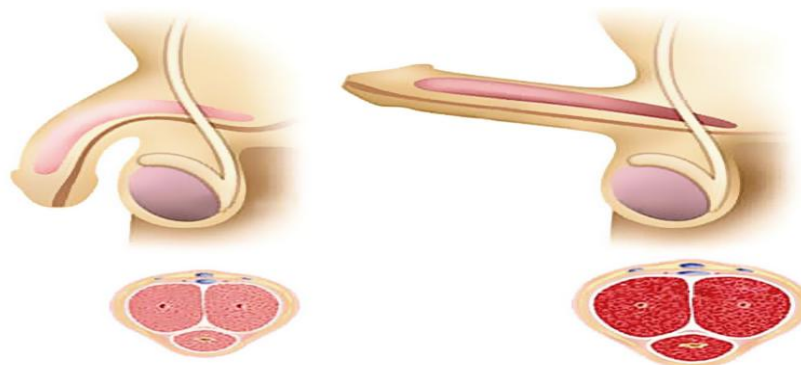
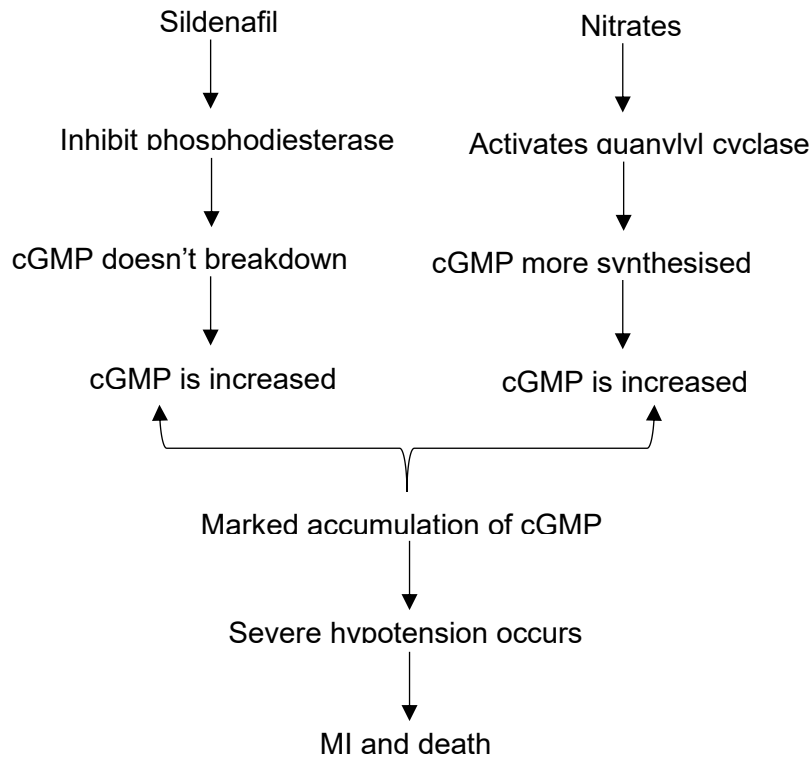


## 6. Methemoglobinemia





## Interactions



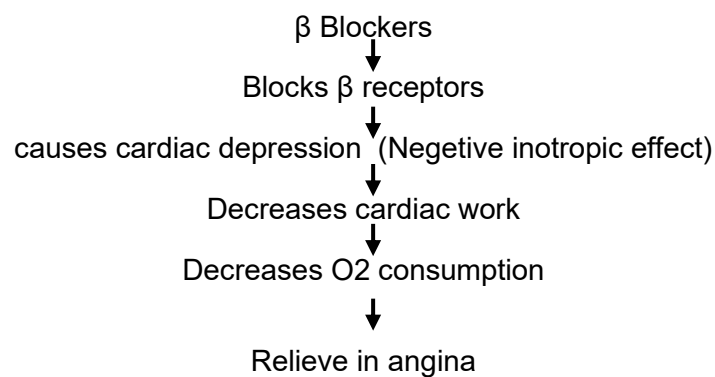
## B BLOCKERS

### Drugs

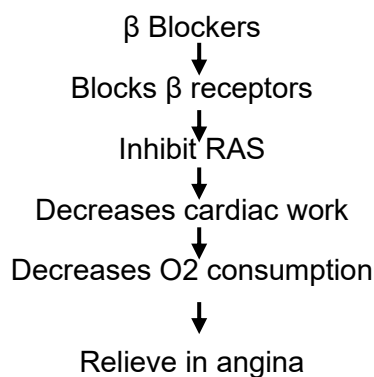
- Propranolol
- Metoprolol
- Atenolol

### MOA

- 2 MOA
- $\beta_1$  receptors  $\rightarrow$  causes cardiac stimulation

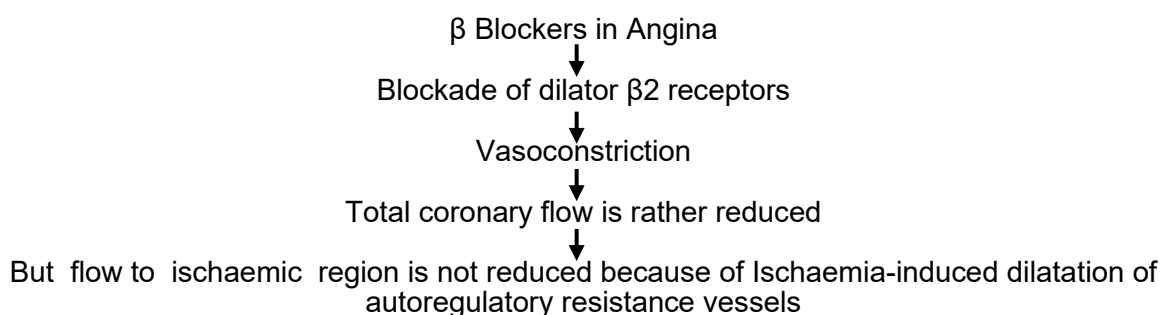


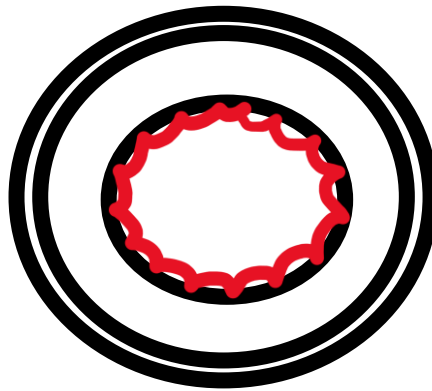
- $\beta_1$  receptors  $\rightarrow$  causes release of renin  $\rightarrow$  stimulate RAAS  $\rightarrow$  increase in aldosterone



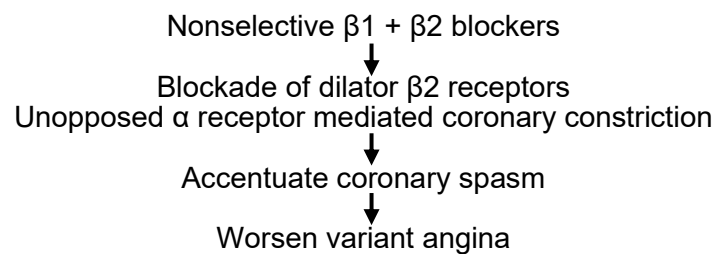
### Remember

- $\beta$  Blockers  $\rightarrow$  do not dilate coronarie arteries
- $\beta$  Blockers  $\rightarrow$  directly acts on heart to decrease cardiac work
- $\beta$  Blockers although causes Vasoconstriction but do not reduce flow to ischaemic region





- Cardioselective agents (atenolol, metoprolol) are preferred over nonselective  $\beta_1 + \beta_2$  blockers (e.g. propranolol)



## CALCIUM CHANNEL BLOCKERS

### Calcium channels

3 types →

1. Voltage sensitive channel
  2. Receptor operated channel
  3. Leak channel
- Only the voltage sensitive L-type channels are blocked by the CCBs.

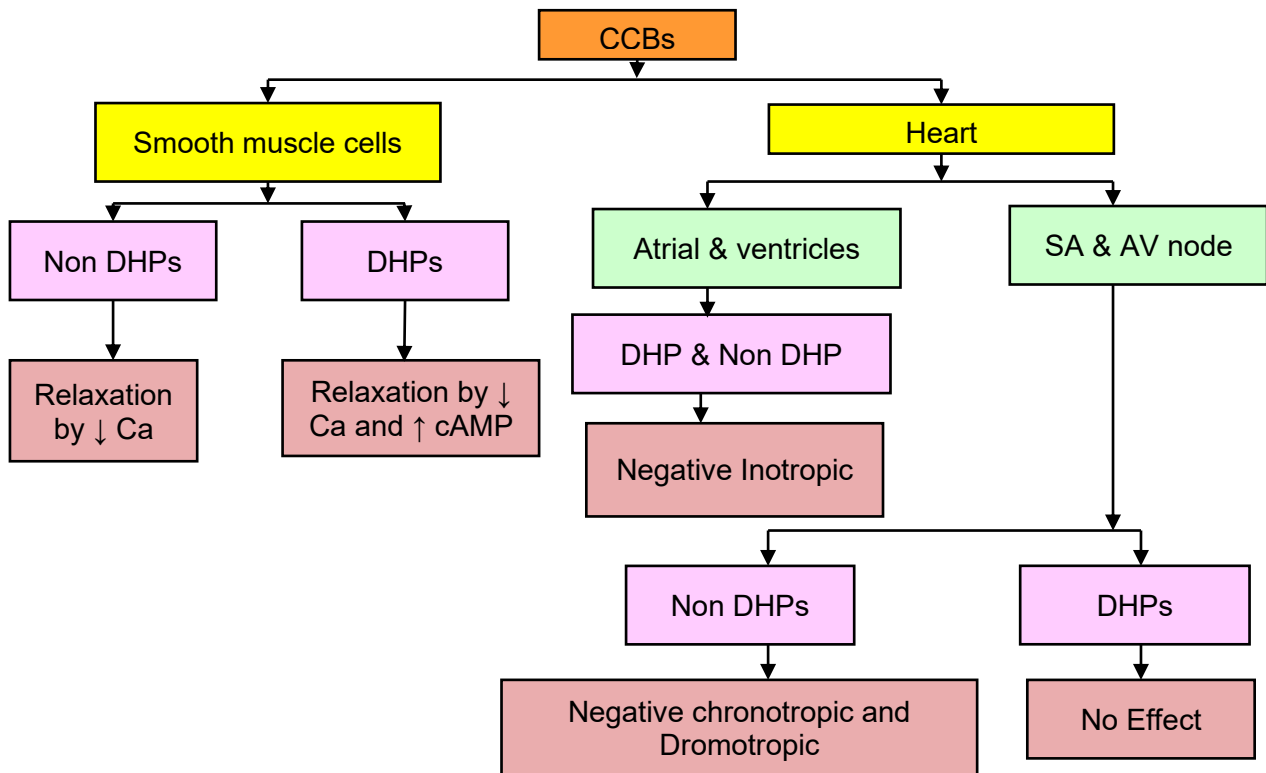
### Drugs

3 groups →

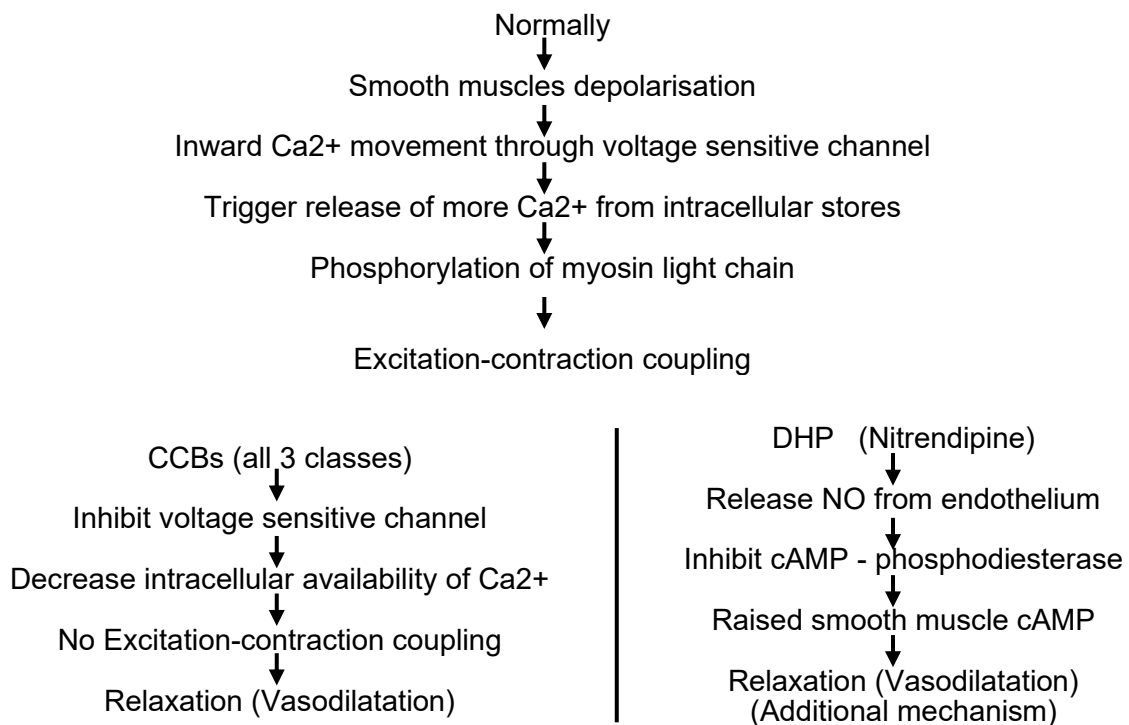
- |                                                       |   |          |
|-------------------------------------------------------|---|----------|
| 1. Phenylalkylamines (Verapamil)                      | } | Non DHPs |
| 2. Benzothiazepine (Diltiazem)                        |   |          |
| 3. Dihydropyridines □ DHPs (nifedipine, Nitrendipine) |   |          |

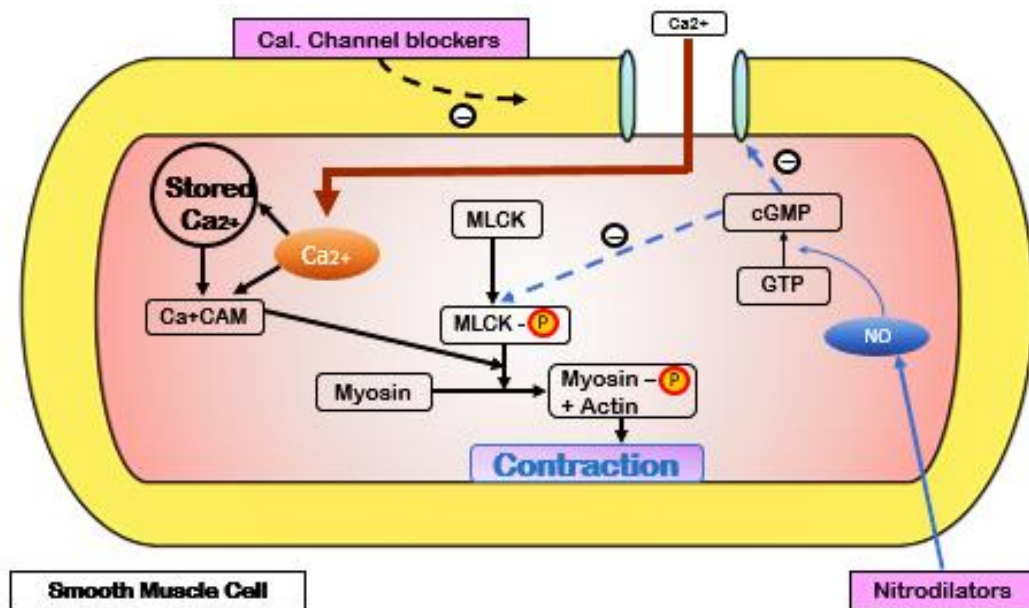
### MOA

1. Smooth muscle (especially vascular) → Relaxation
2. Heart → Negative chronotropic, inotropic and dromotropic



## 1. Smooth muscle



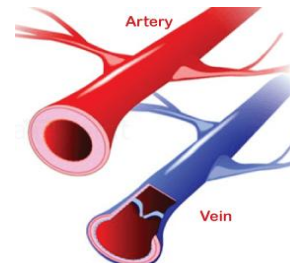


## Remember

- Arterioles are relaxed more markedly than veins.

## Order of blockage

- DHPs > Phenylalkylamines > Benzothiazepine
- Nifedipine > verapamil > Diltiazem

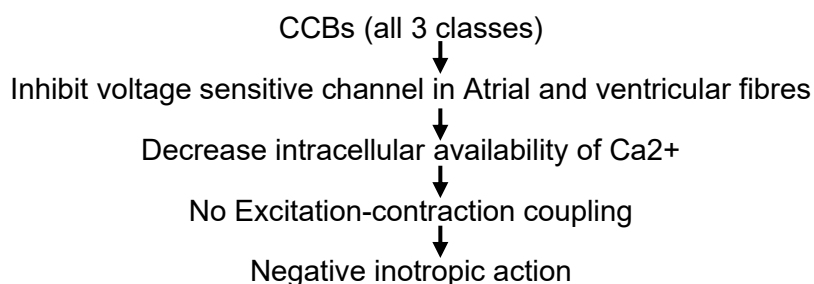


## 2. Heart

### 2 MOA →

- Atrial and ventricular fibres
- SA and A-V nodes

### A) Atrial and ventricular fibres



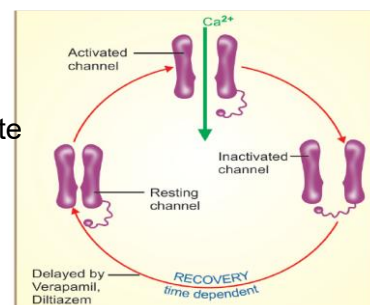
## Remember

- Channel blockade by verapamil is enhanced at higher rates of stimulation
- Channel blockade by nifedipine is independent of frequency
- Channel blockade by Diltiazem is intermediate

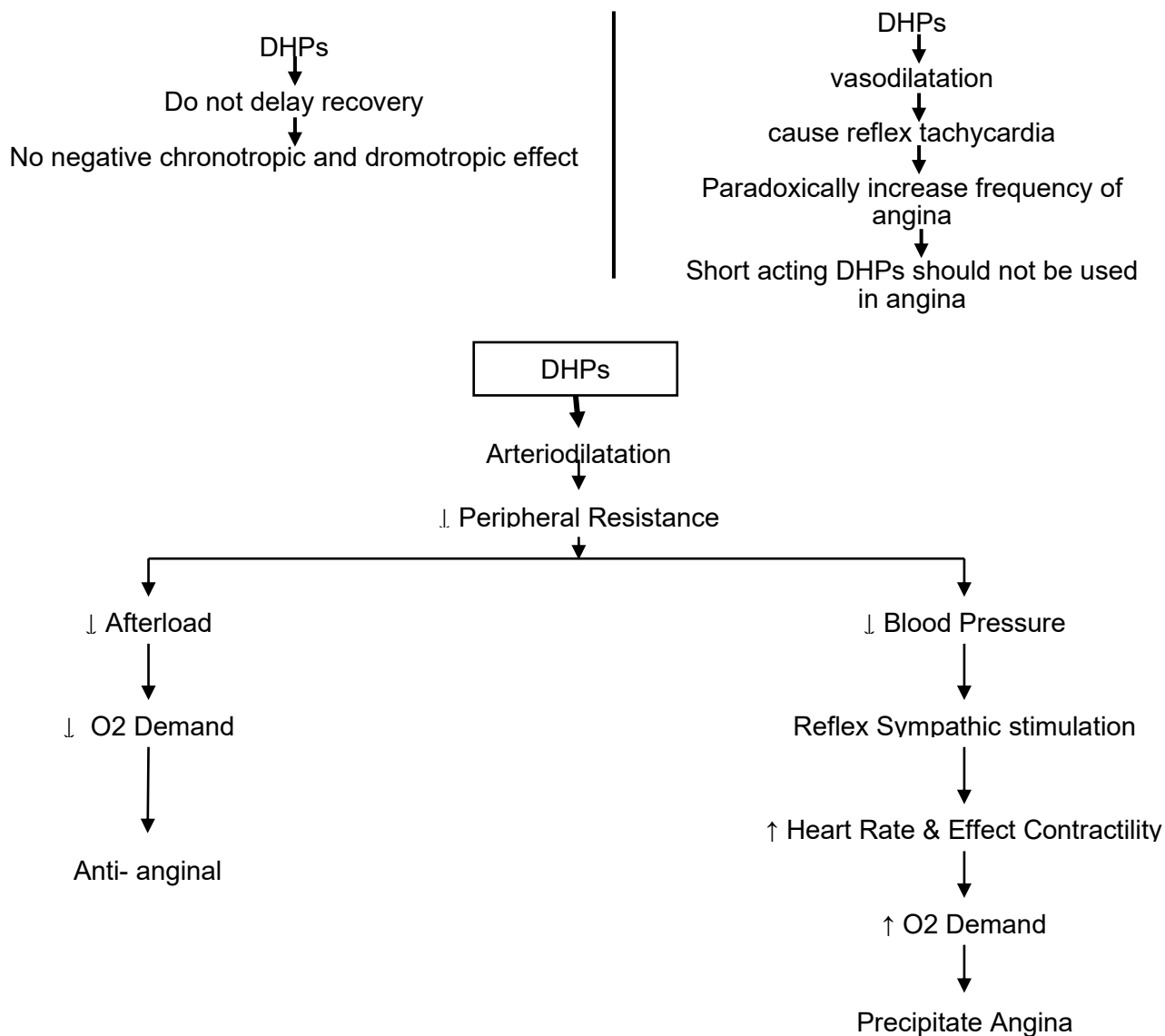
## B) SA and A-V nodes

- Automaticity and conductivity of SA and A-V nodes cells appear to be dependent on the rate of recovery of the  $\text{Ca}^{2+}$  channel.

Verapamil and Diltiazem not DHPs  
 ↓  
 Delay recovery of L type calcium channel from inactivated state to resting state  
 ↓  
 Depression of pacemaker activity and conduction  
 ↓  
 Negative chronotropic and Dromotropic effect



## Remember



| Cardiac effects | Verapamil | Diltiazam | Nifedipine |
|-----------------|-----------|-----------|------------|
| Contractility   | ↓         | ↓         | ↑          |
| Heart rate      | ↓         | ↓         | ↑          |
| AV conduction   | ↓↓        | ↓         | -          |

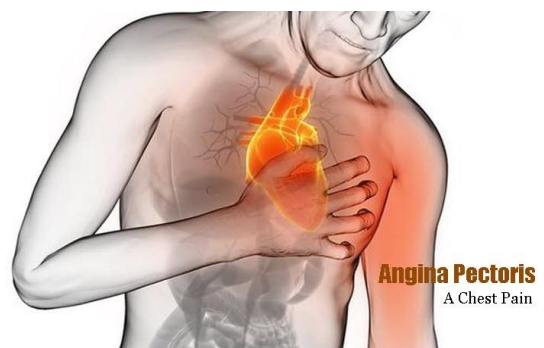
|                                    | DHP                                                            | Non-DHP                                                                                    |
|------------------------------------|----------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| <b>Blood Vessels</b>               | Potent vasodilatation                                          | Less Potent vasodilatation                                                                 |
| <b>Heart</b>                       | No Direct effect                                               | Direct depressant effect                                                                   |
| <b>Reflex effect</b>               | ↑ Sympathetic so ↑ Heart rate & contractility                  | Direct effect dominates so no change in heart rate (Verapamil) or ↓ Heart rate (diltiazem) |
| <b>Antiarrhythmic effect</b>       | No, since conduction is not blocked                            | Yes                                                                                        |
| <b>Common adverse effect</b>       | ↓ BP, headache, dizziness flushing, peripheral edema           | Constipation, bradycardia, heart block, CCF, cardiac arrest                                |
| <b>Combination with β Blockers</b> | Beneficial, since block reflex ↑ in heart rate & contractility | Contraindicated, since ↑ risk of bradycardia, heart block, CCF, Cardiac arrest             |

## Uses

1. Angina pectoris
2. Myocardial infarction
3. Hypertension
4. Cardiac arrhythmias
5. Hypertrophic cardiomyopathy
6. Other uses

### 1. Angina pectoris

- All CCBs (Except Short acting DHPs ) → effective in reducing frequency and severity of classical as well as variant angina.
- Short acting DHPs like nifedipine can cause reflex tachycardia due to vasodilatation and paradoxically increase the frequency of angina → short acting DHPs should not be used in angina.





## 2. Myocardial infarction

- Verapamil / diltiazem may be employed for secondary prophylaxis when  $\beta$  blockers are contraindicated
- Verapamil /diltiazem should not be given with  $\beta$  blockers—additive sinus depression, conduction defects or asystole may occur



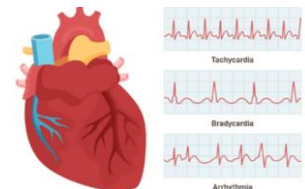
## 3. Hypertension

- All DHPs, diltiazem and verapamil are among the first line drugs for hypertension



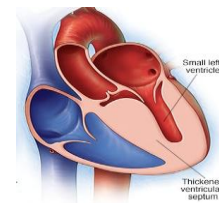
## 4. Cardiac arrhythmias

- Verapamil and diltiazem are highly effective in PSVT and for control of ventricular rate in supraventricular arrhythmias



## 5. Hypertrophic cardiomyopathy

- Negative inotropic action of verapamil salutary in this condition.



## 6. Other uses

- **DHPs** → reduce severity of Raynaud's episodes
- **Nifedipine** → alternative drug for premature labour
- **Verapamil** → used to suppress nocturnal leg cramps
- **Flunarizine** → weak  $\text{Ca}^{+2}$  channel blocker ☐ used for prophylaxis of migraine.

## Adverse effects

- Verapamil
- Diltiazem
- Nifedipine

## Verapamil

1. Nausea, constipation
2. Bradycardia are more common
3. Verapamil can accentuate conduction defect → should be avoided in 2nd & 3rd degree block, in sick sinus syndrome and along with B-blocker.

## Diltiazem

- Side effects are milder, but the profile is similar to verapamil.

## Nifedipine

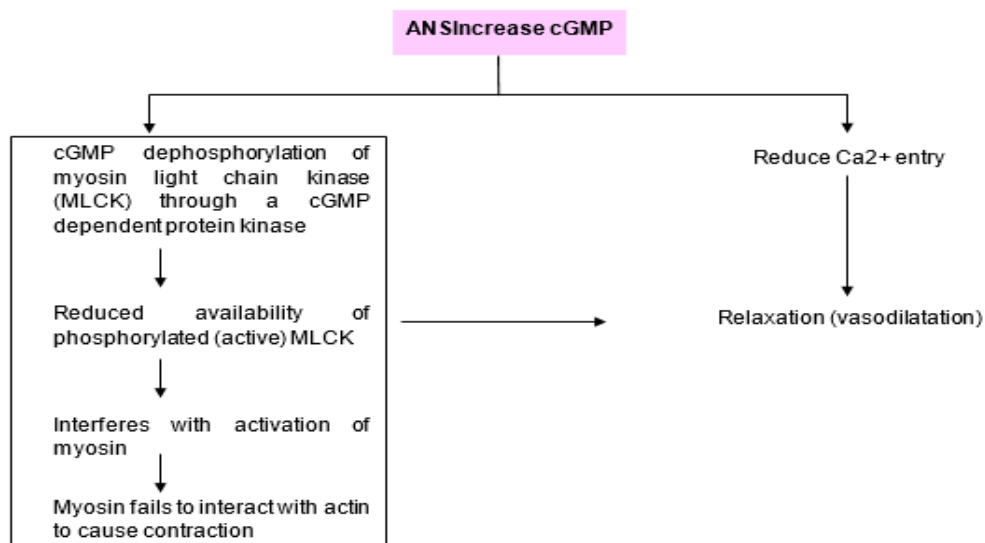
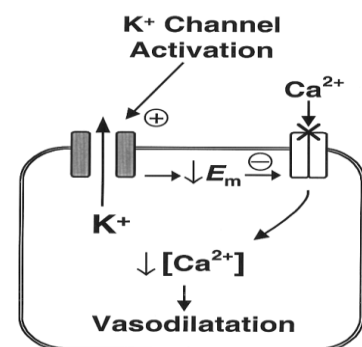
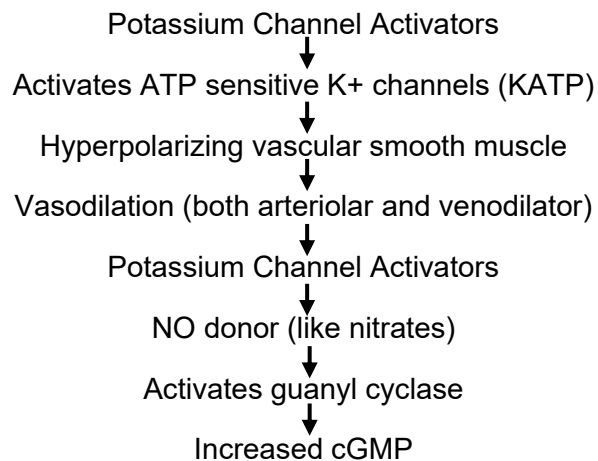
1. Hypotension
2. Palpitation
3. Flushing
4. Headache
5. Ankle edema,
6. Drowsiness and nausea.
7. Nifedipine can paradoxically increase the frequency of angina in some patients
8. Nifedipine can cause voiding difficulty in elderly (relaxant effect on bladder) and glucose intolerance (decreases insulin release).

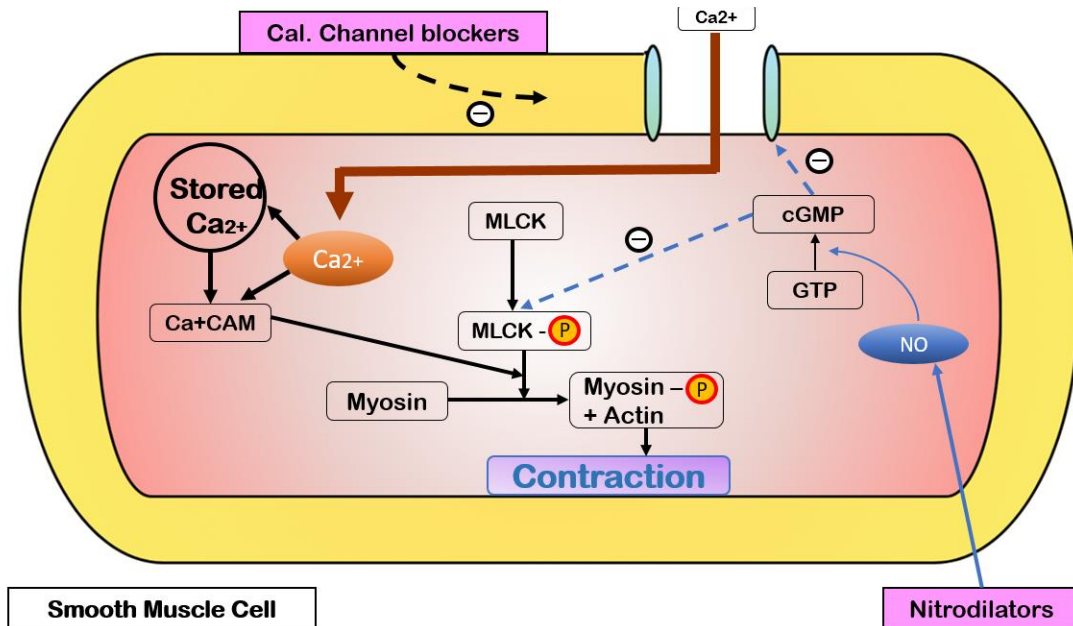
## POTASSIUM CHANNEL ACTIVATORS

### Drugs

- Crofnoalim
- Nicorandil

### MOA





## Uses

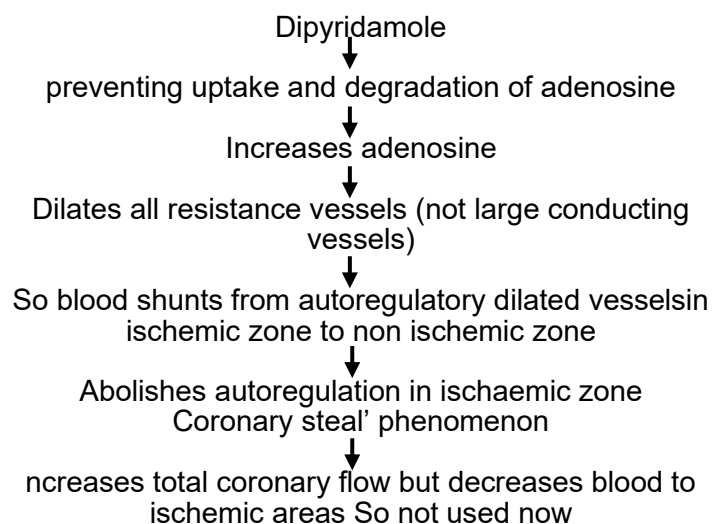
- They are arteriolar as well as venodilators
- Used as adjuvant in chronic stable angina and vasospastic angina.

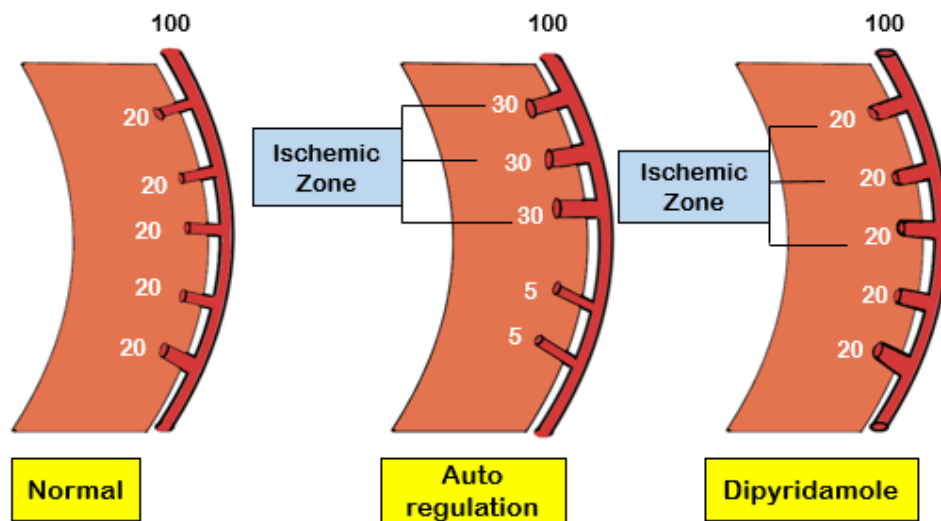
## Adverse effects

- Headache
- Flushing
- Dizziness

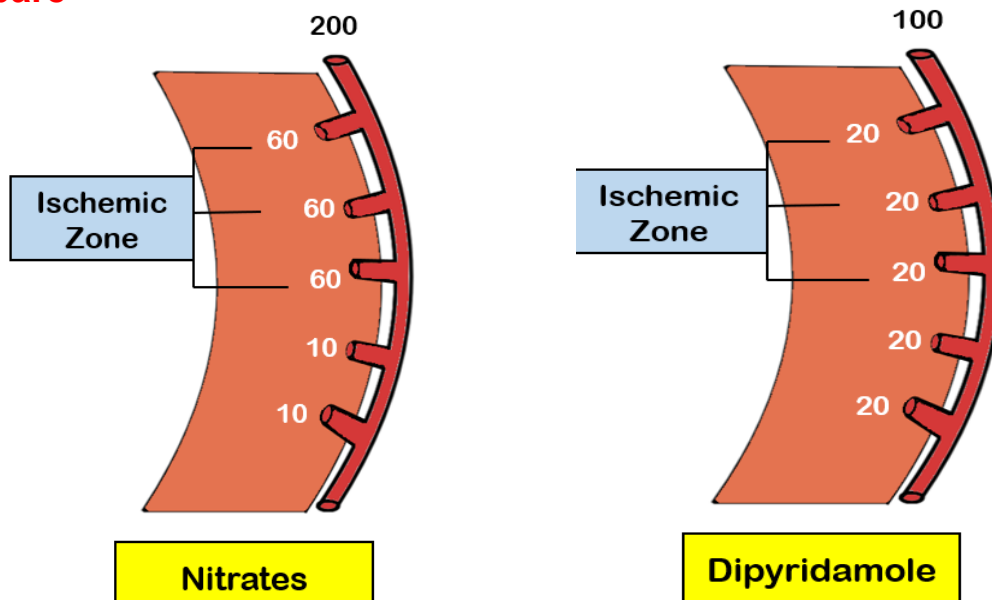
# DIPYRIDAMOLE

## MOA





## Compare



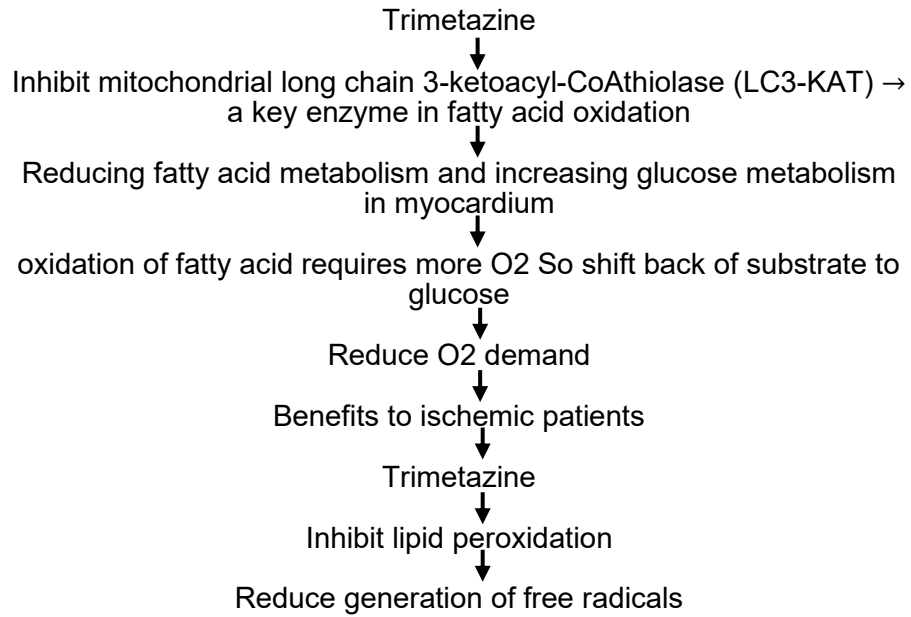
## PFOX INHIBITOR

### Drugs

- Trimetazine

### MOA

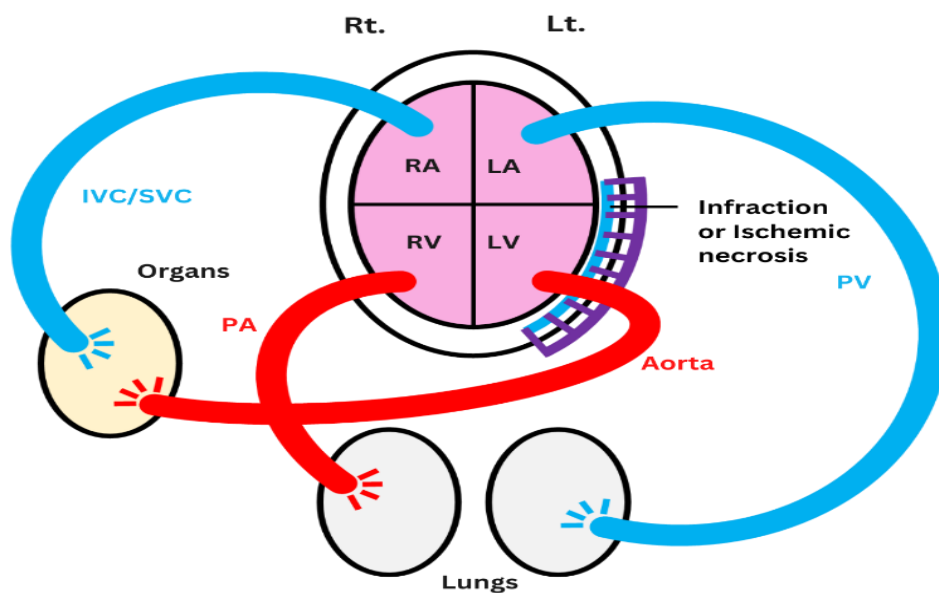
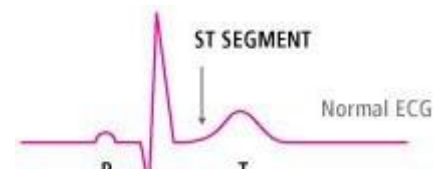
During ischemia  
 ↓  
 Heart utilizes fatty acids as energy sources.  
 (Fatty acids are not very efficient fuel as they require more ATPs for oxidation than required by glucose)



## CORONARY SYNDROMES

### Coronary Syndromes

1. Unstable angina (UA)
2. Non ST segment elevation myocardial infarction (NSTEMI)
3. ST segment elevation myocardial infarction (STEMI)



1. Unstable angina (UA)
  - Vascular obstruction is incomplete
  - Myocardial necrosis is absent
  - Biochemical markers of ischaemia do not appear in blood,
  - ST segment is not elevated in ECG
2. Non ST segment elevation myocardial infarction (NSTEMI)
  - Vascular obstruction is incomplete
  - Smaller area of myocardial necrosis
  - Biochemical markers appear in blood
  - ST segment is not elevated.
3. ST segment elevation myocardial infarction (STEMI)
  - Vascular obstruction is complete
  - Larger area of myocardium is necrosed,
  - Biochemical markers are prominent
  - ST segment in ECG is elevated.

### Remember

- UA and NSTEMI may progress to STEMI.

## DRUG THERAPY IN MYOCARDIAL INFARCTION

### 1. Pain, anxiety and apprehension

- 3 doses of GTN given 5 min apart
- If not relieved ,an opioid analgesic (morphine/pethidine) or diazepam is administered parenterally.

### 2. Oxygenation

- O2 inhalation
- Assisted respiration, if needed

### 3. Maintenance of blood volume, tissue perfusion and microcirculation

- Slow i.v. infusion of saline / low molecular weight dextran
- Avoid volume overload

### 4. Correction of acidosis

- Acidosis occurs due to lactic acid production
- Can be corrected by i.v. sod. bicarbonate infusion.

### 5. Prevention and treatment of arrhythmias

- Prophylactic i.v. infusion of a  $\beta$  blocker (unless contraindicated) as soon as the MI patient is seen
- Its continuation orally for a few days has been shown to reduce the incidence of arrhythmias and mortality.
- Tachyarrhythmias may be treated with i.v. lidocaine, procainamide or amiodarone

### 6. Pump failure

- Objective is to increase C.O. and/or decrease filling pressure without unduly increasing cardiac work or lowering BP.

- (a) **Furosemide:** indicated if pulmonary wedge pressure is > 20 mm Hg. It decreases cardiac preload.
- (b) **Vasodilators:** venous or combined dilator is selected according to the monitored haemodynamic parameters. Drugs like GTN (i.v.), or nitroprusside have been mainly used.
- (c) **Inotropic agents:** dopamine or dobutamine i.v. infusion (rarely digoxin if AF present) may be needed to augment the pumping action of heart and tide over the crisis

## 7. Prevention of thrombus extension, embolism, venous thrombosis

- **Aspirin (162–325 mg)** → given for chewing and swallowing as soon as MI is suspected
- **Anticoagulants (heparin followed by oral anticoagulants)** → used primarily to prevent deep vein thrombosis (increased risk due to bed rest) and pulmonary/ systemic arterial embolism.

## 8. Thrombolysis and reperfusion

- **Fibrinolytic agents, i.e. plasminogen activators** → streptokinase/ urokinase/alteplase to achieve reperfusion of the infarcted area
- Unless thrombolysis can be started within 1–2 hours of MI symptom onset, primary percutaneous coronary intervention (PCI) with stenting is now the preferred revascularization procedure

## 9. Prevention of remodeling and subsequent CHF

- **ACE inhibitors/ARBs** → proven efficacy and afford long-term survival benefit

## 10. Prevention of future attacks

- (a) **Platelet inhibitors** → aspirin or clopidogrel given on long-term basis are routinely prescribed
  - (b) **Control of hyperlipidaemia** → dietary substitution with unsaturated fats, hypolipidemic drugs especially statins
  - (c) **β blockers** → reduce risk of reinfarction, CHF and mortality.
- All patients not having any contraindication are put on a β blocker for at least 2 years.

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# ANTIHYPERTENSIVE DRUGS

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## Introduction

- Drugs used to lower BP in hypertension

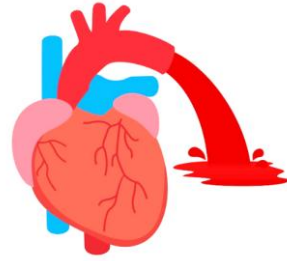


## Hypertension

- Sustained increase in blood pressure
- BP has 2 components → Systolic and Diastolic
- Very common disorder, particularly past middle age.
- It is not a disease in itself, but is an important risk factor for cardiovascular mortality and morbidity.



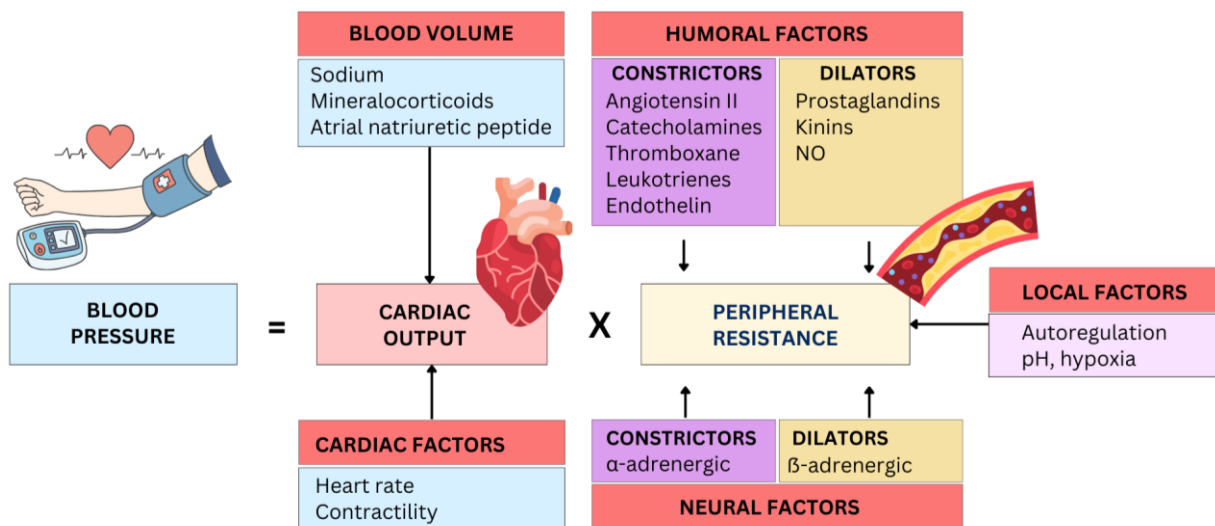
- $BP = CO \times PR$ 
  - SBP → determined by cardiac output



- DBP → determined by blood vessel status



## Blood Pressure Regulation



## Types

1. **Essential hypertension** → RAS is overactive
2. **Secondary hypertension** → Secondary to other disease processes → Renal, Endocrine, Cardiovascular, Neurogenic

|                        | Systolic<br>mm Hg |            | Diastolic<br>mm Hg |
|------------------------|-------------------|------------|--------------------|
| <b>Normal</b>          | <120              | <b>and</b> | <80                |
| <b>Prehypertension</b> | 120 - 139         | <b>or</b>  | 80-89              |
| <b>Stage I</b>         | 140- 159          | <b>or</b>  | 90-99              |
| <b>Stage II</b>        | ≥160              | <b>or</b>  | ≥100               |

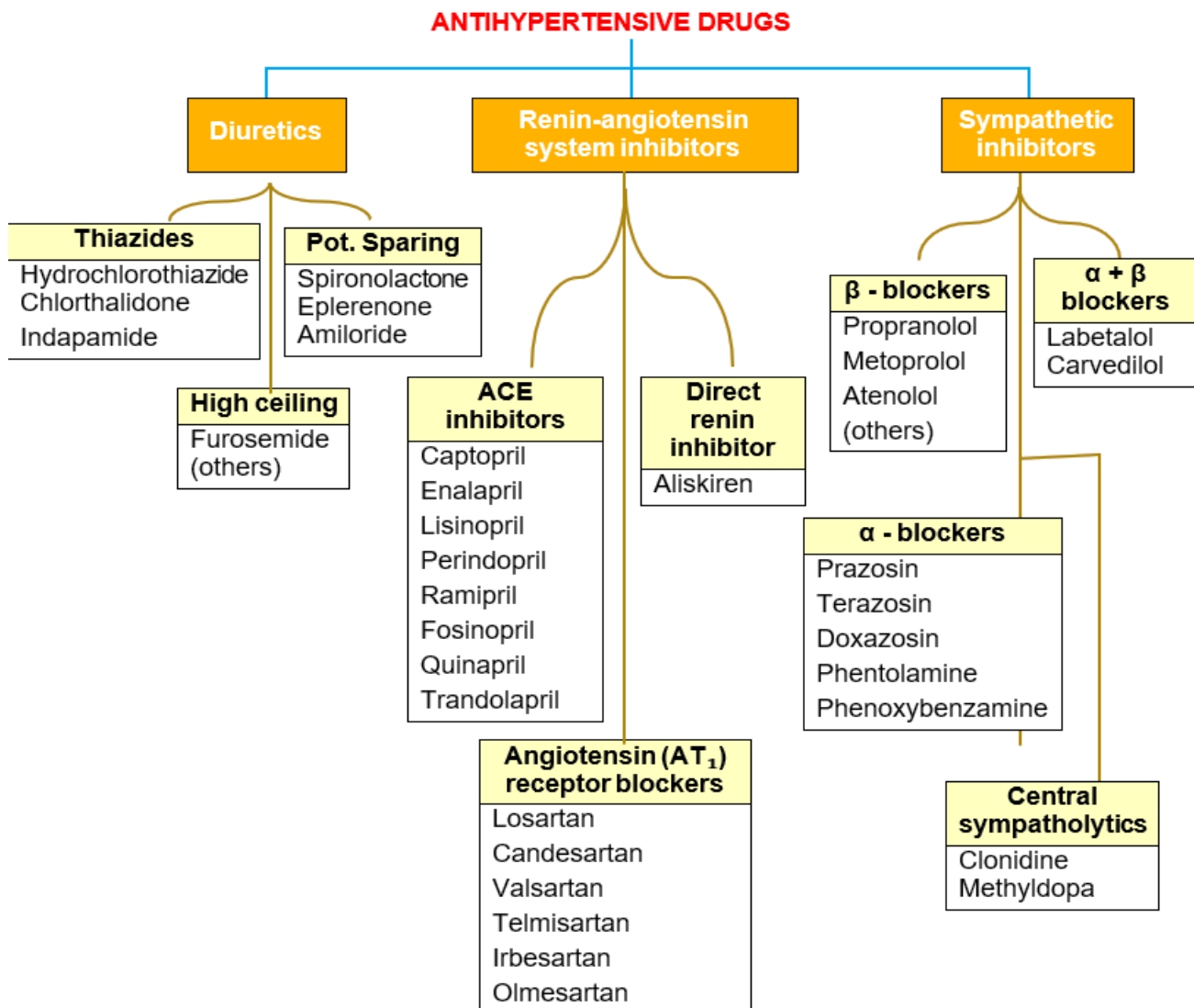
- For practical purposes 'hypertension' could be that level of BP at or above which long-term antihypertensive treatment will reduce cardiovascular mortality.

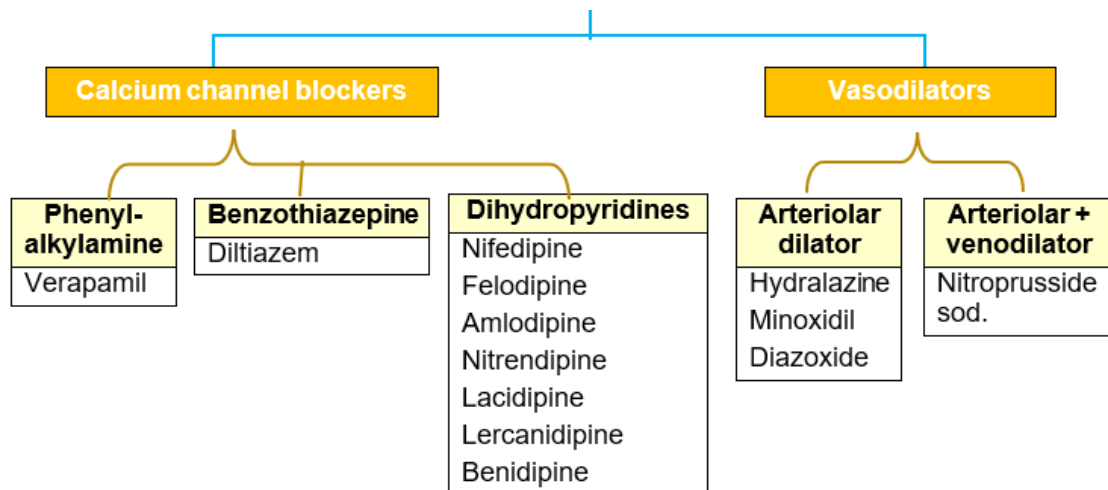
- JNC 7 (2003) and WHO-ISH guidelines (2003) have defined it to be 140 mm Hg systolic and 90 mm Hg diastolic

## ANTIHYPERTENSIVE DRUGS

### Classification (ABCDV)

- RAS inhibitors (ACE inhibitors, ARBs)
- Sympathetic inhibitors ( $\alpha$  – blockers,  $\beta$  – blockers, Central sympatholytics)
- Calcium channel blockers (CCBs)
- Diuretics
- Vasodilators





## DIURETICS

### Classification (ABCDV)

|                     | Diuretics |              |                   |
|---------------------|-----------|--------------|-------------------|
|                     | Thiazides | High ceiling | Potassium sparing |
| Drugs               |           |              |                   |
| MOA                 |           |              |                   |
| Use in hypertension |           |              |                   |
| Adverse effect      |           |              |                   |
| Preferred in        |           |              |                   |
| Avoided in          |           |              |                   |

## THIAZIDES

### Drugs

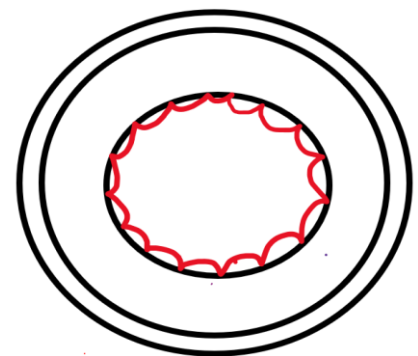
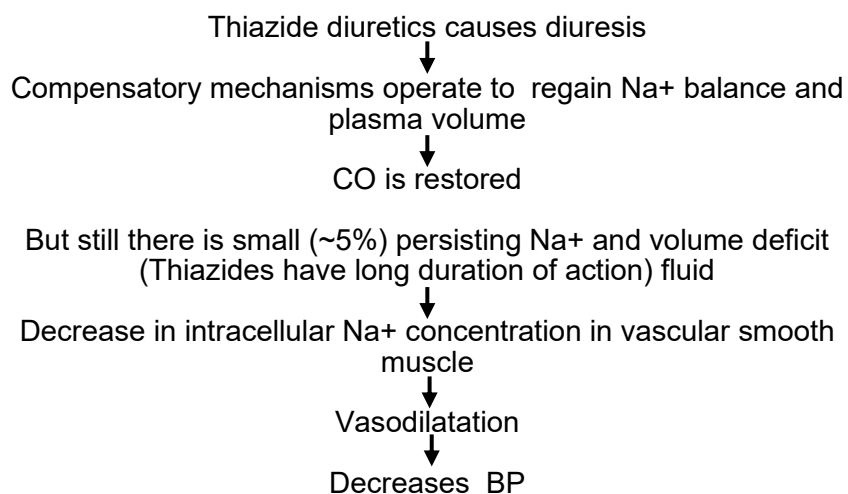
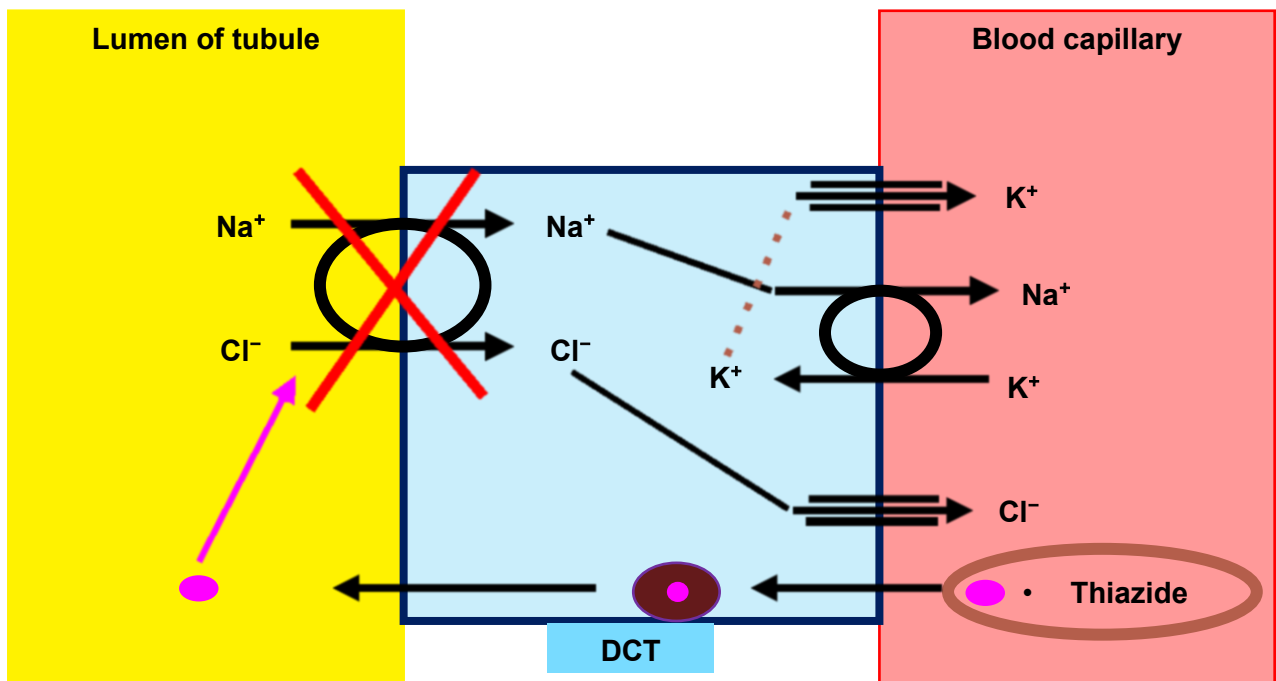
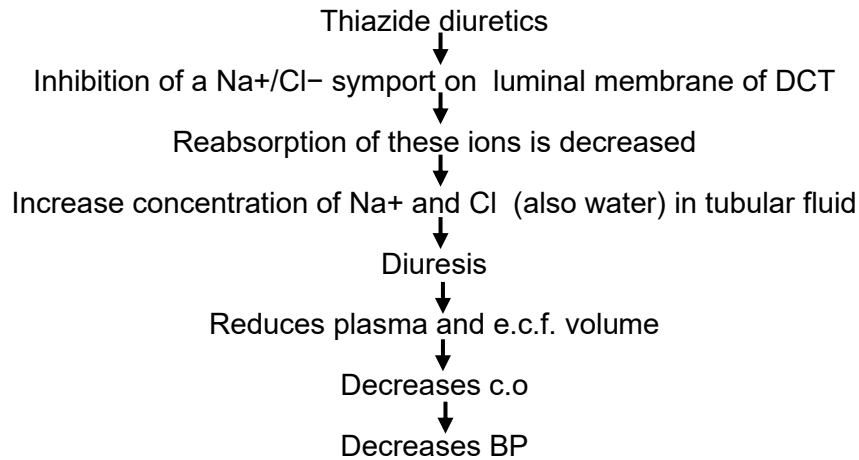
- Hydrochlorothiazide
- Chlorthalidone
- Indapamide

### MOA

- **Site of Action** → Thiazide diuretics acts on distal convoluted tubule (DCT)



- Thiazide diuretics causes fall in BP by 2 MOA →
  - Reduces plasma and Decreases c.o
  - Vasodilatation



## Remember

- Similar effects are produced by salt restriction
- Antihypertensive action of diuretics is lost when salt intake is high.

Use in hypertension

- Diuretic of choice for uncomplicated hypertension → first line antihypertensive drugs.
- Thiazides are mild antihypertensives → average fall in mean arterial pressure is ~10 mm Hg.
- They potentiate all other antihypertensives (except DHPs)
- They prevent development of tolerance to other antihypertensive drugs by not allowing expansion of plasma volume.
- Thus, in combination, they are useful in any grade of hypertension.

## Advantages to other antihypertensives

1. Once a day dosing and flat dose-response curve permitting simple standardized regimens.
2. No fluid retention
3. No tolerance
4. Low incidence of postural hypotension and relative freedom from side effects, especially CNS (compared to sympatholytics)
5. Lessened risk of hip fracture in the elderly due to hypocalciuric action of thiazides (as compared to furosemide)
6. Low cost

## Adverse effects

### Hypo PMNH

1. Potassium
2. Mg
3. Na
4. H<sub>2</sub>O

### Hyper GLUC

5. Glycemia
6. Lipidemia
7. Uricemia (Gout)
8. Calcium

9. Not safe in pregnancy (all diuretics)
10. Sulphonamide hypersensitivity
11. Renal insufficiency

## Preferred in

- Elderly patients
- Isolated systolic hypertension (ISH)

## Avoided in

- Diabetes
- Hyperlipidemia

# HIGH CEILING DIURETICS

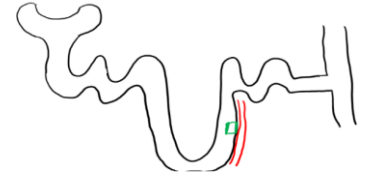
## Drugs

### High ceiling

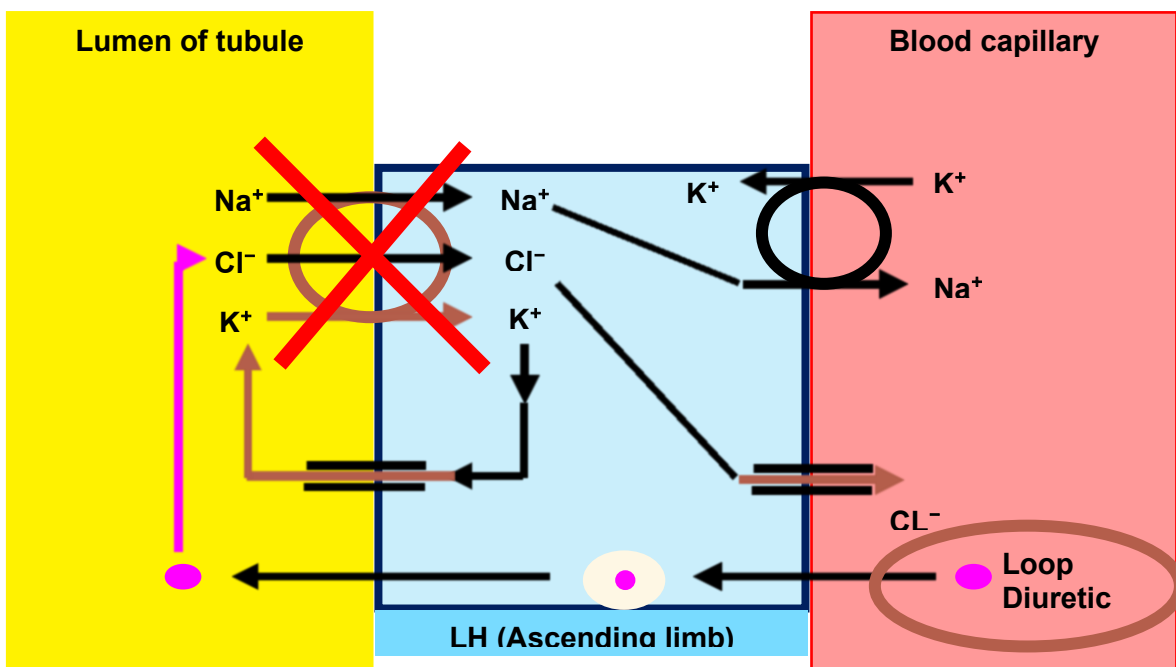
- Furosemide
- Bumetanide
- Torsemide

## MOA

- Site of Action** → Loop diuretics acts on ascending limb of loop of Henle



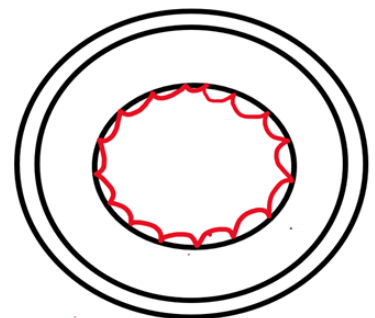
Loop diuretics  
 ↓  
 Enter tubular lumen via proximal tubular secretion (organic acid transport)  
 ↓  
 Inhibit cotransport of  $\text{Na}^+/\text{K}^+/2\text{Cl}^-$  in luminal membrane  
 ↓  
 Reabsorption of these ions is decreased  
 ↓  
 Increase concentration of  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cl}^-$  (also water) in tubular fluid  
 ↓  
 Reduces plasma and e.c.f. volume  
 ↓  
 Decreases c.o.  
 ↓  
 Decreases BP



## Remember

- Here fall in BP is entirely dependent on reduction in plasma volume and c.o.
- Vasodilatation does not occur in High ceiling diuretics because of their brief duration of action.

High ceiling diuretics  
 ↓  
 Brief duration of action  
 ↓  
 $\text{Na}^+$  deficient state in vascular smooth muscle may not be maintained round-the-clock  
 ↓  
 So there is compensatory increase in  $\text{Na}^+$  balance  
 ↓  
 So no vasodilatation fluid  
 ↓  
 Reduces plasma and e.c.f. volume  
 ↓  
 No fall in BP by this mechanism



## Use in hypertension

- Furosemide is a strong diuretic
- But the antihypertensive efficacy does not parallel diuretic potency.
- Furosemide is a weaker antihypertensive than thiazides
- They are indicated in hypertension only when it is complicated by:
  - (a) Chronic renal failure: thiazides are ineffective, both as diuretic and as antihypertensive.
  - (b) Coexisting refractory CHF.
  - (c) Resistance to combination regimens containing a thiazide

## Adverse effects

### Hypo PMNHC

1. **P**otassium
2. **M**g
3. **N**a
4. **H**<sub>2</sub>O
5. **C**alcium

### Hyper GLU

6. **G**lycemia
7. **L**ipidemia
8. **U**ricemia (Gout)

9. Not safe in pregnancy (all diuretics)
10. Sulphonamide hypersensitivity
11. Ototoxicity- hearing loss

## POTASSIUM SPARING DIURETICS

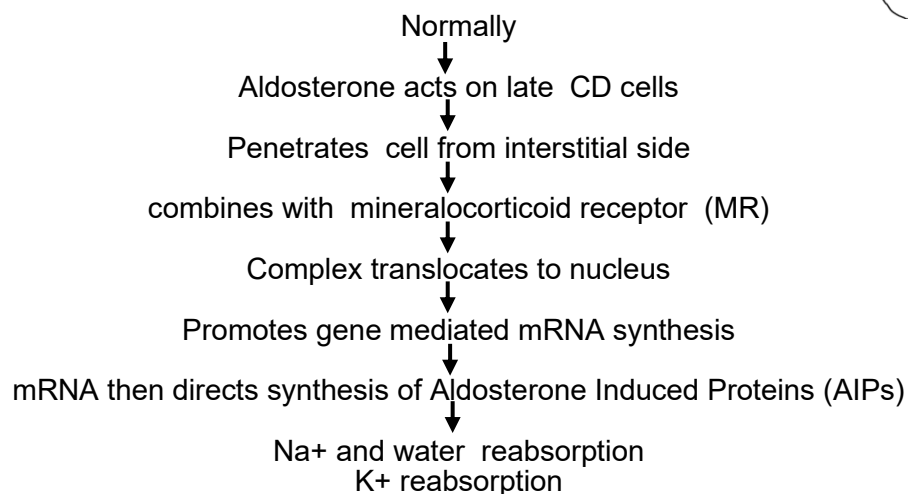
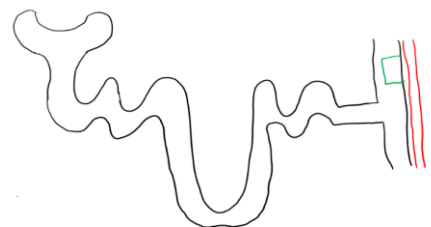
### Drugs

#### Pot. Sparing

- Spironolactone
- Eplerenone
- Amiloride

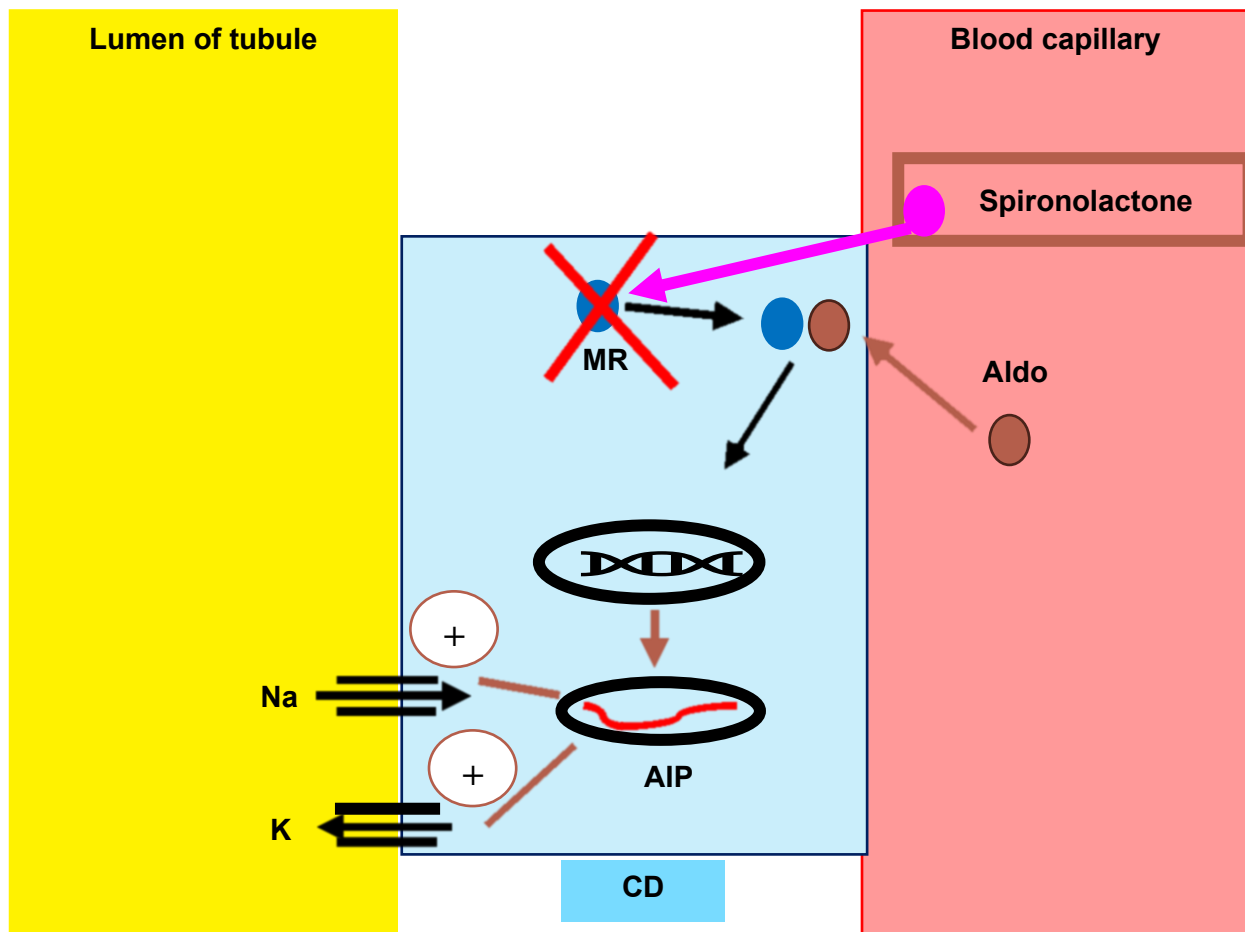
### MOA

**Site of Action** → Potassium sparing diuretics acts on collecting ducts





Spironolactone  
 ↓  
 Combines with mineralocorticoid receptor on interstitial side of CD cell  
 ↓  
 Inhibits formation of AIPs  
 ↓  
 Antagonises effects of Aldosterone  
 ↓  
 Increases Na<sup>+</sup> and water excretion → Diuresis  
 Decreases K<sup>+</sup> excretion → Hyperkalemia



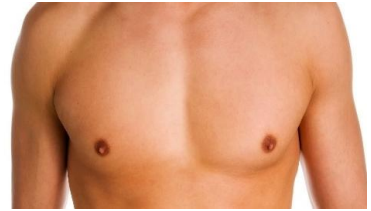
## Use in hypertension

- Used only in conjunction with a thiazide diuretic
  1. To prevent K<sup>+</sup> loss
  2. To augment antihypertensive action
- Spironolactone is not favoured because of its hormonal side effects (gynaecomastia, impotence, menstrual irregularities).
- This problem has been offset in the newer aldosterone antagonist Eplerenone □ increasingly used.

## Adverse Effects

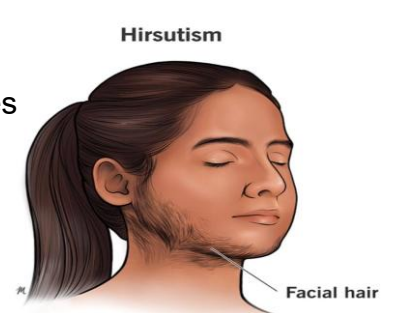
### 1. Hyperkalemia risk

- In CRF patients
- Patients taking ACEI (Enalapril) or ARB (Losartan)
- KCl supplement



### 2. Antiandrogen

- Males → Gynaecomastia, Impotence
- Female → Hirsutism, menstrual irregularities



## Preferred in

- Used only in conjunction with a thiazide diuretic to prevent K<sup>+</sup> loss

## Avoided in

### Hyperkalemia risk →

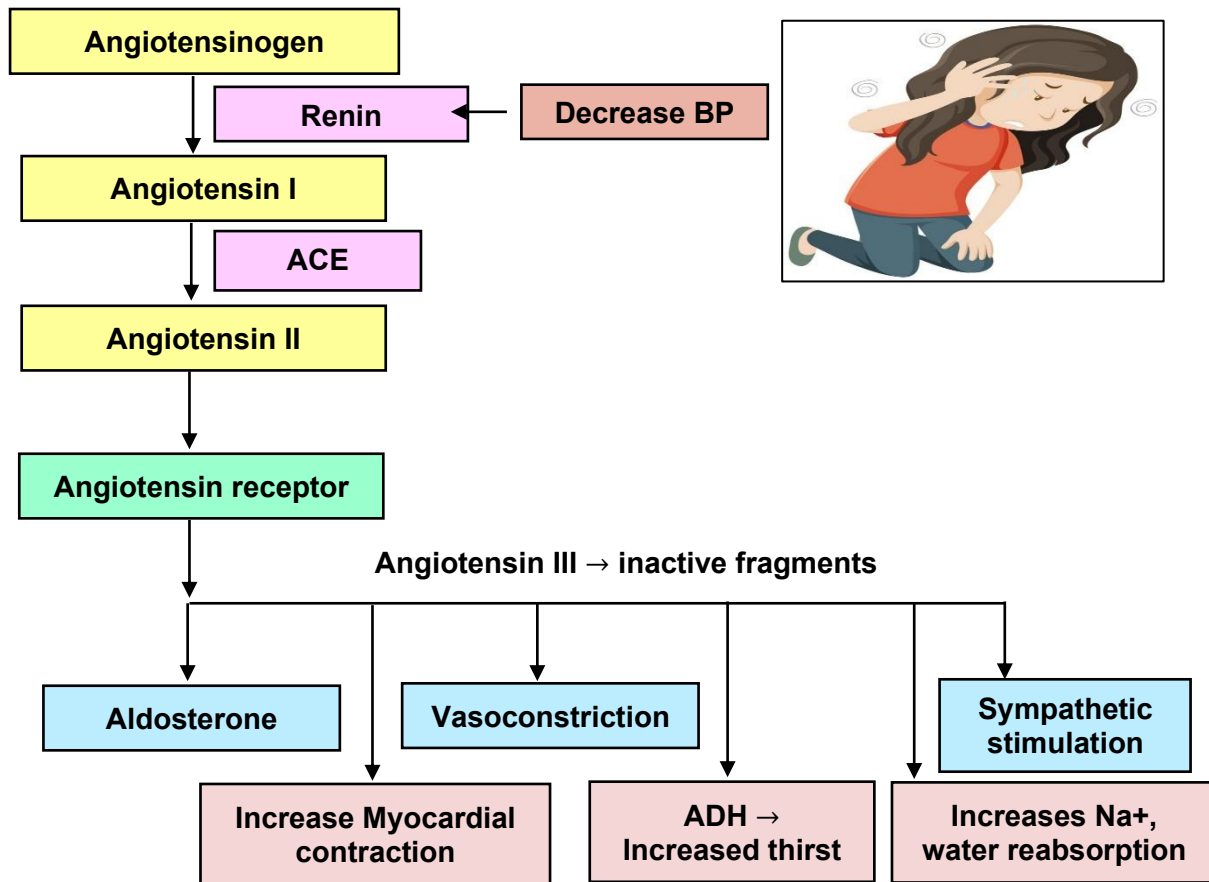
- In CRF patients
- Patients taking ACEI (Enalapril) or ARB (Losartan)

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## RAS INHIBITORS

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|                     | RAS inhibitors |      |                         |
|---------------------|----------------|------|-------------------------|
|                     | ACE inhibitors | ARBs | Direct Renin Inhibitors |
| Drugs               |                |      |                         |
| MOA                 |                |      |                         |
| Use in hypertension |                |      |                         |
| Adverse effect      |                |      |                         |
| Preferred in        |                |      |                         |
| Avoided in          |                |      |                         |

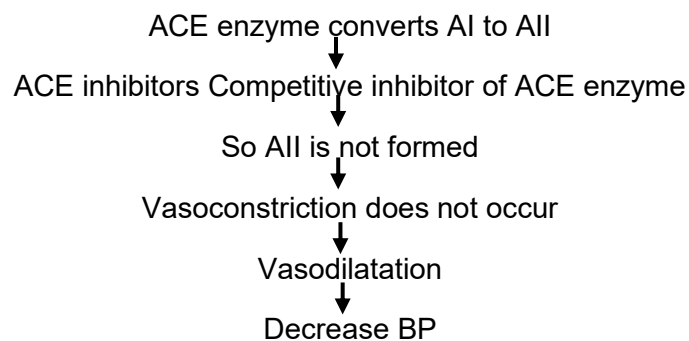


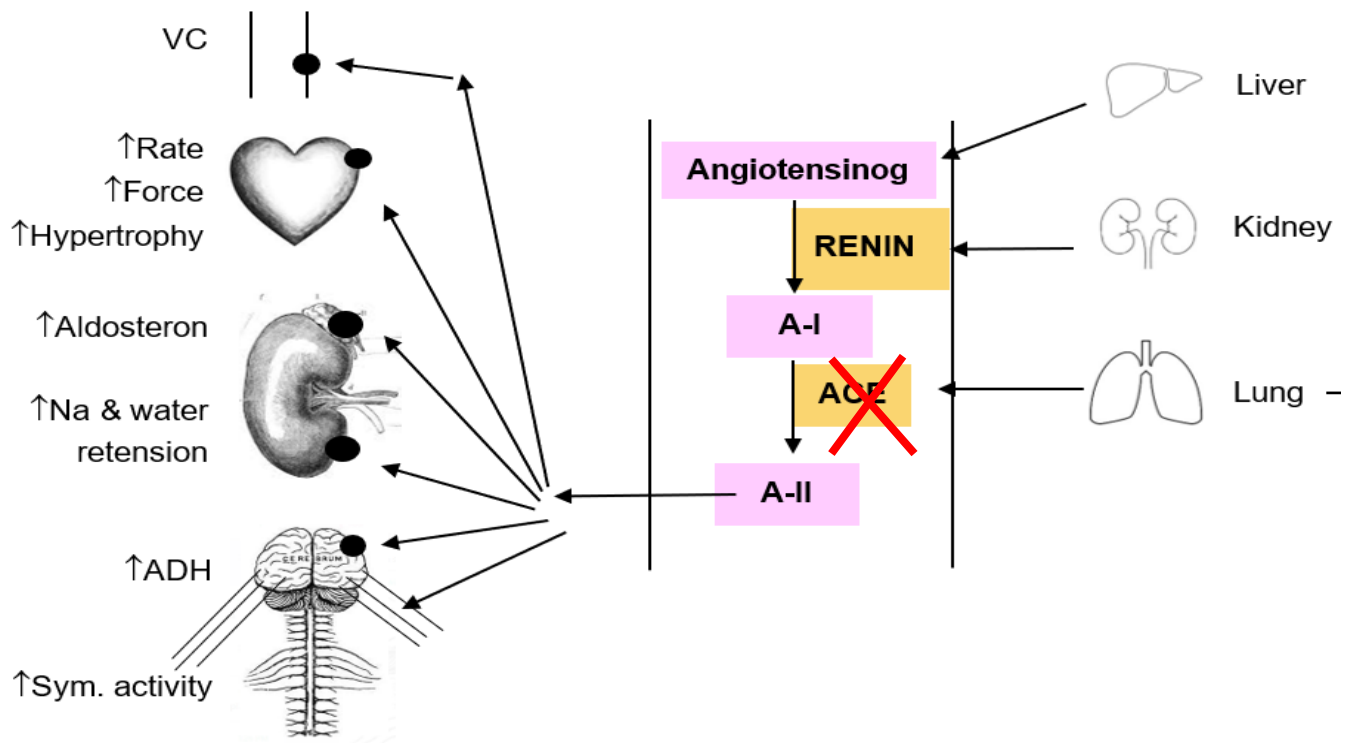
## ACE INHIBITORS

### Drugs

- Captopril (Prototype drug)
- Lisinopril
- Enalapril
- Perindopril
- Ramipril
- Fosinopril
- Quinapril
- Trandolapril

### MOA





## Use in hypertension

- ACE inhibitors are one of the first choice drugs in all grades of essential as well as renovascular hypertension (except those with bilateral renal artery stenosis)
- Used alone they control hypertension in ~50% patients, and addition of a diuretic/ $\beta$  blocker extends efficacy to ~90%
- More effective in younger (< 55 year) hypertensives than in the elderly

## Advantages over other antihypertensives

- No postural hypotension
- No electrolyte imbalance (no fatigue or weakness)
- Safe in asthmatics and diabetics
- Renal perfusion well maintained
- Reverse ventricular hypertrophy and increase in lumen size of vessel
- No hyperuraecemia
- No deleterious effect on plasma lipid profile
- No rebound hypertension
- Minimal worsening of quality of life – general wellbeing, sleep and work performance etc.

## Adverse effects

### CAPTOPRIL

|          |   |                                                         |
|----------|---|---------------------------------------------------------|
| <b>C</b> | - | <b>C</b> ough                                           |
| <b>A</b> | - | <b>A</b> ngioneurotic oedema                            |
| <b>P</b> | - | <b>P</b> roteinuria                                     |
| <b>T</b> | - | <b>T</b> aste disturbance/ Teratogenic in 1st trimester |
| <b>O</b> | - | <b>O</b> ther (fatigue, headache)                       |
| <b>P</b> | - | Potassium increased                                     |

- |          |   |                           |
|----------|---|---------------------------|
| <b>R</b> | - | <b>R</b> enal impairment  |
| <b>I</b> | - | <b>I</b> tch              |
| <b>L</b> | - | <b>L</b> ow BP (1st dose) |

### Preferred in

- Most appropriate antihypertensives in patients with
  1. Diabetes
  2. Asthmatics
  3. Gout
  4. Nephropathy (even nondiabetic)
  5. Left ventricular hypertrophy and CHF
  6. Angina and post MI cases

### Avoided in

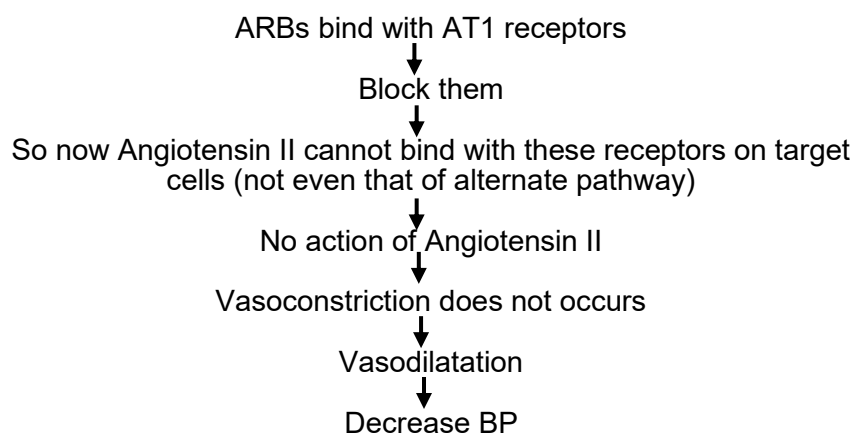
- ACE inhibitors not given along with potassium sparing diuretics because both causes hyperkalemia (So severe hyperkalemia)
- They can be combined with thiazides and loop diuretics ( because these diuretics causes hypokalemia)

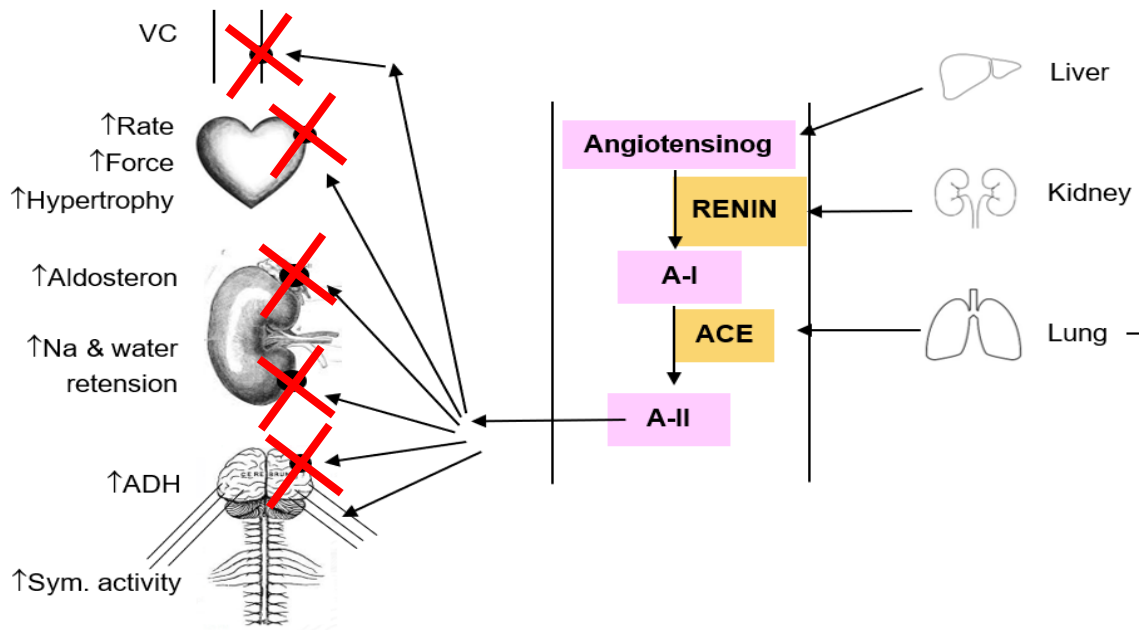
## ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

### Drugs

- Losartan (Prototype drug)
- Candesartan
- Valsartan
- Telmisartan
- Irbesartan
- Olmesartan

### MOA

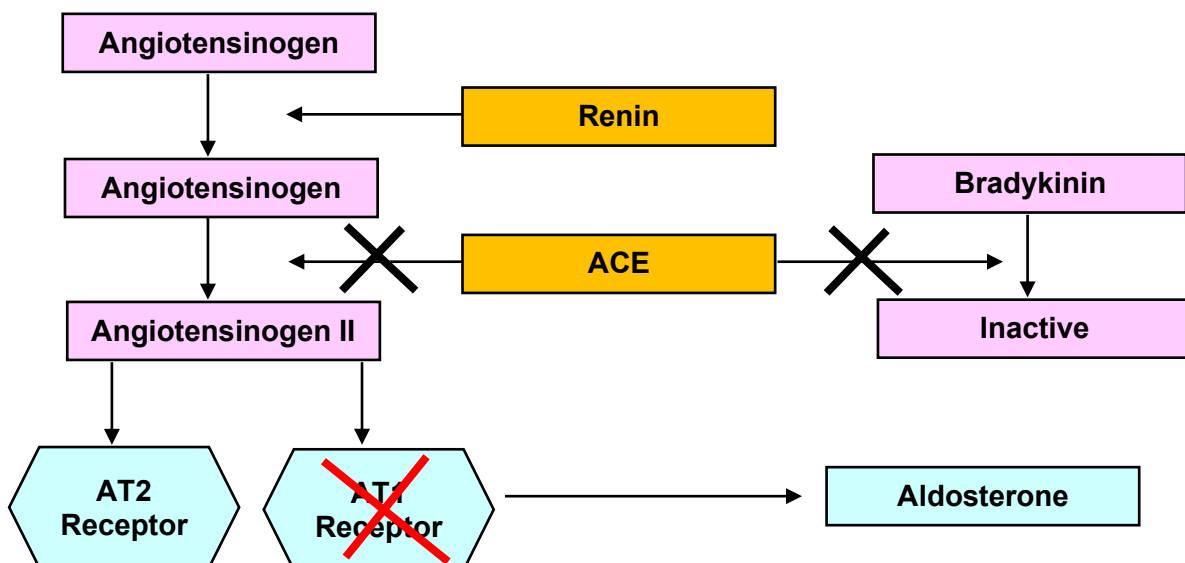




## Use in hypertension

- First choice drugs in all grades of essential as well as renovascular hypertension
- As effective antihypertensives as ACE inhibitors
- As antihypertensive, use of ARBs has outstripped that of ACE inhibitors because →  
Do not interfere with degradation of bradykinin and P substrate

↓  
No rise in level of bradykinin, substance P  
↓  
Cough, rashes and dysgeusia is absent (ACE inhibitor related)



## Adverse effects

1. Hypotension
2. Hyperkalemia
3. Teratogenic

## Preferred in

- Most appropriate antihypertensives in patients with
  1. Diabetes
  2. Asthmatics
  3. Gout
  4. Nephropathy (even nondiabetic)
  5. Left ventricular hypertrophy and CHF
  6. Angina and post MI cases

## Avoided in

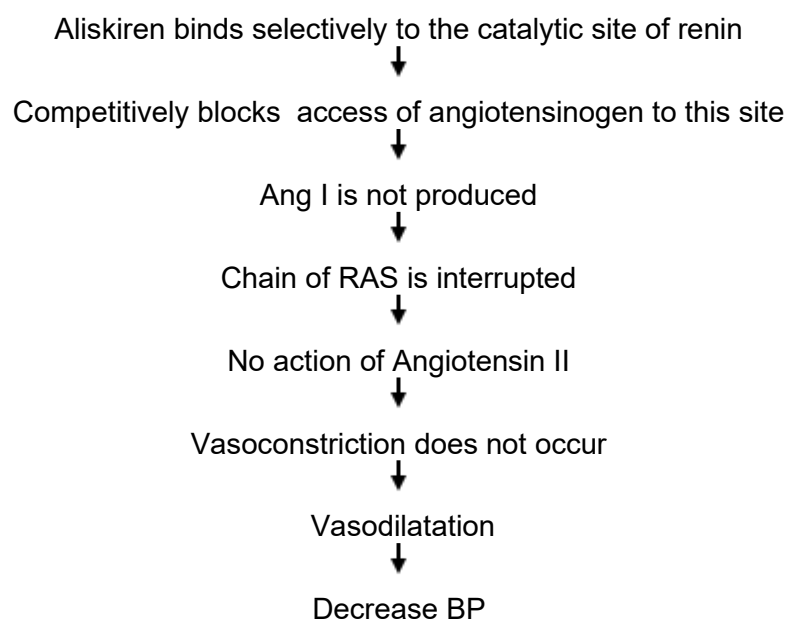
- ARBs not given along with potassium sparing diuretics because both causes hyperkalemia (So severe hyperkalemia)
- They can be combined with thiazides and loop diuretics ( because these diuretics causes hypokalemia)

# DIRECT RENIN INHIBITORS

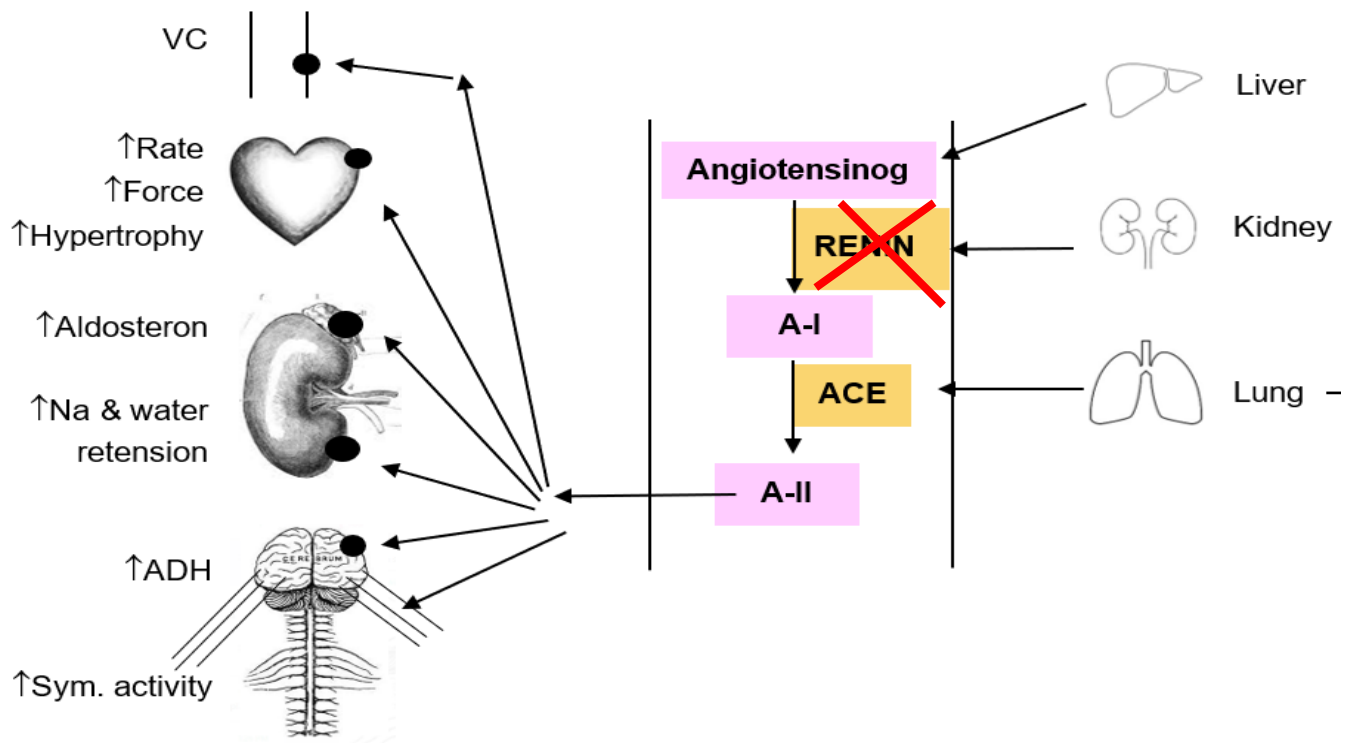
## Drugs

- Aliskiren
- Remikiren

## MOA







Use in hypertension

- Aliskiren is an equally effective antihypertensive as ACE inhibitors and ARBs, but experience with it so far is limited.
- Presently it is a second line antihypertensive which may be employed when the more established ACE inhibitors or ARBs cannot be used, or to supplement them.

### Adverse effects

1. Mild side effects → Dyspepsia, abdominal pain, loose motions, headache and dizziness
2. Acute hypotension
3. Hyperkalaemia

## CALCIUM CHANNEL BLOCKERS

|                     | CCBs |
|---------------------|------|
| Drugs               |      |
| MOA                 |      |
| Use in hypertension |      |
| Adverse effect      |      |
| Preferred in        |      |
| Avoided in          |      |

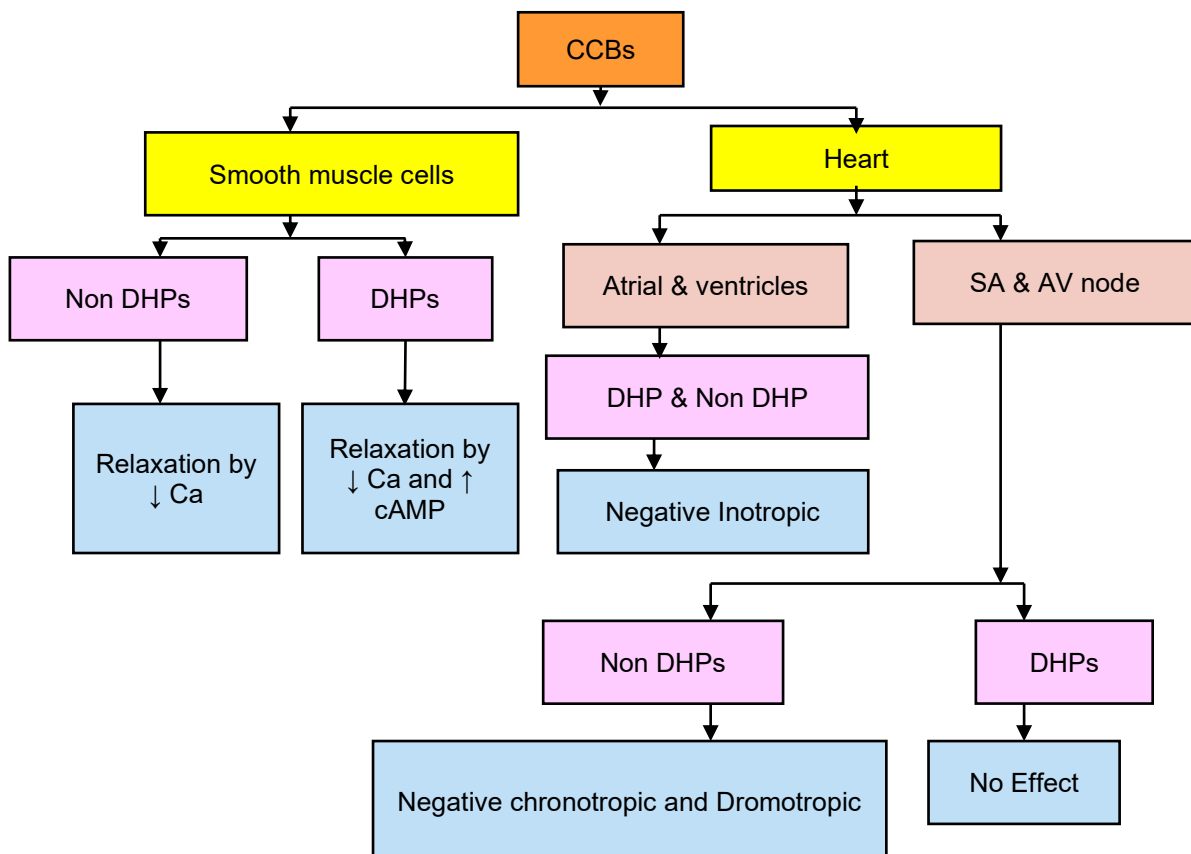
## Drugs

3 groups →

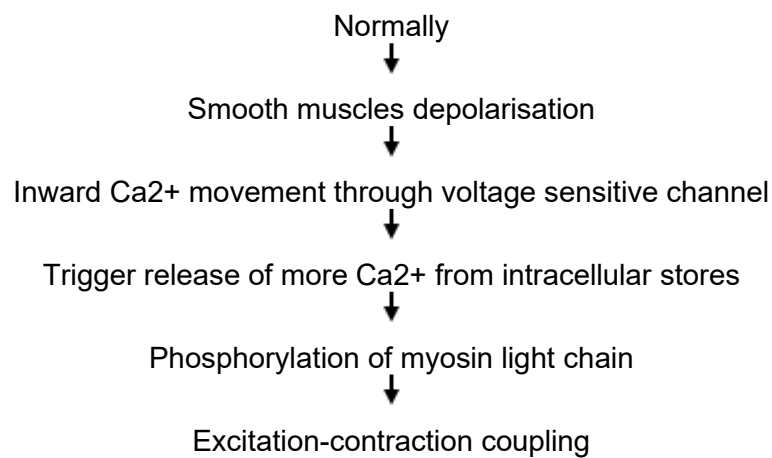
1. Phenylalkylamines (Verapamil) } Non DHPs
2. Benzothiazepine (Diltiazem) }
3. Dihydropyridines □ DHPs (nifedipine, Nitrendipine)

## MOA

1. **Smooth muscle (especially vascular)** → Relaxation
2. **Heart** → Negative chronotropic, inotropic and dromotropic

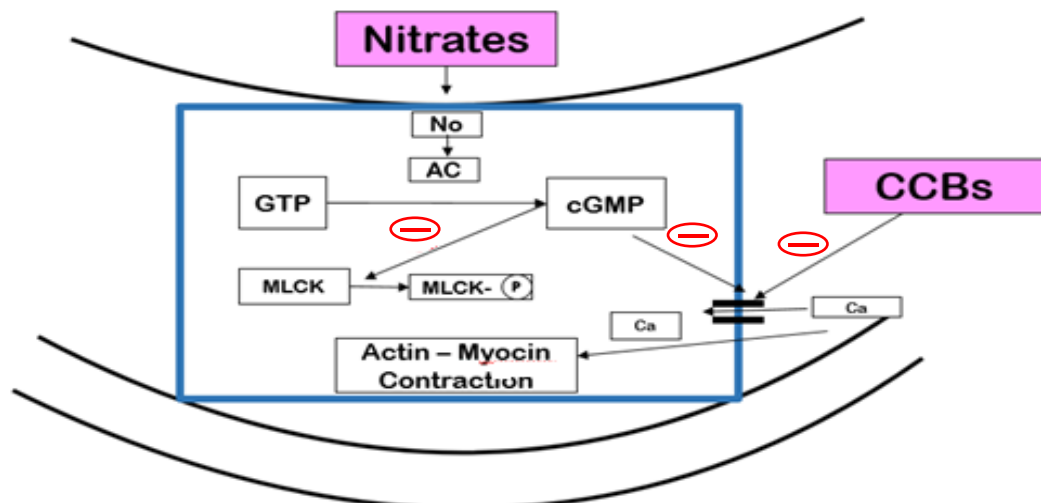
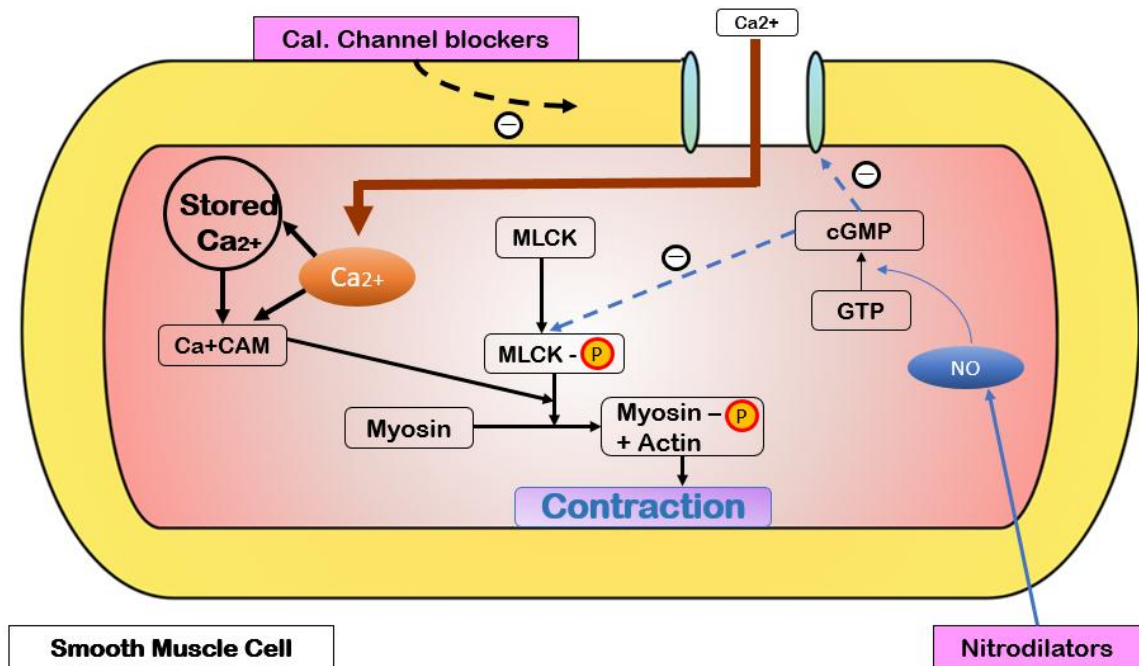


## 1. Smooth muscle



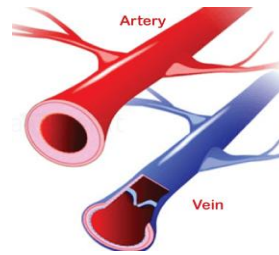
CCBs (all 3 classes)  
 ↓  
 Inhibit voltage sensitive channel  
 ↓  
 Decrease intracellular availability of  $\text{Ca}^{2+}$   
 ↓  
 No Excitation-contraction coupling  
 ↓  
 Relaxation (Vasodilatation)  
 ↓  
 Fall in BP

DHP (Nitrendipine)  
 ↓  
 Release NO from endothelium  
 ↓  
 Inhibit cAMP - phosphodiesterase  
 ↓  
 Raised smooth muscle cAMP  
 ↓  
 Relaxation (Vasodilatation)  
 (Additional mechanism)  
 ↓  
 Fall in BP  
 ↓  
 cause reflex tachycardia



## Remember

- Arterioles are relaxed more markedly than veins.



## Order of blockage

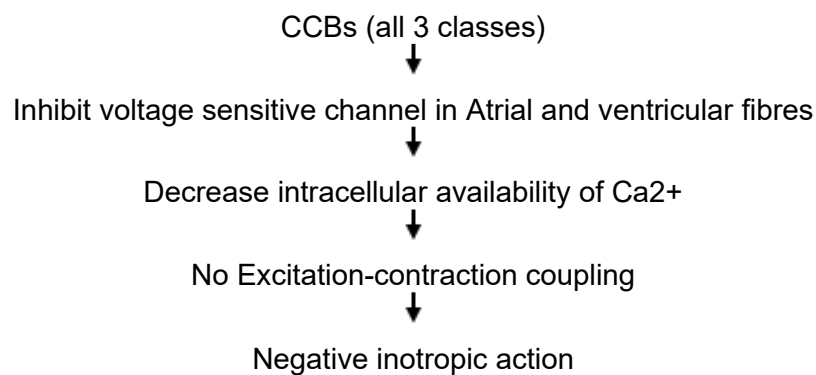
- DHPs > Phenylalkylamines > Benzothiazepine
- Nifedipine > verapamil > Diltiazem

## 2. Heart

### 2 MOA →

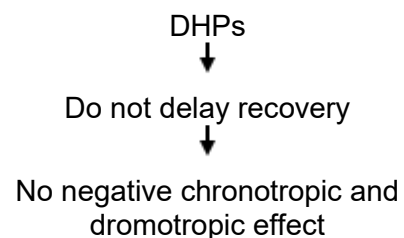
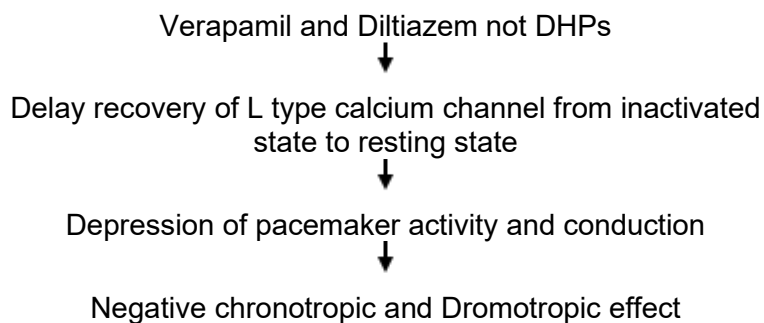
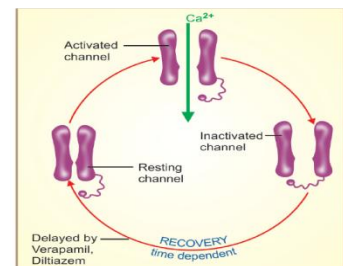
- Atrial and ventricular fibres
- SA and A-V nodes

### A) Atrial and ventricular fibres



### B) SA and A-V nodes

- Automaticity and conductivity of SA and A-V nodes cells appear to be dependent on the rate of recovery of the Ca<sup>2+</sup> channel.



## Use in hypertension

- Calcium channel blockers (CCBs) are also first line antihypertensive drugs.
- All 3 subgroups of CCBs, ie. dihydropyridines (DHPs, e.g. amlodipine), phenylalkylamine (verapamil) and benzothiazepine (diltiazem) are equally efficacious antihypertensives.
- DHPs (especially short-acting) also tend to increase HR and c.o. by invoking reflex sympathetic stimulation

## Advantages over other Antihypertensives

- Their action is independent of patient's renin status
- Do not compromise haemodynamics: no impairment of physical work capacity.
- No sedation or other CNS effects; cerebral perfusion is maintained.
- Not contraindicated in asthma, angina (especially variant) and PVD patients: may benefit these conditions.
- Do not impair renal perfusion.
- Do not affect male sexual function.
- No deleterious effect on plasma lipid profile, uric acid level and electrolyte balance.
- No adverse foetal effects; can be used during pregnancy (but can weaken uterine contractions during labour).

## Preferred in

1. Long-acting DHPs are next to ACE inhibitors in reducing albuminuria and slowing disease progression in diabetic nephropathy.
2. Most useful antihypertensives in cyclosporine induced hypertension
3. In renal transplant recipients.
4. Use of rapid acting oral nifedipine for urgent BP lowering in hypertensive emergencies is outmoded.

## Avoided in

1. Negative inotropic/dromotropic action of verapamil/diltiazem may worsen CHF and cardiac conduction defects (DHPs are less likely to do so).
2. By their smooth muscle relaxant action □ DHPs can worsen gastroesophageal reflux.
3. CCBs (especially DHPs) may accentuate bladder voiding difficulty in elderly males.

## SYMPETHTIC INHIBITORS

|                     | Sympathetic inhibitors |                    |                        |
|---------------------|------------------------|--------------------|------------------------|
|                     | $\alpha$ - blockers    | $\beta$ - blockers | Central sympatholytics |
| Drugs               |                        |                    |                        |
| MOA                 |                        |                    |                        |
| Use in hypertension |                        |                    |                        |
| Adverse effect      |                        |                    |                        |
| Preferred in        |                        |                    |                        |
| Avoided in          |                        |                    |                        |

### $\alpha$ – BLOCKERS

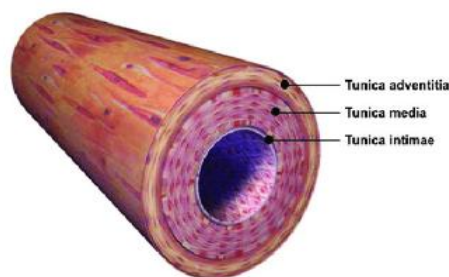
#### Drugs

| $\alpha$ - blockers                                                    |
|------------------------------------------------------------------------|
| Prazosin<br>Terazosin<br>Doxazosin<br>Phentolamine<br>Phenoxybenzamine |

#### MOA

Blockade of vasoconstrictor  $\alpha_1$  (also  $\alpha_2$ ) receptors

↓  
 Vasodilatation  
 ↓  
 Fall in BP  
 ↓  
 Hypotension



- Reflex tachycardia occurs due to fall in mean BP
- Only selective for  $\alpha_1$  receptors (prazosin-like) are used→ they decreases BP by vasodilatation
- $\alpha$  blockers other than those selective for  $\alpha_1$  are not used because reflex tachycardia, postural hypotension, impotence, nasal blockage and other side effects produced

## Use in hypertension

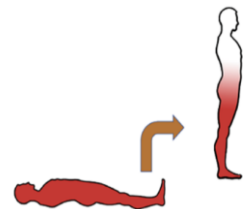
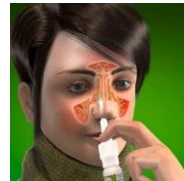
- Prazosin is a moderately potent antihypertensive, but is not used as a first line drug because fluid retention and tolerance gradually develops
- May be added to a diuretic +  $\beta$  blocker in those not achieving target BP.

## Advantages over other antihypertensives

- Does not impair carbohydrate metabolism; suitable for diabetics
- Has a small but favourable effect on lipid profile: lowers LDL cholesterol and triglycerides, increases HDL.
- Affords symptomatic improvement in coexisting benign prostatic hypertrophy.
- Affords symptomatic improvement in coexisting PVD

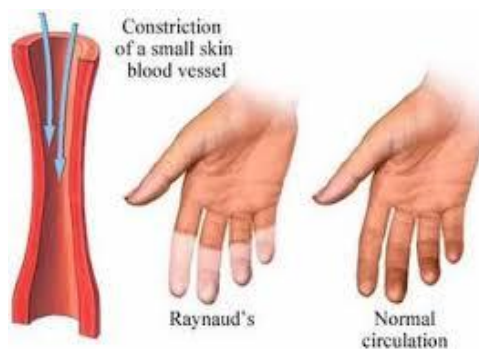
## Adverse effect

1. Postural hypotension → seen with first few doses (first dose effect)
2. Nasal blockade
3. Palpitation
4. Loose motions
5. Inhibition of ejaculation and impotence.



## Preferred in

1. DOC for hypertension in patients with BPH
2. PVD



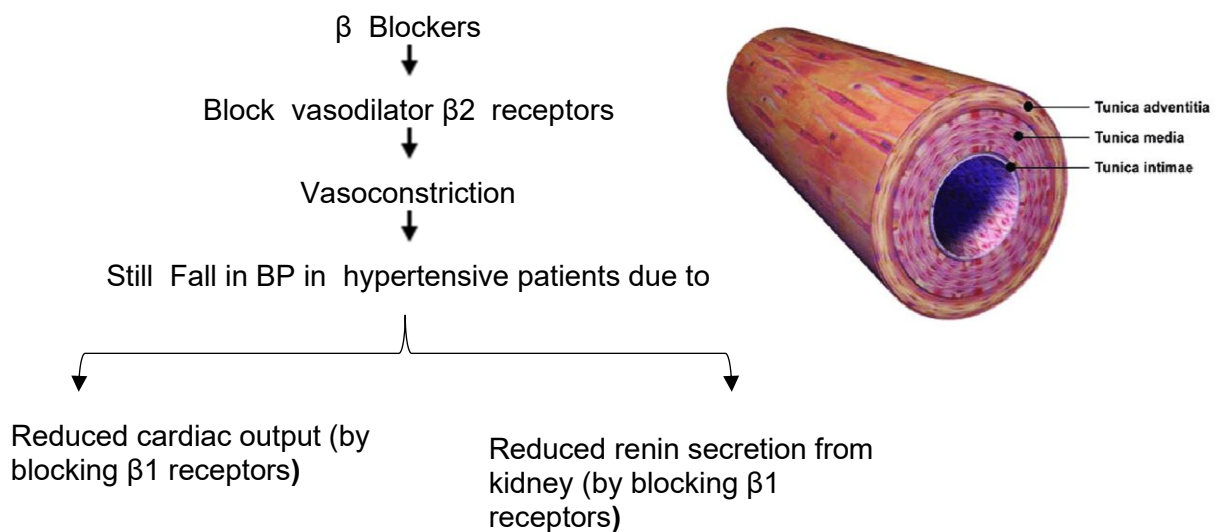
## $\beta$ – BLOCKERS

### Drugs

| $\beta$ - blockers                              |
|-------------------------------------------------|
| Propranolol<br>Metoprolol<br>Atenolol<br>Others |



## MOA



## Use in hypertension

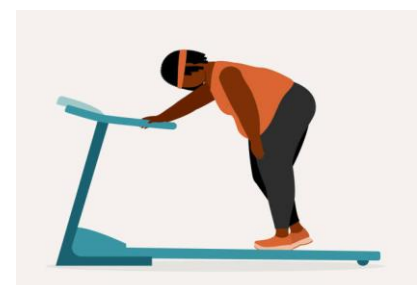
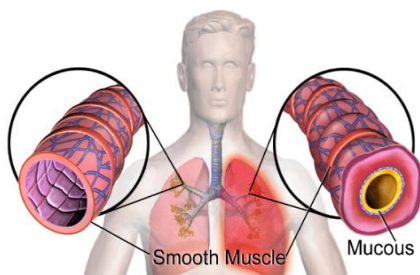
- Among the first choice drugs of hypertension
- Cardio selective B blockers like metoprolol and atenolol are preferred.

## Adverse Effects

1. Cold hands and feet, worsening of peripheral vascular disease
2. Bradycardia: resting HR may be reduced to 60/min or less. Patients of sick sinus are more prone to severe bradycardia.
3. Contraindicated in partial and complete heart block: arrest may occur
4. Worsens COPDs → can precipitate life-threatening attack of bronchial asthma: contraindicated in asthmatics
5. Carbohydrate tolerance may be impaired in prediabetics.
6. Plasma lipid profile is altered → total triglycerides and LDL-cholesterol tend to increase while HDL-cholesterol falls. This may enhance risk of coronary artery disease.
7. Tiredness and reduced exercise capacity → inhibition of glycogenolysis and lipolysis.



Bradycardia



## Advantages over other antihypertensives

1. Reflex vasoconstriction is preserved hence there is no postural hypotension and exercise-induced hypotension.

2. Additional advantages of reducing the load and survival in patients of angina, infarction and arrhythmia.
3. Reduction in anxiety and tremors improves working of a young tense person.

### Preferred in

- For relatively young non-obese hypertensives
- Those prone to psychological stress
- Those with ischaemic heart disease

### Avoided in

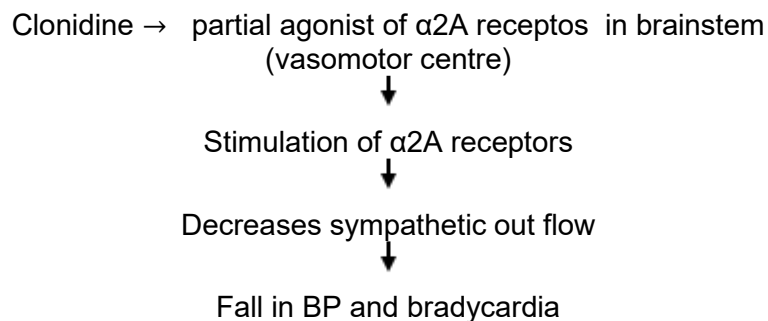
- Bradycardia, heart block
- Asthma
- PVD
- Impotency
- Hyperlipidemia, and metabolic disturbances
- Diabetics

## CENTRAL SYMPATHOLYTICS

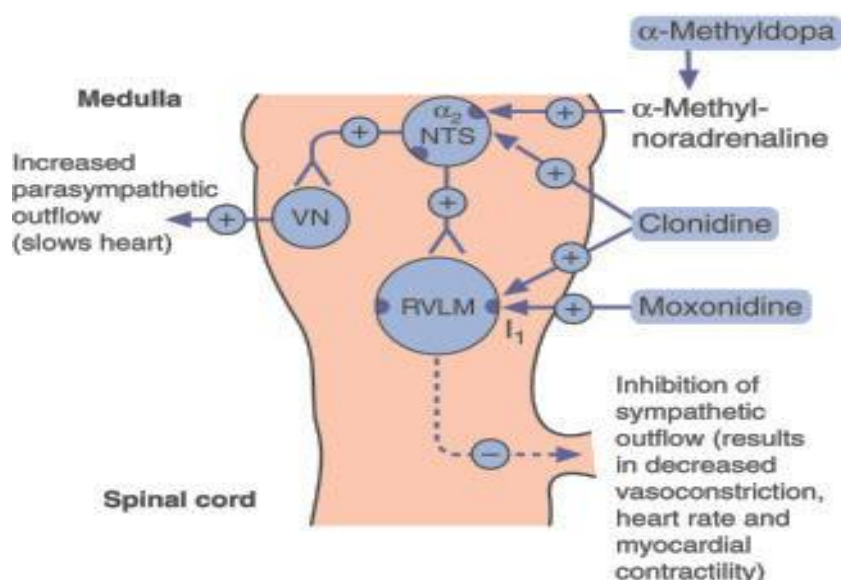
### Drugs

1. Clonidine
2. Methyldopa
3. Guanabenz
4. Guanfacine
5. Rilmenidine
6. Moxonidine
7. Reserpine

### Clonidine MOA



- Clonidine → also binds to a nonadrenergic receptor, imidazoline receptor, which may also mediate antihypertensive effect.



## Use in hypertension

- 3rd or 4th choice drug.

## Adverse effects

1. Decreases sympathetic out flow □ Sedation, mental depression, disturbed sleep; dryness of mouth, nose and eyes (secretion is decreased by central action), constipation (antisecretory effect on the intestines)
2. Impotence
3. Postural hypotension
4. When doses of clonidine are missed for 1–2 days □ Alarming rise in BP (rebound hypertension) with tachycardia, restlessness, anxiety, sweating, headache, nausea and vomiting

## VASODILATORS

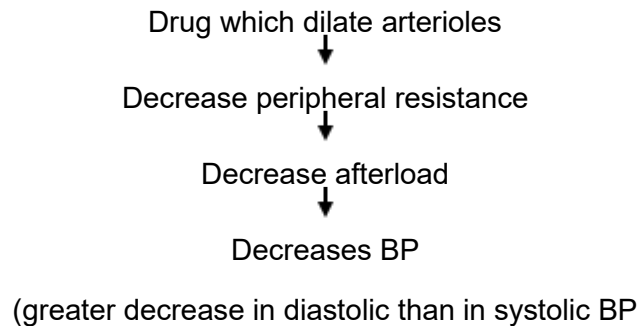
|                     | Vasodilator        |                          |
|---------------------|--------------------|--------------------------|
|                     | Arteriolar dilator | Arteriolar + venodilator |
| Drugs               |                    |                          |
| MOA                 |                    |                          |
| Use in hypertension |                    |                          |
| Adverse effect      |                    |                          |
| Preferred in        |                    |                          |
| Avoided in          |                    |                          |

## ARTERIOLEAR DILATOR

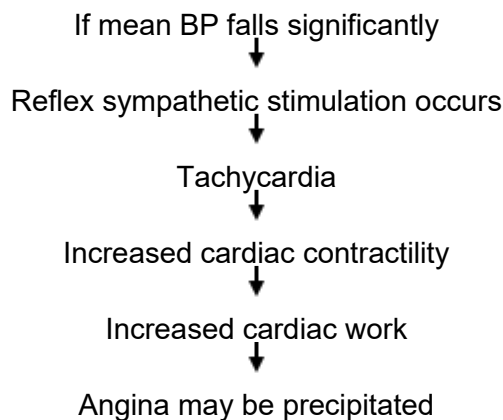
### Drugs

- Hydralazine
- Dihydralazine

## MOA



## Remember



## Use in hypertension

1. Hydralazine is now used as a second line alternative only in combination with a diuretic and/or  $\beta$  blocker for patients not achieving target BP with first line drugs.
2. It is one of the preferred antihypertensives during pregnancy, especially preeclampsia, because of safety record.
3. Parenterally, it is occasionally employed in hypertensive emergencies.

## Adverse effects

1. Facial flushing, conjunctival injection, throbbing headache, dizziness, palpitation, nasal stuffiness, fluid retention, edema, CHF.
2. Angina and MI → precipitated in patients with coronary artery disease.
3. Lupus erythematosus or rheumatoid arthritis like symptoms □ develop on prolonged use of doses above 100 mg/day

## Preferred in

- Antihypertensives during pregnancy, especially preeclampsia
- Hypertensive emergencies.

## Avoided in

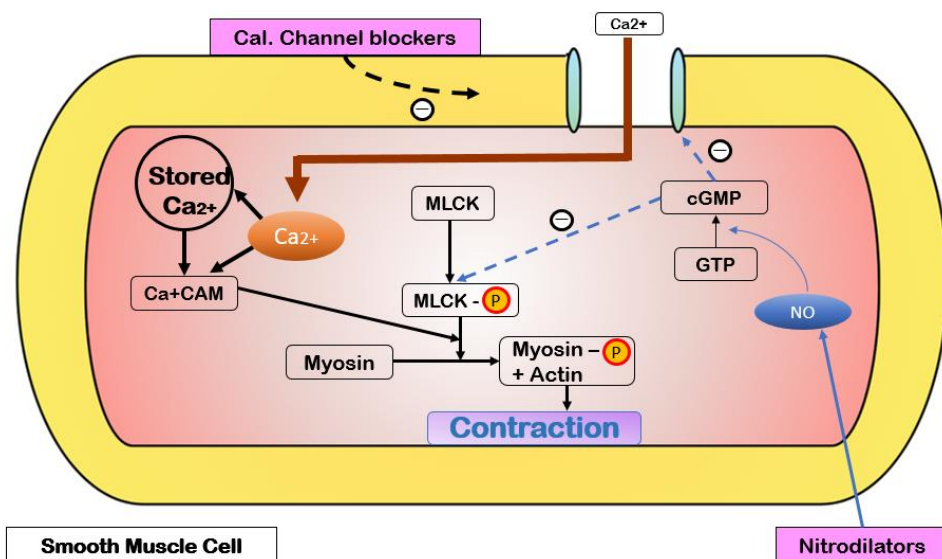
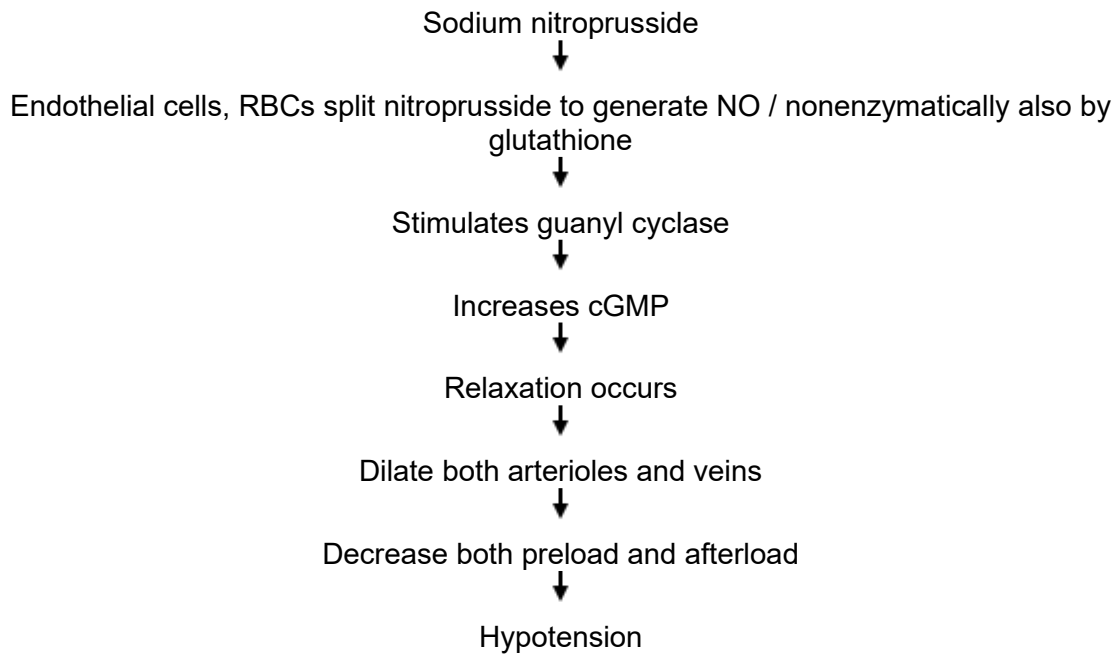
- Angina (with care)
- Ischaemic heart disease.

## ARTERIOLAR + VENODILATOR

### Drugs

- Sodium nitroprusside

### MOA



- It is a rapidly (within seconds) and consistently acting vasodilator
- Has brief duration of action (2–5 min)
- so that vascular tone can be titrated with rate of i.v. infusion.

### Use in hypertension

- In management of hypertensive emergencies

### Adverse effects

- Cyanide toxicity

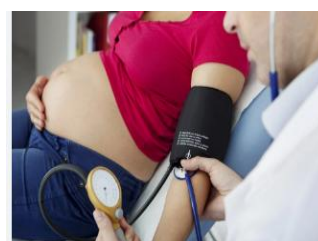
## SUMMARY

| Antihypertensives             | Preferred in                                                                                                                                                                               | Avoided in                                                                                             |
|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Diuretics</b>              | CCF, old age, Isolated systolic hypertension, obesity Osteoporosis (thiazides only)                                                                                                        | Gout, pregnancy, dyslipidemia, metabolic syndrome                                                      |
| <b>Aldosterone antagonist</b> | CCF, hyperaldosteronism, refractory hypertension                                                                                                                                           | Hyperkalemia, renal insufficiency                                                                      |
| <b>B-Blockers</b>             | Angina, tachyarrhythmias, post MI, heart failure, tremors, migraine, tense young people, hyperthyroidism, pregnancy                                                                        | Asthma, severe COPD, heart block, metabolic syndrome, PVD, athletes, depression, erectile dysfunctions |
| <b>ACE I and ARB</b>          | CCF, post infarct, nephropathy, diabetes                                                                                                                                                   | Pregnancy, hyperkalemia, renal artery stenosis, cough (for ACE I)                                      |
| <b>CCB</b>                    | Angina, old age, isolated systolic hypertension, supraventricular tachyarrhythmias (NDHP), carotid atherosclerosis, PVD, diabetes, pregnancy, asthma, migraine and low renin hypertension. | CCF, heart block (NDHP)                                                                                |

## HYPERTENSION IN PREGNANCY

### Introduction

- A sustained BP reading above 140/90 mm Hg during pregnancy has implications both for the mother and the foetus



### Types

- (a) A woman with preexisting essential hypertension becomes pregnant.
- (b) Pregnancy induced hypertension; as in toxemia of pregnancy → preeclampsia

### Antihypertensives found safer during pregnancy

1. Hydralazine
2. Methyldopa
3. Dihydropyridine CCBs → if used, they should be discontinued before labour as they weaken uterine contractions.
4. Cardioselective  $\beta$  blockers and those with ISA (e.g. atenolol, metoprolol, pindolol, acebutolol) → may be used if no other choice.
5. Prazosin

## 6. Clonidine

### Mnemonic

|                     |                                                                                   |
|---------------------|-----------------------------------------------------------------------------------|
| <b>Better</b>       | Beta blockers (Cardioselective and Labetalol)                                     |
| <b>Mother</b>       | Methyl dopa (Preferred drug)                                                      |
| <b>Care</b>         | Clonidine                                                                         |
| <b>During</b>       | Dihydropyridine CCB (sustained release nifedipine, amlodipine)                    |
| <b>Hypertensive</b> | Hydralazine (DOC for hypertensive emergencies in pregnancy, according to JNC-VII) |
| <b>Pregnancy</b>    | Prazosin (and other alpha blockers)                                               |

### Antihypertensives to be avoided during pregnancy

1. ACE inhibitors, ARBs → Risk of foetal damage, growth retardation.
2. Diuretics → Tend to reduce blood volume → accentuate uteroplacental perfusion deficit (of toxemia) → increase risk of foetal wastage, placental infarcts, miscarriage, stillbirth.
3. Nonselective  $\beta$  blockers → Propranolol has been implicated to cause low birth weight, decreased placental size, neonatal bradycardia and hypoglycaemia.
4. Sod. Nitroprusside → Contraindicated in eclampsia

## HYPERTENSIVE EMERGENCIES AND URGENCIES

### Introduction

- **Hypertensive emergency** → Systolic BP > 220 or diastolic BP > 120 mm Hg with evidence of active end organ damage
- **Hypertensive urgency** → Systolic BP > 220 or diastolic BP > 120 mm Hg without overt signs of endorgan damage



### Oral therapy

#### 1. Nifedipine (10 mg soft geletine cap.)

- Orally or s.c. every 30 min was widely employed in urgencies.
- This practice has now been abandoned because it often causes abrupt fall in BP and precipitates MI or stroke, or may be fatal.

#### 2. Captopril (25 mg oral every 1–2 hours)

- Response is variable
- It carries risk of excessive hypotension.



### 3. Clonidine (100 µg every 1–2 hours oral)

- Acts in 30–60 min
- But produces sedation and rebound rise in BP on stopping the drug.

## Parenteral therapy

1. Sodium nitroprusside
2. Hydralazine
3. Esmolol
4. Phentolamine
5. Labetalol
6. Furosemide

### 1. Sodium nitroprusside

- Nitroprusside → 20–300 µg/min) → DOC for most hypertensive emergencies
- Predictable, instantaneous, titratable and balanced arteriovenous vasodilatory action which persists without tolerance till infused

### 2. Hydralazine

- 0–20 mg i.m. or slow i.v. injection; acts in 20–30 min
- Keeps BP low for 4–8 hours
- Less predictable, and not a first line drug.
- Especially used in eclampsia.

### 3. Esmolol

- 0.5 mg/kg bolus followed by slow i.v. injection (50–100 µg/kg/min)
- Acts in 1–2 min
- Action lasts for 10–20 min.
- Particularly useful when cardiac contractility and work is to be reduced, such as in aortic dissection.

### 4. Phentolamine

- Nonselective  $\alpha_1 + \alpha_2$  blocker
- Injected i.v. (5–10 mg)
- Acts in 2 min
- Action lasts 5–15 min.
- DOC for hyperadrenergic states, e.g. hypertensive episodes in pheochromocytoma, cheese reaction or clonidine withdrawal.

### 5. Labetalol

- Injected i.v.
- An alternative to an  $\alpha$  blocker for lowering BP in pheochromocytoma, etc.

- Used to lower BP in MI, unstable angina, eclampsia as well.
- Also good for patients with altered consciousness, because it does not cause sedation or increase intracranial pressure.

## 6. Furosemide

- 20–80 mg oral or i.v.
- Given as an adjunct with any of the above drugs if there is volume overload (acute LVF, pulmonary edema, CHF) or cerebral edema (in encephalopathy)
- Avoided when patient may be hypovolemic states

## DRUG PREFERENCE IN PATIENT WITH CO-EXISTING MORBIDITY

| Associated disorders | Drugs preferred | Reason                                                           | Drugs avoided | Reason                         |
|----------------------|-----------------|------------------------------------------------------------------|---------------|--------------------------------|
| Diabetes             | ACE I           | Improves glucose tolerance<br>Slows development of complications | Diuretics     | Hyperglycemia                  |
| Bronchial asthma     | CCB             | No bronchospasm                                                  | β-Blockers    | Bronchospasm                   |
| Angina               | B-Blockers      | Reduce cardiac energy consumption                                | Vasodilators  | Reflex sympathetic stimulation |
|                      | CCB             | Reduce afterload                                                 |               | increase energy consumption    |

| Associated disorders | Drugs preferred       | Reason                                    | Drugs avoided            | Reason                                                                        |
|----------------------|-----------------------|-------------------------------------------|--------------------------|-------------------------------------------------------------------------------|
| Heart failure        | ACE I, diuretics      | Reduces load                              | First generation CCB     | Reduce contractility                                                          |
| Dyslipidemia         | α blockers            | Reduces LDL<br>Increases HDL              | β -Blockers, Diuretics   |                                                                               |
| Pregnancy            | Methyldopa            | Established safety with a long experience | ACE I and ARB, Diuretics | Fetal toxicity Affects placental blood flow by reducing intra-vascular volume |
| PVD                  | Labetalol, CCB<br>CCB | Relaxes blood vessels                     | B-Blockers               | Constriction of peripheral vessels                                            |

| Associated disorders  | Drugs preferred                           | Reason                                                      | Drugs avoided                                                | Reason                                              |
|-----------------------|-------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------|
| Physically active     | $\alpha$ blockers,<br>ACE I,<br>CCB (DHP) | Exercise induced increase in cardiac output is not affected | B-Blockers                                                   | Decrease COP by reducing the rate and contractility |
| Intellectual activity | ACE I,<br>CCB                             |                                                             | B-Blockers                                                   | Mild intellectual impairment                        |
| Sexual dysfunction    | ACE I                                     | No sexual dysfunctions                                      | Diuretics,<br>B-Blockers,<br>centrally acting sympatholytics | Sexual dysfunctions (Erectile dysfunctions)         |

## TREATMENT OF HYPERTENSION

### A B C D rule (first choice antihypertensive drugs)

- **A** → ACE inhibitor/ARB
  - **B** →  $\beta$  blocker
  - **C** → CCB
  - **D** → Diuretic
- **A and B** → preferred in younger patients (<55 years)
  - **C and D** → preferred in the older (> 55 years)

### British Hypertension Society Guidelines

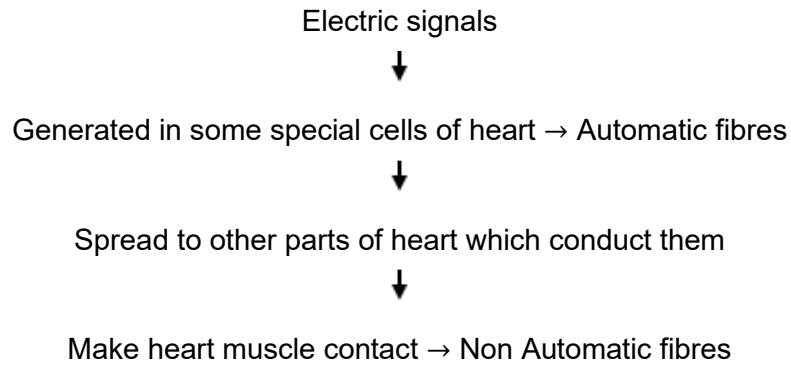
#### Stepped care approach → 4 Steps

- **Step 1** → monotherapy → Start with one drug as monotherapy out of A , B , C or D
- **Step 2** → when two drugs are to be used □ one out of A or B with one out of C or D
- **Step 3** → Both C and D are combined with A or B
- **Step 4** → 4 drug therapy given to achieve the target BP

## ANTIARRHYTHMIC DRUGS

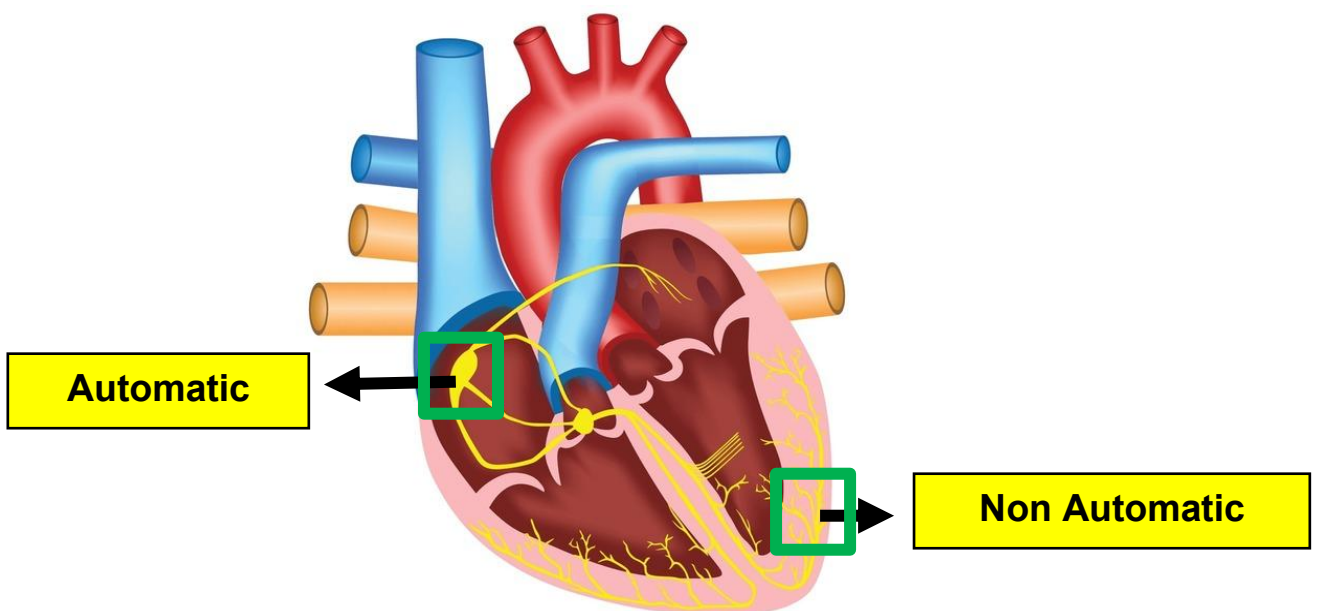
### What makes the heart beat ?

Heart beats due to electric signals

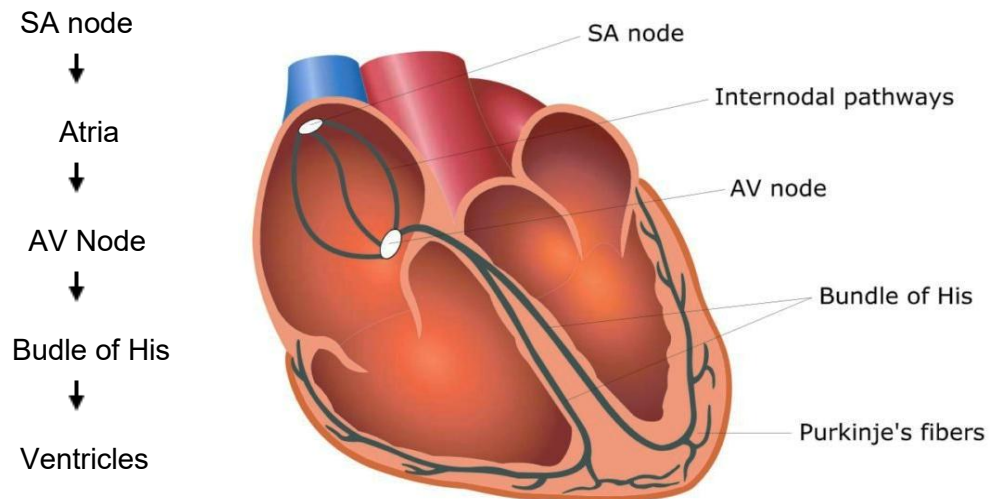


## Types of heart fibers

| Non Automatic                                                                                          | Automatic                                                                                             |
|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Ordinary working myocardial fibers</li> </ul>                 | <ul style="list-style-type: none"> <li>• Specialised myocardial fibers</li> </ul>                     |
| <ul style="list-style-type: none"> <li>• Cannot generate signal but only conduct the signal</li> </ul> | <ul style="list-style-type: none"> <li>• Can generate their own signal</li> </ul>                     |
| <ul style="list-style-type: none"> <li>• Contractile fibers</li> </ul>                                 | <ul style="list-style-type: none"> <li>• Pacemaker fibers</li> </ul>                                  |
| <ul style="list-style-type: none"> <li>• Atrial and ventricular muscle fibers</li> </ul>               | <ul style="list-style-type: none"> <li>• SA node, AV node, Bundle of His, Purkinjee fibers</li> </ul> |



## Impulse generation

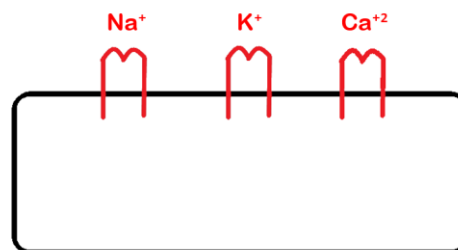


## Action potential (AP)

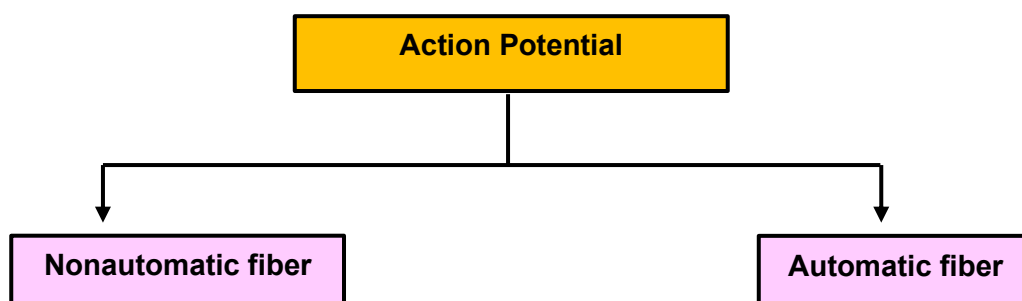
- Electric change that travels through heart cells and contract them
- It's different in Automatic and Non Automatic fibres

### Resting membrane potential

- Resting Membrane potential (RMP) of →
  - Non Automatic fibres → -90 mV
  - Automatic fibres → -60 mV
- Determined by →  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{+2}$ , and  $\text{Cl}^-$  ic
- $\text{K}^+ \rightarrow \text{ICF} > \text{ECF}$
- $\text{Na}^+, \text{Ca}^{+2}, \text{Cl}^- \rightarrow \text{ECF} > \text{ICF}$



## ACTION POTENTIAL

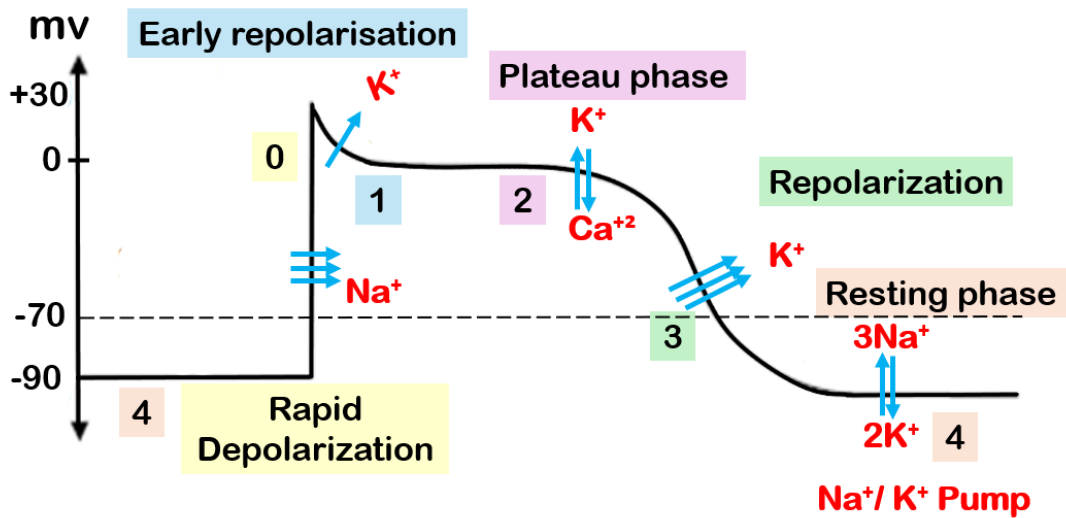


## Action Potential of Nonautomatic fibre

### 5 Phases →

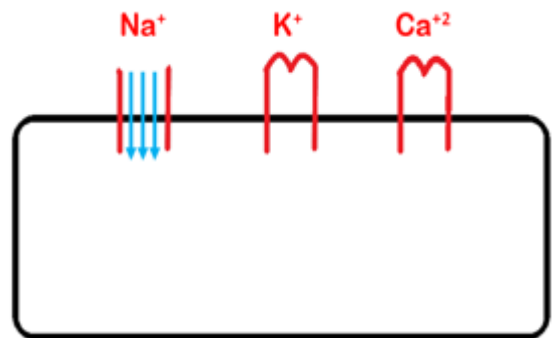
1. Phase 0

2. Phase 1
3. Phase 2
4. Phase 3
5. Phase 4



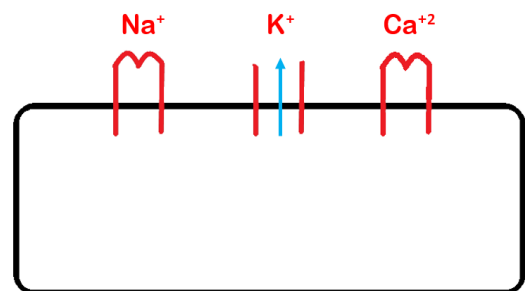
### 1) Phase 0 (Rapid depolarisation)

Stimulus  
 ↓  
 Na<sup>+</sup> channel opens fast  
 ↓  
 Rapid influx of Na<sup>+</sup>  
 ↓  
 Bundle of His  
 ↓  
 Depolarise very fast with overshoot (+30 mV)



### 2) Phase 1 (Early fast Repolarisation)

Na<sup>+</sup> channel Close  
 ↓  
 K<sup>+</sup> channels Briefly opens  
 ↓  
 Small out flow of K<sup>+</sup>  
 ↓  
 Slight drop in membrane potential (return to near iso electric level → 0 mv)



### 3) Phase 2 (Plateu phase)

Voltage gated slow  $\text{Ca}^{+2}$  channels opens



$\text{Ca}^{+2}$  influx into cell

$\text{K}^{+}$  continues to leave cell



Inward  $\text{Ca}^{+2}$  = Outward  $\text{K}^{+}$



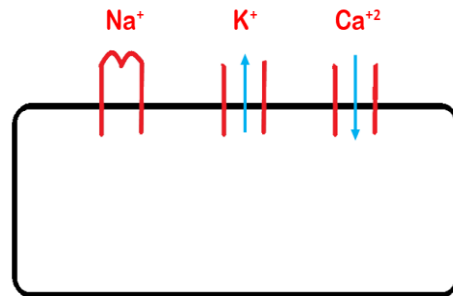
Brings about contraction



Flat platue



Maintainance of Isoelectric level for a considerable period



### 4) Phase 3 (Repolarisation)

$\text{Ca}^{+2}$  Channels close



$\text{K}^{+}$  channels Fully open



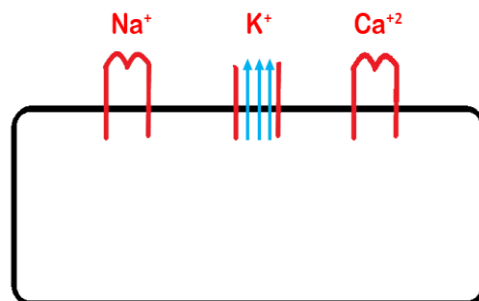
$\text{K}^{+}$  Rush out of the cell



Inside become negative again



Return to resting membrane potential (-90mv)



### 5) Phase 4 (Resting phase)

All ion Channels closed



$\text{Na}^{+}/\text{K}^{+}$  Pump maintains balance (3  $\text{Na}^{+}$  out / 2  $\text{K}^{+}$  In)



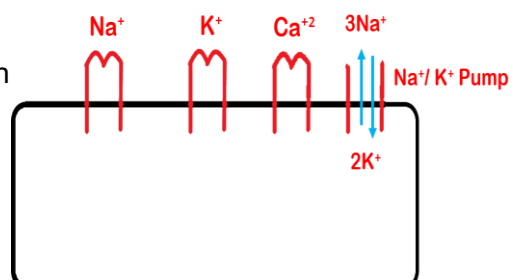
Stable RMP (-90 mv)



RMP once attained do not decay



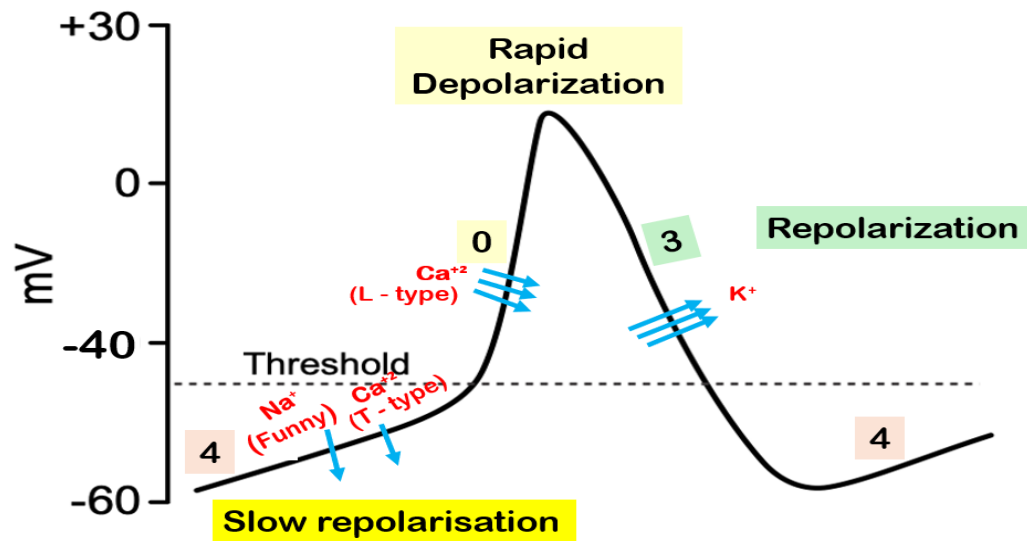
Ready for next cxde



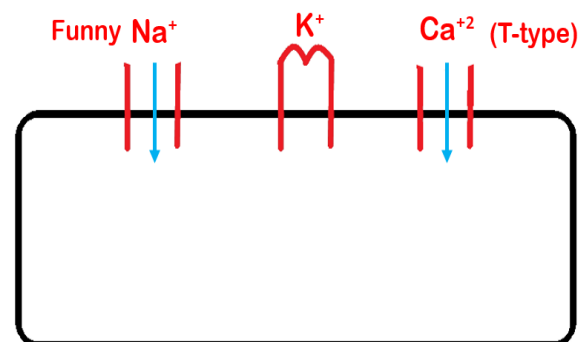
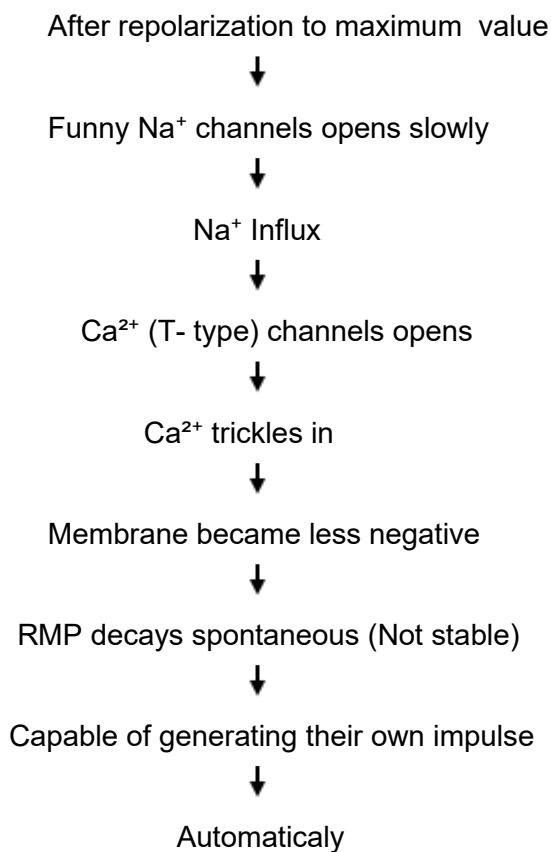


## Action Potential of Automatic fibre

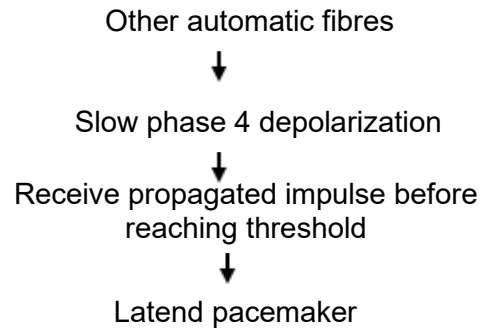
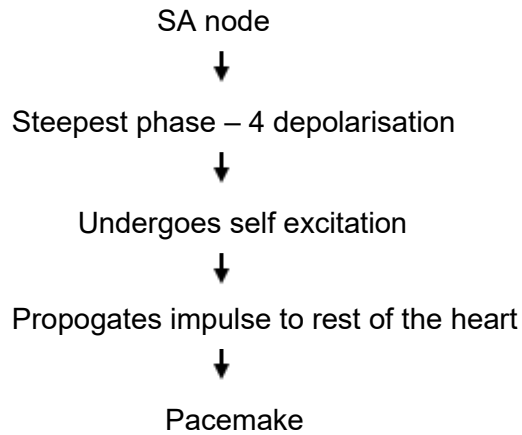
- 1) Phase 4
- 2) Phase 0
- 3) Phase 1 → Absent
- 4) Phase 2 → Very brief
- 5) Phase 3



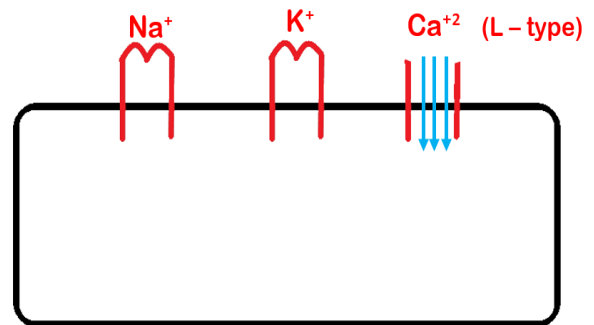
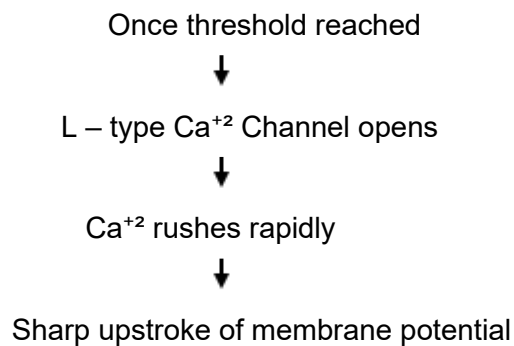
### 1) Phase 4 (Slow repolarisation) → Pacemaker potential



- Rate of impulse generation is steepness of slope of Phase 4



## 2) Phase 0 (Rapid depolarisation)



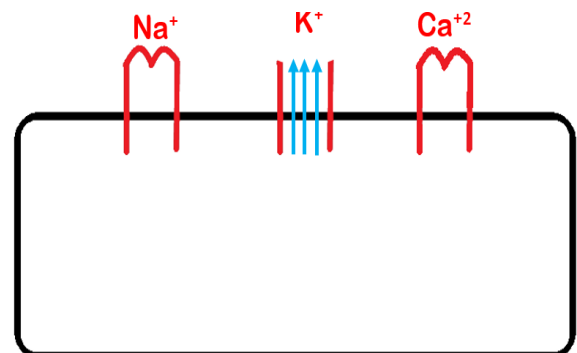
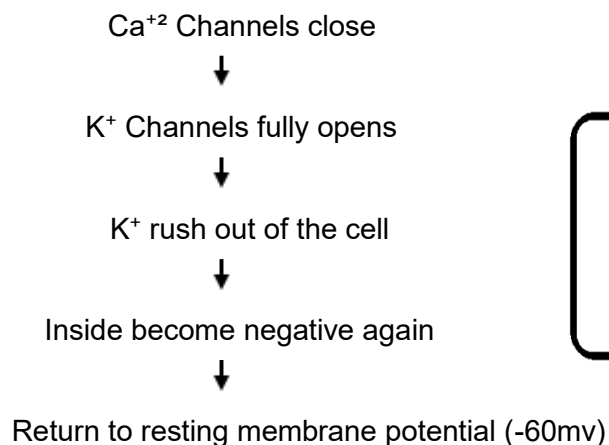
## 3) Phase 1

- Absent

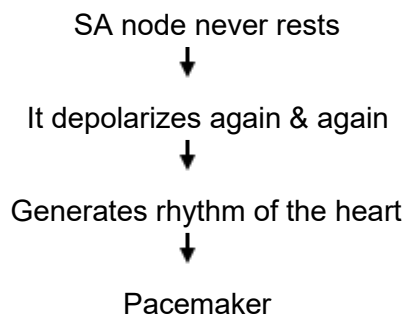
## 4) Phase 2

- Very breif

## 5) Phase 3



## Cycle repeats Automatically



|                                           | Non – Automatic fibres<br>(e.g. ventricular myocytes)         | Automatic fibres<br>(e.g. SA node)                                           |
|-------------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------------------|
| <b>Function</b>                           | Conduction + Contraction                                      | Pacemaker (Initiate impulse)                                                 |
| <b>RMP</b>                                | Stable (-90mv)                                                | Unstable (-60mv)                                                             |
| <b>Phase 0<br/>(depolarization)</b>       | Fast Na <sup>+</sup> influx                                   | Slow Ca <sup>+2</sup> influx (L – type)                                      |
| <b>Phase 1<br/>(early repolarization)</b> | Present<br>(transient K <sup>+</sup> efflux)                  | Absent                                                                       |
| <b>Phase 2<br/>(Plateau)</b>              | Prominent<br>(Ca <sup>+</sup> Influx = K <sup>+</sup> efflux) | Very short                                                                   |
| <b>Phase 3<br/>(Repolarization)</b>       | K <sup>+</sup> efflux                                         | K <sup>+</sup> efflux                                                        |
| <b>Phase 4<br/>(resting /pacemaker)</b>   | Stable (maintained by Na <sup>+</sup> / K <sup>+</sup> pump)  | Pacemaker potential funny Na <sup>+</sup> , Ca <sup>+2</sup> (T-type) influx |
| <b>AP duration</b>                        | Long (250 – 300 ms)                                           | Short (150ms)                                                                |
| <b>RP</b>                                 | Long                                                          | Short                                                                        |

## PROPERTIES OF A CARDIAC CELL

- Automaticity
- Excitability
- Threshold potential
- Conduction velocity
- Effective refractory period (ERP)

### Automaticity

- Ability of cardiac cell to undergo spontaneous depolarization.
- Normally → rate of spontaneous depolarization is fastest in SA node → Pacemaker of the heart.

## Excitability

- Ability of a cell to undergo depolarization in response to a stimulus.

## Threshold potential

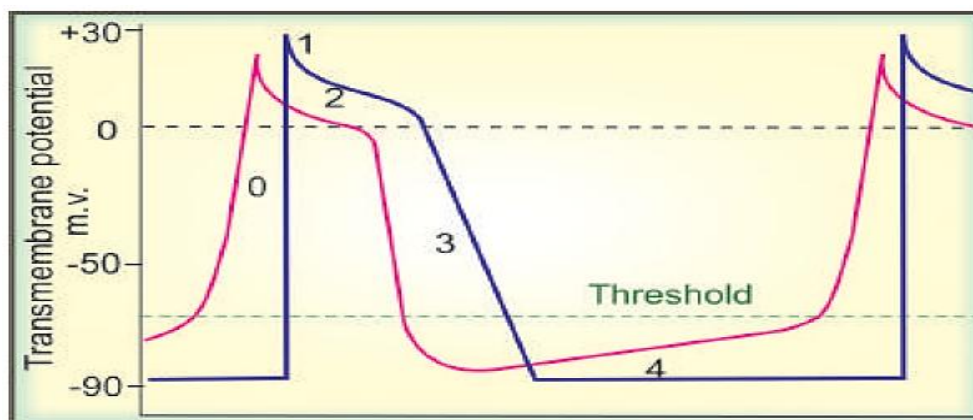
- Potential at which sudden, rapid and complete depolarization occurs resulting in generation of an action potential.

## Conduction velocity

Depends mainly on the slope of action potential and phase 0 depolarization.

## Effective refractory period (ERP)

- Minimal interval between two successive, propagated action potentials.



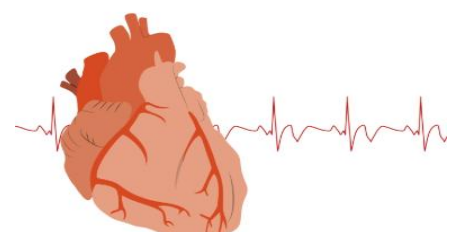
## EFFECTS OF ANS ON CARDIAC ELECTROPHYSIOLOGY

|                                           | Parasympathetic (ACh) | Sympathetic (Adr) |
|-------------------------------------------|-----------------------|-------------------|
| 1. Automaticity<br>SA node                | Bradycardia           | Tachycardia       |
| 2. Refractory period<br>Conducting tissue | Prolonged             | Shortened         |
| 3. Conductivity                           | Decreased             | Increased         |
| 4. Contractility                          | Decreased             | Increased         |

## ARRHYTHMIA

### Introduction

- Disturbances on cardiac rhythm
- Abnormal automaticity or abnormal conduction or both → arrhythmias
- Arrhythmias → MC cause of sudden cardiac death



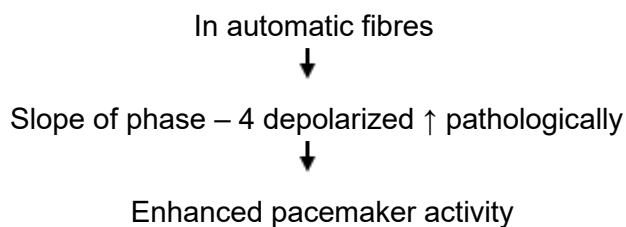
## Causes

- 1) Ischaemia
- 2) Electrolyte and pH imbalance
- 3) Mechanical injury
- 4) Stretching due to heart failure
- 5) Neurogenic
- 6) Pharmacological (Antiarrhythmic drugs themselves)

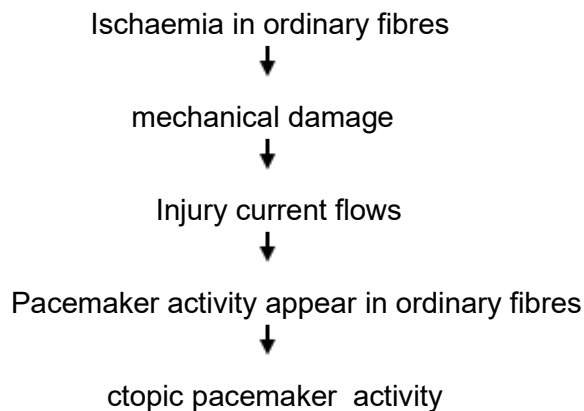
## Mechanisms

- 1) Enhanced pacemaker activity
- 2) Ectopic pacemaker activity
- 3) After depolarizations
- 4) Re entry

### 1. Enhanced pacemaker activity

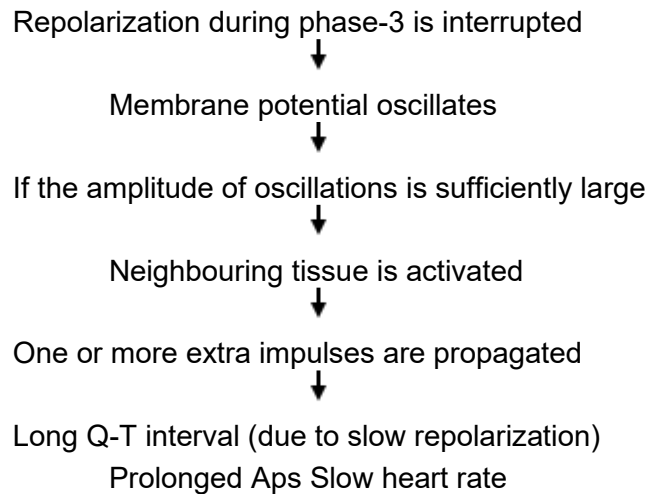
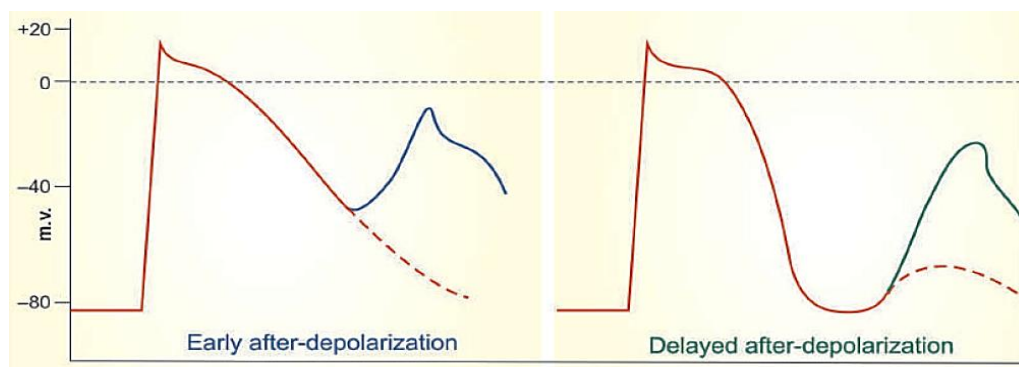
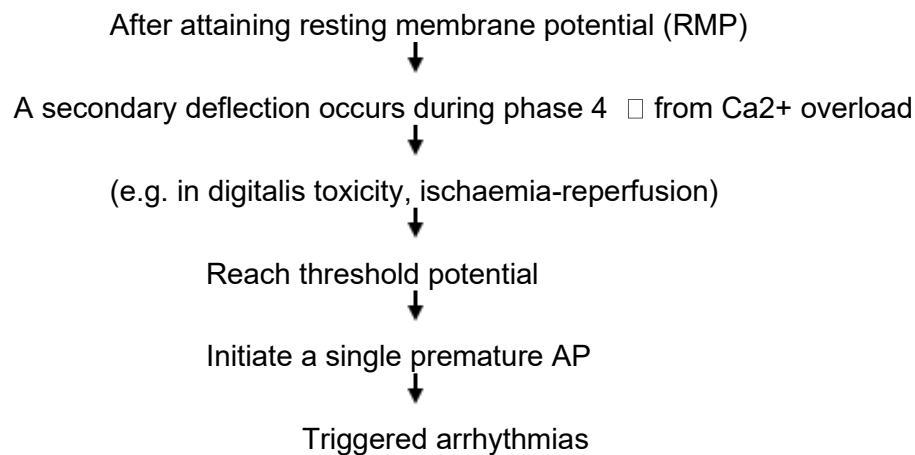
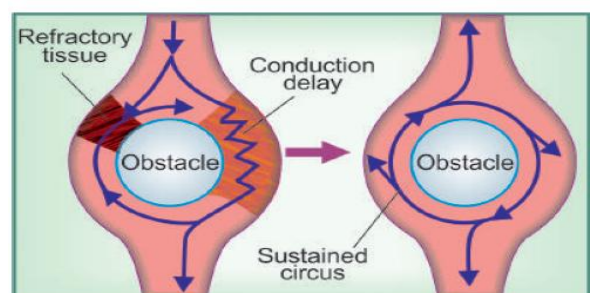
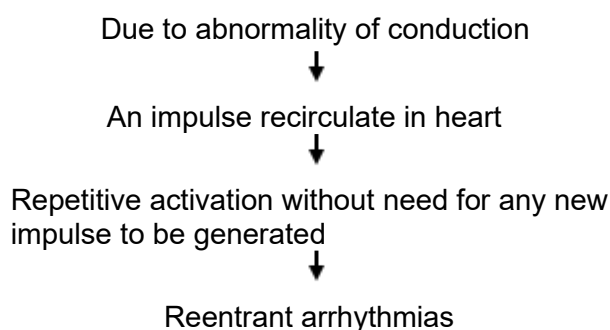


### 2. Ectopic pacemaker activity



### 3. After depolarizations

- Secondary depolarizing accompanying normal or premature AP
  - a) Early After depolarizations (EADs)
  - b) Delayed After depolarizations (DADs)

**a) Early after depolarizations (EAD)****b) Delayed after depolarizations (DAD)****4. Re-entry**

## Types

1. Extrasystoles (ES)
2. Paroxysmal supraventricular tachycardia (PSVT)
3. Atrial flutter (AFI)
4. Atrial fibrillation (AF)
5. Ventricular tachycardia (VT)
6. Ventricular fibrillation (VF)
7. Atrio-ventricular (A-V) block

### 1. Extrasystoles (ES)

- Premature ectopic beats due to abnormal automaticity arising from an ectopic focus in the atrium (AES), A-V node (nodal ES) or ventricle (VES).

### 2. Paroxysmal supraventricular tachycardia (PSVT)

- Sudden onset episodes of atrial tachycardia
- Rate → 150–200/min
- 1:1 atrioventricular conduction

### 3. Atrial flutter (AFI)

- Atria beat at a rate of 200–350/min
- There is a physiological 2:1 to 4:1 or higher A-V block
- Because A-V node cannot transmit impulses faster than 200/min

### 4. Atrial fibrillation (AF)

- Atrial fibres are activated asynchronously → due to electrophysiological inhomogeneity of atrial fibres
- Rate → 350–550/min
- Grossly irregular and often fast (100–160/min) ventricular response.

### 5. Ventricular tachycardia (VT)

- Run of 4 or more consecutive ventricular extrasystoles.

### 6. Ventricular fibrillation (VF)

- Grossly irregular, rapid and fractionated activation of ventricles resulting in incoordinated contraction of its fibres with loss of pumping function.
- It is fatal unless reverted within 2–5 min.
- VF is the most common cause of sudden cardiac death.

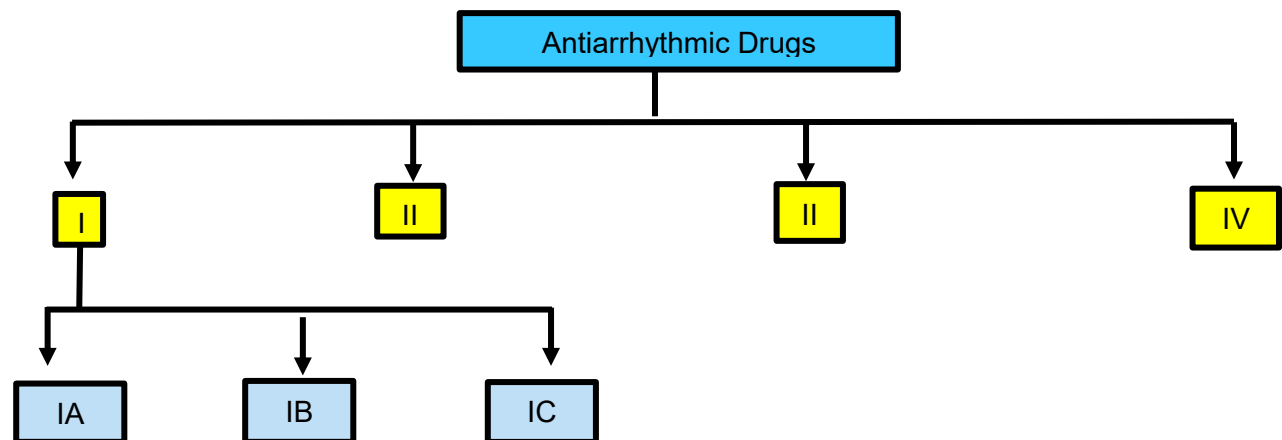
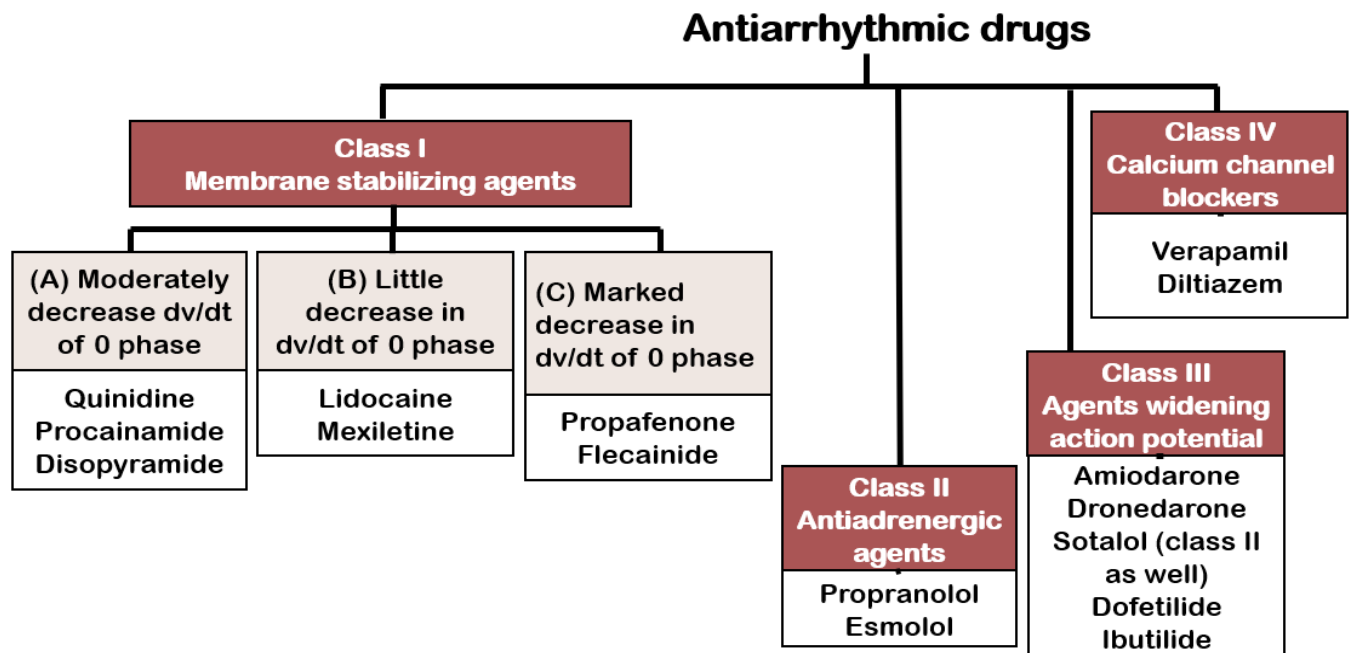
### 7. Atrio-ventricular (A-V) block

- Due to depression of impulse conduction through the A-V node and bundle of His, due to vagal influence or ischaemia.



# ANTIARRYTHMIC DRUGS

## Classification



|                 | IA        |              | IB        | IC          |
|-----------------|-----------|--------------|-----------|-------------|
|                 | Quinidine | Procainamide | Lidocaine | Propafenone |
| Introduction    |           |              |           |             |
| MOA             |           |              |           |             |
| ECG changes     |           |              |           |             |
| Pharmaology     |           |              |           |             |
| Uses            |           |              |           |             |
| Adverse effects |           |              |           |             |

|                 | II        | III        | IV        |
|-----------------|-----------|------------|-----------|
|                 | Propandol | Amiodarone | Virapamil |
| Introduction    |           |            |           |
| MOA             |           |            |           |
| ECG changes     |           |            |           |
| Pharmaology     |           |            |           |
| Uses            |           |            |           |
| Adverse effects |           |            |           |

## CLASS I

- Acts on → Non automatic fibres
- Na<sup>+</sup> channel blockers → LA like activity
- 3 subclass → based on effect on AP duration
  1. **IA** → Moderate Na<sup>+</sup> channel blockers
  2. **IB** → Weak Na<sup>+</sup> channel blockers
  3. **IC** → Strong Na<sup>+</sup> channel blockers

## SUBCLASS IA

- Moderate Na<sup>+</sup> channel blockers → Prolong repolarization
- More in → Open state
- Drugs →
  - Quinidine
  - Procainamine
  - Disopyramide

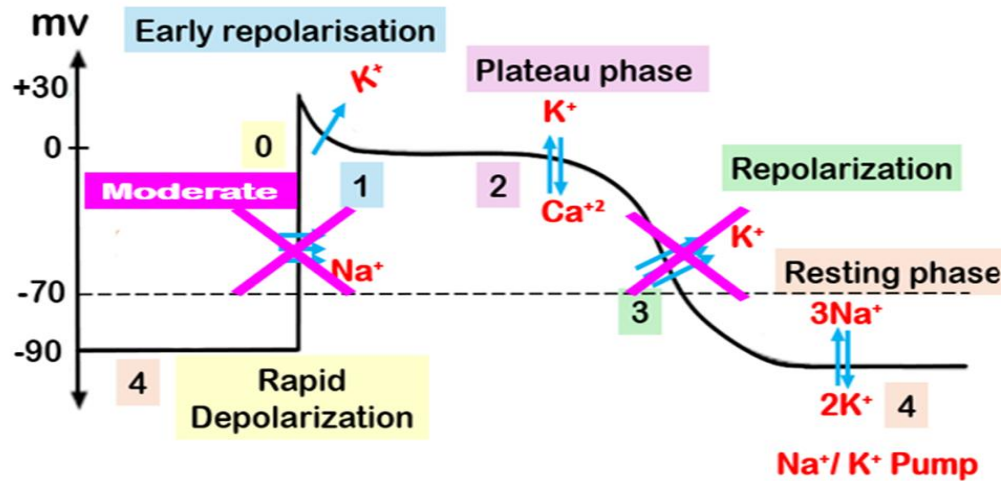
## QUINIDINE

### Introduction

- Class IA antiarrhythmic drug
- Dextro isomer of antimalarial alkaloid quinine
- Found in chinchola bark

## MOA

3 MOA →



Quinidine



Block  $\text{Na}^+$  channel in open state during phase 0 (Moderate block)



↓ Rate of depolarization in frequency def. manner



↓ conduction velocity



↓ Ectopic automaticity

Quinidine



Block  $\text{K}^+$  channel in phase 3



↑ Action potential duration (APD)

Quinidine



Delay in recovery of  $\text{Na}^+$  and  $\text{K}^+$  channel



↑ Effective refractory period (ERP)

## Extracardiac Action

1. Weak  $\alpha$  Block → ↓BP
2. ↓ Skeletal muscle contractility
3. ↑ Uterine contractions
4. GIT → Vomiting, Diarrhea
5. CNS → Chinchonism → Ringing of ears, vertigo, deafness

## ECG changes

1. ↑ P – R
2. ↑ Q – T → Risk of Torsades de Pointes
3. ↑ QRS

## Pharmacokinetics

- Orally
- Highly bound to plasma proteins
- 20% excreted uncharged in urine



## Uses

- Broad spectrum antiarrhythmic activity
- Not DOC in any type of arrhythmia because of its adverse effects
- Used in maintaining normal sinus rhythm in →
  - Atrial fibrillation
  - Atrial flutter

## Adverse effects

1. **GIT** → Diarrhoea
2. **Blood** → Thrombocytopenia
3. **CVS** → ↓BP, Torsades de pointes
4. **CNS** → chinchonism → Tinnitus, deafness, headache, diplopia, photophobia, delirium, Psychosis



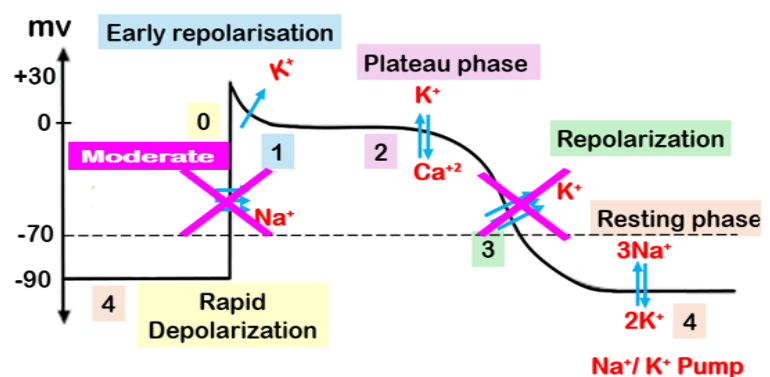
# PROCAINAMIDE

## Introduction

- Class IA antiarrhythmic drug
- Orally active amide derivative of LA Procaine
- Electrophysiological → actions identical to Quinidine

## MOA

- Same as Quinidine with following differences →
  1. ↓ Effective in Suppressing ectopic automaticity than Quinidine
  2. No α Blocking effects → Less fall in BP
  3. No antivagal effects



## ECG changes

1.  $\uparrow$  P – R
2.  $\uparrow$  Q – T  $\rightarrow$  Risk of Torsades de Pointes
3.  $\uparrow$  QRS

## Pharmacokinetics

- Oral or IV
- Metabolised by acetylation to N Acetyl Procainamide (NAPA)  $\rightarrow$ 
  1.  $\text{Na}^+$  channel blocking  $\rightarrow$  Absent
  2.  $\text{K}^+$  channel blocking  $\rightarrow$  Present  $\rightarrow$  APD
    - $\uparrow$
- Slow and fast acetylators



## Uses

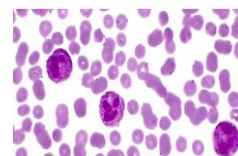
- 2nd line drug to terminate  $\rightarrow$ 
  - Monomorphic VT
  - Supraventricular arrhythmias

## Adverse effects

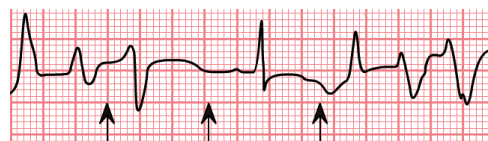
1. **GIT**  $\rightarrow$  Diarrhoea (less than Quinidine)



2. **Blood**  $\rightarrow$  Agranulocytosis and Aplastic anemia



3. **CVS**  $\rightarrow$  Torsades de pointes



4. **Drug induced Lupus erythematosus (DILE)**  $\rightarrow$  in slow acetylators



## SUBCLASS IB

- Weakly Block  $\text{Na}^+$  Channels
- More in  $\rightarrow$  inactivated state than open
- Do not delay channel recovery
- Do not  $\downarrow$  conduction,  $\uparrow$ APD, ERP and QT
- Drugs  $\rightarrow$ 
  - Lidocaine
  - Mexiletine

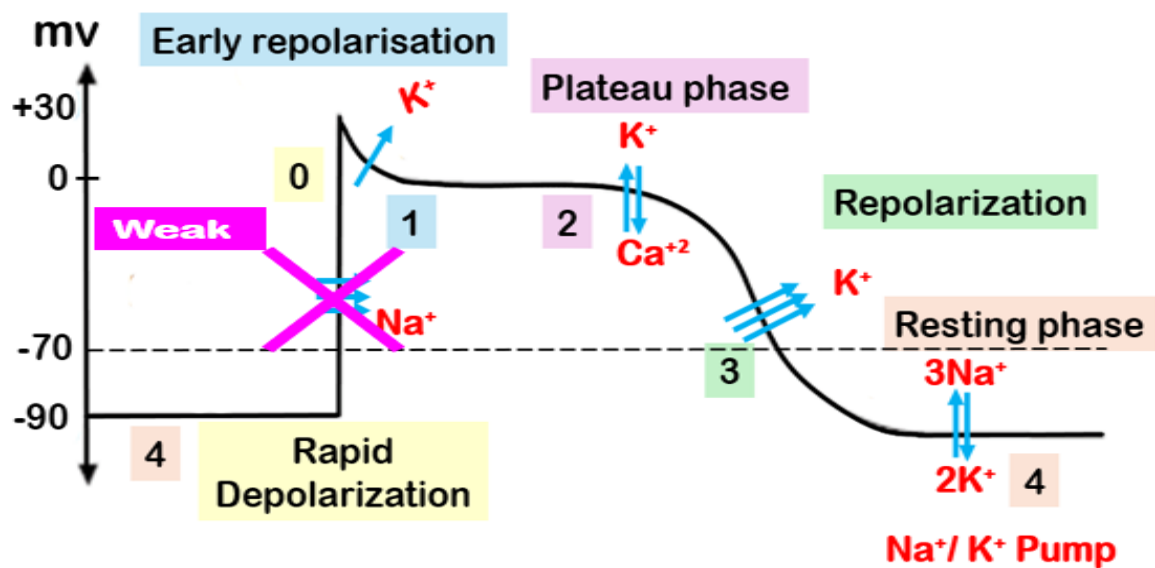
## LIDOCAINE

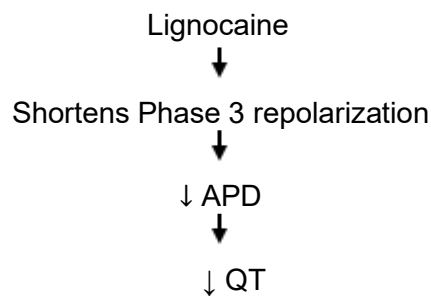
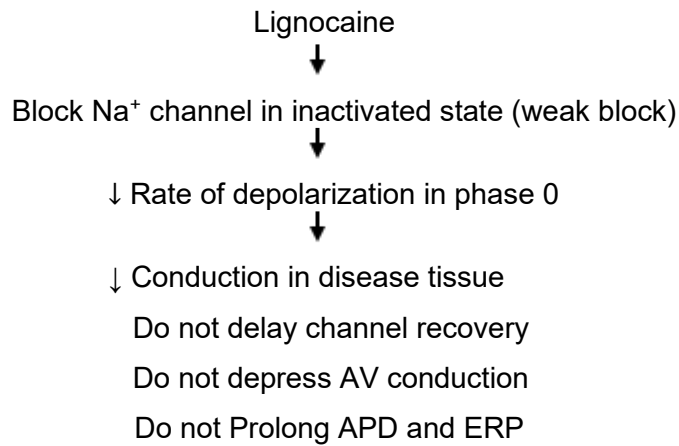
### Introduction

- Class IB antiarrhythmic drug
- Most commonly used LA
- Minimal effect on normal cardiac tissue
- Prominent effect on ischemic (depolarized tissue)
- No proarrhythmic potential

### MOA

2 MOA  $\rightarrow$





## ECG changes

1. ↓ Q - T
2. No effect on QRS and P - R

## Pharmacokinetics

- IV route (extensive 1st pass metabolism)
- Short t / 2
- Hepatic metabolism



## Uses

- Rapidly developing and titrable action it is good drug in emergency setting
  1. Post - MI Ventricular arrhythmias
  2. Post cardiac sx Ventricular arrhythmias
  3. Digitalis induced arrhythmias

## Adverse effects

1. CNS → Tremors, confusion, paresthesia, nystagmus
2. CVS → ↓ BP





## SUBCLASS IC

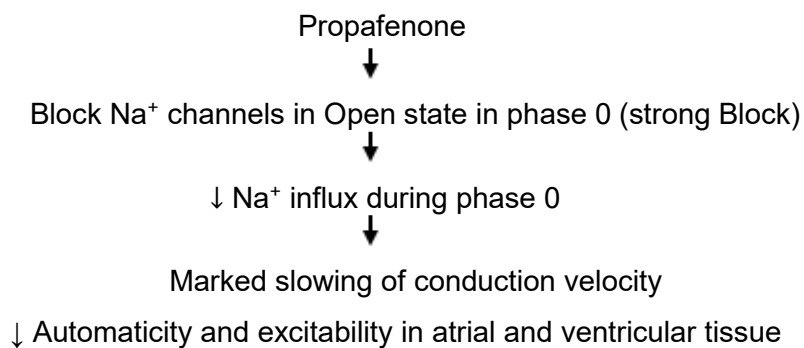
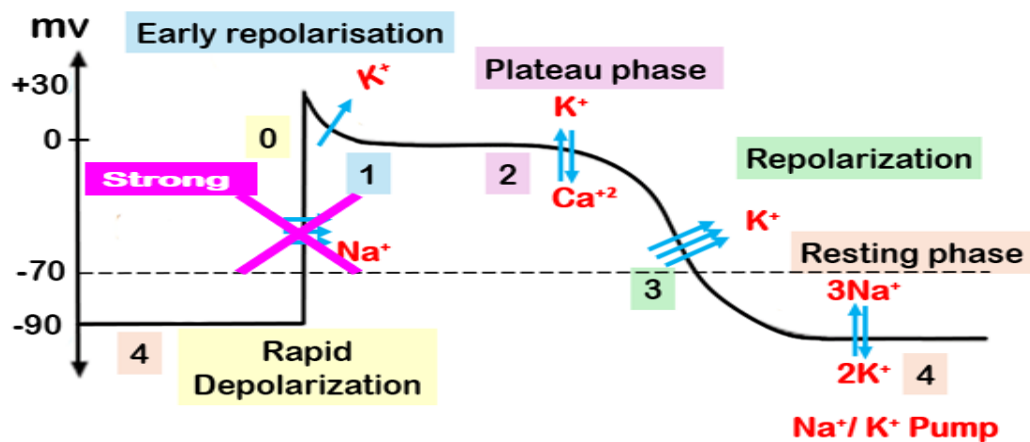
- **Most potent Na channel blockers**
- **More in** → open state
- Longest recovery time
- High proarrhythmic potential
- **Drugs** →
  - Propafenone
  - Flecainide

## PROPAFENONE

### Introduction

- Class IC antiarrhythmic drug

### MOA



Propafenone  
↓  
No effect on  $K^+$  channels  
↓  
APD is unchanged  
Q – T is unchanged

---

Propafenone  
↓  
 $\beta$  Blocking property  
↓  
Precipitate CHF and Bronchospasm

### ECG change

1.  $\uparrow$  QRS
2.  $\uparrow$  P – R
3. No effect on QT

### Pharmacokinetics

- Oral Bioavailability varies due to 1st pass metabolism
- Metabolised in liver via CYP2D6

### Uses

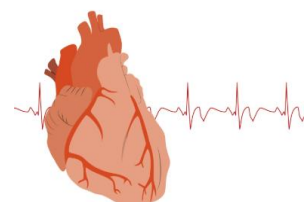
1. Atrial fibrillation (AF) → For rhythm control in structurally normal heart
2. PSVT
3. Ventricular arrhythmias

### Adverse effects

1. Proarrhythmic risk in Structural heart disease or Post MI
2. Bradycardia or AV block



3. Worsen asthma (Due to  $\beta$  Blocking property)



## CLASS II

- **Antiadrenergic drugs** →  $\beta$  blockers
- **Acts primarily on** → Automatic fibres □ SA and AV node which are rich in  $\beta_1$  receptors
- **Drugs** →
  - Propranolol
  - Esmolol

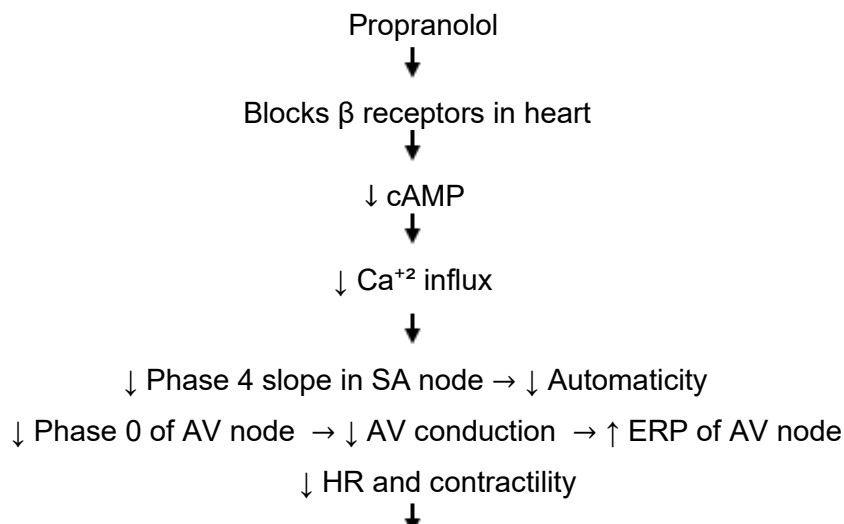
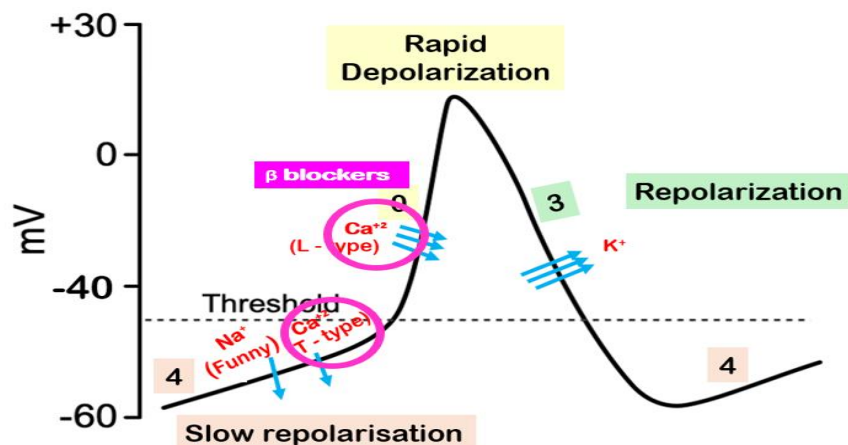
## PROPRANOLOL

### Introduction

- Class II antiarrhythmic drug
- Non selective  $\beta$  blocker (block  $\beta_1$  and  $\beta_2$  receptors)
- Low dose → Block  $\beta$  receptors → Reduces sympathetic stimulation of heart → slowing SA node rate and AV node conduction
- High dose → Block  $\text{Na}^+$  channel → Membrane stabilizing effect

### MOA

#### 2 MOAs



↓ Arrhythmogenic effect of catecholamines  
(during stress or MI)

Propranolol



↓  $\text{Ca}^{+2}$  influx



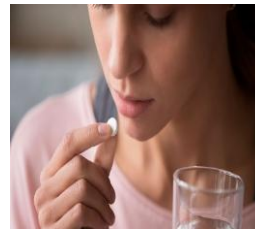
↓ DADs

## ECG change

1. ↑ P – R
2. ↓ HR

## Pharmacokinetics

- Oral and IV
- Highly lipophilic
- Extensive 1st pass metabolism → Variable bioavailability
- Hepatic metabolism → CYP450



## Uses

1. Inappropriate sinus tachycardias
2. Supraventricular arrhythmias (PSVT, AF, Atrial flutter) of Post – MI arrhythmias
3. Performance anxiety, essential tremors
4. Migraine prophylaxis
5. Adjunct in pheochromocytoma (after  $\alpha$  blockers)
6. Sympathetically mediated arrhythmias seen in pheochromocytoma
7. Digitalis induced and thyrotoxicosis associated tachyarrhythmias
8. Arrhythmias during anaesthesia with halothane

## Adverse effects

1. **Blood vessels** → VC → cold extremities



2. **CVS** → Bradycardia, AV Block



3. **Lung** → Bronchospasm



4. **CNS** → Depression, Vivid dreams



5. **Metabolic** → Fatigue, hypoglycemia



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## CLASS III

---

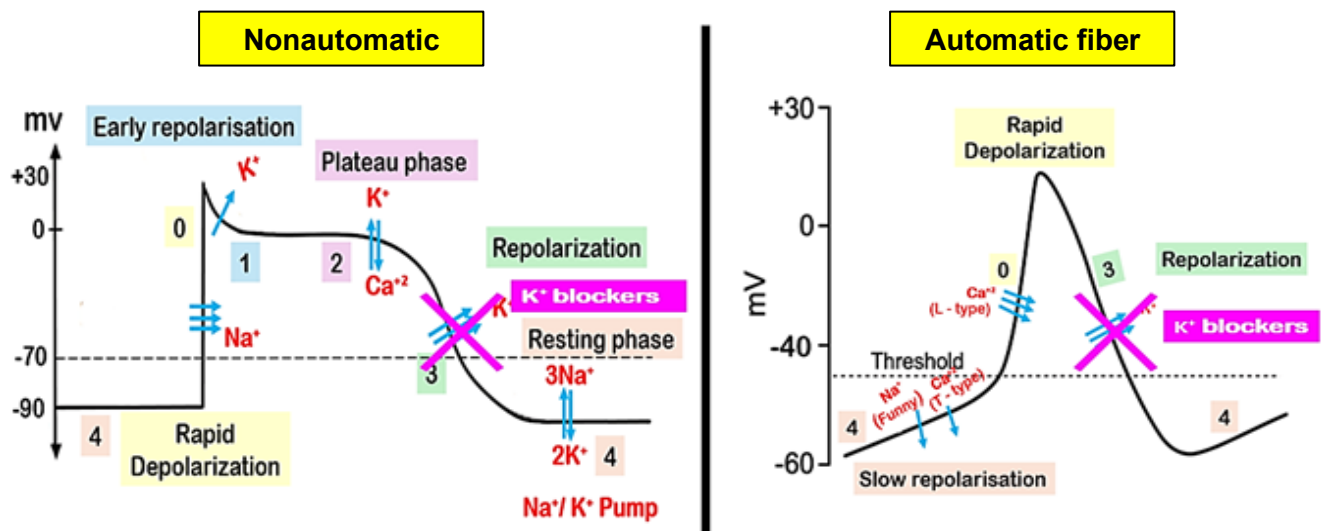
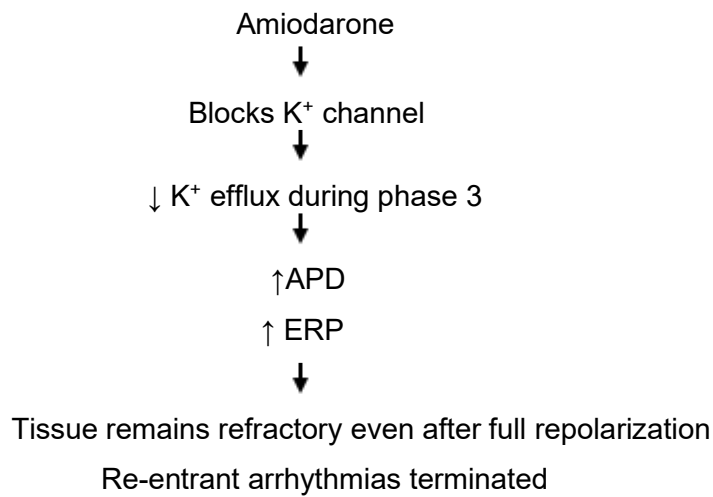
- **K<sup>+</sup> channel blockers** → ↑ duration of repolarization (phase 3)
- **Acts on** → both Automatic as well as Non Automatic fibres
- **Drugs** →
  - Amiodarone
  - Dronedarone
  - Sotalol (Class 2 also)
  - Dofetilide
  - Ibutilide

## AMIODARONE

### Introduction

- Class III antiarrhythmic drug
- Broad Spectrum
- Exerts multiple actions → Class I, II, III, IV
- Long acting
- Highly lipophilic
- Iodine containing compound

## MOA



## Additional MOA

- ↓  $Na^+$  influx (Class I) → ↓ Conduction
- ↓  $\beta$  Activity (Class II) → ↓ HR
- ↓  $Ca^{2+}$  influx (Class IV) → ↓ AV node conduction
- Combination of MOA → Makes Amiodarone → Effective for most arrhythmias

## ECG Changes

- ↑ Q – T (due to prolonged repolarization)
- ↓ HR (due to  $\beta$  Block and  $Ca^{2+}$  block)

## Pharmacokinetics

- Highly lipophilic
- Very long  $t_{1/2}$  (25 – 60 days)

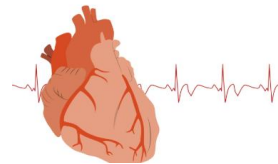
- Onset is slow
- Hepatic metabolism → CYP3A4

## Uses

1. Broad spectrum →
2. Atrial fibrillation
3. Atrial flutter
4. Ventricular tachycardia (VT)
5. Ventricular Fibrillation (VF)
6. Refractory or resistance arrhythmias

## Adverse effects

1. CVS: Hypotension (due to vasodilation), CHF and exacerbation of arrhythmias.



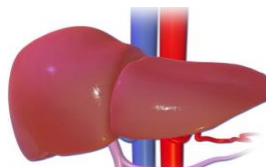
2. Neurological: Peripheral neuropathy.



3. Respiratory: Pulmonary fibrosis.



4. GIT: Nausea and hepatitis.



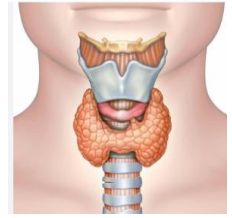
5. Skin : Photosensitivity and pigmentation of the skin.



6. Eye: Corneal deposits.



7. Thyroid: Hypothyroidism and hyperthyroidism → TSH, T3 and T4 levels should be monitored during long-term therapy with amiodarone.



## CLASS IV

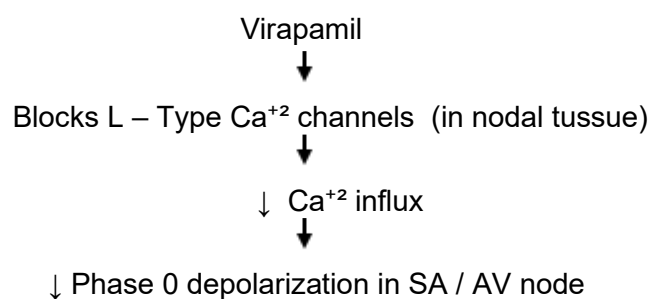
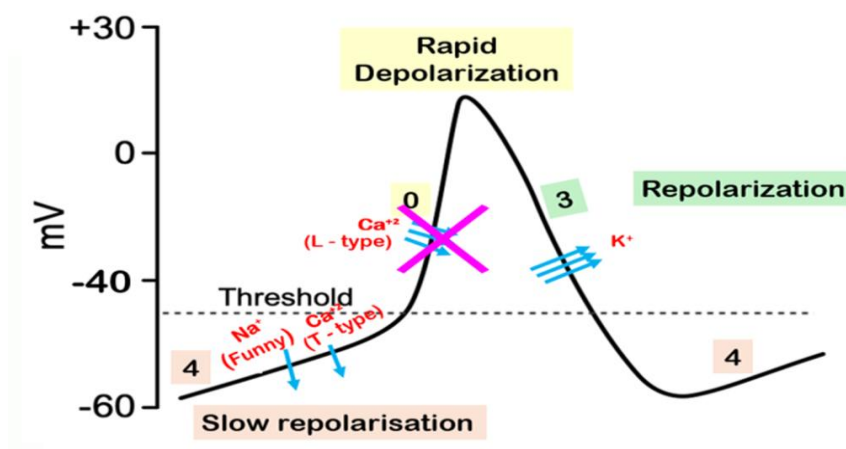
- **Inhibit  $\text{Ca}^{+2}$  Med. Slow channel inward current**
- **Acts on** → Automatic fibres
- **Drugs** →
  1. Virapamil
  2. Diltiazem

## VIRAPAMIL

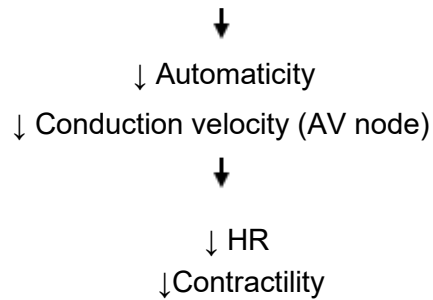
### Introduction

- Class IV antiarrhythmic drug
- Non dihydropyridine CCB
- Acts on L- type  $\text{Ca}^{+2}$  channels in SA and AV nodes
- Used for rate control in supraventricular arrhythmias

### MOA







- Selectively slows conduction through AV Node → ideal for supraventricular arrhythmias

## ECG Changes

- ↑P – R (Slow AV Condition)
- ↓Heart rate

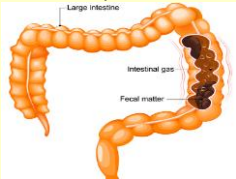
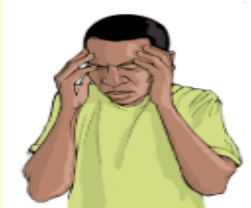
## Pharmacokinetics

- Oral and IV
- Short  $t_{1/2}$
- Hepatic Met → CYP3A4

## Uses

1. Supraventricular tachycardius
2. Rate control in atrial flutter and fibrillation
3. Variant angina
4. Hypertension
5. HOCM

## Adverse effects

|                  |                                                                                                                            |
|------------------|----------------------------------------------------------------------------------------------------------------------------|
| <b>Cardiac →</b> | Bradycardia, AV block, hypotension<br> |
| <b>GIT →</b>     | Constipation (most common)<br>         |
| <b>CNS →</b>     | Dizziness, headache<br>                 |

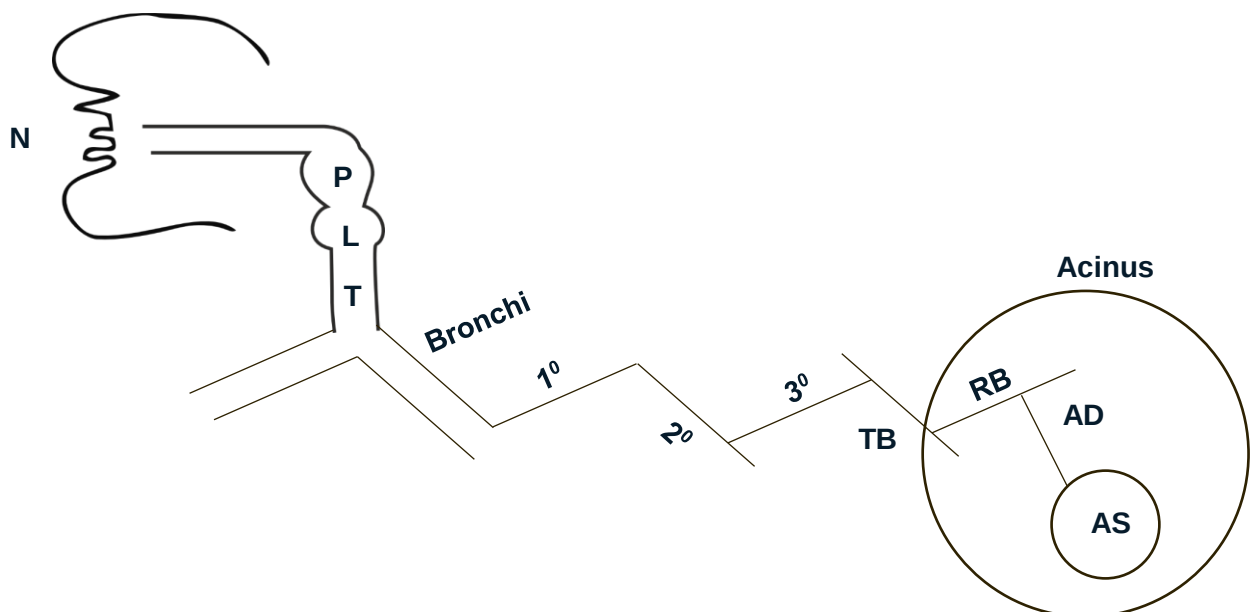
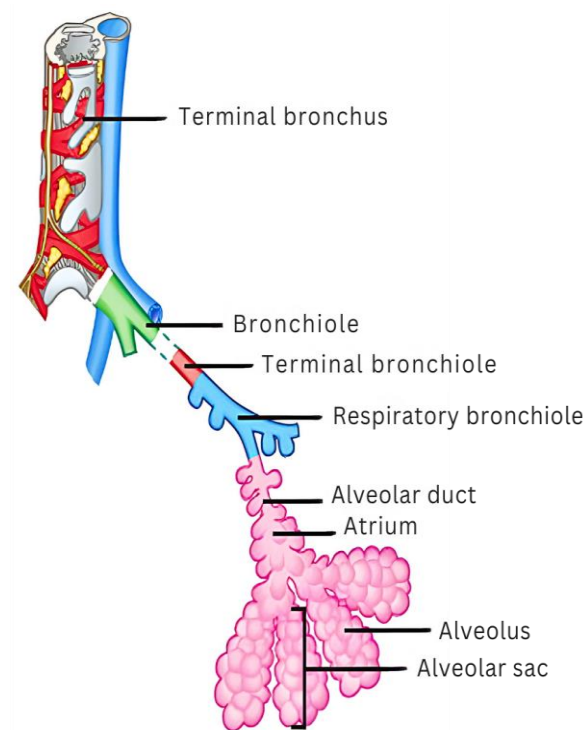
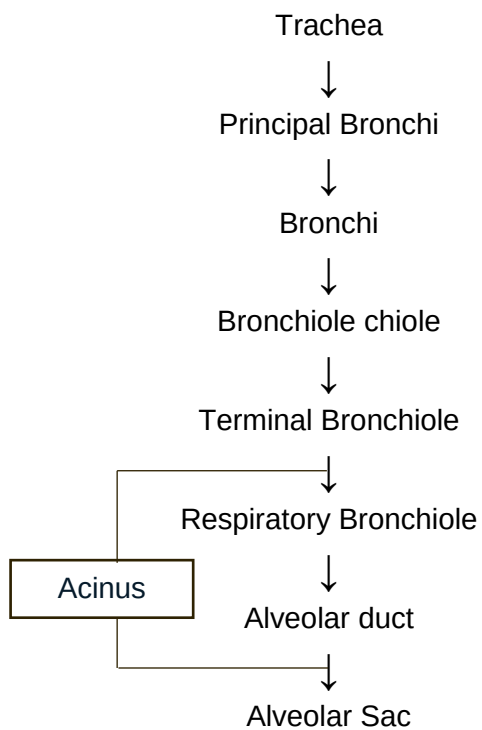


# Respiratory System Drugs

CHAPTER

7

## Normal anatomy of Respiratory tract



## Asthma

Asthma is a disease of airways that is characterised by increased responsiveness of tracheobronchial tree to a variety of stimuli



Widespread spasmodic narrowing of air passages

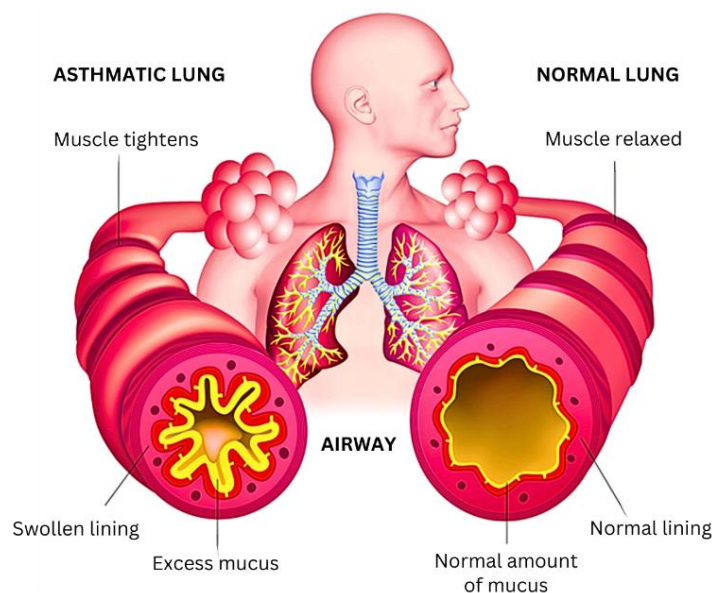
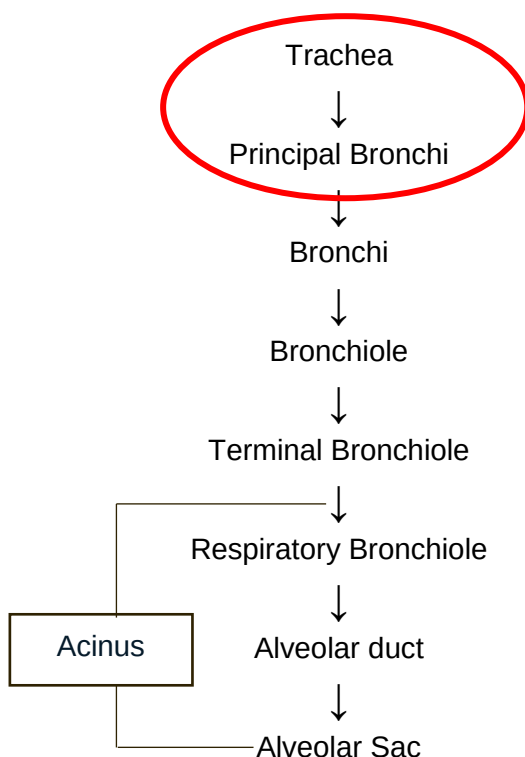


Relieved spontaneously or by therapy



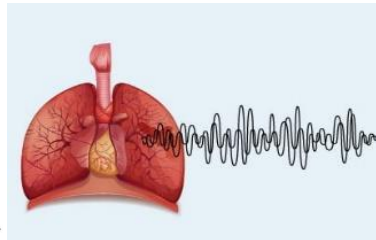
## Location

- Trachea and Bronchi



## Symptoms

- Dyspnoea
- Wheezing
- Cough



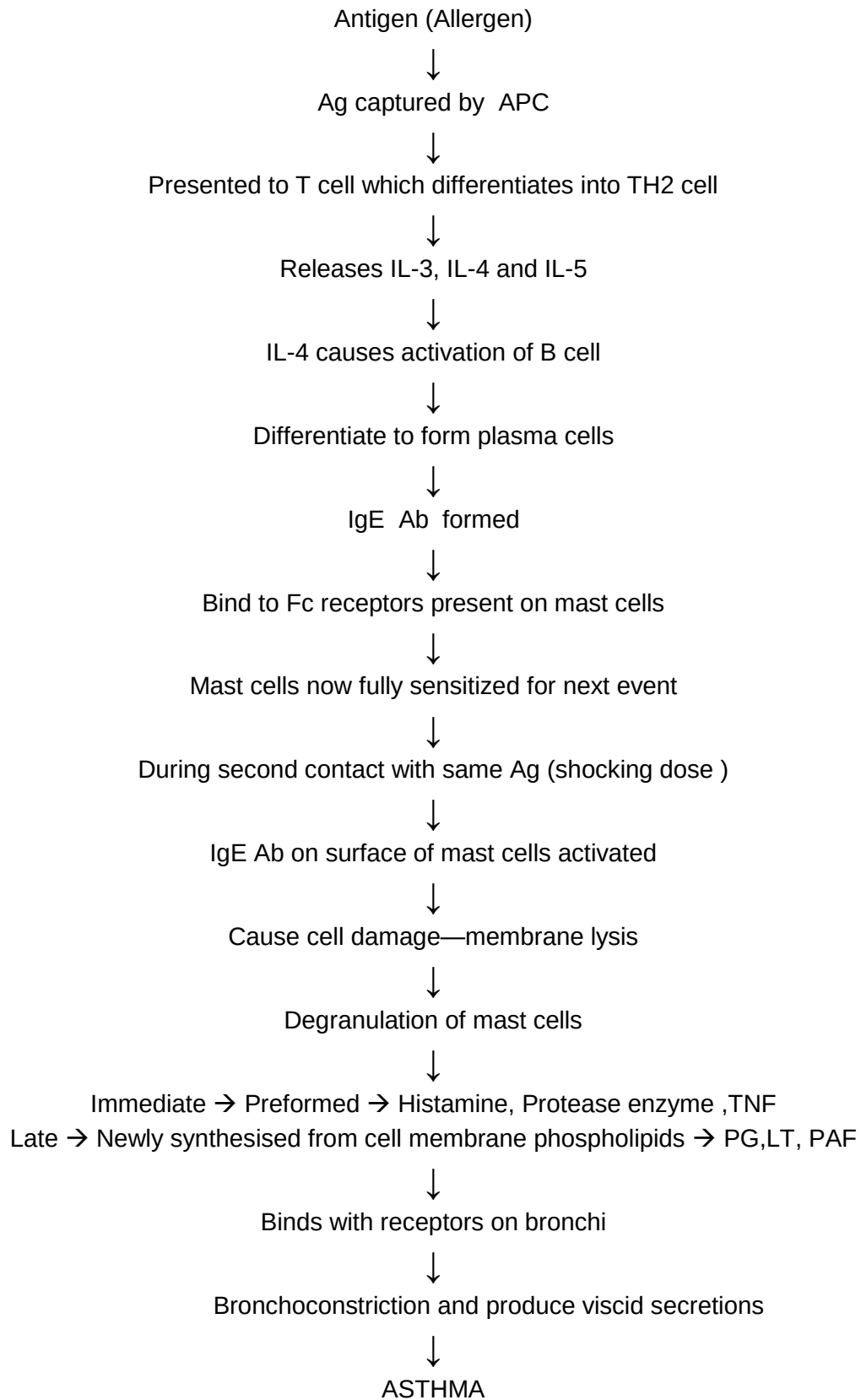
## Clinical categorization

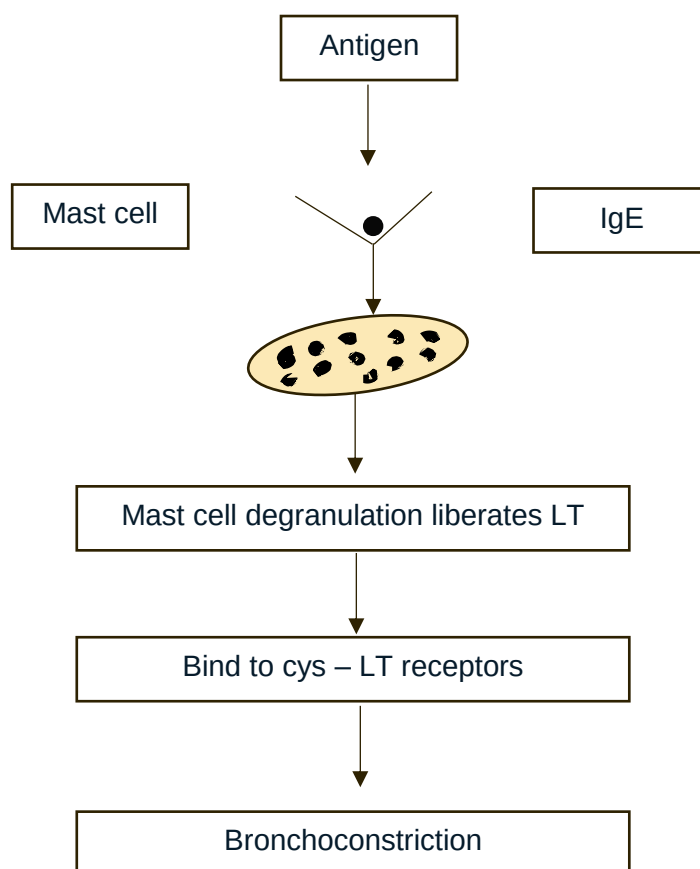
1. **Mild intermittent:** Symptoms not more than 2/week
2. **Mild persistent:** Symptoms more than 2/week but not daily
3. **Moderate persistent:** Daily symptoms
4. **Severe persistent:** Continued symptoms with limited physical activity.



## Pathogenesis

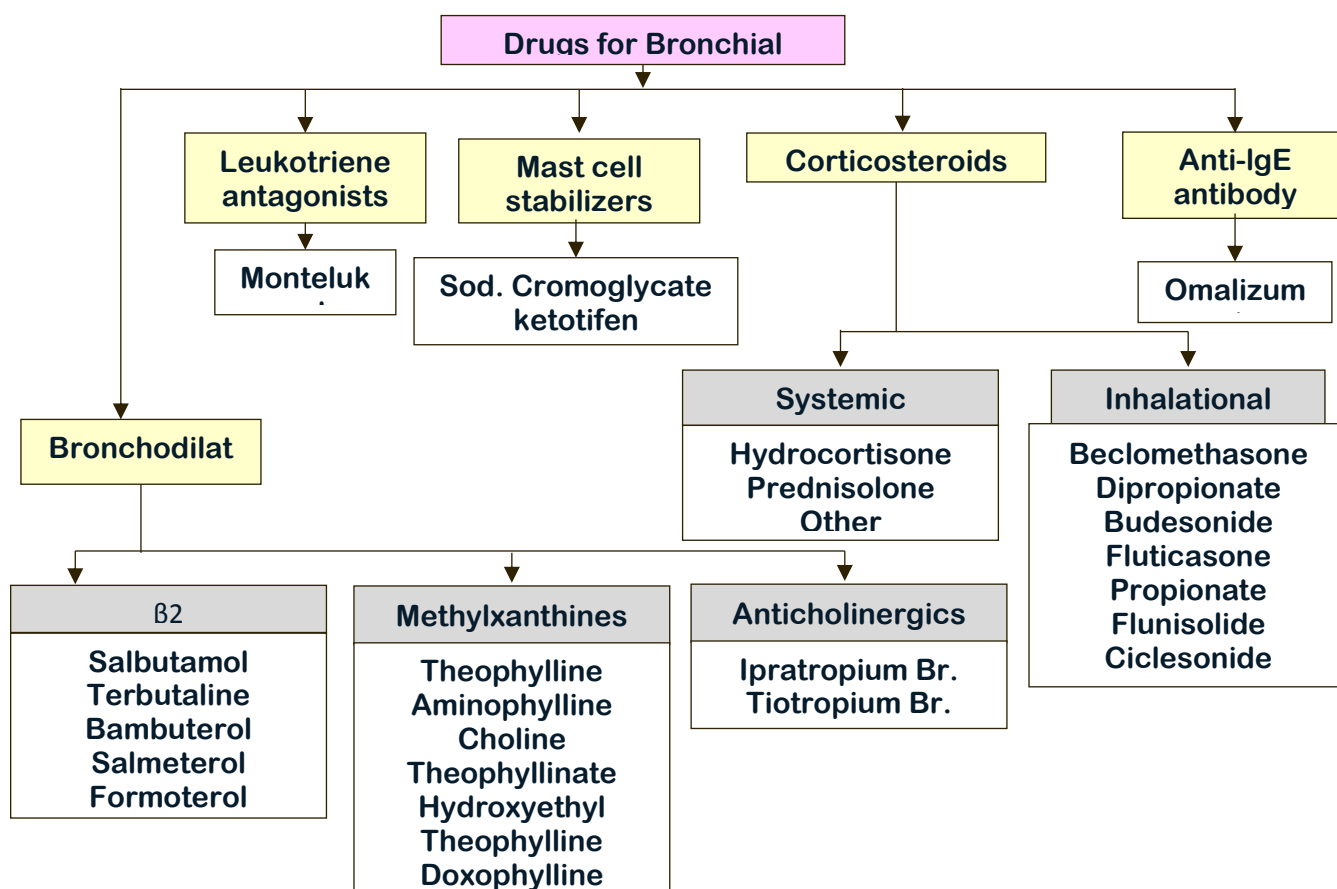
- Asthma is type I hypersensitivity

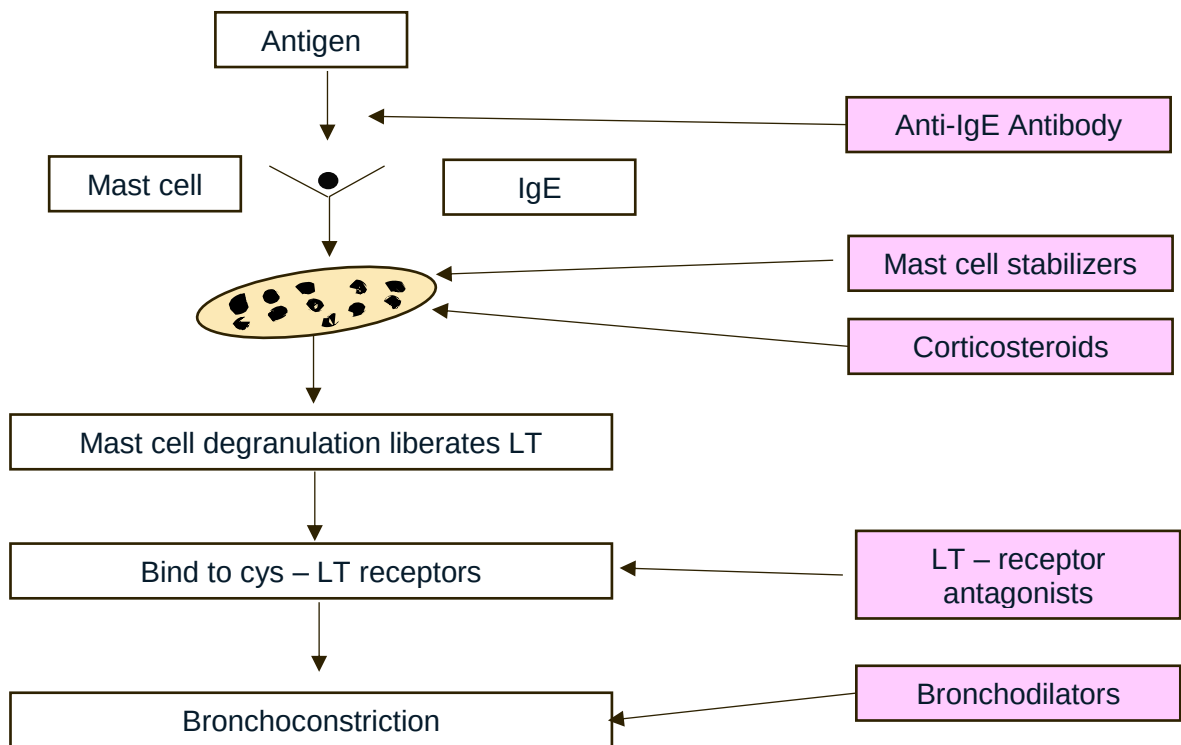




## DRUGS FOR ASTHMA

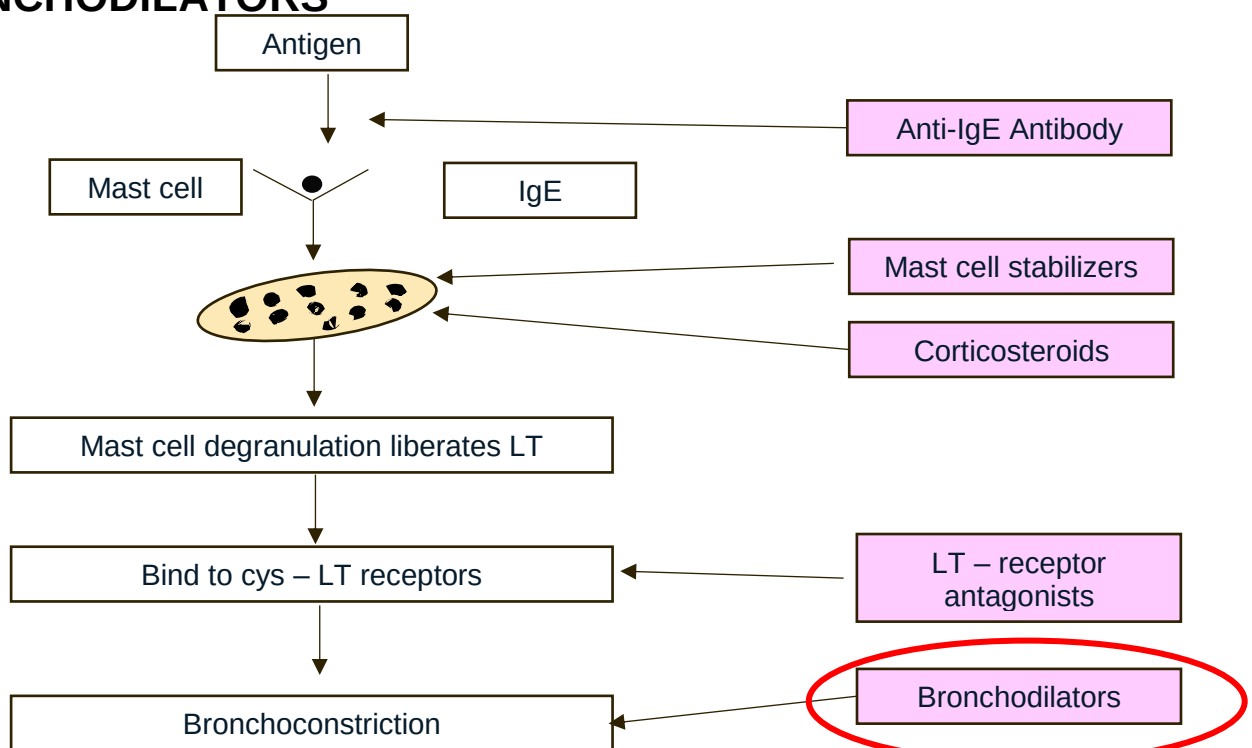
### Classification





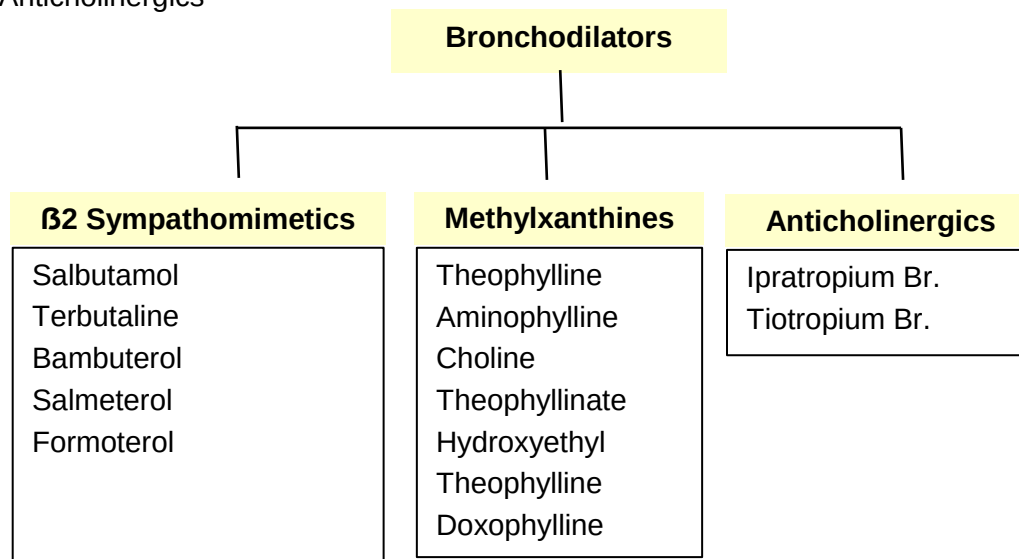
|                 | Bronchodilators | LT Antagonists | Mast Cell Stabilizers | Corticosteroids | Anti-IgE Antibody |
|-----------------|-----------------|----------------|-----------------------|-----------------|-------------------|
| Classification  |                 |                |                       |                 |                   |
| MOA             |                 |                |                       |                 |                   |
| Use             |                 |                |                       |                 |                   |
| Adverse effects |                 |                |                       |                 |                   |
| Interaction     |                 |                |                       |                 |                   |

## BRONCHODILATORS

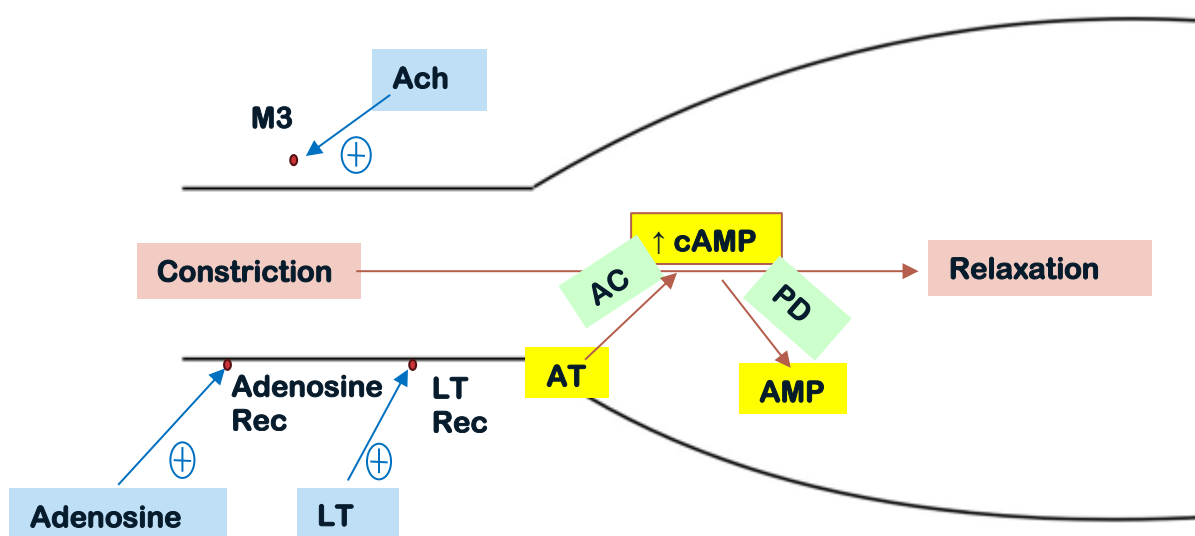
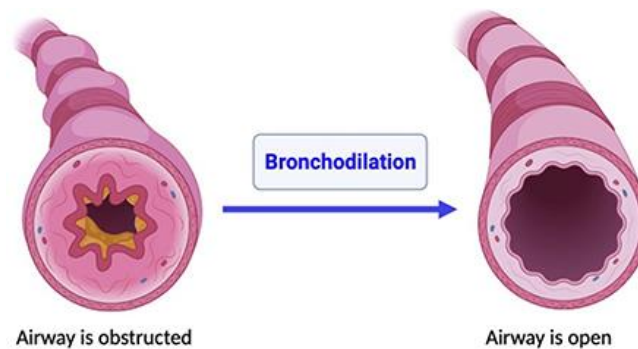


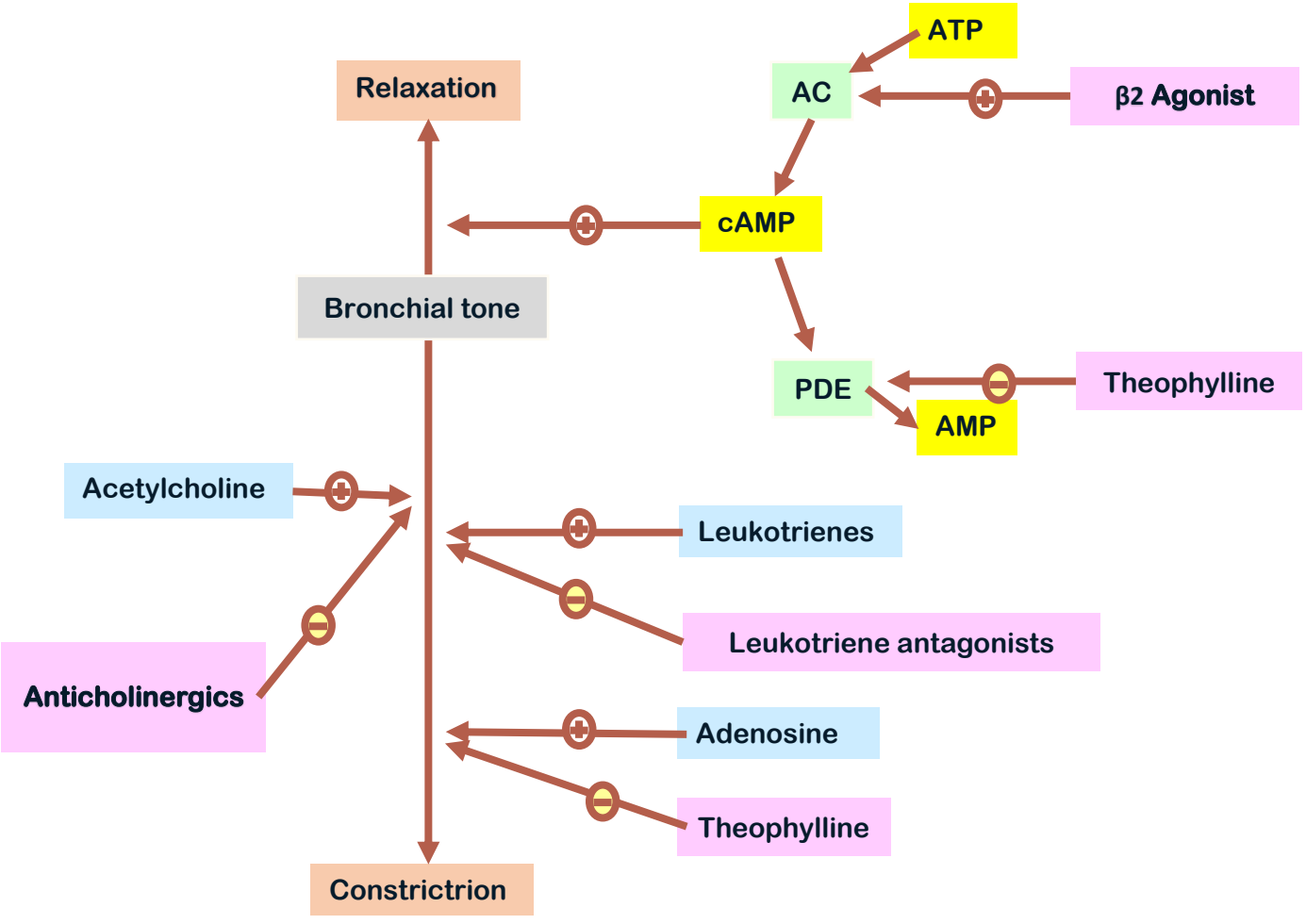
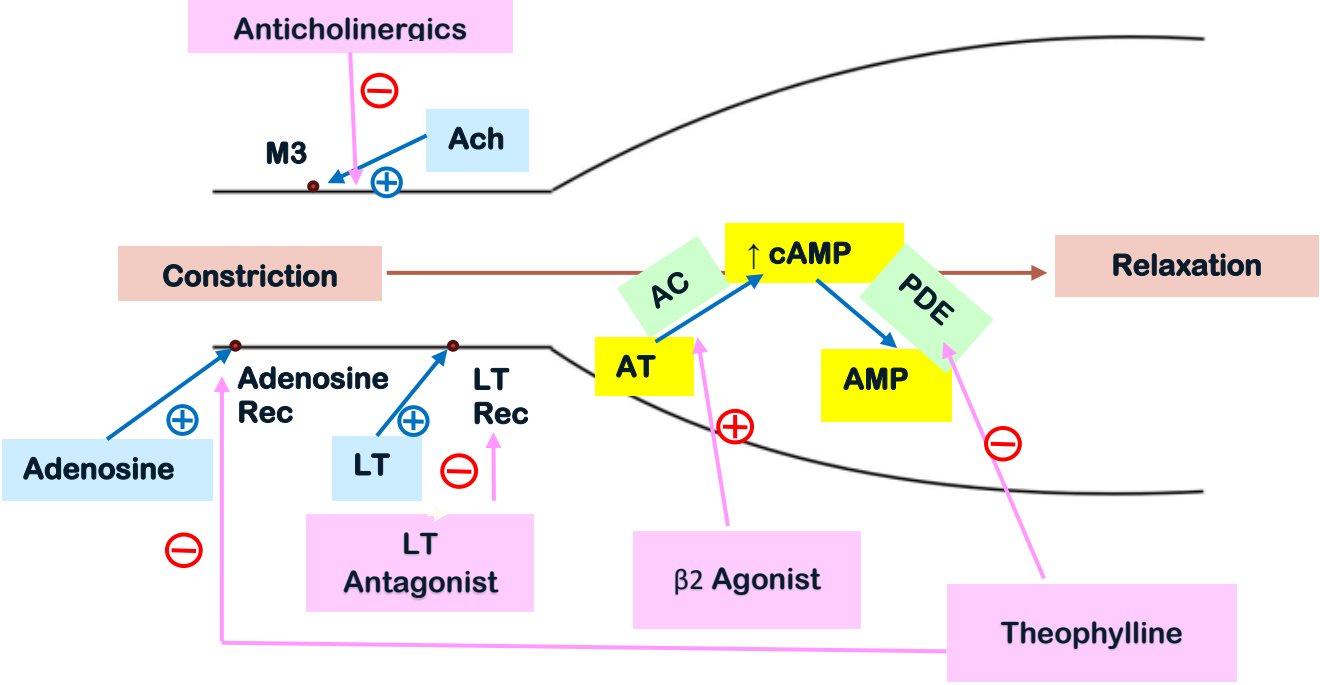
## Classification

- $\beta_2$  Sympathomimetics
- Methyl Xanthines
- Anticholinergics



## Physiology of Bronchus constriction and Dilatation





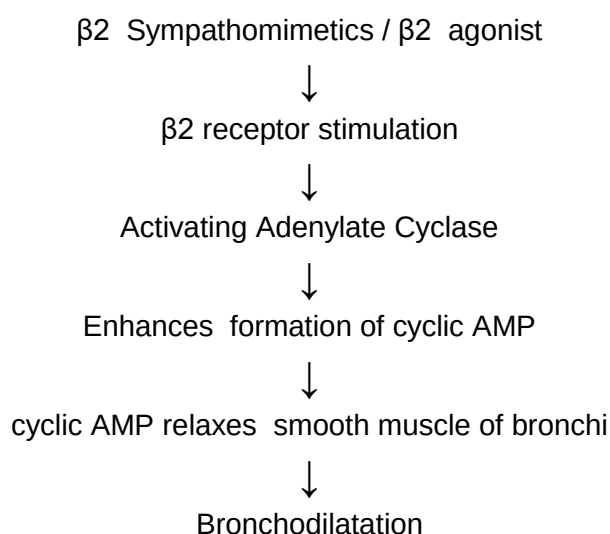


## A) B2 SYMPATHOMIMETICS

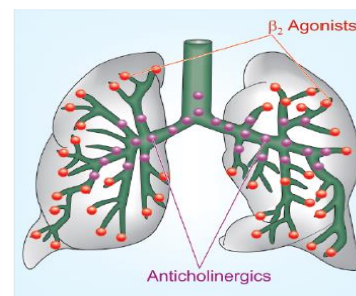
### Classification

| <b>β2 Sympathomimetics</b> |
|----------------------------|
| Salbutamol                 |
| Terbutaline                |
| Bambuterol                 |
| Salmeterol                 |
| Formoterol                 |

### MOA

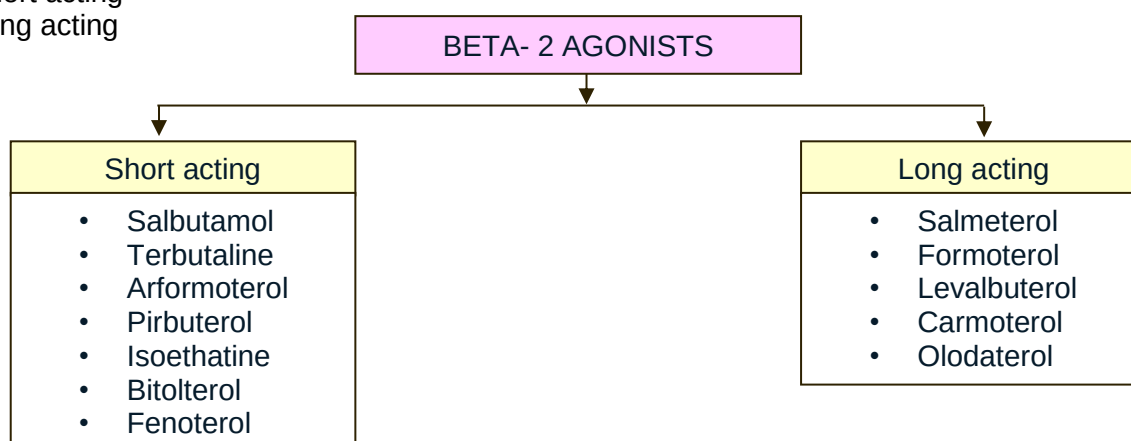


- Non-specific β activation leads to β mediated stimulation of heart with potential of producing tachycardia, palpitation and arrhythmia.
- Hence specific β2 agonists are preferred in asthma
- β2 agonists have no antiinflammatory action.
- Act primarily in small airways



### Types

- Short acting
- Long acting



## Route

- To achieve a rapid, local effect and minimize systemic toxicity, inhalation therapy is preferred.
- By inhalational route → these are fastest acting drugs
- Success inhalation depends on maintenance of size of particles and breathing co-ordination.



## Size of particles

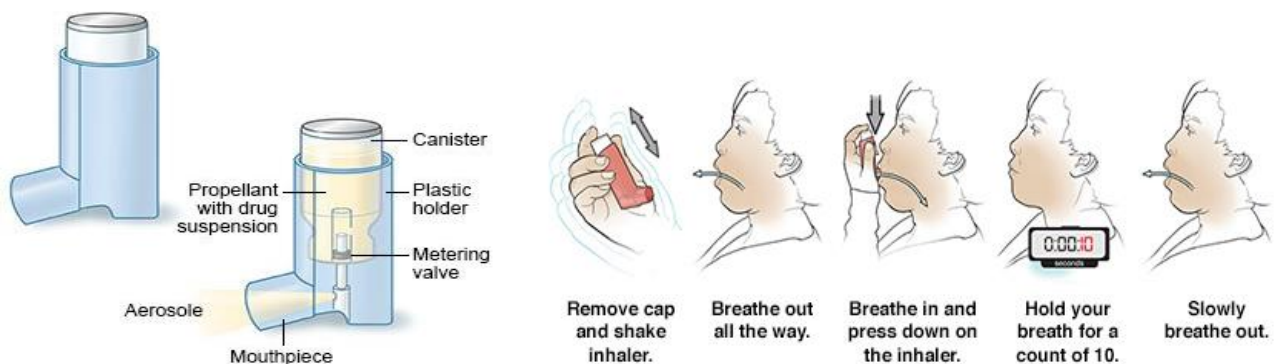
- **Particles more than 10  $\mu\text{m}$  size** → get deposited in the mouth and oropharynx
- **Particles less than 0.5  $\mu\text{m}$**  → inhaled and immediately exhaled without being deposited in lungs.
- **Particles size 1 to 5  $\mu\text{m}$**  → Optimum size of particles for an effective deposition in the lungs

## Inhalational devices

1. MDI (meter dose inhaler)
2. Nebulizer
3. Dry powder inhalation → rotacaps

### 1. MDI (Meter dose inhaler)

- Micronized drug in suspension or solution
- It needs hand-breathing coordination and a propellant to push it.
- Chlorofluorocarbon (CFC) is used as propellant but it is an environmental pollutant, disrupts the protective ozone layer
- It is now being replaced with hydro-fluoroalkane that does not deplete ozone layer.



### 2. Nebulizer

- Nebulizer needs minimum coordination of the patient and therefore it is suitable for severely ill patient.
- It retains a large amount of drug
- It is costly
- Needs the maintenance
- Takes time to administer drug.



### 3. Dry powder inhalation

- Portable devices
- Capsule (rotacap) containing drug is punctured/cut across
- Powder is aerosolized by inspiratory air flow of the patient.
- It is environmental friendly since no propellant is required.
- It needs minimum co-ordination
- But needs sufficient inspiratory rate (60 L/minute), which is difficult to maintain with active bronchospasm.



### Uses

- First-line drugs for bronchial asthma.
  - **Short acting** → Used for aborting an attack of acute asthma
  - **Long acting** → Useful only for prophylaxis

### Adverse effects

1. Tachycardia palpitation, arrhythmia
2. Tremors
3. Hypokalemia
4. Hyperglycemia
5. Tolerance develops with continuous use due to desensitization of the receptor

### Contraindications

- Ischaemic heart disease patients

## B) METHYL XANTHINES

### Classification

#### Methylxanthines

Theophylline  
Aminophylline  
Choline  
Theophyllinate  
Hydroxyethyl  
Theophylline  
Doxophylline

### MOA

3 MOA→

#### 1. Inhibition of PDE

Methylxanthines

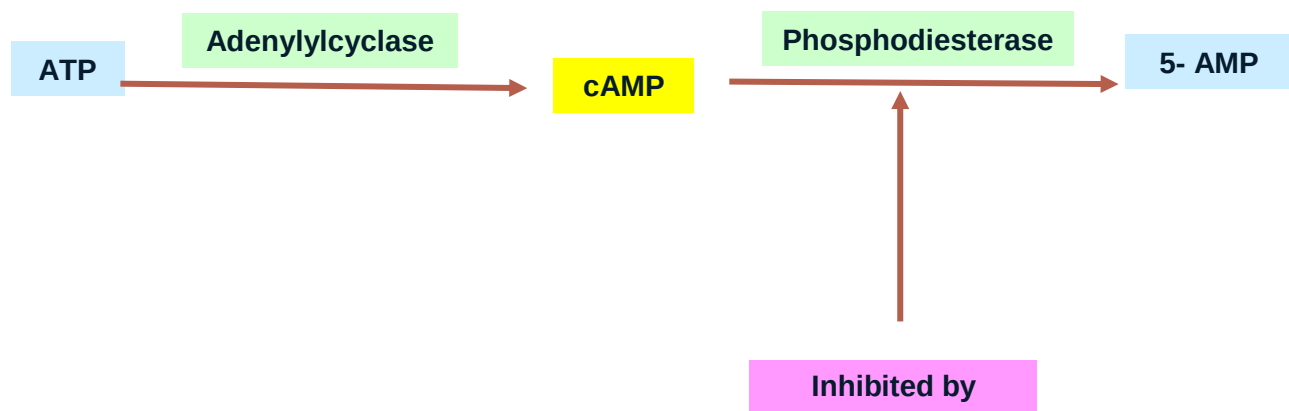


Inhibit of phosphodiesterase (PDE) (which degrades cAMP)

↓  
cAMP is not degraded

↓  
Concentration of cAMP is increased

↓  
Bronchodilatation



## 2. Blockade of adenosine receptors

- Adenosine →
  - Acts as a local mediator in smooth muscles
  - Contracts smooth muscles in bronchi

Methylxanthines

↓  
Causes Blockade of adenosine receptors  
↓  
Bronchodilatation

## 3. On mast cells

Theophylline

↓  
Decreases release of histamine and other mediators from mast cells and activated inflammatory cells.  
↓  
Therapeutic effect in bronchial asthma

## Other Actions

### 1. CNS

- CNS stimulants
- Higher doses cause nervousness, restlessness, panic, insomnia and excitement. Still higher doses produce tremors, delirium and convulsions.

## 2. CVS

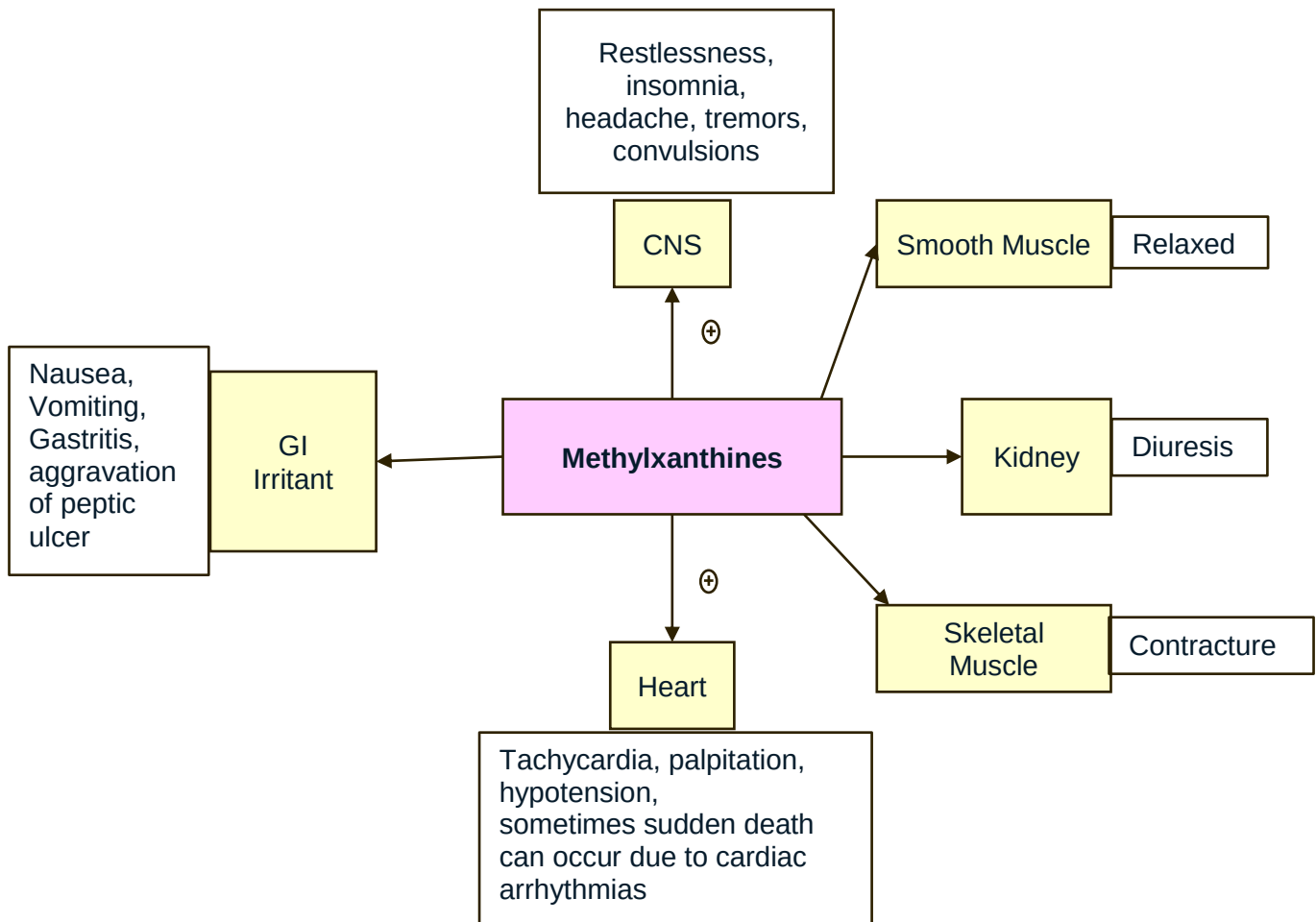
- Directly stimulate heart
- Increase force of myocardial contractions → Positive inotropic and chronotropic
- At high doses cardiac arrhythmias may be produced

## 3. Smooth muscles → Relaxed

## 4. Kidney → Mild diuretics

## 5. Skeletal muscles → Enhances contractile power of skeletal muscle. At toxic doses contracture is produced.

## 6. Stomach → Enhance secretion of acid and pepsin



## Pharmacokinetics

- Theophylline work within a narrow therapeutic window.
  - 5-20 µgm/ml → Optimum concentration
  - 20-40 µgm/ml → Arrhythmia appears
  - >40 µgm/ml → produces convulsions

## Uses

1. **Bronchial asthma and COPD** → Theophylline is used as an additional drug in moderate or severe persistent bronchial asthma.
2. **Apnoea in premature infants** → Aminophylline/cafeine is used intravenously to reduce the duration of apnoea episodes. Caffeine is safer than aminophylline

## Adverse effects

- Nausea, vomiting
- Hyperacidity
- Tachycardia
- Palpitation
- Arrhythmia
- Restlessness
- Insomnia
- Tremors
- Seizures

## Interactions

- Theophylline is metabolized by CYP3A4
  - So extensively metabolized in liver.
1. Theophylline metabolism is increased by enzyme inducers (phenytoin, rifampicin, phenobarbitone, carbamazepine, smoking) → Thus the dose should be increased with concomitant use of enzyme inducers
  2. Theophylline metabolism is inhibited and toxicity level is increased by enzyme inhibitors (cimetidine, erythromycin, ciprofloxacin, oral contraceptives) → Thus the dose should be decreased with concomitant use of enzyme inhibitors.

### Enzyme Inhibitors

- |              |   |                   |
|--------------|---|-------------------|
| ➤ Vitamin    | - | Valproate         |
| ➤ K          | - | Ketoconazole w ww |
| ➤ Cannot     | - | Cimetidine        |
| ➤ Cause      | - | Ciprofloxacin     |
| ➤ Enzyme     | - | Erythromycin      |
| ➤ Inhibition | - | INH               |

### Enzyme Inducers

- |           |   |                |
|-----------|---|----------------|
| ➤ G       | - | Griseofulvin   |
| ➤ P       | - | Phenytoin      |
| ➤ R       | - | Rifampicin     |
| ➤ S       | - | Smoking        |
| ➤ Cell    | - | Carbamazepine  |
| ➤ Phone   | - | Phenobarbitone |
| ➤ Battery | - | Barbiturate    |
| ➤ Dead    | - | DDT            |

## C) ANTICHOLINERGICS

### Classification

1. Ipratropium bromide → short acting (duration 4–6 hours) inhaled anticholinergic bronchodilator
2. Tiotropium bromide → long acting (duration 24 hours).

### MOA

Ach  
↓

Acts on M3 receptor on bronchi



Bronchoconstriction

Anticholinergics

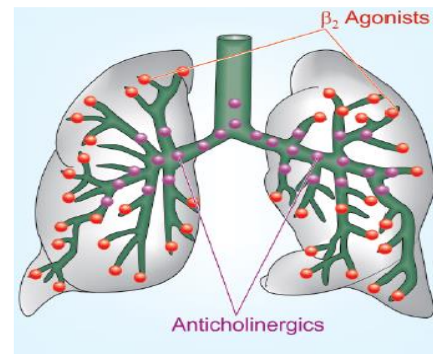


Block M3 receptor on bronchi



Bronchodilatation

- Act primarily in the larger airways (not bronchi like  $\beta_2$  agonists)



## Uses

- Less efficacious than inhaled  $\beta_2$  sympathomimetics in bronchial asthma
- Produce slower response than inhaled  $\beta_2$  sympathomimetics and
- Better suited for regular prophylactic use than for quick relief of breathlessness.
- Combination of inhaled ipratropium with  $\beta_2$  agonist produces more marked and longer lasting bronchodilatation → their effects are additive

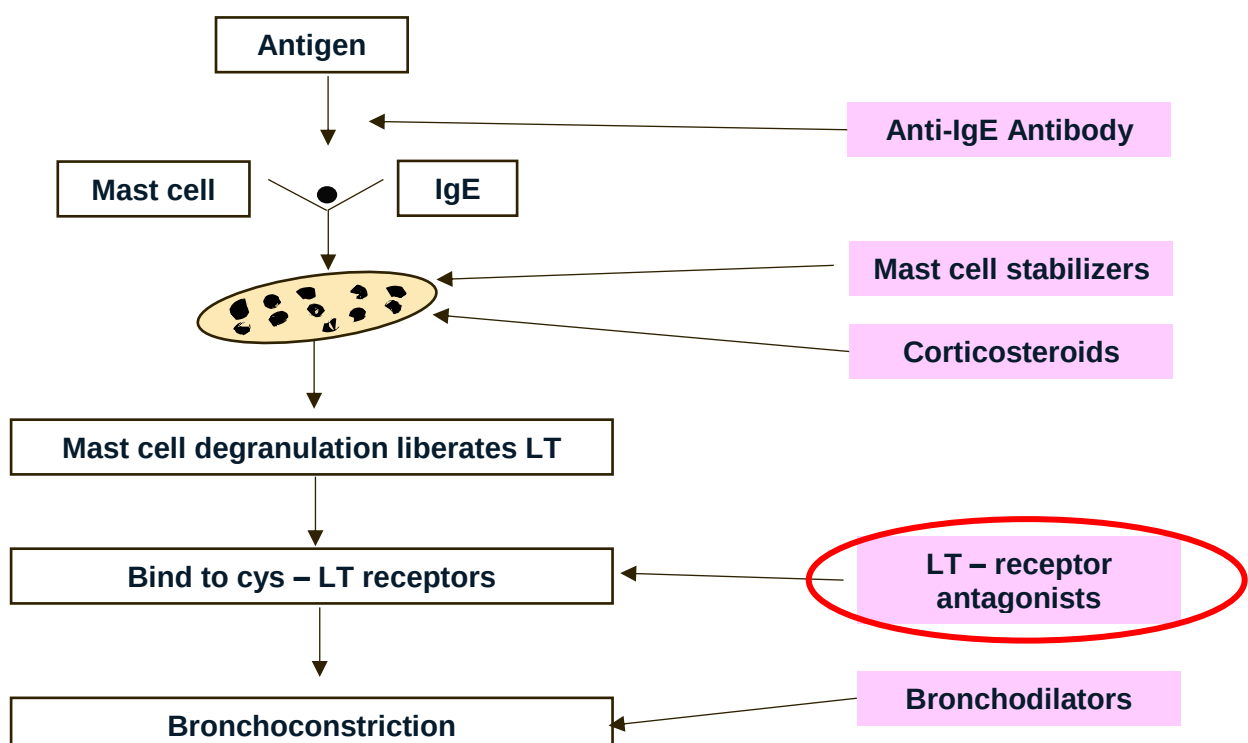
## Adverse effects

- Dryness of mouth
- Scratching of trachea
- Cough

## Contraindication

- BPH and urinary retention

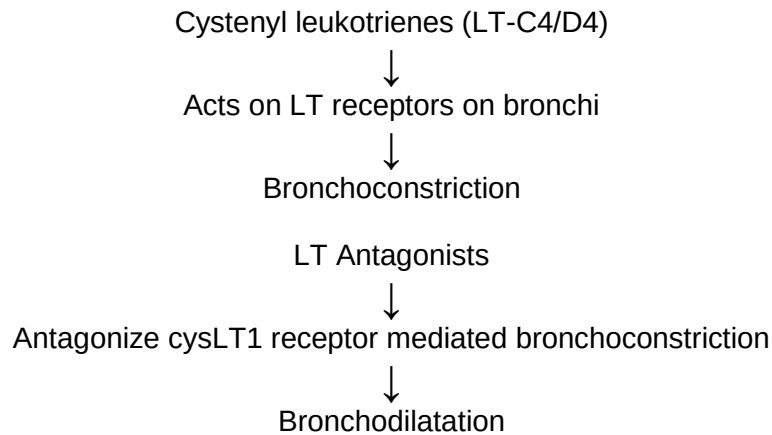
## LT ANTAGONISTS



## Classification

- Montelukast
- Zafirlukast

## MOA



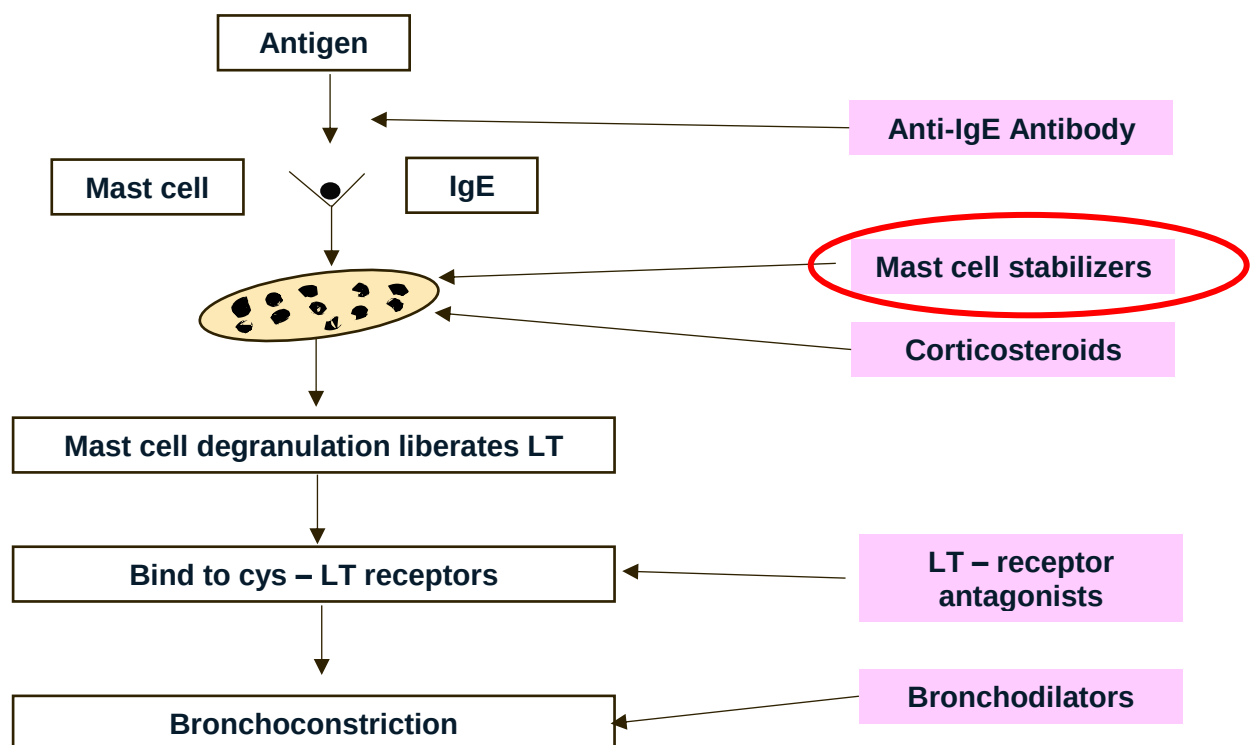
## Uses

1. Prophylactic therapy of mild-to-moderate asthma
2. Aspirin-induced asthma
3. Exercise induced asthma
  - They are not used for terminating asthma episodes
  - Efficacy is low

## Adverse effects

- Headache
- Rashes
- Eosinophilia
- Neuropathy
- Few cases of Churg-Strauss syndrome have been reported

## MAST CELL STABILIZERS

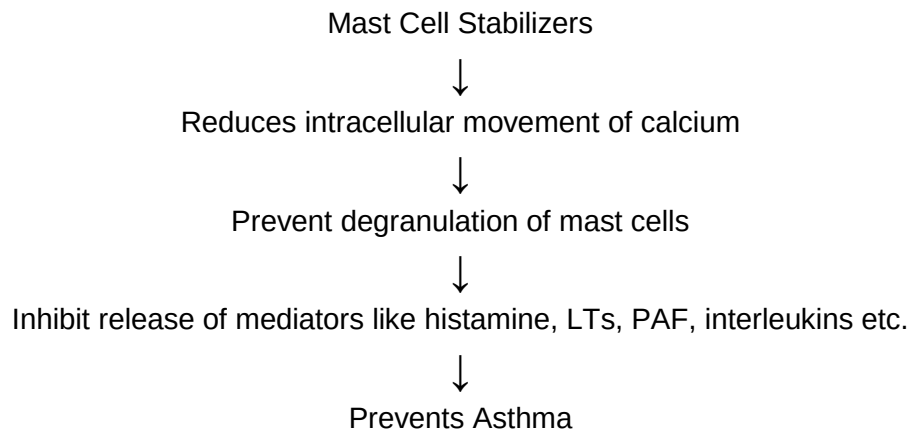




## Classification

- Sodium cromoglycate
- Ketotifen
- nedocromil

## MOA



## Route

- **Sodium cromoglycate** → not absorbed orally, therefore it is used by inhalational route.
- **Ketotifen** → absorbed orally and is used by this route

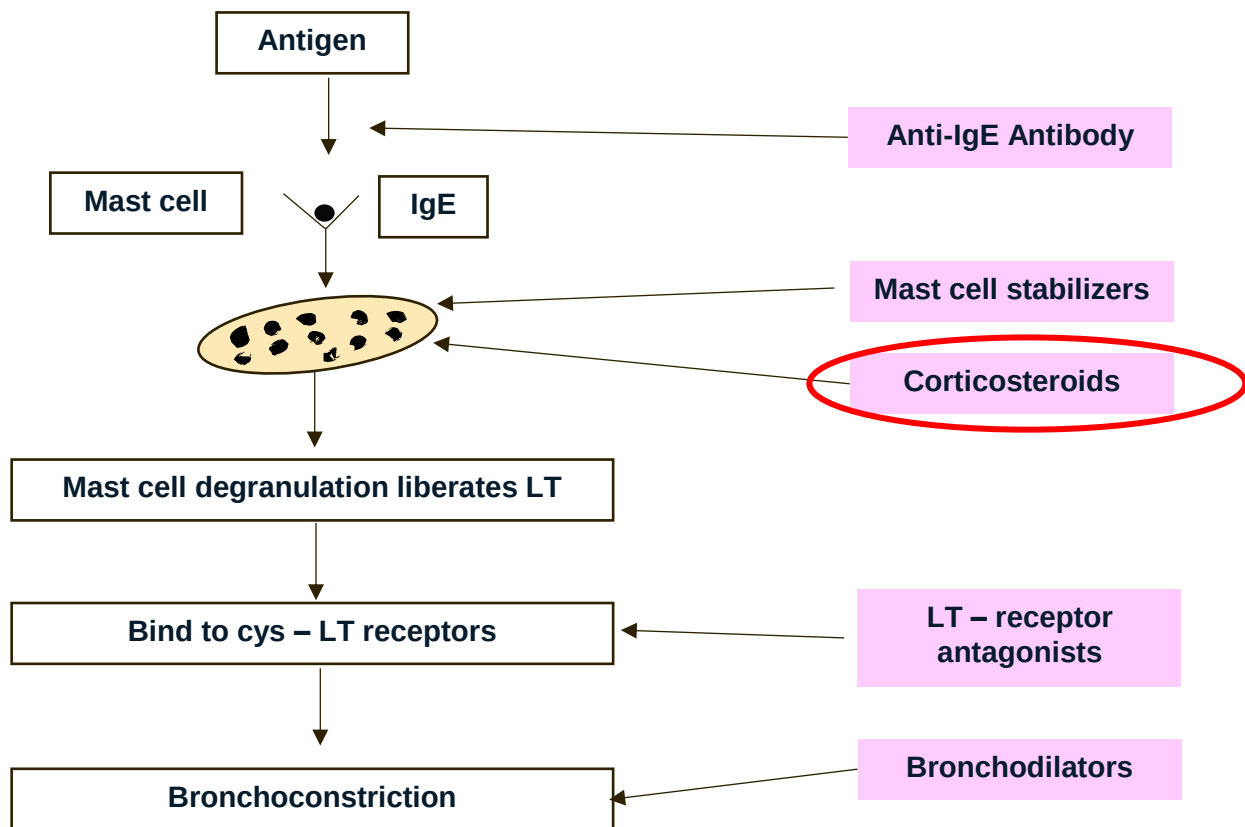
## Uses

- Preventive therapy in asthma
- Allergic rhinitis
- Allergic conjunctivitis
- Systemic mastocytosis
- Food allergies
- Ulcerative colitis
- Not suitable for an acute attack since →
  - About 4-6 weeks are required for sufficient response.
  - Degranulation of mast cells with release of inflammatory mediators has already occurred.

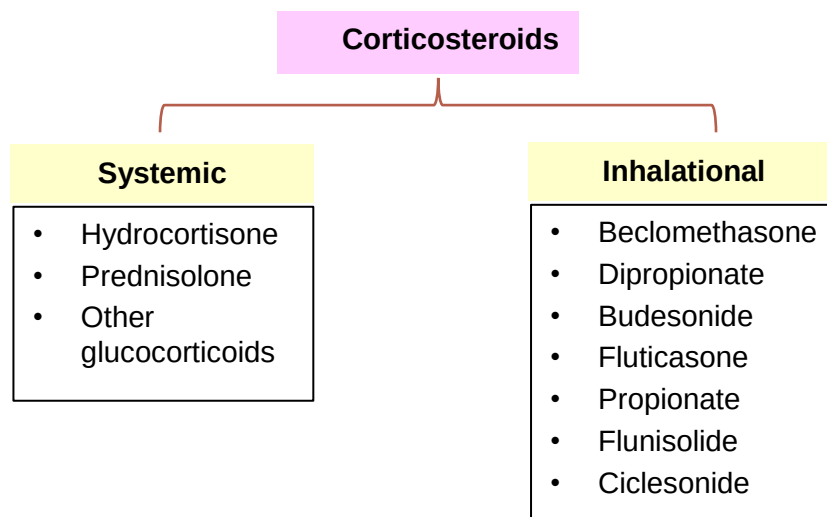
## Adverse effects

- Bitter taste
- Throat irritation
- Allergic reactions

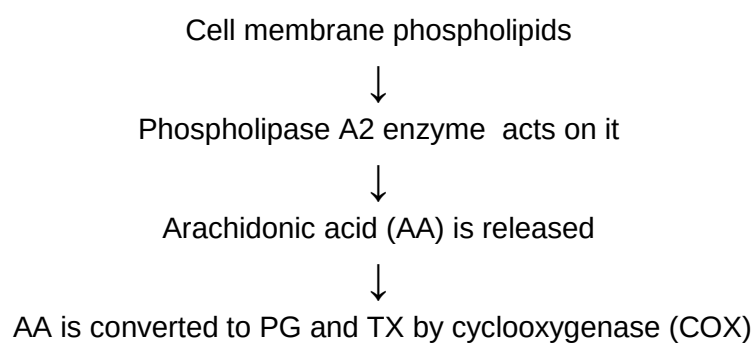
# CORTICOSTEROIDS

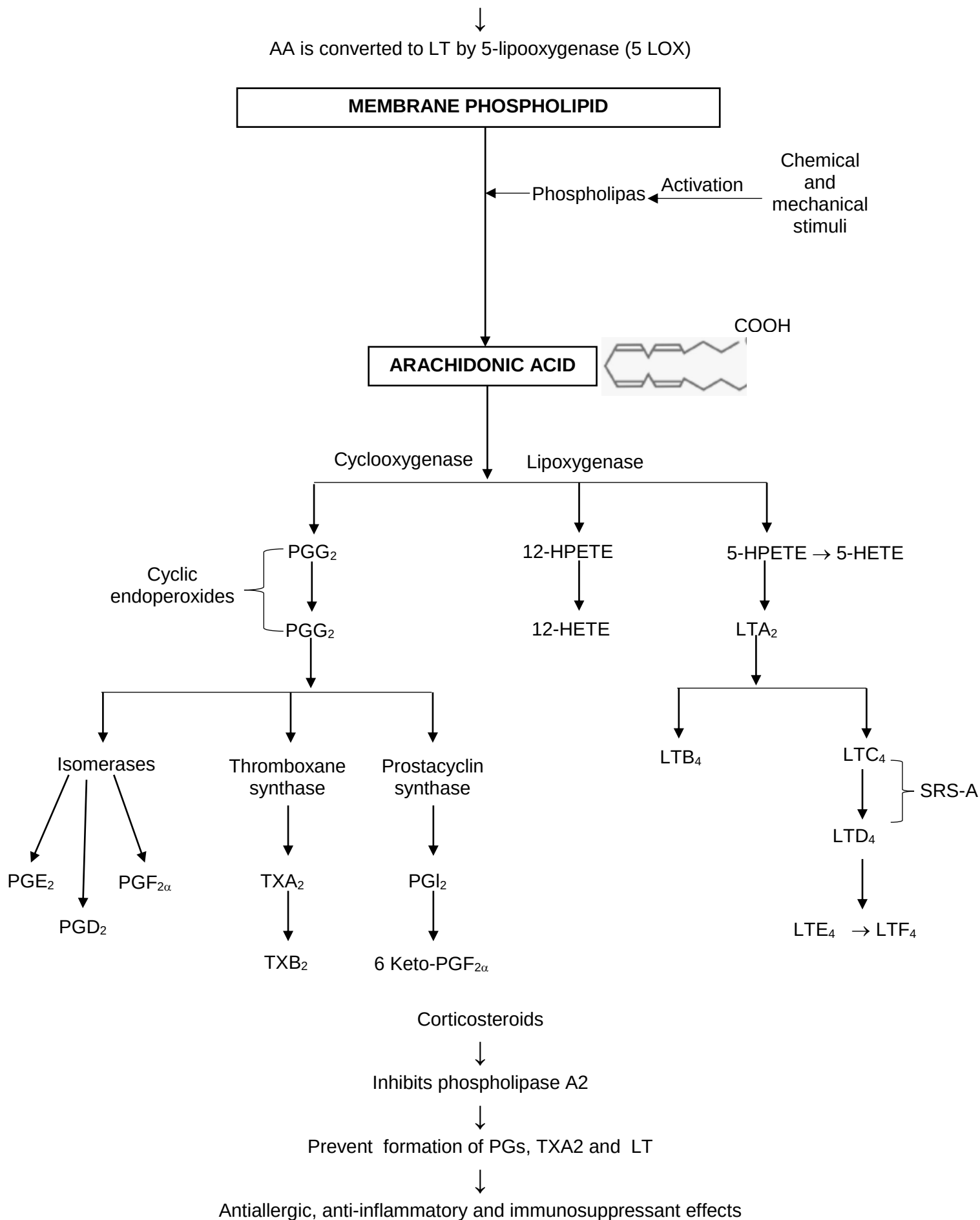


## Classification



## MOA





## Remember

- They are not bronchodilators
- They benefit by Antiinflammatory action
- Antiinflammatory action is due to decreased recruitment of inflammatory cells as well as decreased production of PGs and LTs.
- Corticosteroids afford more complete and sustained symptomatic relief than bronchodilators or cromoglycate
  1. Improve airflow
  2. Reduce asthma exacerbations
  3. May influence airway remodeling
  4. Retarding disease progression.
  5. Increase airway smooth muscle responsiveness to  $\beta_2$  agonists and reverse refractoriness to these drugs.

## Uses

- A. Inhaled steroids
- B. Systemic Steroid

### A. Inhaled steroids

- Inhaled steroids are not considered necessary for patients with mild and episodic asthma.
- They are indicated when inhaled  $\beta_2$ -agonists are required almost daily
- They have no role during acute attack or in status asthmaticus

### B. Systemic Steroid

- Systemic steroid therapy is resorted to in asthma under the following 2 situations:
  1. Severe chronic asthma: not controlled by bronchodilators and inhaled steroids
  2. Status asthmaticus/acute asthma exacerbation → Asthma attack not responding to intensive bronchodilator therapy

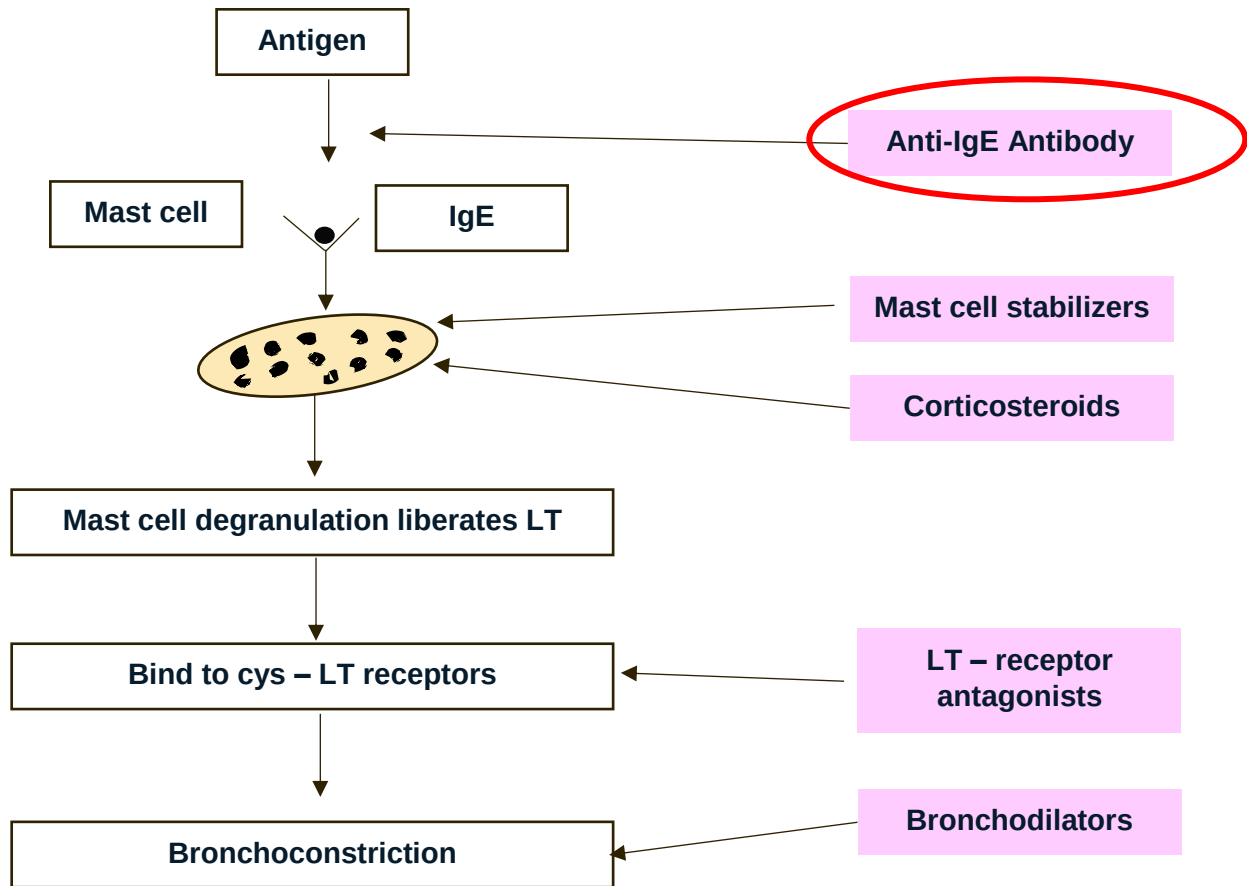
## Dose

1. Start with high dose of a rapidly acting i.v. glucocorticoid which generally acts in 6–24 hours
2. Shift to oral therapy for 5–7 days
3. Then taper rapidly.

## Adverse effects

1. Suppression of HPA axis
2. Bone resorption
3. Skin atrophy
4. Cataract
5. Hypertension
6. Diabetes
7. Growth retardation
8. Psychosis
9. Peptic ulcer

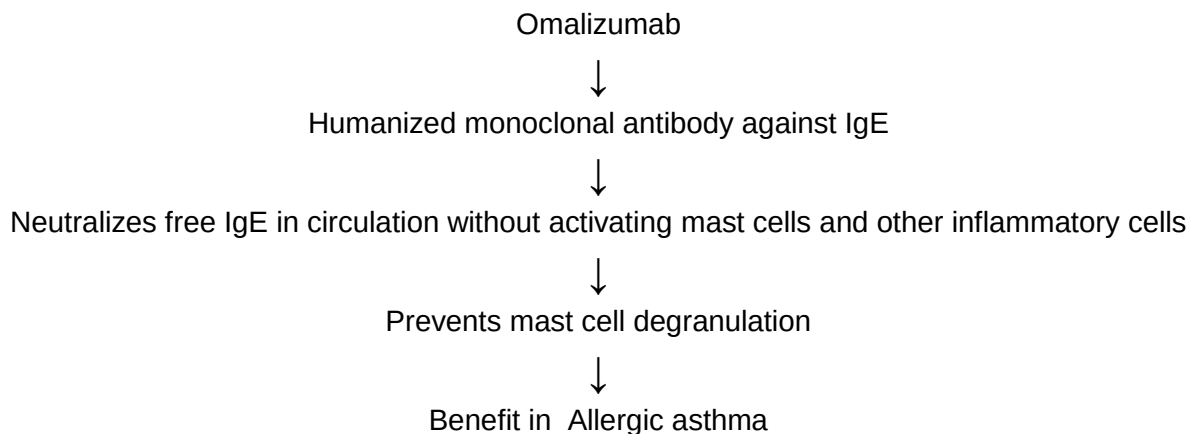
## ANTI - IGE ANTIBOD



### Classification

- Omalizumab

### MOA



- It has no effect on IgE already bound to mast cells

### Uses

- Administered s.c.
- Use is reserved for resistant asthma patients with positive skin tests or raised IgE levels

## Adverse effects

- Local side effects → redness, stinging, itching and induration.
- Very expensive
- No benefit has been noted in nonallergic asthma.

## CHOICE OF TREATMENT IN ASTHMA

- Seasonal asthma
- Mild episodic asthma
- Mild chronic persistent asthma
- Moderate asthma
- Severe asthma
- Status asthmaticus / Refractory asthma

### Seasonal asthma

#### Treatment →

- Start regular low-dose inhaled steroid (200–400 µg/day) or cromoglycate 3–4 weeks before anticipated seasonal attacks and Continue till 3–4 weeks after the season is over.
- Treat individual episodes with inhaled short-acting β<sub>2</sub> agonist.

### Mild episodic asthma

- Symptoms less than once daily, normal in between attacks

#### Treatment →

- Inhaled short-acting β<sub>2</sub> agonist at onset of each episode.
- Since asthma is intermittent, it does not require continuous prophylactic therapy

### Mild chronic (persistent) asthma

- Symptoms once daily or so, subnormal ventilatory performance

#### Treatment →

- Regular low-dose (100–500 µg/day) inhaled steroid or Inhaled cromoglycate or oral theophylline, but these are less effective.
- Episode treatment with inhaled short acting β<sub>2</sub> agonis

### Moderate asthma with frequent exacerbations

- Attacks affect activity, occur > 1 per day or mild baseline symptoms

#### Treatment →

- Increasing doses of inhaled steroid (up to 800 µg/day) + Inhaled long-acting β<sub>2</sub> agonist

### Severe asthma

- Continuous symptoms; activity limitation; frequent exacerbations/ hospitalization

#### Treatment →

1. Regular high dose inhaled steroid (800–2000 µg/day) through a large volume spacer device + Inhaled long-acting β<sub>2</sub> agonist (salmeterol) twice daily
2. Additional treatment with one or more of the following :

- Leukotriene antagonist
  - sustained release oral theophylline
  - oral  $\beta_2$  agonist
  - inhaled ipratropium bromide.
3. Rescue treatment with short-acting inhaled  $\beta_2$  agonist
  4. In patients not adequately controlled or those needing frequent emergency care—institute oral steroid therapy

## Status Asthmaticus

- Severe bronchospasm that does not respond to aggressive therapies within 30-60 minutes
- Severe asthmatic attack with one or more of the following:
  - Dyspnea (precluding speech), accessory muscle use
  - RR 35/min
  - HR > 140/min Peak expiratory flow < 100 l/min
- Hypercapnea ( $\geq 50$  mmHg)
- Any patient of asthma has the potential to develop acute severe asthma which may be life-threatening.
- Upper respiratory tract infection is the most common precipitant.

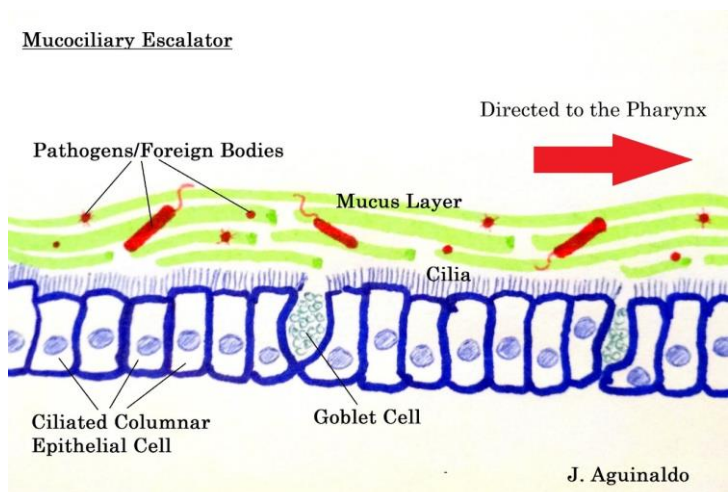
## Treatment →

1. Hydrocortisone hemisuccinate 100 mg (or equivalent dose of another glucocorticoid) i.v. stat, followed by 100–200 mg 4–8 hourly infusion; may take up to 6 hours to act.
2. Nebulized salbutamol (2.5–5 mg) + ipratropium bromide (0.5 mg) intermittent inhalations driven by O<sub>2</sub>
3. High flow humidified oxygen inhalation.
4. Salbutamol/terbutaline 0.4 mg i.m./s.c. may be added, since inhaled drug may not reach smaller bronchi due to severe narrowing/ plugging with secretions.
5. Intubation and mechanical ventilation, if needed.
6. Treat chest infection with intensive antibiotic therapy.
7. Correct dehydration and acidosis with saline + sod. bicarbonate/lactate infusion.

## DRUGS FOR COUGH

### Respiratory defence mechanisms

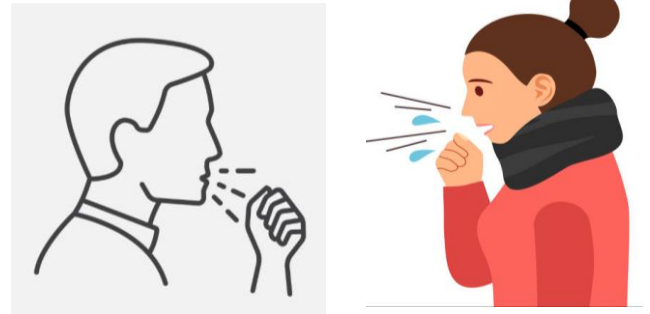
- Normal lung is free of bacteria because of the presence of a number of lung defense mechanisms at different levels such as →
  1. Nasopharyngeal filtering action
  2. Mucociliary action of the lower respiratory airways
  3. Cough reflex
  4. Presence of phagocytosing alveolar macrophages and immunoglobulin



- Macrophages and mucociliary system clears the airways from secretion and foreign materials.
- When these mechanism fail → cough occurs

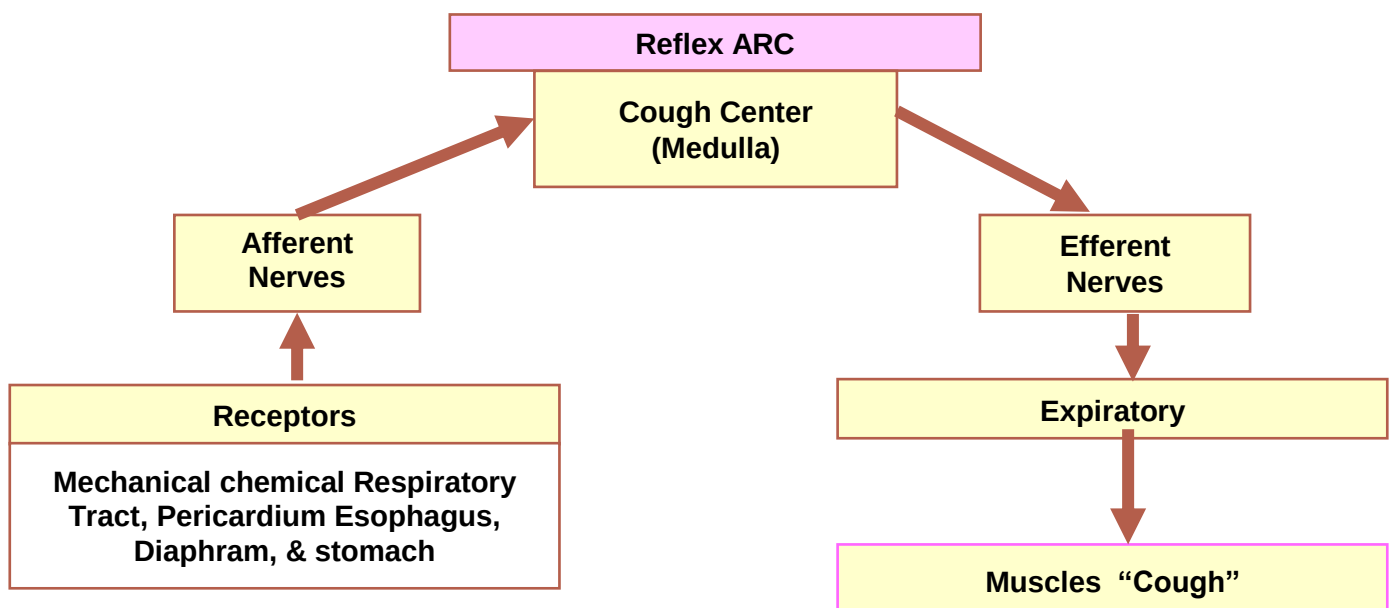
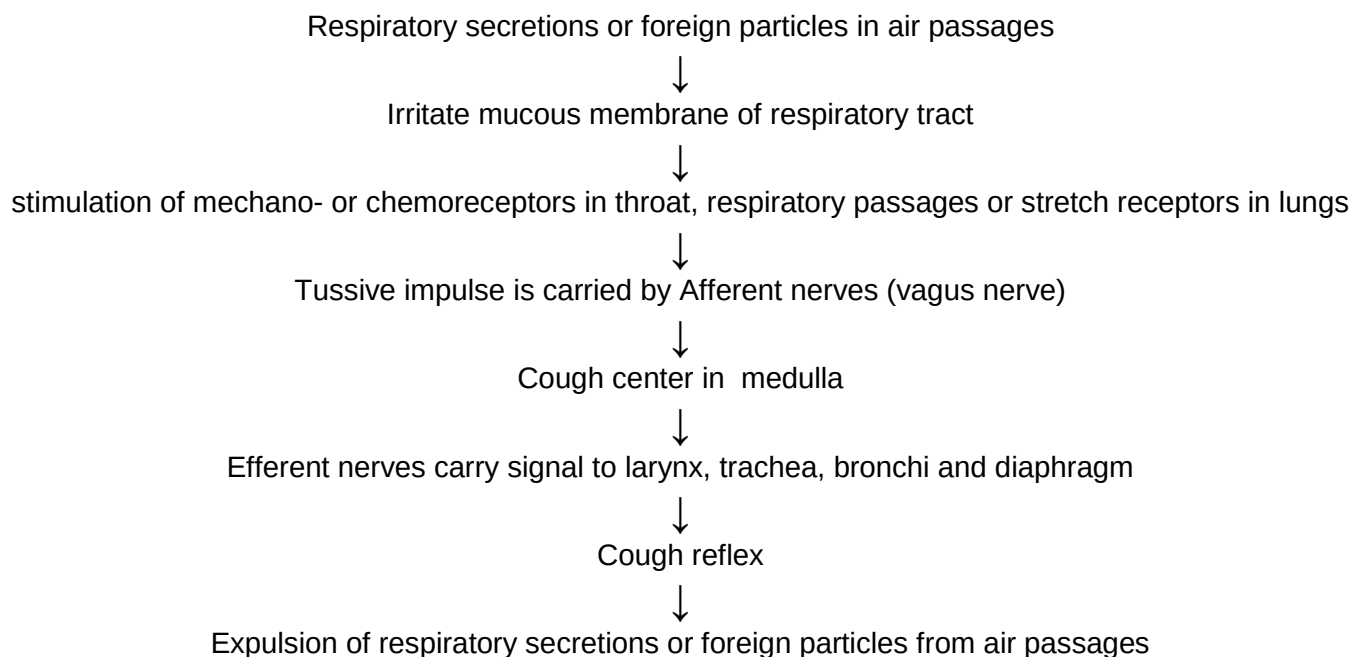
## Cough

- Coughing is the forceful expulsion of air from the lung
- Cough is a protective reflex that clears the respiratory tract, rapidly and efficiently.



## Cough reflex

- **Initiation** → Initiated by irritation of mucous membrane of respiratory tract and coordinated by a cough center in the medulla
- **Stimulation** → Occurs due to stimulation of mechano- or chemoreceptors in throat, respiratory passages or stretch receptors in the lungs.
- **Purpose** → expulsion of respiratory secretions or foreign particles from air passages.





## Types

### 1. Useful or productive:

- When effectively expels the secretion/ with expectoration
- It should not be suppressed
- It should be suppressed only when it is exhausting or dangerous like after eye surgery.



### 2. Useless or non-productive (dry cough):

- When the secretion are not expelled / without expectoration
- It should be suppressed
- If it is ineffective due to thick secretions, convert it to useful, if possible.

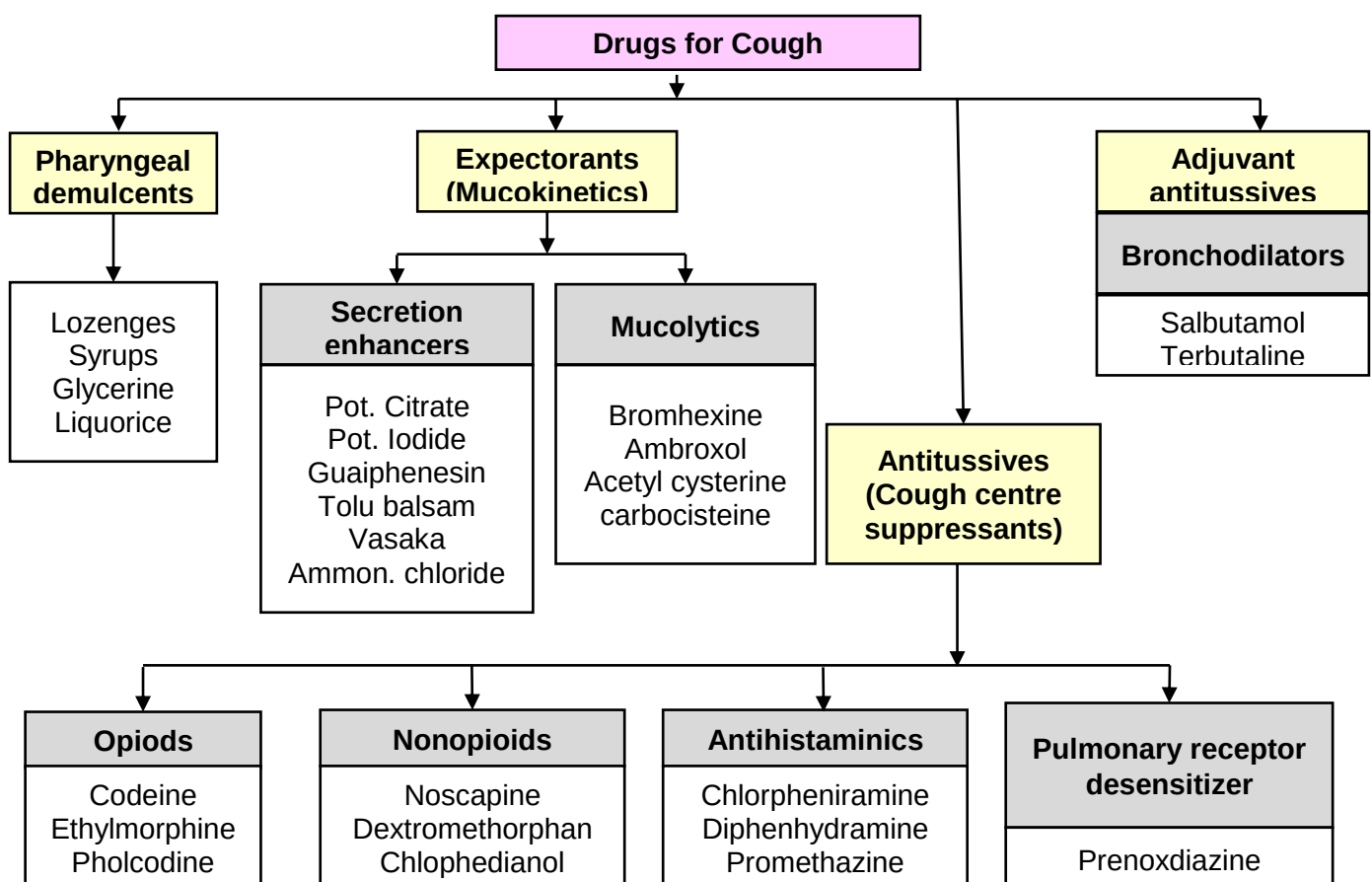


## Cough therapy

1. **No treatment:** For a patient with an acute self-limited illness, causing a nonproblematic cough.
2. **Specific therapy:** To eliminate the cause and the reason for the ineffectiveness of cough.
3. **Symptomatic therapy:** When no specific causes is determined

## Symptomatic therapy

1. Pharyngeal demulcents
2. Expectorants (Mucokinetics)
3. Antitussives (Cough centre suppressants)
4. Adjuvant antitussives



|                  | Pharyngeal demulcents | Expectorants        |            | Antitussives |            |                  |                                 |
|------------------|-----------------------|---------------------|------------|--------------|------------|------------------|---------------------------------|
|                  |                       | Secretion enhancers | Mucolytics | Opioids      | Nonopioids | Anti histaminics | Pulmonary receptor desensitizer |
| Classification   |                       |                     |            |              |            |                  |                                 |
| MOA              |                       |                     |            |              |            |                  |                                 |
| Individual Drugs |                       |                     |            |              |            |                  |                                 |

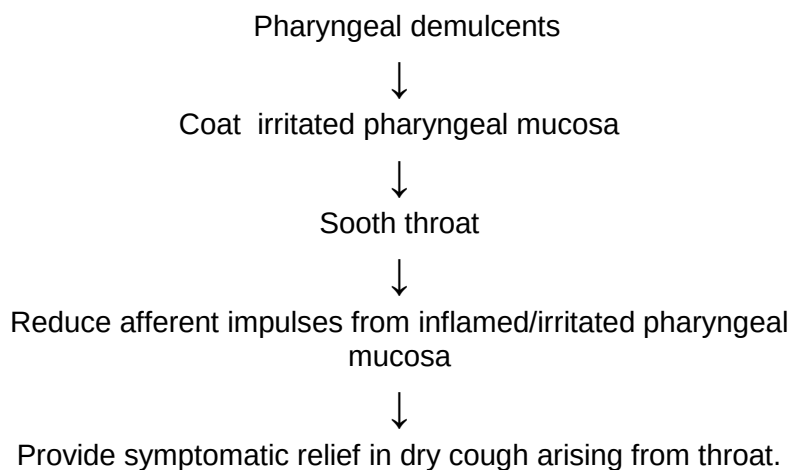
## PHARYNGEAL DEMULCENTS

### Classification

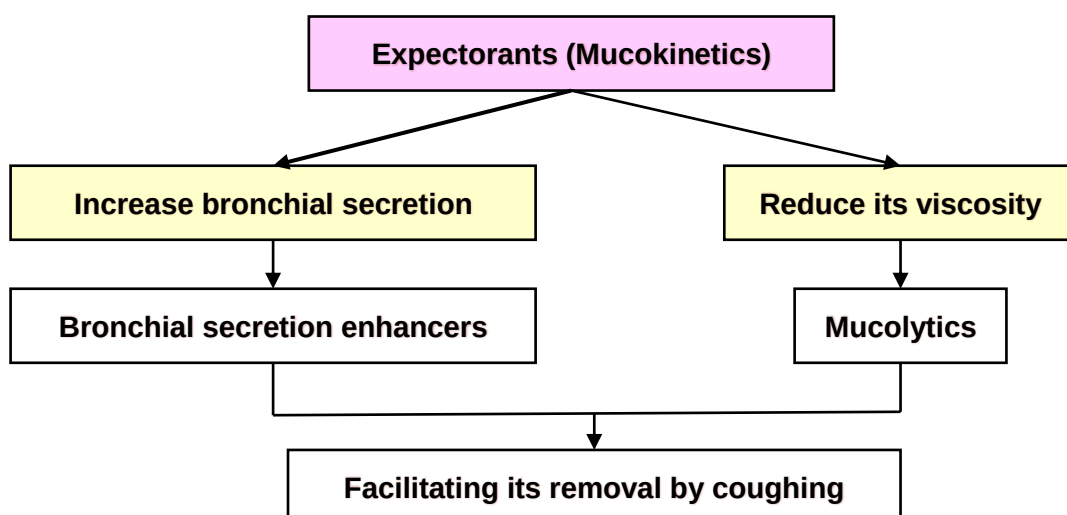
- Lozenges
- Cough drops
- Linctuses containing syrup
- Glycerine
- Liquorice



### MOA



## EXPECTORANTS

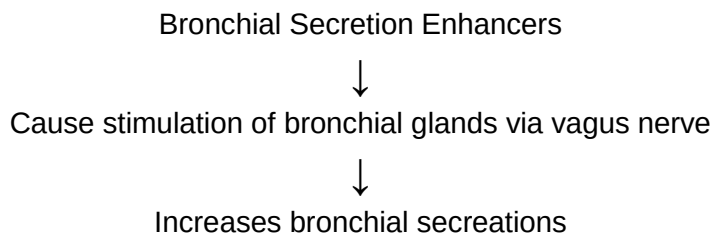


## SECRETION ENHANCERS

### Classification

- Potassium citrate
- Potassium iodide
- Guaifenesin
- Tolu balsam
- Vasaka
- Ammonium chloride

### MOA



### Potassium citrate and Potassium iodide

- Potassium citrate and Potassium iodide are considered to increase bronchial secretion by salt action.
- Potassium iodide is secreted by bronchial glands and irritate the airway mucosa → increase bronchial secretion
- Side effects → Prolonged use can affect thyroid function and produce iodism.
- It is not used now

### Guaifenesin, Vasaka, ammonium chloride.

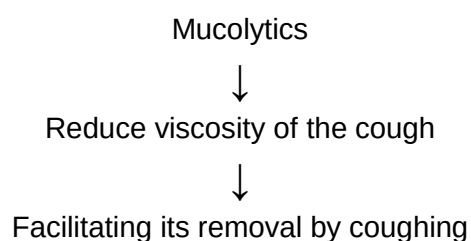
- They irritate gastric mucosa leading to a reflex stimulation of bronchial glands via vagus nerve
- US-FDA has stopped marketing of all expectorants, except guaifenesin.

## MUCOLYTICS

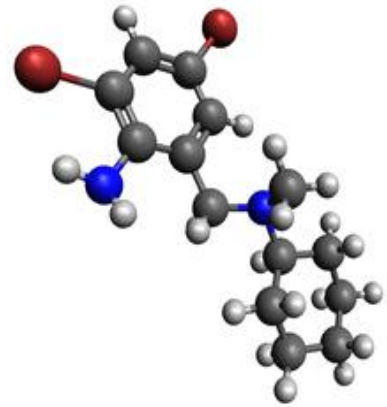
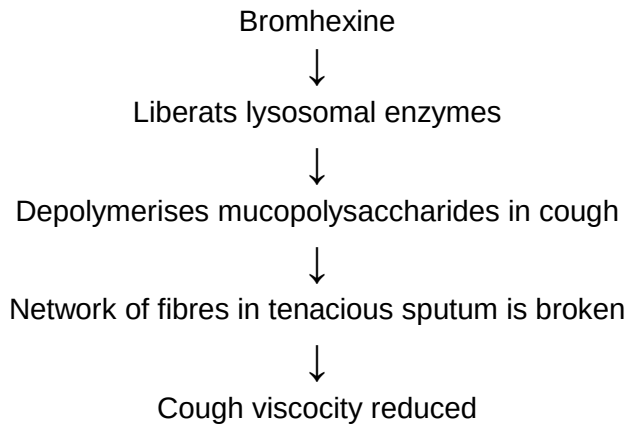
### Classification

- Bromhexine
- Ambroxol
- Acetyl cysteine
- Carbocisteine

### MOA



## Bromhexine

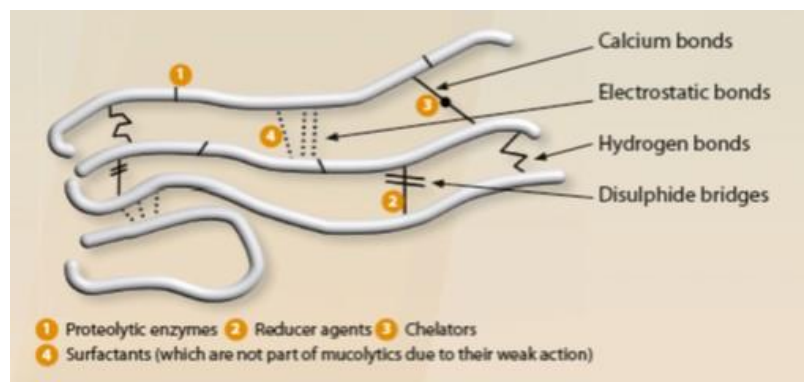
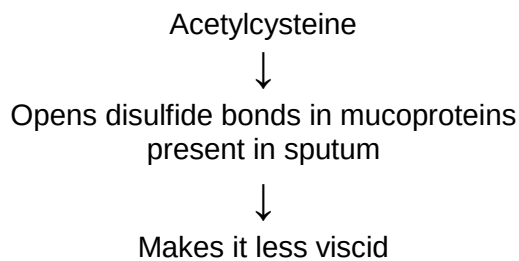


- Side effects → rhinorrhoea and lacrimation, nausea, gastric irritation, hypersensitivity

## Ambroxol

- A metabolite of bromhexine having similar mucolytic action, uses and side effects.

## Acetylcysteine



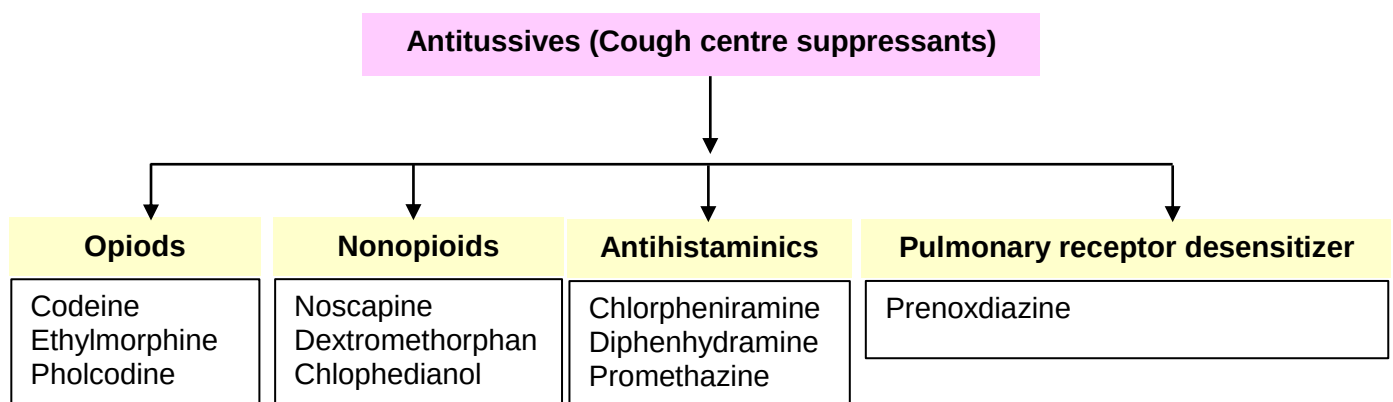
- Administered directly into respiratory tract

## Carbocisteine

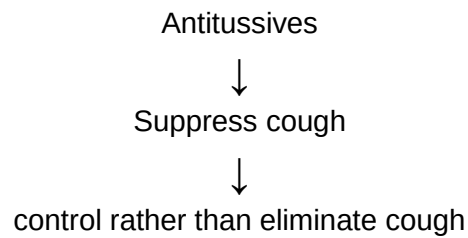
- It liquefies viscid sputum in the same way as acetylcysteine
- Administered orally

# ANTITUSSIVES

## Classification



## MOA



- Used only for dry nonproductive cough or if cough is unduly tiring, disturbs sleep or is hazardous (hernia, piles, cardiac disease, ocular surgery).

## Types

### 1. Centrally acting antitussives

- Act in the CNS to raise the threshold of cough centre
- Eg Opioids, Nonopioids, Antihistamines

### 2. Peripherally acting antitussives

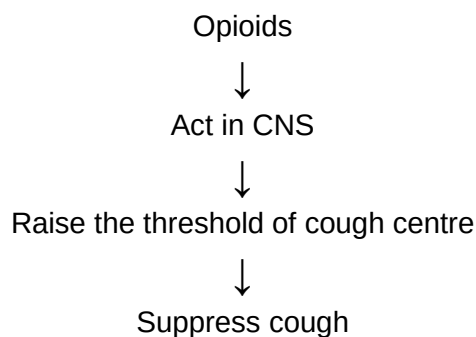
- Act peripherally in the respiratory tract to reduce tussal impulses→
- Eg. Prenoxdiazine

## OPIOIDS

### Classification

- Morphine
- Codeine
- Hydromorphone
- Pholcodeine

## MOA



### Codeine

- Antitussive action is exerted through opioid receptors in brain.
- Antitussive action is blocked by naloxone indicating that it is exerted through opioid receptors in the brain.
- It depresses cough but also has narcotic, analgesic or dependence inducing properties.
- Codeine is regarded as the standard antitussive; suppresses cough for about 6 hours

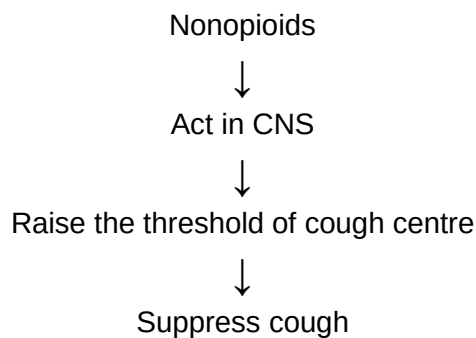
- Side effects, such as addiction, nausea; vomiting, biliary colic, ureteric spasm, constipation, bronchospasm and respiratory depression (contraindicated in asthmatics)

## NONOPIOIDS

### Classification

- Noscapine (Narcotine)
- Dextromethorphan
- Chlophedianol

### MOA



### Noscapine (Narcotine)

- It depresses cough but has no narcotic, analgesic or dependence inducing properties.
- It is nearly equipotent antitussive as codeine
- Side effects → Headache and nausea can occur. It can release histamine and produce bronchoconstriction in asthmatics (contraindicated in asthmatics)

### Dextromethorphan

- A synthetic central NMDA (N-methyl D-aspartate) receptor antagonist
- d-isomer → antitussive action
- l-isomer → analgesic
- Antitussive action of dextromethorphan has been rated equivalent to codeine
- Side effect → Dizziness, nausea, drowsiness; at high doses hallucinations and ataxia may occur

### Chlophedianol

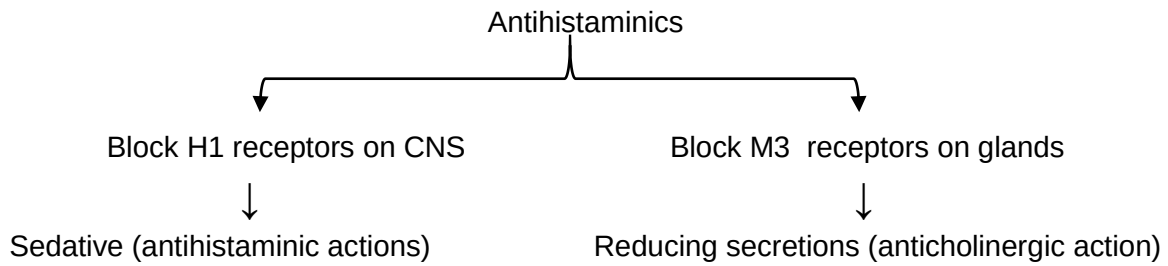
- Slow onset
- Longer duration of action.
- Side effect → Dryness of mouth, vertigo, irritability

## ANTI HISTAMINICS

### Classification

- Chlorpheniramine
- Diphenhydramine
- Promethazine

## MOA



## Remember

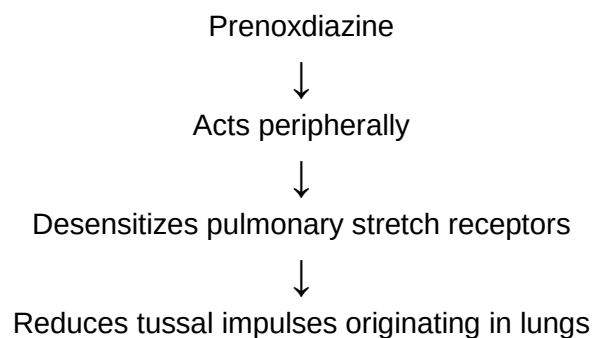
- They lack selectivity for the cough centre.
- They have no expectorant property,
- They may even reduce secretions by anticholinergic action.

## PULMONARY RECEPTOR DESENSITIZER

### Classification

- Prenoxdiazine

## MOA



- It is indicated in cough of bronchial origin
- Introduced recently in India.



# Gastrointestinal Drugs

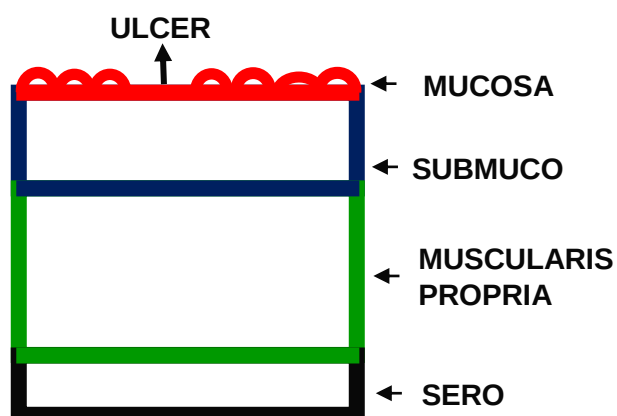
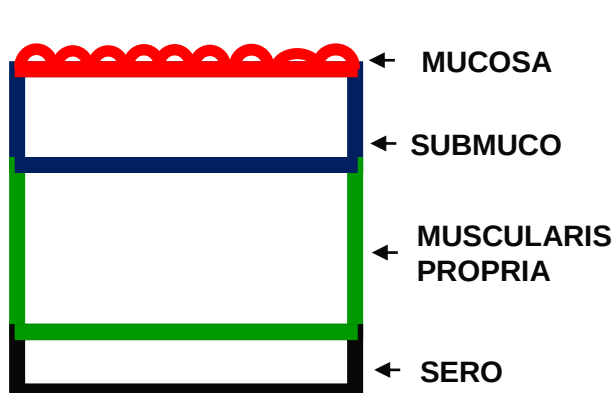
CHAPTER

8

## DRUGS FOR PEPTIC ULCER

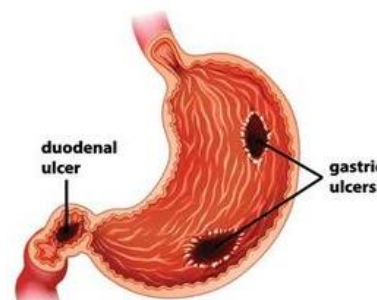
### Introduction

- **Ulcers** → a breach in the mucosa of alimentary tract that extends through submucosa into muscularis mucosa or deep.
- **Peptic ulcers** → areas of degeneration and necrosis of gastrointestinal mucosa exposed to acid-peptic secretions.



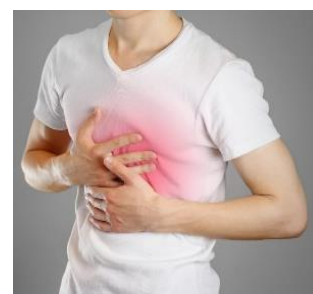
### Types

- 2 types →
  1. Gastric ulcer
  2. Duodenal ulcer



### Clinical Features

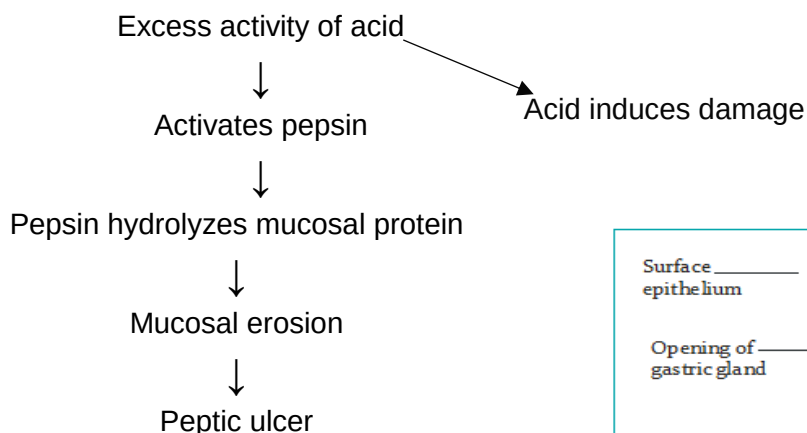
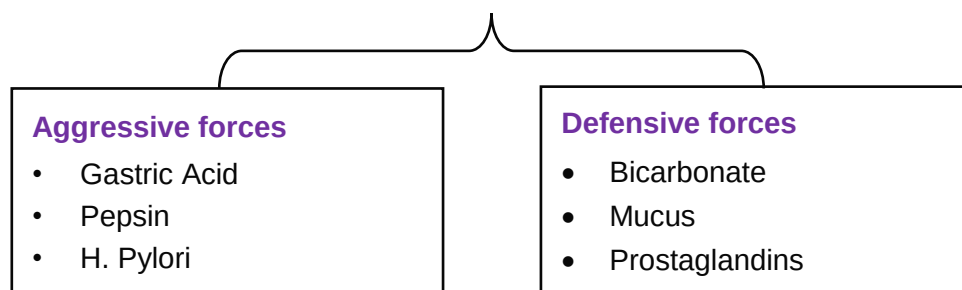
1. Dyspepsia (upper abdominal pain or discomfort)
2. Epigastric pain
3. Nausea
4. Vomiting
5. Heart burn



### Etiology

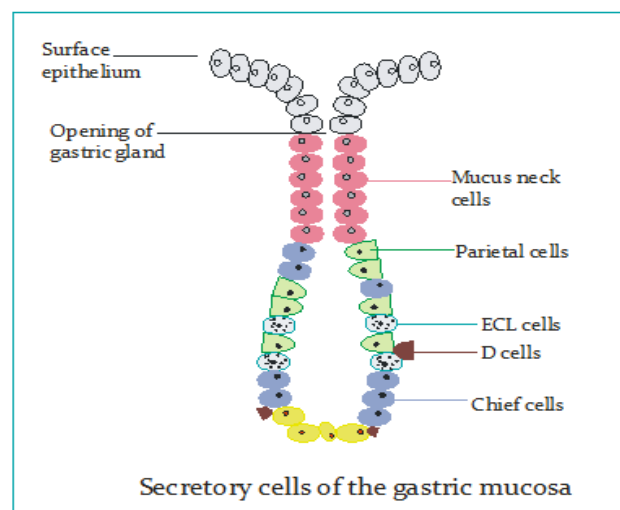
- Imbalance between → Mucosal Damaging factors/ Aggressive factors and Defense mechanisms





## Gastric acid secretion

- Acid is secreted from parietal cells



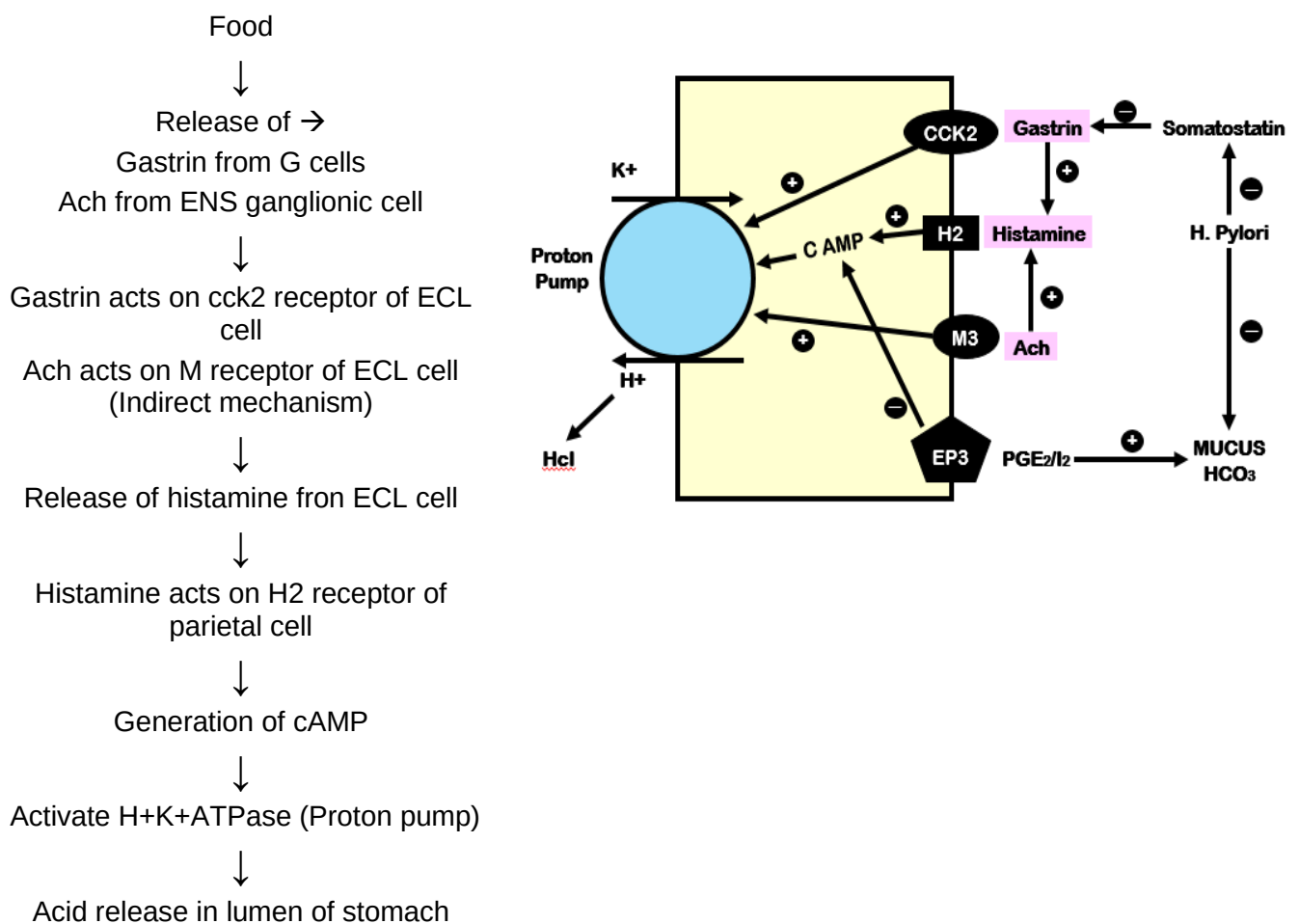
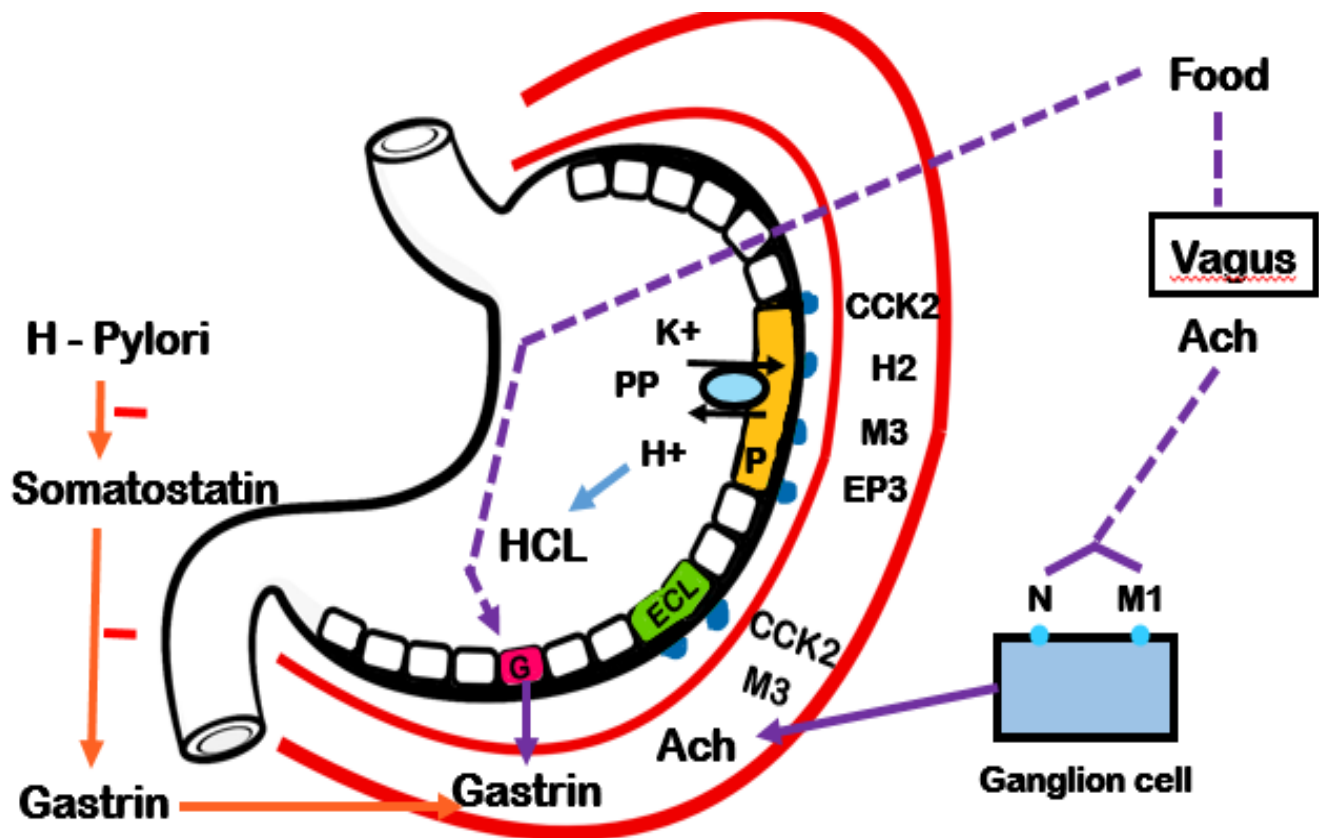
| Cell types       | Substance secreted           | Function of secretion                                                              |
|------------------|------------------------------|------------------------------------------------------------------------------------|
| Parietal cells   | HCL<br>Intrinsic factor      | Kills microbes and activates pepsinogen<br>Binds vit. B12 to allow it's absorption |
| Chief cells      | Pepsinogen<br>Gastric lipase | Protein digestion<br>Fat digestion                                                 |
| G cells          | Gastrin                      | Stimulates gastric acid secretion                                                  |
| ECL cells        | Histamine                    | Stimulates gastric acid secretion                                                  |
| Mucus-neck cells | Mucus and bicarbonate        | Protects stomach epithelium from acid                                              |
| D cells          | Somatostatin                 | Inhibits gastric acid secretion                                                    |

## Major secretagogues

- Histamine** → through H<sub>2</sub> receptors
- Acetylcholine** → through M<sub>3</sub> receptors
- Gastrin** → through CCK<sub>2</sub> receptors

- Their receptors are located on basolateral membrane of paraietal cells.
- They stimulate proton pump to exchange potassium with H ions for formation of HCl

## Physiology of Gastric acid formation and Secretion

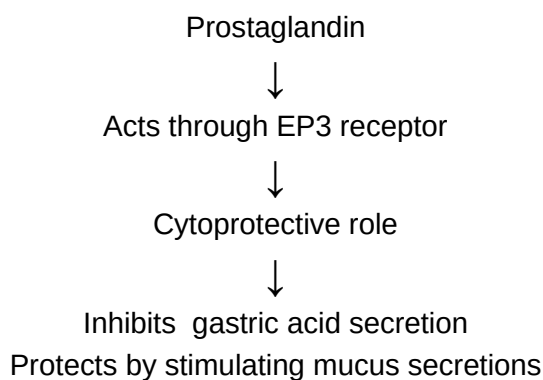


- Out of these 3 secretagogues → Histamine → plays a dominant role
- Other two → Acetylcholine and Gastrin act indirectly → by releasing histamine from enterochromaffin-like (ECL) cells and only partly by direct action.

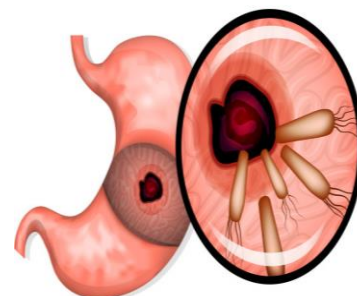
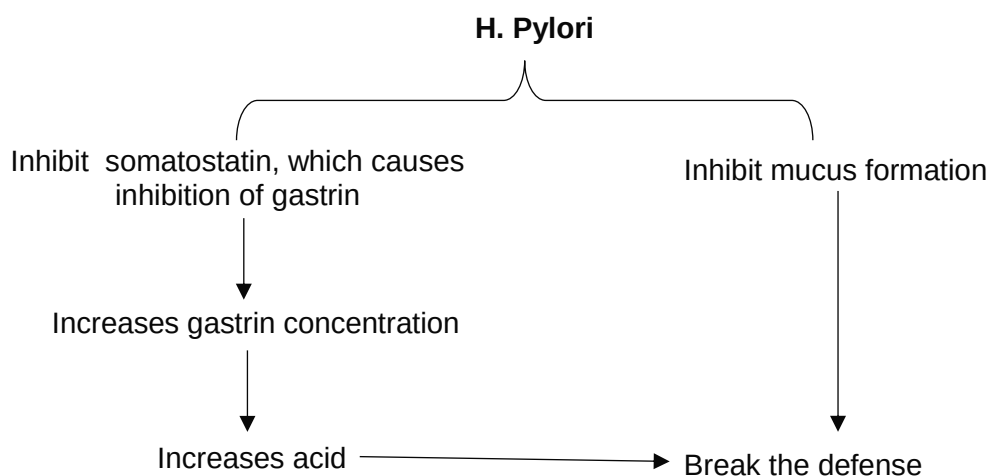
## Remember

1. **H<sub>2</sub> receptors** → activate H<sup>+</sup>K<sup>+</sup>ATPase by generating cAMP
2. **M<sub>3</sub> and CCK<sub>2</sub> receptors** → function through phospholipase C → IP<sub>3</sub>–DAG pathway

## Prostaglandin



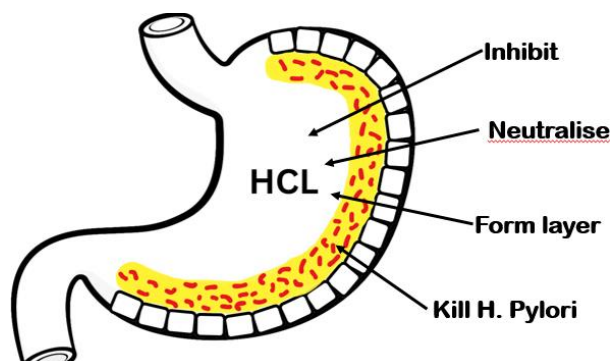
## H. Pylori



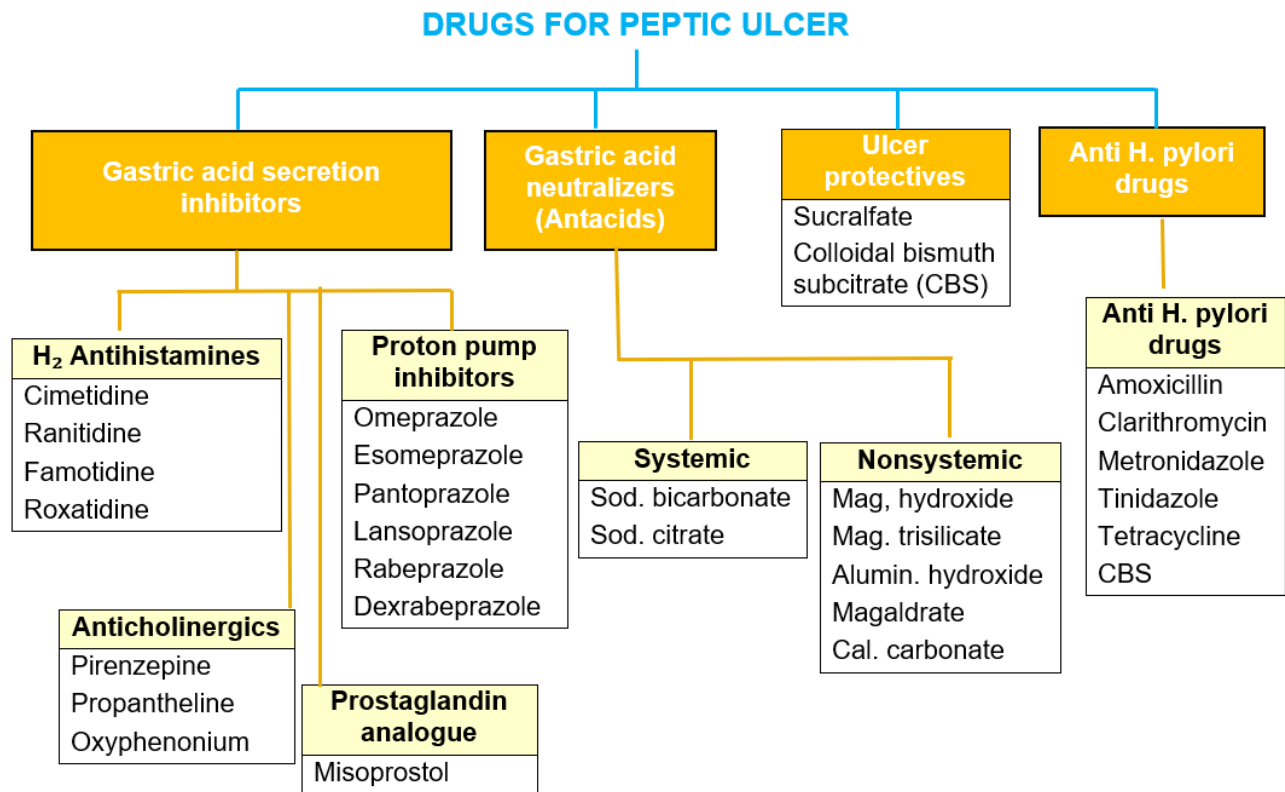
## APPROACH FOR TREATMENT OF PEPTIC ULCER

### 4 approaches

1. Decrease/ inhibit secretion of acid in stomach.
2. Neutralize gastric acid by antacids.
3. Protect the ulcer by forming a layer over it
4. Kill H. pylori associated with peptic ulcer disease



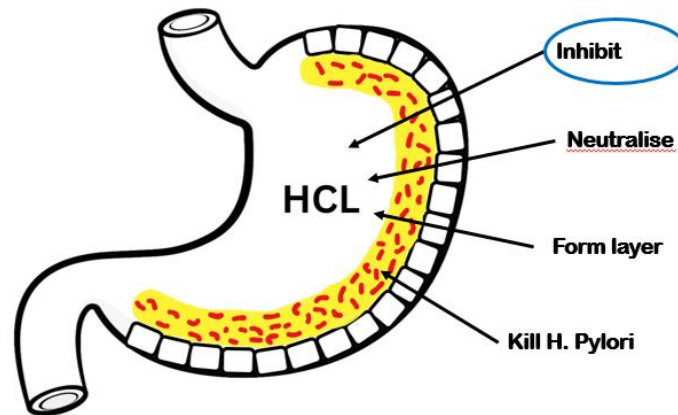
## Classification



| Drugs for Peptic ulcer            |               |     |                  |                        |
|-----------------------------------|---------------|-----|------------------|------------------------|
| Gastric acid secretion Inhibitors |               |     |                  |                        |
|                                   | H2 Antagonist | PPI | Anticholinergics | Prostaglandin Analogue |
| <b>Drugs</b>                      |               |     |                  |                        |
| <b>MOA</b>                        |               |     |                  |                        |
| <b>Pharmacokinetics</b>           |               |     |                  |                        |
| <b>Uses</b>                       |               |     |                  |                        |
| <b>Adverse effects</b>            |               |     |                  |                        |
| <b>Interactions</b>               |               |     |                  |                        |

| Drugs for Peptic ulcer  |                          |                   |                     |
|-------------------------|--------------------------|-------------------|---------------------|
|                         | Gastric acid Neutralizer | Protect ulcer     | Kill H. pylori      |
|                         | Antacid                  | Ulcer protectives | Anti H.pylori drugs |
| <b>Drugs</b>            |                          |                   |                     |
| <b>MOA</b>              |                          |                   |                     |
| <b>Pharmacokinetics</b> |                          |                   |                     |
| <b>Uses</b>             |                          |                   |                     |
| <b>Adverse effects</b>  |                          |                   |                     |
| <b>Interactions</b>     |                          |                   |                     |

## GASTRIC ACID SECRETION INHIBITORS

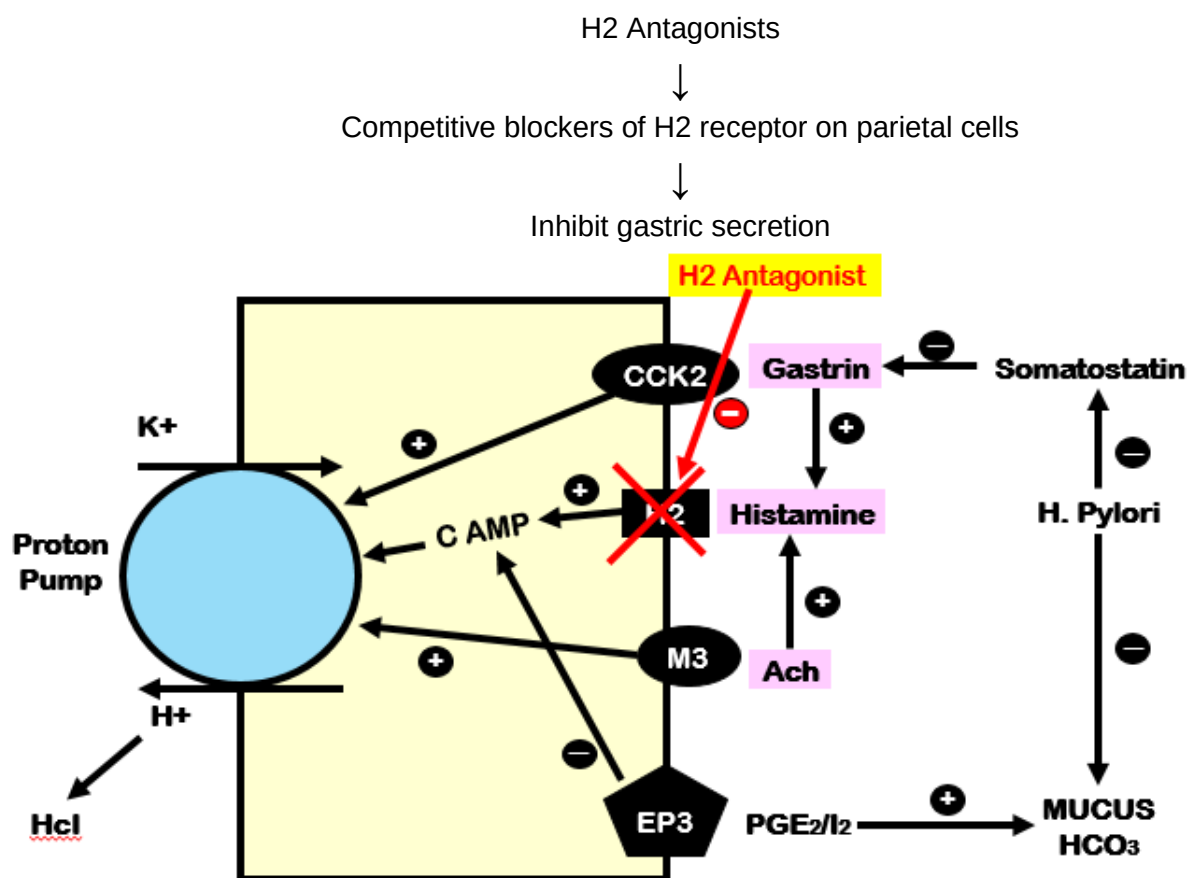


## H2 ANTAGONIST

### Drugs

- Cimetidine → first H2 blocker and prototype
- Ranitidine
- Famotidine
- Roxatidine
- Nizatidine
- Loxatidine

### MOA



## Remember

- These drugs reduce basal acid secretion with little effect on stimulated acid secretion (Contrast PPIs inhibit both basal as well as stimulated acid secretion).
- Volume, pepsin content and intrinsic factor secretion are reduced, but most marked effect is on acid (Contrast PPIs have no effect on volume, pepsin content and intrinsic factor secretion).
- 60–70% inhibition of 24 hr acid output
- No effect on motility
- They have been surpassed by proton pump inhibitors (PPIs)

## Pharmacokinetics

- **Cimetidine** →
  - Absorbed orally
  - Bioavailability is 60–80% due to first pass hepatic metabolism.
  - Absorption is not interfered by presence of food in stomach.
  - Crosses placenta and reaches milk
  - About 2/3 of a dose is excreted unchanged in urine and bile
  - Elimination  $t_{1/2}$  is 2–3 hr

## Uses

1. Peptic ulcer
2. Stress ulcers and gastritis
3. Zollinger-Ellison syndrome
4. Gastroesophageal reflux disease (GERD)
5. Prophylaxis of aspiration pneumonia

### 1. Peptic ulcer

- **Duodenal ulcer**
  - H<sub>2</sub> blockers produce rapid and marked pain relief (within 2–3 days)
  - 60–85% ulcers heal at 4 weeks
  - 70–95% ulcers at 8 weeks
- **Gastric ulcer**
  - Healing rates obtained in gastric ulcer are somewhat lower
  - 50–75% heal at 8 weeks
- PPI are DOC for peptic ulcer

### 2. Stress ulcers and gastritis

- Acutely stressful situations like hepatic coma, severe burns and trauma, prolonged surgery, prolonged intensive care, renal failure, asphyxia neonatorum, etc. are associated with gastric erosions and bleeding.
- H<sub>2</sub> blockers are DOC

### 3. Zollinger-Ellison syndrome

- It is a gastric hypersecretory state due to a rare tumour of G cells secreting gastrin.

- H2 blockers in high doses control hyperacidity and symptoms in many patients
- PPIs are DOC
- Definitive treatment is surgical.

#### 4. Gastroesophageal reflux disease (GERD)

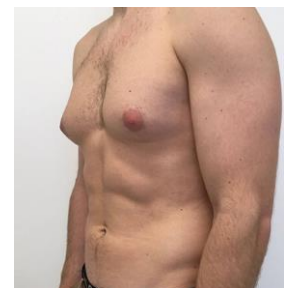
- H2 blockers afford symptomatic relief and facilitate healing of esophageal erosions, but are less effective than PPIs
- Indicated only in mild or stage-1 cases of GERD

#### 5. Prophylaxis of aspiration pneumonia

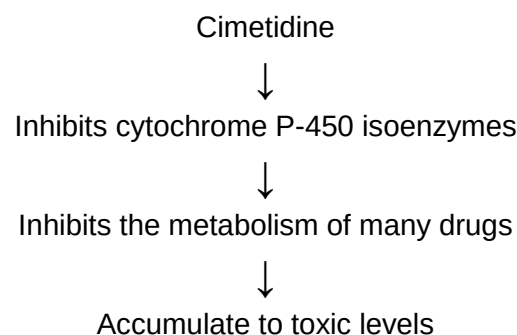
- H2 blockers given preoperatively (preferably evening before also) reduce the risk of aspiration of acidic gastric contents during anaesthesia and surgery.
- Now PPI are DOC

#### Adverse effects

1. **CNS effects** → Headache, dizziness, confusional state (Delirium), restlessness, convulsions, coma, headache dizziness, hallucination
2. **GIT** → Bowel upset, dry mouth
3. **CVS** → Bolus i.v. injection can cause histamine release → arrhythmias and cardiac arrest.
4. **Liver** → Transient elevation of plasma aminotransferases
5. **Cimetidine (but not other H2 blockers)** →
  - Antiandrogenic effects due to inhibition of binding of testosterone to receptor and reduced metabolism of estrogen.
  - Enhanced release of prolactin → loss of libido, impotence, gynecomastia and galactorrhea.



#### Interactions



- e.g. theophylline, phenytoin, carbamazepine, phenobarbitone, sulfonylureas, metronidazole, warfarin, imipramine, lidocaine, nifedipine, quinidine.

#### Substrate /Object drug

- **C** - Cyclosporin, CCB
- **T** - Tacrolimus
- **S** - Statins
- **C** - Cisapride
- **A** - Amiodaron, Astemizole

- **N - Navirs** (Protease inhibitors)t

#### Enzyme Inhibitors

- |                      |   |                       |
|----------------------|---|-----------------------|
| • <b>V</b> itamin    | - | <b>V</b> alproate     |
| • <b>K</b>           | - | <b>K</b> etoconazole  |
| • <b>C</b> annot     | - | <b>C</b> imetidine    |
| • <b>C</b> ause      | - | <b>C</b> iprofloxacin |
| • <b>E</b> nzyme     | - | <b>E</b> rythromycin  |
| • <b>I</b> nhibition | - | <b>I</b> NH           |

### Ranitidine Versus Cimetidine

- Ranitidine several desirable advantages over cimetidine
  1. 5 times more potent
  2. No antiandrogenic effects
  3. Less penetration to brain (less CNS effects)
  4. Less effect on metabolism of other drugs

### Remember

- **Cimetidine** → least potent H<sub>2</sub> blocker.
- **Famotidine** → most potent H<sub>2</sub> blocker.
- All H<sub>2</sub> blockers are competitive blockers except **famotidine** (competitive - noncompetitive) and **loxatidine** (non competitive).
- **Nizatidine** → anticholinesterase activity → cause bradycardia and increased gastric emptying.
- **Nizatidine** → negligible first pass metabolism → 100% bioavailability).
- All H<sub>2</sub> blockers except **famotidine** inhibits gastric first pass metabolism of ethanol.
- Absorption of **cimetidine** is not affected by food

## PROTON PUMP INHIBITORS (PPI)

### Drugs

- Omeprazole → prototype
- Esomeprazole
- Lansoprazole
- Pantoprazole
- Rabeprazole
- Dexrabeprazole

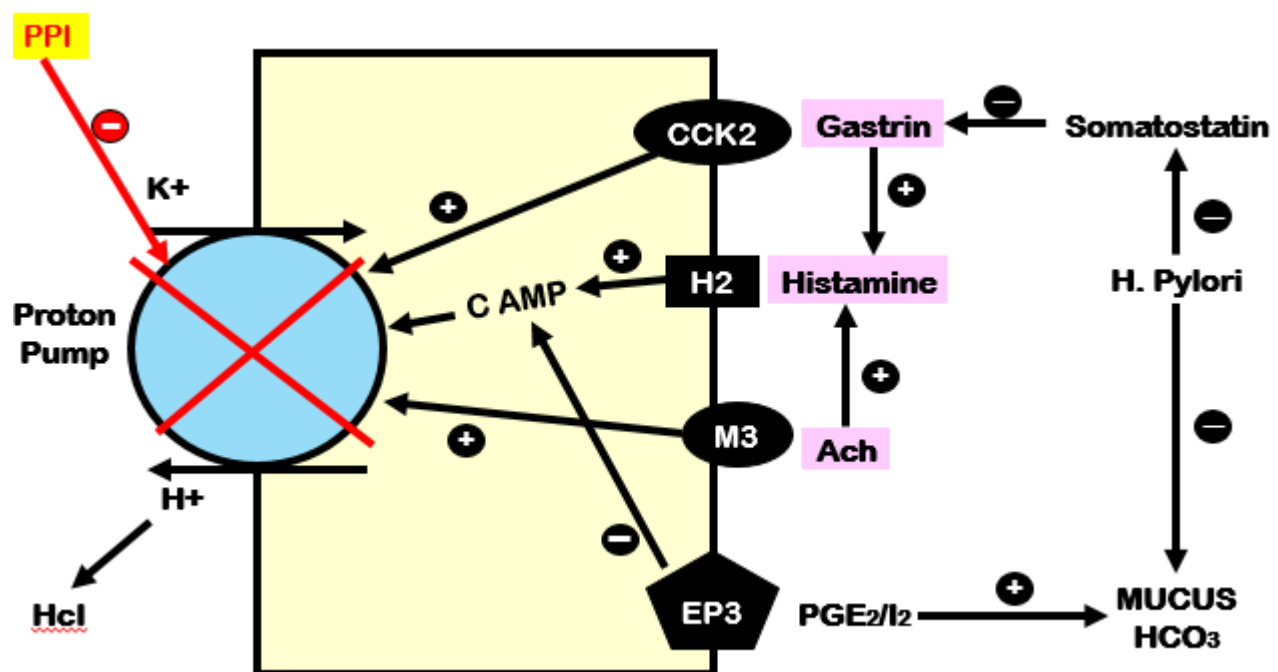
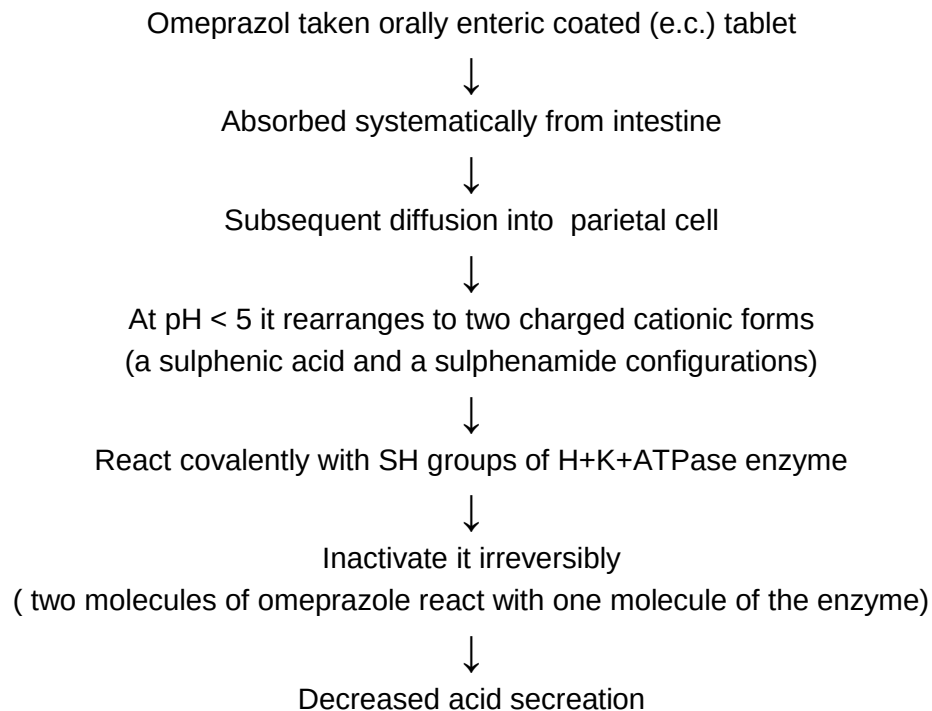
### Introduction

- Ultimate mediator of acid secretion is proton pump i.e. H<sup>+</sup>K<sup>+</sup> ATPase → so inhibitors block ultimate stage
- PPIs have overtaken H<sub>2</sub> blockers for acid-peptic disorders.

### MOA

- Omeprazole is inactive at neutral pH





## Remember

- They decrease a basal acid secretion by 90-95%.
- There is reduction in acid secretion but no change in volume, secretion of pepsin, intrinsic factors and gastric motility.

## Pharmacokinetics

1. All PPIs are administered orally in enteric coated (e.c.) form to protect them from molecular transformation in the acidic gastric juice.
  - e.c. tablet or granules filled in capsules should not be broken or crushed before swallowing.



- Esomeprazole, lansoprazole and pantoprazole can also be given intravenously
- 2. PPI are prodrugs
  - On reaching the parietal cells, active moiety, i.e. sulfenamide is formed and gets trapped which inhibits  $H^+$ ,  $K^+$  ATPase irreversibly.
- 3. PPI→
  - Short half life → 1.5 hours
  - Long Duration of action → lasts for 24 to 48 hours
    - This is due to irreversible inactivation of proton pump
    - Until new proton pumps are synthesized and incorporated into the luminal membrane of parietal cells.
- 4. Because not all proton pumps are inactivated with first dose of medication as not all proton pumps are active simultaneously
  - Maximal suppression of acid requires several doses of proton pump inhibitors, i.e. 2 to 5 days of therapy is required before the full acid-inhibiting potential is reached.
- 5. Bioavailability of all PPIs is reduced by food
  - They should be taken in empty stomach
  - Followed 1 hour later by a meal to activate the  $H^+K^+$  ATPase and make it more susceptible to the PPI.

## Uses

1. Peptic ulcer
2. Stress ulcers and gastritis
3. Zollinger-Ellison syndrome
4. Gastroesophageal reflux disease (GERD)
5. Prophylaxis of aspiration pneumonia

### 1. Peptic ulcer

- Omeprazole 20 mg OD is equally or more effective than  $H_2$  blockers.
  - Relief of pain is rapid and excellent.
  - Faster healing has been demonstrated with 40 mg/day
  - Duodenal ulcers heal (over 90%) at 4 weeks.
  - Gastric ulcer generally requires 4–8 weeks.
  - Continued treatment (20 mg daily or thrice weekly) can prevent ulcer relapse
  - DOC for peptic ulcer

### 2. Stress ulcers

- Intravenous pantoprazole/ rabeprazole is as effective prophylactic (if not more) for stress ulcers as i.v.  $H_2$  blockers

### 3. Zollinger-Ellison syndrome

- Omeprazole is more effective than  $H_2$  blockers in controlling hyperacidity in Z-E syndrome.
- 60–120 mg/day or more (in 2 divided doses) is often required for healing of ulcers
- PPIs are DOC

- Definitive treatment is surgical.

#### 4. Gastroesophageal reflux disease(GERD)

- Omeprazole produces more complete round-the-clock inhibition of gastric acid resulting in rapid symptom relief
- It is more effective than H2 blockers in promoting healing of esophageal lesions.
- PPIs are DOC for GERD

#### 5. Aspiration pneumonia

- PPIs are preferred to H2 blockers for prophylaxis of aspiration pneumonia due to prolonged anaesthesia.

#### Adverse effects

1. Nausea, loose stools, abdominal pain
2. Muscle and joint pain, dizziness
3. Rashes
4. Hepatic dysfunction
5. On prolonged treatment → atrophic gastritis

#### Interactions

1. Interferes with activation of clopidogrel by inhibiting CYP2C19.
2. Omeprazole inhibits oxidation of certain drugs: diazepam, phenytoin and warfarin levels may be increased.

#### Remember

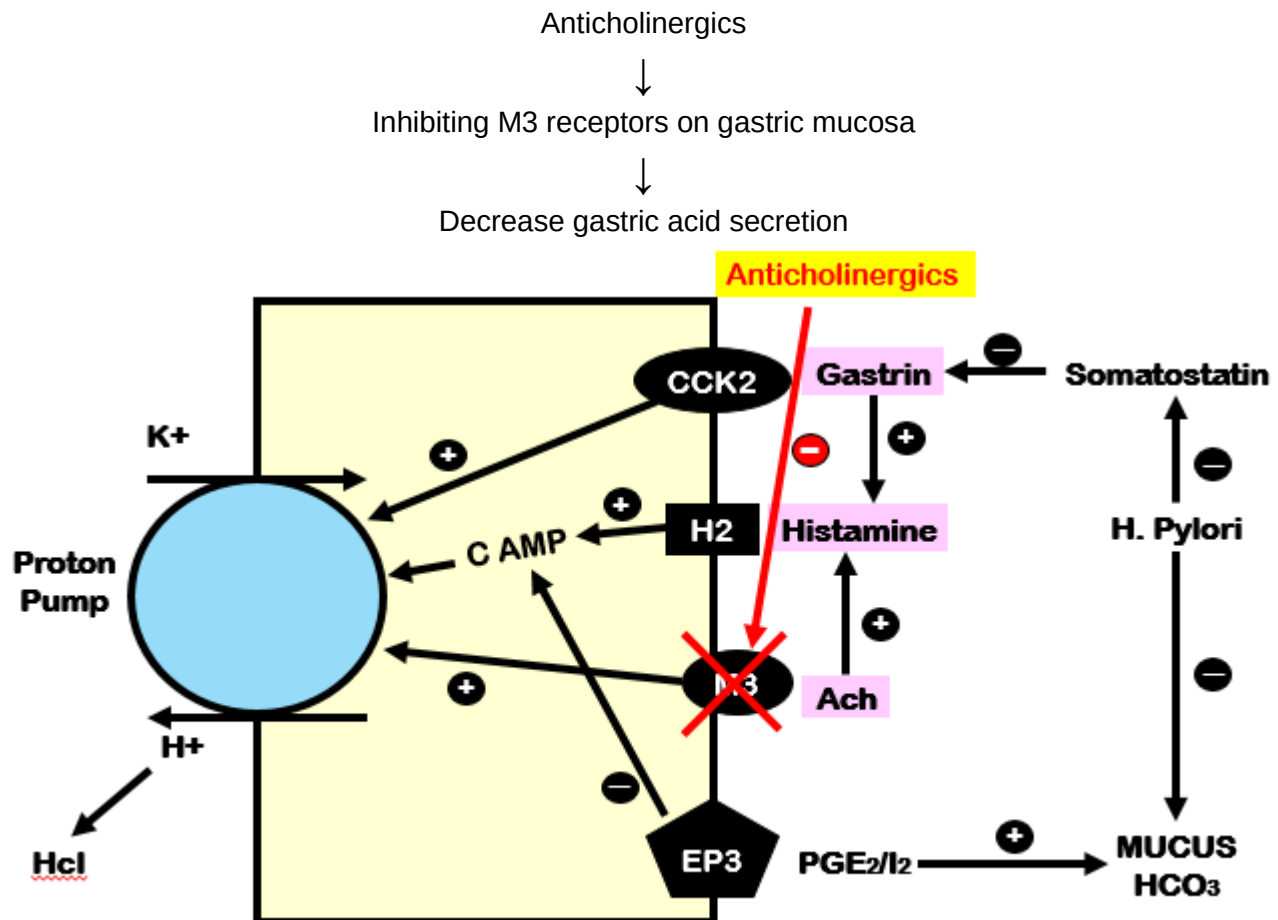
- PPIs given for →
  - 4 weeks for duodenal ulcer
  - 8 weeks for gastric ulcers.
- Refractory ulcer →
  - Duodenal ulcers that fail to heal after 8 weeks
  - Gastric ulcers that fail to heal after 12 weeks.
- **Lansoprazole** → most potent PPI
- **Rabeprazole** → **longest** acting PPI
- **Pantoprazole** → can also be given intravenously
- **Lansoprazole** → safest PPI in pregnancy
- **Omeprazole and esomeprazole** → enzyme inhibitors and may decrease the metabolism of diazepam.
- **Lansoprazole** → enhances the metabolism of theophylline.

## ANTICHOLINERGICS

### Drugs

- Pirenzapine
- Propantheline
- Oxyphenonium

### MOA



### Not preferred because

1. Exhibit a weak antisecretory effect as compared to H2 blockers.
2. Decrease basal acid secretion by 40-45%.
3. In doses need to reduce acid secretion there are typical anticholinergic adverse effects like dryness of mouth, blurring of vision, tachycardia, urinary retention and glaucoma, therefore they are not preferred.
4. Reduce volume of gastric juice without raising its pH

## PROSTAGLANDIN ANALOGUE

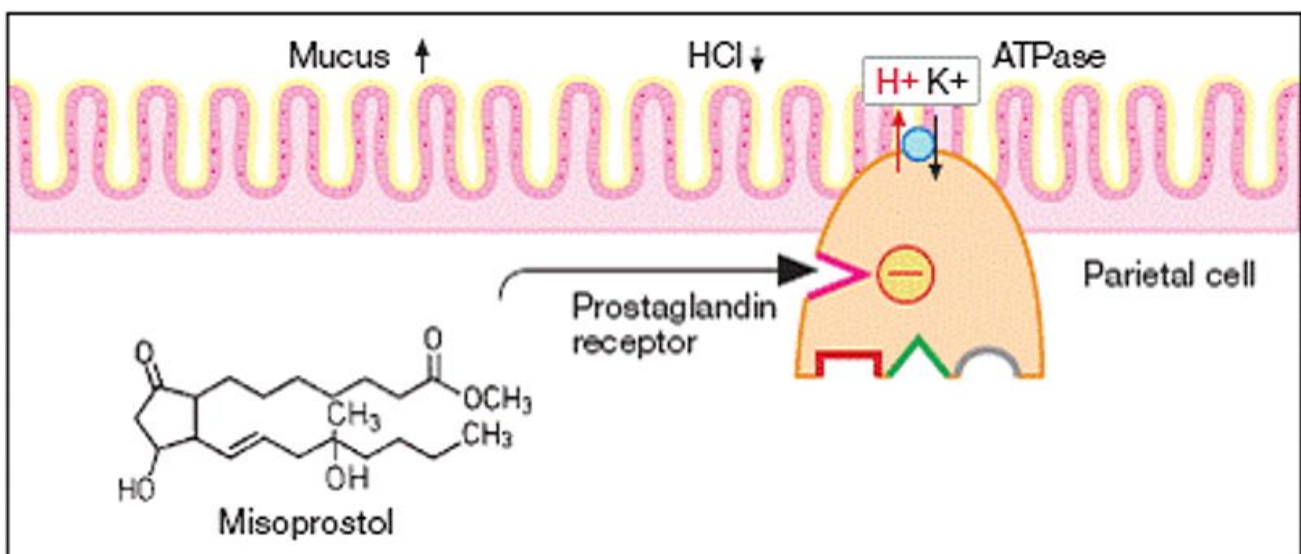
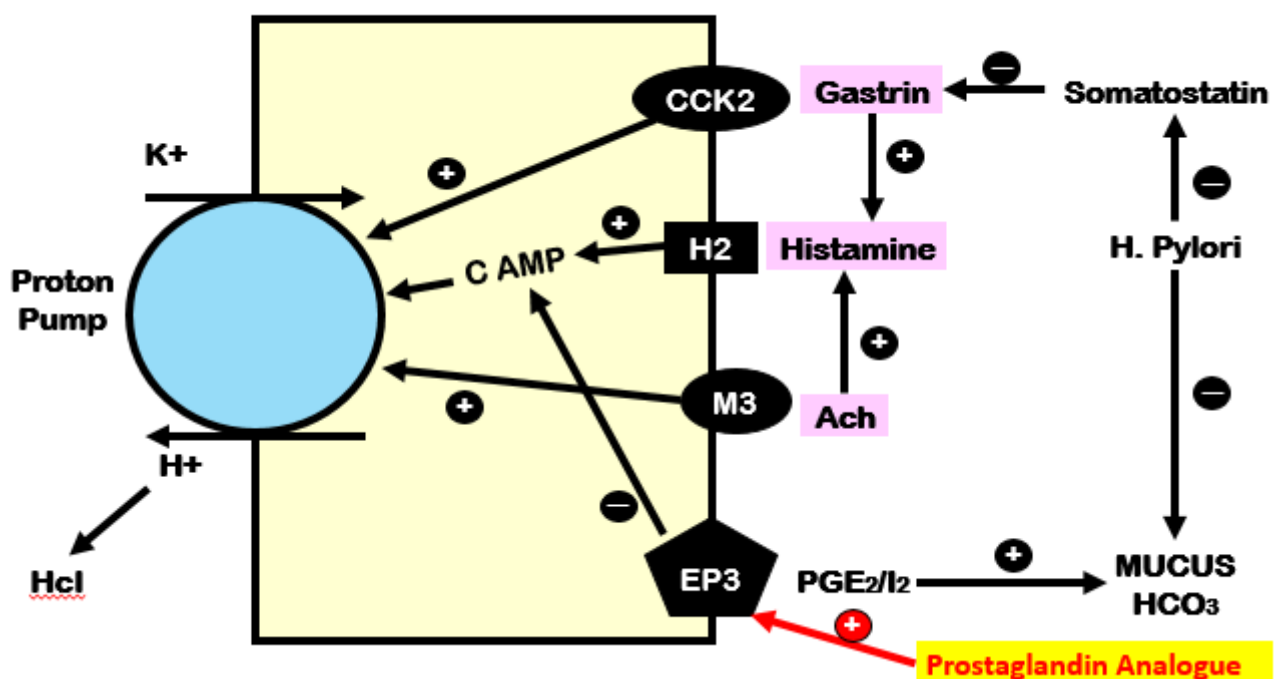
### Drugs

- Misoprostol (PGE1 analogue)
- Enprostil (PGE2 analogue)

- Rioprostil (PGE<sub>2</sub> analogue)

## MOA

- Cytoprotective antisecretory action
  1. Inhibiting acid secretion
  2. Inhibit gastrin release
  3. Promoting mucus as well as HCO<sub>3</sub><sup>-</sup> secretion
  4. Increase mucosal blood flow
  5. Ability to reinforce the mucus layer covering gastric and duodenal mucosa which is buffered by HCO<sub>3</sub><sup>-</sup> secreted into this layer
- Reduction in 24 hour acid production is less than H<sub>2</sub> blockers



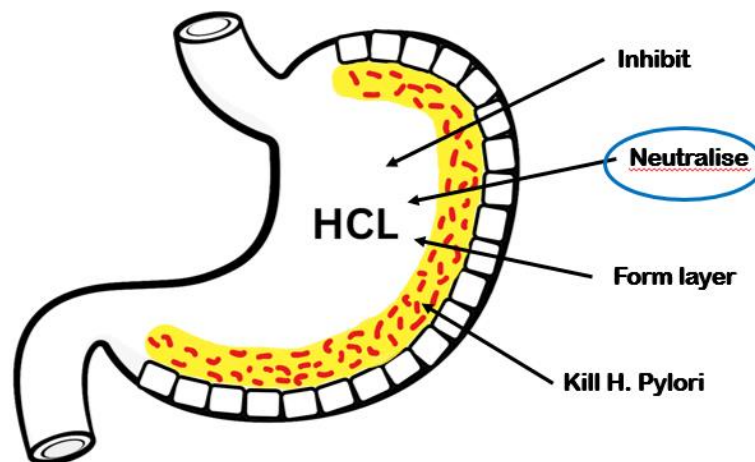
## Uses

- Misoprostol (PGE1 analogue) is used for prevention and treatment of NSAID induced ulcer
- But DOC is PPI

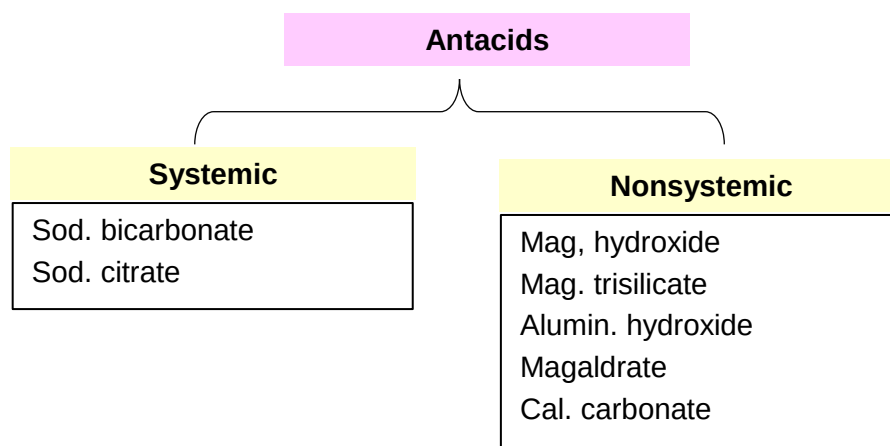
## Adverse effects

- Abdominal cramps
  - Diarrhea
  - Headache
  - Fever
  - Potential for abortion
- 
- It is seldom employed now because PPIs are more effective, more convenient, better tolerated and cheaper.

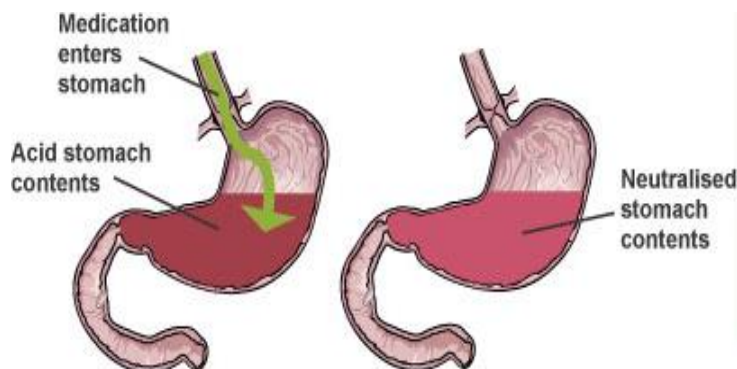
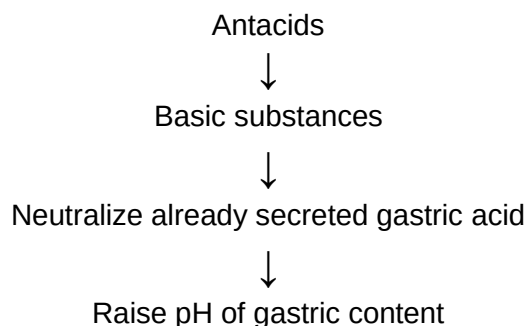
## GASTRIC ACID NEUTRALIZER → ANTACID



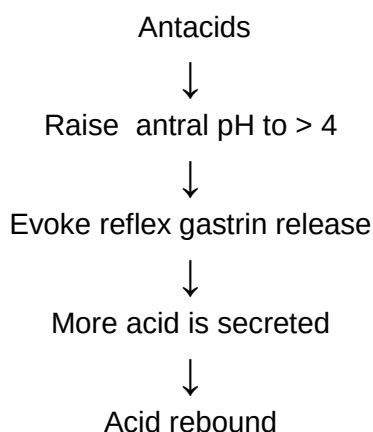
## Drugs



## MOA



2. Peptic activity is indirectly reduced if pH rises above 4 because →
  - Pepsin is secreted as a complex with an inhibitory terminal moiety that dissociates below pH 5. so optimum peptic activity is exerted between pH 2 to 4.
  - Antacids do not decrease acid production rather →



## Potency of an antacid

- **Acid neutralizing capacity (ANC)** → It is defined as number of mEq of 1N HCl that are brought to pH 3.5 in 15 min (or 60 min in some tests) by a unit dose of the antacid preparation.

## Pharmacokinetics

- Taken in empty stomach → acts for 30–60 min only, since in this time any gastric content is passed into duodenum.
- Taken with meals → act for at the most 2–3 hr

## Types

1. Systemic Antacids
2. Non-systemic antacids

### 1. Systemic Antacids

- Sodium bicarbonate
  - It gets absorbed leading to systemic (metabolic) alkalosis

- Hence not preferred as antacid.

## 2. Non-systemic antacids

- Aluminum and magnesium salts
  - Insoluble salts
  - Not absorbed significantly
  - Do not disturb systemic pH.

### Aluminum compounds

- Weak antacids
- Slow acting
- Inhibit motility so delays gastric emptying → produces constipation.
- Inhibits phosphate absorption, increase in calcium resorption from bones → chronic use may lead phosphate depletion syndrome hypercalcemia, hypercalciuria and osteomalacia.

### Magnesium compounds

- Strong antacids
- Rapidly acting
- Increase GI motility → produce diarrhea.
- 5-10% of magnesium may get absorbed and then eliminated by kidney → magnesium salts are contraindicated to a patient of renal insufficiency

### Calcium Salts

- Strong antacid
- Rapidly acting
- Longer duration of action but not preferred owing to following problems →
  - Acid rebound: Calcium, in small intestine, increases release of gastrin and acid.
  - Hypercalcemia.
  - Milk alkali syndrome
  - Constipation.
  - Belching, abdominal discomfort and flatulence due to production of gas.

## Antacid combinations

- Combination of Magnesium salts and aluminium salts has many advantages →
- Mag. salts → Fast, Alum. salts → slow
- Mag. salts → laxative, Alum. salts → constipation
- Mag./cal. salts → hasten Gastric emptying, Alum. salts → delay Gastric emptying → Gastric emptying is least affected



## Interactions

- By raising gastric pH and by forming complexes → non-absorbable antacids decrease absorption of many drugs →
  - Tetracyclines
  - Iron salts
  - fluoroquinolones
  - Ketoconazole



- H<sub>2</sub> blockers
- Diazepam
- Phenothiazines
- Indomethacin
- Phenytoin
- Isoniazid
- ethambutol
- Nitrofurantoin

## Uses

- Antacids are now employed only for intercurrent pain relief and acidity
- Mostly self-prescribed by the patients as over counter preparations

## Adverse effects

- Acid rebound
- Bowel upset

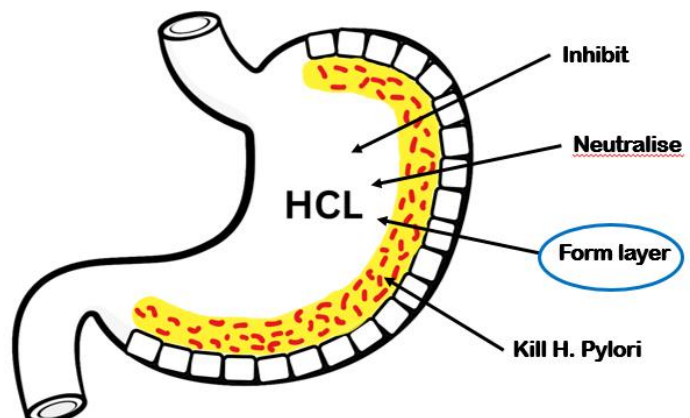
## ULCER PROTECTIVES

### Drugs

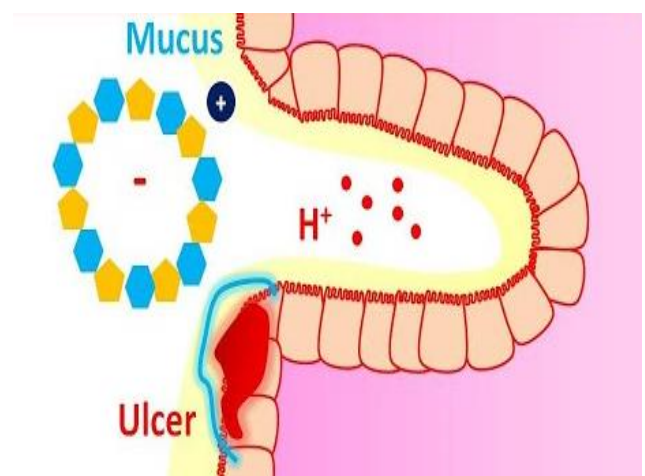
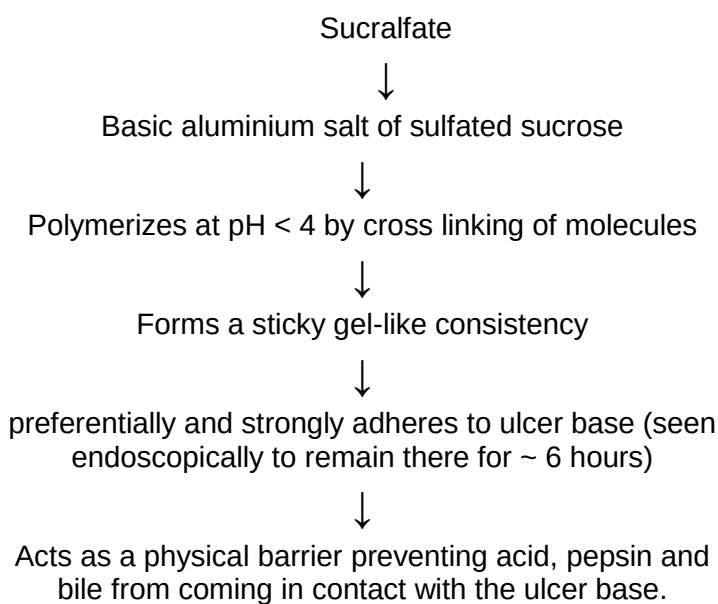
1. Sucralfate
2. Colloidal bismuth subcitrate (CBS; Tripotassium dicitratobismuthate)

### Sucralfate

- Sucralfate is an ulcer protective agent.



### MOA



↓  
Promotes healing

## Remember

- **Sucralfate** →
  - Minimally absorbed after oral administration.
  - No acid neutralizing action
  - Delays gastric emptying
  - Action is entirely local.
  - Viscous and gel like properties that are responsible for its action.
  - This protective action is attributed to sucralfate only in acidic medium

## Dose

- Ulcer healing dose of sucralfate is 1 g taken in empty stomach 1 hour before the 3 major meals and at bed time for 4–8 weeks.

## Interactions

- Antacids should not be taken with sucralfate because its polymerization is dependent on acidic pH

## Adverse effects

1. Constipation is reported by 2% patients.
2. It has potential for inducing hypophosphatemia by binding phosphate ions in the intestine.
3. Dry mouth and nausea

## Uses

- Sucralfate is infrequently used now because of need for 4 large well-timed daily doses and availability of simpler and more effective H<sub>2</sub> blockers/PPIs.

## Colloidal bismuth subcitrate (CBS)

- It is a colloidal bismuth compound
- Precipitates at pH < 5

## MOA

1. Increase gastric mucosal PGE<sub>2</sub>, mucus and HCO<sub>3</sub> production.
2. Precipitate mucus glycoproteins and coat the ulcer base.
3. Detach and inhibit H.pylori directly

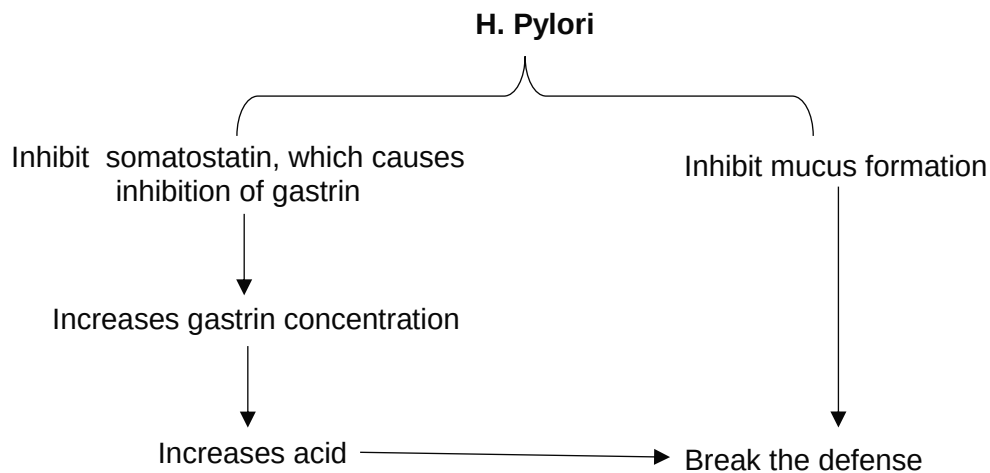
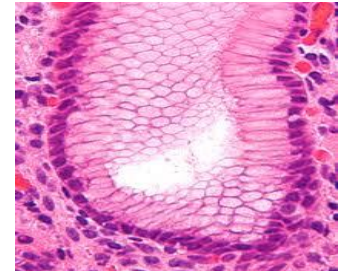
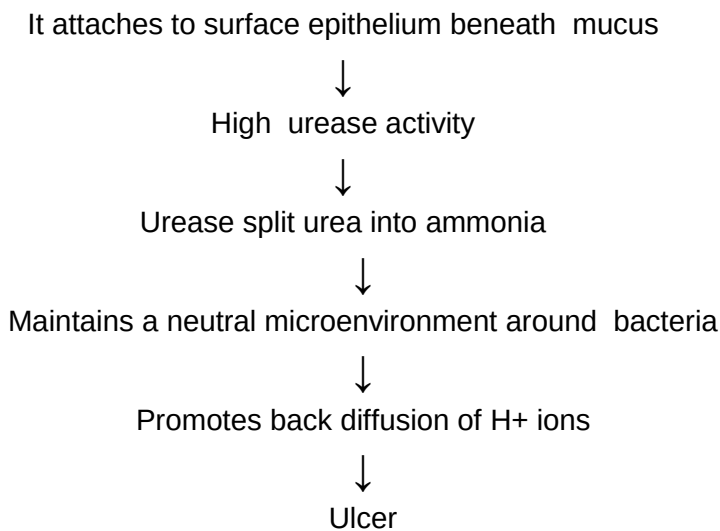
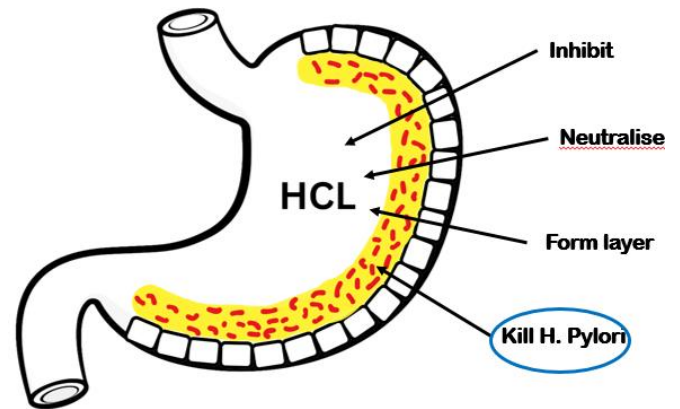
## Adverse effects

- Diarrhoea
- Headache
- Dizziness
- Blackening of tongue, dentures and stools

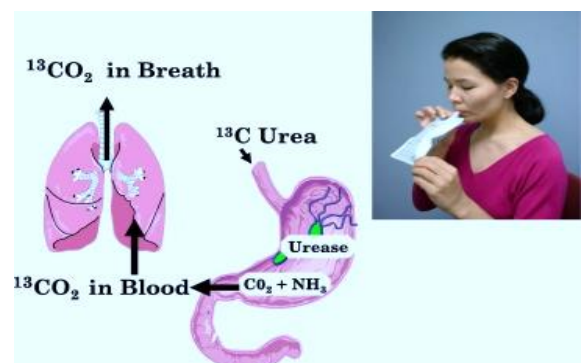
## ANTI H.PYLORI DRUGS

### Introduction

- Helicobacter Pylori are gram-negative bacteria



- It has been found as a commensal in 20–70% normal individuals
- 70-90% of peptic ulcers are associated with H. pylori.
- Eradication of H. pylori concurrently with H<sub>2</sub> blocker/PPI therapy of peptic ulcer has been associated with faster ulcer healing and largely prevents ulcer relapse.



- H. pylori infection can be detected by → urea breath test
  1. All H. pylori positive ulcer patients should receive H. pylori eradication therapy.
  2. In the absence of H. pylori testing, all cases with failed conventional ulcer therapy and relapse cases must be given the benefit of H. pylori eradication.

## Antimicrobials against H. pylori

1. Amoxicillin
2. Clarithromycin
3. Tetracycline
4. Metronidazole/Tinidazole

## Combinations are used

- Any single antibiotic is ineffective.
- Resistance develops rapidly,
- Acid suppression by PPIs/H<sub>2</sub> blockers enhances effectiveness of anti-H. pylori antibiotics, and optimum benefits are obtained when gastric pH is kept >5 for at least 16–18 hours per day.
- Therefore combinations are used → combination of one PPI and two anti H pylori

## Therapies Used

- A. Triple therapy → Regimen (LCA), Regimen (OAM)
- B. Quadruple therapy → Regimen (OBTM)

### A) Triple therapy

- A number of 3 drug regimens →
- Combination of one PPI and two anti H pylori for 1 or 2 weeks are being used
- 2 week regimens achieve higher (upto 96%) eradication rates, though compliance is often poor due to side effects.

### Regimen 1 (LCA)

- US-FDA approved regimen is:
  1. Lansoprazole 30 mg
  2. Clarithromycin 500 mg
  3. Amoxicillin 1000 mg
- All given twice daily for 2 weeks.

### Regimen 2 (OAM)

- National Formulary of India suggests a model H. pylori eradication regimen
  1. Omeprazole 40 mg OD
  2. Metronidazole 400 mg TDS
  3. Amoxicillin 500 mg TDS
- All given twice daily for 1 weeks.

### B) Quadruple therapy

- For eradication failure cases
- Combination of one PPI and CBS and two anti H pylori

## Regimen (OBTM)

1. Omeprazole 20 mg BD
2. CBS 120 mg QID
3. Metronidazole 400 mg TDS
4. Tetracycline 500 mg QID

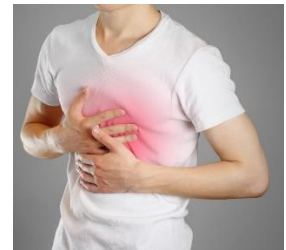
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# DRUGS FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)

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## Introduction

- Reflux is sensation of stomach contents coming back in foodpipe
- Patient complains of 'heart-burn', acid eructation, especially after a large meal
- Aggravated by stooping or lying flat.



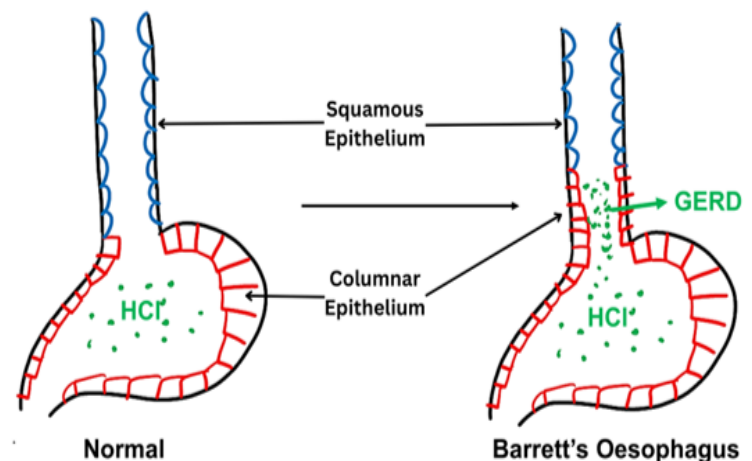
## Etiology

Relaxation of lower esophageal sphincter (LES) in the absence of swallowing

↓  
Reflux of acid from stomach to lower 1/3rd of oesophagus

↓  
Repeated reflux of acid gastric contents into lower 1/3rd of esophagus

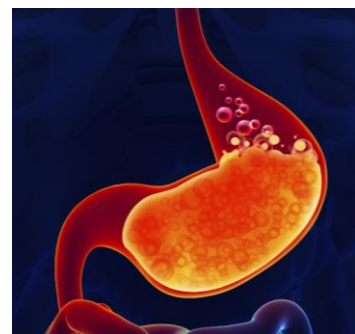
↓  
Causes esophagitis, erosions, ulcers, pain on swallowing, dysphagia, strictures, and increases the risk of esophageal carcinoma



- Though GERD is primarily a GI motility disorder, acidity of gastric contents is the most important aggressive factor in causing symptoms and esophageal lesions.

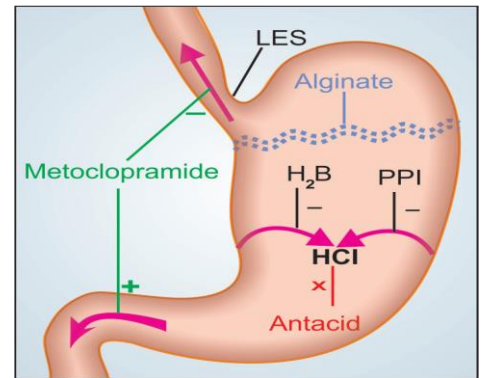
## Staging

- **Stage 1:** occasional heartburn (<3 episodes/ week), mostly only in relation to a precipitating factor, mild symptoms, no esophageal lesions.
- **Stage 2:** > 3 episodes/week of moderately severe symptoms, nocturnal awakening due to regurgitation, esophagitis present or absent.
- **Stage 3:** Daily/chronic symptoms, disturbed sleep, esophagitis/erosions/stricture/extraesophageal symptoms like laryngitis, hoarseness, dry cough, asthma.



## TREATMENT OF GERD

1. Proton pump inhibitors (PPIs)
2. H<sub>2</sub> blockers
3. Antacids
4. Sodium alginate
5. Prokinetic drugs



### 1. PROTON PUMP INHIBITORS (PPI)

- Reduce acidity of gastric contents
- No effect on LES tone
- Most effective drugs, both for symptomatic relief as well as for healing of esophageal lesions
- Intragastric pH >4 for ~18 hr/day is considered optimal for healing of esophagitis.
- 80–90% esophageal lesions heal in 4–8 weeks
- PPIs → DOC for patients with all stages of GERD

### 2. H<sub>2</sub> BLOCKERS

- Reduce acidity of gastric contents
- No effect on LES tone
- H<sub>2</sub> blockers cause less complete acid suppression than PPIs, ie elevate intragastric pH to >4 for less than 8 hours in 24 hours
- H<sub>2</sub> antagonists are indicated in stage-1 cases, or as alternative to PPIs in stage 2 or 3 cases.

### 3. ANTACIDS

- Used only for pain relief
- No longer employed for healing of esophagitis
- No effect on LES tone.

### 4. SODIUM ALGINATE

- Forms a thick frothy layer which floats on gastric contents like a raft may prevent contact of acid with esophageal mucosa.
- No effect on LES tone.

### 5. PROKINETIC DRUGS

1. Metoclopramide
2. cisapride

### MOA

1. By increasing LES tone
2. Improving esophageal clearance



3. Facilitating gastric emptying,

- Do not affect gastric acidity or promote healing of esophagitis.
- Symptom control afforded by prokinetic drugs is much inferior to that by PPIs/H2 blockers.
- Prokinetic drugs are often coprescribed with PPI/H2 blocker therapy, but whether this improves outcome is not clear

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## ANTIEMETIC AND PROKINETIC DRUGS

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### Emesis

- **Vomiting** → occurs due to stimulation of emetic (vomiting) centre situated in the medulla oblongata.
- Close to vomiting centre are other visceral centre, including those for respiration, salivation and vascular control, which give rise to the prodromal sensations of vomiting.

➤ **Motion sickness** → Vomiting due to travelling



➤ **Morning sickness** → Vomiting in early pregnancy

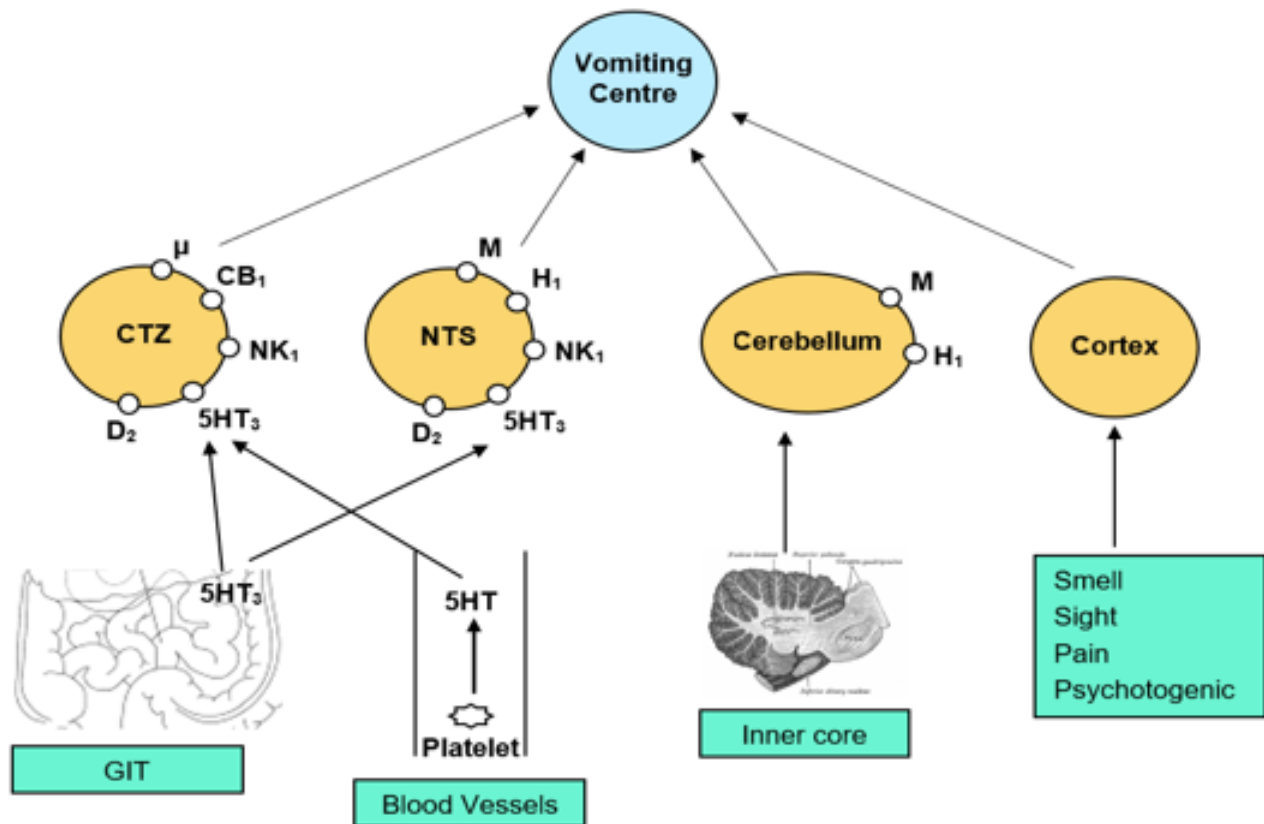


➤ **Sea sickness** → Vomiting in sea



### Pathways

- Multiple pathways can elicit vomiting→
  1. Chemoreceptor trigger zone (CTZ)
  2. Nucleus tractus solitarius (NTS)
  3. Cerebellum
  4. Cortex higher centre



## 1. Chemoreceptor trigger zone (CTZ)

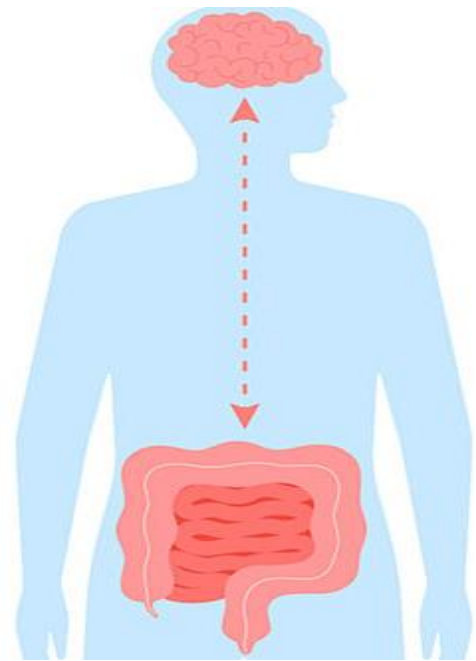
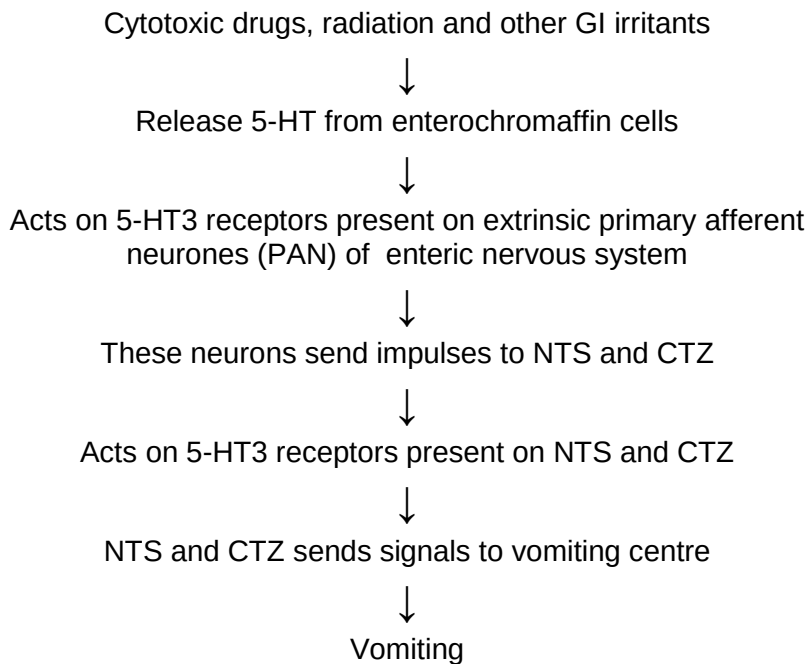
- Located in area postrema
- Unprotected by BBB
- **Expresses** → dopamine  $D_2$ , serotonin  $5-HT_3$ , neurokinin  $NK_1$  (activated by substance P), cannabinoid  $CB_1$  and opioid  $\mu$  receptors
- **Receives impulses arising in** →
  - GIT
  - Bloodborne → drugs, mediators, hormones, toxins, etc. because it is unprotected by the blood-brain barrier

## 2. Nucleus tractus solitarius (NTS)

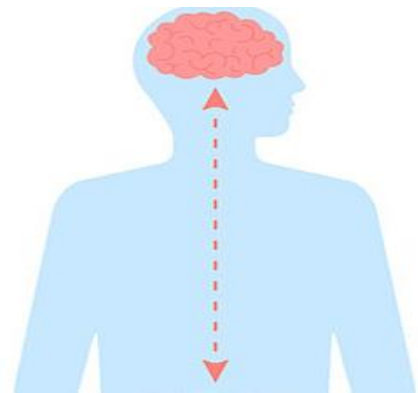
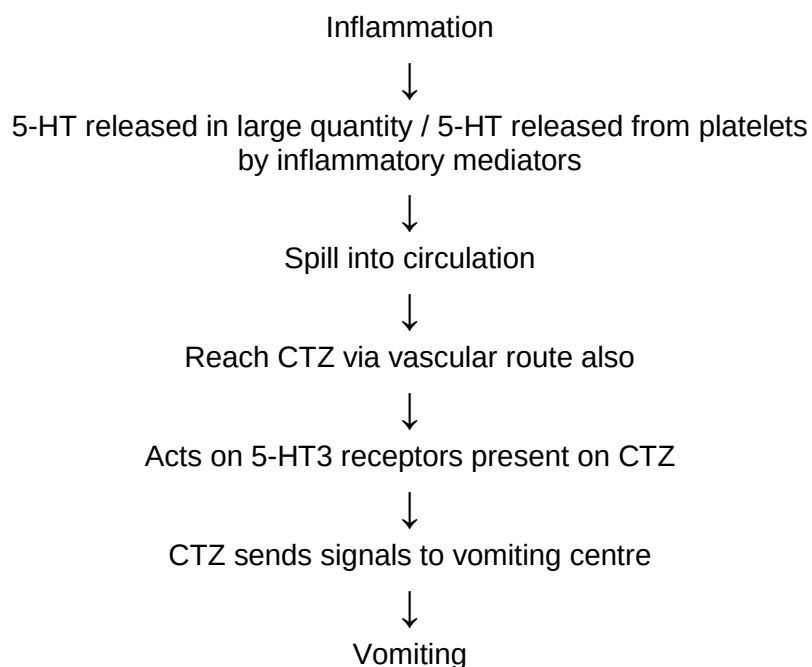
- Protected by BBB
- **Expresses** → dopamine  $D_2$ , serotonin  $5-HT_3$ , neurokinin  $NK_1$  (activated by substance P), histamine  $H_1$ , cholinergic  $M$  receptors
- **Receives impulses arising in** →
  - GIT



### Impulse from GIT



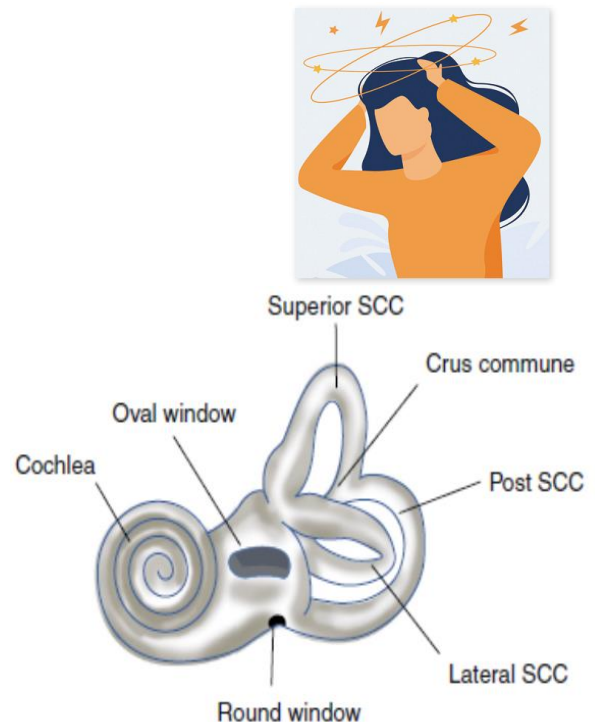
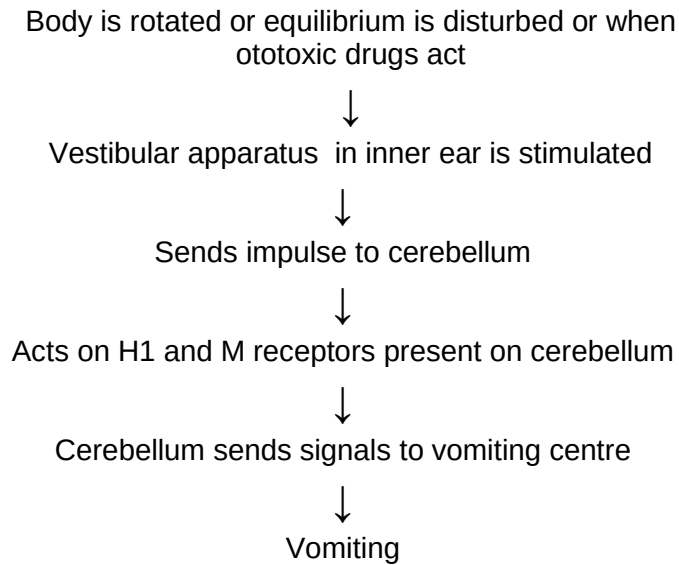
### Impulse from Blood



### 3. Cerebellum

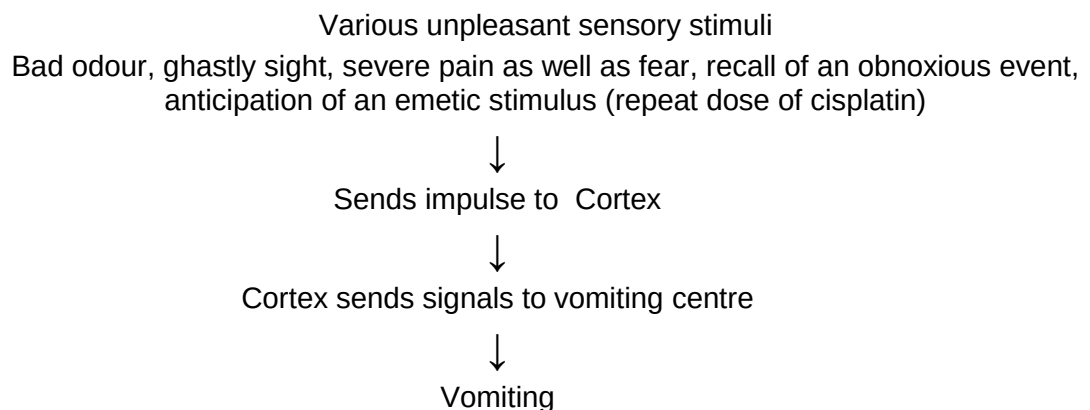
- **Expresses** → histamine H<sub>1</sub>, cholinergic M receptors
- **Receives impulses arising in** →
  - Vestibular apparatus in inner ear

### Impulse from Vestibular apparatus



### 4. Cortex higher centres

- **Receives impulses arising in** →
  - Various unpleasant sensory stimuli



### Reduced gastric emptying

- Vomiting is accompanied by reduced gastric tone and peristalsis

In the emetic response →

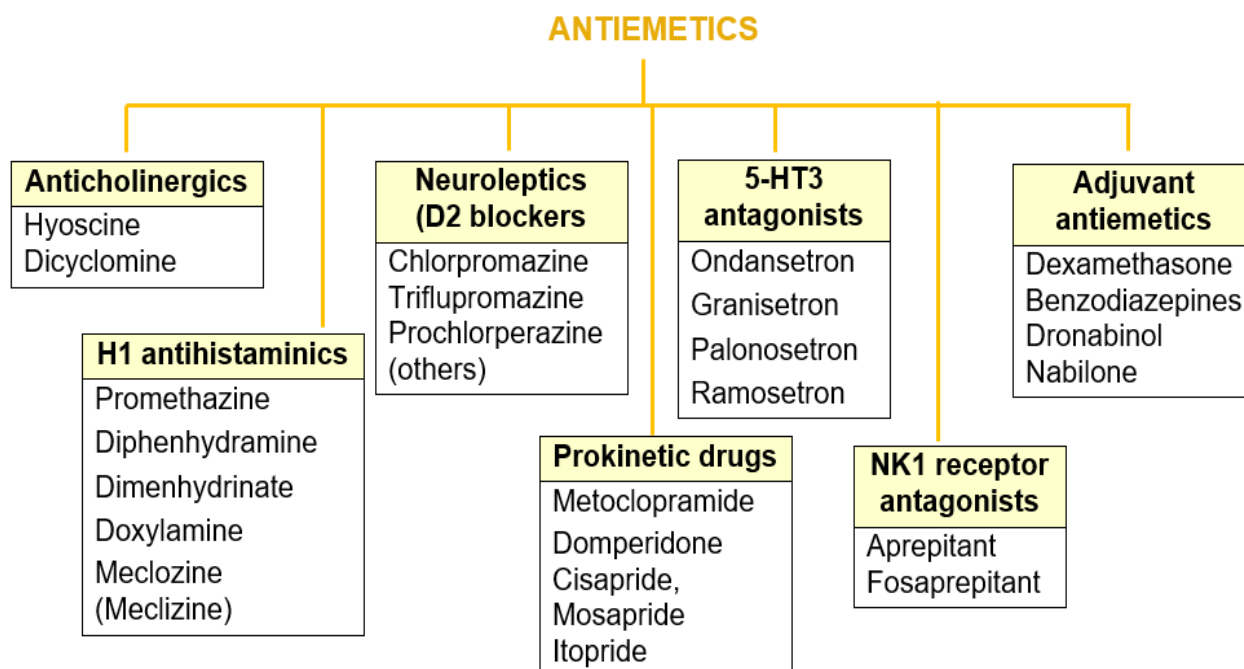
1. LES, esophagus, fundus and body of stomach relax
  2. Duodenum and pyloric stomach contract in a retrograde manner.
- **Conditions that inhibit gastric emptying** → Predispose to vomiting
  - **Conditions that stimulates gastric emptying** → Suppress vomiting

## ANTIEMETIC DRUGS

### Introduction

- Drugs used to prevent or suppress vomiting

### Classification



| Antiemetic Drugs |                  |                    |              |                          |                   |
|------------------|------------------|--------------------|--------------|--------------------------|-------------------|
|                  | Anticholinergics | H1 Antihistaminics | Neuroleptics | Nk1 Receptor Antagonists | 5-HT3 Antagonists |
| Drugs            |                  |                    |              |                          |                   |
| MOA              |                  |                    |              |                          |                   |
| Pharmacokinetics |                  |                    |              |                          |                   |
| Uses             |                  |                    |              |                          |                   |
| Drawbacks        |                  |                    |              |                          | Interactions      |

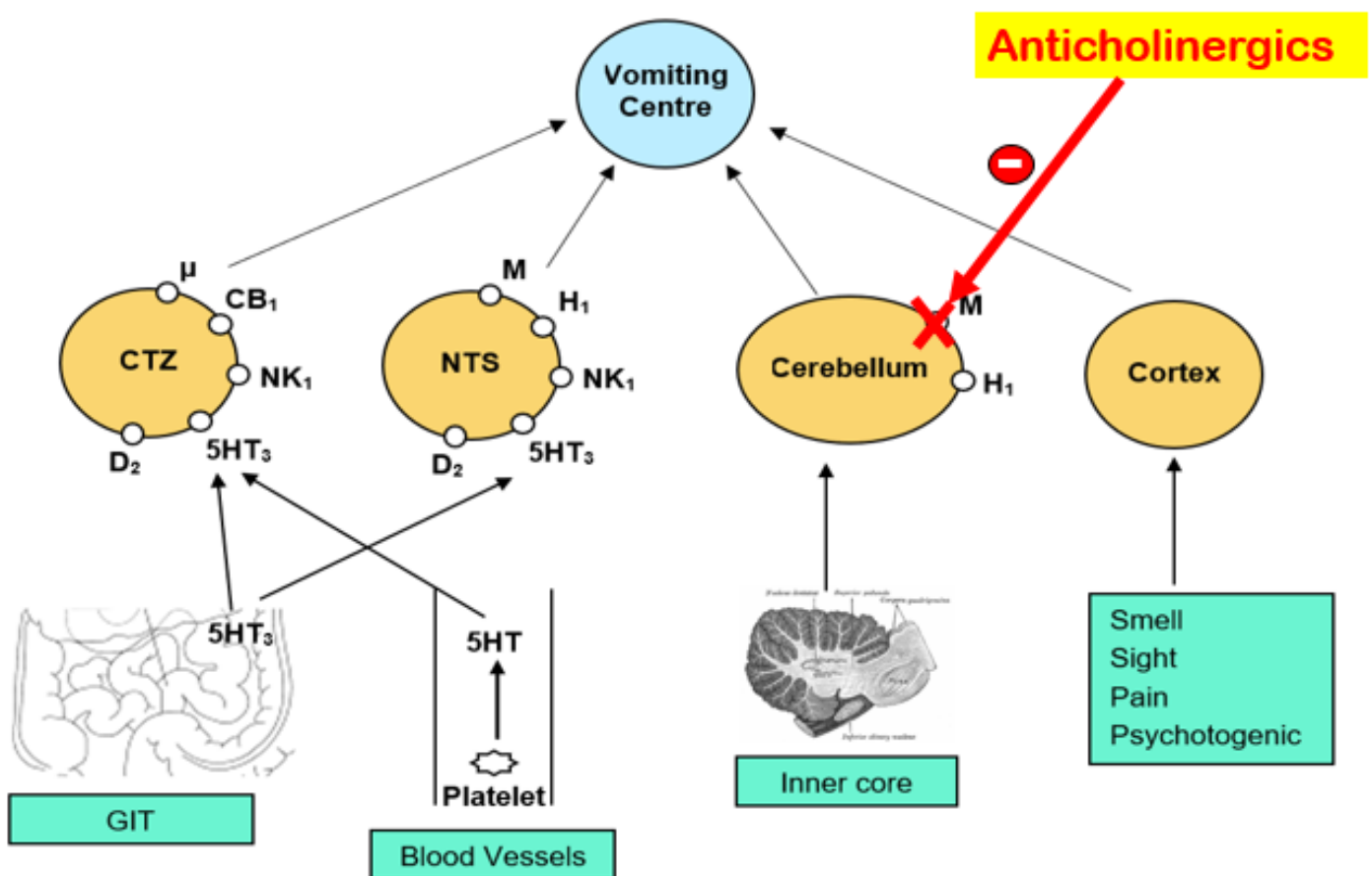
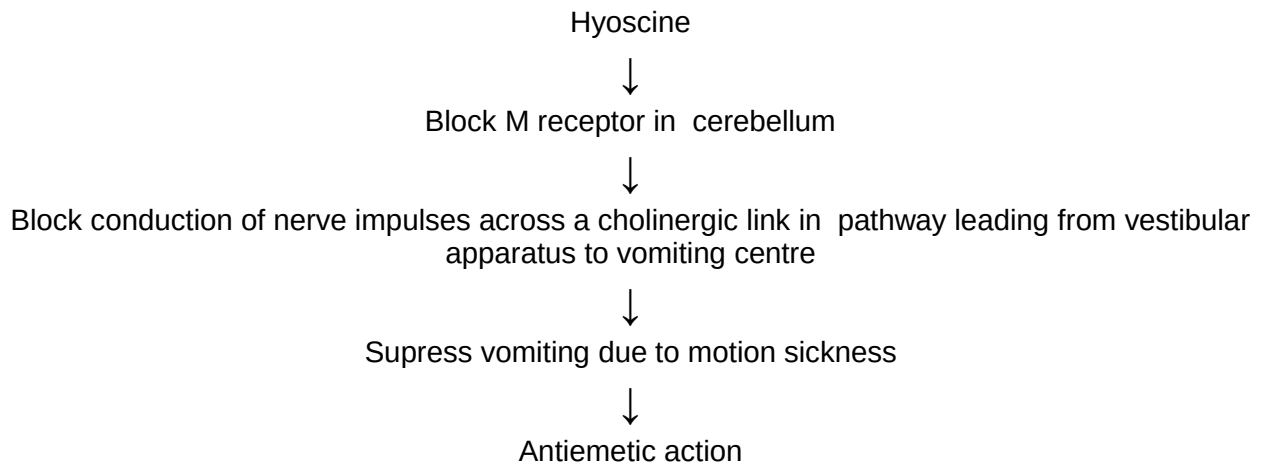
## ANTICHOLINERGICS

### Drugs

- Hyoscine
- Dicyclomine

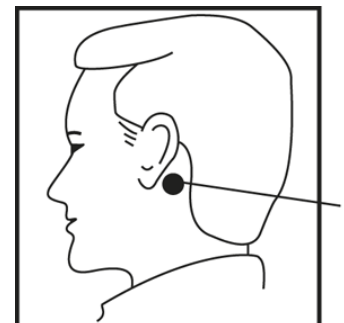
### Hyoscine

## MOA



## Route

- A transdermal patch containing 1.5 mg of hyoscine, to be delivered over 3 days has been developed.
- Applied behind the pinna, it suppresses motion sickness while producing only mild side effects



## Uses

- Most effective drug for motion sickness.



## Drawbacks

1. It has a brief duration of action; so suitable only for short brisk journeys
2. Produces sedation
3. Dry mouth and other anticholinergic side effects
4. Has poor efficacy in vomiting of other etiologies.

## Dicyclomine

- Use → for prophylaxis of motion sickness and for morning sickness.



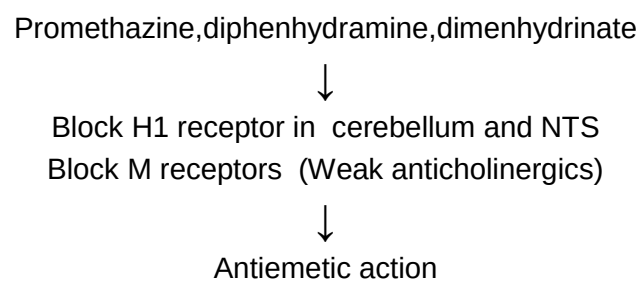
# H1 ANTIHISTAMINICS

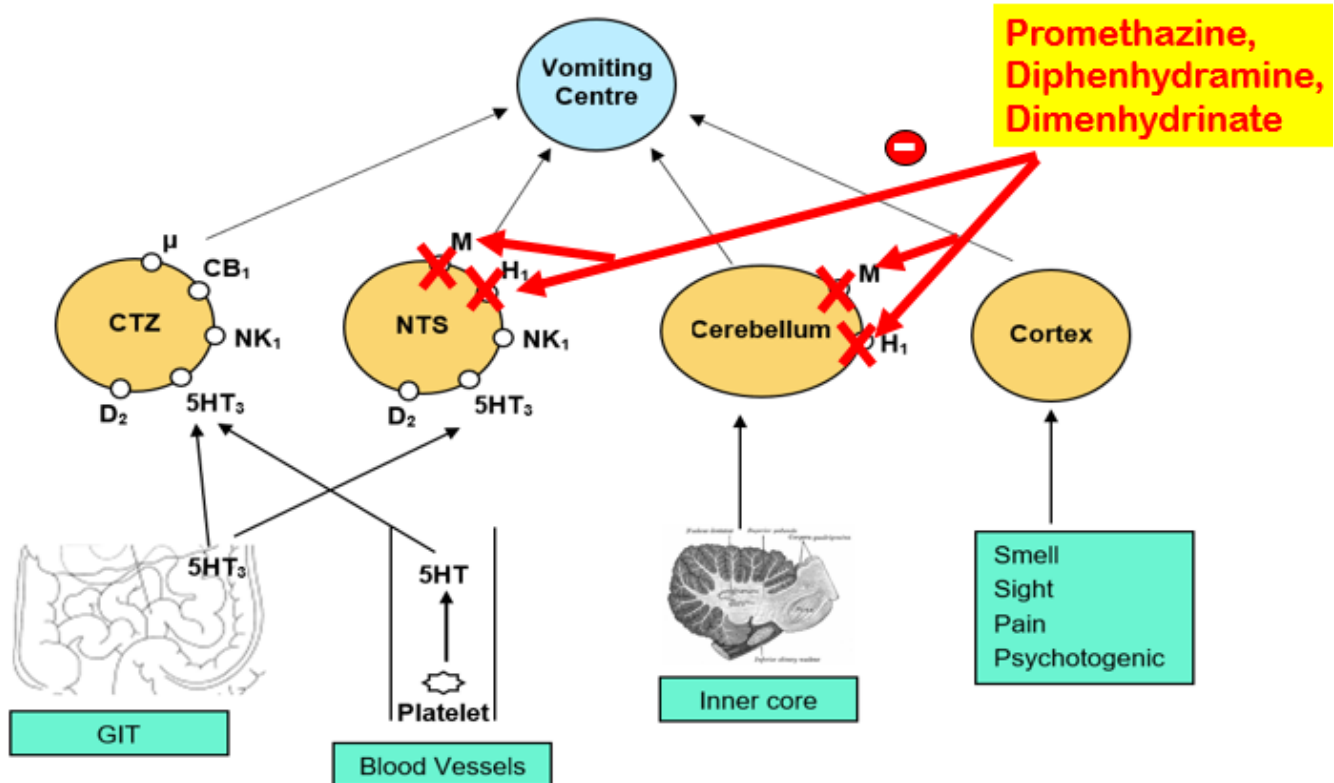
## Drugs

- Promethazine
- Diphenhydramine
- Dimenhydrinate
- Doxylamine
- Meclozine (Meclizine)
- Cinnarizine

## Promethazine, diphenhydramine, dimenhydrinate

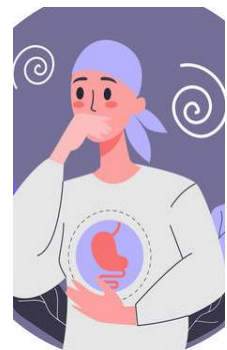
## MOA





## Uses

- Protection of motion sickness for 4–6 hours
- Chemotherapy induced nausea and vomiting (CINV).



## Drawbacks

1. Produces sedation
2. Dry mouth and other anticholinergic side effects (they are also weak anticholinergics)



## Doxylamine

- It is a sedative  $H_1$  antihistaminic with prominent anticholinergic activity.
- Specifically promoted in India for morning sickness

## Meclozine (meclizine)

- Less sedative
- Longer-acting
- Protects against sea sickness for nearly 24 hours.



## Cinnarizine

- Additional MOA  $\rightarrow$  acts by inhibiting influx of  $Ca^{2+}$  from endolymph into vestibular sensory cells which mediates labyrinthine reflexes



- Use → Motion sickness

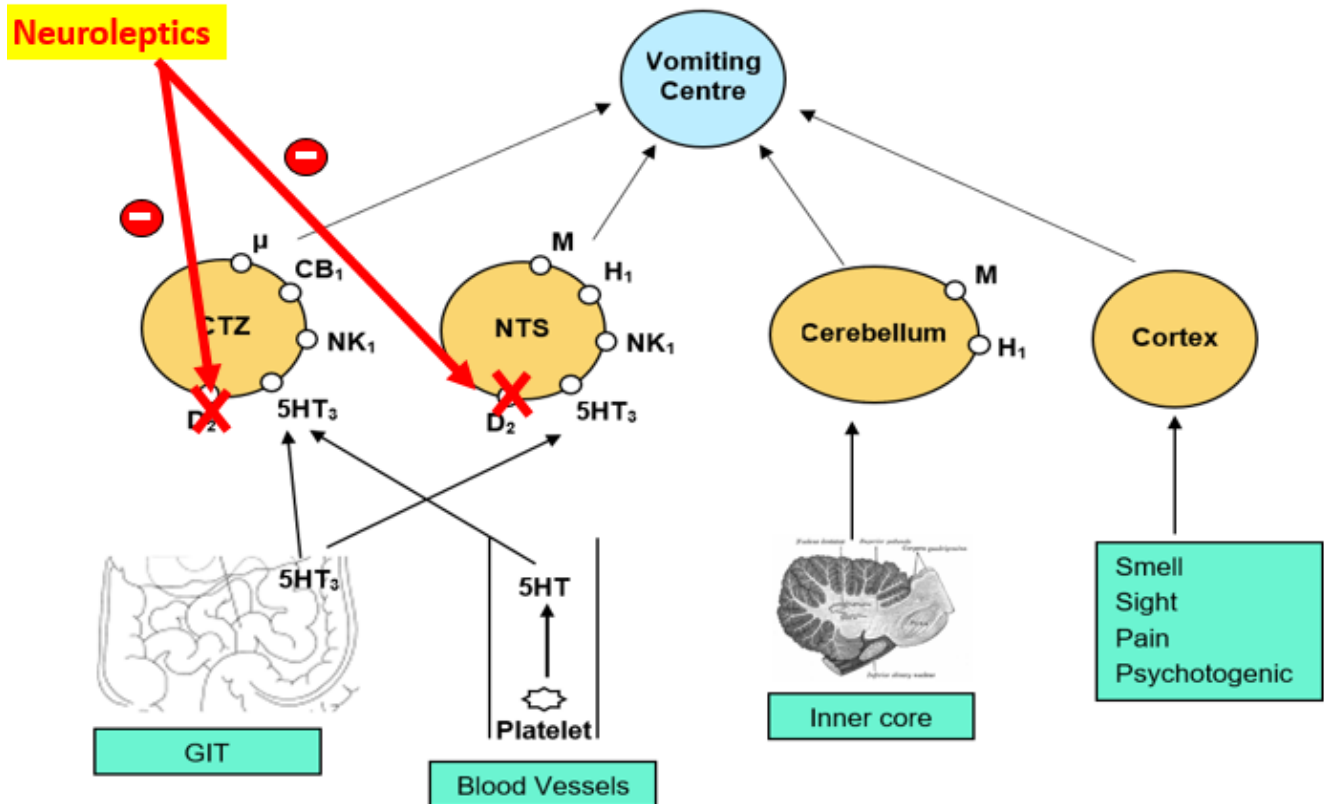
## NEUROLEPTICS

### Drugs

- Chlorpromazine
- Triflupromazine
- Prochlorperazine
- Haloperidol

### MOA

1. Block D<sub>2</sub> receptors in CTZ and NTS
2. Also Block M receptors → Additional antimuscarinic property
3. Also Block H<sub>1</sub> receptors → Additional antihistaminic property



### Uses

1. Drug induced and postoperative nausea and vomiting (PONV).
2. Disease induced vomiting: gastroenteritis, uraemia, liver disease, migraine, etc.
3. Malignancy associated and cancer chemotherapy (mildly emetogenic) induced vomiting.
4. Radiation sickness vomiting (less effective).
5. Morning sickness: should not be used except in hyperemesis gravidarum.

### Remember

- Neuroleptics are less effective in motion sickness: vestibular pathway does not involve dopaminergic link.



## Drawbacks

1. Sedation
2. Acute muscle dystonia

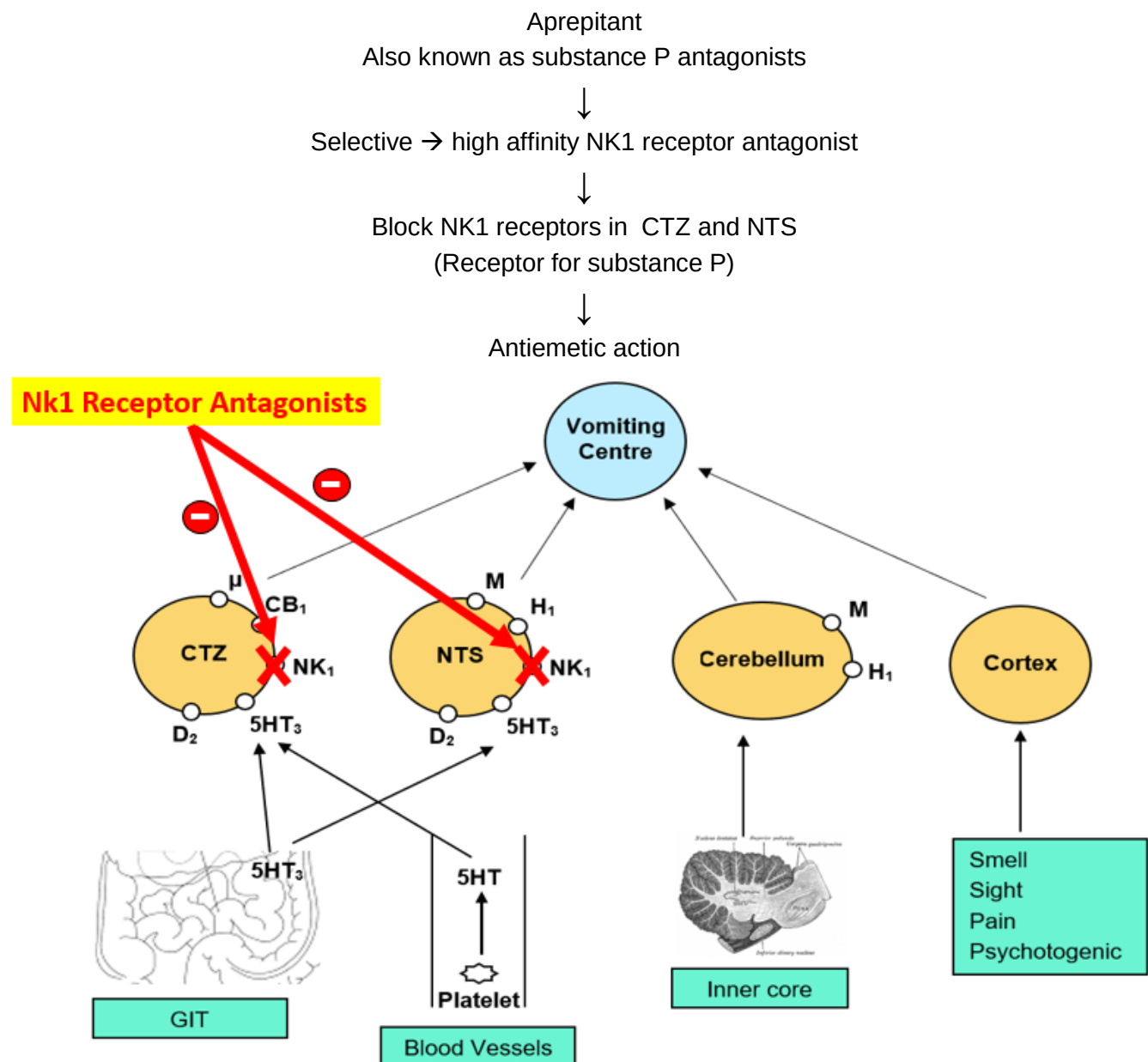
## NK1 RECEPTOR ANTAGONISTS

### Drugs

- Aprepitant
- Fosaprepitant

### Aprepitant

### MOA





## Pharmacokinetics

- Metabolized primarily by hepatic CYP 3A4
- Aprepitant is contraindicated in patients on cisapride or pimozone, in which life threatening QT prolongation has been reported.

## Uses

1. Antiemetic efficacy against high emetogenic cisplatin based chemotherapy.
  - Greater additional protection was afforded against delayed vomiting than against acute vomiting.
  - It was particularly useful in patients undergoing multiple cycles of chemotherapy.
2. PONV

## Drawbacks

- Weakness
- Fatigue
- Flatulence
- Rise in liver enzymes

## Fosaprepitant

- Parenterally administered prodrug of aprepitant.

# 5-HT<sub>3</sub> ANTAGONISTS

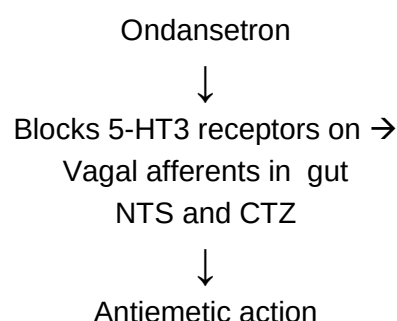
## Drugs

- Ondansetron
- Granisetron
- Palonosetron
- Ramosetron

## Ondansetron

- Blocks emetogenic impulses both at their peripheral origin and their central relay.

## MOA





- **Ondansetron** → shortest acting.
- **Dolasetron** → cause QT prolongation.
- **Alosetron** → withdrawn because of fatal GI side effects like constipation and ischemic colitis.
- **Dolasetron, Tropisetron and Palonasetron** → newer 5-HT<sub>3</sub> antagonists.

## PROKINETIC DRUGS

### Drugs

- Metoclopramide
- Domperidone
- Cisapride, Mosapride, Itopride
- Tegaserod

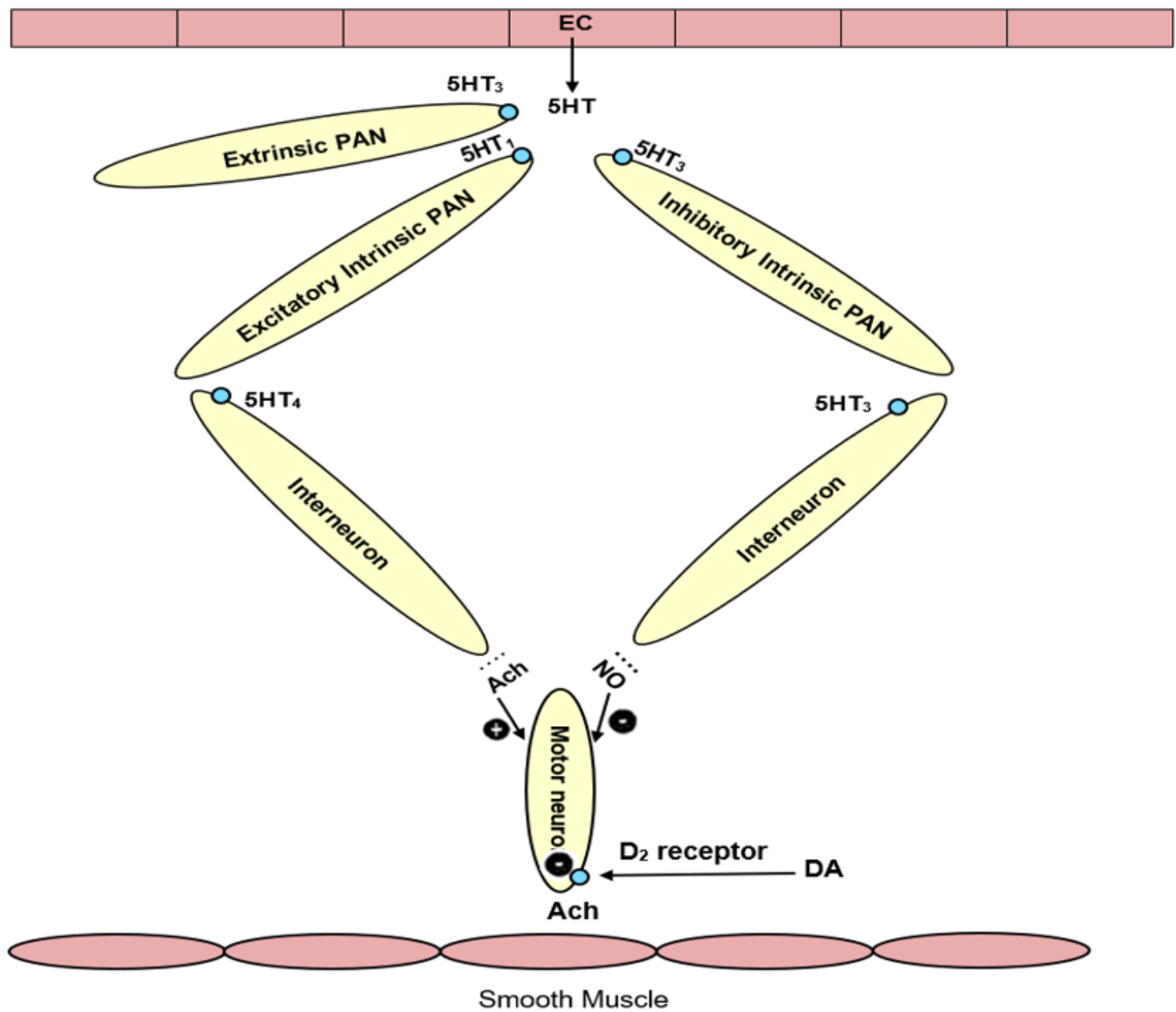
| Prokinetic Drugs |                |             |           |           |
|------------------|----------------|-------------|-----------|-----------|
|                  | Metoclopramide | Domperidone | Cisapride | Tegaserod |
| Introduction     |                |             |           |           |
| MOA              |                |             |           |           |
| Pharmacokinetics |                |             |           |           |
| Uses             |                |             |           |           |
| Adverse effects  |                |             |           |           |
| Interactions     |                |             |           |           |

### Introduction

- Promote gastrointestinal transit
- Speed gastric emptying by enhancing coordinated propulsive motility.

### Pathophysiology of gastrokinetic drugs

- **Acetylcholine** → major neurotransmitter in the GIT which is responsible for peristaltic movement.
- Its secretion is affected by other neurotransmitter →
  1. Activation of prejunctional excitatory 5-HT<sub>4</sub> receptors increases release of Ach.
  2. Activation of prejunctional inhibitory D<sub>2</sub> and 5-HT<sub>3</sub> receptors inhibits release of Ach.



Prokinetic drugs act by



5HT<sub>4</sub> agonistic activity

D<sub>2</sub> antagonistic activity

5-HT<sub>3</sub> antagonistic activity



Increase release of ACh



Increase motility of GIT

## METOCLOPRAMIDE

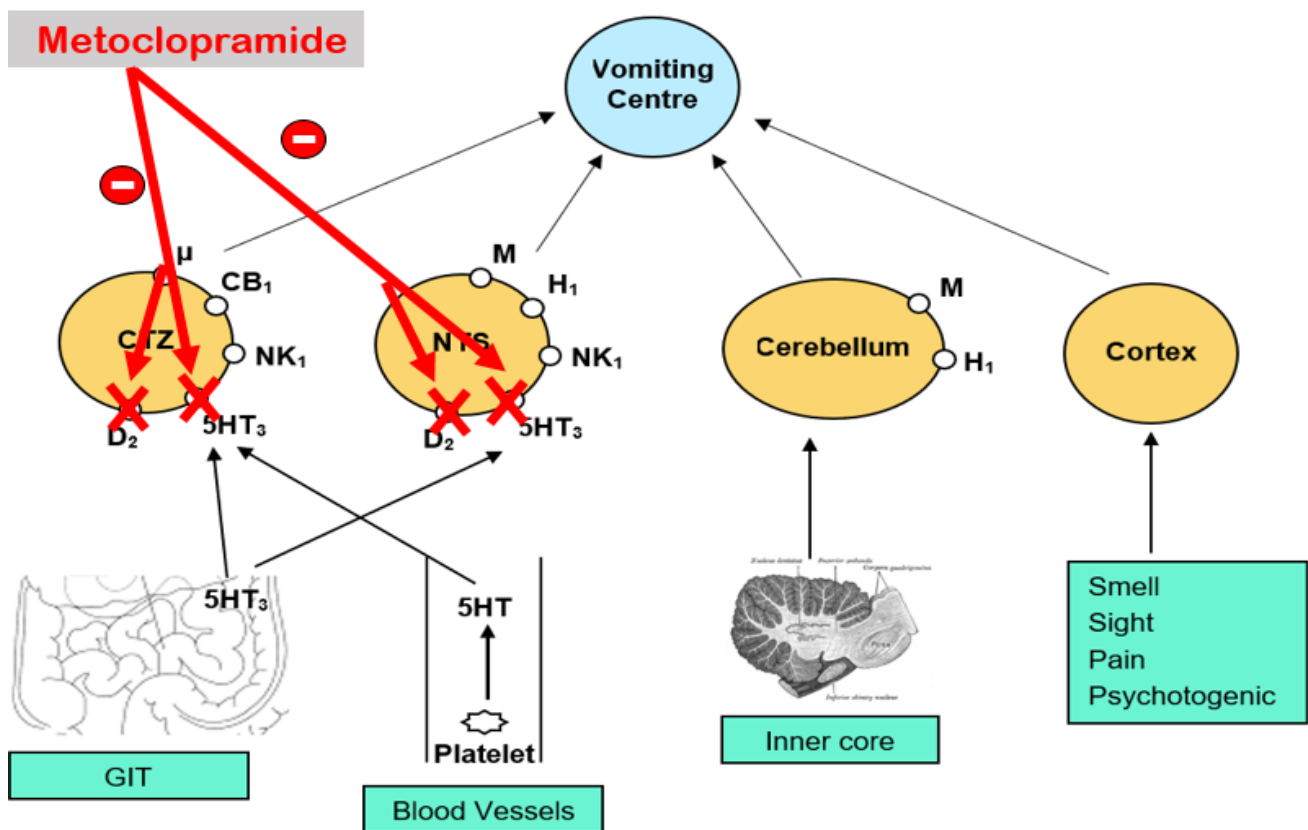
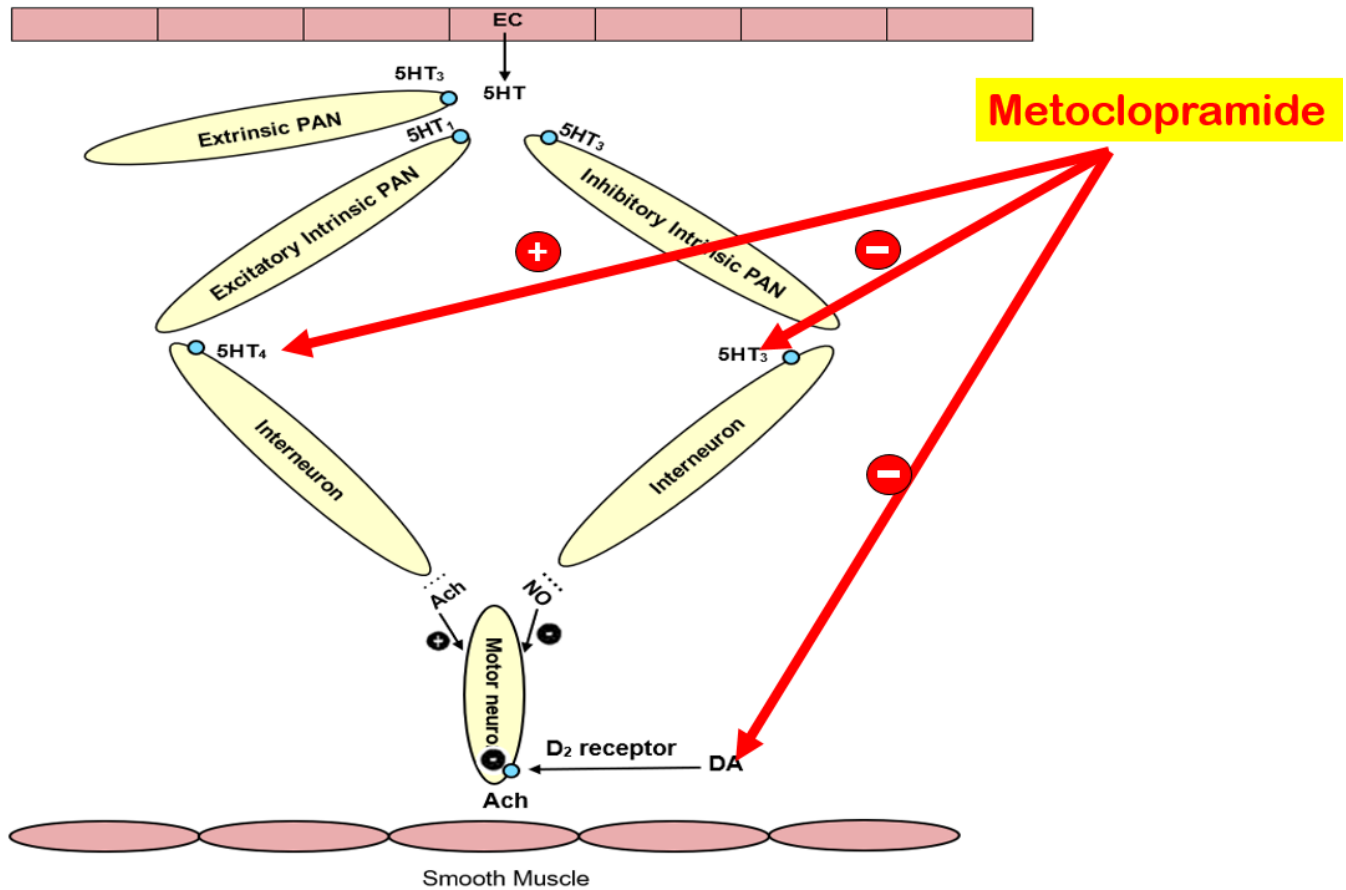
### Introduction

- Metoclopramide (a benzamide, like procainamide<sup>1</sup>) is a prokinetic drug

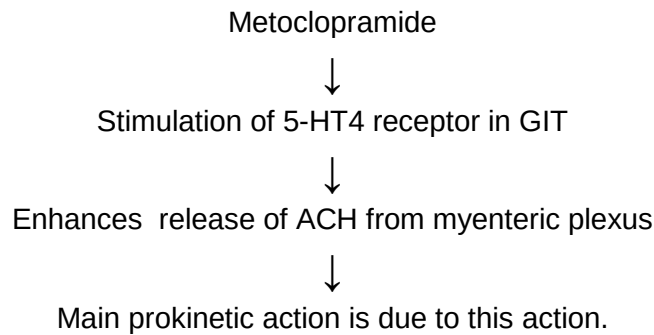
### MOA

- 5-HT<sub>4</sub> agonism in GIT

2. D2 antagonism in GIT and CTZ / NTS
3. 5-HT3 antagonism in GIT and CTZ / NTS



## 1. 5-HT<sub>4</sub> agonism

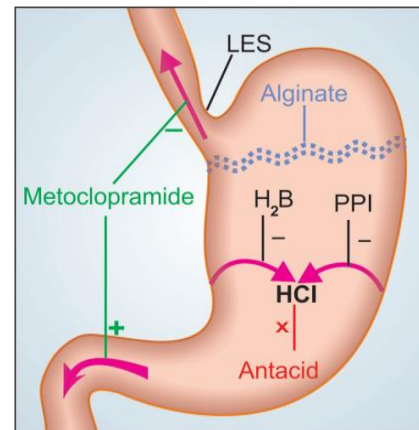


## 2. D<sub>2</sub> antagonism

- Blockade of D<sub>2</sub> receptor in GIT → responsible for prokinetic action
- Blockade of D<sub>2</sub> receptor in CTZ / NTS → responsible for antiemetic effect

## 3. 5-HT<sub>3</sub> antagonism

- Blockade of 5-HT<sub>3</sub> receptor in GIT → responsible for prokinetic action
- Blockade of 5-HT<sub>3</sub> receptor in CTZ/NTS → responsible for antiemetic effect
- Increases tone of lower esophageal sphincter (LES) → GERD opposed
- Relax pylorus and first part of duodenum → speed gastric emptying
- More prominent effect on upper GIT → increases gastric peristalsis
- Less prominent effect on lower GIT → increases intestinal motility to some extent
- But has no significant action on colonic motility



## Pharmacokinetics

- Metoclopramide is rapidly absorbed orally, enters brain, crosses placenta and is secreted in milk.
- Plasma  $t_{1/2}$  is 3–6 hours.
- Orally it acts in  $\frac{1}{2}$ –1 hr, but within 10 min after i.m. and 2 min after i.v. injection.
- Action lasts for 4–6 hours.

## Uses

1. As an antiemetic
2. Gastrokinetic
3. Dyspepsia
4. GERD

### 1. As an antiemetic →

- Effective for many types of vomiting— postoperative, drug induced, disease associated (especially migraine), radiation sickness, etc
- But is less effective in motion sickness.
- Though no teratogenic effects have been reported, metoclopramide should be used for morning sickness only when not controlled by other measures.

## 2. **Gastrokinetic:** To accelerate gastric emptying:

- (a) When emergency general anaesthesia has to be given and the patient has taken food less than 4 hours before.
- (b) To relieve postvagotomy gastroparesis associated gastric stasis.

## 3. **Dyspepsia**

- Metoclopramide may succeed in stopping persistent hiccups

## 4. **GERD**

- Metoclopramide may benefit milder cases of GERD, but is much less effective than PPIs/H2 blockers.
- Used as adjuvant to acid suppressive therapy.

## **Adverse effects**

1. Sedation, dizziness, loose stools, muscle dystonia (especially in children) are main side effects.
2. D2 - blocking action cause extrapyramidal symptoms (Akathisia, Parkinsonism) and hyperprolactinemia (galactorrhea, gynecomastia).

## **Interactions**

- **Levodopa** → By blocking DA receptors in basal ganglia, it abolishes the therapeutic effect of levodopa

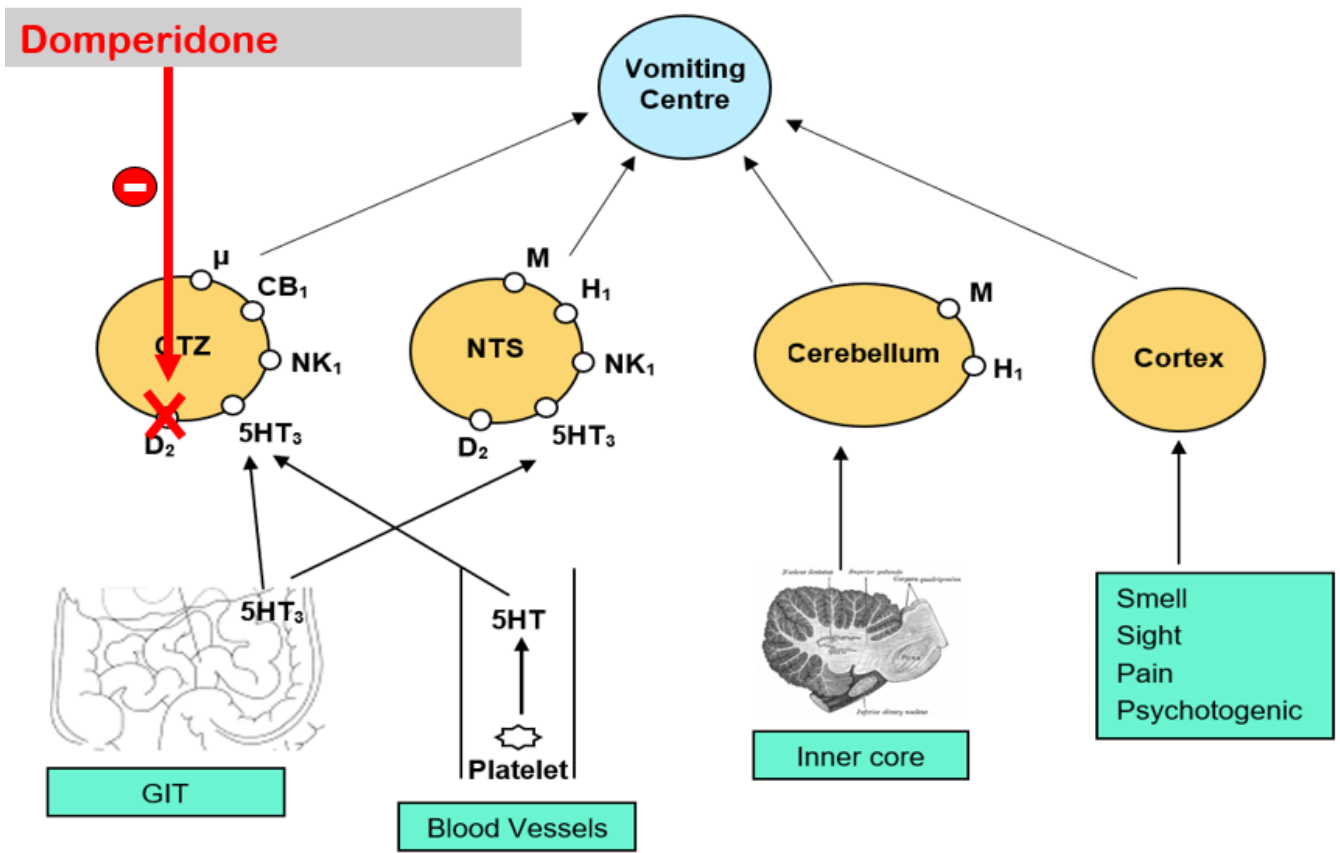
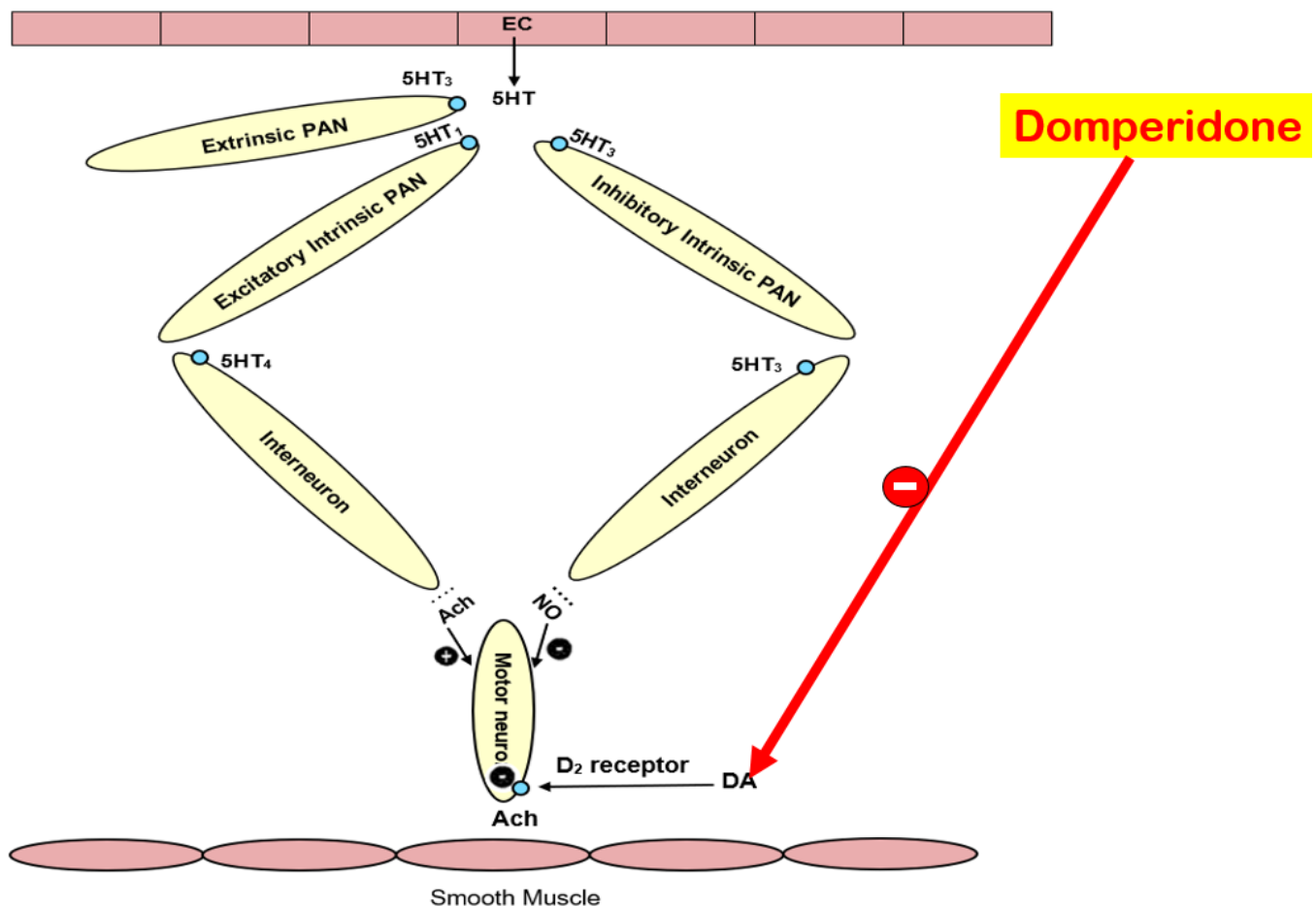
# **DOMPERIDONE**

## **Introduction**

- It is a D2 receptor antagonist

## **MOA**

- D2 antagonism in GIT and CTZ
  - Blockade of D2 receptor in GIT → responsible for prokinetic action
  - Blockade of D2 receptor in CTZ → responsible for antiemetic effect





### It does not cross blood brain barrier

1. Exerts antiemetic effect, because CTZ lies out side the BBB
2. No extrapyramidal side effects and hyperprolactinemia (in contrast to metoclopramide)
3. It can be given with levodopa → Domperidone decreases levodopa induced vomiting (by acting on CTZ) without interfering its therapeutic effects

### Pharmacokinetics

- Domperidone is absorbed orally.
- Bioavailability is only ~15% due to first pass metabolism.
- Plasma  $t_{1/2}$  is 7.5 hr.

### Uses

- Same as metaclopramide

### Adverse effects

- Less than with metoclopramide.
  1. Dry mouth, loose stools, headache, rashes, galactorrhoea are generally mild.
  2. Cardiac arrhythmias have developed on rapid i.v. injection

## CISAPRIDE

### Introduction

- It is a prokinetic with little antiemetic property.

### MOA

1. 5-HT<sub>4</sub> agonism in GIT → Stimulation of 5-HT<sub>4</sub> receptor in GIT enhances release of ACH from myenteric plexus
  2. Weak 5-HT<sub>3</sub> antagonistic activity in GIT → suppresses inhibitory transmission in myenteric plexuses → enhances release of ACH from myenteric plexus
- No D<sub>2</sub>-antagonistic activity



## Pharmacokinetics

- Cisapride is primarily inactivated by CYP3A4
- Plasma  $t_{1/2}$  of ~ 10 hours.

## Uses

1. GERD
2. Dyspepsia
3. Impaired gastric emptying
4. Chronic constipation

## Adverse effects

1. At high concentrations, cisapride blocks delayed rectifying K<sup>+</sup> channels in heart—prolongs Q-Tc interval and predisposes to torsades de pointes/ventricular fibrillation → Banned
2. Ventricular arrhythmias and death, mainly among patients who took CYP3A4 inhibitors like azole antifungals, macrolide antibiotics, antidepressants

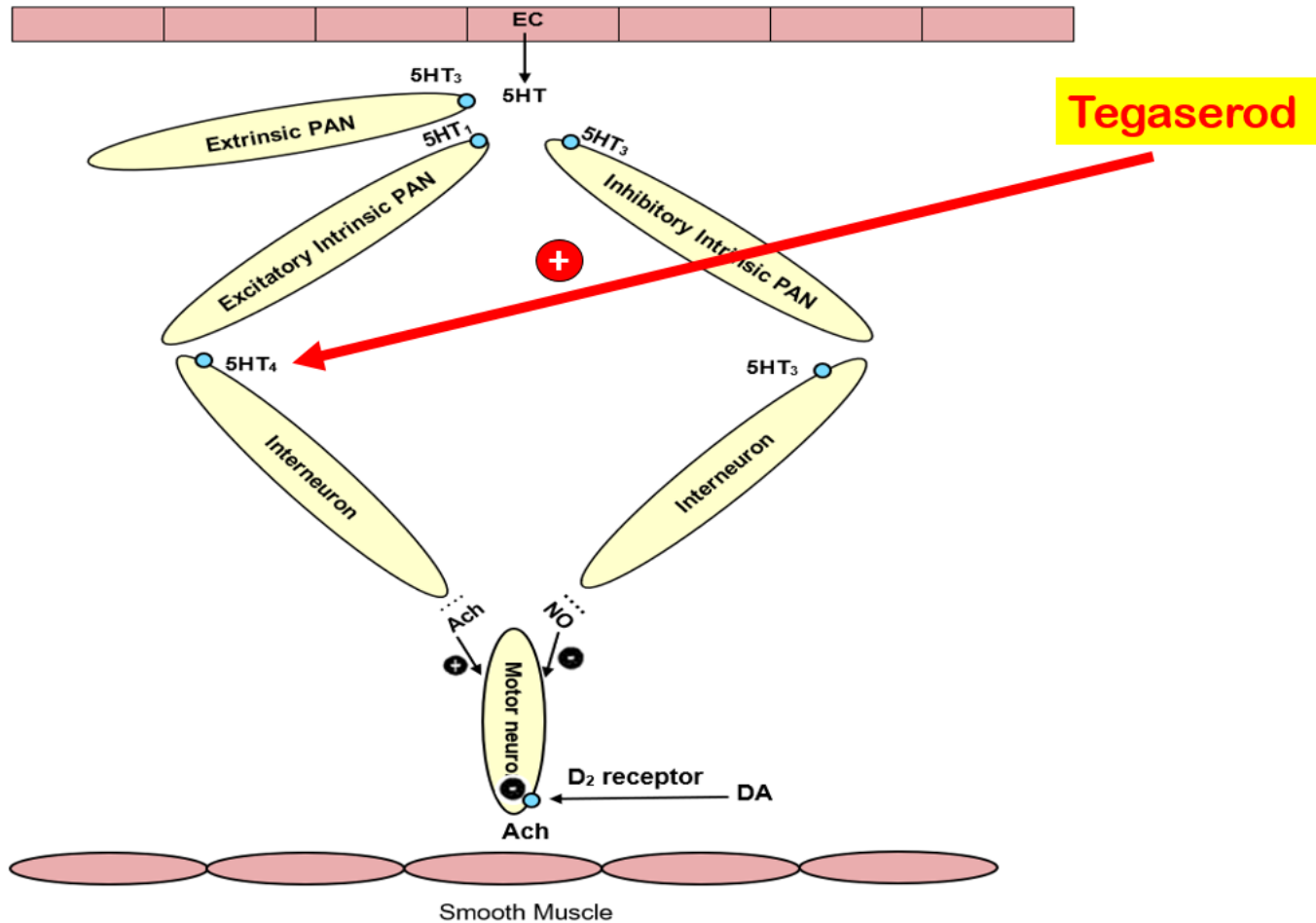
## Misapride

- Similar to cisapride, but does not cause QT prolongation.

# TEGASEROD

## MOA

- Selective 5-HT<sub>4</sub> agonist in GIT with no action on 5-HT<sub>3</sub> receptor (contrast cisapride also has weak 5-HT<sub>3</sub> antagonistic action).
- It mainly augments colonic motility along with promotion of gastric emptying and intestinal transit, and less effect on LES tone.



## Use

1. Constipation
2. Irritable bowel syndrome

## Remember

### Motion sickness

- Anticholinergic → Hyoscine (scopolamine) and H<sub>1</sub> antihistaminic drugs are more effective in motion sickness.
  - a) Anticholinergics → Hyoscine (Scopolamine) Dicyclomine
  - b) H<sub>1</sub> antihistaminic → Promethazine, cyclizine, meclizine, cinnarizine, etc.

### Morning sickness

H<sub>1</sub> antihistaminic is preferred

1. Combination of doxylamine (an antihistaminic) with pyridoxine is preferred.

2. Promethazine is an alternative to doxylamine

### Chemotherapy induced nausea and vomiting

- Cisplatin is most common culprit causing chemotherapy induced nausea and vomiting.
- Cytotoxic drugs and radiation cause cellular damage which leads to release of 5-HT from intestine and activation of emetogenic 5-HT<sub>3</sub> receptors.
- Therefore, 5-HT<sub>3</sub> receptor antagonists (e.g. ondansetron) are the DOC for this condition.
- Cisplatin can induce vomiting within 24 hours or after 2 days.
  - DOC for early vomiting → Ondansetron
  - DOC for delayed vomiting → Aprepitant (substant P antagonist)

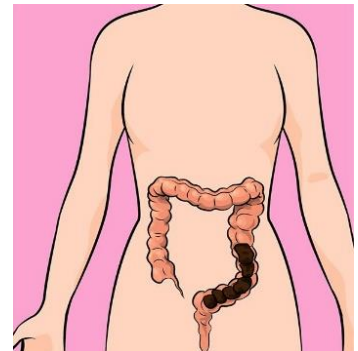
### Post-operative nausea and vomiting (PONV)

- Prevention of PONV
  - For high risk patients, propofol is the drug of choice for induction and maintenance.
  - As prophylaxis droperidol or metoclopramide or ondansetron can be given before surgery.
- Control of PONV
  - All the mentioned antiemetic drugs can be used.

## DRUGS FOR CONSTIPATION

### Constipation

- A stool frequency of once in 2 days to 2–3 times per day is considered normal by different individuals
- Constipation is infrequent production of hard stools requiring straining to pass, or a sense of incomplete evacuation.
- Constipation is a symptom rather than a disease.



### Etiology

- Various aspects of patient's lifestyle may contribute:
  - (a) Misconception about the normal/necessary frequency, amount or consistency of stools.
  - (b) Inadequate fibre in diet, less fluid intake.
  - (c) Lack of exercise, sedentary nature of work.
  - (d) Irregular bowel habits, rushing out for job

### Types

#### 1. Spastic constipation (irritable bowel):

- Excessive tone of colonic muscles which narrows cavity and the forward movement of faeces is retarded
- The stools are hard, rounded, stone like and difficult to pass.

#### 2. Atonic constipation (sluggish bowel):

- Due to advanced age, debility or laxative abuse.

【Spastic constipation】



【Atonic constipation】



## DRUGS FOR CONSTIPATION

### 1. Laxative or aperient:

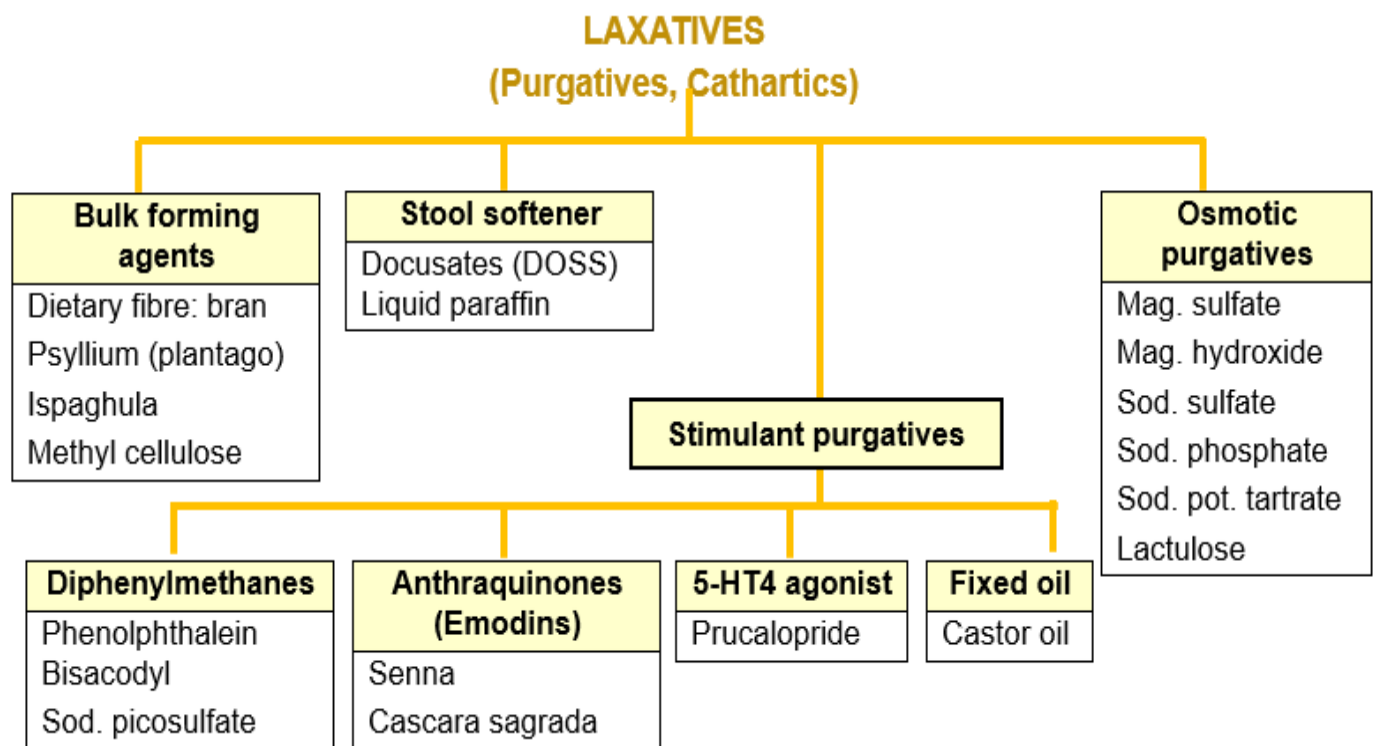
- Milder action
- Elimination of soft but formed stools.

### 2. Purgative or cathartic:

- Stronger action
- Resulting in more fluid evacuation.

- Many drugs in low doses act as laxative and in larger doses as purgative

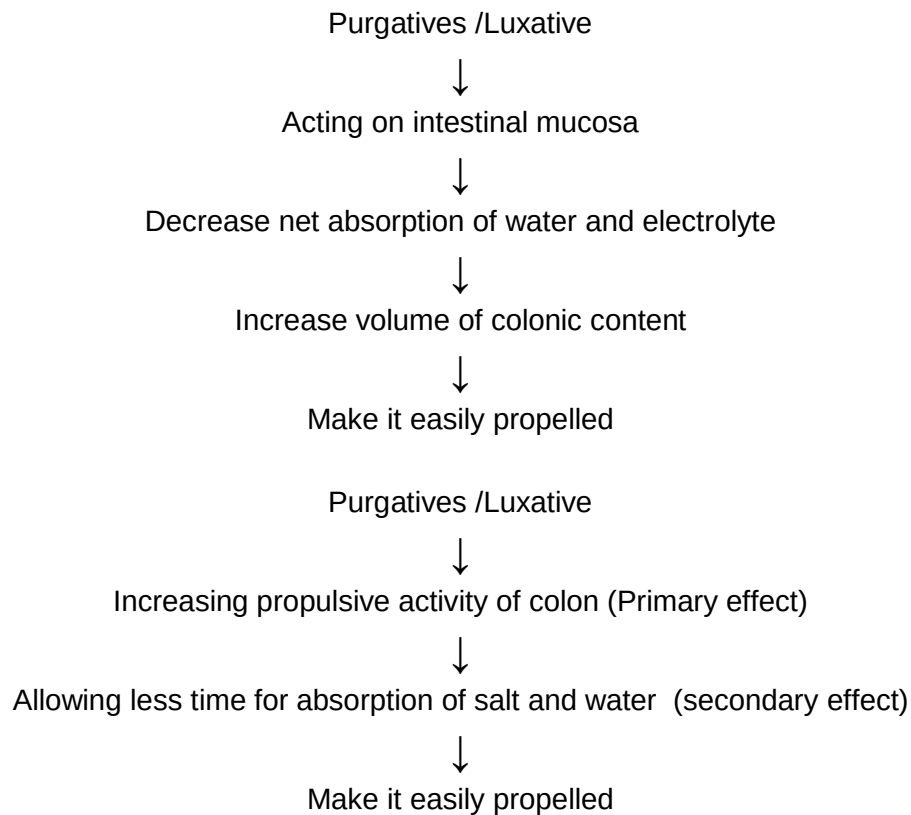
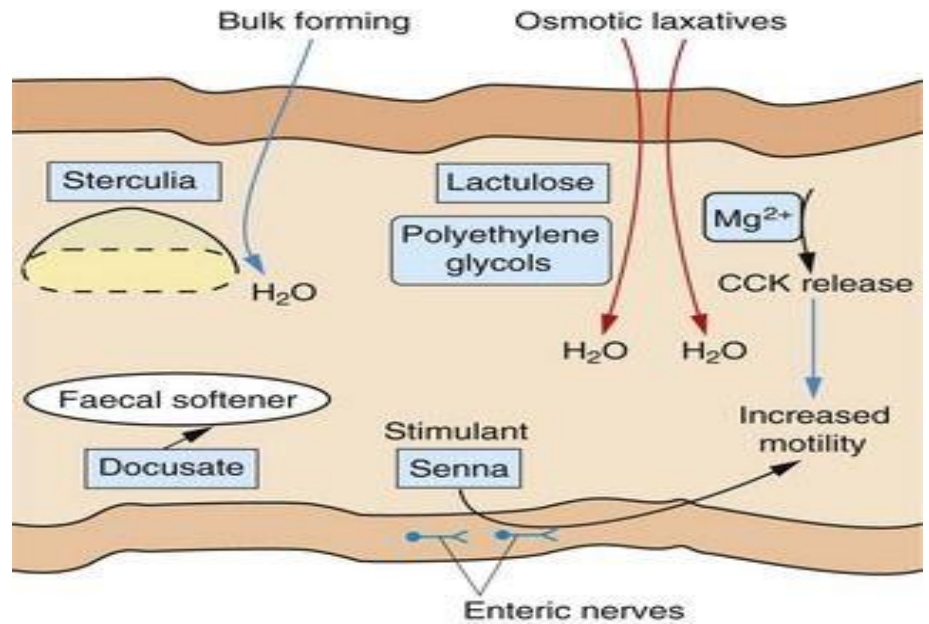
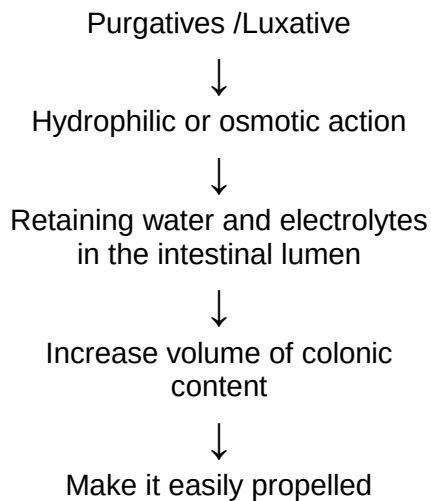
## Classification



| Drugs for constipation |                 |                |                      |                      |
|------------------------|-----------------|----------------|----------------------|----------------------|
|                        | Bulk Purgatives | Stool Softener | Stimulant Purgatives | Stimulant Purgatives |
| Drugs                  |                 |                |                      |                      |
| MOA                    |                 |                |                      |                      |
| Uses                   |                 |                |                      |                      |
| Adverse effects        |                 |                |                      |                      |
| Contraindications      |                 |                |                      |                      |

## Overall MOA

- All Purgatives /Luxative increase water content of faeces by:



## BULK PURGATIVES

### Drugs

- Dietary fibre: bran
- Psyllium (Plantago)
- Ispaghula
- Methylcellulose

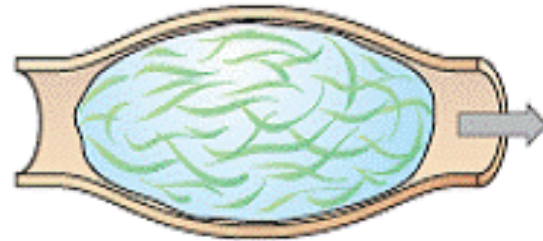
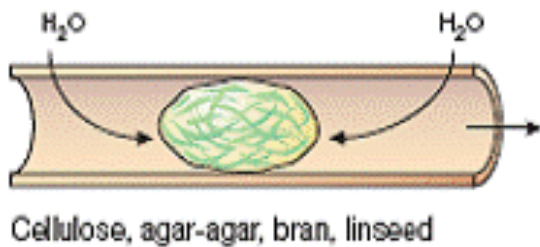
## Dietary fibre: bran

- Dietary fibre is the plant cell wall that resists digestion, consist of cellulose, lignin, polysaccharides like pectin and hemicellulose
- Bran is the residual product of flour industry which consists of ~40% dietary fibre.



## MOA

- 3 Mechanisms →



It

absorbs water in the intestines



Swells



Increases water content of faeces



softens it



Facilitates colonic transit

Dietary fibre supports bacterial growth in colon



Bacterial degradation of pectins, gums, etc.



Osmotically active products are formed in colon



Retain water



Softens faeces



Facilitates colonic transit

Dietary fibre bind bile acids



Increase their excretion



↓  
so stimulate their synthesis from cholesterol in liver  
↓  
So decrease plasma cholesterol

## Uses

1. First line approach for simple constipation.
2. Prolonged intake reduces rectosigmoid intraluminal pressure and helps to relieve symptoms of irritable bowel syndrome (IBS)
3. Chronic diverticulosis
4. Useful when straining at stools has to be avoided.

## Drawbacks

1. Unpalatable
2. Large quantity (20–40 g/day) needs to be ingested
3. Full effect requires daily intake for at least 3–4 days.
4. It does not soften faeces already present in colon or rectum. So bran is useful for prevention of constipation, but not for treating already constipated subjects.
5. Flatulence may occur.

## Contraindications

1. Patients with gut ulcerations
2. Adhesions
3. Stenosis
4. when faecal impaction is a possibility

## Psyllium (Plantago) and Ispaghula

- Contain natural colloidal mucilage which forms a gelatinous mass by absorbing water.
- Refined ispaghula husk 3–8 g is freshly mixed with cold milk, fruit juice or water and taken once or twice daily.
- It should not be swallowed dry (may cause esophageal impaction).
- It acts in 1–3 days.



## Methylcellulose

- A semi-synthetic, colloidal, hydrophilic derivative of cellulose that remains largely unfermented in colon.
- It takes up water to swell (about 25 times).
- A dose of 4–6 g/day is satisfactory in most individuals.

# STOOL SOFTENER

## Introduction

- Also known as Surfactants / Emollients



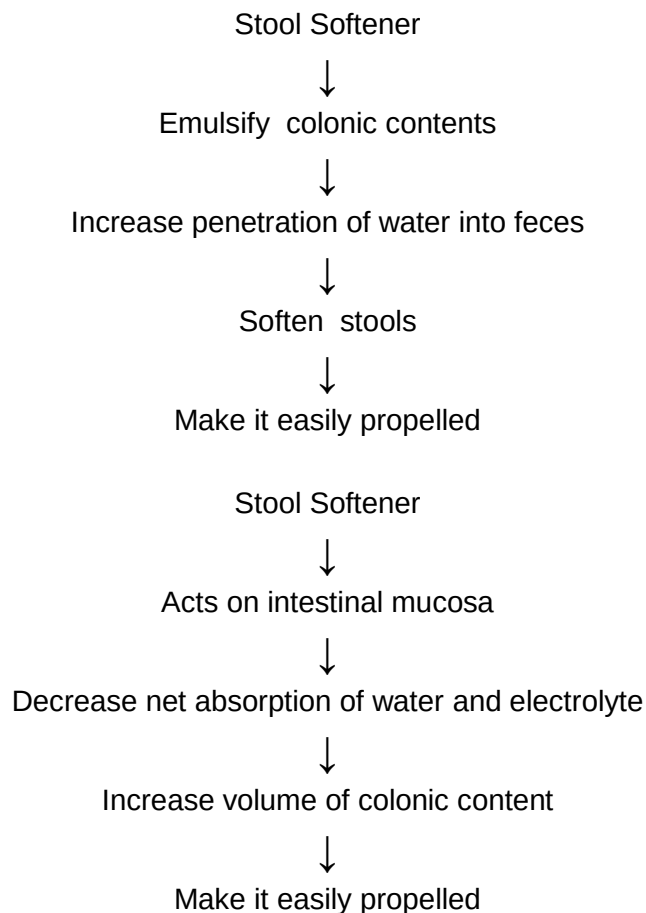
## Drugs

- Docusates (Dioctyl sodium sulfosuccinate : DOSS)
- Liquid paraffin

## Docusates (Dioctyl sodium sulfosuccinate: DOSS)

### MOA

- 2 mechanisms →



### Uses

Mild laxative → indicated when straining at stools must be avoided.

### Side effects

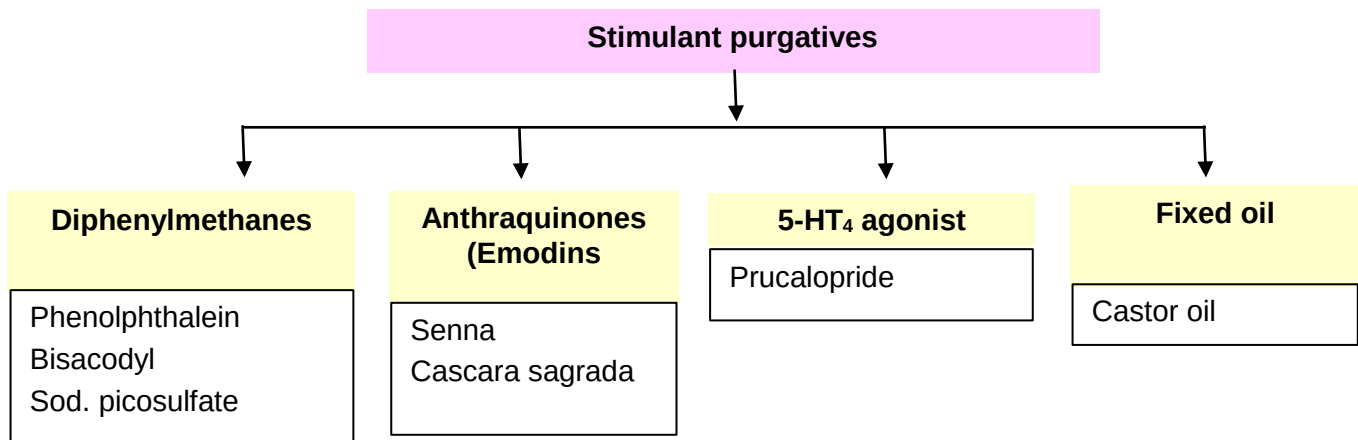
- It is bitter
- Cramps and abdominal pain can occur
- Liquid preparations may cause nausea.
- Hepatotoxicity on prolonged use

## Liquid paraffin

- It is a viscous liquid; a mixture of petroleum hydrocarbons
- Indigestible and non absorbable
- It is pharmacologically inert.
- Takes 2–3 days for action

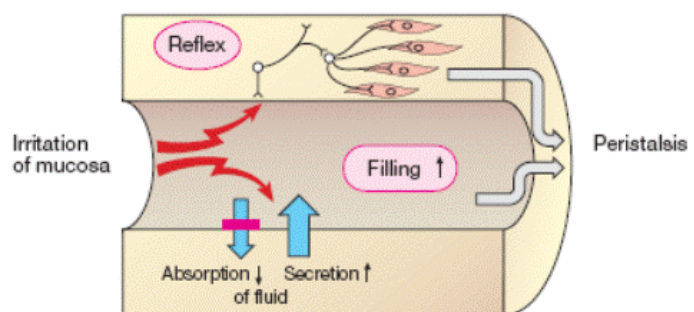
# STIMULANT PURGATIVES

## Drugs



## MOA

- 2 mechanisms →  
Stimulant Purgatives  
↓  
Act on myenteric plexuses of intestine  
↓  
Directly increase motility



- (a) Inhibiting Na<sup>+</sup>K<sup>+</sup>ATPase of villous cells— impairing electrolyte and water absorption.
- (b) Stimulating adenylyl cyclase in crypt cells— increasing water and electrolyte secretion.
- (c) Enhancing PG synthesis in mucosa which increases secretion.
- (d) Increasing NO synthesis which enhances secretion

Increase volume of colonic content

↓  
Make it easily propelled

## Adverse effects

1. Hypokalaemia
2. Routine and long-term use must be discouraged, because it can produce colonic atony

## Contraindication

1. They can reflexly stimulate gravid uterus, therefore are contraindicated during pregnancy
2. Subacute or chronic intestinal obstruction

## Diphenylmethanes

- **Phenolphthalein**
  - It is a litmus-like indicator which is in use as purgative

- It turns urine pink if alkaline
- About 15% is absorbed and eliminated by kidney so urine becomes pink or red if it is alkaline.
- It has a prolonged effect owing to enterohepatic circulation

- **Bisacodyl**

- Intestinal enzymes convert bisacodyl in to the active disacetyl metabolite.
- Available as enteric coated preparation that has to be. swallowed with out chewing or crushing
- Also used in suppository form, which may produce burning sensation in rectum

## Anthraquinones

- **Senna and Cascara**

- Plant purgatives contain anthraquinone glycosides, also called emodins.
- Unabsorbed in the small intestine, they are passed to the colon where bacteria liberate the active anthrol form
- Take 6–8 hours to produce action.
- Taken by lactating mothers, the amount secreted in milk is sufficient to cause purgation in the suckling infant

## Prucalopride

- It is a selective 5-HT<sub>4</sub> receptor agonist
- It activates 5-HT<sub>4</sub> receptors on intrinsic enteric neurones to enhance intestinal contractions

## Castor oil

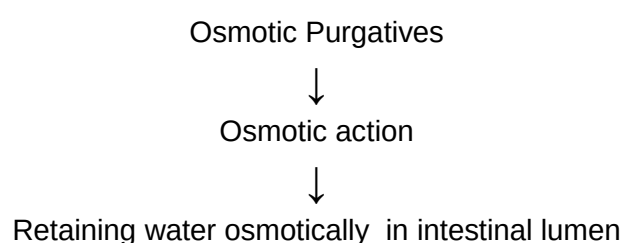
- Obtained from the seeds of *Ricinus communis*.
- In small intestine, pancreatic lipase converts it into glycerol and ricinoleic acid.
- Ricinoleic acid irritate the mucosa and stimulate intestinal contractions
- Onset of action is in 1-3 hours since the site of action is small intestine.

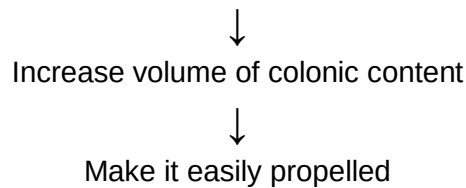
# OSMOTIC PURGATIVES

## Introduction

- Osmotic Purgatives are solutes that are
  1. Not absorbed in the intestine
  2. They retain water osmotically

## MOA





## Uses

1. First line approach for simple constipation.
2. Useful when straining at stools has to be avoided.
3. Hepatic encephalopathy →
  - Patients have reduced capacity to detoxify ammonia produced by colon bacteria
  - Lactulose causes reduction of blood  $\text{NH}_3$  concentration by 25–50%.
  - The breakdown products of lactulose are acidic—lower the pH of stools.
  - Ammonia produced by bacteria in colon is converted to ionized  $\text{NH}_4^+$  salts that are not absorbed.

## Adverse effects

- Flatulence
- Cramps
- Abdominal discomfort
- Nausea and vomiting
- Diarrhea

## VALID INDICATIONS OF LAXATIVES

### 1. Functional constipation

- Spastic constipation (irritable bowel)
  - First choice laxative is dietary fibre or bulk forming agents taken over weeks/months.
  - Stimulant purgatives are Contraindicated
- Atonic constipation (sluggish bowel):
  - Non-drug measures like plenty of fluids, exercise, regular habits and reassurance should be tried.
  - In resistant cases a bulk forming agent should be prescribed. In case of poor compliance or if the patient is not satisfied—bisacodyl or senna may be given once or twice a week for as short a period as possible.

### 2. Bedridden patients

- Myocardial infarction, stroke, fractures, postoperative
- Bowel movement may be sluggish and constipation can be anticipated.
  - (a) To prevent constipation: bulk forming agents on a regular schedule; docusates, lactulose and liquid paraffin are alternatives.
  - (b) To treat constipation: Enema (soap-water/ glycerine) is preferred; bisacodyl or senna may be used.

### 3. To avoid straining at stools

- Hernia, cardiovascular disease, eye surgery) and in perianal afflictions (piles, fissure, anal surgery)

- It is essential to keep the faeces soft.
- Bulk forming agent, lactulose or docusates.

#### 4. Preparation of bowel

- For surgery, colonoscopy, abdominal X-ray
- Bowel needs to be emptied of the contents including gas.
- Saline purgative, bisacodyl or senna may be used

#### 5. After certain anthelmintics

- Saline purgative or senna may be used to flush out the worm and the anthelmintic drug.

### CONTRAINDICATIONS OF LAXATIVES

1. Undiagnosed abdominal pain, colic or vomiting.
2. Organic (secondary) constipation due to stricture or obstruction in bowel, hypothyroidism, hypercalcaemia, malignancies and certain drugs, e.g.—opiates, sedatives, anticholinergics including antiparkinsonian, antidepressants and antihistaminics, oral iron, clonidine, verapamil and laxative abuse itself.
3. Primary cause should be treated in these cases.

---

## DRUGS FOR DIARRHOEA

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### Introduction

- WHO definition → 3 or more loose or watery stools in a 24 hour period.
- However it is the recent change in consistency of stools rather than the number of stools that is more important feature.
- This may be due to:
  1. Decreased electrolyte and water absorption.
  2. Increased secretion by intestinal mucosa.
  3. Increased luminal osmotic load.
  4. Inflammation of mucosa and exudation into lumen.

### Types

1. **Osmotic Diarrhea** —increase in poorly absorbed substances, which are osmotically active like carbohydrates and fats.
2. **Secretory Diarrhea** —increase in secretion of fluid and electrolytes in lumen due to toxins, bile salt and mucosal abnormality.
3. **Transit Disorders** —hypermotility that leads to abnormality in contact of luminal contents with mucosal surface.

### TREATMENT OF DIARRHEA

- A. Treatment of fluid depletion, shock and acidosis → Rehydration
- B. Drug therapy

## A) REHYDRATION

1. Oral Rehydration Therapy
2. Intravenous Rehydration

### 1. Oral Rehydration Therapy

- With introduction of oral rehydration by WHO it is established that oral rehydration treatment can be safely and successfully used in treating acute diarrhoeas due to all aetiologies, in all age groups, and in all countries.

#### Aim

- To prevent dehydration and reduce mortality.

#### Principle

- Oral fluid therapy is based on the observation that glucose given orally enhances the intestinal absorption of salt and water, and is capable of correcting the electrolyte and water deficit.

#### Composition

- Since January 2004, the new ORS formulation is the only one procured by UNICEF.
- India was the first country in the world to launch this ORS formulation since June 2004.
- Treatment is Home based



| Composition (grams) |             |
|---------------------|-------------|
| Sodium chloride     | 2.6         |
| Potassium chloride  | 1.5         |
| Sodium citrate      | 2.9         |
| Glucose             | 13.5        |
| <b>Total</b>        | <b>20.5</b> |

| Osmolar concentration (mmol/litre) |            |
|------------------------------------|------------|
| Sodium                             | 75         |
| Potassium                          | 20         |
| Chloride                           | 65         |
| Citrate                            | 10         |
| Glucose                            | 75         |
| <b>Total</b>                       | <b>245</b> |

#### Estimated amount of ORS

- If the child's weight is known, the amount of ORS solution required for rehydration during the first four hours may be calculated by setting the deficit at approximately 75 ml/kg.
- If the child's weight is not known, the approximate deficit may be determined on the basis of child's age, although this procedure is less accurate.
- As a general guide, after each loose stool, give →

- children under 2 years of age : 50-100 ml
- children aged 2 up to 10 years : 100-200 ml
- older children and adults : as much fluid as they want
- Try to give the estimated required amount within a 4-hour period.

## 2. Intravenous Rehydration

- Intravenous infusion is usually required only for the initial rehydration of severely dehydrated patients who are in shock or unable to drink
- Such patients are best transferred to the nearest hospital or treatment centre.

### Solutions recommended by WHO for intravenous infusion

(a) **Ringer's lactate solution (Hartmann's solution)** : best commercially available solution. It supplies adequate concentrations of sodium and potassium and the lactate yields bicarbonate for correction of the acidosis. It can be used to correct dehydration due to acute diarrhoeas of all causes

(b) **Diarrhoea Treatment Solution (DTS)**

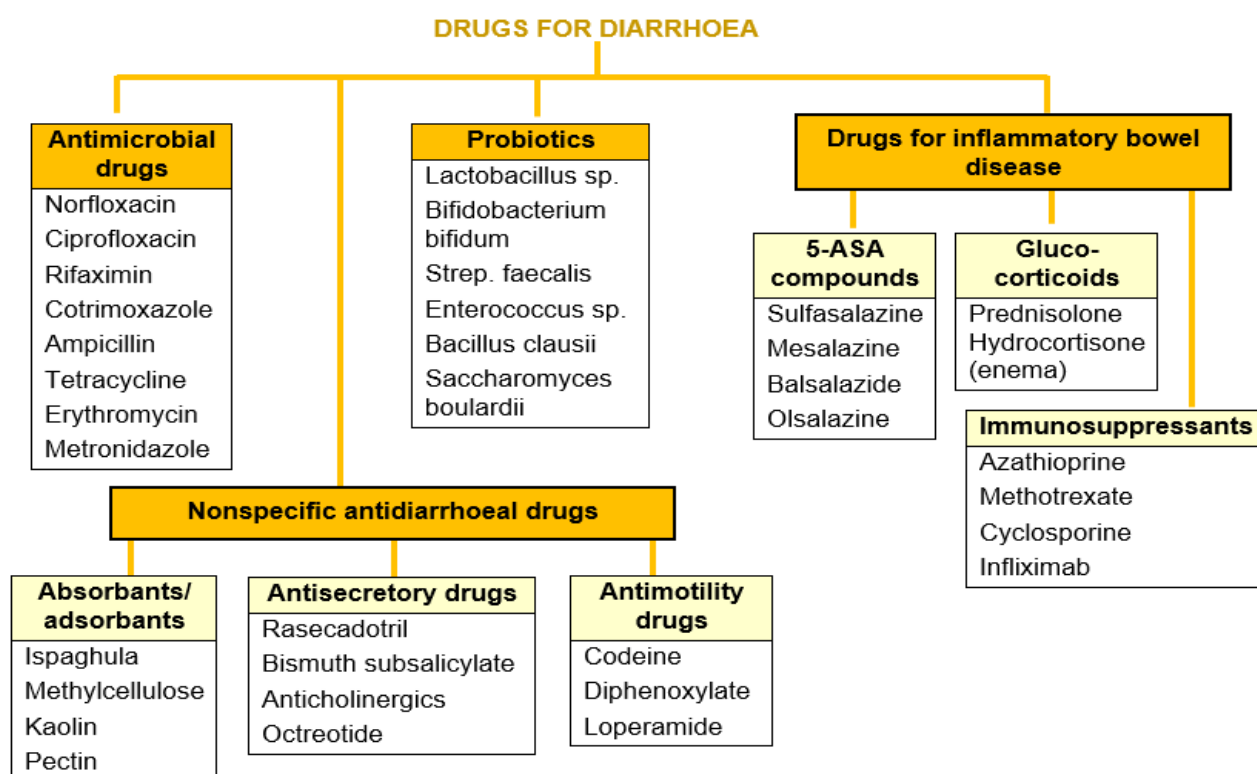
(c) **Normal saline**

### Dose

- The recommended dose of the IV fluid to be given is 100 ml/kg, divided as follows

| Age                       | First give 30 ml/kg in | Then give 70 ml/kg in |
|---------------------------|------------------------|-----------------------|
| Infants (under 12 months) | 1 hour                 | 5 hours               |
| Older                     | 30 minutes             | 2½ hours              |

## B) DRUG THERAPY



## ANTIMICROBIAL DRUGS

- A. Antimicrobials are of no value
- B. Antimicrobials are useful only in severe disease (but not in mild cases)
- C. Antimicrobials are regularly useful

### A. Antimicrobials are of no value

- In diarrhoea due to noninfective causes, such as:
  1. Irritable bowel syndrome (IBS)
  2. Coeliac disease
  3. Pancreatic enzyme deficiency
  4. Tropical sprue
  5. Thyrotoxicosis

### B. Antimicrobials are useful only in severe disease (but not in mild cases)

1. Travellers' diarrhoea: cotrimoxazole, norfloxacin, doxycycline
2. EPEC: Cotrimoxazole, or a fluoroquinolone or colistin
3. Shigella enteritis: ciprofloxacin or norfloxacin, Cotrimoxazole and ampicillin
4. Nontyphoid Salmonella enteritis: fluoroquinolone, cotrimoxazole or ampicillin.
5. Yersinia enterocolitica: Cotrimoxazole

### C. Antimicrobials are regularly useful in

1. Cholera: Tetracyclines, Cotrimoxazole, Ampicillin and erythromycin
2. Campylobacter jejuni: Norfloxacin and other fluoroquinolones
3. Clostridium difficile: metronidazole, while vancomycin given orally is an alternative.
4. Amoebiasis: metronidazole, diloxanide furoate,

## PROBIOTICS

- Microbial cell preparations, either live cultures or lyophilised powders, that are intended to restore and maintain healthy gut flora
- Organisms most commonly used are → Lactobacillus sp., Bifidobacterium, Streptococcus faecalis, Enterococcus sp. and the yeast Saccharomyces boulardii, etc
- Convincing evidence of their efficacy is lacking
- Natural curd/yogurt is an abundant source of lactic acid producing organisms, which can serve as probiotic.

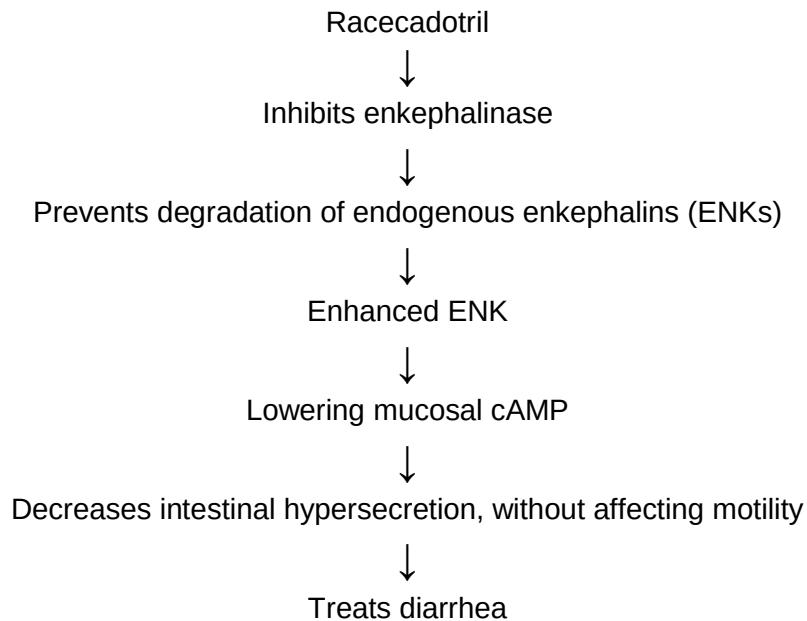
## ANTISECRETORY DRUGS

### Racecadotril

- Prodrug
- Rapidly converted to thiorphan, an enkephalinase inhibitor.



## MOA



## Uses

- Secretory diarrhoeas

## Adverse effects

- Nausea
- Vomiting
- Drowsiness
- Flatulence

# DRUGS FOR INFLAMMATORY BOWEL DISEASE (IBD)

## Introduction

- IBD is a chronic relapsing inflammatory disease of the ileum, colon, or both, that may be associated with systemic manifestations.
  1. Ulcerative colitis (UC)
  2. Crohn's disease (CrD)

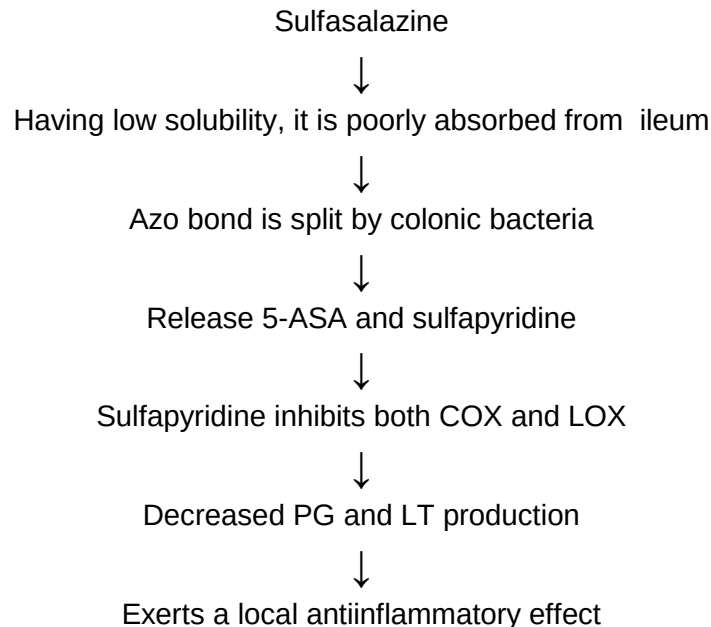
## 5-Amino salicylic acid (5-ASA) compounds

## Sulfasalazine (Salicylazosulfapyridine)

- It is a compound of 5-aminosalicylic acid (5-ASA) with sulfapyridine linked through an azo bond



## MOA



## Uses

- First line of treatment in mild to moderate UC and CD

## Corticosteroids

- Prednisolone (40–60 mg/day) is highly effective in controlling symptoms as well as in inducing remission in both UC and CrD.
- DOC for severe exacerbations
- Corticosteroids are generally used for short term, and discontinued after remission is induced.

## Immunosuppressants

- Because of long latency of response, they are not suitable for acute flare ups of the disease, but have good remission maintaining rates
- Azathioprine, 6-MP** → Can be used for the induction and maintenance of remission of U.C. and C.D.
- Methotrexate** → Can be used in CD, but has no use in U.C.
- Anti TNF-α (Infliximab, adalimumab, certolizumab, etanercept)** → Can be used in CD.
- Cyclosporine** → Used in severe U.C., which is refractory to glucocorticoids.



# Drugs acting on PNS

CHAPTER

9

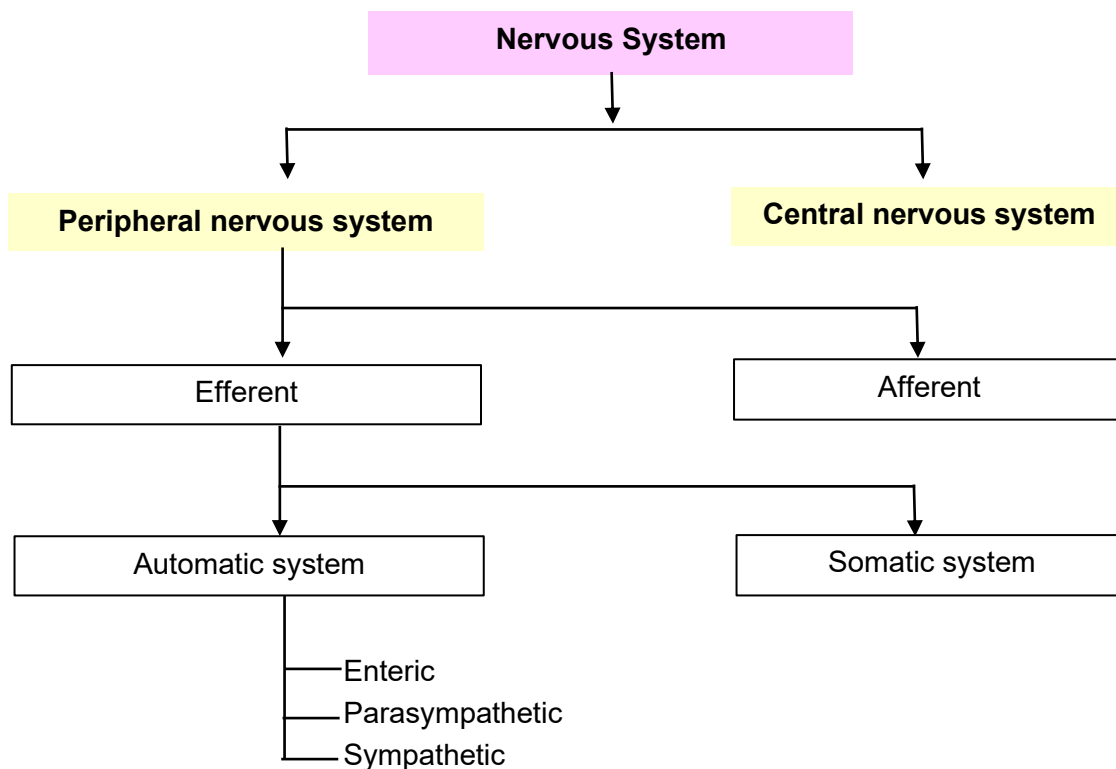
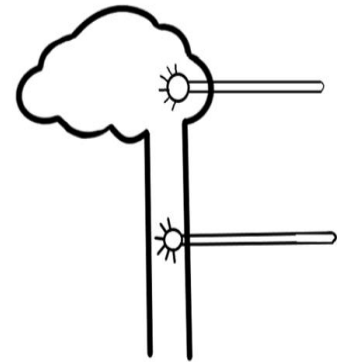
## CONTENT

- Skeletal Muscle Relaxants
- Local Anaesthesia

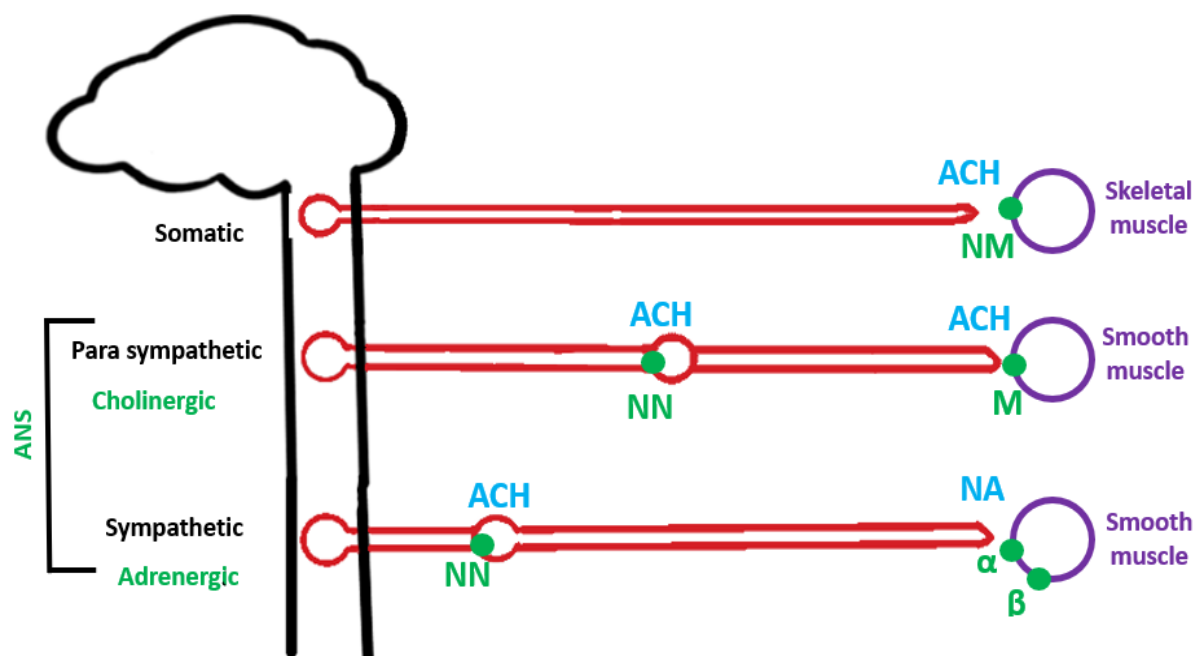
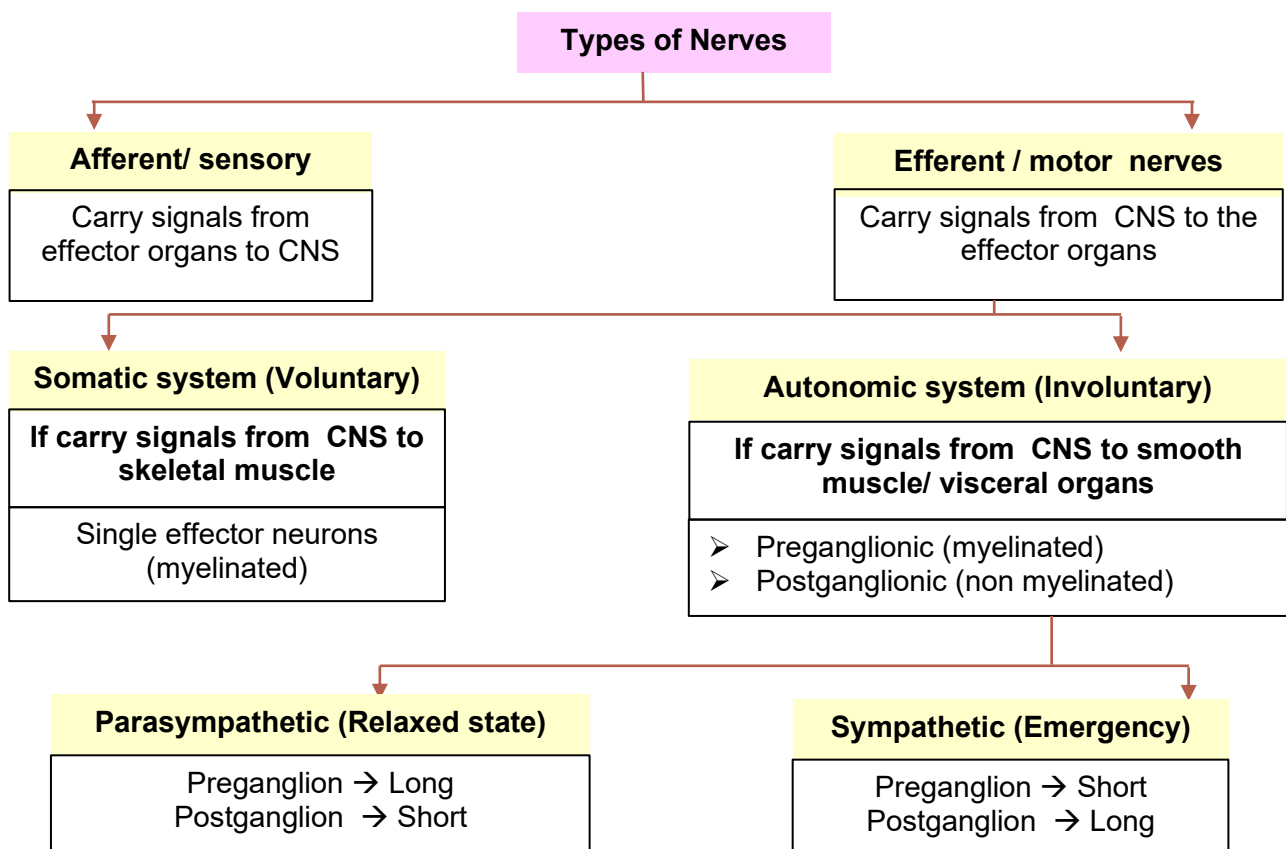
## INTRODUCTION TO NERVOUS SYSTEM

### Nervous system

- **CNS**
  - Brain
  - Spinal cord
- **PNS**
  - Consists of nerves arising from → brain and spinal cord
    - ❖ 12 pairs of cranial nerves
    - ❖ 31 pairs of spinal nerves



## Types of Nerves

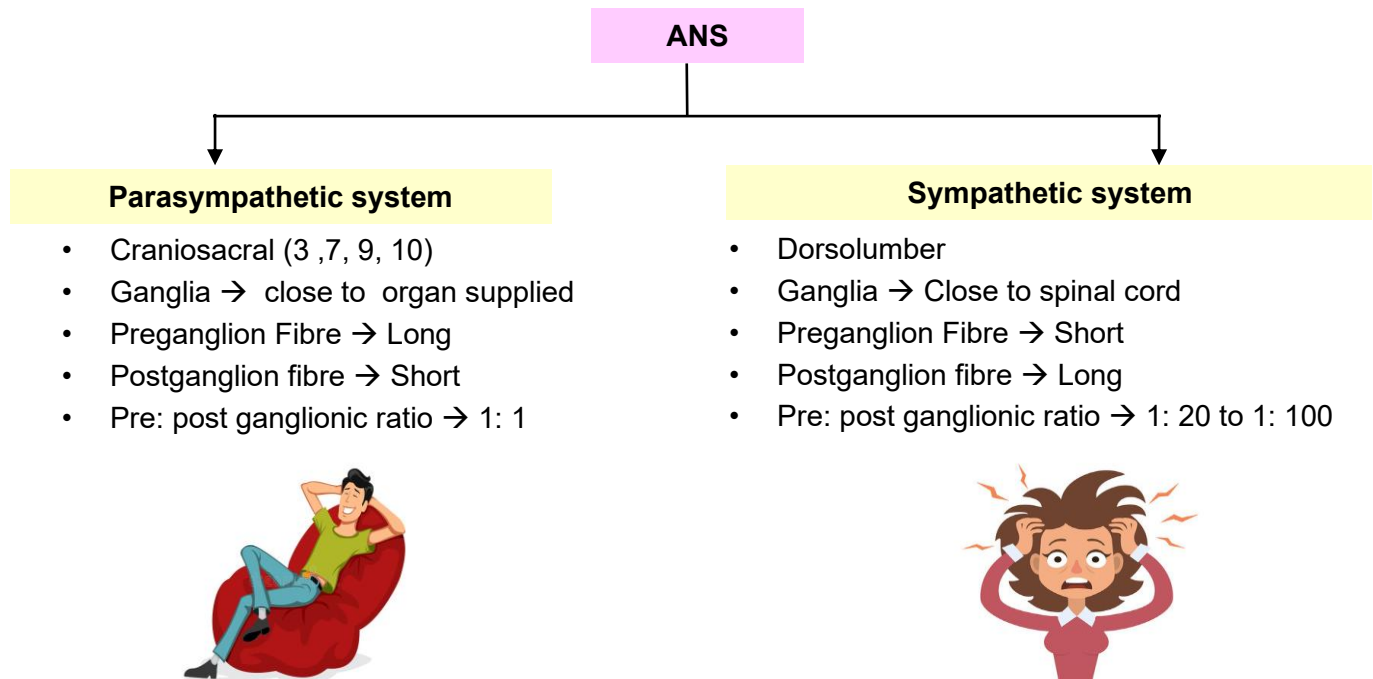


## Somatic versus Autonomic Nervous System

|                     | Somatic nervous system         | Autonomic nervous system         |
|---------------------|--------------------------------|----------------------------------|
| <b>Functions</b>    | To control voluntary functions | To control involuntary functions |
| <b>Target organ</b> | Skeletal muscles               | Visceral organs                  |

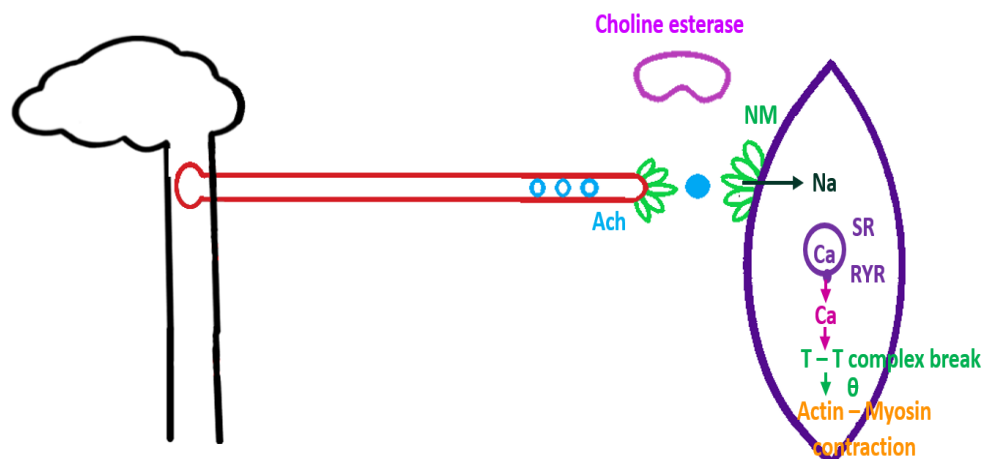
|                      |                      |                                                                                              |
|----------------------|----------------------|----------------------------------------------------------------------------------------------|
| <b>Neuron</b>        | Single myelinated    | Two types of neurons connected with a synapse/ganglion. Preganglionic one is non myelinated. |
| <b>Nerve section</b> | Paralysis or atrophy | No atrophy, activity is maintained, there may be denervation supersensitivity                |

## AUTONOMIC NERVOUS SYSTEM (ANS)



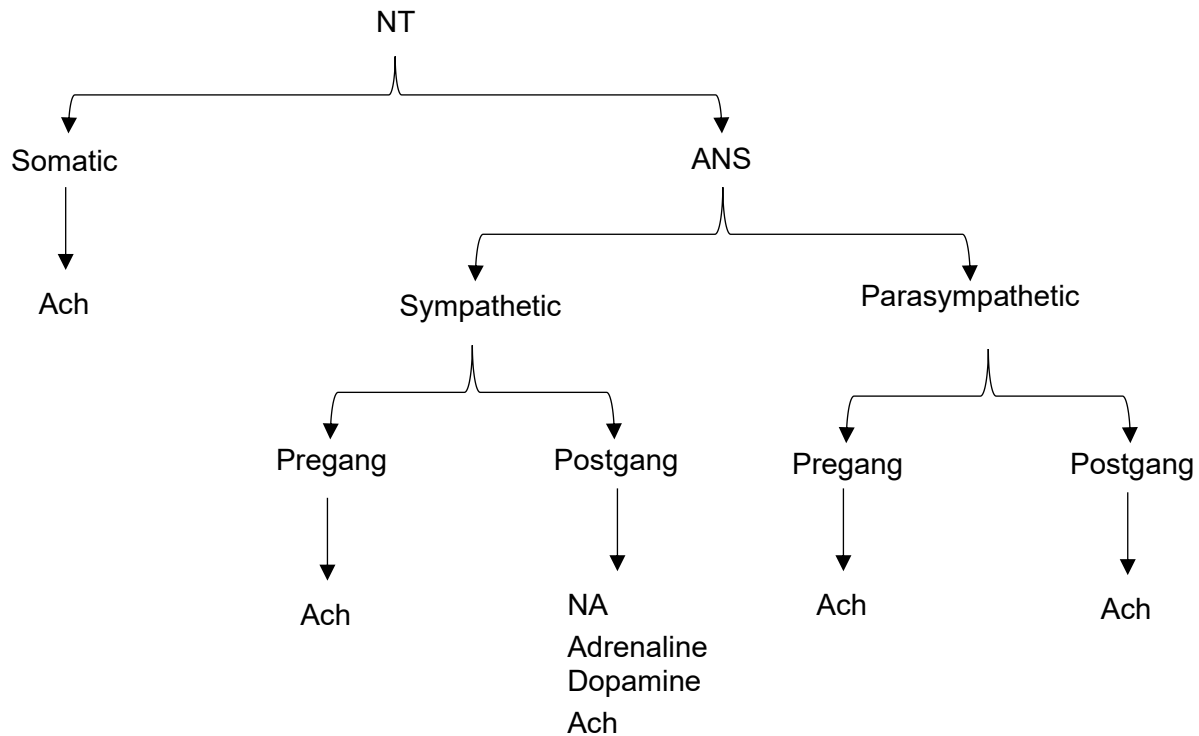
## SOMATIC NERVOUS SYSTEM

- Carries nerve impulses from CNS to effector organs (skeletal muscle) by single effector neurons (myelinated)

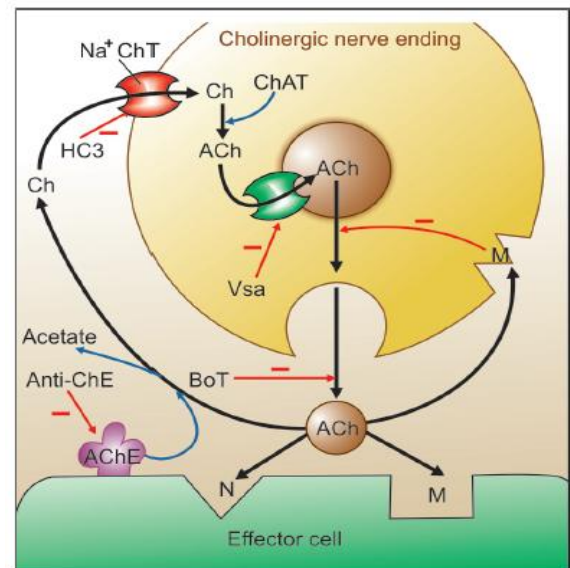
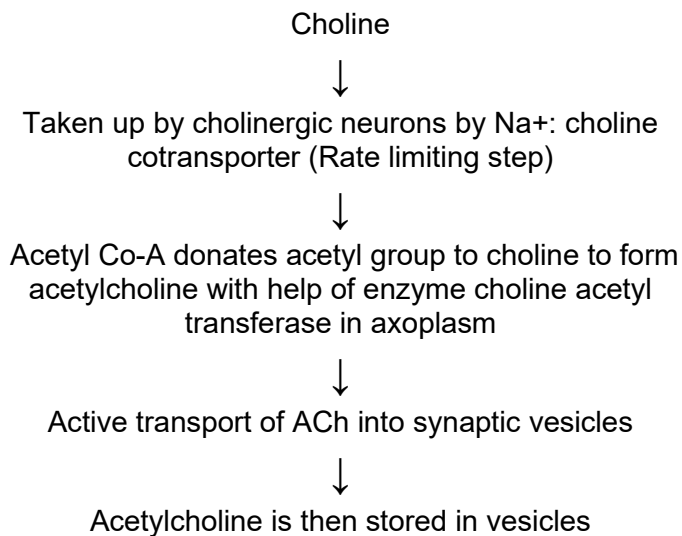


### Neurotransmitter (NT)

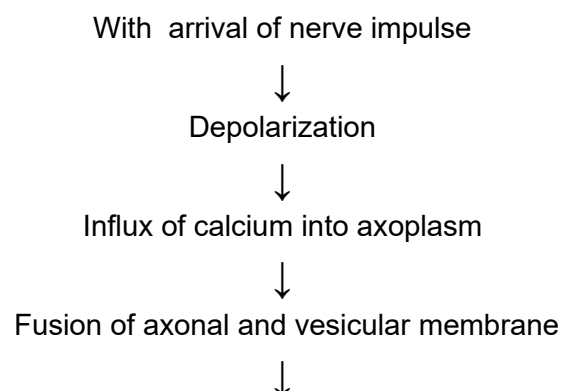
NT at somatic fibres → Acetylcholine (ACh) is principal neurotransmitter (NT)



## Synthesis and storage of ACh



## Release of ACh



Release of acetylcholine  
↓  
Acts on M and N receptors

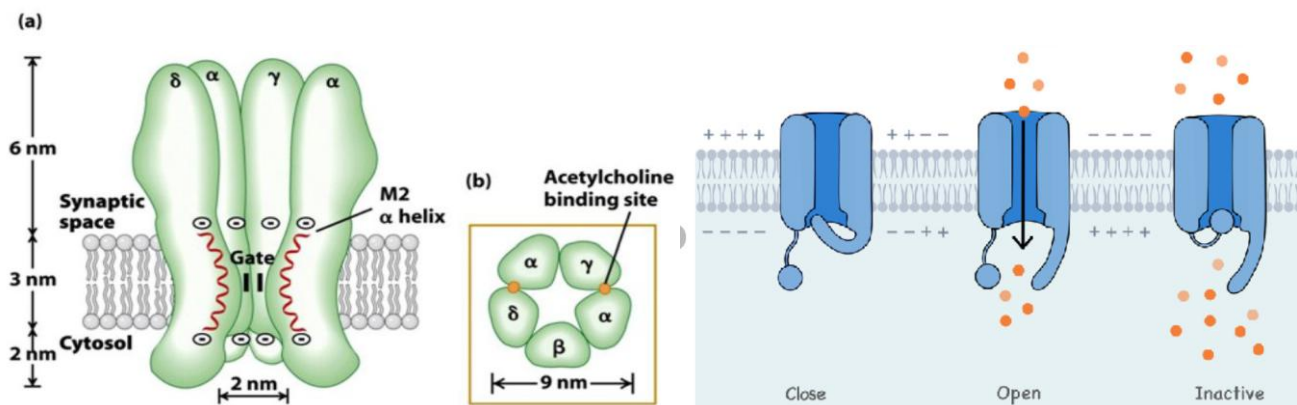
## Destruction of ACh

Acetylcholine acts on M and N receptors  
↓  
Remains bound there for less than a millisecond  
↓  
Hydrolyzed by cholinesterase enzyme  
(acetyl cholinesterase)  
↓  
Half of choline is recaptured by neurons  
Rest is carried away in circulation  
(No reuptake of acetylcholine as occurs with other transmitters)

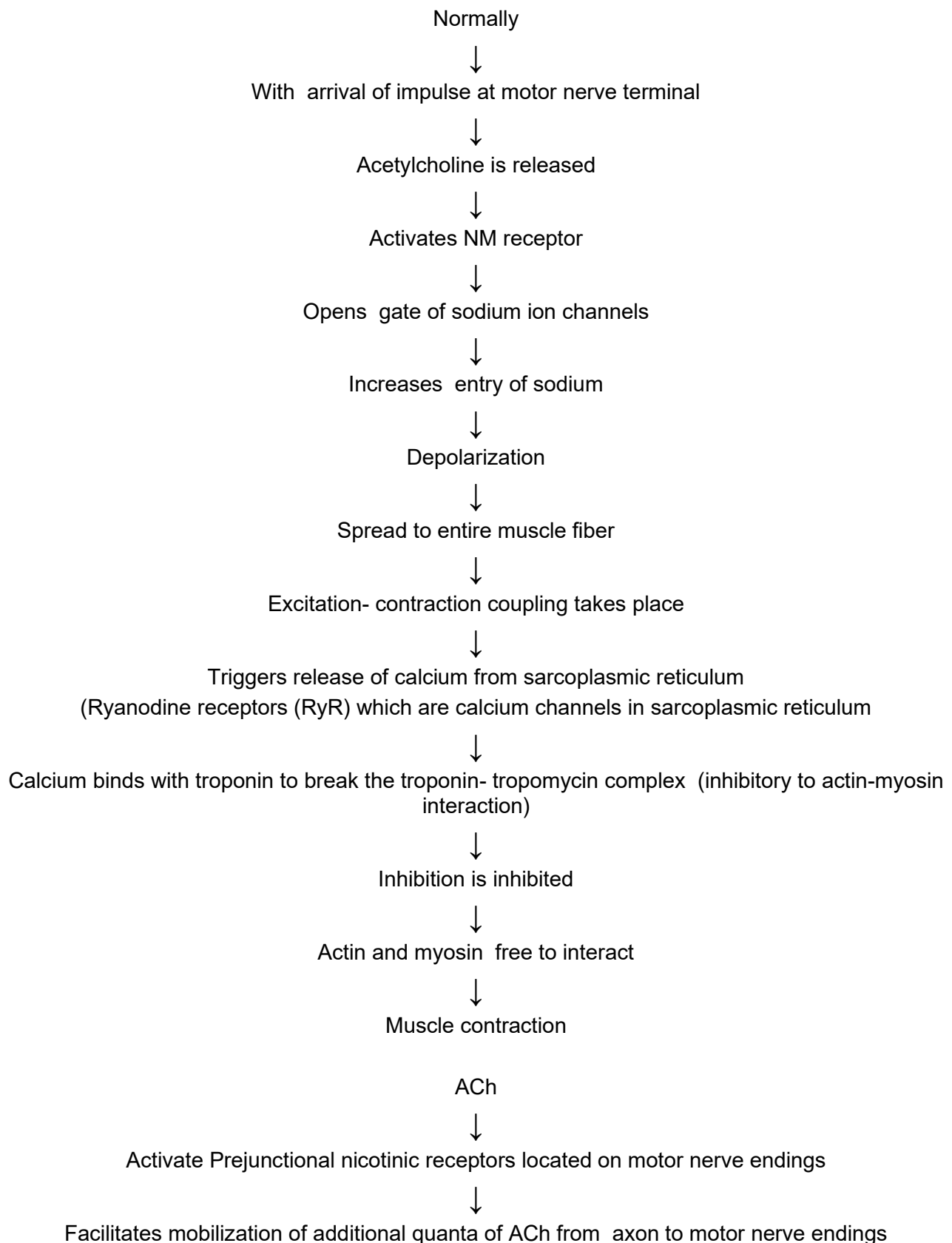
## NM receptor

- A protein with 5 subunits ( $\alpha$ 2,  $\beta$ ,  $\epsilon$  or  $\gamma$  and  $\delta$ ) → arranged like a rosette surrounding the Na<sup>+</sup> channel

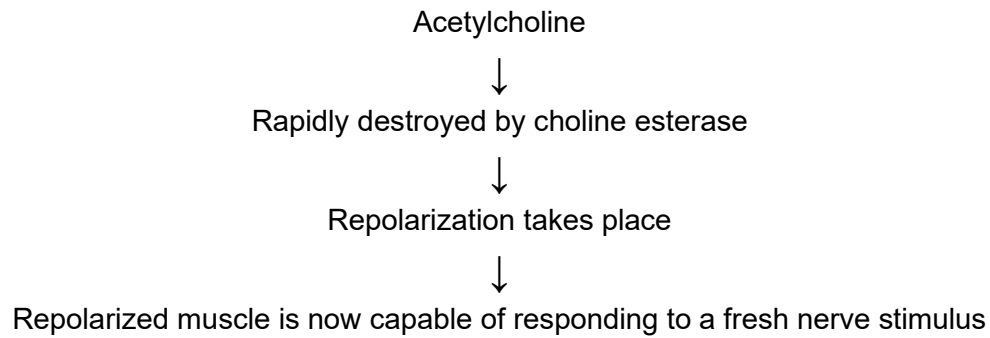
2  $\alpha$  subunits  
↓  
Carry two ACh binding sites  
↓  
Have negatively charged groups  
↓  
Combine with cationic head of ACh  
↓  
Opening of Na<sup>+</sup> channel



## Normal Skeletal muscle → Contraction and Relaxation



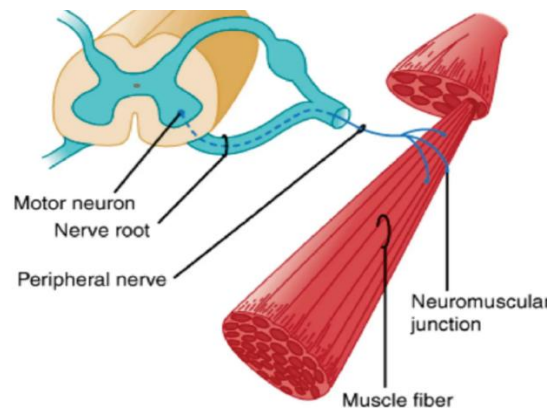




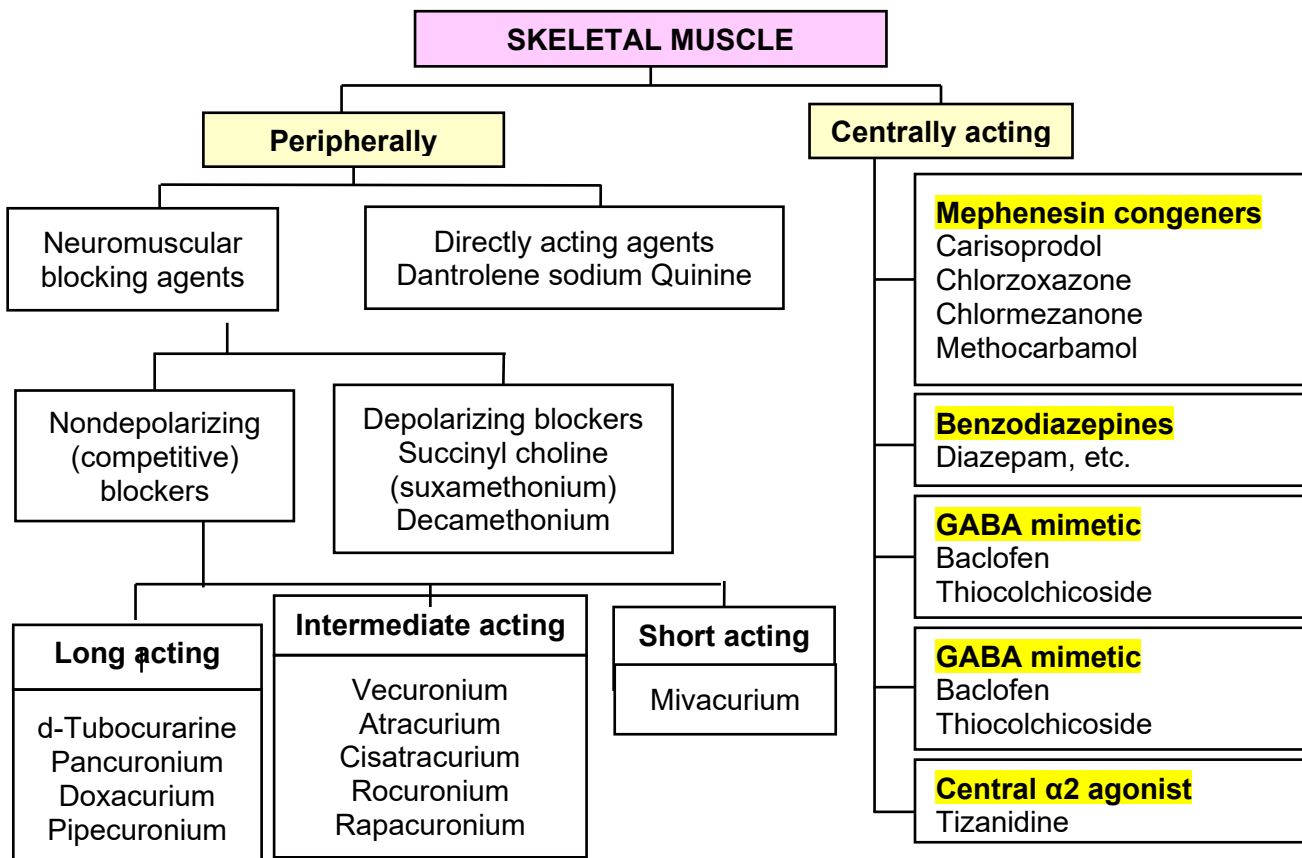
## SKELETAL MUSCLE RELAXANTS

### Definition

- Drugs that act →
  - **Peripherally** → neuromuscular junction / muscle fibre itself or
  - **Centrally** → cerebrospinal axis
- To reduce muscle tone and/or cause paralysis.
- Skeletal Muscle relaxants → relax skeletal muscles without affecting level of consciousness to a significant level.



### Classification



| Peripherally Acting |                               |                        | Centrally Acting |
|---------------------|-------------------------------|------------------------|------------------|
|                     | Neuromuscular blocking agents | Directly acting agents |                  |
| Drugs               |                               |                        |                  |
| MOA                 |                               |                        |                  |
| Reversal            |                               |                        |                  |
| Actions             |                               |                        |                  |
| Pharmacokinetics    |                               |                        |                  |
| Interactions        |                               |                        |                  |
| Adverse effects     |                               |                        |                  |
| Contraindications   |                               |                        |                  |
| Uses                |                               |                        |                  |

## PERIPHERALLY ACTING MUSCLE RELAXANTS → NEUROMUSCULAR BLOCKING AGENTS

### Drugs

- A. Nondepolarizing (Competitive) blockers
- B. Depolarizing blockers

### A. Nondepolarizing (Competitive) Blockers

- 2 Classification →
  - Based on chemical structure
  - Based on duration of action

#### Based on chemical structure

##### 1. Benzylisoquinolone derivatives

- No vagolytic action
- Propensity for histamine release
  - d-tubocurarine
  - Atracurium
  - Cis-atracurium
  - Metocurine
  - Dexacurium
  - Mivacurium
  - Alcuronium

##### 2. Amino-steroid derivatives

- Very less propensity for histamine release.
- Have vagolytic action (can cause tachycardia)
  - Pancuronium
  - Rocuronium
  - Vecuronium
  - Pipecuronium

- Rapacuronium

## Based on duration of action

### 1. Long acting

- d-Tubocurarine
- Pancuronium
- Doxacurium
- Pipecuronium

### 2. Intermediate acting

- Vecuronium
- Atracurium
- Cisatracurium
- Rocuronium
- Rapacuronium

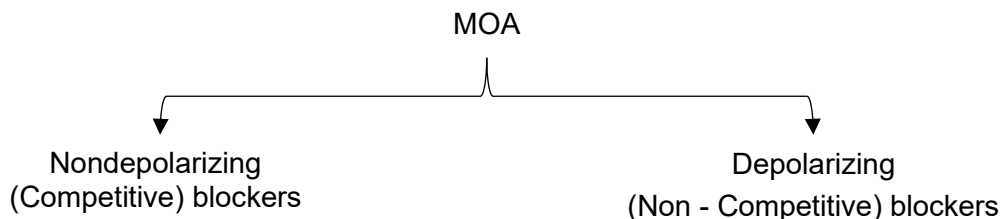
### 3. Short acting

- Mivacurium

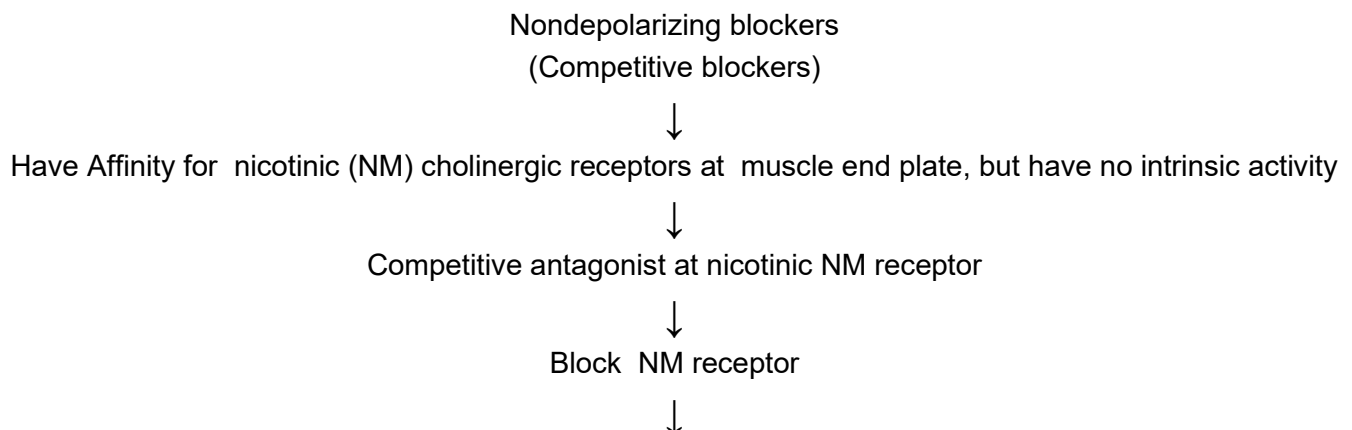
## B. Depolarizing blockers

- Succinylcholine (SCh., Suxamethonium)
- Decamethonium

## MOA



### A) MOA of Nondepolarizing (Competitive) blockers



Reduces frequency of channel opening but not its duration or conductance of a channel once it has opened



ACh released from motor nerve endings is not able to combine with its receptors



End plate potential (EPP) not generated



Magnitude of EPP falls below a critical level



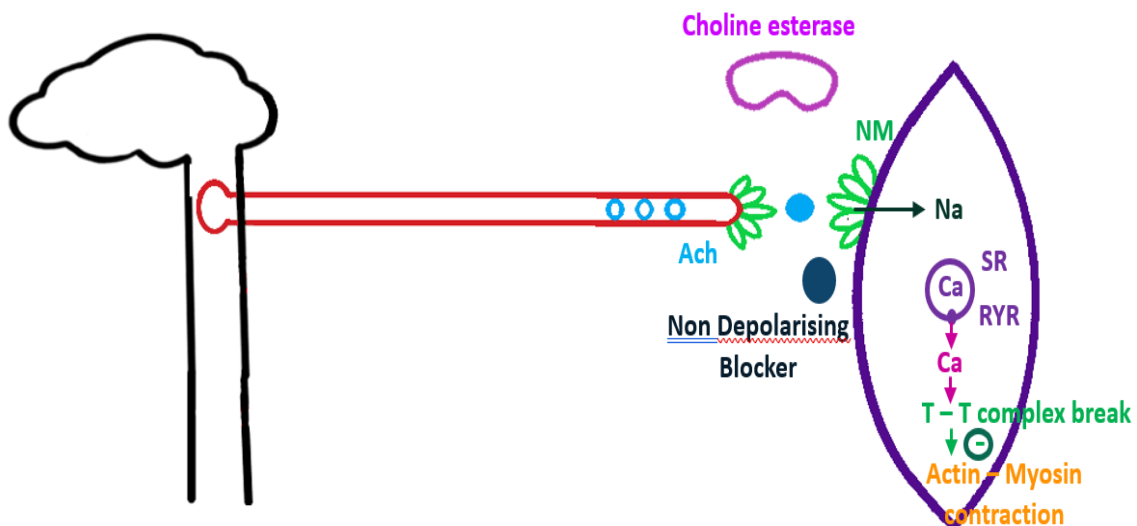
Unable to trigger propagated muscle action potential (MAP)



Muscle fails to contract in response to nerve impulse



Muscle relaxation



Nondepolarizing blockers  
(Competitive blockers)



Also block prejunctional nicotinic receptors located on motor nerve endings



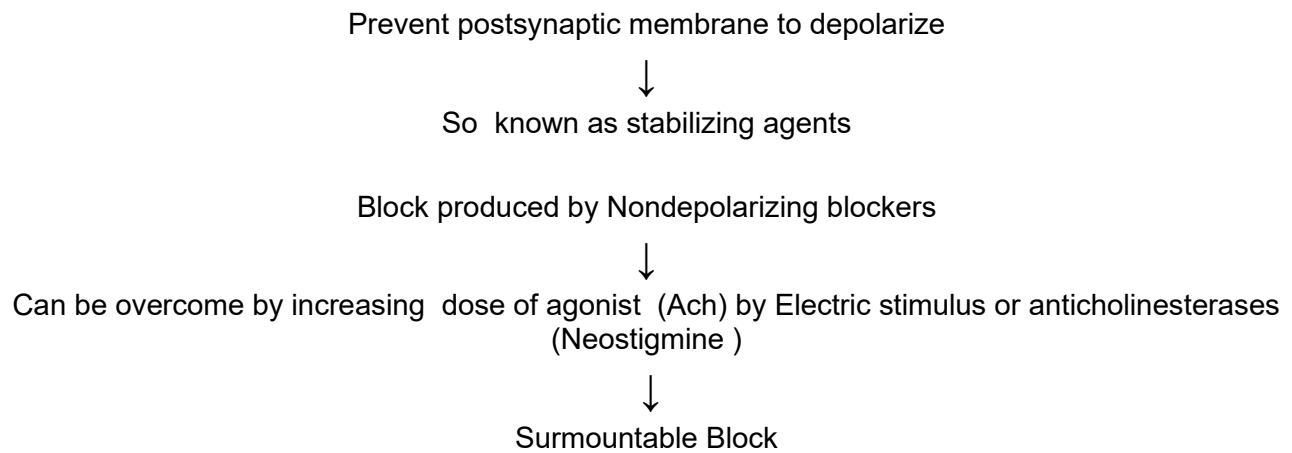
Depression of neuromuscular transmission

- (Activation of these receptors by ACh normally → facilitates mobilization of additional quanta of ACh from axon to the motor nerve endings)

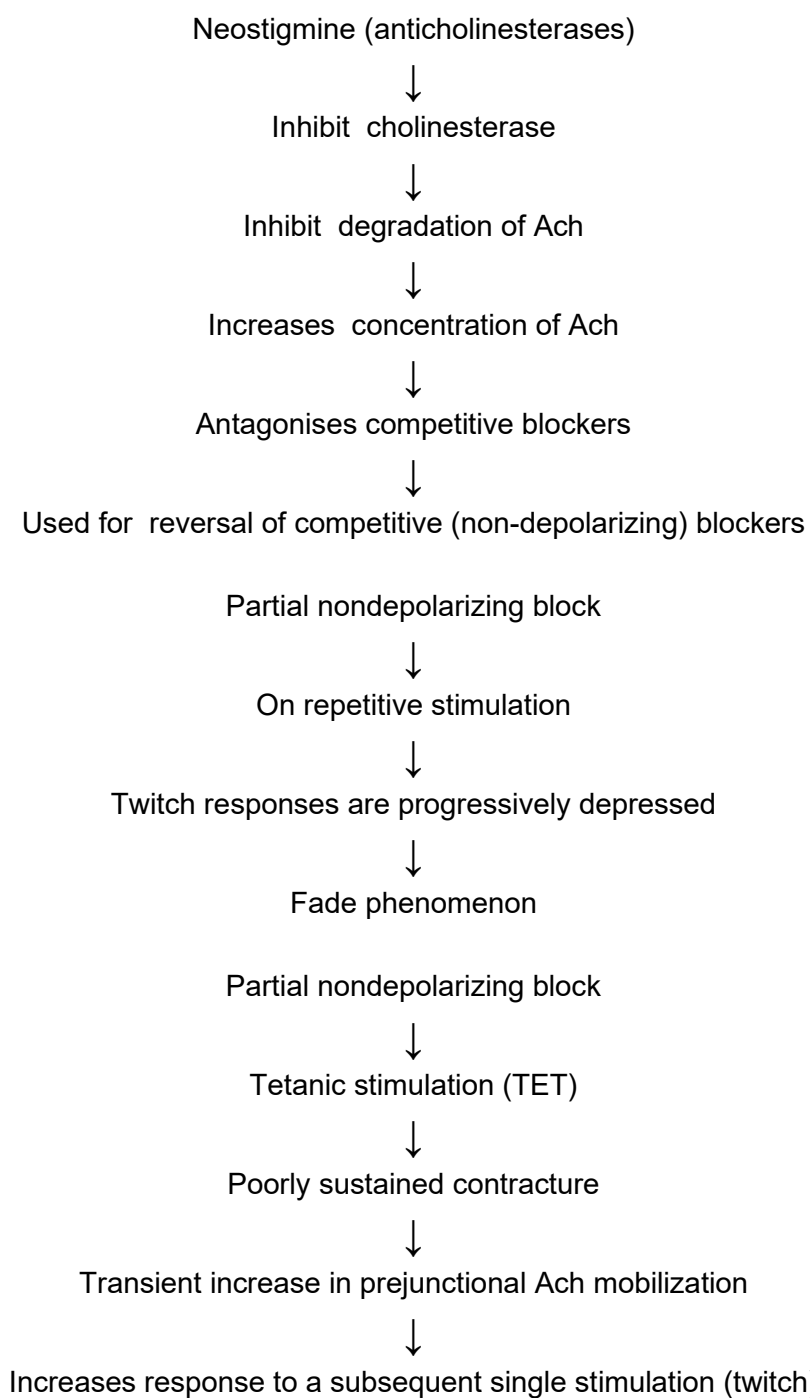
## Remember

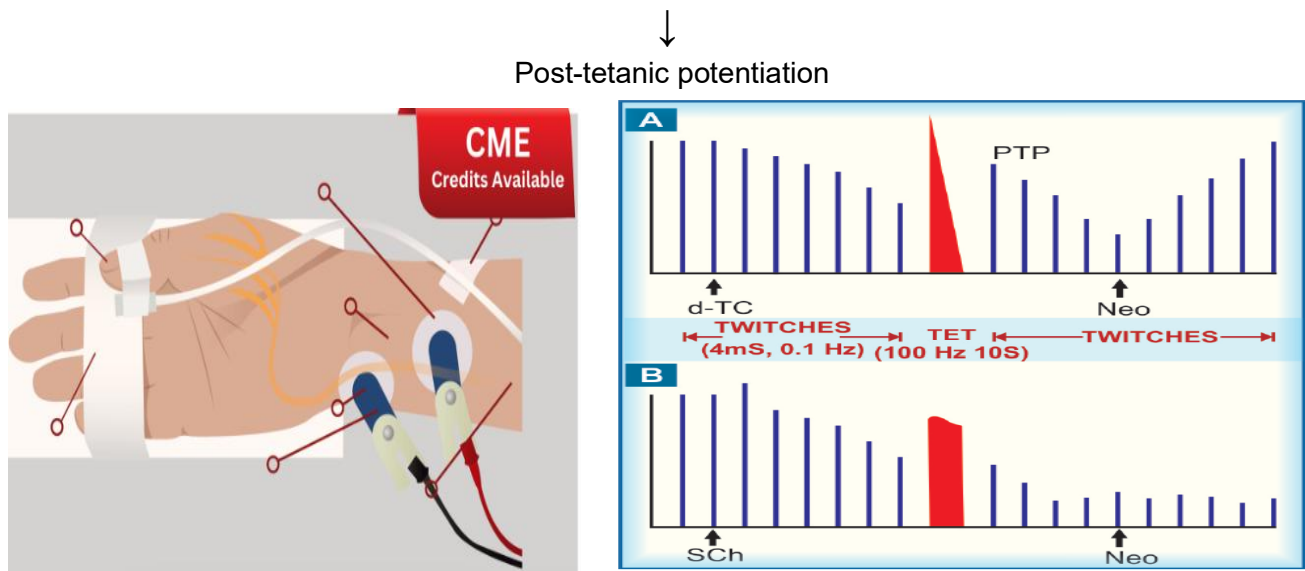
Nondepolarizing blockers





## Neostigmine



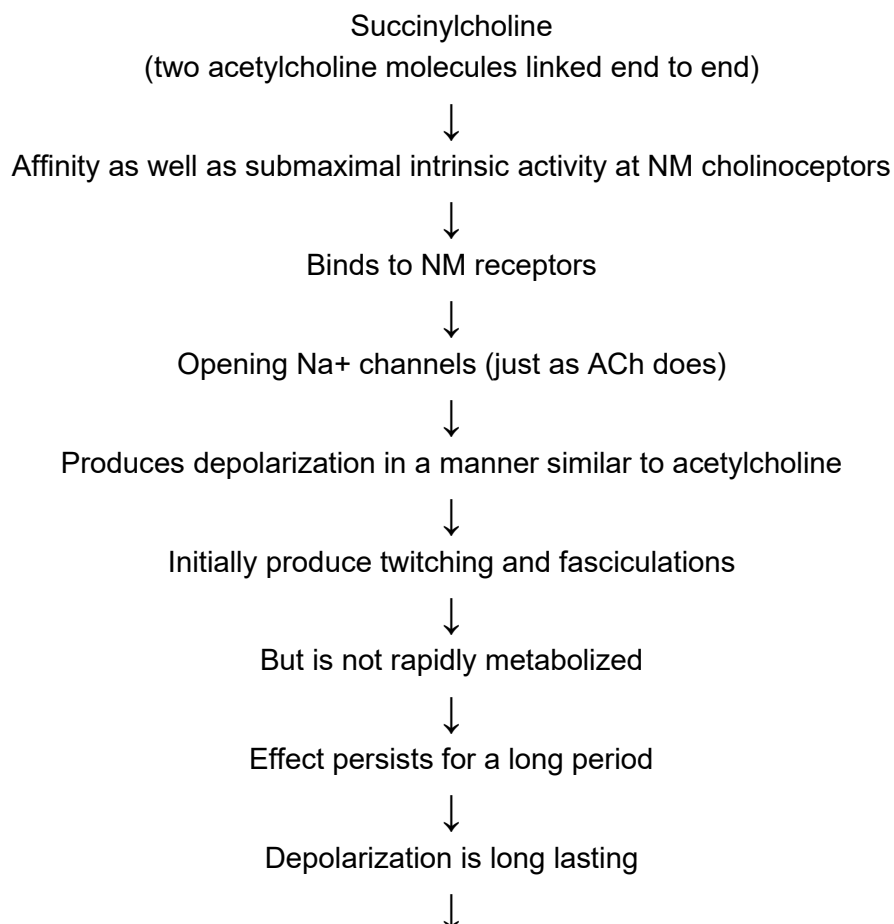


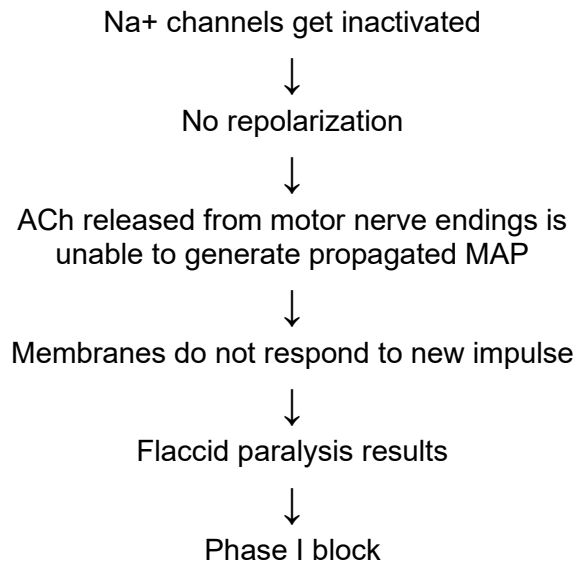
## B) MOA of Depolarizing (Non - Competitive) blockers

### Dual block

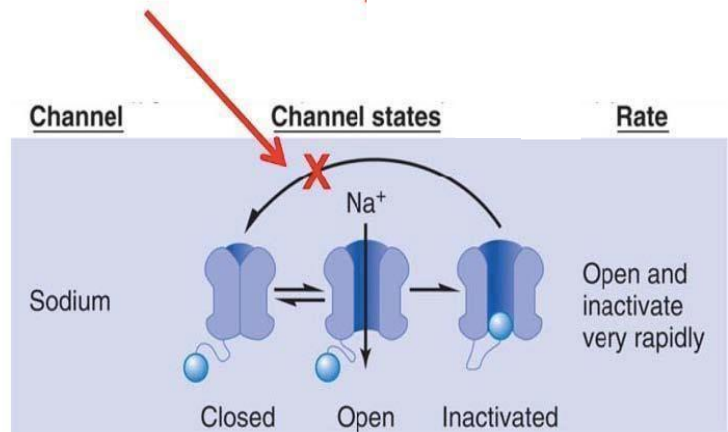
- Phase I block
- Phase II block

### Phase I block

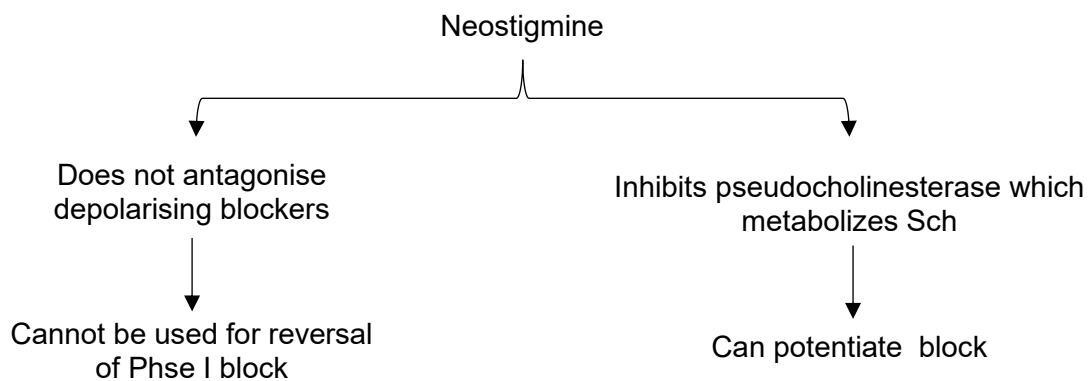




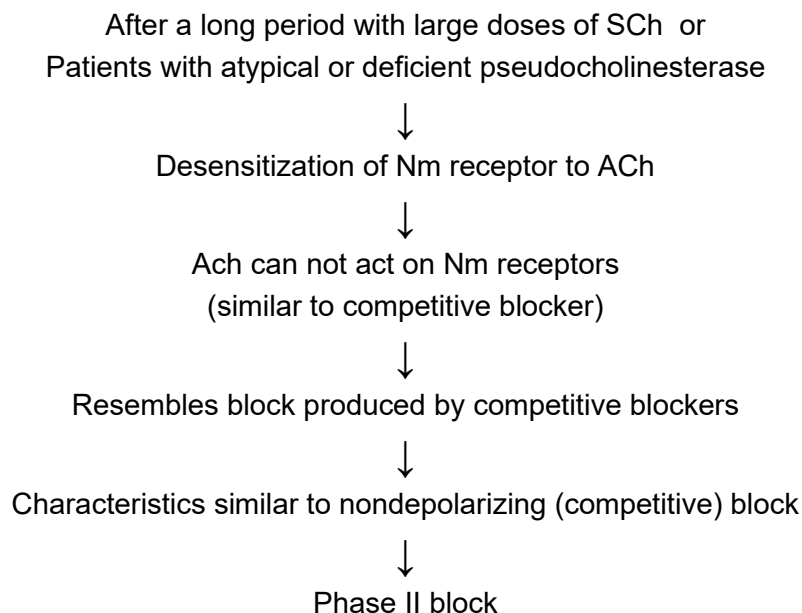
## Depolarizing NMBs

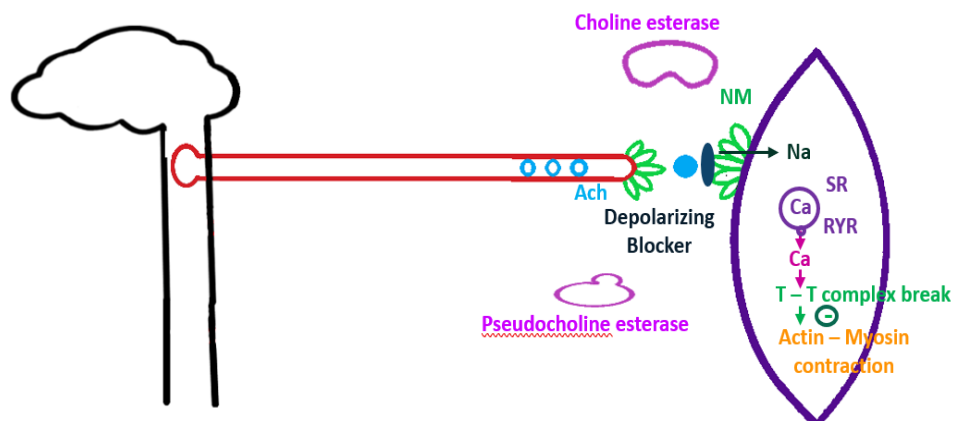


## Neostigmine



## Phase II block





## Neostigmine

Neostigmine  
↓  
Partially reversed Phase II block

| Phase I block                                                                                                                                                        | Phase II block                                                                                                                                                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Rapid in onset</li> </ul>                                                                                                   | <ul style="list-style-type: none"> <li>• Slow in onset</li> </ul>                                                                                                       |
| <ul style="list-style-type: none"> <li>• Result from persistent depolarization of muscle end plate → Typical mechanism of action of depolarizing blocker.</li> </ul> | <ul style="list-style-type: none"> <li>• Results from desensitization of receptor to ACh → ACh can not act on Nm receptors (similar to competitive blocker).</li> </ul> |
| <ul style="list-style-type: none"> <li>• Has classical features of depolarization block.</li> </ul>                                                                  | <ul style="list-style-type: none"> <li>• Resembles block produced by competitive blockers → characteristics similar to nondepolarizing block.</li> </ul>                |
| <ul style="list-style-type: none"> <li>• Block is not antagonized by anticholinesterases (neostigmine)</li> </ul>                                                    | <ul style="list-style-type: none"> <li>• Block is partially reversed by anticholinesterases (Neostigmine).</li> </ul>                                                   |

## Remember

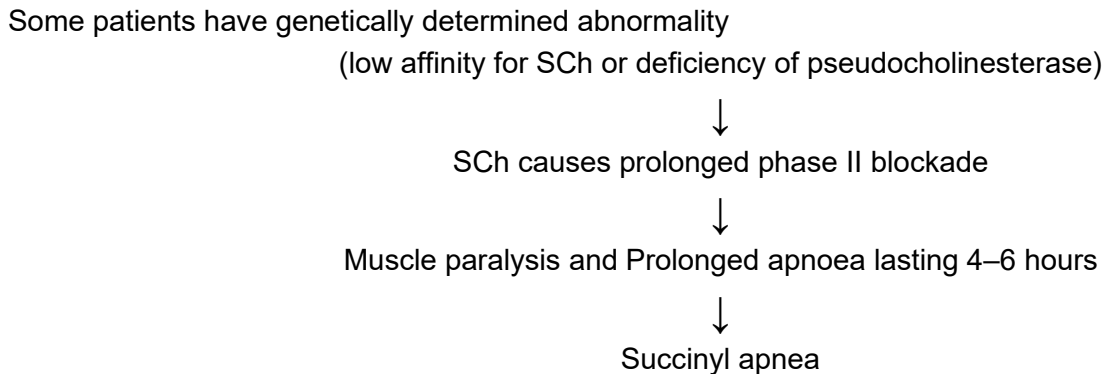
- In man normally → only phase I block is seen → typical depolarizing block.
- Phase II block is seen when →
  - Fluorinated anaesthetics have been given
  - SCh is injected in high dose
  - SCh given by IV infusion
  - Patients with atypical or deficient pseudocholinesterase.

Sch  
↓  
Rapidly hydrolysed by plasma pseudocholinesterase  
↓  
Succinylmonocholine  
↓  
Succinic acid + choline



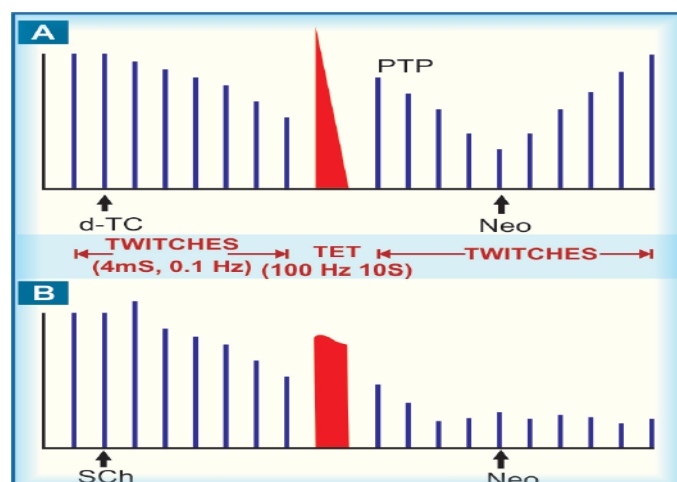
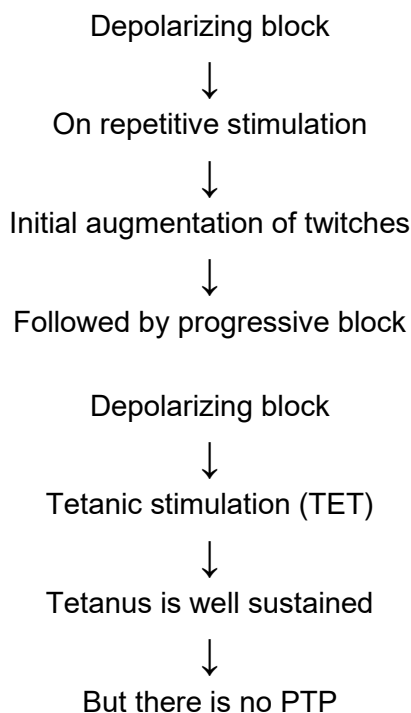
↓  
Action lasts 5–8 min

## Succinyl apnea



Treatment → →

- Mechanical ventilation
- Fresh blood transfusion to replace the enzyme



## Succinylcholine

- Prior to paralysis of muscles → transient muscular fasciculation due to initial depolarization → not marked in anesthetized patient.
- Shortest and fastest acting neuromuscular blocker
- After a single dose of 10-30mg i/v the effect starts within 1 minute, reaches peak in 2 minutes and lasts for 5 minutes.
- Brief effect is due to its rapid hydrolysis by pseudocholinesterase present in plasma and liver.
- Effect is prolonged in conditions with low levels of enzyme like malnutrition, uremia, liver disease, occupational exposure to anticholinesterase and abnormal genetic variants (atypical pseudo-cholinesterases)

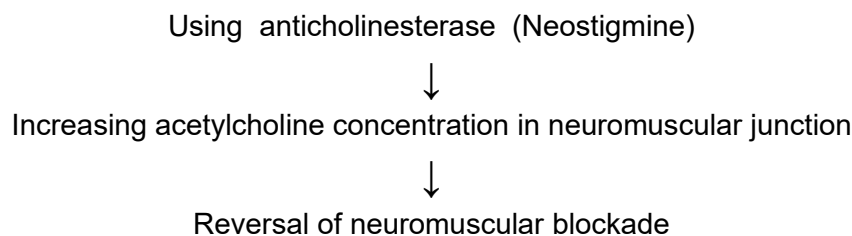
- Atypical pseudo- cholinesterases → not able to metabolize succinylcholine → Prolonged paralysis and apnea (succinyl apnea).

|                                                 | Competitive block (d-TC)     | Depolarizing (phase 1) block (SCh)           |
|-------------------------------------------------|------------------------------|----------------------------------------------|
| <b>Paralysis in man</b>                         | Flaccid                      | I → Fasciculations → flaccid<br>II → Flaccid |
| <b>Tetanic stimulation during partial block</b> | Poorly sustained contraction | Well sustained contraction                   |
| <b>Neostigmine</b>                              | Antagonises block            | No effect                                    |
| <b>Post tetanic potentiation</b>                | Present                      | Absent                                       |
| <b>Ether anaesthesia</b>                        | Synergistic                  | No effect                                    |
| <b>Effect of lowering temperature</b>           | Reduces block                | Intensifies block                            |
| <b>Effect of cathodal current to end plate</b>  | Lessens block                | Enhances block                               |

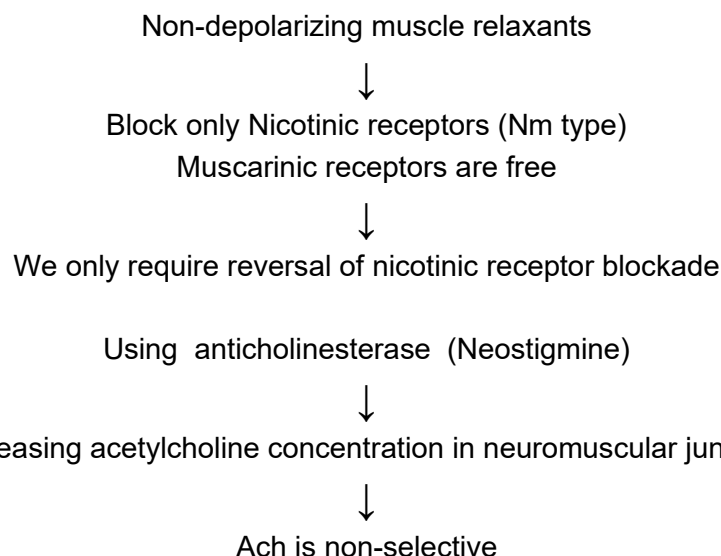
## Reversal of neuromuscular blockade

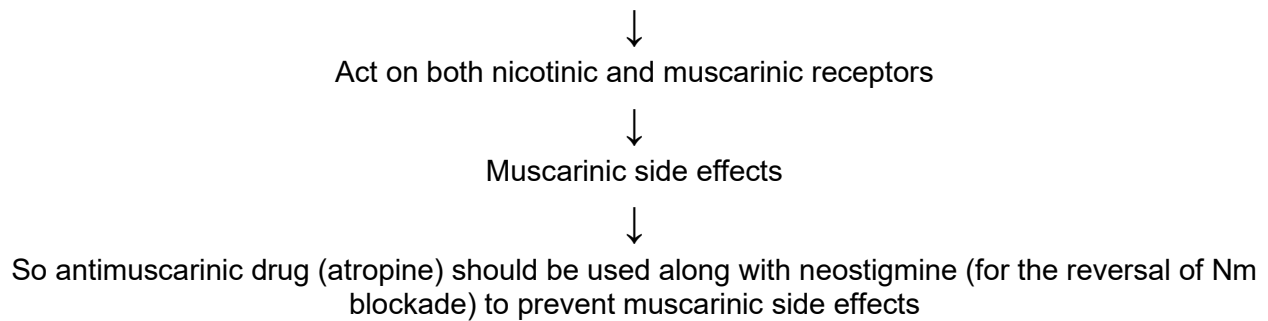
- A) Non-depolarizing block
- B) Depolarizing block

### A) Non-depolarizing block



- Most commonly used drug → Neostigmine
- Neostigmine 0.5–2 mg (30–50 µg/kg) i.v. is almost routinely used after neuromuscular blockers to hasten recovery at the end of operation.
- Other drugs → edrophonium, pyridostigmine & physostigmine.





### Sugamadex

- Novel reversing agent developed for terminating the action of nondepolarizing muscle relaxants ie. rocuronium and vecuronium.
- It is a modified  $\gamma$ -cyclodextrin with high affinity for rocuronium and vecuronium

### B) Depolarizing block

- Neostigmine is used for reversal of non-depolarizing blocker but not for depolarizing blockers (succinylcholine) as it also inhibits the enzyme pseudocholinesterase which metabolizes the Sch  
→ Block may increase (instead of reversal).

### Actions

1. Skeletal muscles
2. Autonomic ganglia
3. Histamine release
4. CVS
5. GIT

#### 1. Skeletal muscles

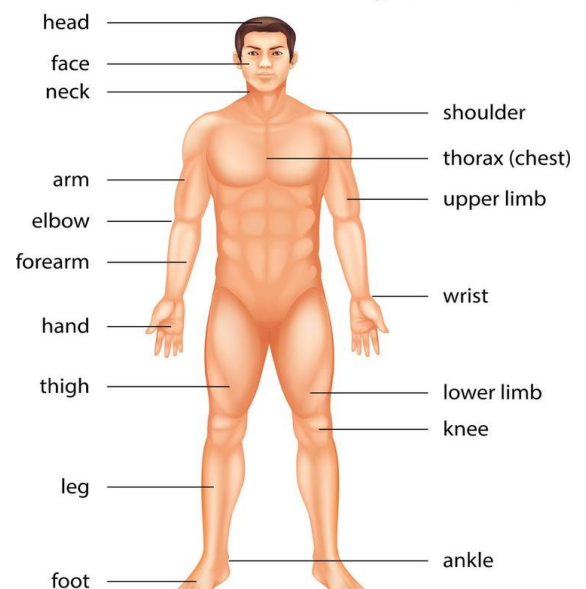
- Neuromuscular blockade (both depolarized and non-depolarized) →
  - Centrally located muscles → i.e., face, jaw, pharynx, larynx, and muscles of respiration (including diaphragm) → Blockage develops faster
  - Peripherally located muscles → e.g., limb muscles (adductor pollicis) → involved later.

#### Sequence of blockade

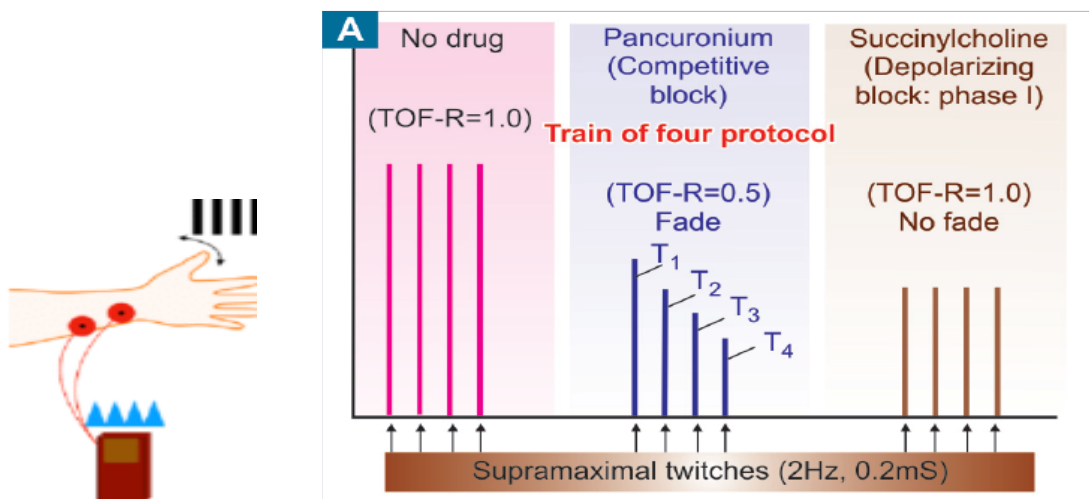
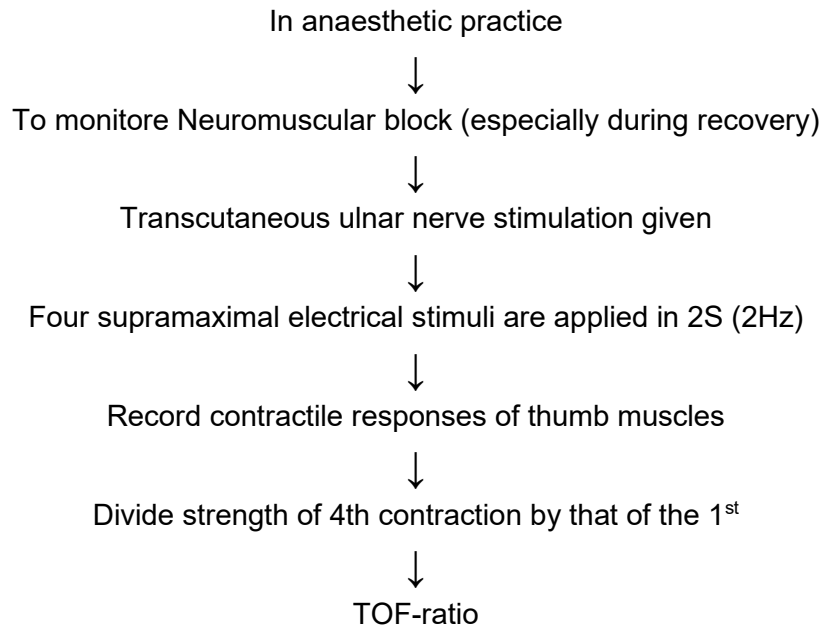
- Face → Jaw → Pharynx → Larynx → Respiratory (including diaphragm) → Trunk muscle → Limb muscle
- Face muscles are involved earliest
- Reversal occurs in reverse order

#### First clinical sign

- a) In non-depolarizing blocker (d-Tc) → Ptosis & Diplopia
- b) In depolarizing blocker (SCh) → Fasciculation of eye lids



## Clinical monitoring of neuromuscular block



### Untreated subject

- All the 4 contractions remain equal
- TOF-ratio is 1.0

### Competitive block

- During partial competitive block → degree of block corresponds to decrease in TOF-ratio, because competitive blockers exhibit 'fade' phenomenon.
- As the muscles recover, the TOF-ratio improves and becomes 1.0 at complete recovery

### Classical or phase-I depolarizing block

- Classical or phase-I depolarizing block does not exhibit fade
- TOF-ratio remains 1.0, though all the 4 twitches are depressed equally depending on degree of block.

## 2. Autonomic ganglia

- Cholinergic receptors in autonomic ganglia → Nicotinic (though of a different subclass NN)

Competitive neuromuscular blockers



Block NN on ganglion

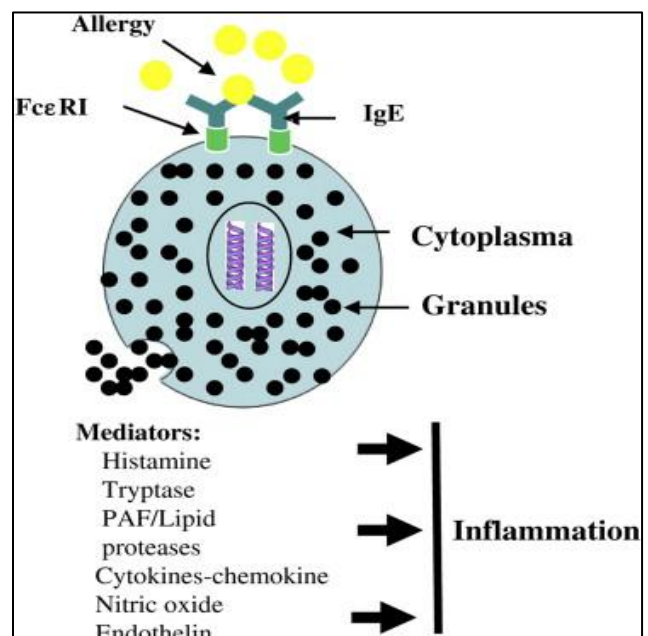


Produce ganglionic blockade

- d-TC → maximum propensity in this regard
- Newer drugs (vecuronium, etc.) → practically devoid of it.
- SCh → cause ganglionic stimulation by its agonistic action on nicotinic receptors

## 3. Histamine release

- d-TC releases histamine from mast cells.
- Histamine release contributes to →
  - Hypotension Flushing
  - Bronchospasm
  - Increased respiratory secretions
  - Intradermal injection of d-TC produces a wheal similar to that produced by injecting histamine.



## 4. CVS

- d-Tubocurarine produces significant fall in BP due to →
  - Ganglionic blockade
  - Histamine release
  - Reduced venous return → a result of paralysis of limb and respiratory muscles.
- Heart rate may increase due to vagal ganglionic blockade

## 5. GIT

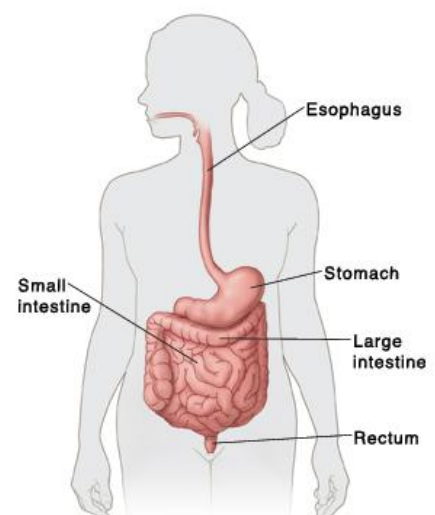
Competitive blockers



Ganglion blocking activity of



Postoperative paralytic ileus after abdominal operations



## Pharmacokinetics

All neuromuscular blockers  
↓  
Polar quaternary compound  
↓  
Not absorbed orally  
↓  
Do not cross cell membranes  
↓  
Practically always given i.v.



Muscles with higher blood flow  
↓  
Receive more drug  
↓  
Affected earlier  
↓  
Drugs that are metabolized in plasma  
↓  
e.g. vecuronium, atracurium, cisatracurium, rocuronium, and mivacurium  
↓  
Have Shorter  $t_{1/2}$   
Shorter duration of action  
(20–40 min)

Drugs that are excreted by kidney  
↓  
e.g. pancuronium, d-Tc, doxacurium and pipecuronium  
↓  
Have Longer  $t_{1/2}$   
Longer duration of action  
(>60 min)

## Interactions

- A) Drugs that enhance neuromuscular blocking effect
- B) Drugs that inhibit neuromuscular blocking effect

### A) Drugs that enhance neuromuscular blocking effect

- a) Inhalational anesthetics like ether, halothane, isoflurane and enflurane, stabilize the membrane so synergistic.

- b) Local anesthetics: Lignocaine, procaine by stabilizing the membrane;
- c) Antimicrobials:
  - Aminoglycosides by decreasing acetylcholine release
  - Tetracyclines by chelating calcium
  - Polymyxin B, clindamycin, vancomycin and colistin by neuromuscular blocking effect.
- d) Antiarrhythmics: Quinidine and procainamide owing to neuromuscular blockade.
- e) CCBs → enhance effect of competitive neuromuscular blocker.
- f) Magnesium—by reducing release and sensitivity of acetylcholine.

## B) Drugs that inhibit neuromuscular blocking effect

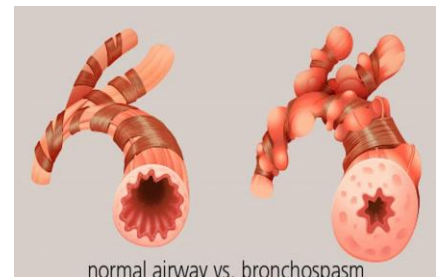
- (a) Anticholinesterase (neostigmine, Pyridostigmine & edrophonium) reverse the action of competitive blockers, they can enhance depolarizing neuromuscular blockers.
- (b) Calcium salts by increasing the release of acetylcholine.
- (c) Corticosteroids, if patient is receiving for a long period, antagonize effect of certain NMB
- (d) Competitive NMB antagonizes depolarizing blockers → This property is utilized to prevent muscle twitching and soreness induced by depolarizing blocker, by prior use of a little dose of competitive NMB

## Adverse Effects

- A) Adverse Effects Due to Nondepolarizing (Competitive) blockers
- B) Adverse Effects Due to Depolarizing blockers

### A) Adverse Effects due Nondepolarizing (Competitive) blockers

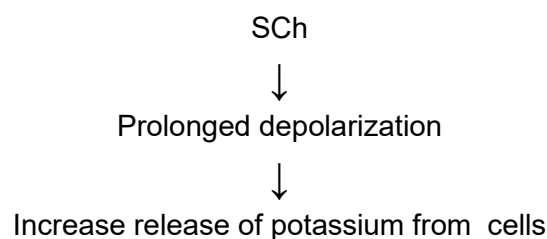
1. Prolonged apnea and respiratory failure
2. Cardiovascular collapse
3. Effects of histamine release →
  - Bronchospasm
  - Hypotension
  - Excessive bronchial and salivary secretions.

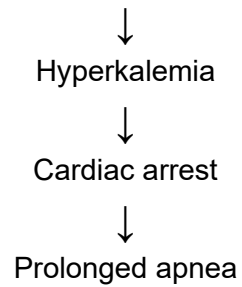


### B) Adverse effects Due to Depolarizing blockers

1. Hyperkalemia
2. Increase intra ocular pressure
3. Intra gastric pressure
4. Muscle soreness (pain)
5. Succinyl apnea
6. Malignant hyperthermia

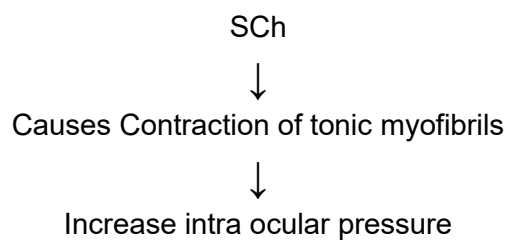
#### 1. Hyperkalemia



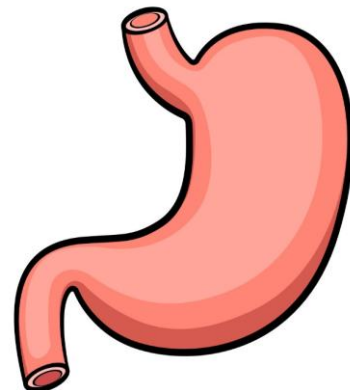
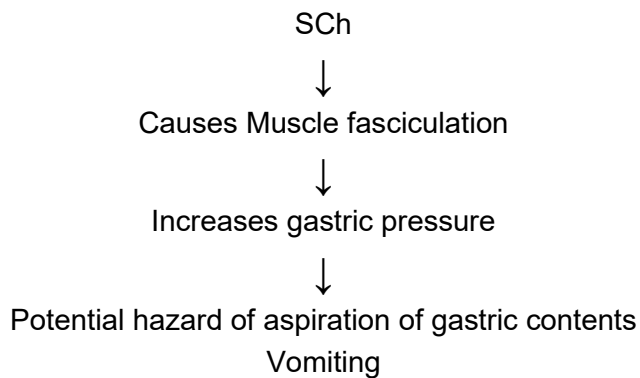


- In patients with extensive injury to soft tissues like burns, trauma, peritoneal infections and renal failure → life threatening.

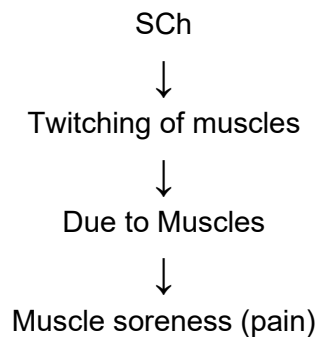
## 2. Increase intra ocular pressure



## 3. Intra gastric pressure



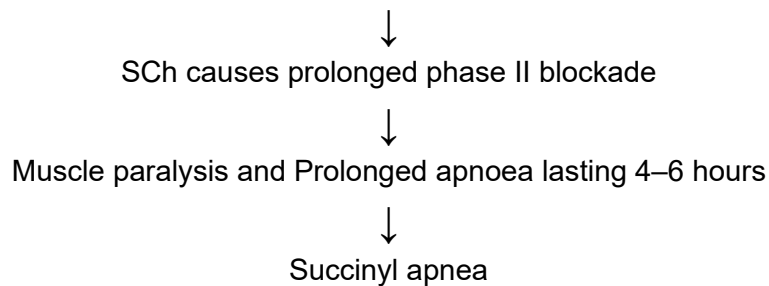
## 4. Muscle soreness (pain)



## 5. Succinyl apnea

Some patients have genetically determined abnormality  
(low affinity for SCh or deficiency of pseudocholinesterase)





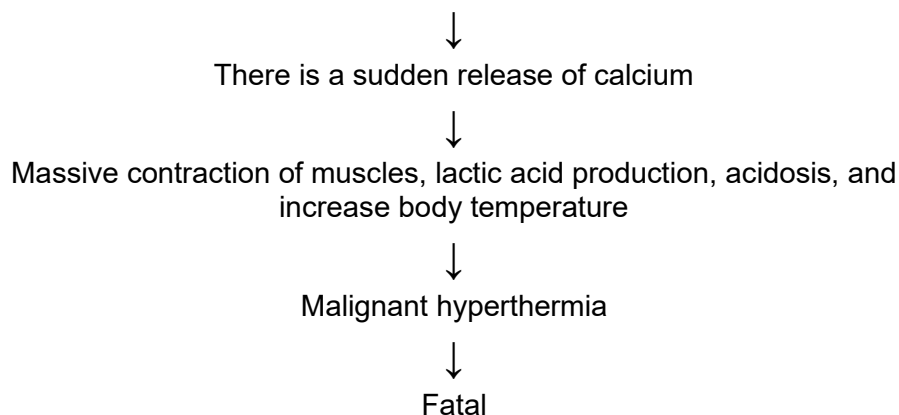
Treatment → →

- Mechanical ventilation
- Fresh blood transfusion to replace the enzyme



## 6. Malignant hyperthermia

SCh If used with halothane or isoflurane in patients with hereditary disorder and familiar tendency



**Treatment** →

- (a) Rapid cooling
- (b) Control of acidosis
- (c) 100% oxygen inhalation
- (d) Dantrolene

## Contraindications to Succinylcholine

1. Patients with extensive soft tissue injury such as burn, trauma and peritoneal infections
2. Tetanus
3. Rhabdomyolysis
4. Ocular lacerations
5. Head injury
6. Spinal cord injury with paraplegia or quadriplegia or with muscle dystrophies
7. Child below age of 8 years
8. Renal failure (hyperkalemia becomes life threatening)

## Uses

1. As adjuvants to general anaesthesia
2. Assisted ventilation

3. Electroconvulsive therapy
4. Tetanus and status epilepticus

## 1. As adjuvants to general anaesthesia

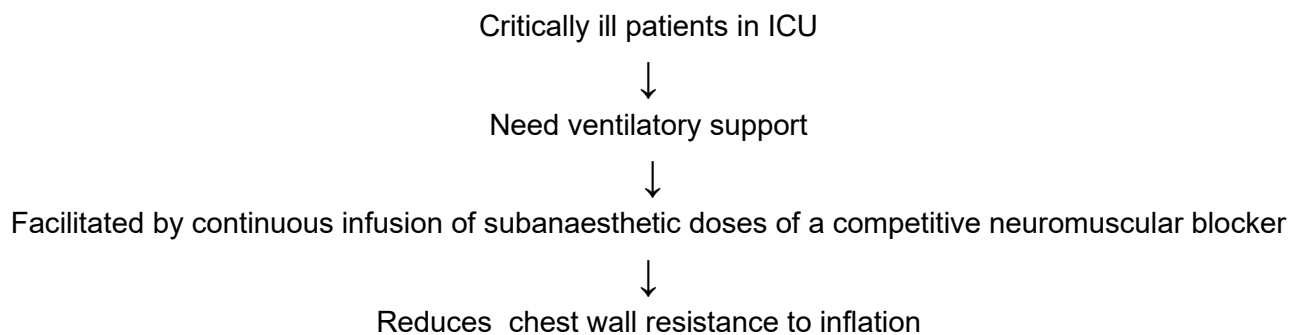
- Particularly helpful in → abdominal and thoracic surgery, intubation and endoscopies, orthopedic manipulations, etc.
- Muscle relaxants →
  - (a) Reduce reflex muscle contraction in region undergoing surgery
  - (b) Assist maintenance of controlled ventilation during anaesthesia



### Remember

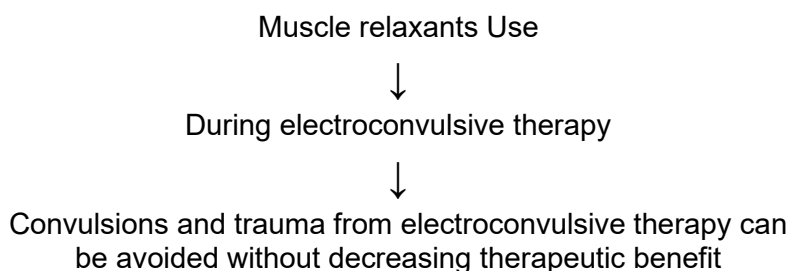
- Vecuronium and rocuronium → most frequently selected nondepolarizing blockers.
- SCh → employed for brief procedures, e.g. endotracheal intubation, laryngoscopy, bronchoscopy, esophagoscopy, reduction of fractures, dislocations, and to treat laryngospasm.

## 2. Assisted ventilation

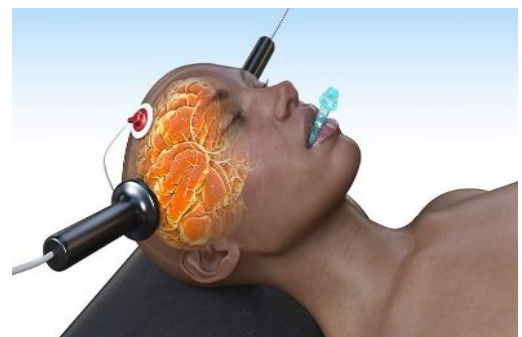


- Vecuronium → most commonly used

## 3. Electroconvulsive therapy



- SCh → most commonly used for this purpose.
- Mivacurium → alternative



#### 4. Tetanus and status epilepticus

Tetanus and status epilepticus, who are not controlled by diazepam or other drugs



Paralysed by a neuromuscular blocker  
(repeated doses of a competitive blocker)



Maintained on intermittent positive pressure respiration till disease subsides.



## INDIVIDUAL COMPOUNDS

### d-Tubocurarine

- d-TC is not used now because of its →
  - Prominent histamine releasing
  - Ganglion blocking
  - Cardiovascular actions
  - Long duration of paralysis needing pharmacological reversal

### Succinylcholine

- SCh → depolarising skeletal muscle relaxant
- Causes sustained partial depolarization of muscle end plate → Initially produce twitching and fasciculation followed by flaccid paralysis.
- Shortest and fastest acting skeletal muscle relaxant
- Only muscle relaxant which stimulate autonomic ganglia and vagus → Bradycardia occurs due to vagal stimulation
- Most commonly used muscle relaxant for passing endotracheal tube (rapacuronium and rocuronium are alternatives).
- Rapidly hydrolysed by plasma pseudocholinesterase
- Some patients have genetically determined abnormality or deficiency of pseudocholinesterase → SCh causes phase II block (dual block)
- Post-operative muscle pain (myalgia, muscle soreness) is a very common problem
- It can accentuate malignant hyperthermia caused by halothane
- SCh causes increases in all pressures → intraocular, intracranial, BP, and intrabdominal
- SCh can cause Trismus (masseter spasm) especially in patients susceptible for malignant hyperthermia.

### Mivacurium

- Shortest acting competitive blocker
- Does not need reversal → can be used as an alternative to SCh for endotracheal intubation.
- Metabolized rapidly by plasma cholinesterases → Prolonged paralysis can occur in pseudocholinesterase deficiency.
- Only nondepolarising (competitive) blocker that is metabolized by plasma cholinesterase (pseudocholinesterases).

## Atracurium

- Unique feature of atracurium is inactivation in plasma by spontaneous nonenzymatic degradation (Hofman elimination) in addition to that by alkaline ester hydrolysis.
- So its duration of action is not altered in patients with hepatic/renal insufficiency or hypodynamic circulation -> Preferred muscle relaxant for such patients as well as for neonates and the elderly.
- Atracurium is metabolised to laudanosine that is responsible for seizures

## Cisatracurium

- R-Cis enantiomer of atracurium
- 4 times more potent, slower in onset but similar in duration of action.
- Like atracurium it undergoes Hofman elimination, but in contrast it is not hydrolysed by plasma cholinesterase.
- It does not provoke histamine release.
- Reversal of atracurium and cisatracurium by neostigmine is not required because of spontaneous nonenzymatic degradation (Hofmann elimination)
- So, Atracurium/cisatracurium can be used in patient with neostigmine hypersensitivity

## Vecuronium

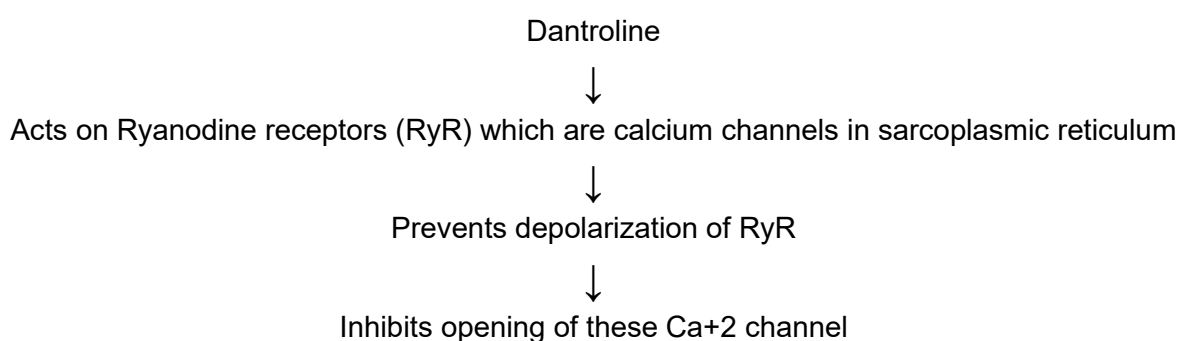
- Vecuronium is a steroidal (amino-steroid) non-depolarizing neuro-muscular blocker with intermediate duration (20- 50 min) of action
- Vecuronium is lipid soluble and the lipophilic effect of single quaternary nitrogen enhances rapid uptake into hepatocytes.
- It is mainly metabolized in liver and excreted in bile. Only slightly (< 20%) excreted in urine → Not affected by renal failure
- Vecuronium is cardiovascular stable, even at high doses, vecuronium is devoid of significant cardiovascular side effect.
- Therefore vecuronium is the most commonly used muscle relaxant during surgery.

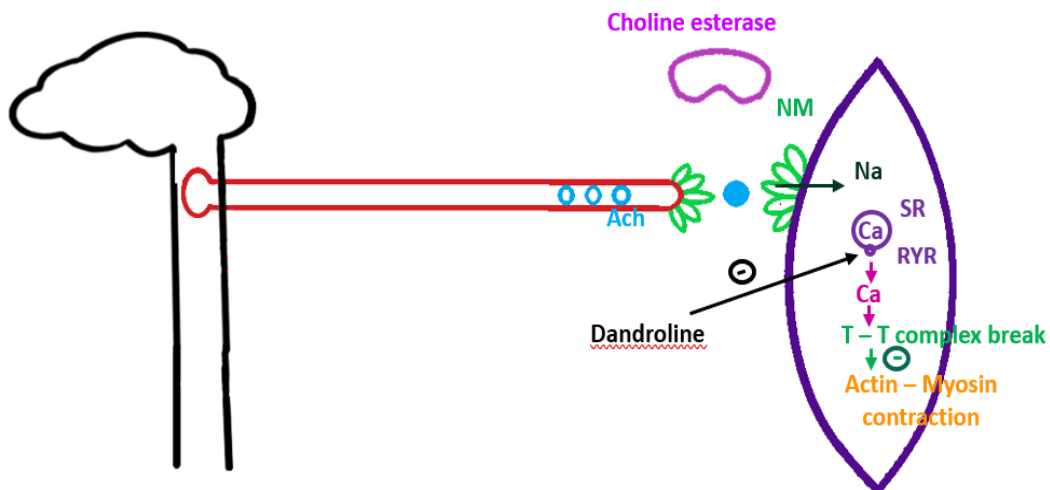
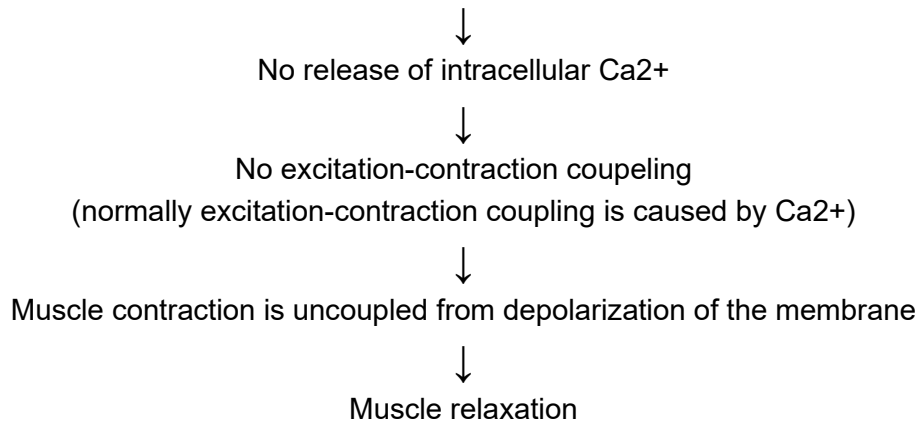
## PERIPHERALLY ACTING MUSCLE RELAXANTS → DIRECTLY ACTING AGENTS

### Drugs

1. Dantroline
2. Quinine

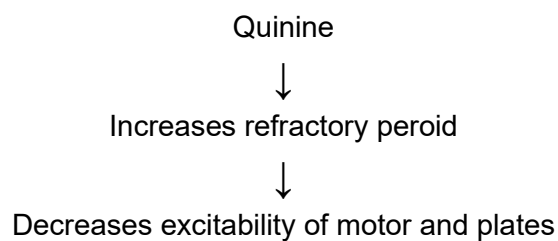
### MOA





### Remember

- Neuromuscular transmission or MAP are not affected
- Only Muscle contraction is uncoupled from depolarization of the membrane
- $\text{Ca}^{2+}$  channels in sarcoplasmic reticulum of cardiac and smooth muscles are of a different subtype (RyR2) → these muscles are affected little by dantrolene.



- Used in → Nocturnal leg cramps

### Adverse effects

1. Generalized muscle weakness
2. Sedation
3. Diarrhea
4. Hepatitis

## Use

### 1. Used orally →

- Reduces spasticity in upper motor neurone disorders, hemiplegia, paraplegia, cerebral palsy and multiple sclerosis.



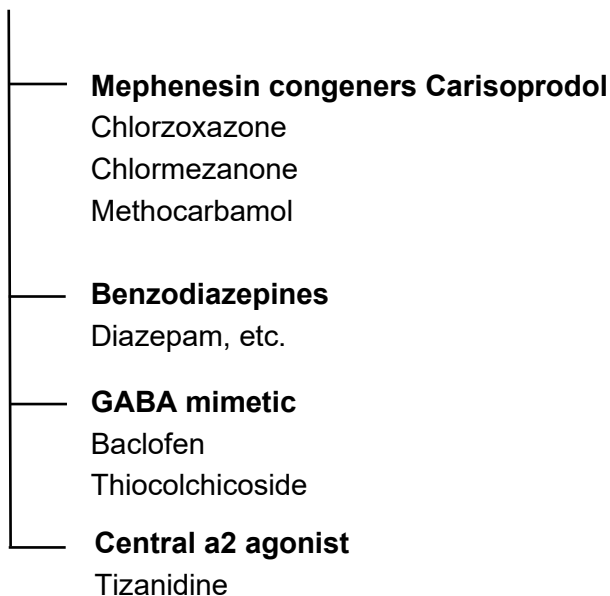
### 2. Used IV →

- DOC → for malignant hyperthermia → due to persistent release of  $\text{Ca}^{2+}$  from sarcoplasmic reticulum (induced by fluorinated anaesthetics and SCh in genetically susceptible individuals with abnormal RyR1)

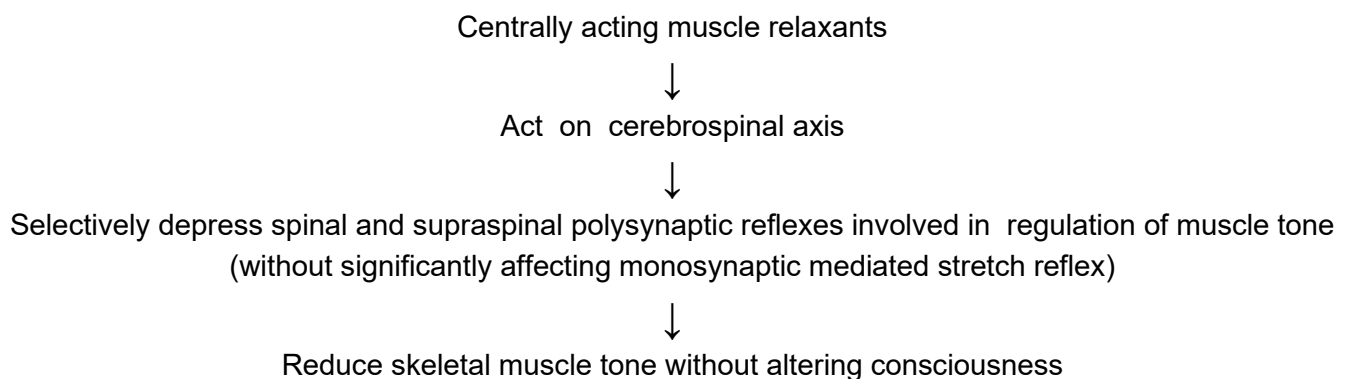


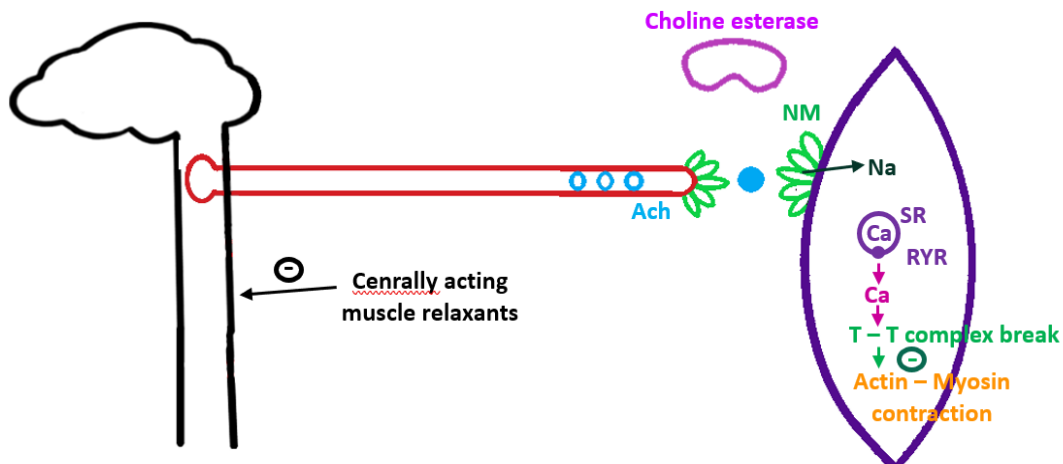
## CENTRALLY ACTING MUSCLE RELAXANTS

### Drugs



### MOA





- Reduce →
  - Decerebrate rigidity
  - Upper motor neurone spasticity
  - Hyperreflexia

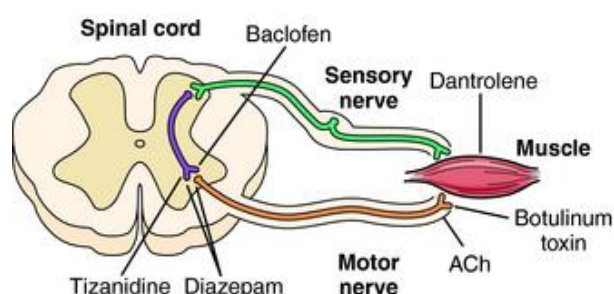
### Remember

- No effect on neuromuscular transmission
- No effect on muscle fibres

Centrally acting muscle relaxants  
 ↓  
 Also depresses Polysynaptic pathways in ascending reticular formation which are involved in maintenance of wakefulness  
 ↓  
 Sedative property



| Centrally acting                                                           | Peripherally acting                                |
|----------------------------------------------------------------------------|----------------------------------------------------|
| 1. <b>Decrease muscle tone without reducing voluntary power</b>            | Cause muscle paralysis, voluntary movements lost   |
| 2. <b>Selectively inhibit polysynaptic reflexes in CNS</b>                 | Block neuromuscular transmission                   |
| 3. <b>Cause some CNS depression</b>                                        | No effect on CNS                                   |
| 4. <b>Given orally, sometimes parenterally</b>                             | Practically always given i.v.                      |
| 5. <b>Used in chronic spastic conditions, acute muscle spasms, tetanus</b> | Used for short-term purposes (surgical operations) |





## Uses

1. Acute muscle spasms
2. Torticollis, lumbago, backache, neuralgias
3. Anxiety and tension
4. Spastic neurological diseases
5. Tetanus
6. Electroconvulsive therapy
7. Orthopedic manipulations

### 1. Acute muscle spasms

- Painful spasm of muscles in →
  - Overstretching of a muscle, sprain
  - Tearing of ligaments and tendons
  - Dislocation
  - Fibrositis
  - Bursitis
  - Rheumatic disorders



### 2. Torticollis, lumbago, backache, neuralgias

- Painful spasm of muscles



### 3. Anxiety and tension

- Increased tone of muscles also associated with these
- Diazepam and chlormezanone → Antianxiety as well as muscle relaxant actions.



### 4. Spastic neurological diseases

Hemiplegia, paraplegia, spinal injuries, multiple sclerosis, ALS and cerebral palsy



Impairment of descending pathways in cerebrospinal axis



Withdrawal of inhibitory influence over stretch reflex



Chronic increase in muscle tone



Spasticity





## 5. Tetanus

- Diazepam → Most commonly infused i.v.
- Methocarbamol → alternative.



## 6. Electroconvulsive therapy

- Diazepam → decreases intensity of convulsions resulting from ECT, without diminishing its therapeutic effect.
- SCh → used in addition for total suppression of the muscular component of ECT.



## 7. Orthopedic manipulations

- Under the influence of diazepam or methocarbamol given i.v.



# INDIVIDUAL COMPOUNDS

## 1. Mephenesin

- Selectively inhibit polysynaptic reflex, in CNS.
- Not used clinically because orally it causes marked gastric irritation, and injected i.v., it causes thrombophlebitis, haemolysis and fall in BP.
- Included in counterirritant ointments where its irritant rather than muscle relaxant property could be affording relief.

## 2. Tizanidine

- Central  $\alpha_2$ -adrenergic agonist
- Inhibits release of excitatory amino acids in spinal interneurons.
- Indicated in →
  - Spasticity due to neurological disorder
  - Painful muscle spasm

## 3. Baclofen

- Acts as an agonist on GABA<sub>B</sub> receptor
- Inhibits both polysynaptic and monosynaptic reflexes in spinal cord.
- Reduces spasticity in multiple sclerosis, spinal injuries and flexor spasms, but is ineffective in cerebral palsy, stroke and traumatic & rheumatic muscle spasm.

## 4. Benzodiazepines

- Inhibit both polysynaptic and monosynaptic reflex
- Used in tetanus and spinal injuries.

# REMEMBER

- Longest acting Neuromuscular blocker → **Pancuronium** (DOA → 120-180 minutes).
- Shortest acting neuromuscular blocker → **Succinylcholine** (DOA □ 5-8 minutes)

- Fastest acting neuromuscular blocker → **Succinylcholine**
- Shortest acting competitive (nondepolarizing) neuromuscular blocker → **Mivacurium** (DOA → 12-18 minutes)
- Fastest acting nondepolarizing blocker → **Rocuronium** (can be used for endotracheal intubation as an alternative to Sch).
- Most potent skeletal muscle relaxant → **Doxacurium**.
- Least potent skeletal muscle relaxant → **Succinylcholine**
- Least potent nondepolarising muscle relaxant → **Rocuronium**.
- Most commonly used muscle relaxant for routine surgery → **Vecuronium**
- MR of choice for intubation → Sch > Rapacuroium > **Rocuronium**
- Most nephrotoxic NM blocker that is contraindicated in renal failure → **Gallamine**
- NM blocker that has been withdrawn due to nephrotoxic and tetragenic potential → **Gallamine**
- Only non-depolarizing blocker that is metabolized by plasma cholinesterase → **Mivacurium**
- Non-depolarizing blocker of choice for hepatic and renal disease → **Atracurium / Cisatracurium**
- Non-depolarizing blocker contraindicated in biliary obstruction → **Vecuronium, rocuronium**
- Non-depolarizing blocker with no or less cardiovascular side effects → **Vecuronium**
- Non-depolarizing blocker of choice in cardiac patients → **Vecuronium**.

### Histamine release

- Histamine release caused by → **D-TC > succinylcholine, mivacurium, doxacurium, atracurium**
- Maximum histamine release → **D-TC**
- Virtually no histamine release → **Pancuronium**

### Ganglion block

- Ganglion block is caused by → **d-Tc, Metocurine, Alcuronium**
- Maximum ganglion blockade is caused by → **d-TC**
- Ganglion stimulation is caused by → **Succinylcholine**

### Vagal block

- Vagal block is caused by → **Pancuronium, recuronium, Gallamine**.
- Maximal vagal block and tachycardia is caused by → **Pancuronium**
- Vagal stimulation is caused by → **Succinylcholine (can cause bradycardia)**

### Renal failure

- Nondepolarizing Blocker absolutely contraindicated in renal failure → **Gallamine**
- Non-depolarizing blocker relatively contraindicated in renal failure → **Pancuronium, d-Tc, doxacurium, pipecurium, vecuronium**
- Muscle relaxants completely independent of renal function → **Atracurium, Cisatracurium, Sch, Mivacurium**.
- Non-depolarizing blocker safe in renal failure → **Mivacurium, Atracurium/Atracurium (DOC), vecuronium, Rocuronium, Sch**

## LOCAL ANAESTHETICS

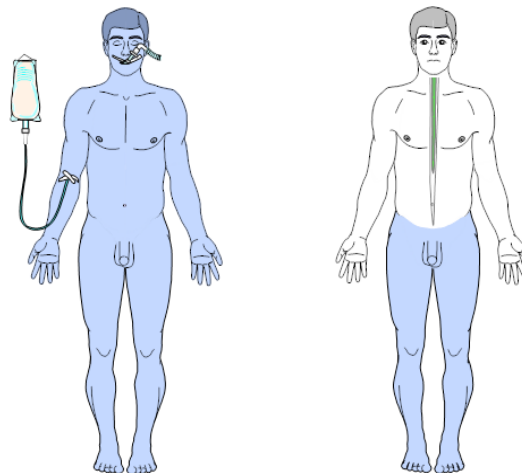
### Anaesthesia

- Anaesthesia is reversible loss of response to a noxious stimuli.

### Types

- General anaesthesia** → if associated with loss of consciousness
- Local anaesthesia** → consciousness is maintained

|                                   | General anaesthesia | Local anaesthesia  |
|-----------------------------------|---------------------|--------------------|
| 1. Site of action                 | CNS                 | Peripheral nerves  |
| 2. Area of body involved          | Whole body          | Restricted area    |
| 3. Consciousness                  | Lost                | Unaltered          |
| 4. Care of vital functions        | Essential           | Usually not needed |
| 5. Poor health patient            | Risky               | Safer              |
| 6. Use in non-cooperative patient | Possible            | Not possible       |
| 7. Major surgery                  | Preferred           | Cannot be used     |
| 8. Minor surgery                  | Not preferred       | Preferred          |



## LOCAL ANAESTHETICS

| Local Anaesthesia |  |
|-------------------|--|
| Introduction      |  |
| Classification    |  |
| MOA               |  |
| Actions           |  |
| Adverse effects   |  |
| Techniques        |  |

## INTRODUCTION

Local anaesthetics (LAs)

↓

Drugs which upon topical application or local injection

↓

Block generation and conduction of nerve impulse at that part of neuron with which they come in contact, without causing any structural damage

↓

Sensory, motor and Autonomic impulses are interrupted

↓

Results in reversible →

Loss of Sensory perception (especially of pain) in a restricted area of body

Muscular paralysis

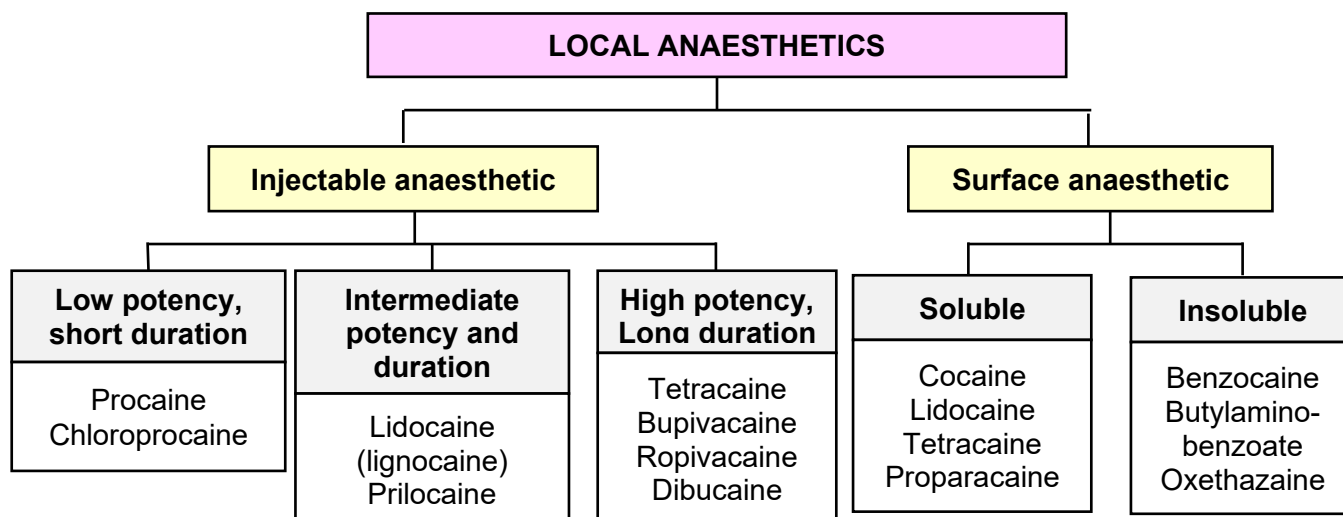
Loss of autonomic control



## CLASSIFICATION

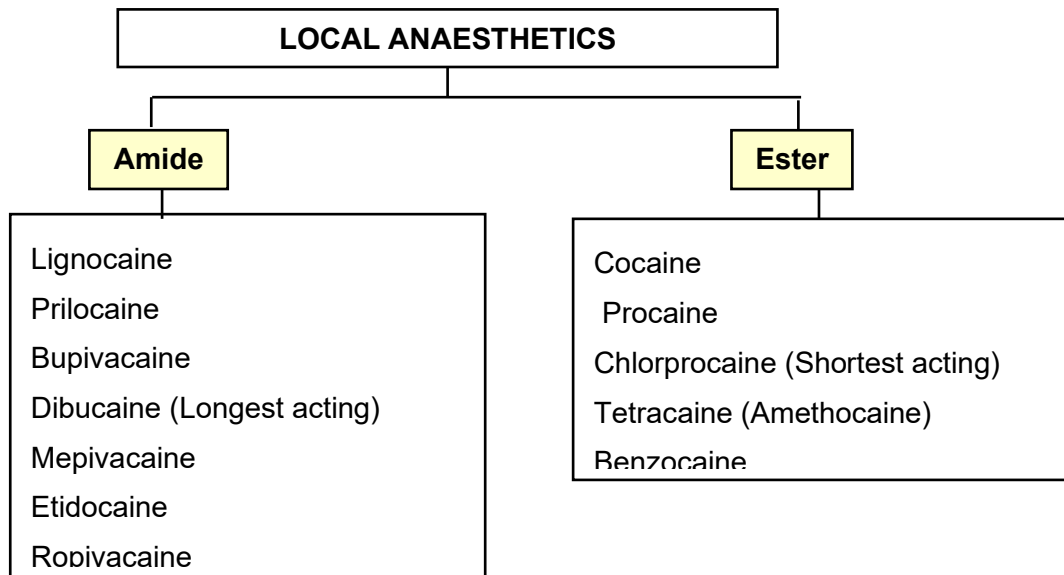
- A) Based on Route
- B) Based on Chemical composition

### A) Based on Route



### B) Based on Chemical composition

| Amides                               | Esters                                                                            |
|--------------------------------------|-----------------------------------------------------------------------------------|
| Metabolized primarily in liver       | Metabolized by pseudocholinesterase except cocaine which is metabolized in liver. |
| Action is longer                     | Action is Shorter                                                                 |
| Low incidence of allergic reactions  | High incidence of allergic reactions due to PABA                                  |
| Bind to $\alpha 1$ acid glycoprotein | Do not bind to plasma protein.                                                    |



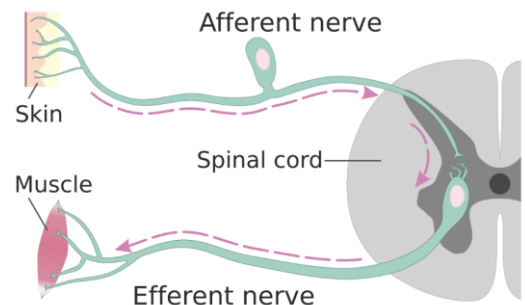
## Remember

### Ester-linked LAs →

- Rarely used for infiltration or nerve block because of →
  - Short duration
  - Less intense analgesia
  - Higher risk of hypersensitivity
- Used topically on mucous membranes

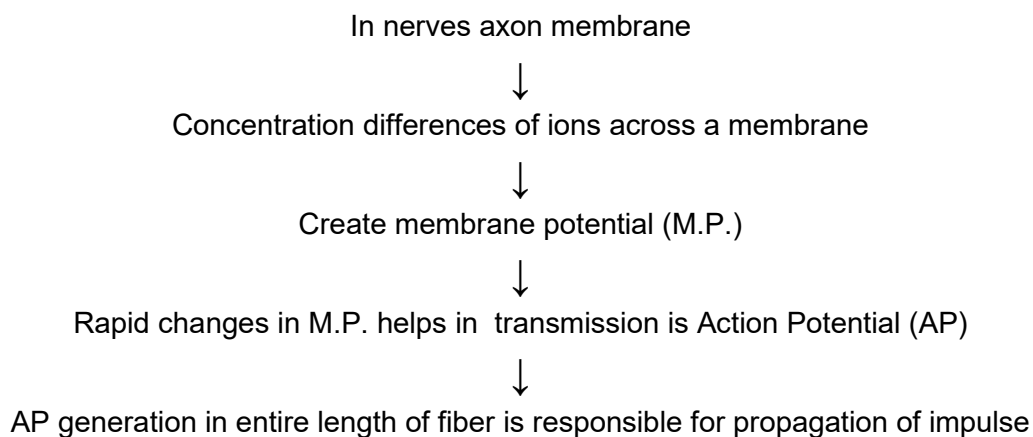
## MOA

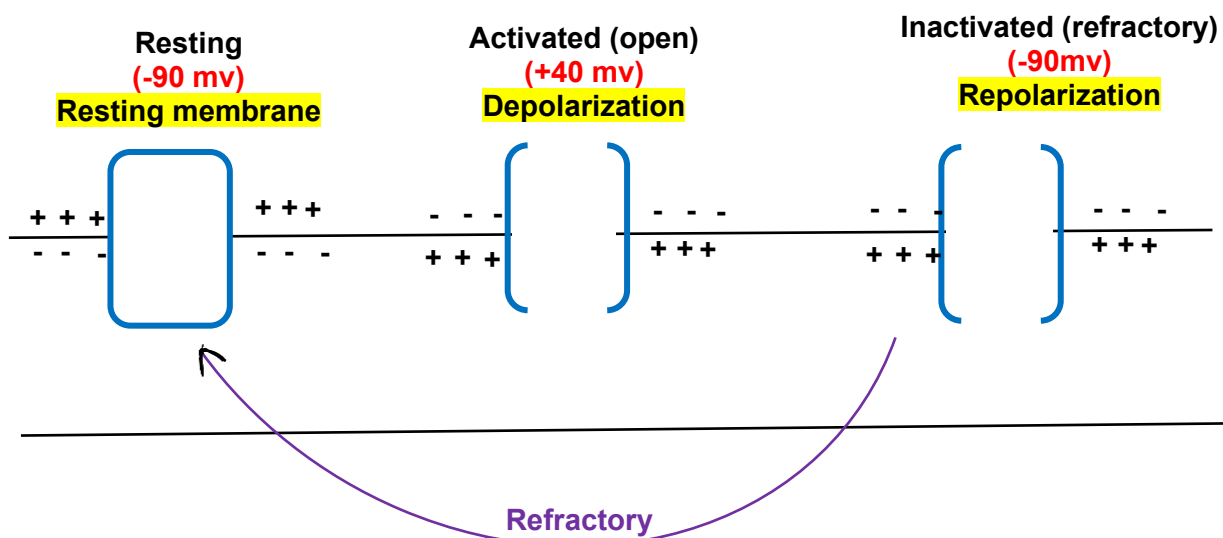
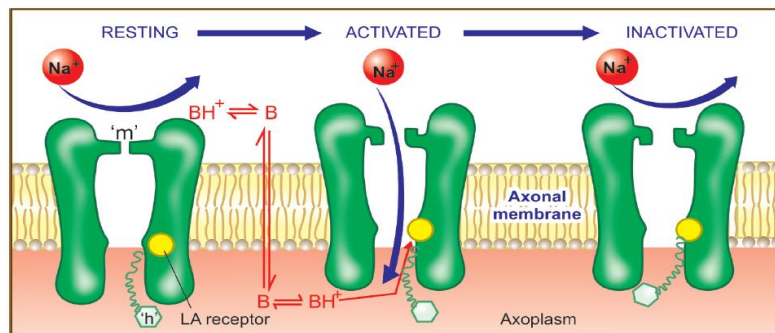
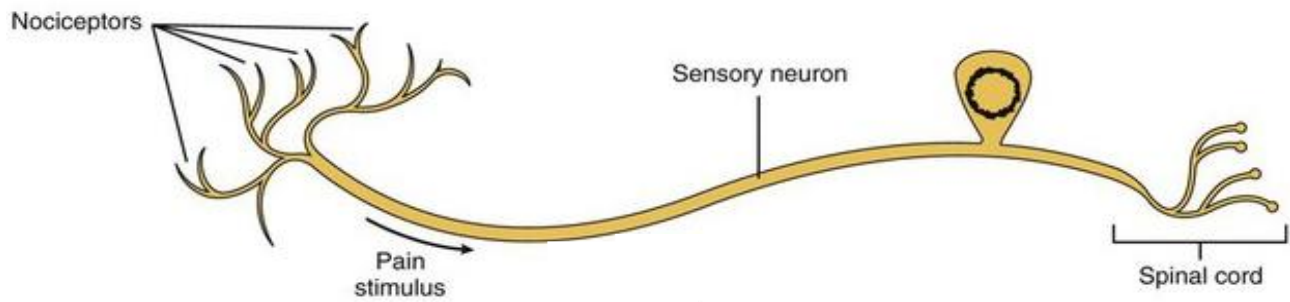
- Local anesthetics prevent generation and conduction of nerve impulse by binding and stabilizing inactivated state of sodium channel



## Normally

- Nerves are excitable i.e. capable of generating and conducting rapid changes in electrochemical impulse at their membrane





Excitable membranes of nerve maintain a transmembrane potential of

-90 to -60 MV



Na channel closed (Resting)



During excitation



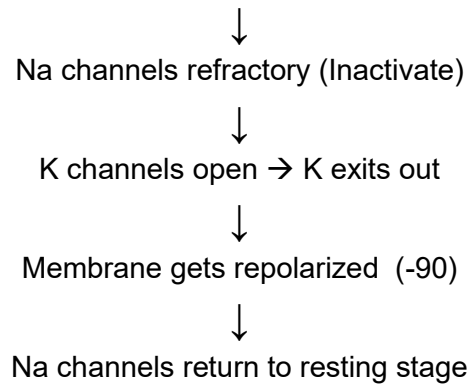
Na channels open (Activated)



Na enters in



Membrane depolarizes (+40 mv)



## States of Action Potential

- **Resting membrane** → polarized due to -90 mv → MP
- **Depolarization** → membrane is permeable to sodium, which enters in, MP rises to positive direction (+40 mv)
- **Repolarization** → Na channels close → K channels open → K comes out → normal negative MP reestablishes (-90mv)

## Voltage gated sodium channels

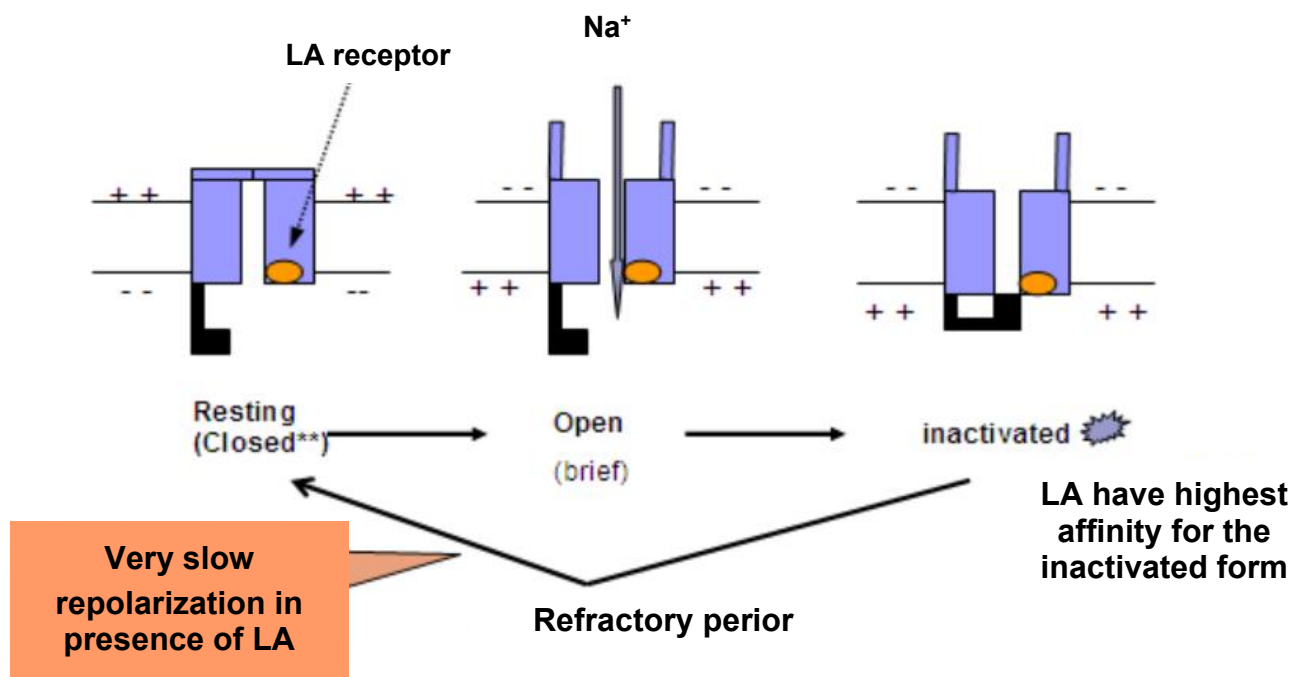
- Three states
- Two Gates

### Three states

1. **Resting** → -90 mv
2. **Activated (open)** → -90 to +40 mv
3. **Inactivated (refractory)** → +40 to -90 mv

### Two gates

1. **Activation (outside) (m or 'm' gate)**
2. **Inactivation (inside) (h or 'h' gate)**

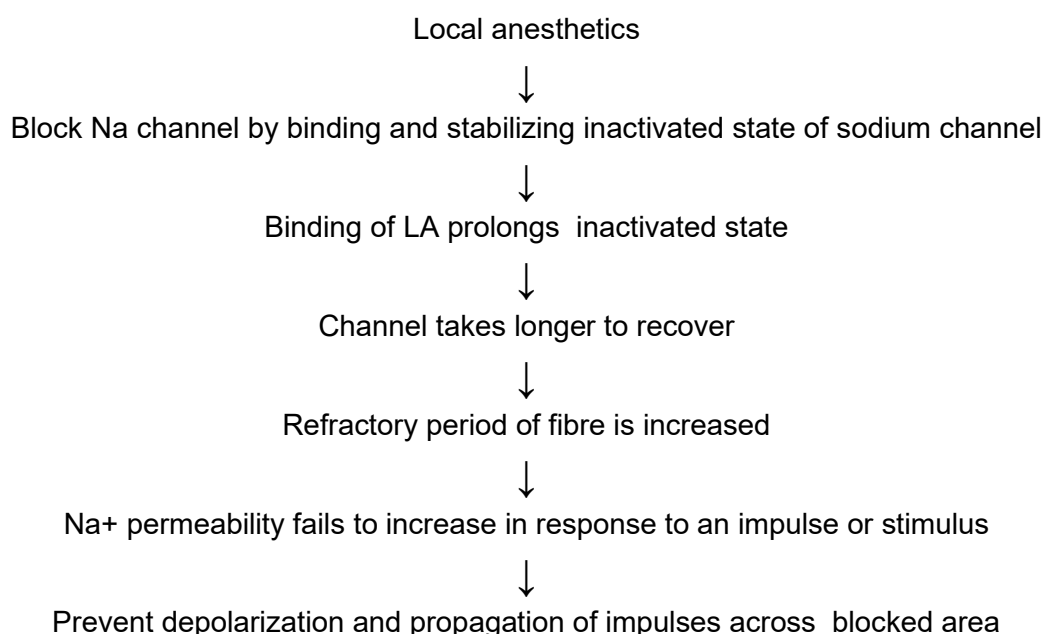


## Gates during 3 states

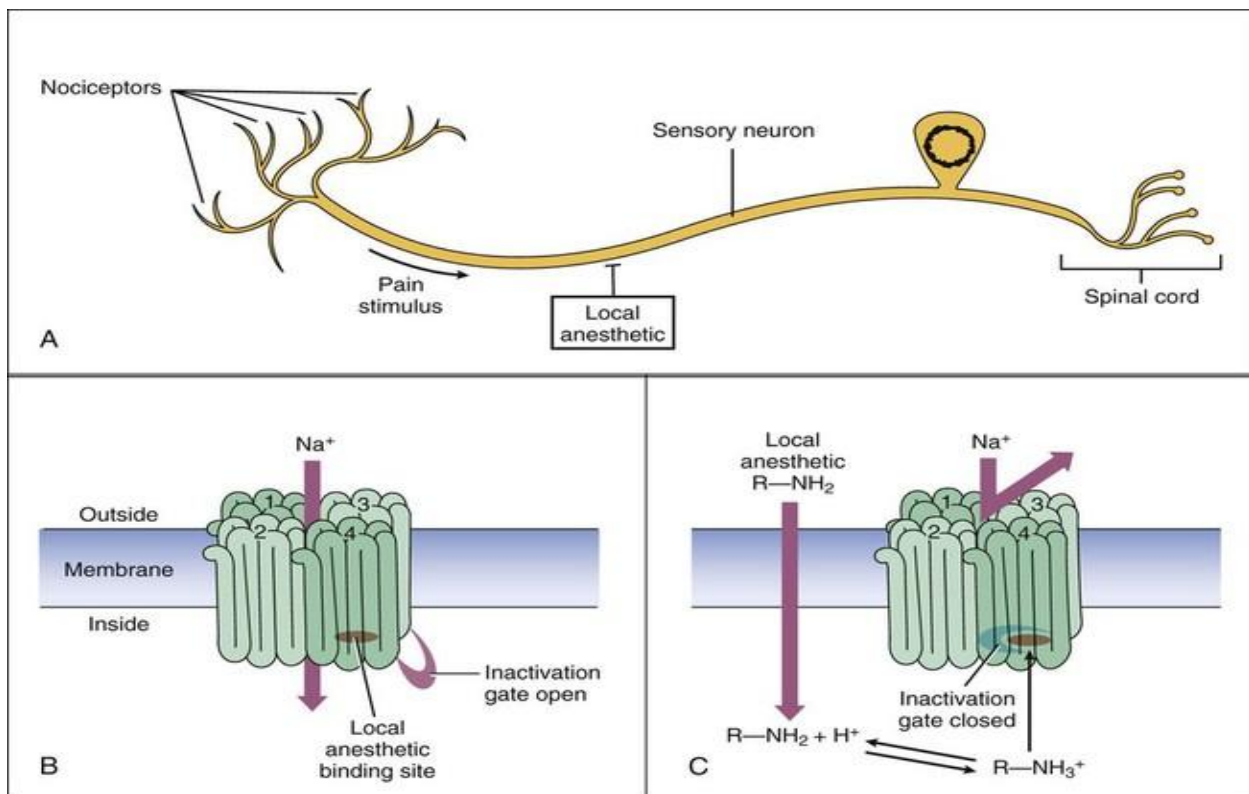
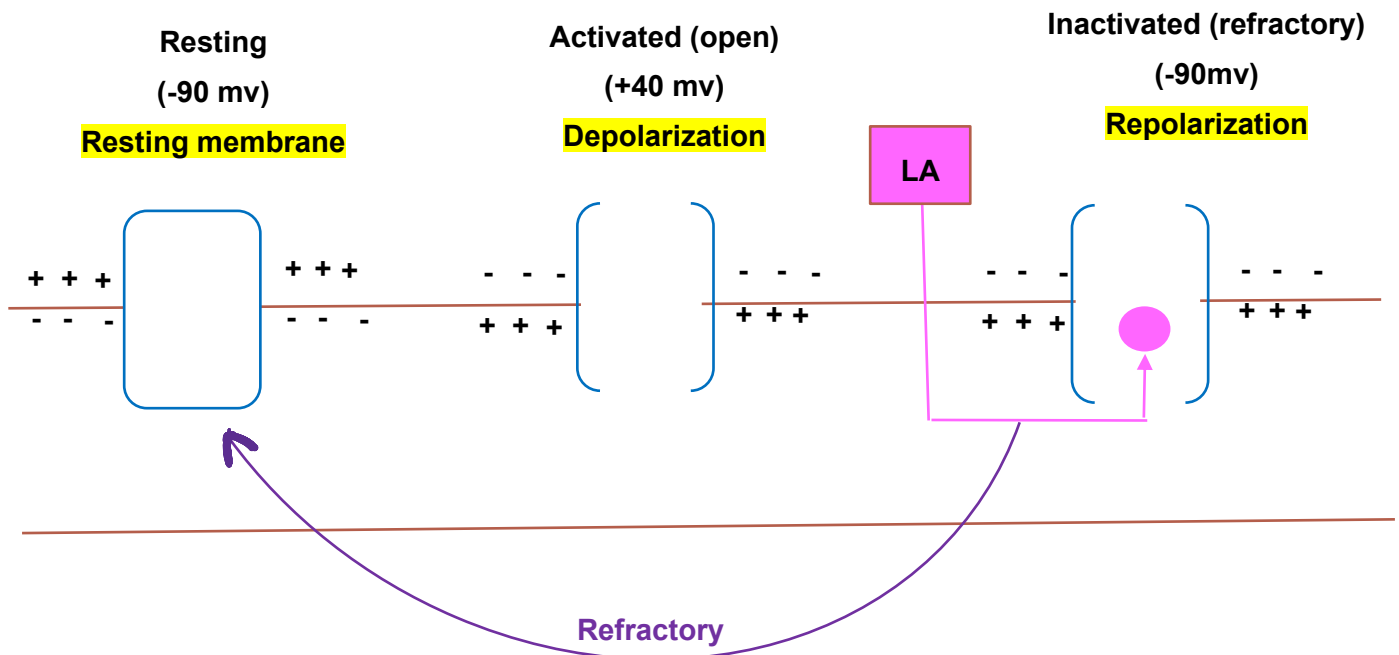
1. **Resting** → m gate closed and h gate open
2. **Activated (open)** → m gate open and h gate open
3. **Inactivated (refractory)** → m gate open and h gate close

## Local anesthetics

- Local anesthetics prevent generation and conduction of nerve impulse by binding and stabilizing inactivated state of sodium channel

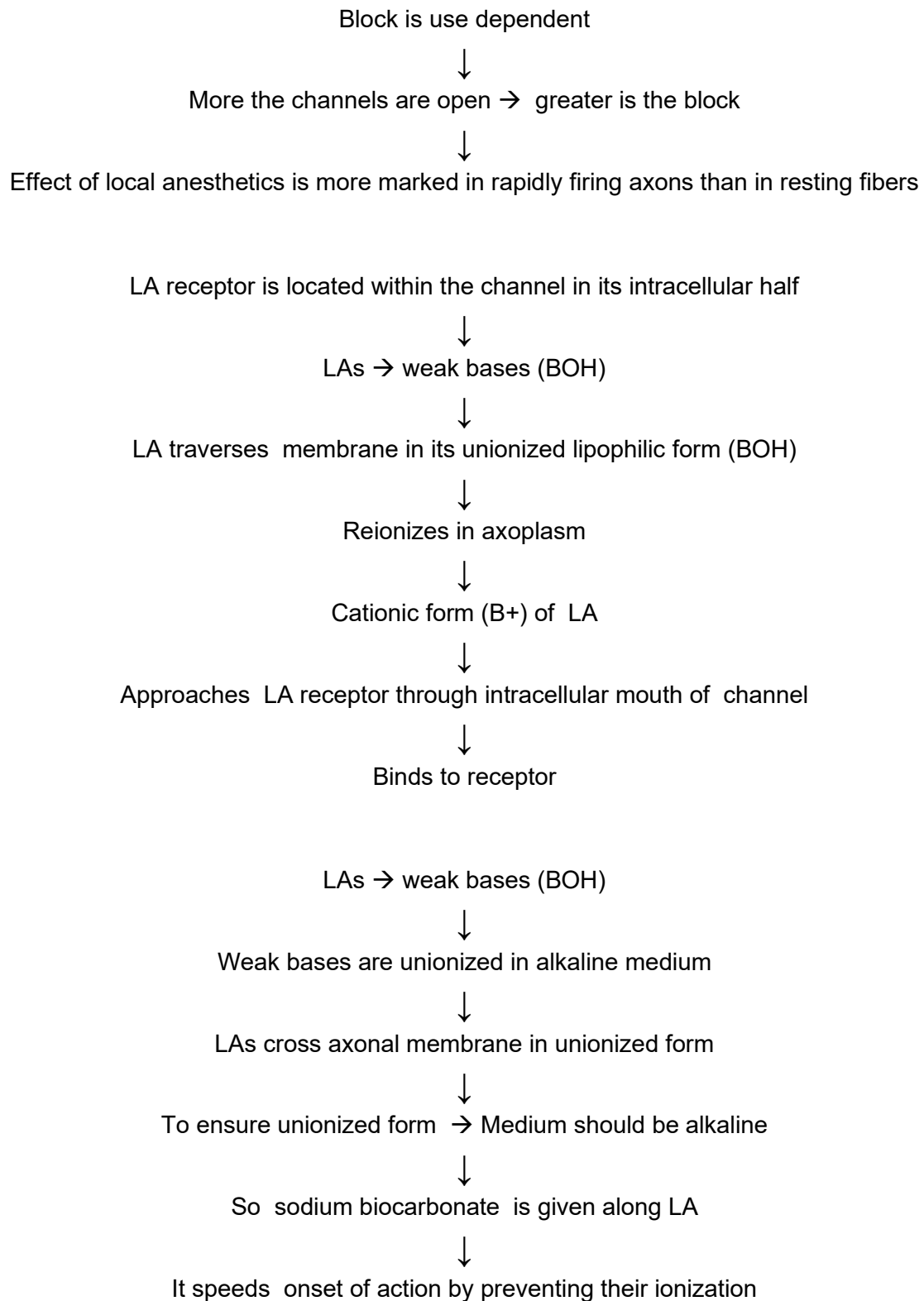






## Remember

- LAs interact with a receptor situated within voltage sensitive Na<sup>+</sup> channel
- Receptor has higher affinity to LA in the activated as well as inactivated states compared to resting state.



## ACTIONS

### Local Actions

- Order of blockade
- LA in Inflammation
- Addition of a vasoconstrictor

## Systemic actions

1. CNS
2. CVS

## A) Local Actions

### 1. Order of blockade

#### Nerve fibres

- Sensory
- Motor
- Autonomic
  - A, B, and C fibers are classified based on diameter, myelination, and conduction velocity

| Fiber Type    | Diameter | Myelination        | Conduction Velocity (m/s) | Function                                                             |
|---------------|----------|--------------------|---------------------------|----------------------------------------------------------------------|
| A $\alpha$    | Largest  | Yes                | 80-120                    | Motor to skeletal muscles; proprioception from muscle spindles & GTO |
| A $\beta$     | Large    | Yes                | 35-90                     | Touch, pressure (skin)                                               |
| A $\gamma$    | Medium   | Yes                | 10-45                     | Motor to intrafusal fibers (muscle spindle)                          |
| A $\delta$    | Small    | Yes                | 5-35                      | Pain (sharp), temperature (cold), crude touch                        |
| B             | Smaller  | Lightly myelinated | 3-15                      | Preganglionic autonomic fibers                                       |
| C (somatic)   | Smallest | No                 | 0.5-2                     | Pain (dull/burning), temperature (warm),                             |
| C (autonomic) | Smallest | No                 | 0.5-2                     | Postganglionic autonomic fibers                                      |

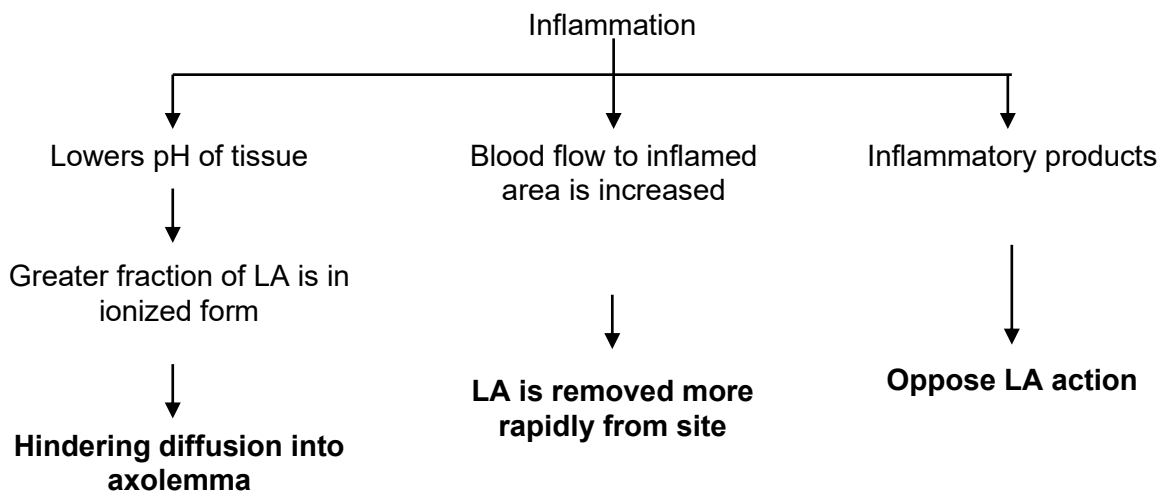
- **Order of blockade of fibres** →
  - Autonomic > Sensory > Motor
  - B > C > A $\delta$  > A $\alpha$ ,  $\beta$  &  $\gamma$
- **Order of recovery of fibres** → in reverse order.
- **Myelinated nerves > nonmyelinated**
- **Smaller fibres > larger fibres**
- **Sensory nerve block** →
  - Among sensory afferent order of block is →
    - Temperature (cold > heat) > Pain > touch > deep pressure
  - Taste → When applied to tongue →
    - Bitter taste is lost first > sweet > sour > salty taste
- **Motor nerve block** → desirable but it also limits patient's ability to cooperate for example during labor.



- **Autonomic nerve block** → lead to hypotension.

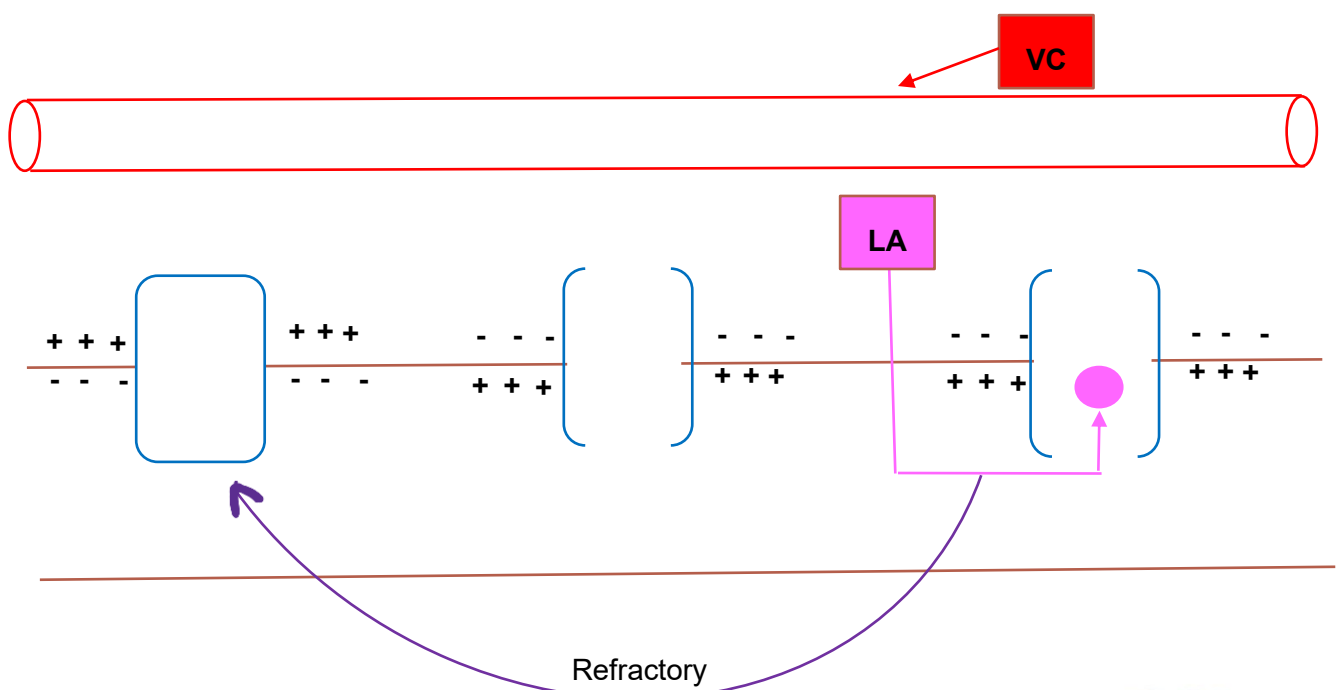
## 2. LA in Inflammation

- LA fails to afford adequate pain control in inflamed tissues (like infected tooth) →



## 3. Addition of a vasoconstrictor

- Vasoconstrictors (adrenaline or felypressin) → used along with LAs



## Advantages

1. Prolongs duration of action of LAs → by decreasing their rate of removal from local site into circulation → contact time of LA with the nerve fibre is prolonged.



- Enhances intensity of nerve block.
- Reduces systemic toxicity of LAs → rate of absorption is reduced
- Provides a more bloodless field for surgery



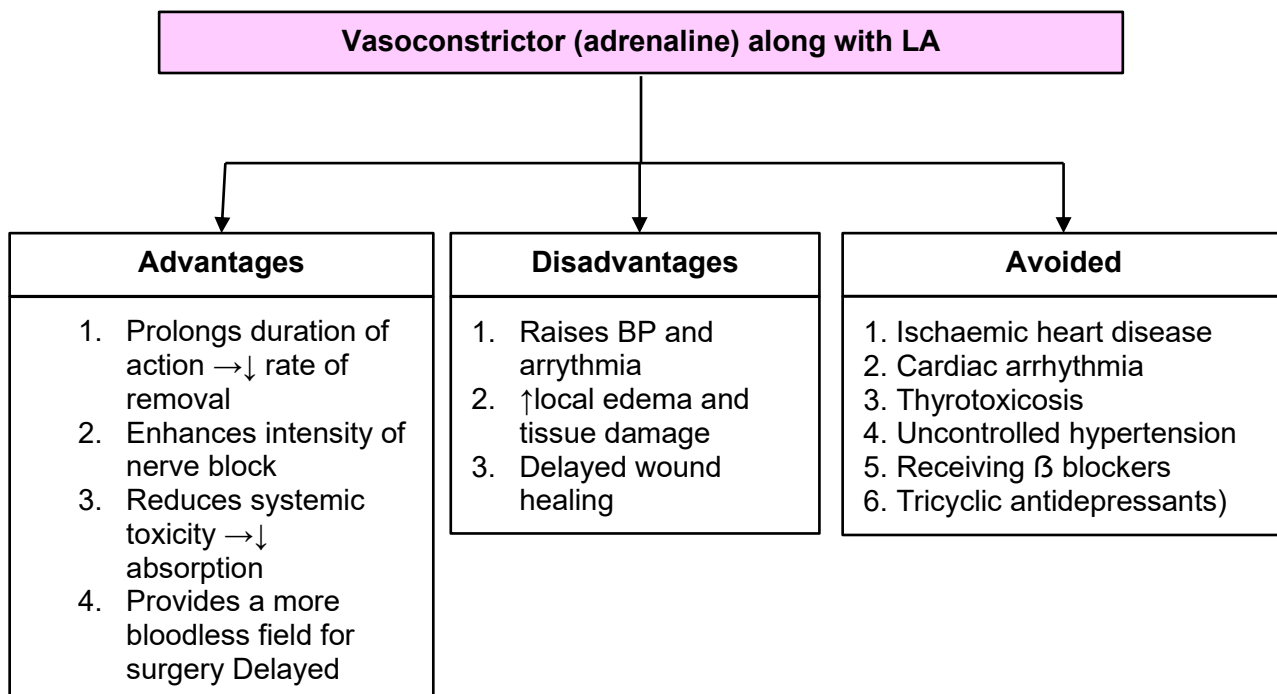
### Disadvantages

- Increases chances of subsequent local tissue edema and necrosis
- Delays wound healing → by reducing oxygen supply in affected area → Co-administration of vasoconstrictor is contraindicated for organs supplied with end arteries like digits, toes, earlobe, nose and penis → there is risk of hypoxia, necrosis and gangrene.
- Raise BP and promote arrhythmia → in susceptible individuals



### Avoided

- Ischaemic heart disease
- Cardiac arrhythmia
- Thyrotoxicosis
- Uncontrolled hypertension
- Receiving  $\beta$  blockers (rise in BP can occur due to unopposed  $\alpha$  action)
- Tricyclic antidepressants (uptake blockade and potentiation of Adrenalin)



## B) Systemic Actions

- Any LA injected or applied locally is ultimately absorbed and can produce systemic effects depending on the concentration attained in the plasma and tissues.

### 1. CNS

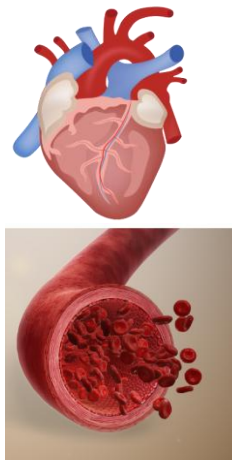
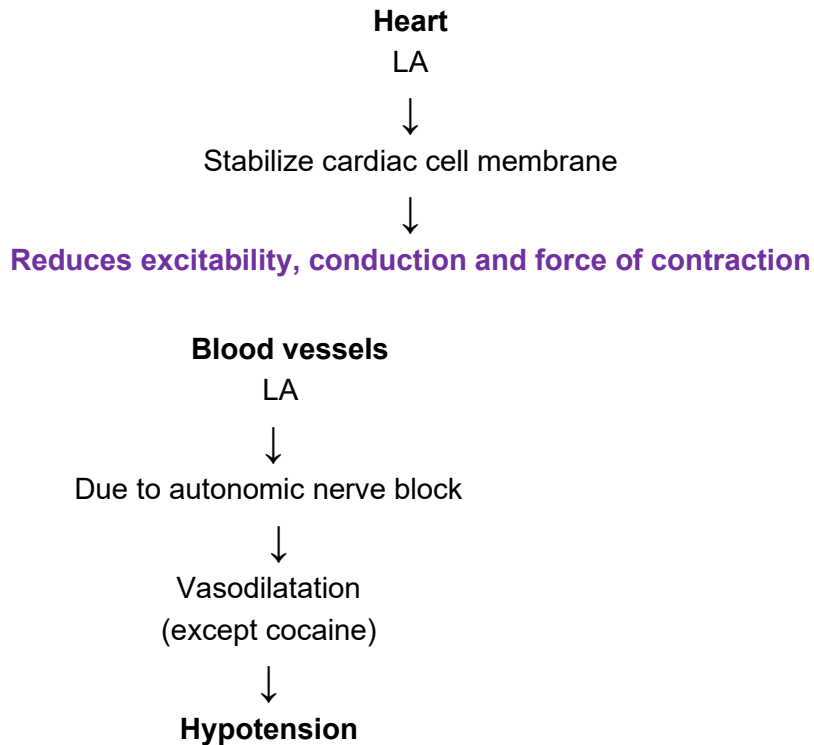
LA  
↓

Initial stimulation  
(due to inhibition of inhibitory neurons)  
↓  
Followed by depression



- So there may be restlessness, tremors, convulsions, respiratory failure and death.

## 2. CVS



## ADVERSE EFFECTS

- (1) CNS effects
- (2) CVS effects
- (3) Local effects
- (4) Hypersensitivity reactions
- (5) Methemoglobinemia

### (1) CNS effects

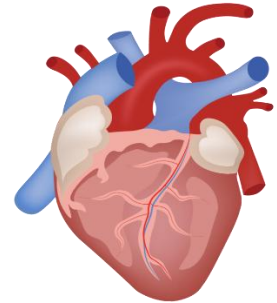
- Light-headedness
- Dizziness, auditory
- Visual disturbances
- Mental confusion
- Disorientation
- Shivering
- Twitchings



- Involuntary movements
- Finally convulsions and respiratory arrest.
- Can be prevented and treated by → **Diazepam**

## (2) CVS effects

- Bradycardia
- Hypotension
- Cardiac arrhythmias
- Vascular collapse



## (3) Local effects

- Injection of LAs may be painful
- Wound healing may be sometimes delayed.
- Addition of vasoconstrictors enhances local tissue damage → rarely necrosis
- **Bupivacaine** → highest local tissue irritancy.

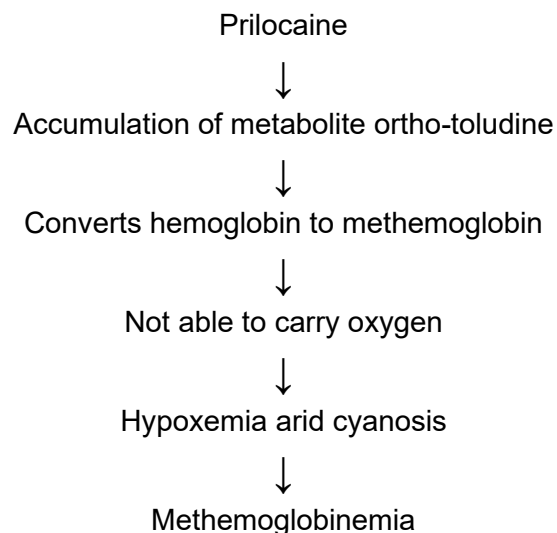


## (4) Hypersensitivity reactions

- Common with **ester-linked LAs**
  - Rashes
  - Angioedema
  - Dermatitis
  - Contact sensitization
  - Asthma
  - Anaphylaxis

## (5) Methemoglobinemia

- Occurs with **prilocaine**



- **Treatment** → oxygen and methylene blue.

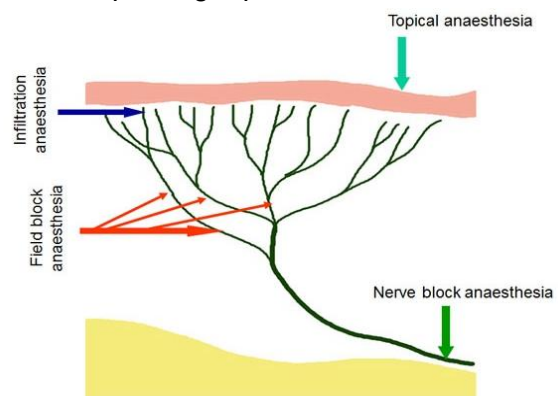
## TECHNIQUES OF LOCAL ANAESTHESIA

- A. Surface anaesthesia
- B. Infiltration anaesthesia
- C. Conduction block
- D. Spinal anaesthesia
- E. Epidural anaesthesia
- F. Intravenous Regional Block (Bier's Block)

### A. SURFACE ANAESTHESIA

#### Technique

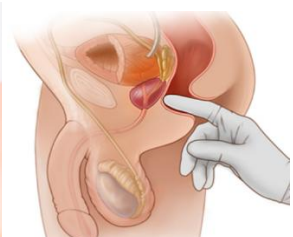
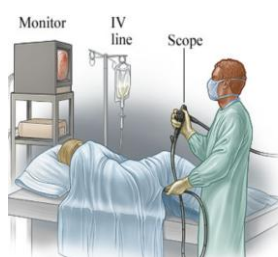
- **Produced by** → Topical application of a surface anaesthetic to → skin, cornea, mucous membrane of nose, mouth, throat, tracheobronchial tree, esophagus and genitourinary tract.
- Only superficial layer is anaesthetised
- No loss of motor function.
- Addition of Adr does not affect duration of topical anaesthesia
- Phenylephrine can cause mucosal vasoconstriction and prolong topical anaesthesia.



#### Uses

##### 1. Lignocaine

- Commonly used agent for topical anaesthesia of mucous membranes of nose, ear, eye, mouth and pharynx.
- Used during →
  - Proctoscopy
  - Catheterization
  - Per rectal examinations
- Lignocaine is ineffective on intact skin



##### 2. A mixture of 2.5% prilocaine and 2.5% lignocaine in 1:1 ratio

- Anaesthetize even unbroken skin.



A mixture of 2.5% prilocaine and 2.5% lignocaine in 1:1 ratio  
 ↓  
 Combination of these two agents lowers melting point of individual drugs  
 ↓  
 Helps to form a semi-solid ointment.  
 ↓  
 Eutectic mixture



### 3. Oxethazaine (mucaine)

- Remains unionized in the acidic pH of stomach
- Used to provide symptomatic relief in gastritis



## B. INFILTRATION ANAESTHESIA

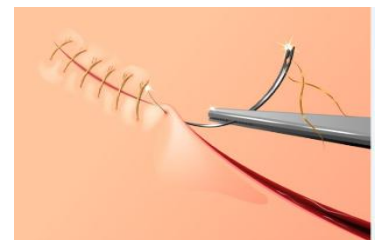
### Technique

- **Dilute solution of LA is infiltrated under skin** → in area of operation without taking into consideration course of cutaneous nerve → blocks sensory nerve endings
- **Relatively larger amount of LA** → required compared to the area anaesthetized
- **Motor function is not affected.**
- **Adrenaline** → can be added to LA to prolong its duration of action and to prevent systemic side effects.



### Uses

- Used in minor surgeries like → incisions, excisions, suturing, hydrocele etc.



## C. CONDUCTION BLOCK

### Technique

- LA is injected around nerve trunks so that the area distal to injection is anaesthetised and paralysed

### Types

- Field block
- Nerve block

#### (a) Field block

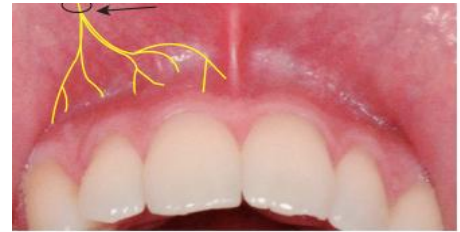
- It is produced by injecting the LA → subcutaneously in a manner that all nerves coming to a particular field are blocked



- **Uses** → for herniorrhaphy, appendicectomy, dental procedures, scalp stitching, operations on forearms and legs, etc

## (b) Nerve block

- It is produced by injecting the LA → around the appropriate nerve trunks or plexuses.
- Area of resulting anaesthesia is still larger compared to the amount of drug used.
- Muscles supplied by the injected nerve/plexus are paralysed.



## D. SPINAL ANAESTHESIA

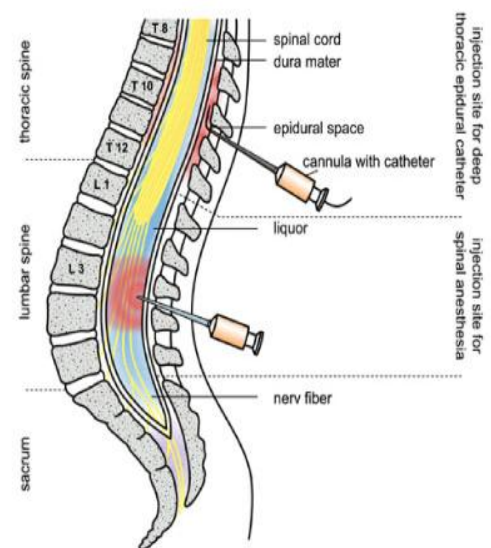
### Technique

Spinal cord terminates above the level of L2



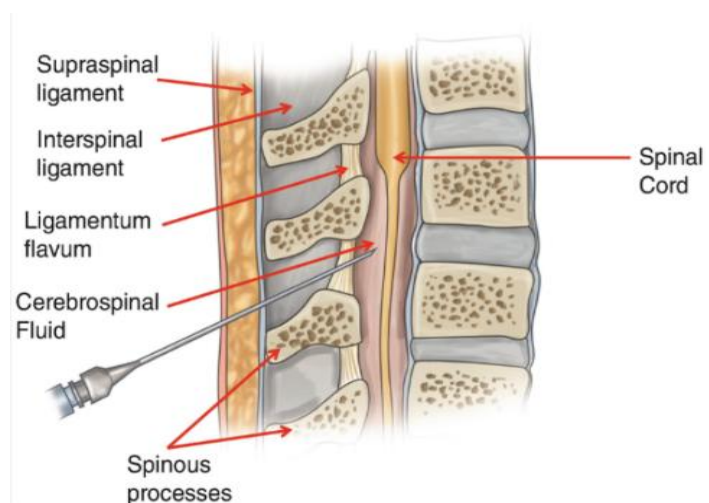
LA is injected below this level (L2) in the subarachnoid space, usually between L2–3 or L3–4

- In a child it terminates at further lower level, at lower border of L3, so spinal injection is given at L4-L5 level
- Primary site of action → nerve roots in the cauda equina rather than the spinal cord.
- Nerve roots rapidly take up and retain the LA, therefore, its concentration in CSF falls quickly after injection.
- Lower abdomen and hind limbs are anaesthetized and paralysed.
- Duration of spinal anaesthesia depends on → drug used and its concentration.
- Addition of 0.2–0.4 mg of Adrenaline to LA prolongs spinal anaesthesia by about 1/3rd



### Structures encountered during lumbar puncture

1. Skin
2. Subcutaneous tissue
3. Supraspinous ligament
4. Interspinous ligament
5. Ligamentum flavum
6. Duramater
7. Arachnoidmater



## Positions

1. Sitting



2. Lying



## Factors affecting Level of anaesthesia

Depends on →

1. Volume of injection
2. Speed of injection
3. Specific gravity of drug solution
4. Posture of patient

### 1. Volume of injection

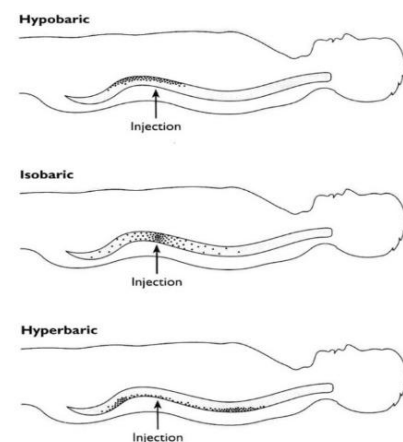
- **Higher volume** → spreads the anesthetic further up the spinal cord → leading to a higher level of block.

### 2. Speed of injection

- **Faster injection** → creates greater turbulence → promoting wider and higher spread of the drug.

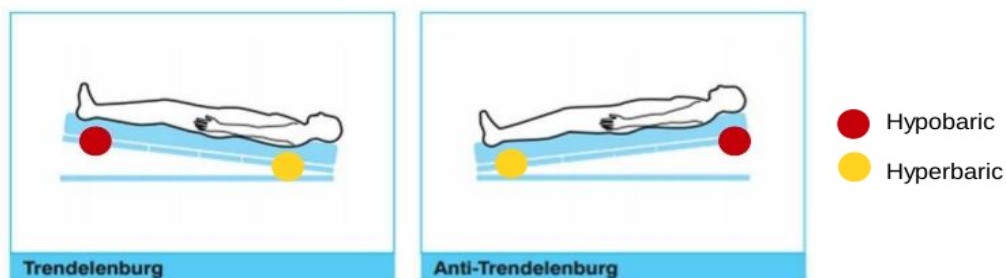
### 3. Specific gravity of drug solution

- **Injection of solution heavier than CSF** → Hyper baric
- **Injection of solution lighter than CSF** → Hypo baric
- Addition of glucose makes the solution Hyperbaric



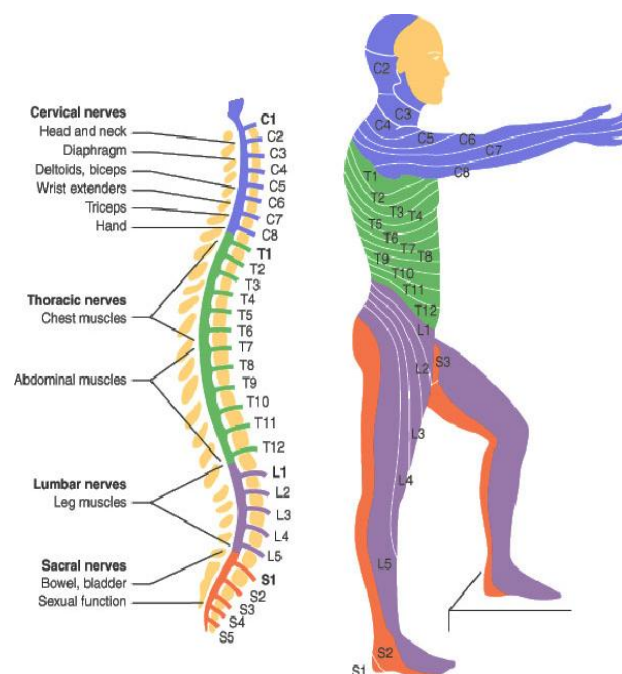
### 4. Posture of patient

- **With Head down position** → hyperbaric solution ascends in subarachnoid space
- **With Head up position** → hypobaric solution ascends in subarachnoid space



## Dermatomes

| Dermatomal Levels of Spinal Anesthesia for Common Surgical Procedures |                         |
|-----------------------------------------------------------------------|-------------------------|
| Procedure                                                             | Dermatomal Level        |
| Upper abdominal surgery                                               | T4                      |
| Intestinal, gynecologic, and urologic surgery                         | T6                      |
| Transurethral resection of the prostate                               | T6                      |
| Vaginal delivery of a fetus, and hip surgery                          | T10                     |
| Thigh surgery and lower leg amputations                               | L1                      |
| Foot and ankle surgery                                                | L2                      |
| Perineal and anal surgery                                             | S2 to S5 (saddle block) |



## Sequence of block

- Autonomic preganglionic fibres are more sensitive
- Somatic motor fibres less sensitive than somatic sensory fibres
- **Autonomic > Sensory > Motor**
  - Level of sympathetic block is about 2 segments higher than the level of cutaneous analgesia
  - Level of motor paralysis about 2 segments lower than the level of cutaneous analgesia

## Uses

- Spinal anaesthesia is used for operations on→
  1. Lower limbs
  2. Pelvis
  3. Lower abdomen, e.g. prostatectomy
  4. Fracture setting
  5. Obstetric procedures
  6. Caesarean section

## Advantages of spinal anaesthesia over general anaesthesia

1. It is safer
2. Produces good analgesia and muscle relaxation without loss of consciousness.
3. Cardiac, pulmonary, renal disease and diabetes pose less problem.

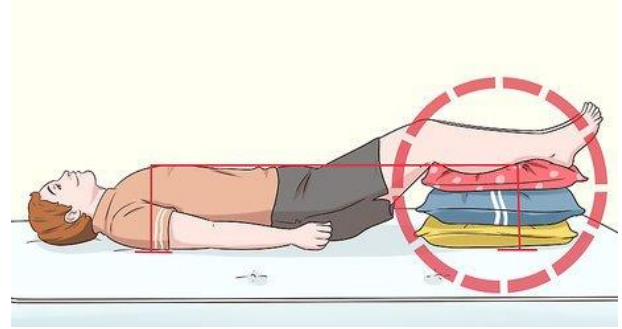
## Complications

1. Hypotension
2. Respiratory paralysis
3. Headache
4. Cauda equina syndrome
5. Septic meningitis
6. Nausea and vomiting



## 1. Hypotension

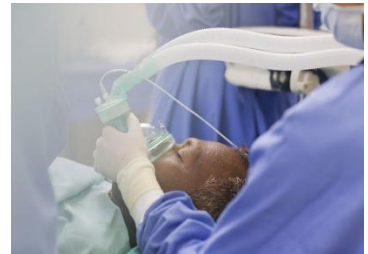
- **Due to** → Blockade of sympathetic vasoconstrictor outflow to blood vessels →
  - Arteriolar dilatation
  - Venous pooling → Decreased return to heart
  - Paralysis of skeletal muscles of lower limb → reducing venous return



- **Treatment** →
  - (a) Raising the foot end overcomes the hypotension by promoting venous drainage.
  - (b) Sympathomimetics with prominent constrictor effect on veins (ephedrine, mephentermine)

## 2. Respiratory paralysis

- Intercostal muscles may be paralysed, but diaphragm (supplied by phrenic nerve) maintains breathing.



## 3. Headache

- **Due to** → seepage of CSF
- **Known as** → Post dural puncture headache (PDPH)
- **Prevention** → Can be minimised by using smaller bore needle



## 4. Cauda equina syndrome

- Rare neurological complication resulting in prolonged loss of control over bladder and bowel sphincters.
- Due to traumatic damage to nerve roots or chronic arachnoiditis caused by inadvertent introduction of antiseptic in the subarachnoid space.

## 5. Septic meningitis

- Due to infection introduced during lumbar puncture.
- Actual incidence is very low in majority of hospitals.



## 6. Nausea and vomiting

- After abdominal operations
- Due to reflexes triggered by traction on abdominal viscera.
- **Prevention** → Premedication with opioid analgesics



## Remember

- Most common intraoperative complication → **Hypotension**
- Most common postoperative complication → **Post dural puncture headache (PDPH)**

## Contraindications

1. Hypotension and hypovolemia.
2. Uncooperative or mentally ill patients.
3. Infants and children—control of level is difficult.
4. Bleeding diathesis.
5. Raised intracranial pressure.
6. Vertebral abnormalities e.g. kyphosis, lordosis, etc.
7. Sepsis at injection site.

## E. EPIDURAL ANAESTHESIA

### Technique

- LA Injection in epidural space
- Prolonged by addition of adrenaline.
- Sympathetic block is not prominent → so there is less risk of hypotension and headache.
- But more concentration is absorbed in blood → increases the risk of systemic toxicity.
- Lidocaine (1–2%) and bupivacaine (0.25– 0.5%) → popular drugs for epidural anaesthesia.
- Technically epidural anaesthesia is more difficult than spinal anaesthesia and relatively larger volumes of drug are needed



### Types

- Epidural anaesthesia can be divided into 3 categories depending on site of injection.
  1. Thoracic
  2. Lumbar
  3. Caudal



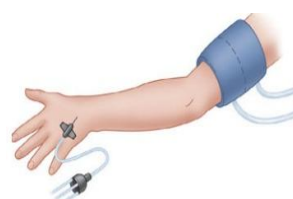
### Uses

1. Mainly used for controlling postoperative pain (by continuous epidural through a catheter).
2. All surgeries which can be performed under spinal anaesthesia.
3. Upper abdominal surgeries, thoracic surgeries and even neck surgeries.
4. Painless labour.
5. Chronic pain due to cancer and other conditions.

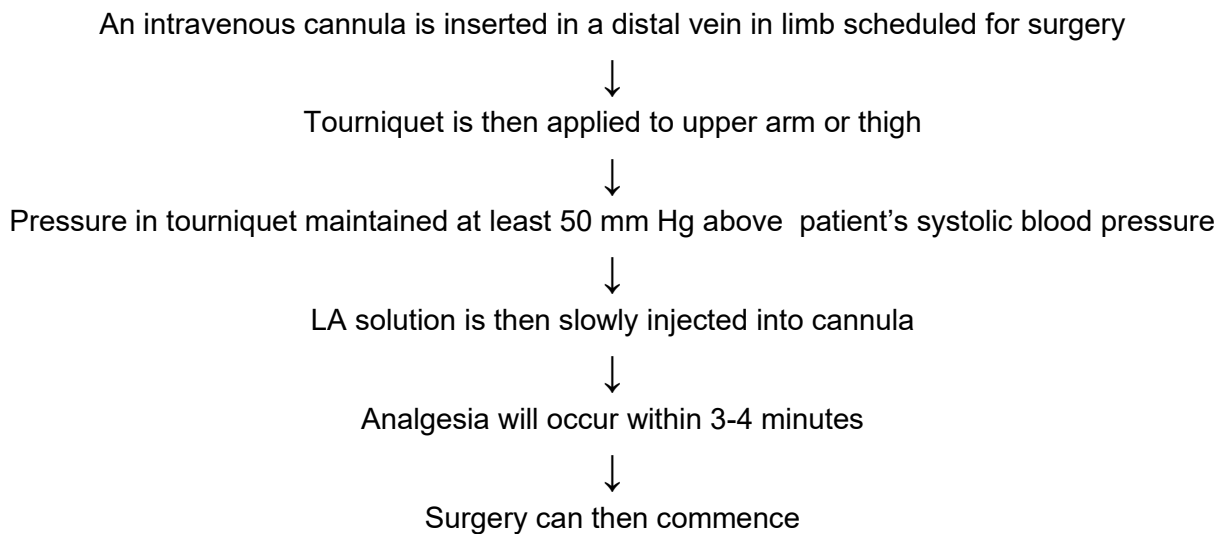
## F. INTRAVENOUS REGIONAL BLOCK (BIER'S BLOCK)

### Indication

- Any procedure on →
  - Arm below the elbow
  - Leg below the knee
 that will be completed within 40-60 minutes



## Technique



- Plain and not adrenaline-containing solutions are used.
- **DOC for IVRA** → Prilocaine → least toxic local anaesthetic and has largest therapeutic index.
- If prilocaine is not available → Lignocaine is an acceptable alternative.
- Bupivacaine should never be employed as it is too toxic, particularly to the myocardium

## INDIVIDUAL COMPOUNDS

### Cocaine

- Cocaine is a natural alkaloid, from leaves of *Erythroxylon coca*
- Blocks noradrenaline uptake so unlike other local Anesthetics → produces vasoconstriction, hypertension, tachycardia and mydriasis.
- All LAs are vasodilators except cocaine (act as sympathomimetic due to inhibition of nor-adrenaline reuptake) which is a vasoconstrictor.
- Therefore all LAs decrease BP except cocaine which increases BP
- Cocaine should NEVER be given by intravenous route or with adrenaline.
- Cocaine is the only ester which is not metabolized by pseudocholinesterase → metabolized in the liver.
- It is the drug of abuse with no tolerance.
- Chronic inhalation may lead to necrosis and perforation of nasal septum.
- It may give black color to teeth and tongue.
- Amyl nitrite inhalation is specific antidote

### Procaine

- First synthetic local anesthetic
- Ester with low potency, slow onset, and short duration of action
- Its use is confined to infiltration anesthesia and occasionally for diagnostic nerve blocks.
- Procaine is most potent vasodilator used for treatment of arteriospasm due to intraarterial injection of thiopental that otherwise could lead to tissue death, gangrene and loss of limb.
- It is also preferred in malignant hyperthermia since lignocaine releases calcium from sarcoplasmic reticulum and hence contraindicated.

## Chlorprocaine

- Shortest acting local anesthetic agent.
- Preservative sodium metabisulfite carries a high potential of producing paraplegia with spinal anesthesia → So it is contra-indicated in spinal anaesthesia
- Newer preparations are having Ca EDTA as preservative.

## Tetracaine

- Rarely used in peripheral nerve blocks because of its potential for toxicity.
- It is incorporated into several topical anesthetic preparations.

## Lidocaine (Lignocaine)

- Prototypical amide local anesthetic that produces an intense, long lasting effect
- Is useful for almost all the form of local anesthesia.
- It is also used as an antiarrhythmic agent by i/v route as a preservative free preparation for ventricular arrhythmias
- Dose is limited to →
  - (a) 7 mg/kg with adrenaline
  - (b) 4 mg/kg without adrenaline.
- A mixture of 2.5% prilocaine and 2.5% lignocaine in 1:1 ratio can anaesthetize even unbroken skin.
- Combination of these two agents lowers the melting point of individual drugs and helps to form a semi-solid ointment → This mixture is known as Eutectic mixture.
- It can precipitate malignant hyperthermia due to release of calcium

## Prilocaine

- Prilocaine is an intermediate-acting amide that causes less vasodilatation and thus can be used without a vasoconstrictor
- It has less potential for CNS toxicity.
- Accumulation of metabolite ortho-toluidine converts hemoglobin to methemoglobin, which is not able to carry oxygen, hence there's hypoxemia and cyanosis.
- It is the most suitable LA for Bier's block

## Bupivacaine

- Bupivacaine is an amide local anesthetic with greater-potency and longer duration but with a high potential for cardiac and neurological toxicity.
- Levobupivacaine the S-enantiomer of bupivacaine is equally effective with a less potential for CNS and cardiotoxicity.
- Most common ECG changes in bupivacaine toxicity → slow idioventricular rhythm with broad QRS complex.
- Bretylium → DOC for bupivacaine induced ventricular tachycardia.
- Best drug for regional block but it is also the most cardiotoxic LA.
- Due to cardiotoxic effect, it should not be used for Bier's block.

## Dibucaine

- Most potent, longest acting



- Most toxic LA

## Ropivacaine

- Suitable for both epidural and regional anesthesia, with duration of action similar to that of bupivacaine.
- Ropivacaine is less cardiotoxic congener of bupivacaine.

## Oxethazaine (mucaine)

- Can be used to provide symptomatic relief in gastritis
- It remains unionized in acidic pH of stomach

## REMEMBER

- **Chlorprocaine** → shortest acting LA.
- **Dibucaine** → longest acting; most potent and most toxic LA
- **Bupivacaine** → most cardiotoxic LA (Ropivacaine is a newer bupivacaine congener with less cardiotoxicity).
- **Bupivacaine** → highest local tissue irritancy
- **Levobupivacaine** → S (-) enantiomer of bupivacaine → less cardiotoxic and less prone to cause seizure.
- **Prilocain** → can cause Methaemoglobinemia
- **Lignocaine** → most commonly used LA.
- **Chorprocaine** → contraindicated in spinal anaesthesia as it can cause paraplegia due to presence of neurotoxic preservative sodium metabisulphite
- **Procaine** → LA of choice in malignant hyperthermia.
- **Cocaine** → In periphery blocks uptake of Adr and NA in adrenergic nerve endings thus producing peripheral sympathetic action
- **All LAs are vasodilators except cocaine** → which causes vasoconstriction.

## LA causing methemoglobinemia

- **B** - Benzocaine
- **P** - Prilocaine (Max)
- **L** - Lignocaine

## Concentration of LA in different uses

|              | Lignocaine | Bupivacaine |
|--------------|------------|-------------|
| Infiltration | 0.5-2      | 0.25-0.5    |
| Spinal       | 5          | 0.5         |
| Epidural     | 2          | 0.5         |

## Potency

- **Dibucaine** → most potent local anaesthetic
- **Procaine and chorprocaine** → least potent

## Decreasing Order of potency

- Dibucaine > Ropivacaine = Bupivacaine = etidocaine - Tetracaine > Lidocaine > Pritocaine > Mepivacaine ~ Cocaine > Procaine & chlorprocaine.
- **D > R = B = E - T > L > P > M ~ C > P & C**

## Mnemonic

**Don't Ride Big Elephants – They're Large, Prickly Monsters Causing Pain Constantly**

- **Don't** → Dibucaine
- **Ride** → Ropivacaine
- **Big** → Bupivacaine
- **Elephants** → Etidocaine
- **They're** → Tetracaine
- **Large** → Lidocaine
- **Prickly** → Pritocaine
- **Monsters** → Mepivacaine
- **Causing** → Cocaine
- **Pain** → Procaine
- **Constantly** → Chlorprocaine

## Duration of action

- **Dibucaine** → longest acting local anaesthetic
- **Chlorprocaine** → shortest acting local anaesthetic

## Decreasing order of duration

- Dibucaine > Bupivacaine = Tetracaine ~ Ropivacaine > Etidocaine > Priocaine = Lignocaine = Mepivacaine > Cocaine > Procaine > Chlorprocaine
- **D > B = T ~ R > E > P = L = M > C > P > C**

## Mnemonic

**Deadly Bats Take Risks Every Party Like Madness, Causing Pain Constantly**

- **Deadly** → Dibucaine (most potent)
- **Bats** → Bupivacaine
- **Take** → Tetracaine
- **Risks** → Ropivacaine
- **Every** → Etidocaine
- **Party** → Prilocaine
- **Like** → Lignocaine
- **Madness** → Mepivacaine
- **Causing** → Cocaine
- **Pain** → Procaine
- **Constantly** → Chlorprocaine (least potent)



# Drugs acting on CNS

CHAPTER

## 10

### CONTENT

1. Sedative-Hypnotics
2. Alcohols
3. Antiparkinsonian Drugs
4. Antiepileptic Drugs
5. Antipsychotic and Antimanic Drugs
6. Antidepressant and Antianxiety Drugs
7. General Anaesthetics
8. Opioid Analgesics and Antagonists

### SEDATIVES AND HYPNOTICS

#### Definition

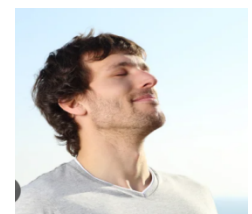
- **Hypnotic**

- Agent that produces sleep (Hypnos (in Greek) = Sleep).
- Drugs are used to treat insomnia



- **Sedative**

- Agent that quietens the patient and makes him drowsy without inducing sleep.
- Calms the patient, i.e. it reduces tension and anxiety.



#### Sleep

- Duration and pattern of sleep varies considerably among individuals.
- Age has an important effect on quantity and depth of sleep.
- Sleep is an architected cyclic process



#### EEG waves

EEG waves have been divided into→

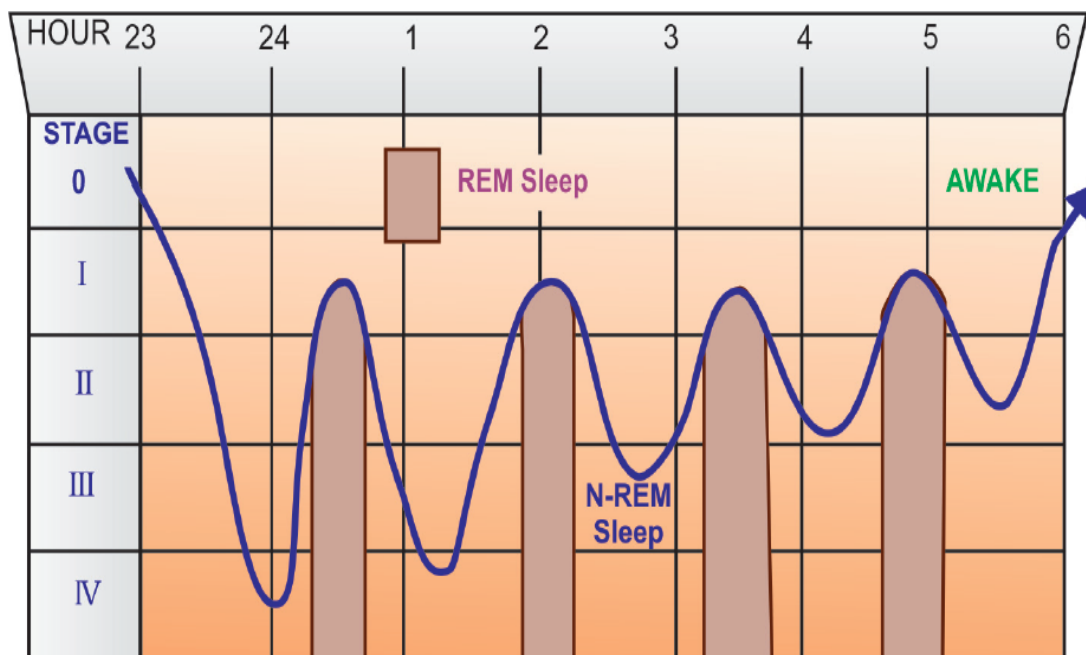
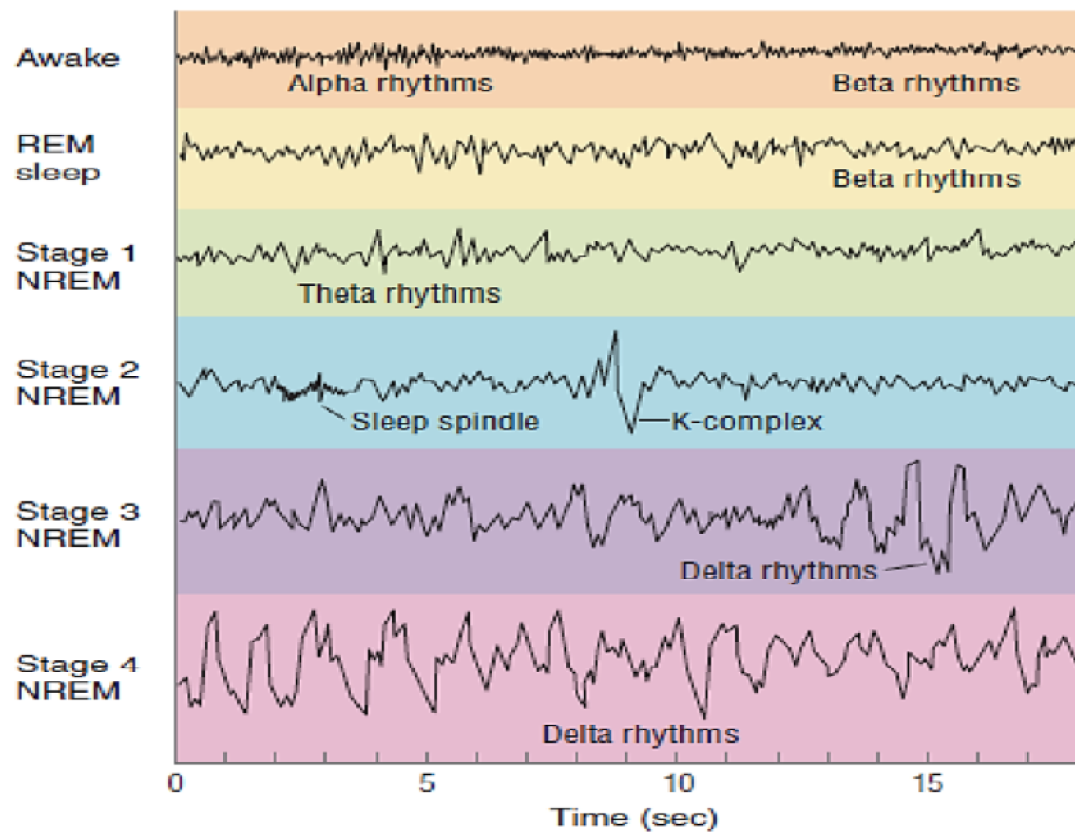
**α:** high amplitude, 8-14 c.p.s. (cycles per second)

**β:** low amplitude, 15-35 c.p.s.

**θ:** low amplitude, 4-7 c.p.s.

**δ:** high amplitude, 0.5-3 c.p.s.

**K complex:** deep negative wave followed by positive wave and a few spindles.



## NREM

1. Stage 0
2. Stage 1
3. Stage 2
4. Stage 3
5. Stage 4

### 1. Stage 0 (awake)

- From lying down to falling asleep and occasional nocturnal awakenings
- EEG shows  $\alpha$  activity when eyes are closed and  $\beta$  activity when eyes are open.
- Eye movements are irregular or slowly rolling
- Constitutes 1–2% of sleep time.

### 2. Stage 1 (dozing)

- $\alpha$  activity is interspersed with  $\theta$  waves.
- Eye movements are reduced but there may be bursts of rolling.
- Neck muscles relax.
- Occupies 3–6% of sleep time.

### 3. Stage 2 (unequivocal sleep)

- $\theta$  waves with interspersed spindles → K complexes
- Can be evoked on sensory stimulation
- Little eye movement
- Subjects are easily arousable.
- Comprises 40–50% of sleep time.

### 4. Stage 3 (deep sleep transition)

- EEG shows  $\theta$ ,  $\delta$  and spindle activity, K complexes
- Can be evoked with strong stimuli only.
- Eye movements are few
- Subjects are not easily arousable;
- Comprises 5–8% of sleep time.

### 5. Stage 4 (cerebral sleep)

- $\delta$  activity predominates in EEG, K complexes cannot be evoked.
- Eyes are practically fixed
- Subjects are difficult to arouse.
- Night terror may occur at this time.
- Comprises 10–20% of sleep time

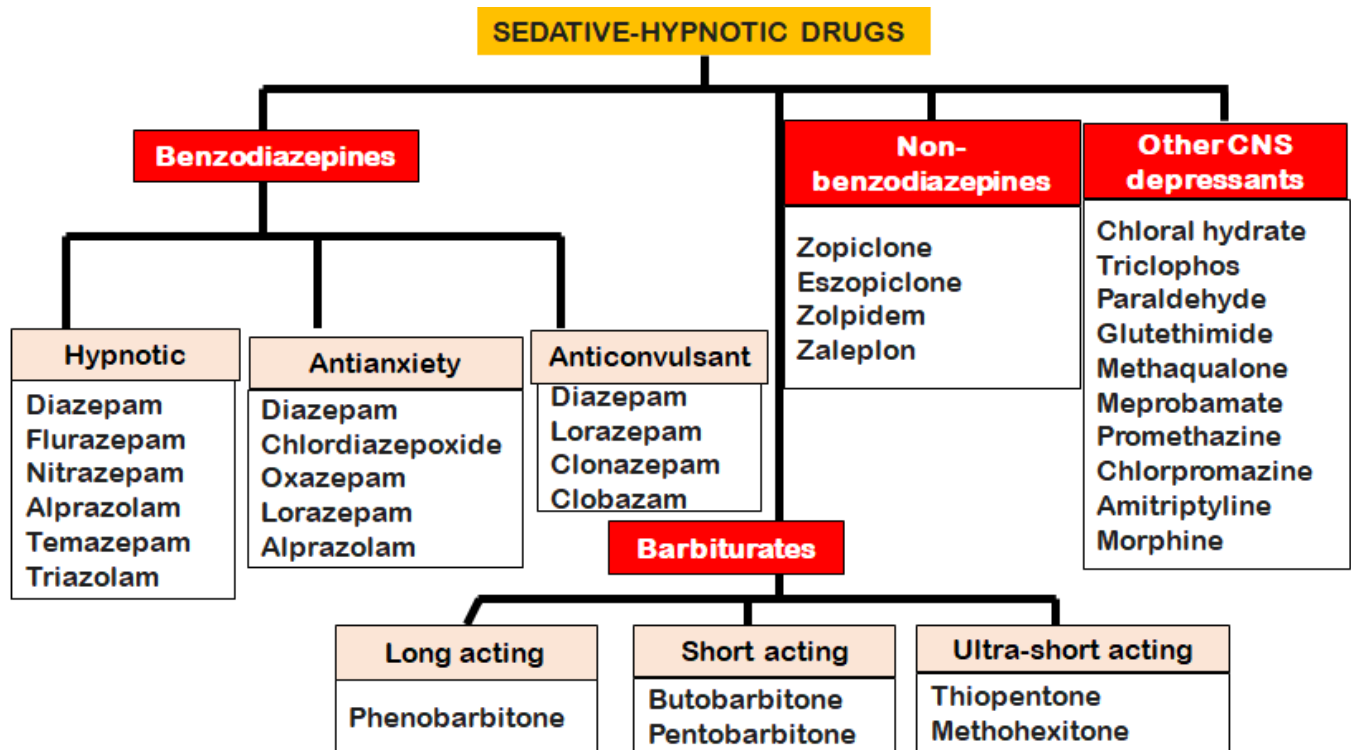
### REM sleep (paradoxical sleep)

- EEG has waves of all frequency, K complexes cannot be elicited.
- Marked, irregular and darting eye movements
- Dreams and nightmares occur, which may be recalled if subject is aroused.
- Heart rate and BP fluctuate
- Respiration is irregular.
- Muscles are fully relaxed, but irregular body movements occur occasionally.
- Erection occurs in males.
- Constitutes 20–30% of sleep time is spent in REM.

## Remember

- Normally stages 0 to 4 and REM occur in succession over a period of 80–100 min.
- Then stages 1–4–REM are repeated cyclically.

## Classification

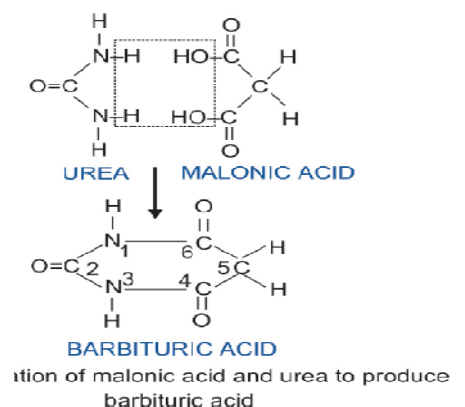


|                         | Barbiturates | Benzodiazepines | Non-benzodiazepine Agonists |
|-------------------------|--------------|-----------------|-----------------------------|
| Introduction            |              |                 |                             |
| Classification          |              |                 |                             |
| MOA                     |              |                 |                             |
| Pharmacological Actions |              |                 |                             |
| Interactions            |              |                 |                             |
| Use                     |              |                 |                             |
| Adverse effects         |              |                 |                             |

## BARBITURATES

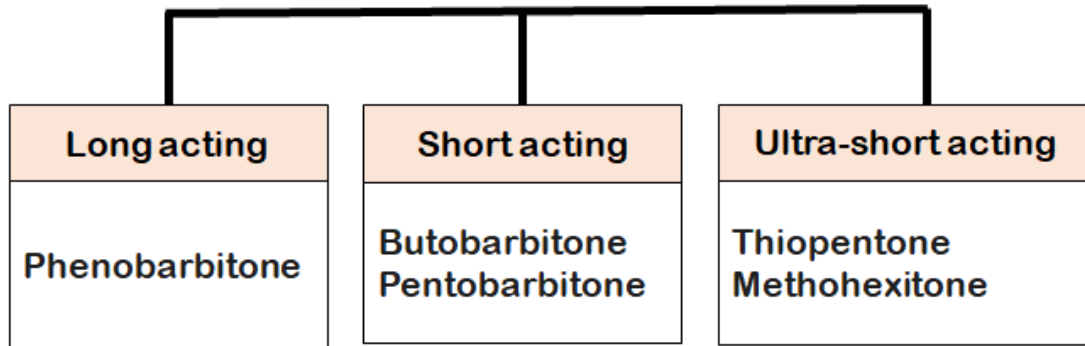
### Introduction

- Barbiturates are substituted derivatives of barbituric acid (malonyl urea).



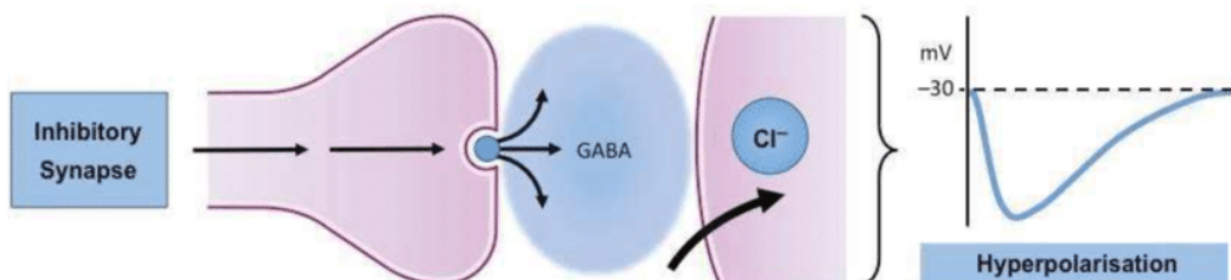
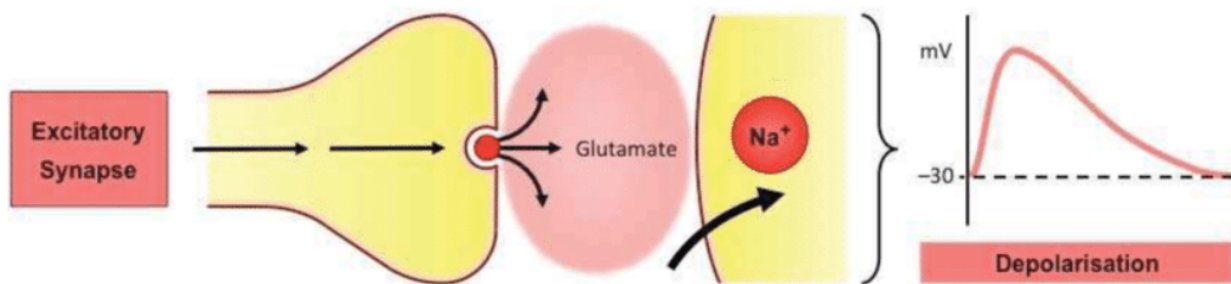
## Introduction

Barbiturates are substituted derivatives of barbituric acid (malonyl

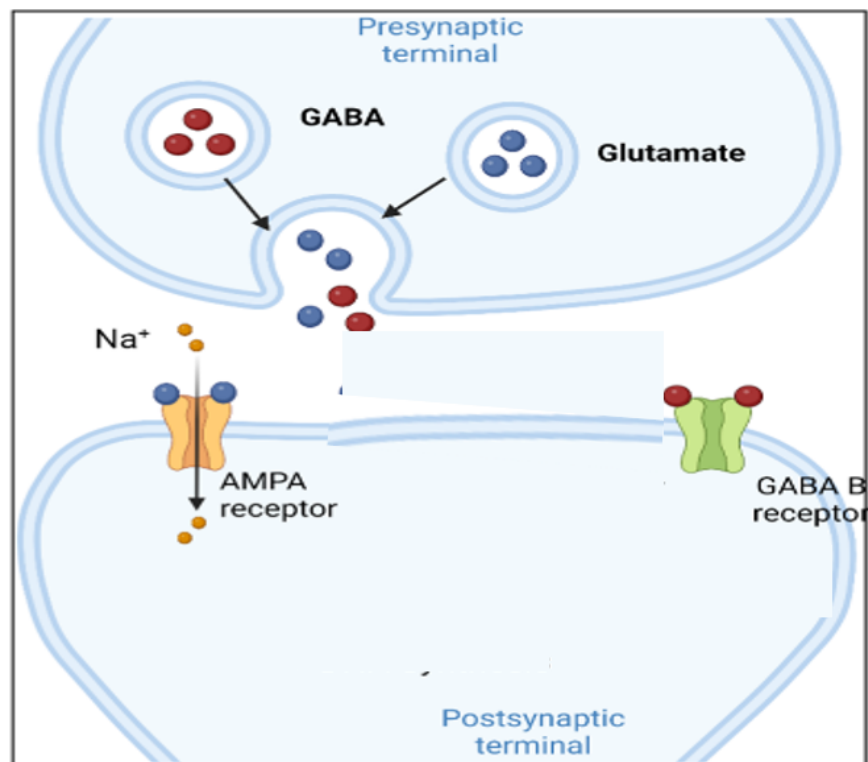


## Introduction

- **GABA** → inhibitory neurotransmitter
- **Glutamate** → excitatory neurotransmitter

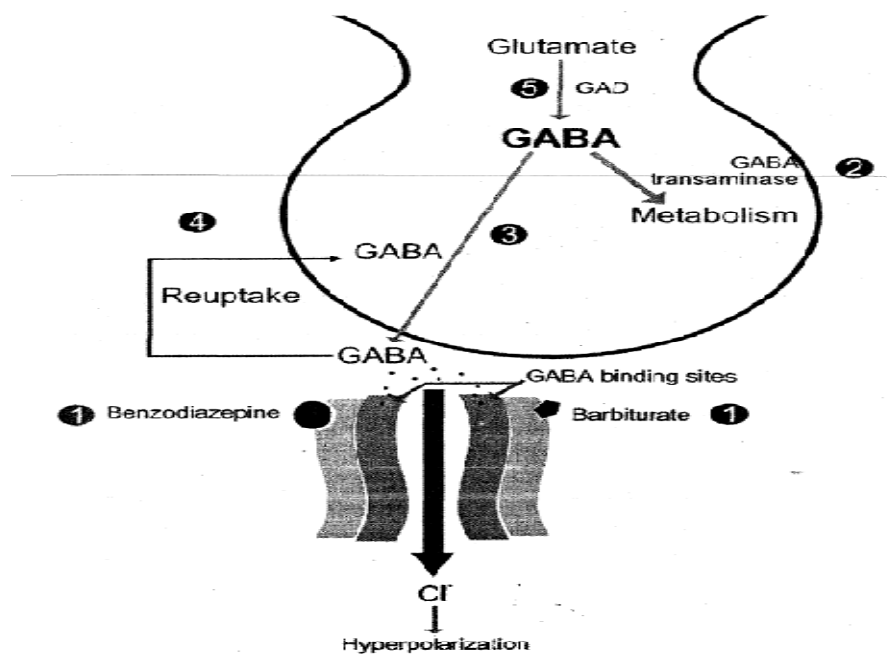






## GABA (gamma amino butyric acid)

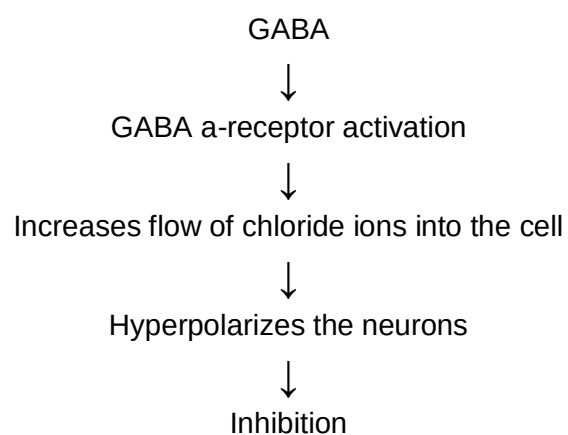
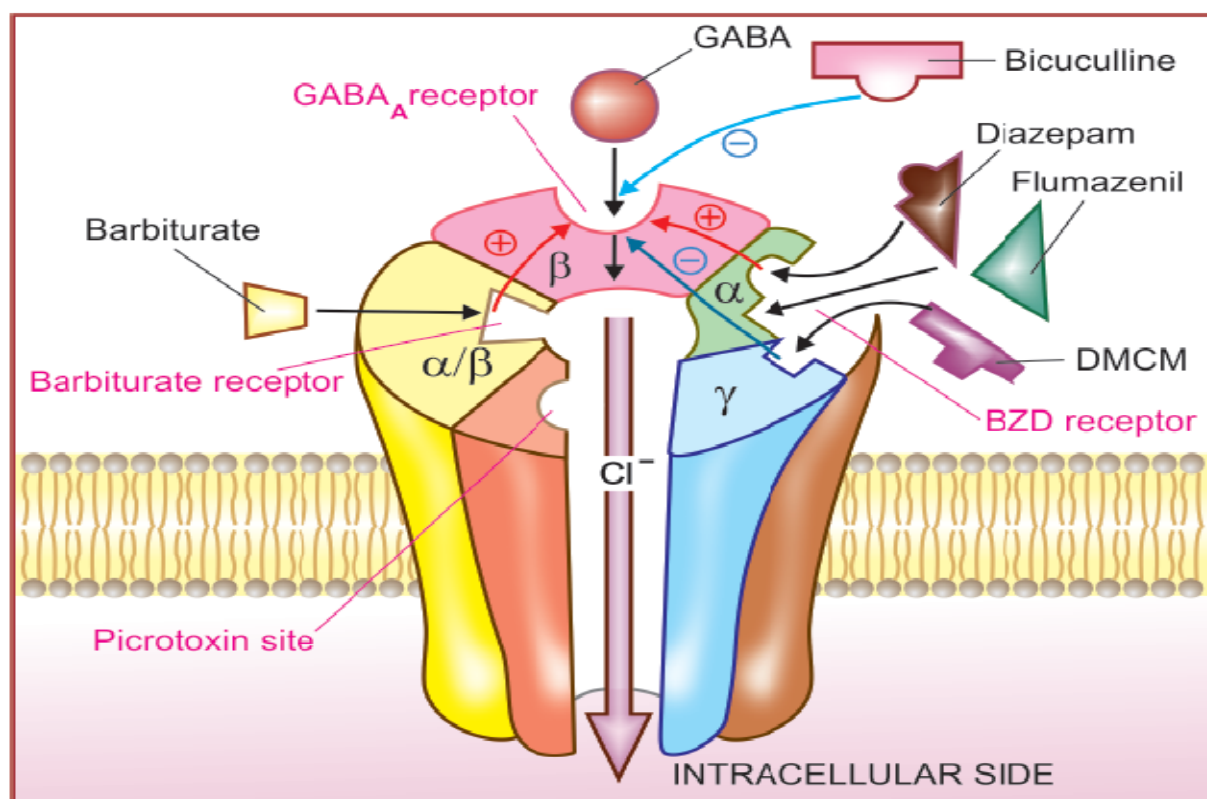
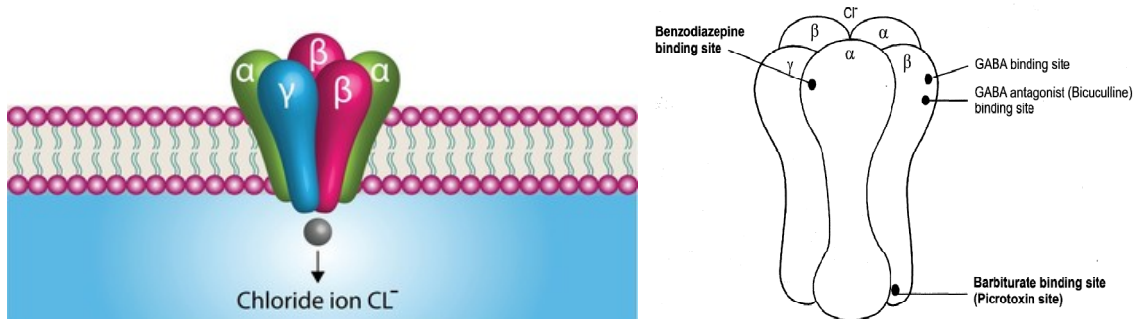
- Inhibitory neurotransmitter in CNS
- Synthesized from glutamate by GAD (glutamic acid decarboxylase).
- Removed mainly by neuronal uptake and partly by deamination catalyzed by GABA transaminase.
- Acts on two different types of receptors namely GABA<sub>A</sub> and GABA<sub>B</sub>





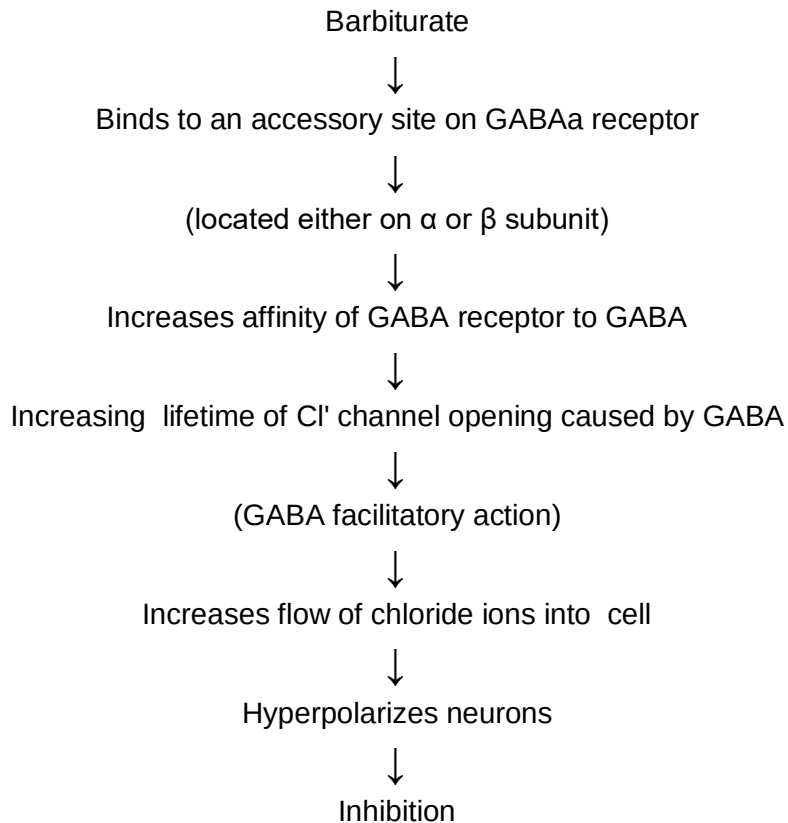
## GABA<sub>A</sub> receptor

- Pentameric structure consisting of → 2α, 2β and 1γ subunits.
- Ionotropic receptor → Directly coupled to chloride channels

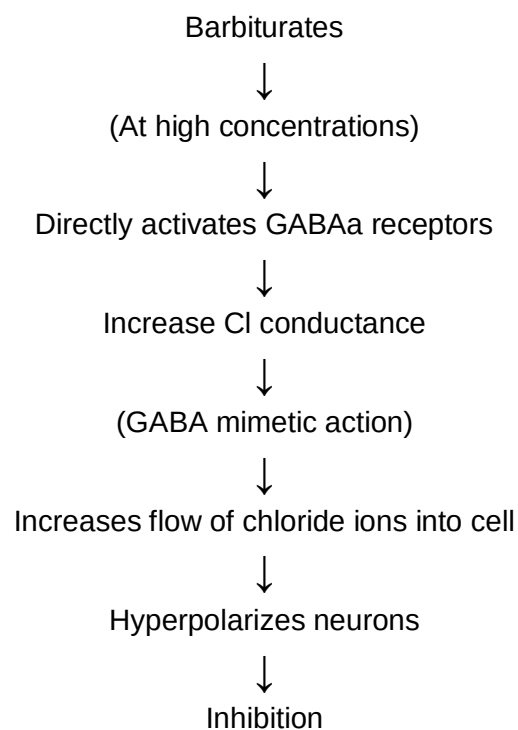


- Barbiturates acts by 3 Mechanisms →
  1. GABA facilitatory action
  2. GABA mimetic action
  3. Through AMPA receptors

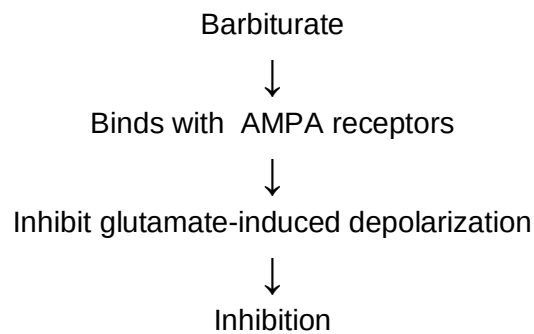
## 1. GABA facilitatory action



## 2. GABA mimetic action



### 3. Through AMPA receptors



## Pharmacological actions

1. CNS
2. Respiration
3. Skeletal muscle
4. CVS
5. Kidney

### 1. CNS

- Barbiturates depress all areas of CNS, but reticular activating system is most sensitive.
- Barbiturates produce dose-dependent effects:

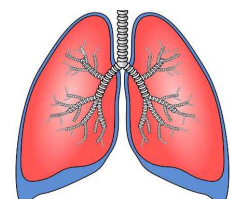
**Sedation → sleep → anaesthesia → coma**

- a) Sleep latency (time taken to fall asleep) is shortened
  - b) Sleep duration is increased.
  - c) Sleep architecture is disturbed (REM, stage 3,4 sleep are decreased).
- Sleep is arousable, but the subject may feel confused and unsteady if woken early.
  - Night awakenings are reduced.
  - Hangover (dizziness, distortions of mood, irritability and lethargy) may occur in the morning after a nightly dose.
  - Impair learning, shortterm memory and judgement
  - No analgesic action, may even cause hyperalgesia (Diazepam has analgesic action).
  - Anticonvulsant property



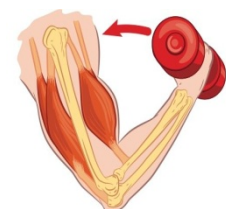
### 2. Respiration

- Respiration is depressed by relatively higher doses.



### 3. Skeletal muscle

- Hypnotic doses have little effect but anaesthetic doses reduce muscle contraction by action on neuromuscular junction.



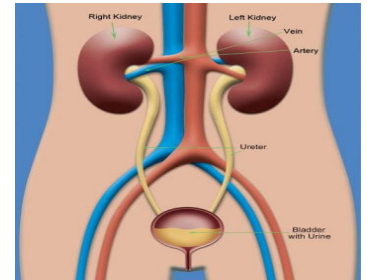
## 4. CVS

- Hypnotic doses of barbiturates produce a slight decrease in BP and heart rate.
- Toxic doses produce → marked fall in BP due to vasomotor centre depression
- Reflex tachycardia occur



## 5. Kidney

- Barbiturates → reduce urine flow by decreasing BP and increasing ADH release.
- Oliguria attends barbiturate intoxication.



## Interactions

1. Barbiturates induce several hepatic microsomal enzymes and increase rate of their own metabolism as well as that of many other drugs → **warfarin, steroids (including contraceptives), tolbutamide, griseofulvin, chloramphenicol, theophylline**
2. **Other CNS depressants** → alcohol, antihistamines, opioids, etc. → Additive action w
3. **Sodium valproate** → increases plasma concentration of phenobarbitone.
4. **Griseofulvin** → Phenobarbitone decreases absorption of griseofulvin from g.i.t

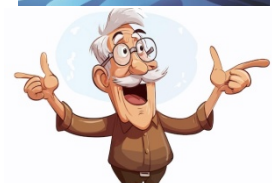
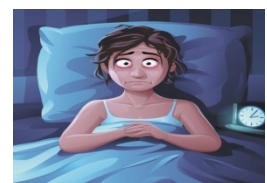
## Uses

1. **Phenobarbitone** → in epilepsy
2. **Thiopentone** → in anaesthesia
  - No other barbiturate is used now.
  - As hypnotic and anxiolytic they have been superseded by BZDs.

## Adverse Effects

### 1. CNS

- Drowsiness/ hangover (residual depression of CNS and feeling tiredness).
- Sleep disturbances on withdrawal.
- Paradoxical excitement especially in debilitated or aged patients.



### 2. Respiratory

- Depression, cough, sneezing, laryngospasm, hiccough, etc.



### 3. Drug automatism

- Owing to amnesia, patient gets confused and he takes repeated doses without remembering that earlier dose has been taken.



### 4. Tolerance



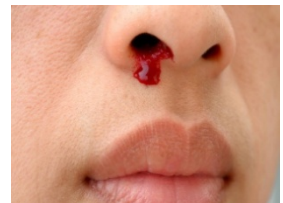
### 5. Drug dependence



### 6. Rapid i / v injection → risk of CVS collapse.



### 7. Increased vitamin D metabolism → Osteomalacia

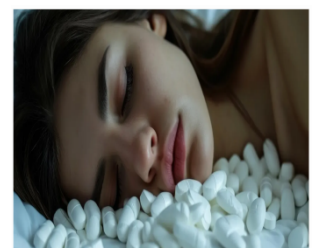


### 8. Increased vitamin K metabolism → Bleeding

### 9. Hypersensitivity reactions

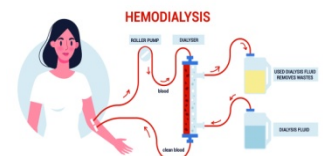
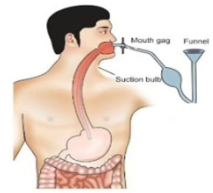
### Barbiturate Poisoning

- Excess amount of a barbiturate leads to →
  1. Unconsciousness
  2. Respiratory depression
  3. Circulatory collapse
  4. Shock
  5. Renal failure
  6. GI bleeding
  7. Pulmonary edema
  8. Cardiac irregularity



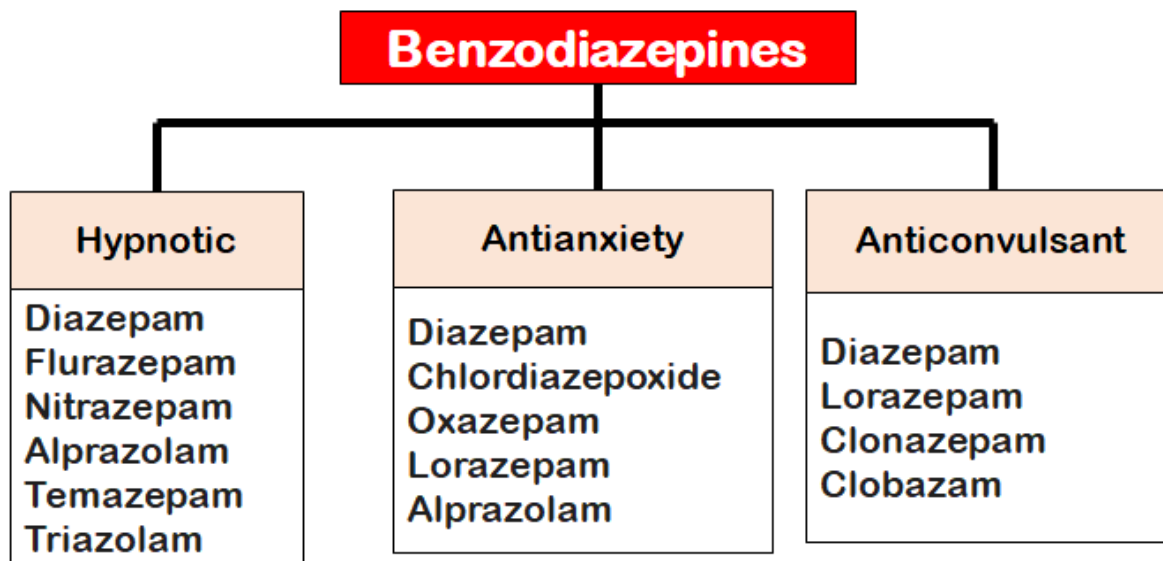
## Management

1. lavage/ emesis/ activated charcoal/ saline cathartic.
2. Airway/oxygen.
3. I/v fluid and dopamine to raise BP.
4. If renal and cardiac functions are satisfactory and patient is hydrated, forced alkaline diuresis for rapid renal excretion.
5. Hemodialysis if there's renal failure.
  - No specific antidote for barbiturates.



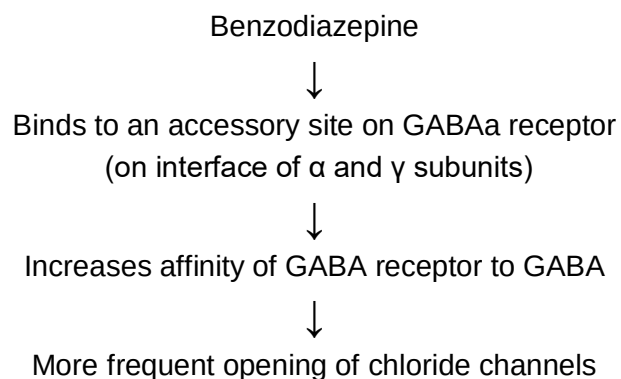
## BENZODIAZEPINES

### Classification

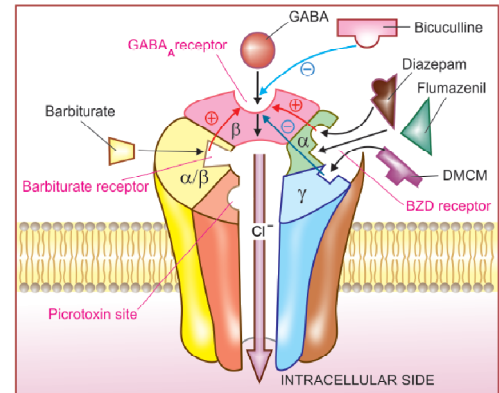
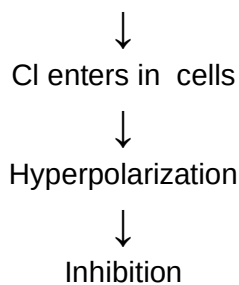


### MOA

- GABA facilitatory effect only



(increases frequency not duration)  
(GABA facilitatory effect)



## BZDs Versus Barbiturates

- BZDs → do not themselves increase Cl conductance, i.e. they have only GABA facilitatory but no GABA mimetic action.
- Barbiturates → both GABA facilitatory and GABA mimetic actions
  - BZDs → require GABA to activate receptor hence safe since effect depends on release of GABA.
  - Barbiturates → do not require GABA to activate the receptor hence not safe

## Remember

- **GABAA antagonist** → Bicuculline → antagonizes BZD action in a noncompetitive manner.
- **Competitive BZD-antagonist** → Flumazenil → blocks the sedative action of BZDs
- **BZD-inverse agonists** → dimethoxyethyl-carbomethoxy-β- carboline (DMCM) → inhibit GABA action and are convulsants.
- **Picrotoxin** → Blocks Cl<sup>-</sup> channel noncompetitively; acts on picrotoxin sensitive site

| Drugs affecting GABAA-receptor gated chloride channel |                                                                                      |
|-------------------------------------------------------|--------------------------------------------------------------------------------------|
| GABA                                                  | Endogenous agonist at GABAA, receptor → promotes Cl <sup>-</sup> influx              |
| Barbiturates                                          | Agonist at an allosteric site; prolong GABA action; and open Cl <sup>-</sup> channel |
| Benzodiazepines                                       | Agonist at an allosteric BZD site → facilitate GABA action                           |
| Muscimol                                              | Agonist at GABAA site                                                                |
| Bicuculline                                           | Competitive antagonist at GABAA receptor                                             |
| Flumazeni                                             | Competitive antagonist at BZD site                                                   |
| B-Carboline (DMCM)                                    | Inverse agonist at BZD site → impede GABA action                                     |
| Picrotoxin                                            | Blocks Cl <sup>-</sup> channel noncompetitively; acts on picrotoxin sensitive site   |
| Alcohol, Inhalational anaesthetics, Propofol          | Open Cl <sup>-</sup> channel directly; allosteric facilitation of GABA               |

## Pharmacological actions

1. CNS
2. GIT



## 1. CNS

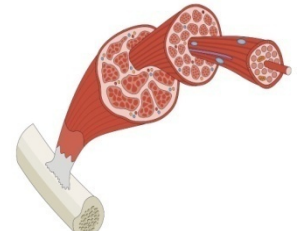
1. **Sedation**
2. **Hypnosis** → (less REM suppression).
3. **Anticonvulsants** → but not preferred for routine management of epilepsy owing to development of tolerance.

- **Anterograde amnesia** →

- Impair recent memory
- Amnesia occurs for events occurring after administration of drug that creates an illusion of anesthesia.
- True general anesthesia is not caused since awareness usually persists.



- **Muscle relaxation** → Transient analgesia after i/v administration, but no hyperalgesia.



- **Analgesia** → Transient analgesia after i/v administration, but no hyperalgesia.

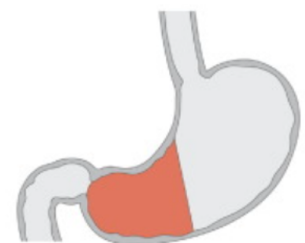


- **Antidepressant** → alprazolam shows additional antidepressant effect.



## 2. GIT

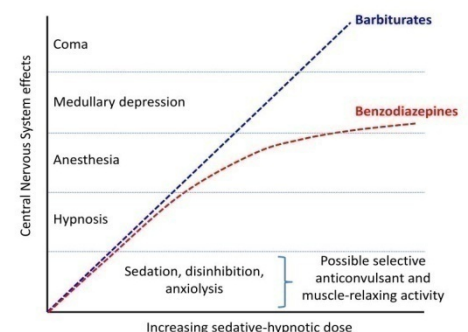
- Diazepam decreases nocturnal gastric secretion → prevents stress ulcers.



## BZP are superior to Barbiturates

1. BZDs → have a high therapeutic index → Ingestion of even 20 hypnotic doses does not usually endanger life → Benzodiazepines have flat dose response curves.

### Dose-response relationship





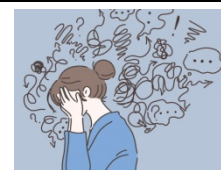
2. BZDs → Hypnotic doses do not affect respiration or cardiovascular function.
3. BZDs → have practically no action on other body system.
4. BZDs → cause less distortion of sleep architecture → rebound phenomena on discontinuation of regular use are less marked.
5. BZDs → do not alter disposition of other drugs by microsomal enzyme induction
6. BZDs → have lower abuse liability → tolerance is mild, psychological and physical dependence and withdrawal syndrome are less marked
7. A specific BZD antagonist 'Flumazenil' is available which can be used in case of poisoning.



|           | BARBITURATES | BENZODIAZEPINES   |
|-----------|--------------|-------------------|
| GABA      | mimetics     | GABA Facilitatory |
| K channel | ↑ duration   | ↑ Frequency       |
| DRC       | Steep        | Flat              |
| Inducers  | +++          | XX                |
| Addiction | +++++        | +                 |
| Amnesia   | No           | +                 |
| Antidote  | XX           | FLUMAZENIL        |

## Uses

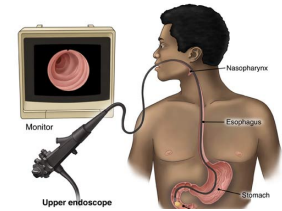
1. **Anxiety** → Alprazolam, chlordiazepoxide, diazepam, lorazepam.
2. **Insomnia** → Triazolam, temazepam, oxazepam, flurazepam.
3. **Epilepsy** →
  - Absence seizures → Clonazepam
  - Convulsive emergencies → Diazepam, lorazepam



**4. Pre-anesthetic medication** → Midazolam, diazepam, and lorazepam.



**5. For procedures** → like endoscopy, ECT, cardioversion and minor surgical or dental procedures to relieve anxiety, tension and to produce amnesia (to decrease patient's recall)→ Midazolam.



**6. Muscle spasm and spasticity** → In muscular strain, spasticity in degenerative disorders such as multiple sclerosis, cerebral palsy, athetosis, and Stiffman syndrome→ Diazepam, clonazepam.



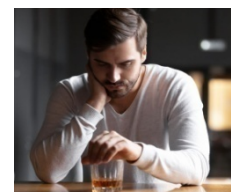
**7. Tetanus** → to control spasm and convulsions→ Diazepam.



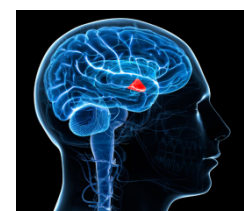
**8. Acute alcohol withdrawal** → for relief of acute agitation, tremor, hallucination and delirium tremens → Diazepam, chlordiazepoxide, and oxazepam.



**9. Alcohol addict as substitution therapy** → Diazepam.

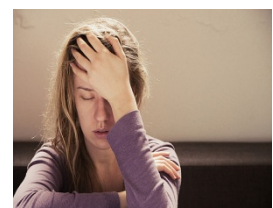


**10. Psychosomatic disorders** → like hypertension, peptic ulcer and angina to relieve anxiety.



## Adverse Effects

1. Tiredness, somnolence, ataxia, headache, vertigo, dizziness and impaired judgment.
2. Prolonged effects and hangover.



3. Tolerance
4. Dependence → Use for more than two weeks need gradual tapering.



## BENZODIAZEPINE ANTAGONIST

- Flumazenil



### MOA

- Flumazenil is competitive antagonist at BZD receptor.

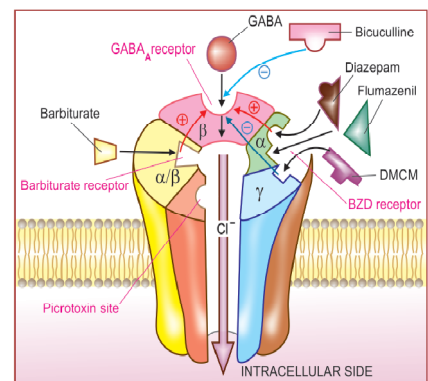
Flumazenil → benzodiazepene analogue



Competes with BZD agonists as well as inverse agonists for BZD receptor



Reverses BZD effects



- It also antagonizes action of Zolpidem, Zopiclone and Zopeplon as these drugs also act on BZD site.
- Duration of action → 30-60 minutes

### Uses

#### 1. To reverse BZD anaesthesia →

- Patients anaesthetized/sedated with a BZD → wakeup, get oriented and regain motor control within 1 min of an i.v. injection of 0.3–1 mg of flumazenil

#### 2. BZD overdose →

- Flumazenil 0.2 mg/min may be injected i.v. till patient regains consciousness.
- Practically all patients intoxicated with a BZD alone respond within 5 min.
- In mixed CNS depressant poisoning, whatever sedation is not abolished by 5 mg of flumazenil should be taken to be due to a non-BZD/non-Zolpidem-like depressant.
- It thus helps in differential diagnosis of such patients.



# NON-BENZODIAZEPINE AGONISTS

## Introduction

- Chemically they are different but act in a similar manner on benzodiazepine receptors with selectivity to bind to isoforms containing  $\alpha 1$  subunits.

## Classification

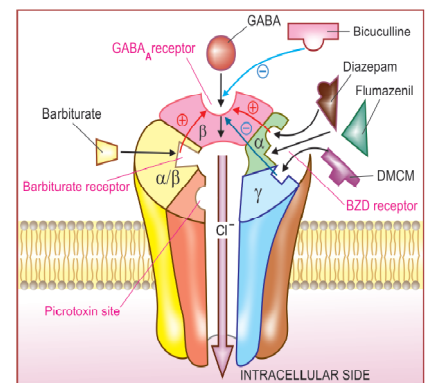
- Non-benzodiazepines** → Zopiclone, Eszopiclone, Zolpidem, Zaleplon

## Major differences

- Lack of muscle relaxant and anticonvulsant effect.
- Lack of memory impairment.
- Short duration of action.
- Effectiveness in sleep onset insomnia.
- Less suppression of REM.
- Less drug withdrawal and rebound effect.

## MOA

- Acts on  $\alpha 1$  subunit of BZD receptors.
- Minimal suppressive effect on REM sleep →
  - Sleep architecture is not disturbed
  - Sleep latency is shortened
  - Sleep duration is prolonged.



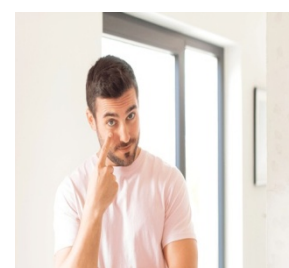
## Uses

- Zolpidem** → Short term treatment of insomnia
- Zopiclone** → To wean off insomniacs taking regular BZD medication.
- Zoleplon** → Sleep onset insomnia → It does not prolong sleep time, but sleep latency is shortened useful in persons having difficulty to fall asleep
  - Currently Zolpidem is one of the most commonly prescribed hypnotic.



## Advantages

- Hangover or withdrawal phenomena on discontinuation is less than BZDs → less day time residual sedation
- Flumazenil blocks the depressant action of BZDs, zolpidem, zoleplon

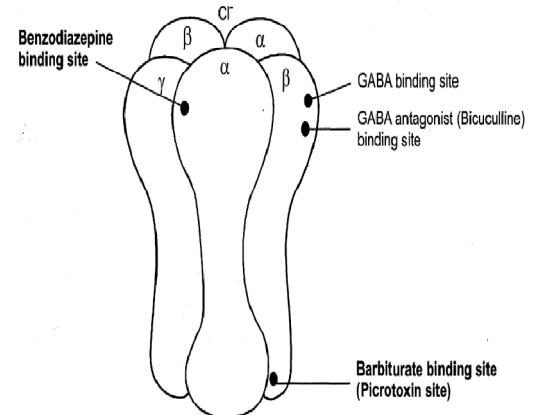


## Adverse effects

1. Metallic or bitter after taste
2. Impaired judgement and alertness
3. Psychological disturbances
4. Dry mouth

## Remember

- **GABA** →  $\beta$  – Subunit
- **BZD** →  $\alpha$  Subunit at  $\alpha$  -  $\gamma$  interface, i.e.  $\alpha/\gamma$  site
- **Barbiturate** →  $\beta$  Subunit at  $\alpha$  -  $\beta$  interface, i.e.  $\alpha/\beta$  site
- **Barbiturates** → Steep dose response curve
- **Benzodiazepines** → Flat dose response curve



## Remember

- **Flurazepam** → longest acting BZD
- **Midazolam** → shortest and fastest acting BZD.
- **Triazolam** → also shortest acting (only slightly longer than midazolam).
- **Clonazepam and diazepam** → more marked muscle relaxant property
- **Clonazepam, diazepam, nitrazepam and flurazepam** → prominent anticonvulsant activity than other BZDs.
- **Diazepam (but not other BZDs)** →
  - Analgesic action.
  - Produces short lasting coronary dilatation on iv. injection.
  - Decreases nocturnal gastric secretion and prevents stress ulcers
  - **Oxazepam, Lorazepam, Temazepam** → not metabolized but directly conjugated -> can be given in liver disease

# ALCOHOLS

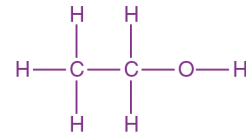
## Alcohols

- Ethyl Alcohol
- Methyl Alcohol

# ETHYL ALCOHOL (ETHANOL)

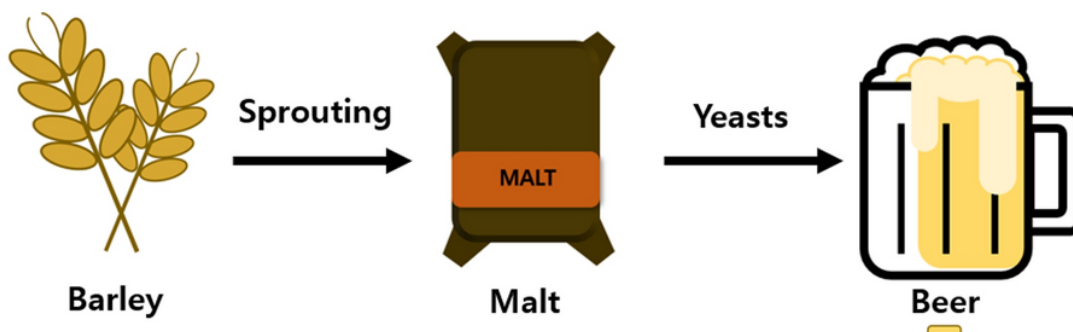
## Introduction

- Ethyl alcohol → CH<sub>3</sub>CH<sub>2</sub>OH
- Amphipathic molecule → Hydroxyl and ethyl moiety confer both hydrophilic and lipophilic properties

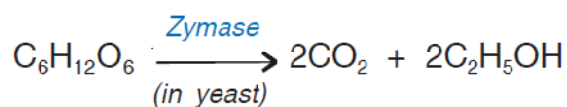


## Preparation

Starchy cereals, e.g. barley soaked  
 ↓  
 Produce maltose  
 ↓  
 Fermented by yeast  
 ↓  
 Produce alcohol



- Prepared from sugar oxidation by yeast (fermentation)





## Distillation

- Process to purify by vaporization and then condensing with cold.

## Alcoholic Beverages

- A. Malted liquors
- B. Wines
- C. Spirits

### A. Malted liquors

- Obtained by → fermentation of germinating cereals
- Undistilled
- Alcohol content is low → 3–6%
- e.g. Beers, Stout.



### B. Wines

- Produced by → fermentation of natural sugars as present in grapes and other fruits.
- Undistilled
- Alcohol content → 16–22%



### C. Spirits

- Distilled after fermentation
- Though alcohol content of these can vary from 40–55%, in India (and almost internationally) for all licenced brands it is standardized to 42.8% v/v or 37% w/w.
- e.g. Rum, Gin, Whiskey, Brandy, Vodka, etc.



## Pharmacological Actions

1. Local effects
2. CNS
3. CVS
4. Blood
5. Body temperature
6. Respiration
7. Liver
8. Kidney
9. Sexual function
10. Teratogenicity

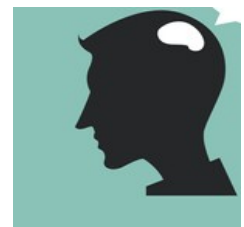
## 1. Local effects

- **On application to skin** → cools by evaporation → alcohol sponging used for fever.
- **Rubbing on skin** → produces redness and burning sensation → used as counterirritant and rubefacient
- **Hardening and cleaning of skin** → prevention of sweating → used in ridden patient to prevent bedsores decubitus ulcer.
- **Precipitation of bacterial protein and dissolution of membrane lipids** →
  - Bactericidal to nearly all the pathogenic organisms but not the spores, fungus and viruses
  - 70% alcohol is effective to kill 90% bacteria within 2 minutes.
  - 70% concentration is preferred over 100% since in higher concentration it gets early evaporation not allowing sufficient time for contact.
  - On raw surface it is irritating and forms a coagulum (a hard covering), under which bacteria may survive, thus it is not used for an open lesion.



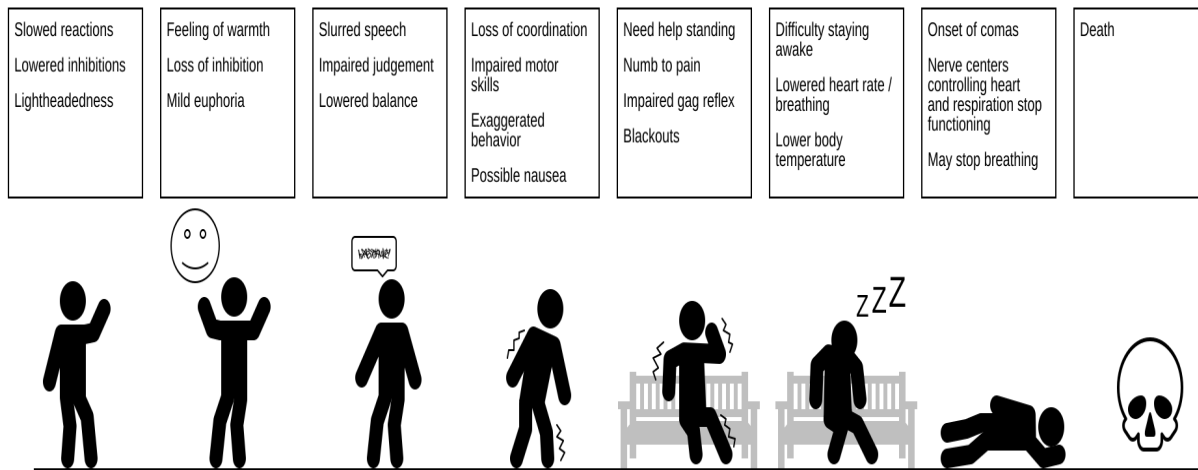
## 2. CNS

- Basic effect of alcohol is to depress various functions of CNS.
- Apparent stimulation is due to depression of inhibitory mechanism.
- Cortex and reticular activating system are most sensitive to alcohol
- Cortex is released from its integrated control →
  - There is loss of inhibition and person enjoys social company.
  - Overconfident, freely speaking and enjoying.
  - Alcohol could be considered as a 'great mimicker'.
  - Mood may swing to extreme happiness or extreme sadness.
- Effect on CNS is directly proportional to concentration in blood.
- Depression progresses as blood concentration increases.





- **Up to 20 mg%** : Person is relaxed
- **Up to 30 mg%** : Relaxed and excessively talking
- **Up to 50mg%** : Yet in control, comfortable and satisfied.
- **More than 50 mg%** : Careless and free
- **More than 100mg%** : Uncoordinated with slurring of speech
- **More than 200mg%** : Intoxicated (drunk) but still mobile
- **More than 300mg%** : Stupor
- **More than 400mg%** : Deadly drunk, coma



- Hangover (headache, dry mouth, laziness, disturbed mood, impaired performance) → occur next morning.



- Initially alcohol exerts anticonvulsant action → but this is followed by lowering of threshold → seizures may be precipitated in epileptics.



### 3. CVS

- Effects are dependent on dose.
- **Small doses:**
  - Produce only cutaneous (especially on the face) and gastric vasodilatation.
  - Skin is warm and flushed
  - BP is not affected
- **Moderate doses:**
  - Cause tachycardia
  - Mild rise in BP due to increased muscular activity and sympathetic stimulation.

- **Large doses:**

- Cause direct myocardial as well as vasomotor centre depression
- Fall in BP.
- Excessive alcohol or withdrawal may lead to atrial fibrillation, which is referred as 'Holiday Heart'.

#### 4. Blood

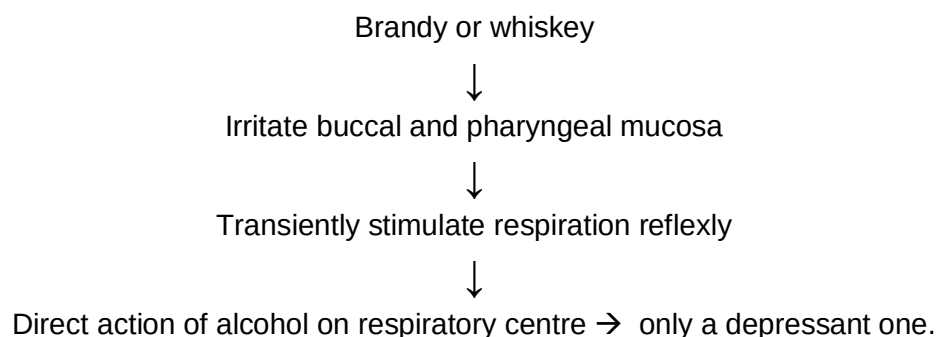
- Regular intake of small to moderate amounts of alcohol (1–2 drinks) →
  - Raise HDL-cholesterol levels and decrease LDL oxidation.
  - 15–35% lower incidence of coronary artery disease in such individuals.
  - Protection is lost if > 3 drinks are consumed daily.
  - But it is considered inappropriate to advise nondrinkers to start drinking on this account, since other adverse consequences may more than nullify this benefit.

#### 5. Body temperature

- Produce a sense of warmth due to cutaneous vasodilatation
- Heat loss is actually increased in cold surroundings.
- High doses depress temperature regulating centre.



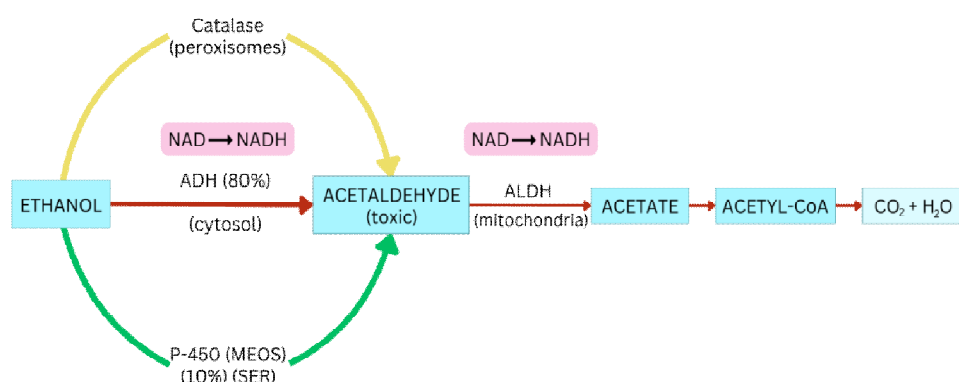
#### 6. Respiration



#### 7. Liver

- **Accumulation of fat and proteins in cells** → cirrhosis
- **Acetaldehyde** → produced during metabolism of alcohol → damage hepatocytes and induce inflammation

#### Ethanol Metabolism



## 8. Kidney

- **Diuresis** → after alcohol intake.
- This is due to water ingested along with drinks as well as alcohol induced inhibition of ADH secretion.
- It does not impair renal function.



## 9. Sexual functions

- Alcohol is considered as an aphrodisiac (substance that stimulates sex drive) due to loss of inhibition.
- It provokes the desire but takes away the performance.
- With chronic use → impotence, testicular atrophy, gynecomastia and sterility.

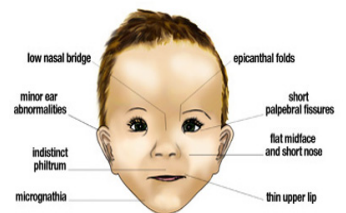


## 10. Teratogenicity

- Fetal alcohol syndrome characterized by→
  - Mental retardation
  - Slow growth
  - Microencephaly
  - Facial abnormality
  - Malformations
  - Increase risk of infections

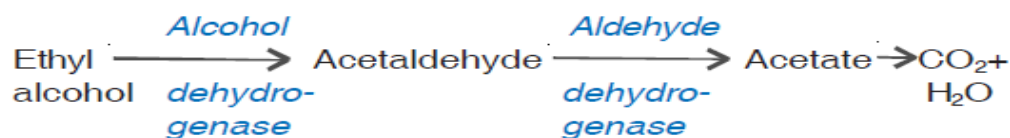


FETAL ALCOHOL SYNDROME



## Pharmacokinetics

- Alcohol absorption from the stomach is slow.
- Absorption from intestines is very fast.
- Peak levels are attained after ~30 min.



- Metabolism of alcohol follows zero order kinetics, i.e. a constant amount (8–12 ml of absolute alcohol/ hour) is degraded in unit time, irrespective of blood concentration.
- Thus, rate of consuming drinks governs whether a person will get drunk

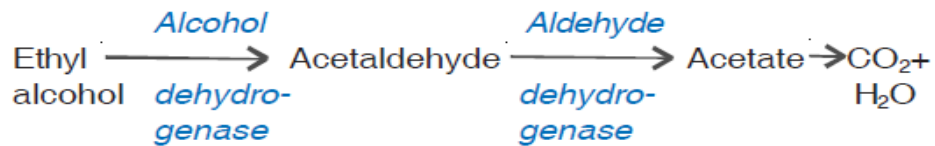
## Interactions

### 1. Anxiolytics, antidepressants, antihistaminics, hypnotics, opioids

- Alcohol synergises
- Marked CNS depression with motor impairment can occur
- Chances of accidents increase.

### 2. Disulfiram

- It inhibits enzyme aldehyde dehydrogenase



Disulfiram and Disulfiram like drugs

↓  
Inhibits enzyme aldehyde dehydrogenase

↓  
When alcohol is ingested after taking disulfiram

↓  
Concentration of acetaldehyde in tissues and blood rises

↓  
Highly distressing symptoms (aldehyde syndrome) are produced



## Drugs Causing Disulfiram Like Reaction

- Sorry - Sulfonylureas (1st generation - like chlorpropamide)
- Pluto - Procarbazine (Anticancer drugs)
- Can't - Cephalosporins (Cefotetan, Cefoperazone)
- Go - Griseofulvin
- to
- Mars - Metronidazole

## Contraindications

1. **Peptic ulcer** → hyperacidity and gastroesophageal reflux patients (alcohol increases gastric secretion and relaxes LES)
2. **Epileptics** → seizures may be precipitated.
3. **Severe liver disease**
4. **Unstable personalities** → likely to abuse it and become excessive drinkers.
5. **Pregnant women** → Even moderate drinking during pregnancy can produce foetal alcohol syndrome resulting in intrauterine and postnatal growth retardation, low IQ, microcephaly, cranio-facial and other abnormalities, and immunological impairment

## Toxicity

- A) Acute alcoholic intoxication
- B) Chronic alcoholism

### A) Acute alcoholic intoxication

#### Symptoms

- Unawareness
- Unresponsiveness
- stupor
- Hypotension
- Gastritis



- Hypoglycaemia
- Respiratory depression
- Collapse
- Coma and death

## Treatment

- First priority is to maintain patent airway → Tracheal intubation and positive pressure respiration may be needed if it is markedly depressed.
- Induction of vomiting.
- Gastric lavage with sodium bicarbonate.
- I/v sodium bicarbonate to correct acidosis
- Maintenance of fluid and electrolyte balance
- Correction of hypoglycaemia by glucose infusion
- Thiamine (100 mg in 500 ml glucose solution infused i.v.)
- Recovery can be hastened by haemodialysis

## B) Chronic alcoholism

### Symptoms

1. Tolerance
2. Dependence
3. Withdrawal syndrome

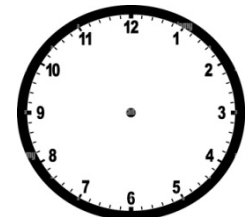
#### 1. Tolerance

- On chronic intake, tolerance develops to subjective and behavioral effects of alcohol, but is generally of a low degree.



#### 2. Dependence

- Psychic dependence occurs only on heavy and round-the-clock drinking (if alcohol is present in body continuously).



#### 3. Withdrawal syndrome

- When a physically dependent subject stops drinking, withdrawal syndrome appears within a day.
- Its severity depends on duration and quantity of alcohol consumed by the subject.
- It consists of →
  - Anxiety
  - Sweating
  - Tachycardia
  - Tremor,
  - Impairment of sleep
  - Confusion
  - Hallucinations
  - Delirium tremens
  - Convulsions and collapse.



## Treatment

- Substitution therapy
- Naltrexone
- Acamprosate
- Disulfiram aversion therapy (Antabuse)

### 1. Substitution therapy

- Alcohol is abruptly withdrawal and substituted with a long acting agent such as diazepam (BZDs are DOC)
- Mean total dose of diazepam needed for loading is 80-120 mg (4-5 doses over 8-10 hours).
- A dose below 180 mg is sufficient in more than 90% of patients.

### 2. Naltrexone

- Several studies have demonstrated involvement of opioid system in the pleasurable reinforcing effects of alcohol through dopamine mediated reward function
- Reinforcement is weakened.
- It helps prevent relapse of alcoholism.
- It reduces → alcohol craving, number of drinking days and chances of resumed heavy drinking.

### 3. Acamprosate

- It is a weak NMDA-receptor antagonist with modest GABAA receptor agonistic activity
- It is being used in USA, UK and Europe for maintenance therapy of alcohol abstinence.

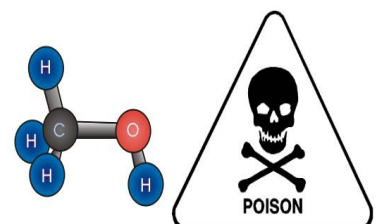
### 4. Disulfiram aversion therapy (Antabuse)

- It inhibits enzyme aldehyde dehydrogenase
- Disulfiram aversion therapy is indicated in abstinent subjects who sincerely desire to leave the habit.
- Subject's resolve not to drink is reinforced by the distressing symptoms that occur if he drinks a little bit.

## METHYL ALCOHOL (METHANOL, WOOD ALCOHOL)

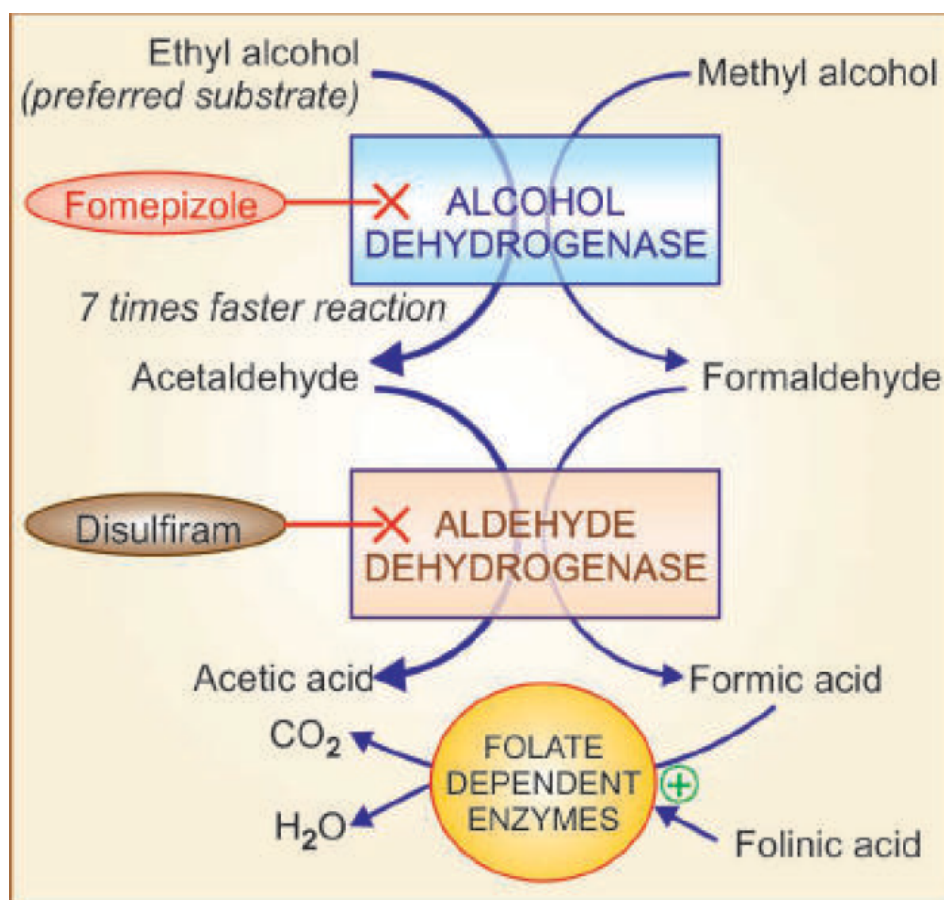
### Introduction

- Methyl alcohol is added to industrial rectified spirit to render it unfit for drinking.
- It is only of toxicological importance.
- Mixing of methylated spirit with alcoholic beverages by bootleggers or its inadvertent ingestion results in methanol poisoning.



## Pharmacokinetics

- Methanol is metabolized to formaldehyde and formic acid by alcohol and aldehyde dehydrogenases respectively, but the rate is 1/7th that of ethanol.
- Like ethanol, metabolism of methanol also follows zero order kinetics
- Methanol also is a CNS depressant, but less inebriating than ethanol.



## Methanol toxicity

- Toxic effects of methanol are largely due to formic acid, since its further metabolism is slow and folate dependent.
- A blood level of >50 mg/dl methanol → associated with severe poisoning.
- **15 ml of methanol** → blindness
- **30 ml of methanol** → death

## Clinical features

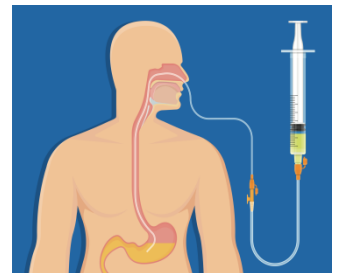
- Vomiting
- Headache
- Epigastric pain
- Uneasiness, drunkenness, disorientation
- Tachypnoea, dyspnoea, bradycardia and hypotension
- Delirium and seizures may occur
- Coma
- Acidosis is prominent and entirely due to production of formic acid



- Specific toxicity of formic acid is retinal damage
- Blurring of vision, congestion of optic disc followed by blindness always precede death which is due to respiratory failure

## Treatment

1. **Keep patient in a quiet, dark room**
2. **Protect eyes from light.**
3. **Supportive measures** → maintain ventilation and BP should be instituted
4. **Gastric lavage** → with sod. bicarbonate if the patient is brought within 2 hours of ingesting methanol.
5. **I.V. Sod. bicarbonate infusion** → Combat acidosis and prevents retinal damage and other symptoms
6. **Pot. chloride infusion** → needed only when hypokalemia occurs due to alkali therapy.
7. **Ethanol** → preferentially metabolized by alcohol dehydrogenase over methanol.
  - At a concentration of 100 mg/dl in blood it saturates alcohol dehydrogenase and retards methanol metabolism.
  - This helps by reducing the rate of generation of formaldehyde and formic acid.
  - Ethanol (10% in water) is administered through a nasogastric tube
  - loading dose of 0.7 ml/kg is followed by 0.15 ml/kg/hour.
8. **Fomepizole (4-methylpyrazole)** → a specific inhibitor of alcohol dehydrogenase and the drug of choice for methanol poisoning by retarding its metabolism.
  - A loading dose of 15 mg/kg i.v. followed by 10 mg/kg every 12 hours till serum methanol falls below 20 mg/dl, has been found effective and safe.
  - It has several advantages over ethanol, viz. longer t<sub>1/2</sub> and lack of inebriating action, but is not available commercially in India.
9. **Haemodialysis** → clears methanol as well as formate and hastens recovery.



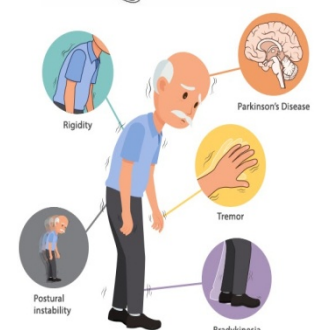
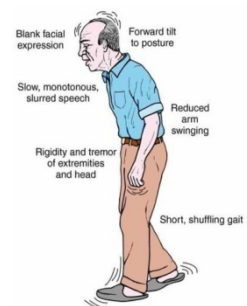
## ANTIPARKINSONIAN DRUGS

### Introduction

- These are drugs that have a therapeutic effect in parkinsonism.

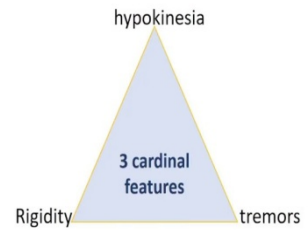
## PARKINSONISM

- Parkinson's disease (PD) is a progressive degenerative disorder, mostly affecting older people
- James Parkinson described it in 1817 as → Paralysis agitans or Shaking palsy
- Age → 45 to 65 years





- It is an extrapyramidal motor disorder characterized by
  1. Tremor
  2. Rigidity
  3. Hypokinesia
- Secondary manifestations like defective posture and gait, mask-like face and sialorrhoea; dementia may accompany



### 1. Tremors

- Present at rest
- Disappear on purposeful movements and sleep
- Increase with anxiety or stress.

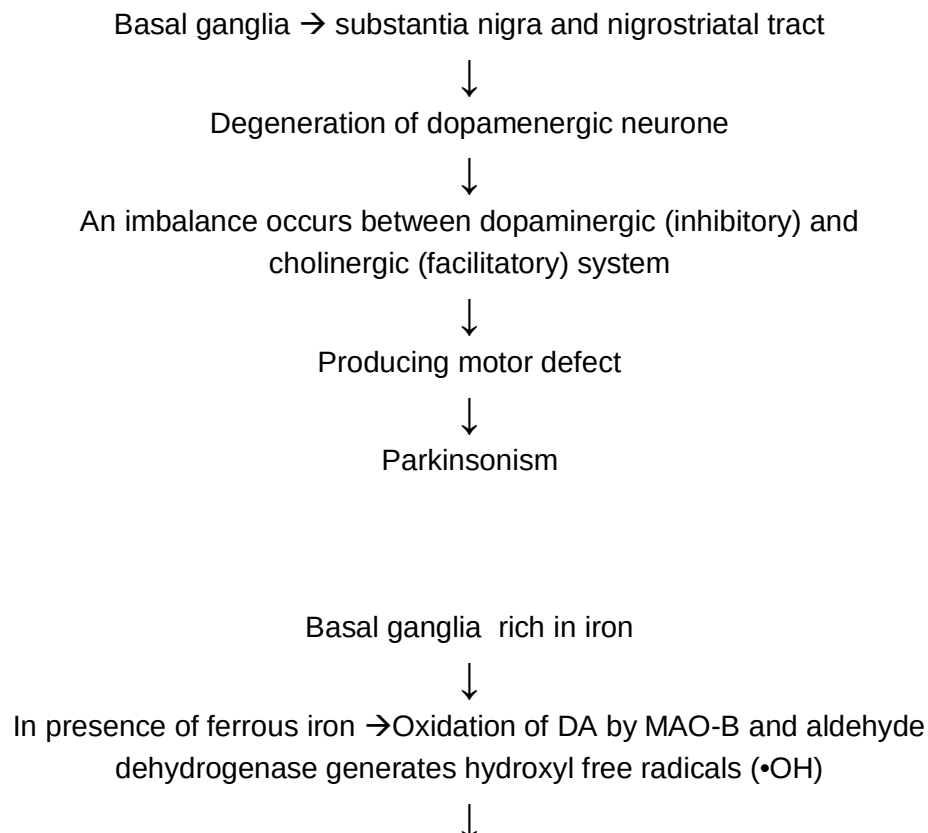
### 2. Hypokinesia / Bradykinesia

- Slow initiation of voluntary movements

### 3. Rigidity

- Increase resistance to passive movements due to increase muscle tone (rigidity)
- Postural defects.
- Patient is unable to maintain the up right posture of trunk while standing.
- There is a change in gait → Festinating gait
- Patient takes a more rapid, smaller and smaller step as if he is chasing his own center of gravity to prevent the fall.

## Pathogenesis



Normally these free radicals are quenched by glutathione



Age-related defect in protective mechanism allows free radicals to damage lipid membranes and DNA



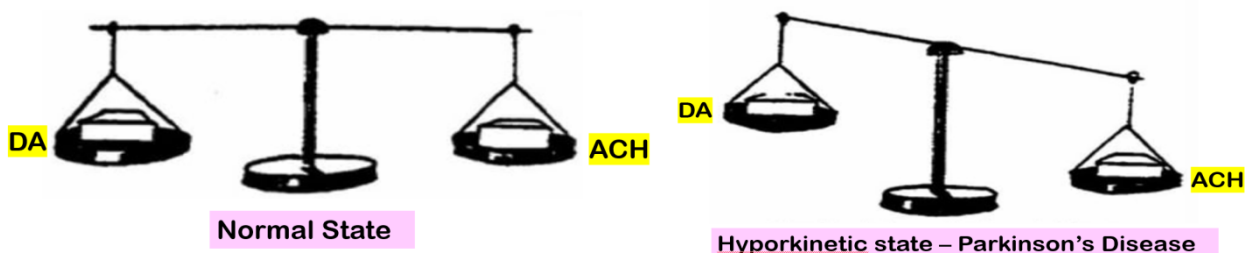
Neuronal degeneration of dopaminergic neurone



An imbalance occurs between dopaminergic (inhibitory) and cholinergic (facilitatory) system



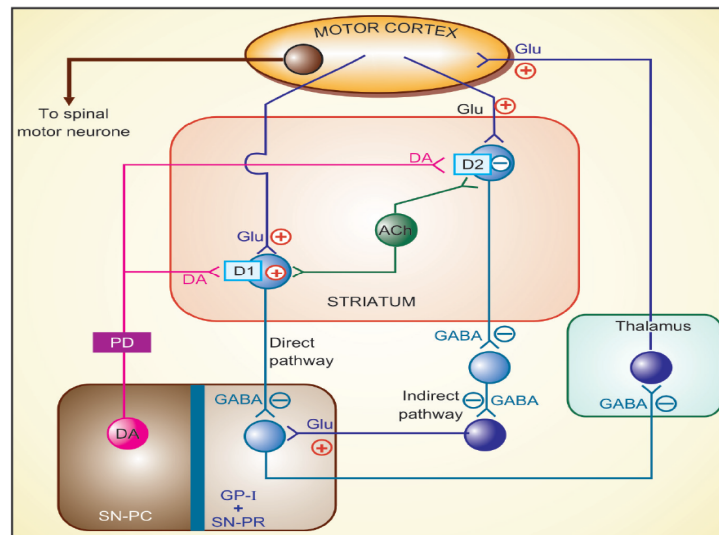
Parkinsonism (Motor defect)



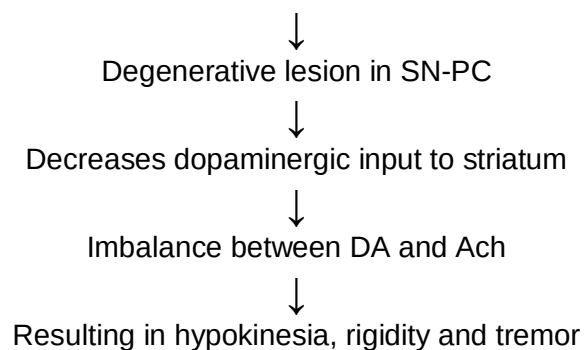
|               |                     |
|---------------|---------------------|
| DA = ACH      | DA ≠ ACH            |
| 100 100       | 50 100              |
| <b>Normal</b> | <b>Parkinsonism</b> |

## Simplified scheme of side loop circuits in basal ganglia

- Striatal GABAergic neurones receive side-loop →
  - Excitatory glutamatergic (Glu) input from motor cortex
  - Modulatory dopaminergic (DA) projections from substantia nigra pars compacta (SN-PC).
  - Balancing cholinergic (ACh) interneurons.
- Striatal neurones express both excitatory D1 and inhibitory D2 receptors.



## Parkinson's disease (PD)



## Aim of Treatment of parkinsonism

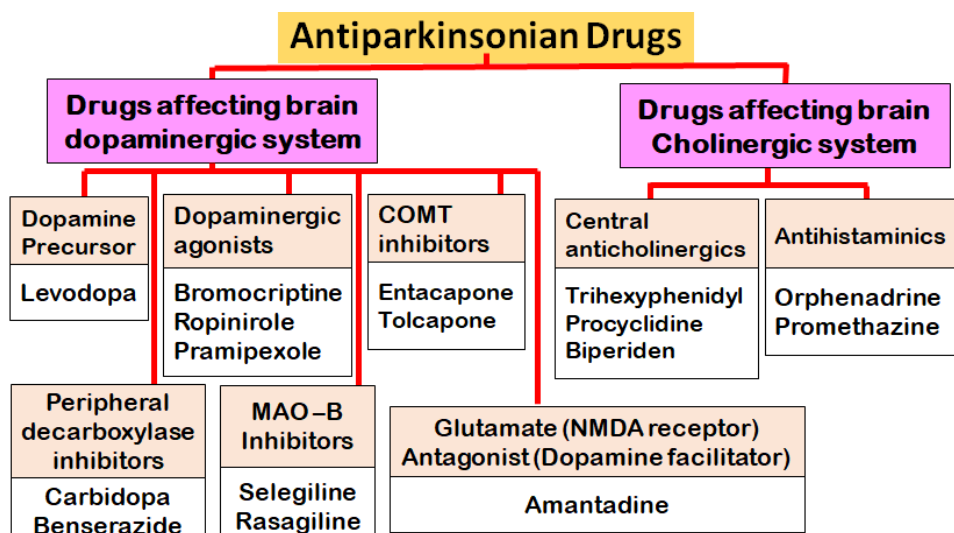
Increase brain dopaminergic activity

OR

Decrease brain cholinergic activity

(though cholinergic is not primarily affected → But its suppression tends to restore balance between cholinergic and dopaminergic system)

## Classification



|                   | Dopamine precursor | Peripheral Decarboxylase Inhibitors | Dopaminergic Agonists |
|-------------------|--------------------|-------------------------------------|-----------------------|
| Classification    |                    |                                     |                       |
| Introduction      |                    |                                     |                       |
| MOA               |                    |                                     |                       |
| Actions           |                    |                                     |                       |
| Pharmacokinetics  |                    |                                     |                       |
| Interactions      |                    |                                     |                       |
| Use               |                    |                                     |                       |
| Adverse effects   |                    |                                     |                       |
| Contraindications |                    |                                     |                       |

|                   | MAO- B Inhibitors | COMT Inhibitors | Glutamate (NMDA) Antagonist | Central Anticholinergics |
|-------------------|-------------------|-----------------|-----------------------------|--------------------------|
| Classification    |                   |                 |                             |                          |
| Introduction      |                   |                 |                             |                          |
| MOA               |                   |                 |                             |                          |
| Actions           |                   |                 |                             |                          |
| Pharmacokinetics  |                   |                 |                             |                          |
| Interactions      |                   |                 |                             |                          |
| Use               |                   |                 |                             |                          |
| Adverse effects   |                   |                 |                             |                          |
| Contraindications |                   |                 |                             |                          |

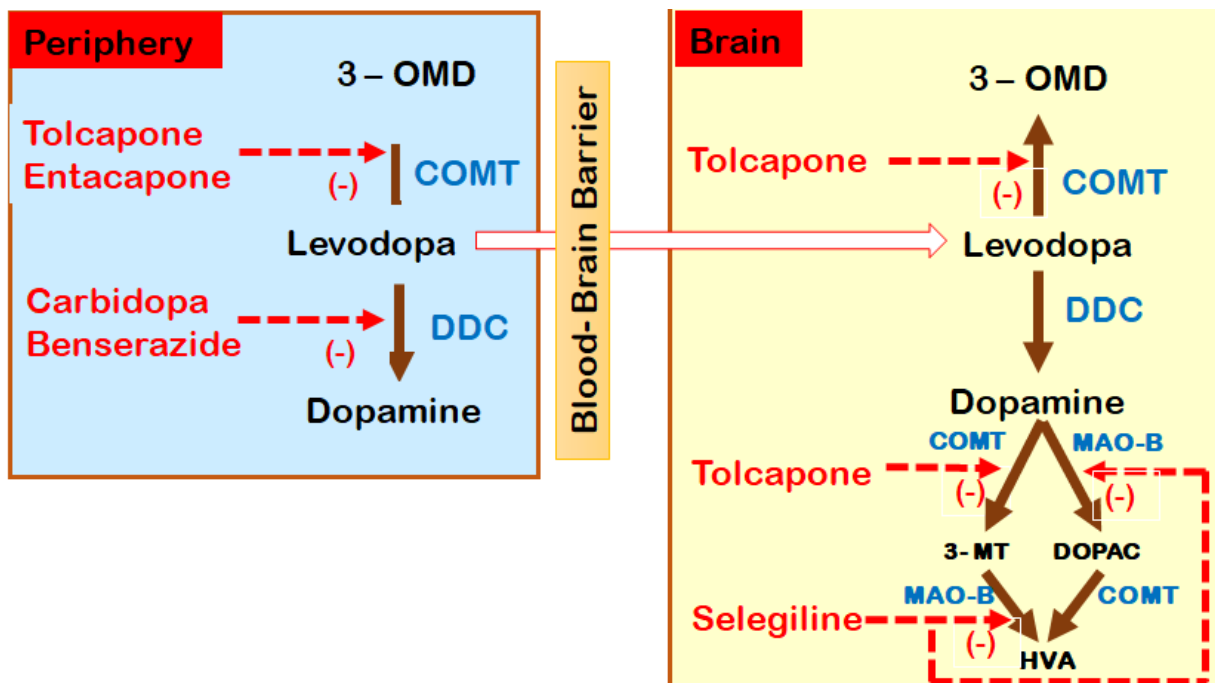
## DOPAMINE PRECURSOR

### Classification

- Levodopa

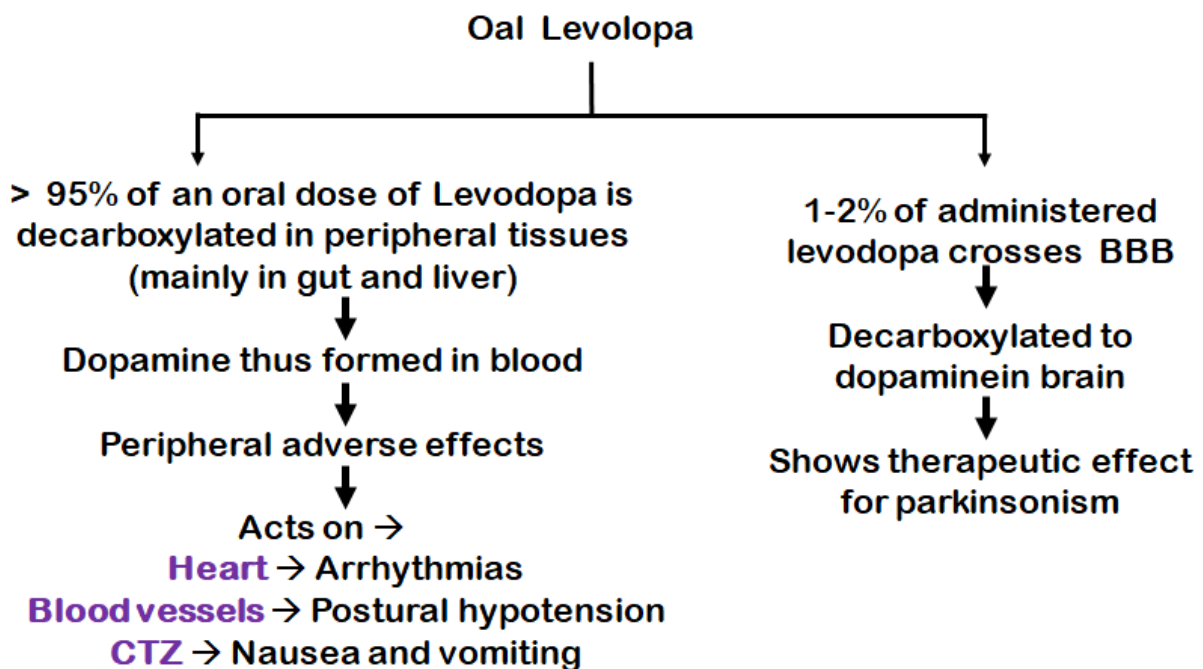
### Introduction

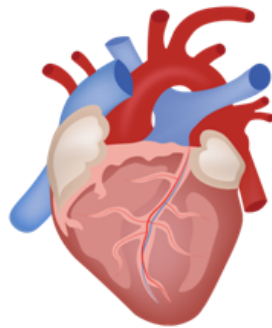
- Dopamine itself cannot cross blood brain barrier (BBB) but its precursor levo-dopa can cross BBB.
- So Levodopa is inactive by itself, but is immediate precursor of the transmitter DA
- It is the most commonly used drug in parkinsonism



Levo-dopa  
 ↓  
 Metabolized by dopa decarboxylase to dopamine  
 (contains pyridoxine as co-factor)  
 ↓  
 This conversion occurs both in periphery as well as in brain

### Peripheral conversion





Heart →  
Arrhythmias

Blood vessels →  
Postural  
hypotension



CTZ → Nausea  
and vomiting

### Disadvantages of Peripheral conversion

1. Dopamine can not cross BBB (so only 1-2% of administered levodopa which crosses BBB is effective).
2. Dopamine produces peripheral adverse effects.
  - Peripherally formed dopamine can lead
    - a) Postural hypotension
    - b) Arrhythmias.
    - c) Nausea and vomiting occurs commonly due to CTZ stimulation by dopamine

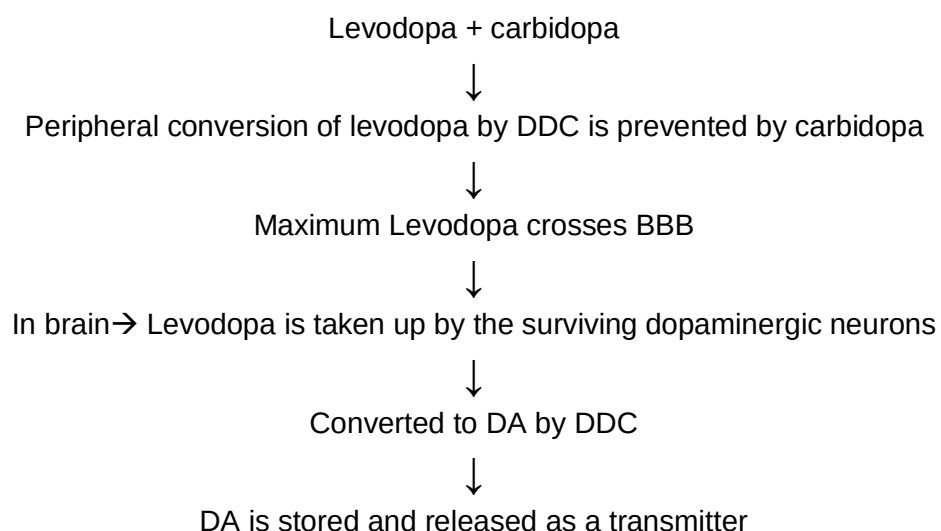
### To overcome Peripheral conversion

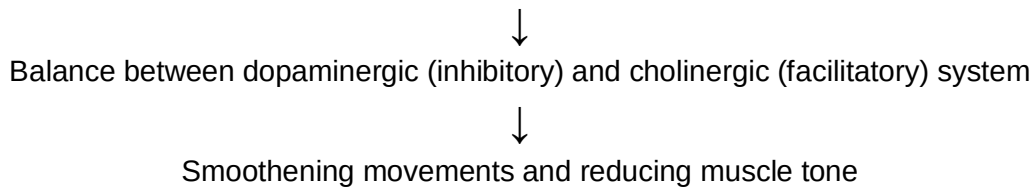
- Therefore levo-dopa is always given in combination with peripheral dopa decarboxylase inhibitors like carbidopa or benserazide.

### Addition of carbidopa to L-dopa therapy

1. Increase entry of L-dopa in brain.
2. Decrease adverse effects due to peripherally formed dopamine

### MOA





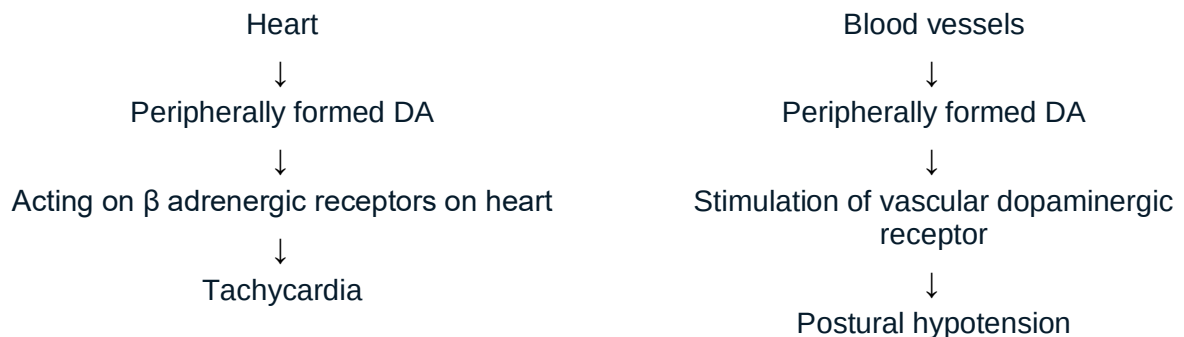
## Actions

1. CNS
2. CVS
3. CTZ
4. Endocrine

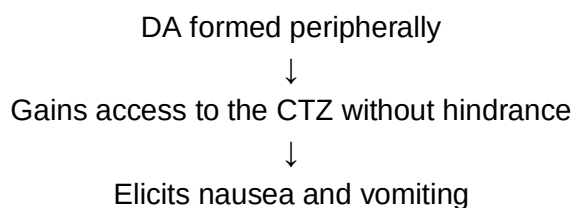
### 1. CNS

- Stimulation of excitatory D1 as well as inhibitory D2 receptors in striatum → net effect of smoothering movements and reducing muscle tone.
- Order of Resolve → **Hypokinesia → Rigidity → Tremor**
- Secondary symptoms → posture, gait, handwriting, speech, facial expression, mood, self care and interest in life are gradually normalized.
- Therapeutic benefit is nearly complete in early disease, but declines as the disease advances.
- Levodopa has alerting response on behavior.
- In some patients this progresses to excitement → frank psychosis

### 2. CVS



### 3. CTZ



### 4. Endocrine

- DA acts on →
  - a) Pituitary mamatotropes → inhibit prolactin release
  - b) Somatotropes → increase GH release

## Pharmacokinetics

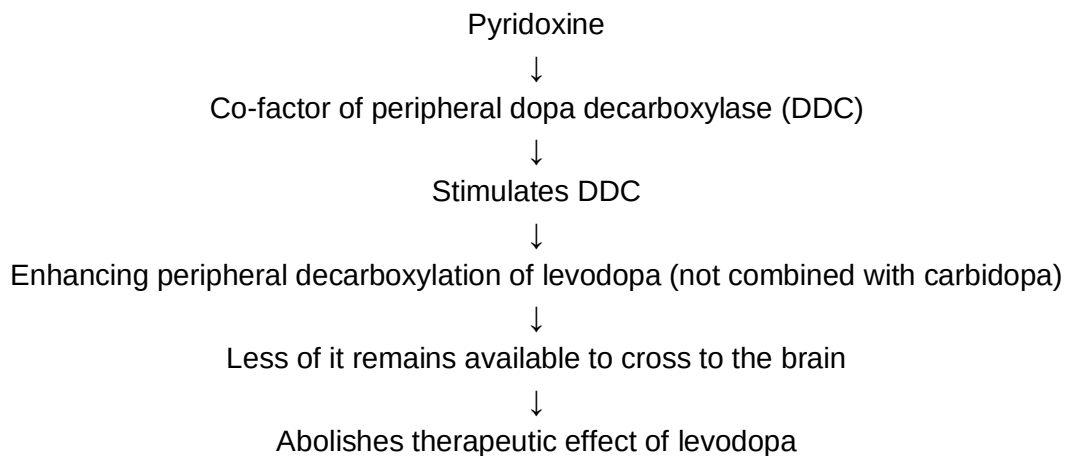
### Levodopa →

- Undergoes high first pass metabolism in g.i. mucosa and liver
- Plasma  $t_{1/2}$  → 1–2 hours
- Metabolized by dopa decarboxylase (contains pyridoxine as co-factor) to dopamine.
- Conversion occurs both in periphery as well as in the brain

## Interactions

1. Pyridoxine
2. Phenothiazines, butyrophenones, metoclopramide
3. Domperidone
4. Reserpine
5. Antihypertensive drugs
6. Atropine and anticholinergic drugs

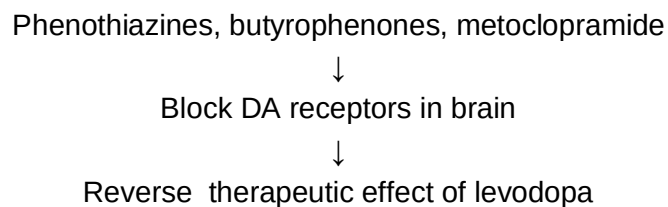
### 1. Pyridoxine



- Multivitamins containing pyridoxine are not given along with levodopa

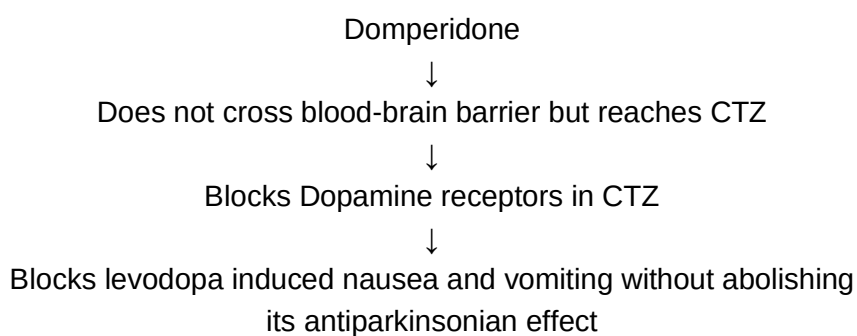


### 2. Phenothiazines, butyrophenones, metoclopramide

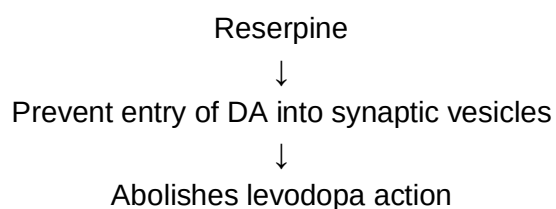




### 3. Domperidone

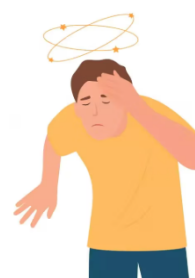


### 4. Reserpine



### 5. Antihypertensive drugs

- Postural hypotension caused by levodopa is accentuated in patients receiving antihypertensive drugs
- Reduce their dose if levodopa is started



### 6. Atropine and anticholinergic drugs

- Have additive therapeutic action with low doses of levodopa

### Uses

- Levodopa → first line therapy

### Adverse Effects

- A. At the initiation of therapy
- B. After prolonged therapy

| A. At the initiation of therapy                   | B. After prolonged therapy          |
|---------------------------------------------------|-------------------------------------|
| 1. Nausea and vomiting                            | 1. Abnormal movements (dyskinesias) |
| 2. Postural hypotension                           | 2. Behavioural effects              |
| 3. Cardiac arrhythmias and Exacerbation of angina | 3. Fluctuation in motor performance |
| 4. Alteration in taste sensation                  |                                     |

## A. At the initiation of therapy

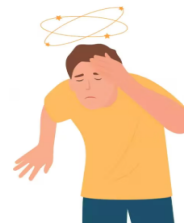
### 1. Nausea and vomiting

- Due to CTZ stimulation by peripherally formed DA .
- It occurs in almost every patient.
- Tolerance gradually develops and then the dose can be progressively increased.
- Reduced by carbidopa



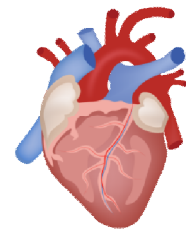
### 2. Postural hypotension

- Due to Stimulation of vascular dopaminergic receptor by peripherally formed DA
- It is more common in patients receiving antihypertensives.
- Tolerance develops with continued treatment and BP normalizes.
- Reduced by carbidopa



### 3. Cardiac arrhythmias and Exacerbation of angina

- Due to  $\beta$  adrenergic action of peripherally formed DA
- Reduced by carbidopa



### 4. Alteration in taste sensation

- Reduced by carbidopa

## B. After prolonged therapy

### 1. Abnormal movements (dyskinesias)

- Facial tics, grimacing, tongue thrusting, choreoathetoid movements of limbs
- Their intensity corresponds with levodopa levels.
- No tolerance develops to this adverse effect
- Dose reduction decreases severity.
- Abnormal movements may become as disabling as the original disease itself, and are the most important dose-limiting side effects.
- This is not reduced by carbidopa

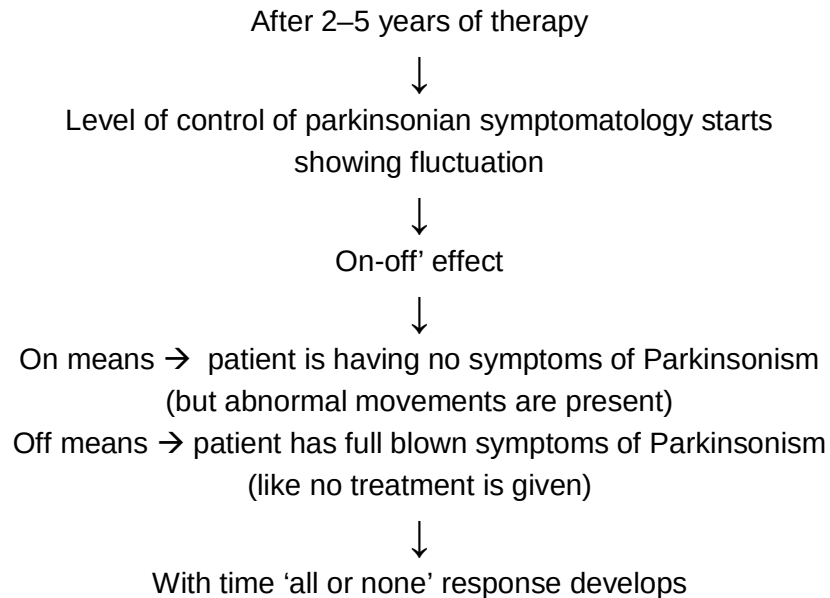


### 2. Behavioural effects

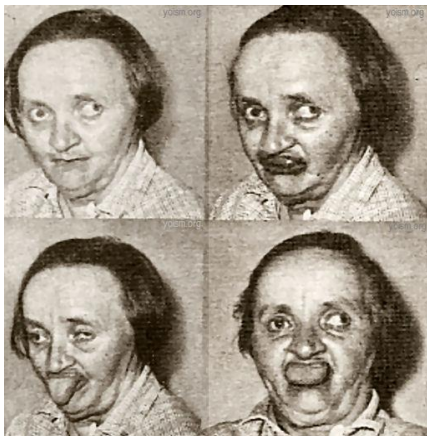
- Excessive DA action in limbic system is probably responsible
- Range from mild anxiety, nightmares, etc. to severe depression, mania, hallucinations, mental confusion or frank psychosis.
- Levodopa is contraindicated in patients with psychotic illness.
- This is not reduced by carbidopa



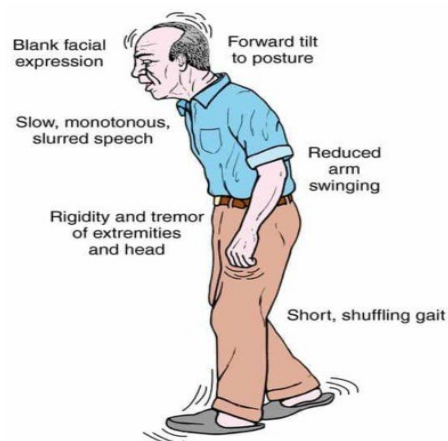
### 3. Fluctuation in motor performance



**On means** → patient is having no symptoms of Parkinsonism (but abnormal movements are present)



**Off means** → patient has full blown symptoms of Parkinsonism (like no treatment is given)



- This effect is due to short half life (1-2hrs) of l-dopa
- This is reduced by carbidopa

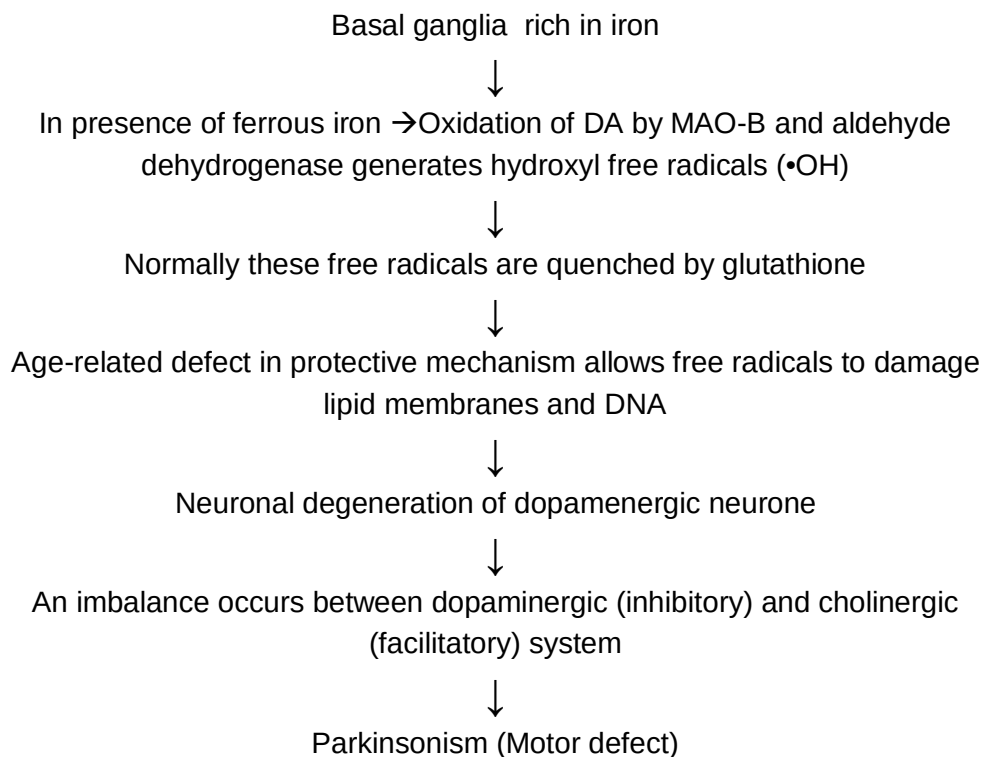
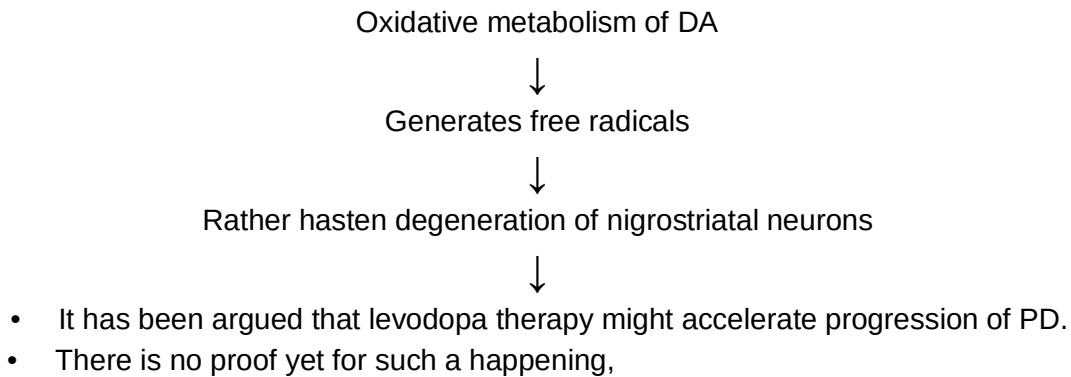
### Contraindications

1. Active peptic ulcer (increased risk of bleeding)
2. Malignant melanoma (levo-dopa is a precursor of melanin)
3. Glaucoma

| Adverse Effect          | Mechanism                  | Remarks                                                  |
|-------------------------|----------------------------|----------------------------------------------------------|
| 1. Nausea, Vomiting     | CTZ stimulation            | Reduced by carbi-dopa                                    |
| 2. Postural hypotension | D <sub>1</sub> stimulation | Reduced by carbi-dopa                                    |
| 3. Arrhythmias          | β <sub>1</sub> stimulation | Reduced by carbi-dopa                                    |
| 4. Hypertension         | α <sub>1</sub> stimulation | Reduced by carbi-dopa More likely when combined with MAO |

|                       |                           | inhibitors                                      |
|-----------------------|---------------------------|-------------------------------------------------|
| 5. Mydriasis          | $\alpha_1$ stimulation    | Contraindicated in acute angle closure glaucoma |
| 6. Dyskinesia         | ↑ Activity of DA in Brain | Not reduced by carbi-dopa                       |
| 7. Psychotic symptoms | ↑ Activity of DA in Brain | Not reduced by carbi-dopa                       |

## Remember

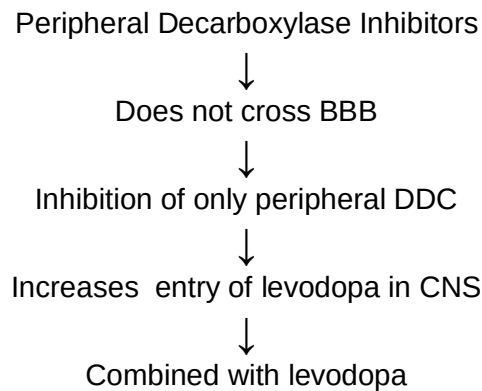


## PERIPHERAL DECARBOXYLASE INHIBITORS

### Classification

- Carbidopa
- Benserazide

## MOA



## Benefits of combination

1. Plasma  $t_{1/2}$  of levodopa is prolonged and its dose is reduced to approximately 1/4th.
2. Systemic concentration of DA is reduced
3. Therapeutic doses of levodopa can be attained quickly.
4. Nausea and vomiting are not prominent
5. Cardiac complications are minimized.
6. Pyridoxine reversal of levodopa effect does not occur.
6. 'On-off' effect is minimized since cerebral DA levels are more sustained.

## Problems not resolved or accentuated

1. Involuntary movements
2. Behavioural abnormalities
3. Excessive day time sleepiness in some patients.

## Uses

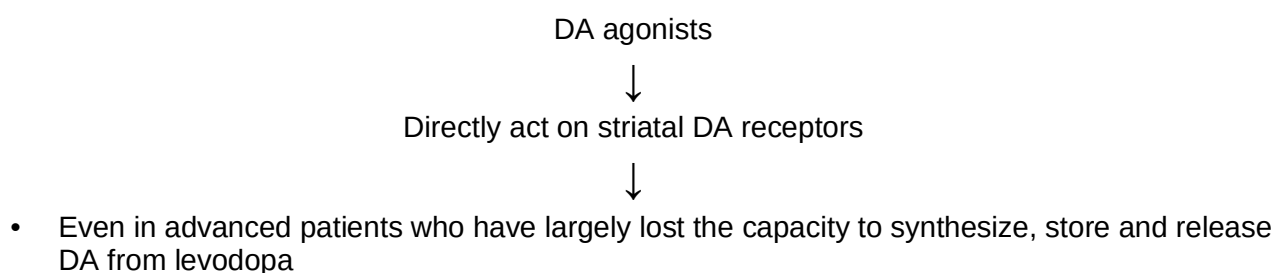
- Currently, levodopa is practically always used along with a decarboxylase inhibitor, except in patients who develop marked involuntary movements with the combination.
- Combination of levodopa with carbidopa has been given the name 'Co-careldopa'

# DOPAMINERGIC AGONISTS

## Classification

1. Ergolines: Ergots with dopaminergic activity, Bromocriptine and pergolide
2. Ropinirole
3. Pramipexole

## MOA



## Ergolines

- Ergots with dopaminergic activity →
  1. Bromocriptine
  2. Pergolide

## Advantages

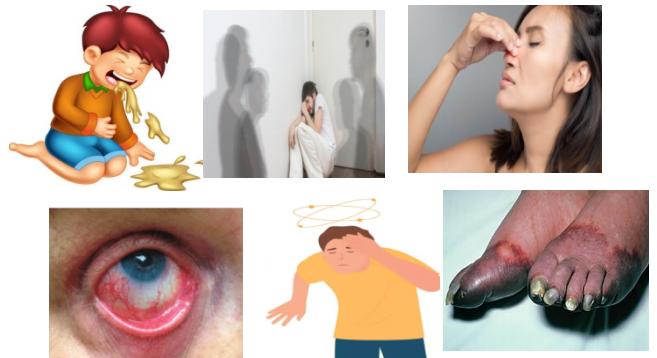
1. Longer duration of action → so useful in patients with on-off phenomenon.
2. Enzymatic conversion is not required → so do not depend on the capacity of neurons hence also effective in late stages of disease.
3. No free radical generation → less risk of any further damage to neurons.
4. More selective

## Uses

- Bromocriptine has been largely replaced by newer DA agonists ropinirole and pramipexole.
- Used in late cases as a supplement to levodopa to improve control and smoothen 'on off' fluctuations.

## Adverse effects

1. Vomiting
2. Hallucinations
3. Nasal stuffiness
4. Conjunctival injection
5. Marked fall in BP with the 'first dose' (especially those on antihypertensive medication)
6. Can cause digital vasospasm → gangrene and pleural, peritoneal and cardiac fibrosis



## Non ergot dopamine agonist

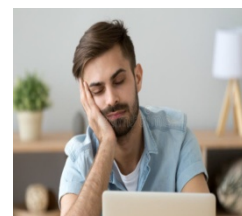
- Pramipexole
- Ropinirole
- These are two nonergoline, selective D2/D3 receptor agonists with negligible affinity for D1 and nondopaminergic receptors.
- Free from ergot specific toxicity.

## Uses

1. DOC in Parkinsonism (In developed countries, these are now first choice drugs for Parkinsonism (preferred over levo-dopa).
2. Hyperprolactinemia in lactation, infertility, amenorrhea, galactorrhea.
3. Pituitary tumors → Acromegaly.
4. Ropinirole is also used for restless le syndrome.

## Adverse effects

- Sudden attack of sleep during daytime activity



# MAO-B INHIBITOR

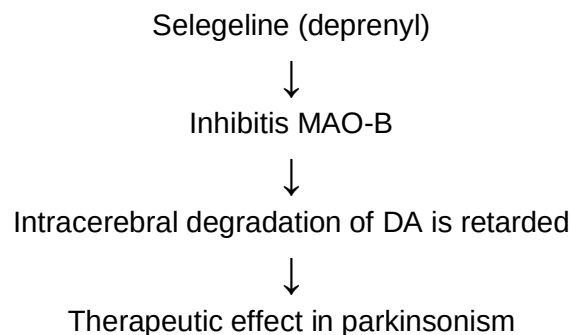
## Classification

- Selegiline (Deprenyl)
- Rasagiline

## Introduction

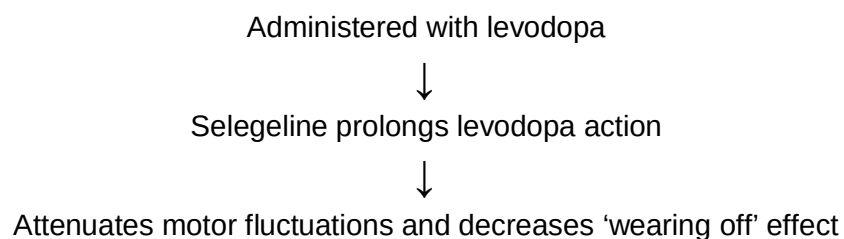
- 2 isoforms of enzyme MAO →
  1. **MAO-A** → Peripheral adrenergic structure, intestinal mucosa.
  2. **MAO-B** → Peripheral adrenergic structures, intestinal mucosa, brain & blood platelets.

## MOA



## Uses

- As an adjuvant to levodopa → it is beneficial in 50–70% patients and permits 20–30% reduction in levodopa dose



## Adverse effects

1. Postural hypotension
2. Nausea
3. confusion
4. Accentuation of levodopa induced involuntary movements and psychosis
5. Selegiline is partly metabolized by liver into amphetamine which sometimes causes insomnia and agitation → Selegiline is contraindicated in patients with convulsive disorders.



## Rasagiline

- It is 5 times more potent,
- Longer acting
- Not metabolized to amphetamine.

## COMT INHIBITORS

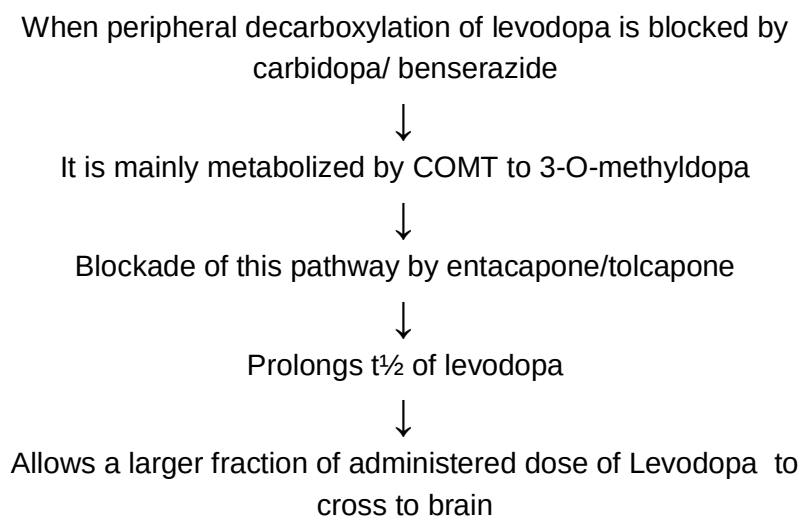
### Classification

- Entacapone
- Tolcapone

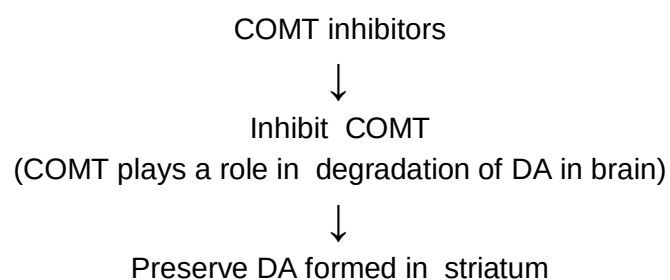
### MOA

- 2 MOA →
  1. Peripheral
  2. Central

#### 1. Peripheral



#### 2. Central





## Remember

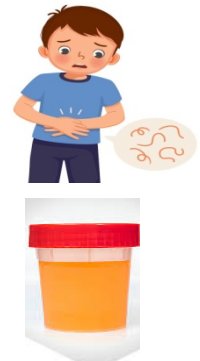
- **Entacapone** → acts only in periphery (probably because of short duration of action ~2 hr).
- **Tolcapone** → acts in periphery and centrally both

## Uses

- Both entacapone and tolcapone enhance and prolong the therapeutic effect of levodopa-carbidopa in advanced and fluctuating PD.
- They are not indicated in early PD cases

## Adverse effects

1. Worsening of levodopa adverse effects such as nausea, vomiting, dyskinesia, postural hypotension, hallucinations, etc.
2. Diarrhoea
3. Yellow orange discolouration of urine



# GLUTAMATE (NMDA RECEPTOR) ANTAGONIST (DOPAMINE FACILITATOR)

## Classification

- Amantadine

## MOA

1. Antagonistic action on NMDA type of glutamate receptors, through which striatal dopaminergic system exerts its influence
2. Promotes presynaptic synthesis and release of DA in brain
3. Has anticholinergic property.

## Uses

- Used in milder cases or in short courses to supplement levodopa for advanced cases.

## Adverse effects

- Insomnia
- Confusion
- Nightmares
- Anticholinergic effects
- Livedo reticularis (bluish discolouration) and edema of ankles → due to local release of CAs → postcapillary vasoconstriction

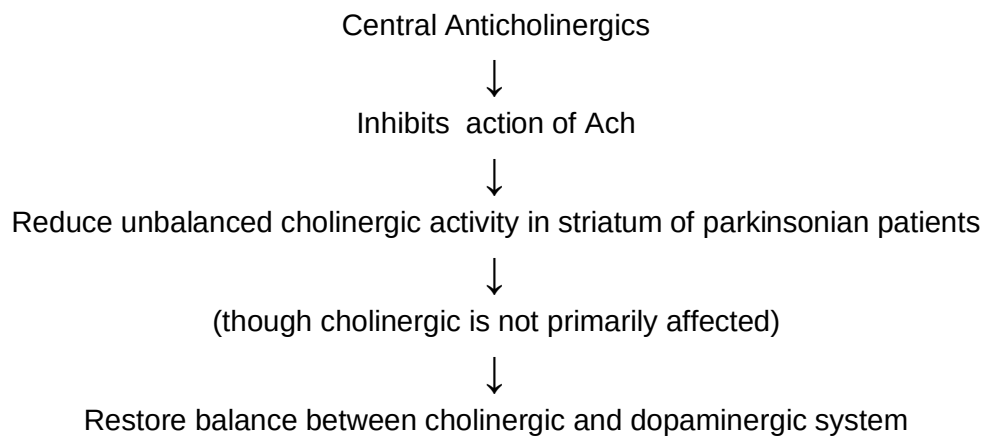


## CENTRAL ANTICHOLINERGICS

### Classification

- Trihexyphenidyl (benzhexol)
- Benztropin
- Biperiden
- Procyclidine
- First generation antihistaminics (promethazine)

### MOA



|                                                                       |                                                                            |
|-----------------------------------------------------------------------|----------------------------------------------------------------------------|
| <p><b>DA = ACH</b></p> <p><b>100     100</b></p> <p><b>Normal</b></p> | <p><b>DA ≠ ACH</b></p> <p><b>50     100</b></p> <p><b>Parkinsonism</b></p> |
|-----------------------------------------------------------------------|----------------------------------------------------------------------------|

### Remember

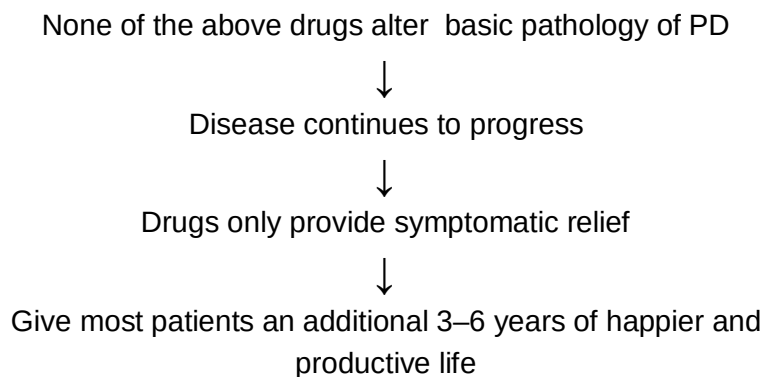
- Tremor is benefited more than rigidity
- Hypokinesia is affected least.
- Central cholinergic drugs → only effective drugs in drug induced parkinsonism

### Adverse effects

- Similar to atropine

### Adverse effects

- Doc for Parkinsonism → **Pramipexole / Ropinirole**
- Most Effective drug for Parkinsonism → **Levodopa + Carbidopa**
- Doc for drug induced Parkinsonism → **Benzhexol**



- Initially, when disease is mild →
  - Central Anticholinergics
  - MAO – B inhibitors → Selegiline
  - Newer DA agonists → Ropinirole or Pramipexole
- Combination of levodopa with a decarboxylase inhibitor → standard therapy → replaced levodopa alone.
- Full benefit lasts for about 2–3 years → then starts declining.
- Subsequently duration of benefit from a levodopa dose progressively shortens → end of dose 'wearing off' effect is seen.
  - Dyskinesias appear, mostly coinciding with the peak of levodopa action after each dose.
  - Still later (4–8 years) the 'on-off' phenomena and marked dyskinesias may become so prominent that the patient is as incapacitated with the drug as without it
  - Levodopa alone → now used only in those patients who develop intolerable dyskinesias with a levodopa-decarboxylase inhibitor combination
- Glutamate (NMDA receptor) Antagonist → Amantadine → used with levodopa for brief periods during exacerbations.
- Direct DA agonists → ropinirole/ pramipexole → used to supplement levodopa in late cases to smoothen 'on off' phenomenon, to reduce levodopa dose and possibly limit dyskinesias.
- COMT inhibitor → entacapone → Used in advanced cases → added to levodopa-carbidopa to prolong its action and subdue 'on off' fluctuation

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## ANTIEPILEPTIC DRUGS

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### Epilepsy

- Epilepsy is a disorder of brain function characterized by periodic and unpredictable occurrence of seizures.
- These are a group of disorders of CNS characterized by paroxysmal cerebral dysrhythmia
- Epilepsy has a focal origin in brain
- Manifestations depend on site of the focus, regions into which the discharges spread and postictal depression of these regions.



## Seizures

- Transient disturbance of cerebral functions
- Due to an abnormal, excessive and temporary neuronal discharge
- Leading to disturbance of sensation, movement, behavior, perception and/or consciousness.
- These episodes are unpredictable and their frequency is highly variable.



## Causes of epilepsy

### 1. Idiopathic

### 2. Secondary to some intracranial causes

- a) Trauma
- b) Infection
- c) Degeneration
- d) Vascular lesions
- e) Tumors

### 3. Secondary to some extracranial causes

- a) Anoxia
- b) Hypoglycemia
- c) Hypocalcaemia
- d) Uremia
- e) Pregnancy (eclampsia)
- f) Poisons (alcohol, lead, insecticides)
- g) Barbiturates withdrawal.

## Types

### A. Generalised seizures

1. Generalised tonic-clonic seizures
2. Absence seizures
3. Atonic seizures
4. Myoclonic seizures
5. Infantile spasms (Hypsarrhythmia)

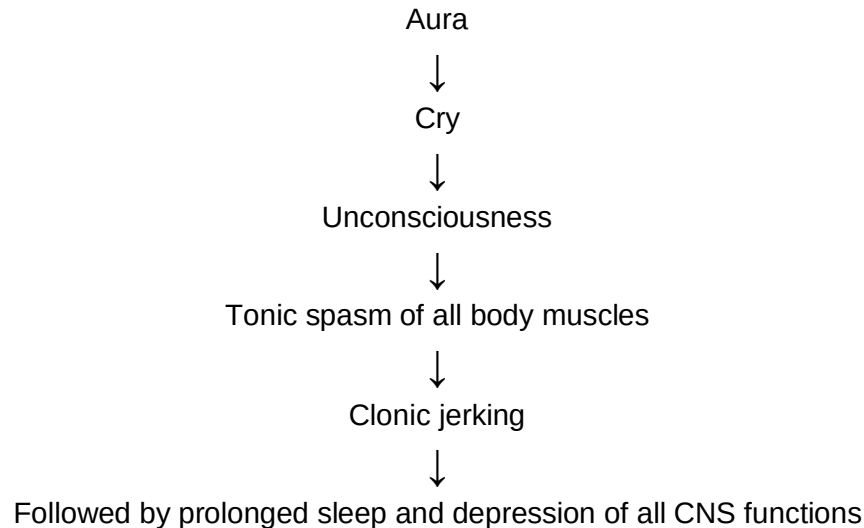
### B. Partial seizures

1. Simple partial seizures
2. Complex partial seizures
3. Simple partial or complex partial seizures secondarily generalized

### A. Generalised seizures

- Also known as GTCS or Major epilepsy
- Commonest
- Lasts 1–2 min

- Usual sequence →



## 2. Absence seizures

- Also known as Minor epilepsy or Petit mal
- Prevalent in children
- Lasts about 1/2 min.
- Momentary loss of consciousness
- Patient apparently freezes and stares in one direction
- No muscular component or little bilateral jerking.
- EEG shows → characteristic 3 cycles per second spike and wave pattern.

## 3. Atonic seizures

- Also known as Akinetic epilepsy
- Unconsciousness with relaxation of all muscles due to excessive inhibitory discharges.
- Patient may fall.

## 4. Myoclonic seizures

- Shock-like momentary contraction of muscles of a limb or the whole body.

## 5. Infantile spasms

- Also known as Hypsarrhythmia
- Seen in infants.
- Probably not a form of epilepsy.
- Intermittent muscle spasm and progressive mental deterioration.
- Diffuse changes in the interseizure EEG are noted.

## B. Partial seizures

### 1. Simple partial seizures

- Also known as SPS or Cortical focal epilepsy
- Lasts 1/2–1 min.
- Convulsions are confined to a group of muscles or localized sensory disturbance depending on the area of cortex involved in the seizure,
- Without loss of consciousness.

## 2. Complex partial seizures

- Also known as CPS or Temporal lobe epilepsy or Psychomotor
- Attacks of bizarre and confused behaviour and purposeless movements, emotional changes lasting 1–2 min along
- With impairment of consciousness.
- An aura often precedes.
- Seizure focus is located in the temporal lobe.

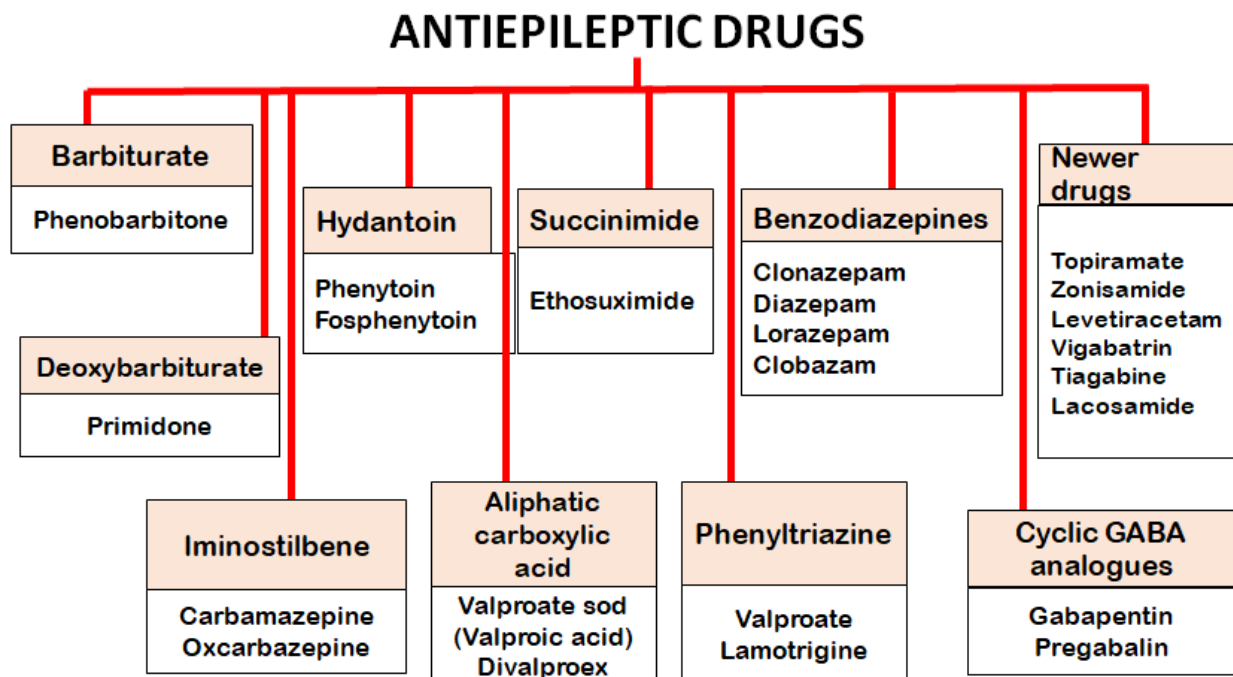
## 3. Simple partial or complex partial seizures secondarily generalized

Partial seizure occurs first



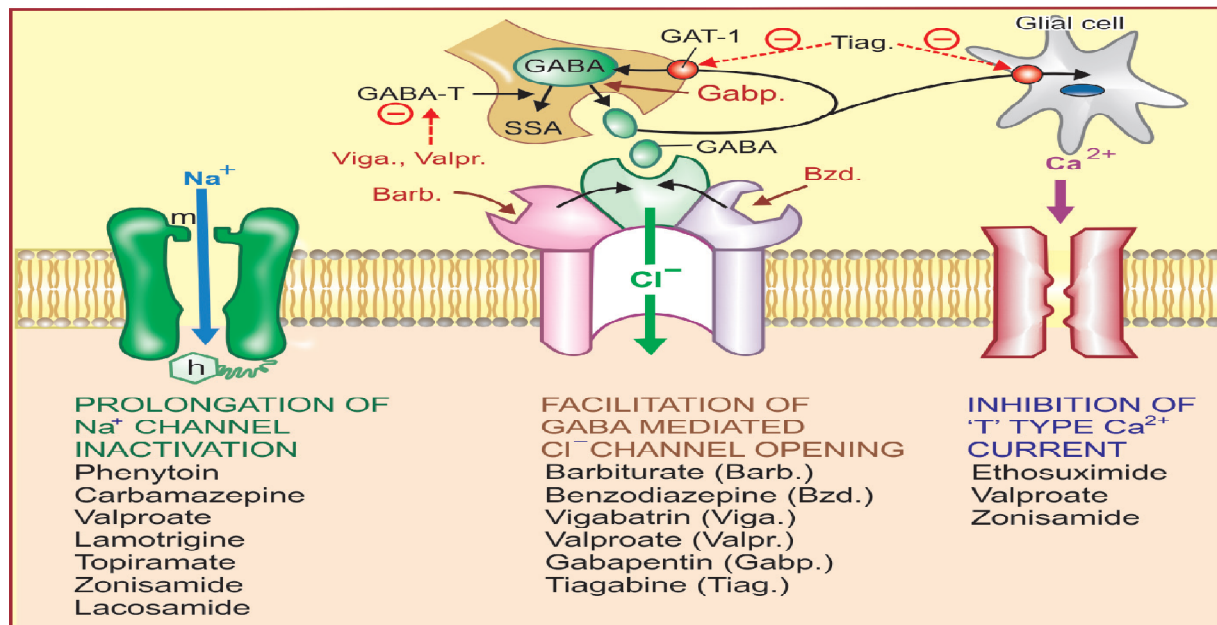
Evolves into generalized tonic-clonic seizures with loss of consciousness.

## Classification



## MOA

- 4 MOA →
  - A) Prolongation of Na<sup>+</sup> channel inactivation
  - B) Facilitation of GABA mediated Cl<sup>-</sup> channel opening
  - C) Decrease in excitatory neurotransmission
  - D) Inhibition of T type Ca<sup>2+</sup> Channels



## A) Prolongation of Na<sup>+</sup> channel inactivation

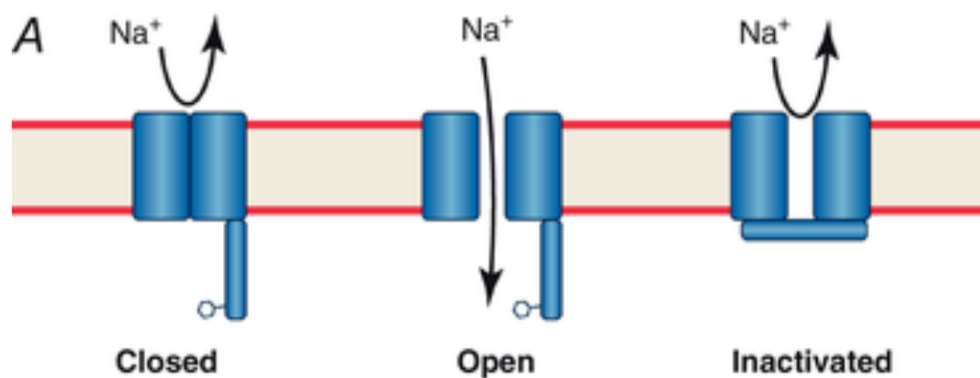
### Drugs acting by this mechanism

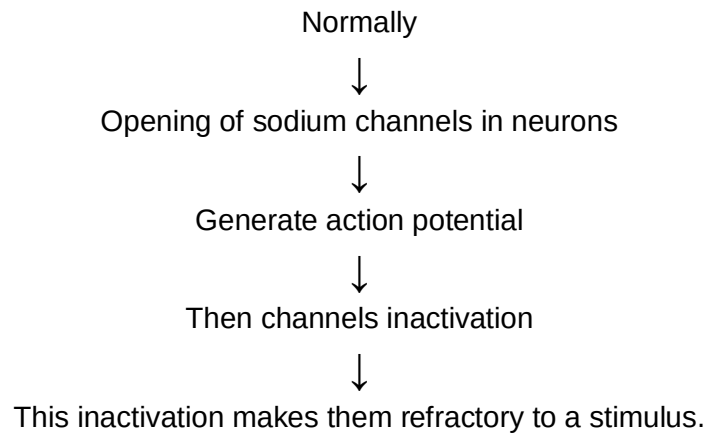
- Phenytoin
- Carbamazepine
- Valproate
- Lamotrigine
- Topiramate
- Zonisamide

### Normally

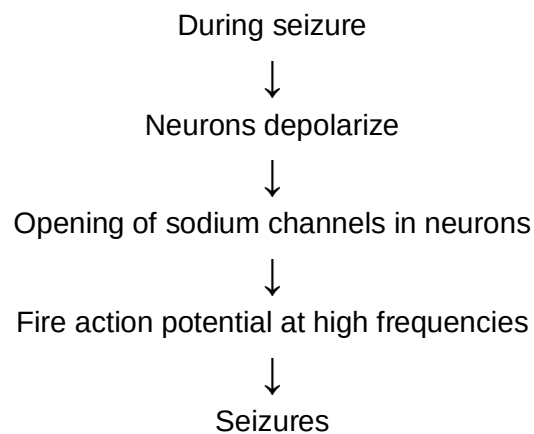
Normally Na<sup>+</sup> channel has following phases →

1. Resting
2. Activated (open)
3. Inactivated (open)

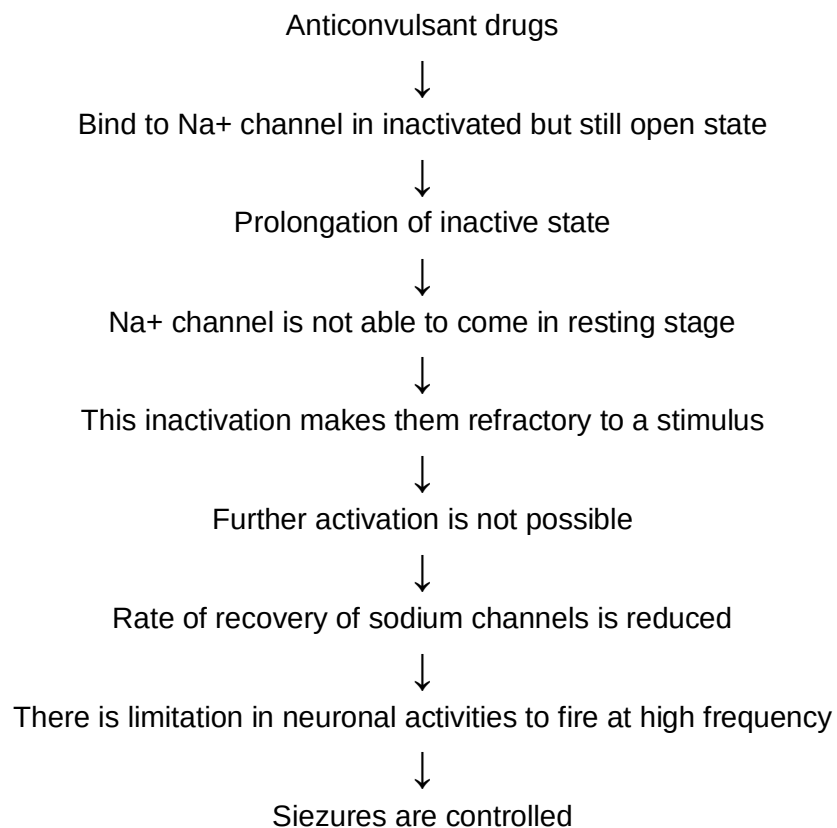




### During seizures



### MOA of antiepileptic drugs





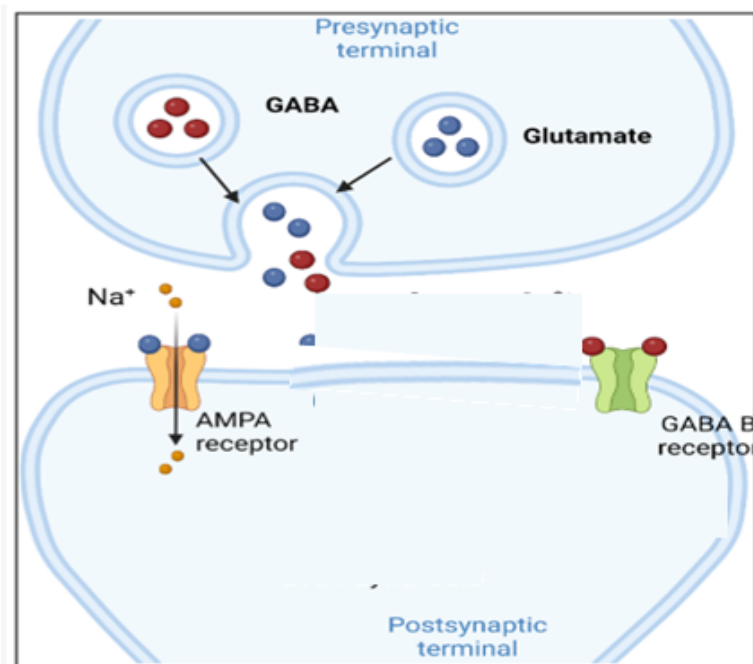
## B) Facilitation of GABA mediated Cl<sup>-</sup> channel opening

### Drugs acting by this mechanism

- Barbiturate (Barb.)
- Benzodiazepine (Bzd.)
- Vigabatrin (Viga.)
- Valproate (Valpr.)
- Gabapentin (Gabp.)
- Tiagabine (Tiag.)

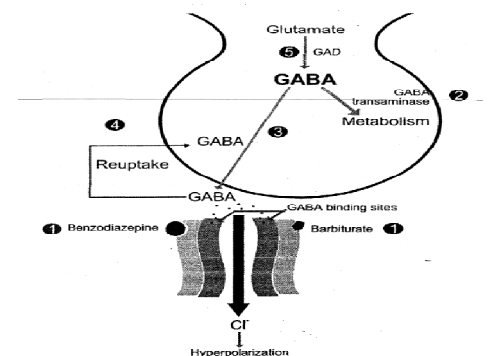
### Normally

- GABA → inhibitory neurotransmitter
- Glutamate → excitatory neurotransmitter
- Seizures are due to →
  1. Reduction in inhibitory synaptic activities (GABA)
  2. Enhancement of excitatory activities (glutamate)



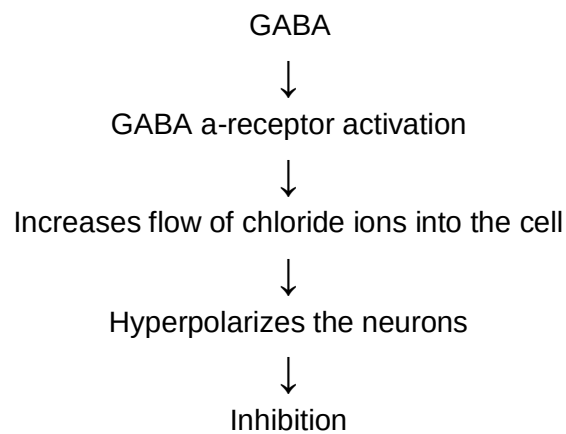
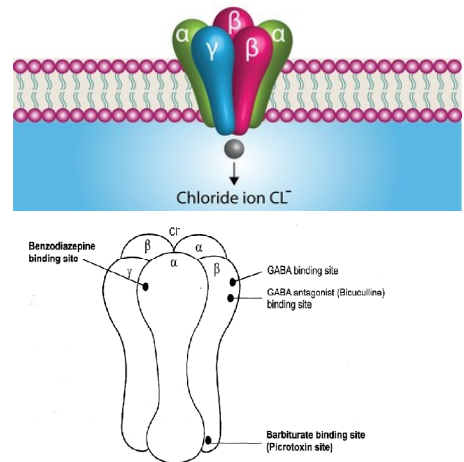
### GABA (gamma amino butyric acid)

- Inhibitory neurotransmitter in CNS
- Synthesized from glutamate by GAD (glutamic acid decarboxylase).
- Removed mainly by neuronal uptake and partly by deamination catalyzed by GABA transaminase.
- Acts on two different types of receptors namely GABA<sub>A</sub> and GABA<sub>B</sub>

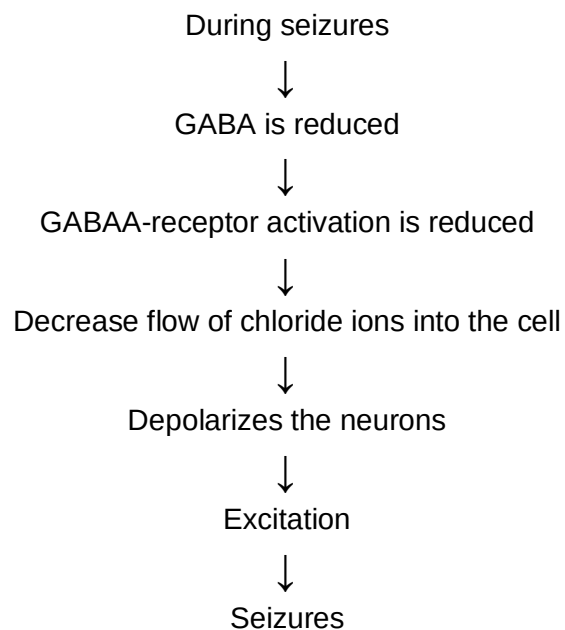


## GABA<sub>A</sub> receptor

- Pentameric structure consisting of → 2α, 2β and 1γ subunits.
- Ionotropic receptor → Directly coupled to chloride channels



## During seizures

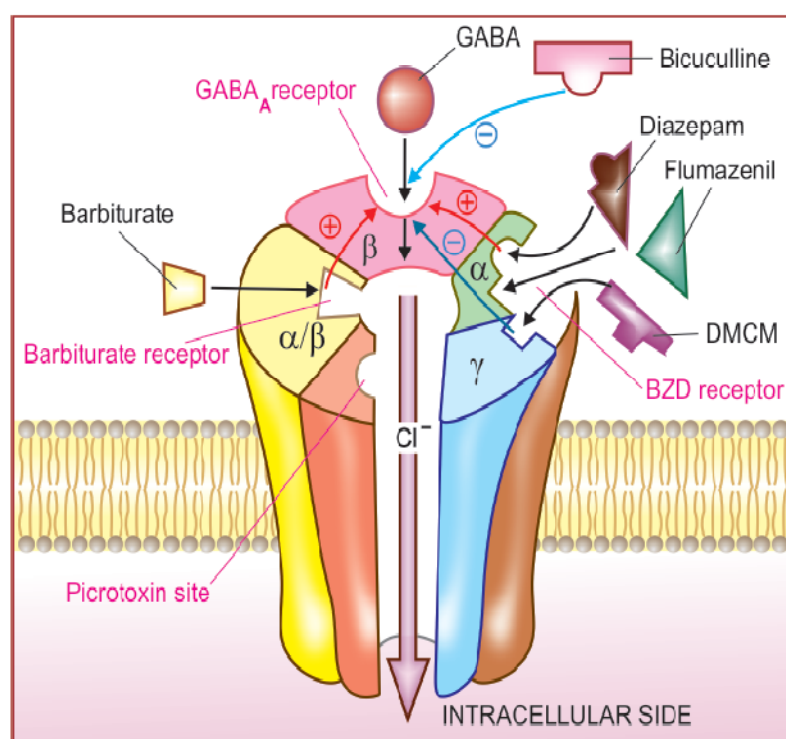
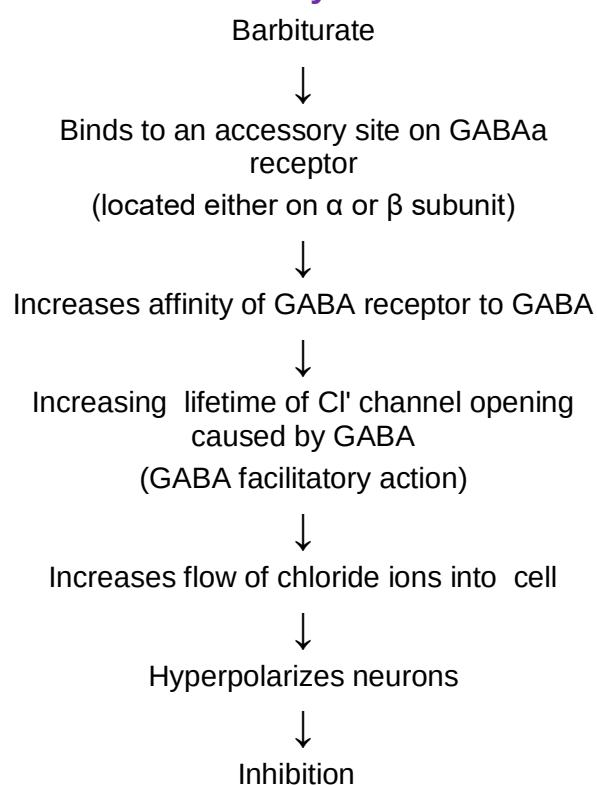


## MOA of antiepileptic drugs

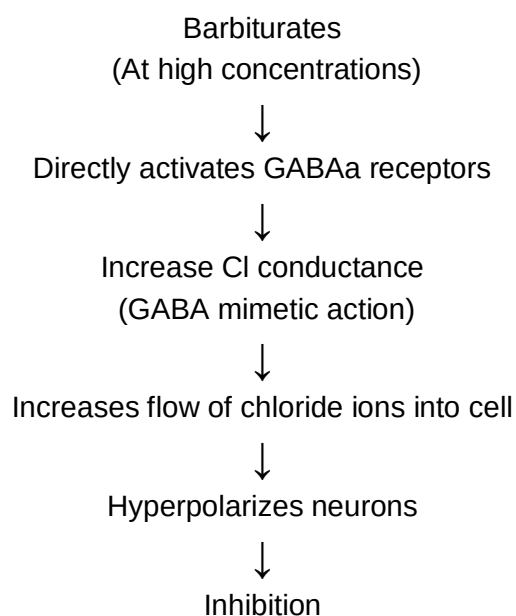
### MOA of Barbiturates

- Barbiturates acts by 3 Mechanisms →
  - GABA facilitatory action
  - GABA mimetic action
  - Through AMPA receptors

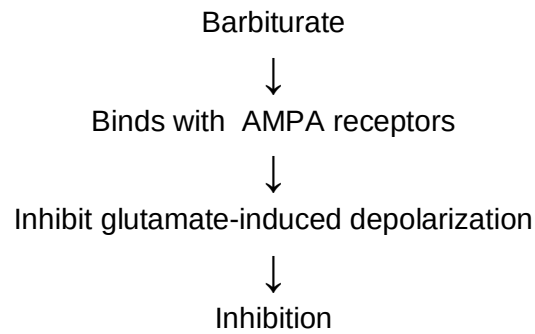
#### 1. GABA facilitatory action



#### 2. GABA mimetic action

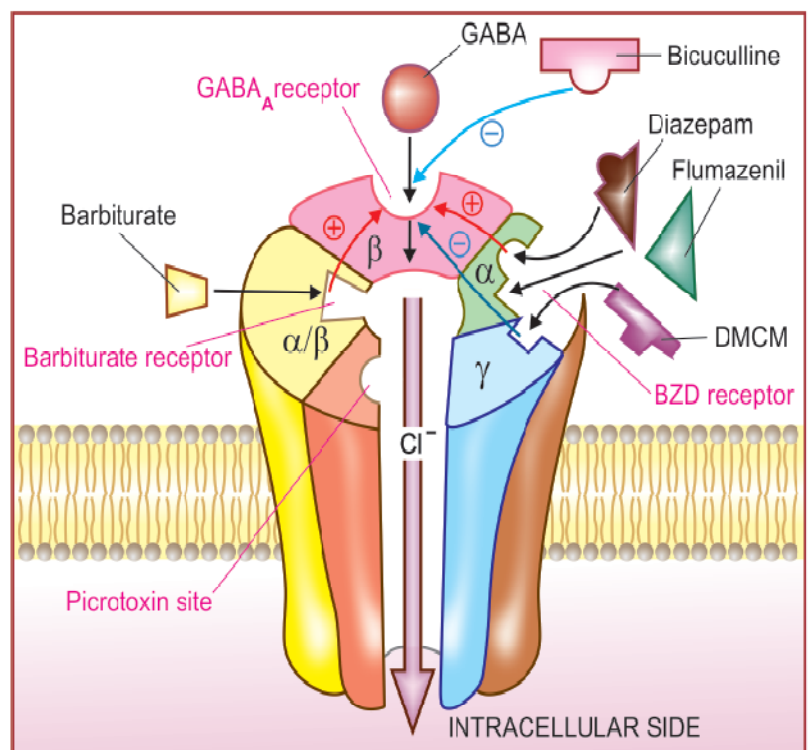
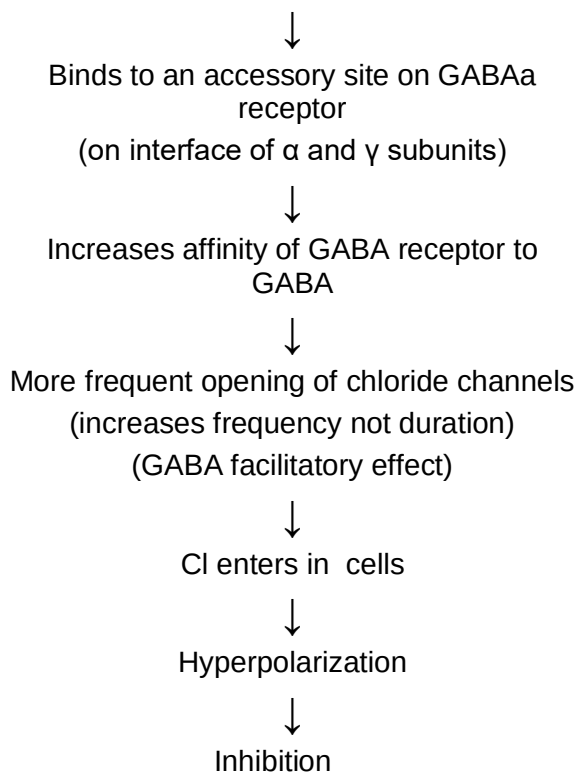


### 3. Through AMPA receptors



### MOA of benzodiazepines (BZDs)

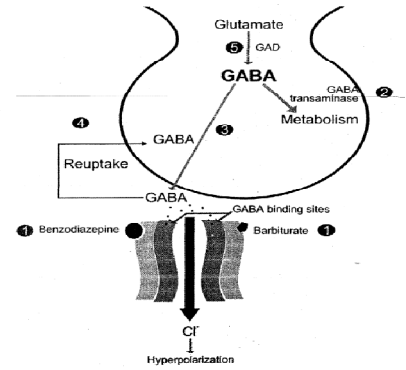
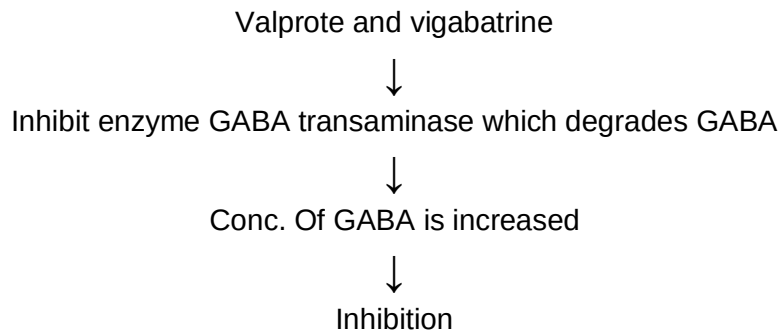
- GABA facilitatory effect only  
Benzodiazepine



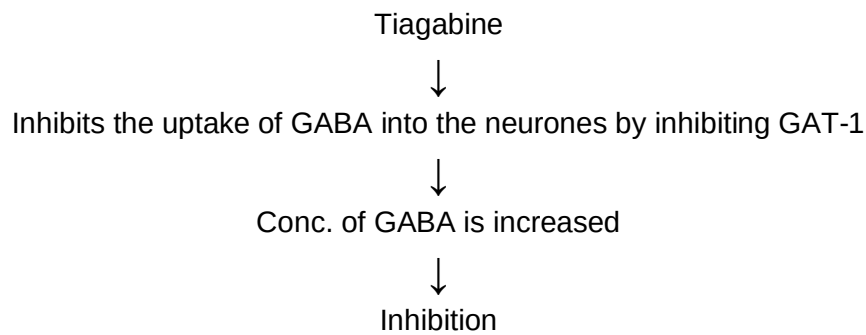
### BZDs Versus Barbiturates

- BZDs → do not themselves increase Cl conductance, i.e. they have only GABA facilitatory but no GABA mimetic action.
- Barbiturates → both GABA facilitatory and GABA mimetic actions
  - BZDs → require GABA to activate receptor hence safe since effect depends on release of GABA.
  - Barbiturates → do not require GABA to activate the receptor hence not safe

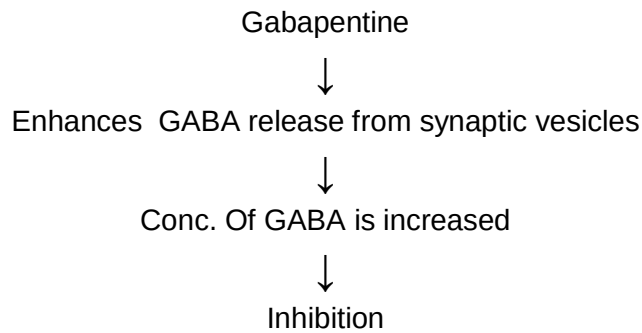
## MOA of Valproate and vigabatrine



## MOA of Tiagabine



## MOA of Gabapentine

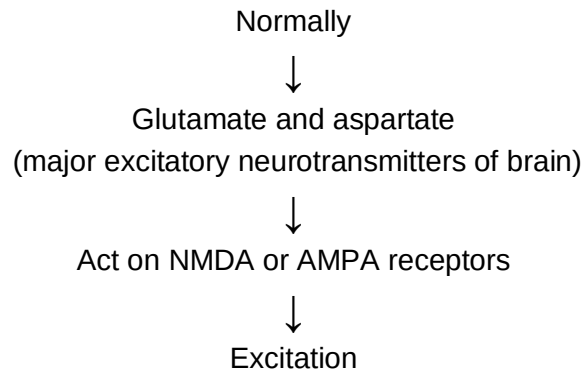


## C) Decrease in excitatory neurotransmission

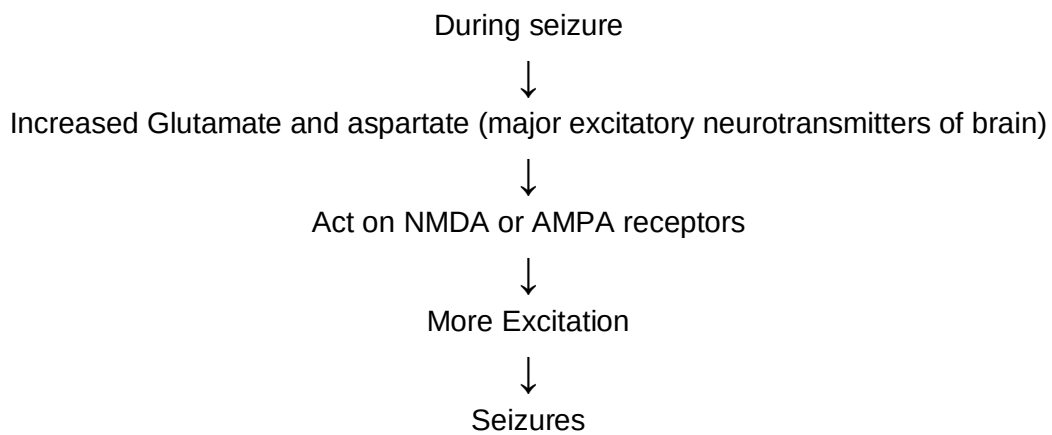
### Drugs acting by this mechanism

- Felbamate

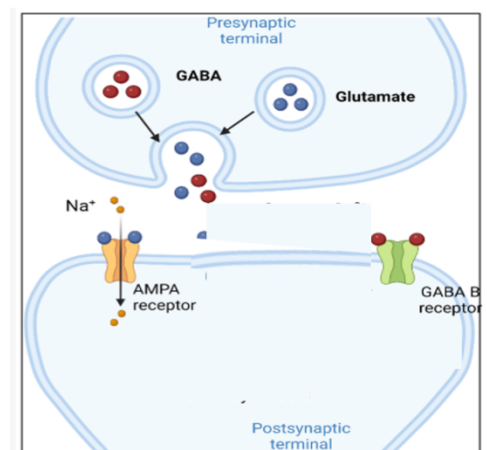
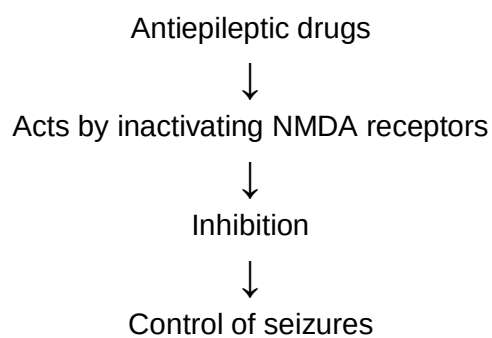
## Normally



## During seizures



## MOA of antiepileptic drugs

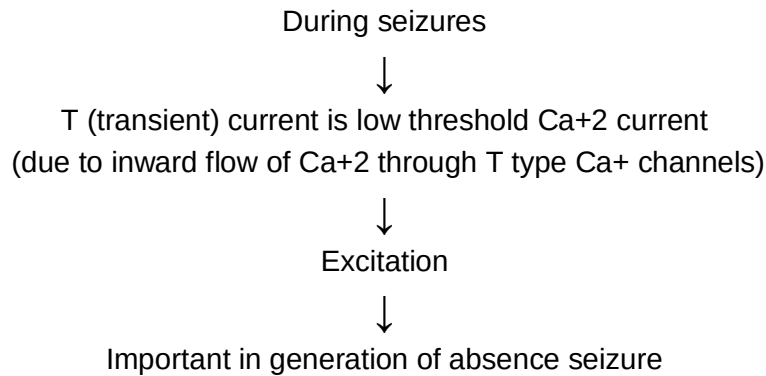


## D) Inhibition of T type $\text{Ca}^{2+}$ Channels

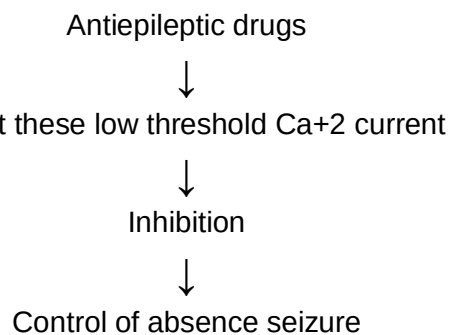
### Drugs acting by this mechanism

- Ethosuximide
- Valproate
- Zonisamide

### During seizures



### MOA of antiepileptic drugs



### Remember

1. Valproate → only drug which acts by all above 3 mechanisms

## PHENYTOIN

### Introduction

- Phenytoin is an antiepileptic without CNS depression.
- There's no increase in seizure threshold so aura is not eliminated.
- Experimentally, it abolishes tonic hind limb response in MES.

### MOA

- It slows the rate of recovery of sodium channels from inactivation so limits the repetitive firing of AP.

## Pharmacokinetics

- Oral absorption is slow, variable and occasionally incomplete.
- Upon i/m injection, it gets precipitated, so absorption is slow and unpredictable hence never used i/m.
- Metabolized by microsomal enzymes mediated hydroxylation in liver and this process becomes saturated so elimination is dose dependant (zero order kinetic).

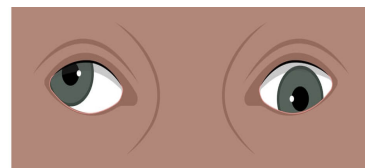
## Adverse effects

### 1. CVS

- Rapid i/v injection cause → cardiovascular collapse, arrhythmia

### 2. CNS

- Nystagmus
- Vertigo
- Diplopia
- Ataxia etc
- Blurring of vision
- Mydriasis
- Ophthalmoplegia.
- Behavioral effects → hyperactivity, confusion, dullness, drowsiness and hallucination.



### 3. Gingival hyperplasia

- Gums grow over the teeth.
- There's an altered collagen metabolism so overgrowth of tissues and hence, there may also be coarseness of facial features.
- It slowly regresses after termination of therapy and so treatment is not stopped.
- Good oral hygiene minimizes the risk.



### 4. GIT

- Nausea
- Vomiting
- Epigastric pain
- Anorexia



### 5. Endocrinal effects

- Decreases insulin release → hyperglycemia and glycosuria.
- Reduces ADH secretion.



## 6. Osteomalacia

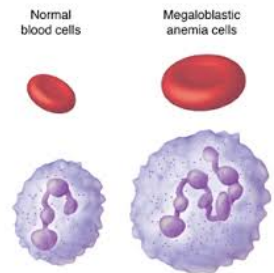
- Decreases absorption of calcium and increases metabolism of vitamin D (due to enzyme induction).
- So osteomalacia is not always improved by vitamin D.

## 7. Hypoprothrombinemia and hemorrhage in newborns

- Hypoprothrombinemia
- Hemorrhage in newborns of mother receiving phenytoin.
- Treatment and prevention → vitamin K.

## 8. Blood

- Megaloblastic anemia due to altered folate absorption and metabolism.



## 9. Hypersensitivity reactions

- Rashes
- Steven's Johnson syndrome
- SLE

## 10. Blood dyscrasias

- Neutropenia, leukopenia, thrombocytopenia, agranulocytosis.

## 11. Hormones

- Hirsutism
- Reduced libido and impotence owing to increase in metabolism of sex hormone

## 12. Fetal malformations

- **Fetal hydantoin syndrome** → Cleft palate, hare lip, CHD, slow growth and mental deformity due to formation of an r epoxide.

## Mnemonic

### Phenytoin: adverse effects

#### PHENYTOIN:

P-450 interactions

Hirsutism

Enlarged gums

Nystagmus

Yellow-browning of skin

Teratogenicity

Osteomalacia

Interference with B12 metabolism (hence anemia)

Neuropathies: vertigo, ataxia, headache

## Therapeutic indications

1. Tonic clonic or partial epilepsy
2. Arrhythmia: ventricular or digitalis induced.
3. Neuralgias.
4. Paroxysmal nightmares.

## Interactions

### A) Increase in concentration and thereby increase risk of toxicity by

- Enzyme inhibitors like chloramphenicol, isoniazid, cimetidine and disulfiram.
- Drugs competing for plasma protein binding site like salicylates and sulfonamides.

### B) Decrease in concentration and thereby risk of reduction in efficacy by

- Enzyme inducers like carbamazepine.
- Folate by reducing the absorption

## Fosphenytoin

1. Prodrug of phenytoin
2. I/ v form has more neutral pH so i/v or i/m administration is without crystallization (no neutralization in glucose) or tissue destruction.
3. Thus it can be administered with any solution with a faster rate but it is too expensive.

# CARBAMAZEPINE

## MOA

- Similar to phenytoin.

## Adverse effects

- Mostly similar to phenytoin
- Except gingival hyperplasia and the reduction in insulin release.
- Additionally there may be cholestatic jaundice and water retention.

## Therapeutic indications

- All but absence seizures.
- Neuralgias.
- Lightning tabetic pain.
- Bipolar affective disorders.

## Oxcarbazepine

- It's a prodrug
- Less potent enzyme inducer than carbamazepine.

## BARBITURATE → PHENOBARBITONE

### MOA

- Increase GABA activity, by prolonging the duration of action of opening of GABA Cl<sup>-</sup> channels, and decreasing glutamate effect.

### Adverse effects

- Tolerance
- Irritation and hyperactivity in children and agitation and confusion in elderly.
- Impairment in school performance.

## ETHOSUXIMIDE

### MOA

- Inhibition of T type Ca<sup>2+</sup> Channels

### Adverse effects

- GIT
- CNS, and Parkinson like symptoms,
- Photophobia
- Hypersensitivity reactions
- Hematological effects.

## VALPROIC ACID (SODIUM VALPROATE)

### Introduction

- Valproic acid is a broad-spectrum antiepileptic that inhibits MES induced hind limb extension as well as PTZ induced seizures.

### MOA

- Valproate is the only drug which acts by all above 3 mechanisms
- Prolonging the recovery of sodium channels from inactivation.
- Increasing the amount of GABA by enhancing the synthesis and decreasing the metabolism.
- Reducing low threshold 'T' calcium current.

### Adverse effects

1. **GIT** → nausea, vomiting, abdominal pain, diarrhea.
2. **CNS** → sedation, ataxia, tremors.
3. **Hepatic toxicity** → occasional but may be fatal.
4. **Acute pancreatitis** → hyperammonemia.
5. **Thinning and curling of hair** → alopecia.
6. **Increase appetite** → weight gain.
7. **Teratogenicity** → Increase risk of neural tube defect.

## Therapeutic indications

1. the varieties of seizures including:
  - Absence seizures.
  - Myoclonic seizures.
  - Partial seizures.
  - Tonic clonic seizures.
2. Bipolar disorders.
3. Neuralgias.
4. Prophylaxis of migraine.
5. Tardive dyskinesias.

## LEVETIRACETAM

### MOA

- It works by the mechanism other than 4 main mechanisms.
- It binds to a synaptic vesicle protein (SV2A), which is involved in vesicle exocytosis.
- Thus it blocks nerve conduction across synapses.

### Adverse effects

- Alopecia
- Pin and needle sensations (reduced by vitamin B6),
- Headache,
- Nausea
- Psychiatric symptoms.

## FIRST LINE DRUG

### MOA

1. **Partial seizure** → Carbamazepine, phenytoin or valproic acid
2. **Tonic-clonic seizures** → Carbamazepine, phenytoin or valproic acid
3. **Myoclonic seizure** → Valproic acid, clonazepam
4. **Absence seizure** → Valproic acid or ethosuximide
5. **Infantile spasm** → ACTH or corticosteroids; vigabatrin is also effective
6. **Lennox- Gastaut syndrome** → Lamotrigine
7. **Seizure of eclampsia** → Magnesium sulfate
8. **Isoniazid induced seizure** → Pyridoxine

| Type of seizure                                                           | First choice drugs        | Second choice drugs       | Alternative/Add-on drugs                                      |
|---------------------------------------------------------------------------|---------------------------|---------------------------|---------------------------------------------------------------|
| 1. Generalised tonic-clonic/simple partial with or without generalization | Carbamazepine, Phenytoin  | Valproate, Phenobarbitone | Lamotrigine, Gabapentin, Topiramate, Primidone, Levetiracetam |
| 2. Complex partial with or without                                        | Carbamazepine, Valproate, | Gabapentin, Lamotrigine,  | Clobazam, Zonisamide, Topiramate                              |

|                       |                                      |                                                       |                              |
|-----------------------|--------------------------------------|-------------------------------------------------------|------------------------------|
| generalization        | Phenytoin                            | Levetiracetam                                         |                              |
| 3. Absence            | Valproate                            | Ethosuximide,<br>Lamotrigine                          | Clobazam, Clonazepam         |
| 4. Myoclonic          | Valproate                            | Lamotrigine,<br>Topiramate                            | Levetiracetam,<br>Clonazepam |
| 5. Atonic             | Valproate                            | Clonazepam,<br>Clobazam                               | Lamotrigine                  |
| 6. Febrile seizures   | Diazepam (rectal)                    | –                                                     | –                            |
| 7. Status epilepticus | Lorazepam (i.v.),<br>Diazepam (i.v.) | Fosphenytoin (i.v.)<br>Phenobarbitone (i.v.,<br>i.m.) | Gen. anaesthetics            |

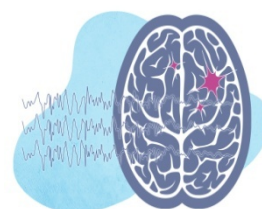
## GENERAL PRINCIPLES IN MANAGEMENT OF A SEIZURE

1. Early diagnosis to achieve a prolonged seizure free period.
2. Detection of cause that may be manageable in some cases.
3. Single seizure, with no brain disorder and normal EEG, and with out family history may not need the therapy.
4. During attack patient must be left undisturbed, in comfortable, lying down, lateral position with loosening of the tight clothes.
  - No drinks and no extra drugs are required.
  - If seizure lasts for more than 10 minutes or a series of seizures occur i/v or per rectal diazepam is indicated.
5. Start with single drug → Gradually increase the dose till maximum limit or adverse effects.
6. If seizure occurs despite adequate treatment, check the patient compliance and achievement of adequate drug- blood level.
  - If still the seizure occurs consider the potential precipitating factors such as sleep disturbances, fever, excess caffeine consumption and use of proconvulsant drugs.
7. If every thing is all right, consider adding another drug, increasing the dose and gradually withdrawing first one.
8. Duration of therapy - 3-5 years after last attack of seizure, thereafter with draw slowly in 1-2 years→ Sudden withdrawal precipitates attack of status epilepticus.
9. If a drug needs immediate withdrawal due to some acute toxicity, maintain on benzodiazepine to cover the withdrawal phase.
10. During pregnancy all the drugs are having risk.
  - Seizures also increase the risk of birth defects due to anoxia.
  - Hence treatment is essential.
  - A single drug with lowest possible dose and risk is preferred. Correction of folic acid deficiency decreases the risk of teratogenecity.

## STATUS EPILEPTICUS

### Introduction

- Frequent attack of convulsions without recovery of consciousness in between.
- It needs immediate control.
- Longer it remains untreated greater is the risk of permanent brain damage.



## Treatment

- **DOC** → intravenous diazepam or lorazepam.
- 10 mg diazepam is administered slowly in 2 minutes.
- Rapid i/v injection carries the risk of respiratory depression and fall in BP
- Onset of action with diazepam is in 3-! minutes and it loss for 20-30 minutes, so simultaneously phenytoin administered in dose of 15 mg/kg, at rate not more than 50 mg/minute

# PSYCHIATRIC DISORDERS

## Introduction

- Psychopharmacological agents or psychotropic drugs are those having primary effects on psyche (mental processes) and are used for treatment of psychiatric disorders

## Types

- **Neuroses** → Insight present
- **Psychoses** → No insight

**Neurosis**  
Neurosis involves chronic distress without delusion or hallucination



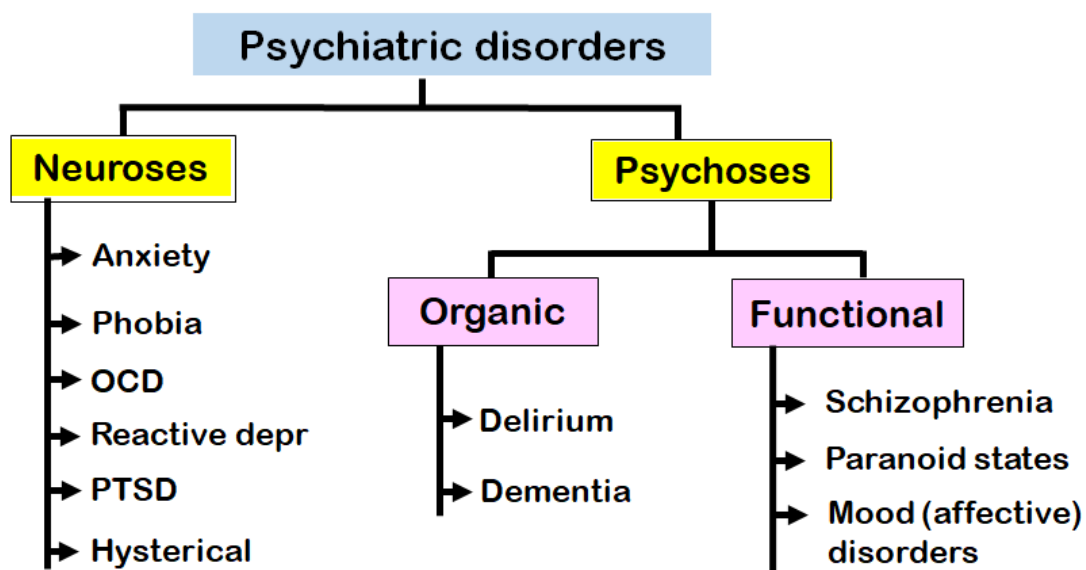
**Vs**

**Psychosis**  
Psychosis entails a loss of contact with reality, often with delusion and hallucination



| Criteria           | Neurosis                                  | Psychosis                                                       |
|--------------------|-------------------------------------------|-----------------------------------------------------------------|
| Definition         | Mild mental disorder causing distress.    | Severe mental disorder causing loss of reality.                 |
| Reality Perception | Generally maintains contact with reality. | Loses touch with reality.                                       |
| Symptoms           | Anxiety, depression, obsessive behaviors  | Hallucinations, delusions.                                      |
| Functionality      | Can function in daily life.               | Significant impairment in daily life.                           |
| Onset              | Gradual, often stress-related.            | Can be sudden or gradual, with a genetic or neurological basis. |
| Insight            | Usually aware of their condition          | Often lacks insight into their condition.                       |

| Criteria         | Neurosis                               | Psychosis                                                                         |
|------------------|----------------------------------------|-----------------------------------------------------------------------------------|
| Hallucinations   | Absent                                 | Present; individuals may see, hear, smell, or feel things that are not there.     |
| Delusions        | Absent                                 | Present; individuals hold strong beliefs that are not based in reality.           |
| Cognition        | Thought processes generally intact.    | Significant cognitive impairment, disorganized thinking.                          |
| Social Impact    | Relationships strained but maintained. | Relationships severely disrupted.                                                 |
| Common Disorders | Anxiety disorders, OCD, depression.    | Schizophrenia, bipolar disorder with psychosis, severe depression with psychosis. |



## I. Neuroses

- Less serious
- Ability to comprehend reality is not lost, though the patient may undergo extreme suffering.

### Includes

1. Anxiety
2. Phobic states
3. Obsessive-compulsive disorder
4. Reactive depression
5. Post-traumatic stress disorder
6. Hysterical

### 1. Anxiety

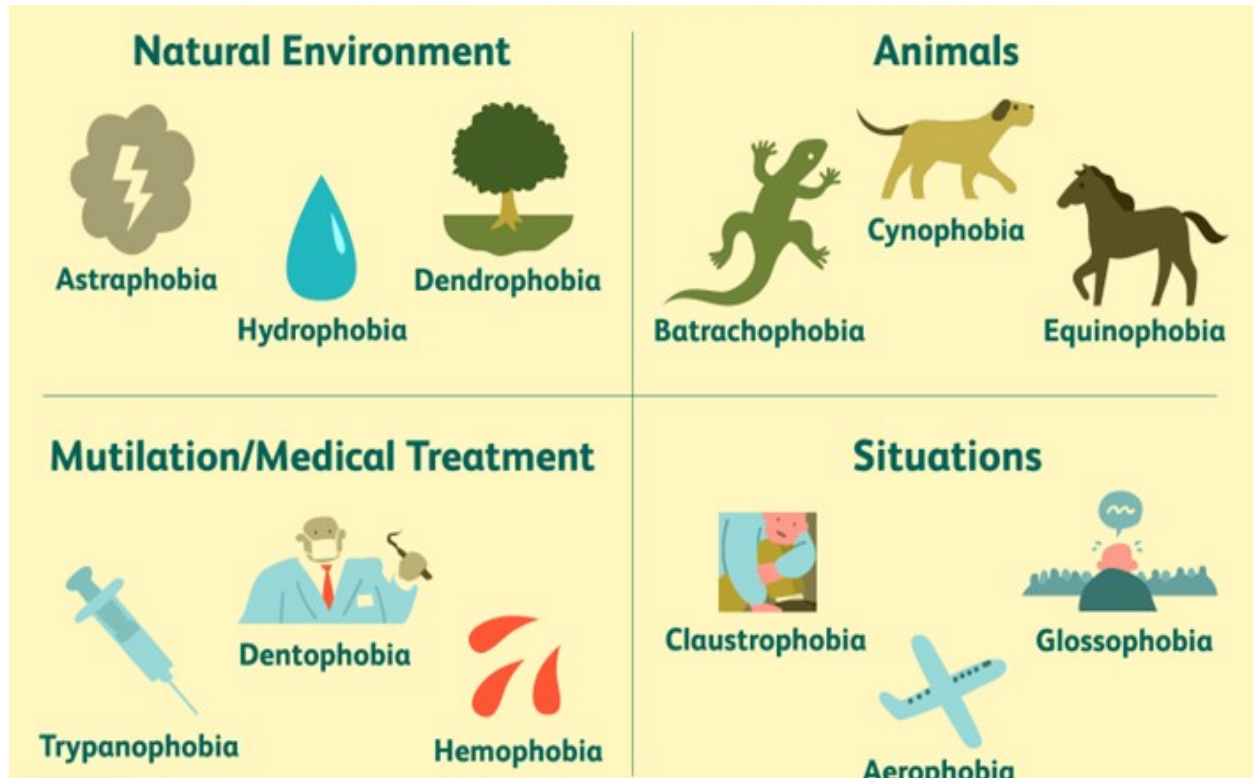
- An unpleasant emotional state associated with uneasiness, worry, tension and concern for the future





## 2. Phobic states

- Fear of the unknown or of some specific objects, person or situations

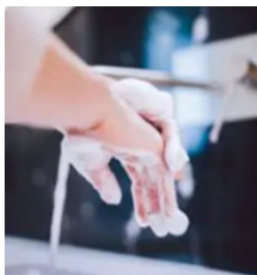


## 3. Obsessive-compulsive disorder

- Limited abnormality of thought or behaviour
- Recurrent intrusive thoughts or ritual like behaviours which the patient realizes are abnormal or stupid, but is not able to overcome even on voluntary effort.
- Obsessions generate considerable anxiety and distress.

### Checking OCD

Individuals experience persistent fears that harm or damage may occur if certain actions, like locking doors or turning off appliances, are not repeatedly verified or checked.



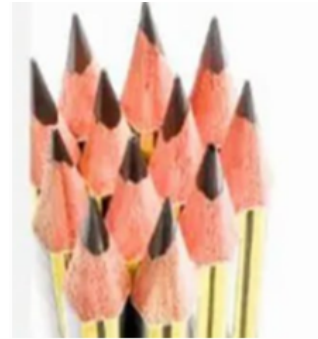
### Contamination OCD

Individuals have an intense fear of germs, dirt, or toxins, leading to compulsive cleaning, washing, or avoidance behaviors to prevent perceived contamination.



## Symmetry and Ordering OCD

Individuals feel an intense need for order, balance, or exactness, often leading to repetitive behaviors to achieve perfect alignment or symmetry.

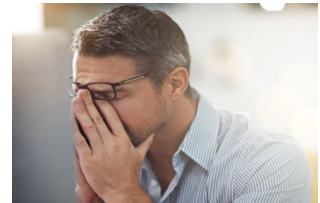


## Ruminations and Intrusive Thoughts OCD

Persistent, unwanted thoughts or mental images that cause distress, often leading individuals to engage in repetitive mental processes to try to neutralize or understand them.

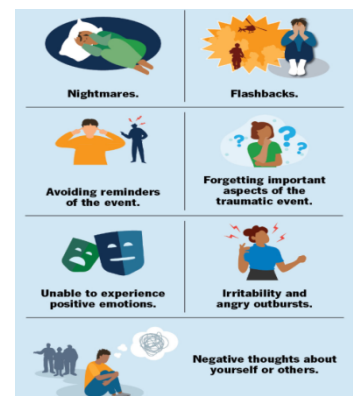
### 4. Reactive depression

- Due to physical illness, loss, blow to self-esteem or bereavement, but is excessive or disproportionate.



### 5. Post-traumatic stress disorder

- Varied symptoms following distressing experiences like war, riots, earthquakes, etc



### 6. Hysterical

- Dramatic symptoms resembling serious physical illness, but situational, and always in the presence of others
- Patient does not feign but actually undergoes the symptoms, though the basis is only psychic and not physical



## I. Psychoses

- Severe psychiatric illness
- Serious distortion of thought, behaviour, capacity to recognise reality and of perception (delusions and hallucinations).

## A. Organic brain syndromes (cognitive disorders)

### ➤ Dementia

### ➤ Delirium

- Some pathological basis can be defined.
- Prominent features → confusion, disorientation, defective memory, disorganized thought and behaviour.



## B. Functional disorders

- No underlying cause can be defined
- Memory and orientation are mostly retained
- But emotion, thought, reasoning and behaviour are seriously altered.
  1. Schizophrenia (split mind)
  2. Paranoid states
  3. Mood (affective) disorders

### 1. Schizophrenia (split mind)

- Splitting of perception and interpretation from reality → hallucinations, inability to think coherently



### 2. Paranoid states

- Marked persecutory or other kinds of fixed delusions (false beliefs) and loss of insight into the abnormality.



### 3. Mood (affective) disorders

- Primary symptom is change in mood state; may manifest as→
  - **Mania** → elation or irritable mood, reduced sleep, hyperactivity, uncontrollable thought and speech, may be associated with reckless or violent behaviour
  - **Depression** → sadness, loss of interest and pleasure, worthlessness, guilt, physical and mental slowing, melancholia, self-destructive ideation.
  - **Bipolar disorder** → with cyclically alternating manic and depressive phases.



## Classification

- Antipsychotic (functional psychosis, especially schizophrenia)
- Antimanic (mania)
- Antidepressants (depression)
- Antianxiety (anxiety and phobic states)

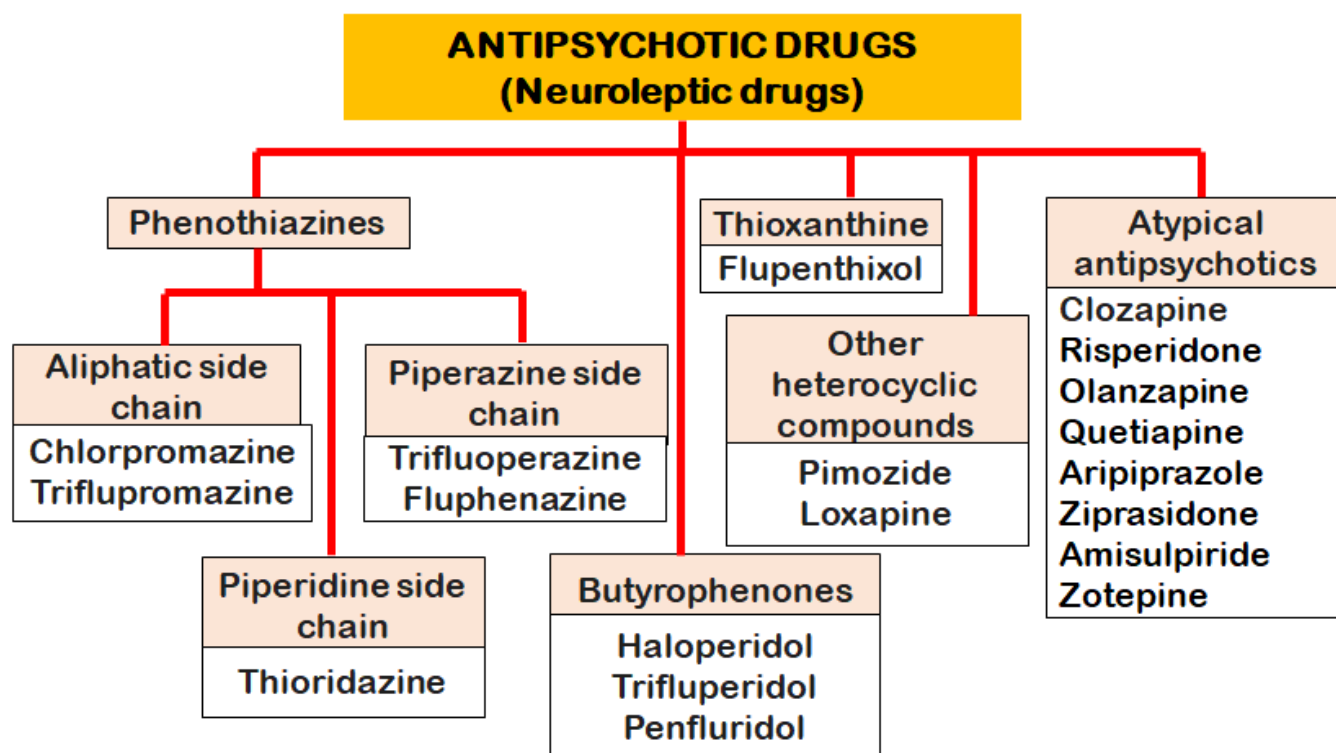
## ANTIPSYCHOTIC DRUGS (NEUROLEPTICS)

|                         | Antipsychotic Drugs (Neuroleptics) |
|-------------------------|------------------------------------|
| Introduction            |                                    |
| Classification          |                                    |
| Pathophysiology         |                                    |
| MOA                     |                                    |
| Pharmacological Actions |                                    |
| Uses                    |                                    |
| Adverse effects         |                                    |

### Introduction

- These are drugs having a salutary therapeutic effect in psychoses.

### Classification



### Pathophysiology

- 3 main neurotransmitters →
  1. Dopamine
  2. Norepinephrine
  3. Serotonin (5-HT)

## Dopamine theory of schizophrenia

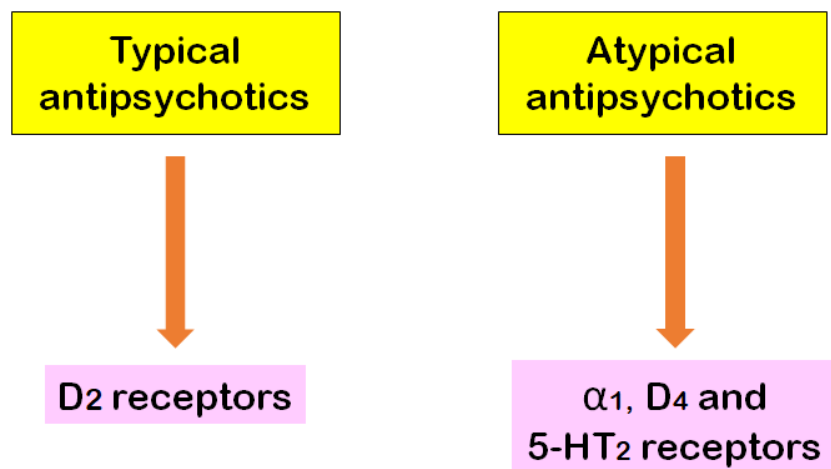
- DA overactivity in limbic area → responsible for schizophrenia

## MOA

- Typical Anti psychotics [ D<sub>2</sub> Blocking ]
- Atypical Anti psychotics [ 5HT<sub>2</sub> Blocking ]
- Most drugs possess both properties

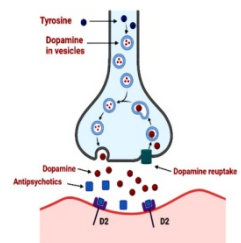
$\frac{D_2 \text{ Blocking}}{5HT_2 \text{ Blocking}} > 1 \longrightarrow \text{Typical Antipsychotics}$

$\frac{D_2 \text{ Blocking}}{5HT_2 \text{ Blocking}} < 1 \longrightarrow \text{Atypical Antipsychotics}$



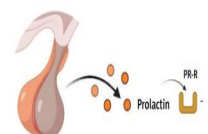
## 1. Typical

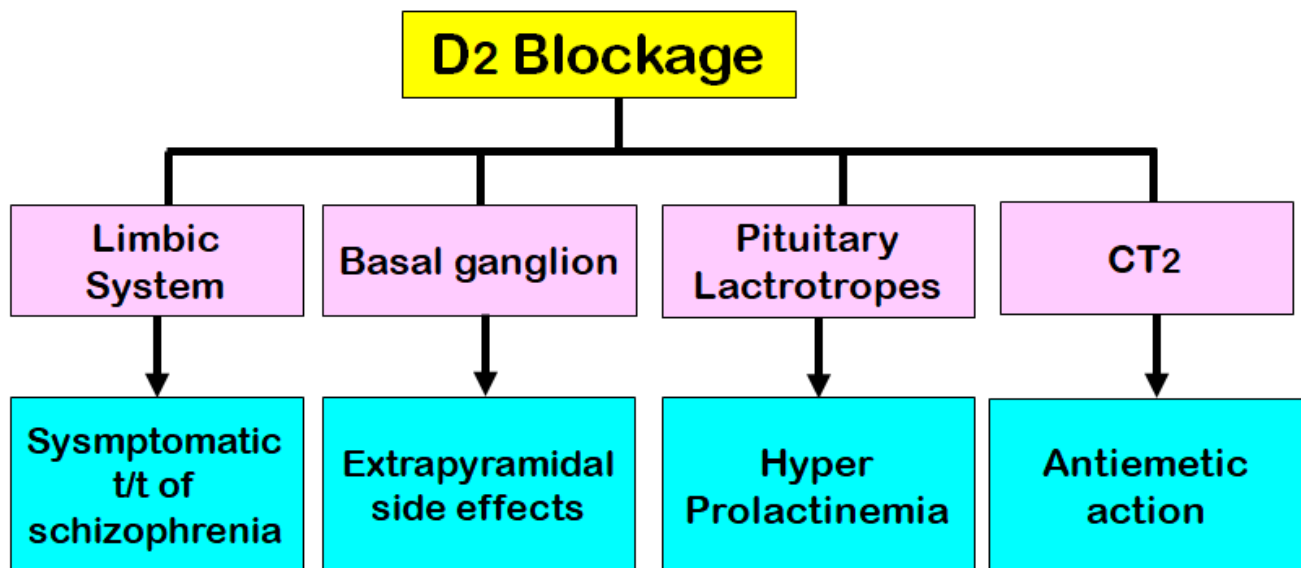
- Potent dopamine D<sub>2</sub> receptor blocking action in temporal and prefrontal areas constituting the 'limbic system' and in mesocortical areas
- Antipsychotic potency has correlation with their capacity to bind to D<sub>2</sub> receptor.



## Other effects

- in basal ganglia** → produces extrapyramidal side effects (Parkinsonism, Acute muscular dystonia, Akathisia, Malignant neuroleptic syndrome, Tardive dyskinesia.)
- Dopaminergic blockade in pituitary lactotropes** → causes hyperprolactinemia
- Dopaminergic blockade in CTZ** → responsible for the antiemetic action.





## 2. Atypical antipsychotics

- Newer generation (second generation) antipsychotics that have weak D2 blocking
- Called atypical because → they have no D2 blocking property (except risperidone).
- Antipsychotic property of atypical antipsychotics depend on a specific profile of action of the drugs on several other neurotransmitter receptors eg.
- 5-HT<sub>2</sub> blocking action
- $\alpha_1$  adrenergic blocking action
- Relatively selective for D<sub>4</sub> receptors.

### Other effects

- Extrapyramidal side effects are minimal (Risperidone can cause some extrapyramidal effects).
- Have minimal effect on prolactin secretion
- Have no antiemetic effect

## Pharmacological Actions

- Chlorpromazine is the prototype
  - A. CNS
  - B. Tolerance
  - C. Dependence

### A. CNS

- In normal individuals
- In psychotic individuals

### In normal individuals

CPZ produces →

- Indifference to surroundings
- Paucity of thought
- Psychomotor slowing
- Emotional quietening

- Tendency to go off to sleep from which the subject is easily arousable.
- Spontaneous movements are minimized but slurring of speech, ataxia or motor incoordination does not occur.
- It is quite different from the sedative action of barbiturates and other similar drugs.
- this has been referred to as the 'neuroleptic syndrome'

## In psychotic individuals

CPZ →

- Reduces irrational behaviour, agitation and aggressiveness and controls psychotic symptomatology.
- Disturbed thought and behaviour are gradually normalized
- Anxiety is relieved.
- Hyperactivity, hallucinations and delusions are suppressed.
- Disturbed sleep pattern in a psychotic is normalized
- Sedative effect is produced promptly, while antipsychotic effect takes weeks to develop.
- Tolerance develops to the sedative but not to the antipsychotic effect.
- Performance and intelligence are relatively unaffected, but vigilance is impaired
- Extrapyramidal motor disturbances are intimately linked to the antipsychotic effect
- Chlorpromazine lowers seizure threshold and can precipitate fits in untreated epileptics.
- Temperature control is knocked off at relatively higher doses rendering the individual poikilothermic.
- Medullary respiratory and other vital centres are not affected, except at very high doses.



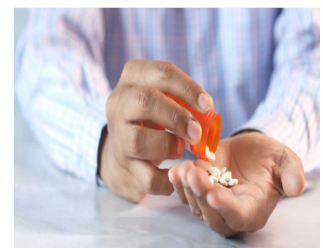
## B. Tolerance

- Tolerance to the sedative actions develops within days or weeks
- Antipsychotic, extrapyramidal and other actions based on DA antagonism do not display tolerance



## C. Dependence

- Hedonically (pertaining to pleasure) bland drugs
- Lack reinforcing effect so that chronic recipients do not exhibit drug seeking behaviour.
- Physical dependence is absent



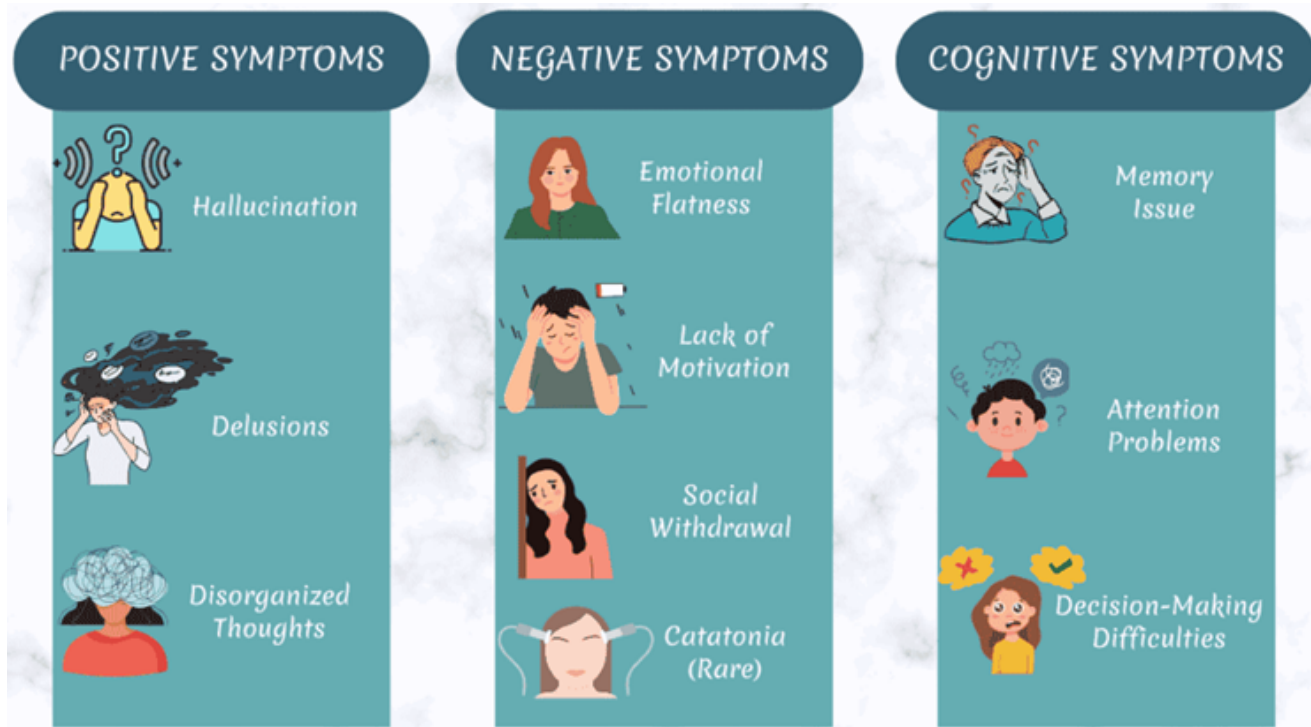
## Uses

- Antipsychotics used primarily in functional psychoses.
  1. Schizophrenia
  2. Mania
  3. Anxiety
  4. As antiemetic
  5. Other uses



## 1. Schizophrenia

- **Positive symptoms** → hallucinations, delusions, disorganized thought, restlessness, insomnia, anxiety, fighting, aggression
- **Negative symptoms** → apathy, loss of insight and volition, affective flattening, poverty of speech, social withdrawal



- They control Positive symptoms better than negative symptoms
- Help upto 90% patients to lead a near normal life in the society
- They are only symptomatic treatment, do not remove the cause of illness
- Judgement, memory and orientation are only marginally improved

## 2. Mania

- Antipsychotics are required in high doses for rapid control of acute mania, and mania patients tolerate them very well.
- CPZ or haloperidol → given i.m. → act in 1–3 days.
- Lithium or valproate → started simultaneously or after the acute phase.
- Such combination therapy is more effective.
- Antipsychotic may be continued for months or may be withdrawn gradually after 1–3 weeks when lithium has taken effect.

## 3. Anxiety

- Antipsychotics have antianxiety action
- But should not be used for simple anxiety because of psychomotor slowing, emotional blunting, autonomic and extrapyramidal side effects.
- Benzodiazepines → preferable.
- Patients having a psychotic basis for anxiety may be treated with a neuroleptic.



#### 4. As antiemetic

- Typical neuroleptics are potent antiemetics.
- They control a wide range of drug and disease induced vomiting
- With the availability of 5-HT<sub>3</sub> antagonists and other antiemetics → use of neuroleptics for control of vomiting has declined

#### 5. Other uses

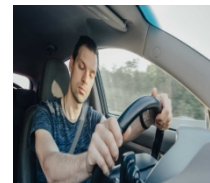
- **Intractable hiccough** → respond to parenteral CPZ.
- **Tetanus** → CPZ is an alternative drug to relieve skeletal muscle spasm.
- **Alcoholic hallucinosis**
- **Huntington's disease**
- **Gilles de la Tourette's syndrome**

#### Adverse Effects

- a. CNS
- b. CVS
- c. Anticholinergic
- d. Endocrine
- e. Extrapyrimal disturbances
- f. Other side effects

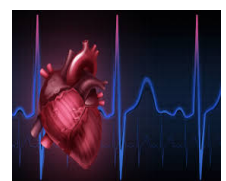
##### A) CNS

- **Drowsiness** → lethargy, mental confusion
- **Increased appetite** → weight gain (not with haloperidol)
- **Aggravation of seizures in epileptics** → even nonepileptics may develop seizures with high doses of some antipsychotics like Clozapine and olanzapine



##### B) CVS

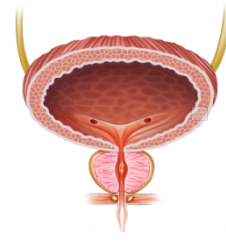
1. **Postural hypotension, palpitation, inhibition of ejaculation** → due to  $\alpha$  adrenergic blockade
  - Maximum → chlorpromazine, thioridazine, clozapine
  - Minimum → Aripiprazole
2. **Q-T prolongation and cardiac arrhythmias** → due to  $\alpha$  adrenergic blockade
  - With thioridazine, pimozide and ziprasidone.





## C) Anticholinergic

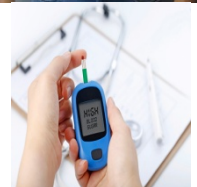
1. Dry mouth
2. Blurring of vision
3. Constipation
4. Urinary hesitancy → in elderly males



➤ Maximum with thioridazine.

## D) Endocrine

1. **Hyperprolactinemia** (due to D2 blockade) is common with typical neuroleptics and risperidone.
  - Amenorrhoea, infertility, galactorrhoea and gynaecomastia occur
  - Atypical antipsychotics, except risperidone, do not appreciably raise prolactin levels.
2. **Worsening of diabetes** → Clozapine, olanzapine.



## E) Extrapyramidal disturbances

- Major dose limiting side effects
- Amongst typical antipsychotics →
  - **Maximum** → with haloperidol
  - **Minimum** → with thioridazine.
  - Amongst atypical antipsychotics →
    - **Maximum** → with risperidone
    - **Minimum** → with clozapine
    - **No extrapyramidal symptoms** → with quetiapine and aripiprazole.

- 1) Acute muscular dystonia
- 2) Parkinsonism
- 3) Akathisia
- 4) Malignant neuroleptic syndrome
- 5) Tardive dyskinesia
- 6) Perioral tremors / Rabbit syndrome

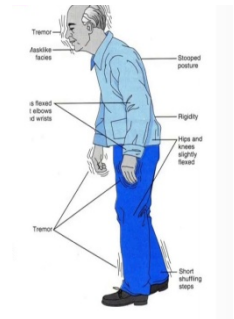
### 1) Acute muscular dystonia

- Earliest appearing symptom (within hours)
- Mostly involving linguo-facial muscles
- Manifest as → torticollis, locked jaw, oculogyric crisis or spasm of other muscles.
- **Treatment** → Central anticholinergics



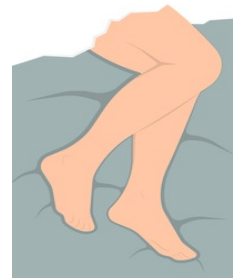
## 2) Parkinsonism

- Appears between 1-4 weeks of therapy.
- With typical manifestations → rigidity, tremor, hypokinesia, mask like facies, shuffling gait;
- Levodopa is not effective since D2 receptors are blocked.
- **Treatment** → DOC → Central anticholinergics like benzhexol



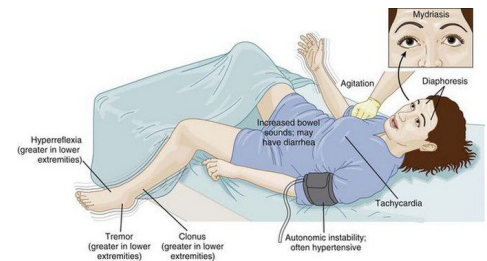
## 3) Akathisia

- Irresistible desire to move about and restlessness in the absence of anxiety is seen in some patients between 1–8 weeks of therapy
- Most common extrapyramidal symptom.
- Cigarette smoking is associated with increased risk of akathisia.
- **Treatment** → Propanolol, central anticholinergics are also useful in the treatment



## 4) Malignant neuroleptic syndrome

- Hyperthermia
- Extreme generalized rigidity
- Autonomic instability
- Altered mental status.
- **Treatment** → i.v. dantrolene (DOC) or bromocriptine.



## 5) Tardive dyskinesia

- Occurs late in therapy
- Characterized by → purposeless involuntary movements like chewing or puffing of cheeks
- **Treatment** →
- Currently no satisfactory treatment for tardive dyskinesia other than discontinuation of drug.
- Terabenazine → currently considered as a first line and most effective medication for treatment of persistent and disabling tardive dyskinesia.
- Reserpine is an alternative to terabenazine.
- Central anticholinergics are contraindicated



## 6. Perioral tremors / Rabbit syndrome

- A rare form of extrapyramidal side effect
- Generally occurs after a few years of therapy.
- **Treatment** → central anticholinergic drugs



## F) Other side effects

- **Corneal and lenticular deposits** → chlorpromazine
- **Retinal deposits** → Thioridazine
- **Blue pigmentation of exposed skin** → Thioridazine
- **Cataract** → Quetiapine
- **Myocarditis** → Clozapine
- **Agranulocytosis** → Clozapine

## Remember

- All typical antipsychotics have antiemetic effects except **thioridazine** → due to blockade of D2 receptor in CTZ
- Maximum extrapyramidal effects → **Haloperidol**
- Least extrapyramidal effects among typical antipsychotics → **Thioridazine**
- Maximum anticholinergic side effects → **Thioridazine**
- Arrhythmogenic action → can cause prolonged QT → **Thioridazine**
- Maximum  $\alpha$  blocking action → **Chlorpromazine and triflupromazine**
- Longest acting antipsychotic → **Penfluridol**
- Most commonly used antipsychotic by IV route → **Haloperidol**
- Most potent typical antipsychotics → **Haloperidol, Fluphenazine**
- Most potent atypical antipsychotic → **Risperidone**

## INDIVIDUAL DRUGS

### Clozapine

- **Blocks D4, 5-HT and  $\alpha$ -adrenergic receptors.**
- Despite its anticholinergic property, it causes hypersalivation (sialorrhea)
- It is highly epileptogenic, can induce seizures even in nonepileptics.
- It suppresses both positive and negative symptoms of schizophrenia.
- Clozapine is more effective than classical agents for resistant schizophrenia
- Clozapine does not cause extrapyramidal side effects

### Olanzapine

- **Blocks D2, 5-HT<sub>2</sub>,  $\alpha$ <sub>2</sub>, muscarinic and H1 receptors.**
- Antimuscarinic (anticholinergic) property → can cause dry mouth, urinary retention and constipation.
- Weight gain
- Worsening of diabetes
- Seizure precipitation (epileptogenic)
- Stroke and death.
- It can also be used in bipolar disorder and acute mania.

### Risperidone

- **Only atypical antipsychotic with potent D2 blocking activity.**
- **Also blocks 5HT<sub>2</sub>,  $\alpha$ <sub>2</sub> and H1 receptors.**

- Due to its D<sub>2</sub> blocking action, it is the only atypical antipsychotic which has marked extrapyramidal effects and can cause hyperprolactinemia.
- Increased risk of stroke (cerebrovascular accident) in elderly.
- Atypical antipsychotic with maximum antipsychotic effects.
- Paliperidone is active metabolite of risperidone which has lesser side effects.

## Quetiapine

- **Blocks 5HT<sub>2</sub>, 5HT<sub>1A</sub>, D<sub>2</sub>, , α<sub>2</sub> , and H<sub>1</sub> receptors with very low D<sub>2</sub> blocking activity.**
- Among atypical neuroleptics, it has maximum sedative effects
- Can cause cataract.
- Shortest acting.

## Aripiprazole

- **Only antipsychotic with D<sub>2</sub> agonistic activity (all others are D<sub>2</sub> antagonists).**
- **Also has 5HT<sub>1A</sub> agonistic and 5HT<sub>2</sub> antagonistic activity**
- Also known as dopamine-serotonin stabilizer.
- Longest acting
- Least sedating (can cause insomnia).
- It has been approved for treatment of irritability in autism.

# ANTIMANIC DRUGS

## Introduction

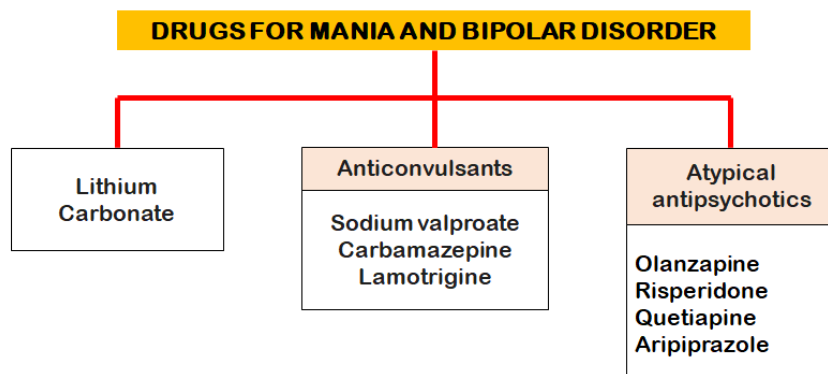
- Major depression and mania → two extremes of affective disorders which refer to a pathological change in mood state.

## Mania

- Elation or irritable mood
- Reduced sleep
- Hyperactivity
- Uncontrollable thought and speech
- Associated with reckless or violent behaviour



## Classification

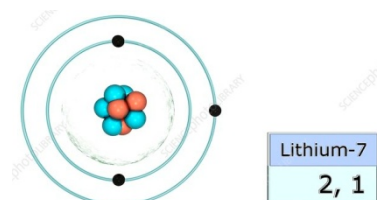


# LITHIUM CARBONATE

|                         | Lithium Carbonate |
|-------------------------|-------------------|
| Introduction            |                   |
| MOA                     |                   |
| Pharmacological Actions |                   |
| Pharmacokinetics        |                   |
| Interactions            |                   |
| Use                     |                   |
| Adverse effects         |                   |

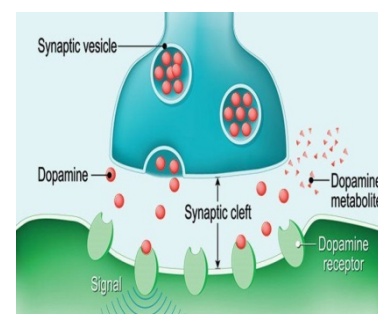
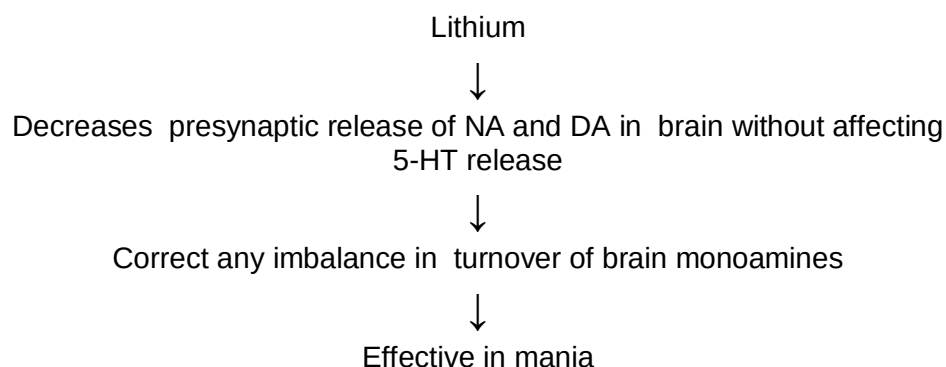
## Introduction

- Lithium is a small monovalent cation.

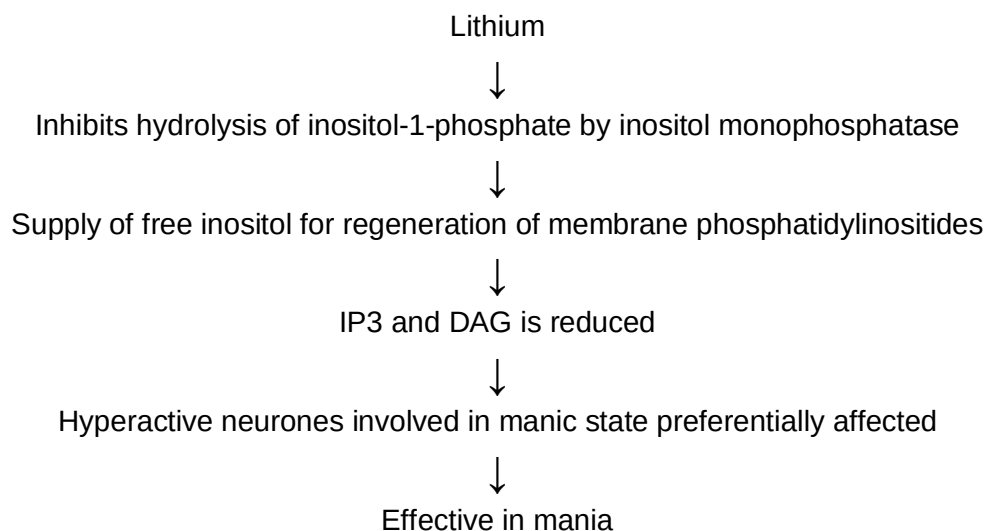


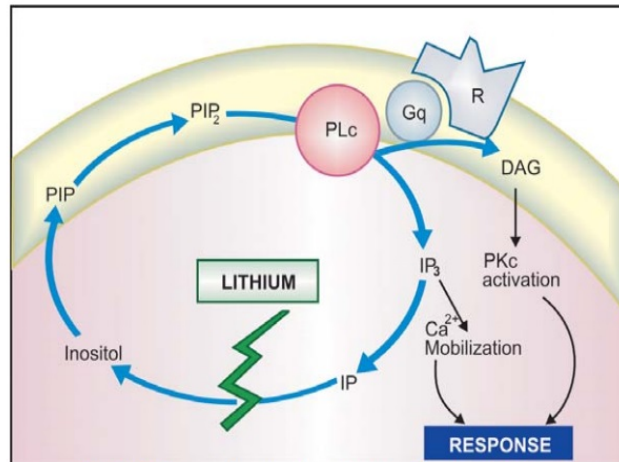
## MOA

- 2 MOA



In mania overactive receptors functioning through phosphatidyl inositol hydrolysis





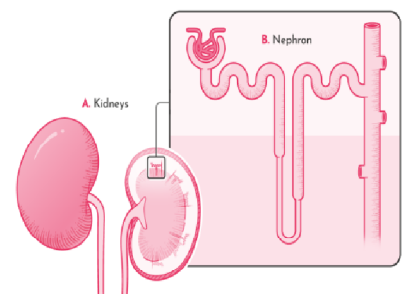
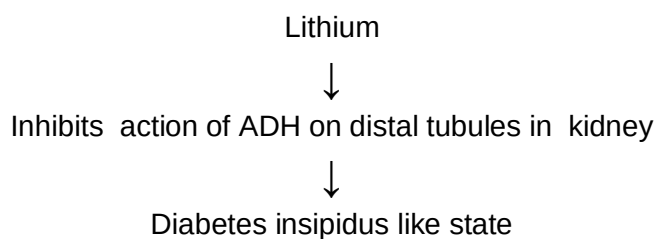
## Pharmacological Actions

1. CNS
2. Kidney
3. Thyroid
4. Endocrine

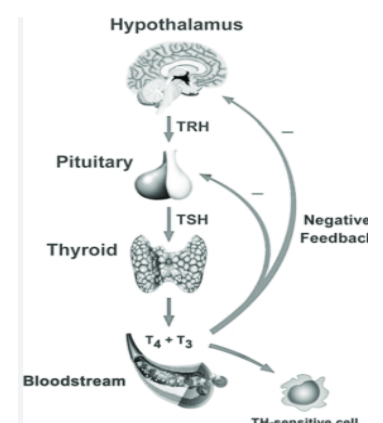
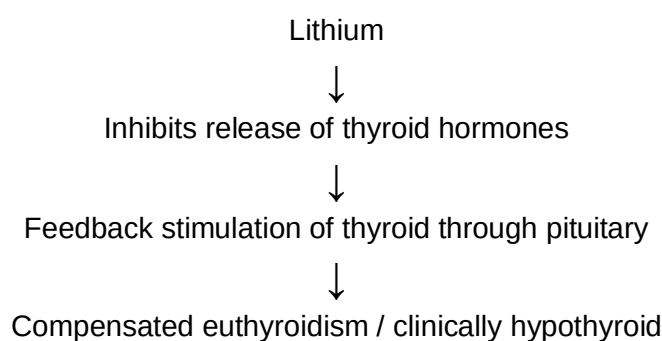
### 1. CNS

- Lithium has practically no acute effects in normal individuals as well as in bipolar patients.
- It is neither sedative nor euphoric
- But on prolonged administration → it acts as a mood stabiliser in bipolar disorder.
- Given to patients in acute mania → it gradually suppresses the episode taking 1–2 weeks
- Continued treatment → prevents cyclic mood changes.
- Markedly reduced sleep time of manic patients is normalized.

### 2. Kidney



### 3. Thyroid

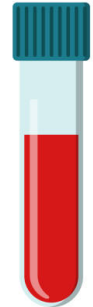


## 4. Endocrine

- An insulin-like action on glucose metabolism is exerted

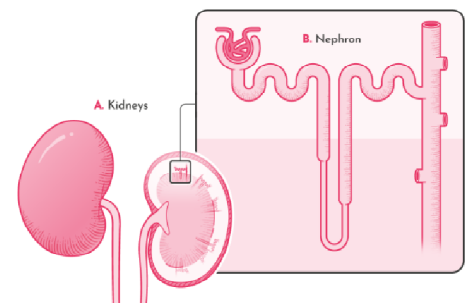
## Pharmacokinetics

- Lithium has narrow (very low) therapeutic index → requires therapeutic drug monitoring (TDM)
- Different serum concentrations have different effect →
  1. Therapeutic level → 0.8-1.2 mEq/L (For tit of acute mania)
  2. Prophylactic level → 0.5-0.8 mEq/L (For relapse prevention in bipolar disorder)
  3. Toxic lithium levels → 2.0 mEq/L



## Interactions

1. **Diuretics (thiazide, furosemide)** → causing Na<sup>+</sup> loss promote proximal tubular reabsorption of Na<sup>+</sup> as well as Li<sup>+</sup> → plasma levels of lithium rise.
2. **NA** → Lithium reduces pressor response to NA.
3. **Insulin/sulfonylurea** → Lithium enhance insulin/sulfonylurea induced hypoglycaemia.



## Uses

### 1. Acute mania

- Though lithium is effective in controlling acute mania, response is slow and control of plasma levels is difficult during the acute phase.
- Most psychiatrists now prefer to use an atypical antipsychotic orally or by i.m. injection, with or without a potent BZD like clonazepam/ lorazepam, and start lithium after the episode is under control.
- Maintenance lithium therapy is generally given for 6–12 months to prevent recurrences.

### 2. Prophylaxis in bipolar disorder

- It lengthens the interval between cycles of mood swings: episodes of mania as well as depression are attenuated
- Patients have been maintained on lithium therapy for over a decade

### 3. Neuropsychiatric illness → cluster headache and as adjuvant to antidepressants in resistant nonbipolar major depression.

### 4. Cancer chemotherapy induced leukopenia and agranulocytosis → Lithium may hasten the recovery of leukocyte count.

### 5. Inappropriate ADH secretion syndrome → Lithium tends to counteract water retention, but is not dependable.

## Adverse effects

- 1) Neurological
- 2) Renal
- 3) Cardiovascular
- 4) Endocrine
- 5) GIT



- 6) Dermatological
- 7) Teratogenicity

### 1) Neurological

- **Tremor** → commonest side effect of lithium.
- **Other CNS side effects** → giddiness, ataxia, motor incoordination, hyperreflexia, mental confusion, nystagmus.
- **DOC for lithium induced tremor** → Propranolol



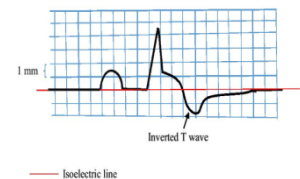
### 2) Renal

- Nephrogenic diabetes insipidus with polyuria & polydipsia.
- **DOC for Lithium induced nephrogenic DI** → Amiloride



### 3) Cardiovascular

- Effects are similar to hypokalemia which causes arrhythmia
- **Most common ECG change** → T wave depression.



### 4) Endocrine

- Goitre
- Hypothyroidism



### 5) GIT

- Vomiting
- Diarrhoea
- Metallic taste
- Abdominal pain



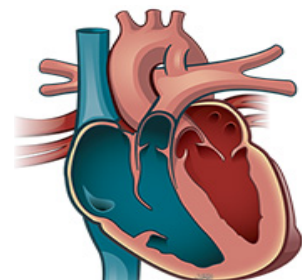
### 6) Dermatological

- Acneiform eruptions
- Papular eruption
- Exacerbation of psoriasis



### 7) Teratogenicity

- Ebstein's anomaly in fetus





## ANTIDEPRESSANT DRUGS

### Introduction

- Major depression and mania → two extremes of affective disorders which refer to a pathological change in mood state.



### Major depression

- Sad mood
- Loss of interest and pleasure
- Low energy
- Worthlessness
- Guilt
- Psychomotor retardation
- Agitation
- Change in appetite and/or sleep
- Suicidal thoughts, etc.
- It may be a unipolar or a bipolar disorder in which cycles of mood swings from mania to depression occur over time.



### Remember

- Mood change (depression) may have a psychotic basis and induce anxiety.
- On other hand, pathological anxiety may lead to depression.
- Anxiety and depression are the leading psychiatric disorders now

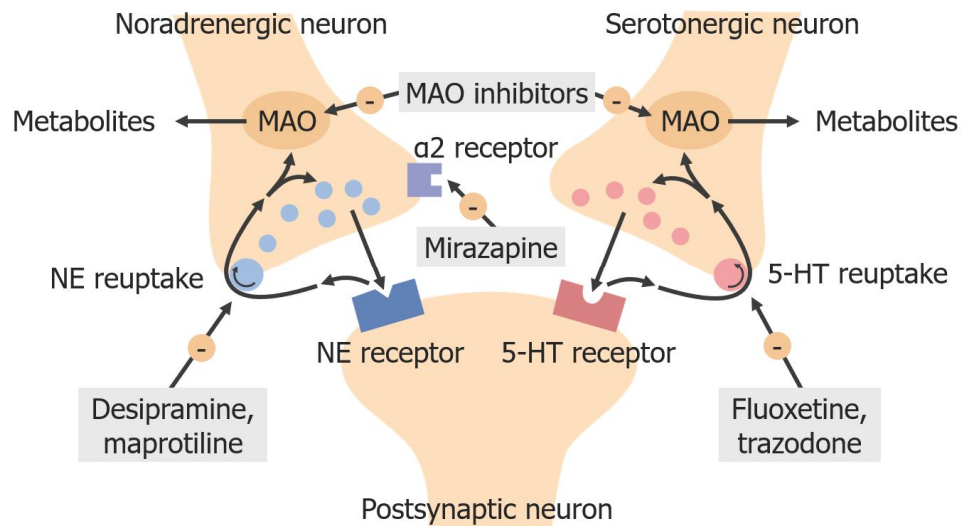


### Pathophysiology

- 3 main neurotransmitters involved in depression →
  - Dopamine
  - Norepinephrine
  - Serotonin (5-HT)
- When brain levels of one or more neurotransmitter are low or unbalanced, depression can result.

### Principle of Antidepressant drugs

- Antidepressant drugs work by →
  - Increasing concentration by decreasing re-uptake
  - Decreasing breakdown of one or more of these neurotransmitters.



## MAO INHIBITORS

### Introduction

- Monoamine oxidase (MAO) is a mitochondrial enzyme involved in the oxidative deamination of biogenic amines (Adr, NA, DA, 5-HT).

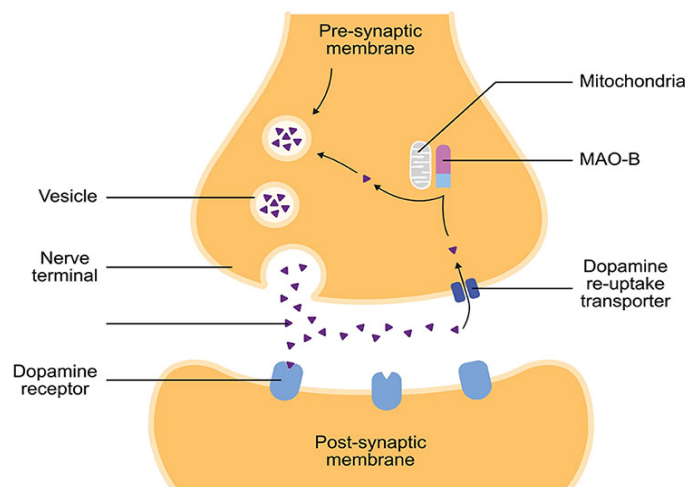
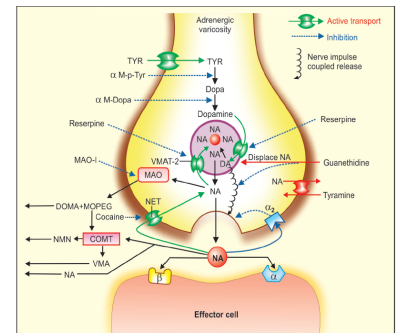
### Types of MAO enzyme

#### 1. MAO-A

- Preferentially deaminates 5-HT & NA, DA
- Found in peripheral adrenergic nerve endings, intestinal mucosa and human placenta.

#### 2. MAO-B

- Preferentially deaminate DA
- Found in brain and platelets
- Dopamine is degraded equally by both isoenzymes.
- Liver contains both isoenzymes



## Classification of MAO inhibitors

1. **Nonselective** → Tranylcypromine, phenelzine, isocarboxazid.
2. **Selective MAO-A** → Moclobemide, clorgyline (used in depression)
3. **Selective MAO-B** → Selegiline (used in parkinsonism)

## Non selective MAO inhibitors

- Nonselective MAO inhibitors inactivate enzyme irreversibly.
- Drugs themselves stay in the body for relatively short periods, but their effects last for 2–3 weeks after discontinuation → they are 'hit and run' drugs.
- Return of MAO activity depends on synthesis of fresh enzyme

## Interactions

- Non selective MAO inhibitors interact with many food constituents and drugs

1. **Cheese reaction** → Hypertensive crisis occurs when cheese, beer, wines, pickled meat and or yeast extract contain large quantities of tyramine is given.



Cheese, beer, wines, pickled meat and or yeast extract



Contain large quantities of tyramine



When given with non selective MAO inhibitors



NA formed too much and not destroyed



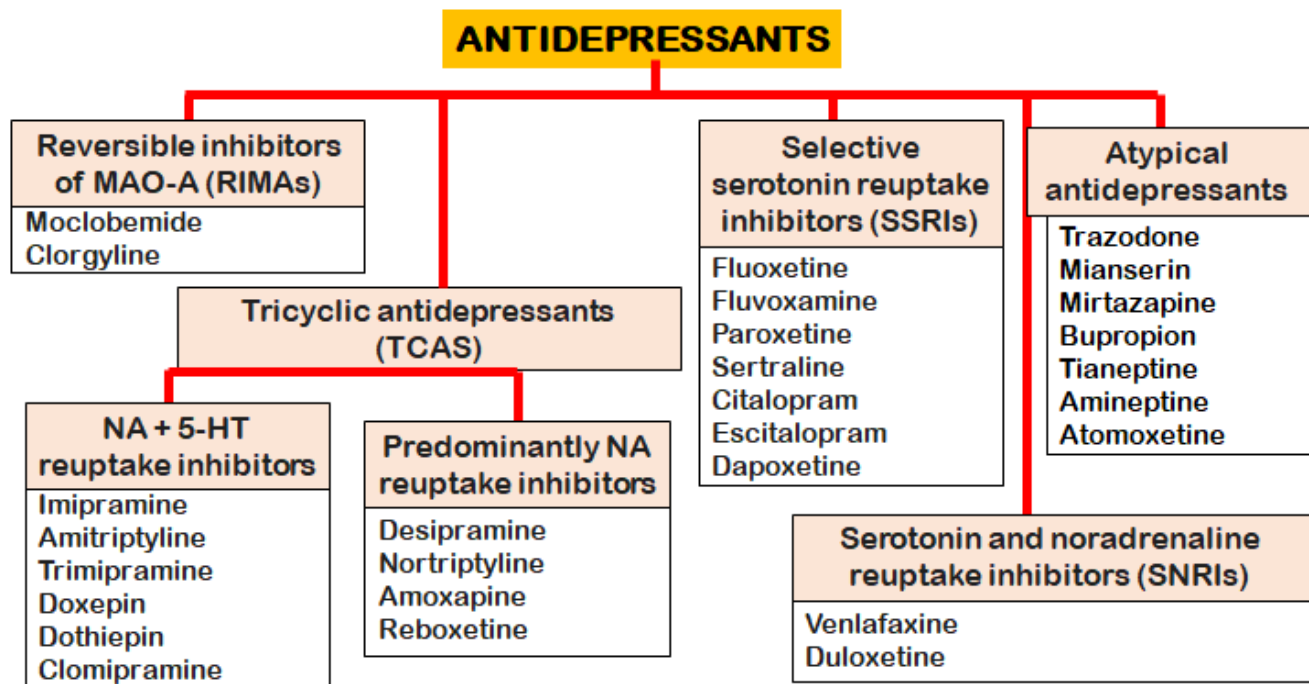
Hypertensive crisis



- It is treated by IV phentolamine (rapidly acting  $\alpha$  blocker)
- Prazosin and chlorpromazine are alternatives.

2. **SSRIs** → Serotonine syndrome occurs
3. **Reserpine, guanethidine or tricyclic antidepressant** → Hypertension and excitment occurs  
→ due to their initial NA releasing or uptake blocking action
4. **Levodopa** → Excitement and hypertension occur due to increase in biological  $t_{1/2}$  of DA and NA that are produced from levodopa.

## Classification of Antidepressants



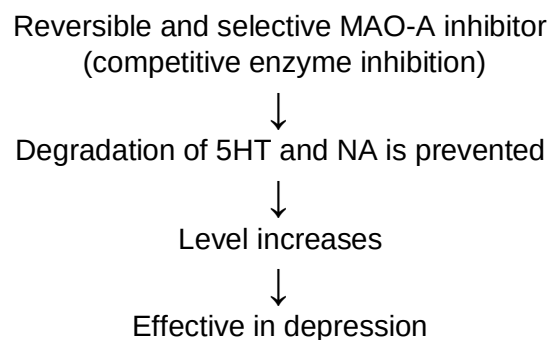
|                         | RIMAs | TCA | SSRI | SNRI |
|-------------------------|-------|-----|------|------|
| Introduction            |       |     |      |      |
| Classification          |       |     |      |      |
| MOA                     |       |     |      |      |
| Pharmacological Actions |       |     |      |      |
| Interactions            |       |     |      |      |
| Adverse effects         |       |     |      |      |
| Use                     |       |     |      |      |

## REVERSIBLE INHIBITORS OF MAO-A (RIMA)

### Classification

- Moclobemide
- Clorgyline

### MOA



- Because of competitive enzyme inhibition, tyramine is able to displace it from the enzyme
- so that potentiation of pressor response to ingested amines is minor
- Dietary restrictions are not required.

## Adverse effects

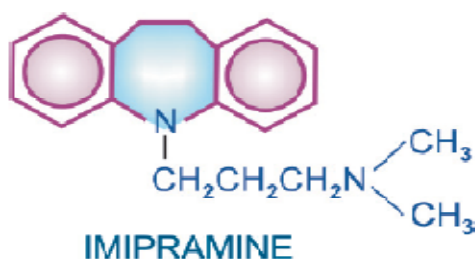
1. Nausea
2. Dizziness
3. Headache
4. Insomnia
5. Liver damage

## Uses

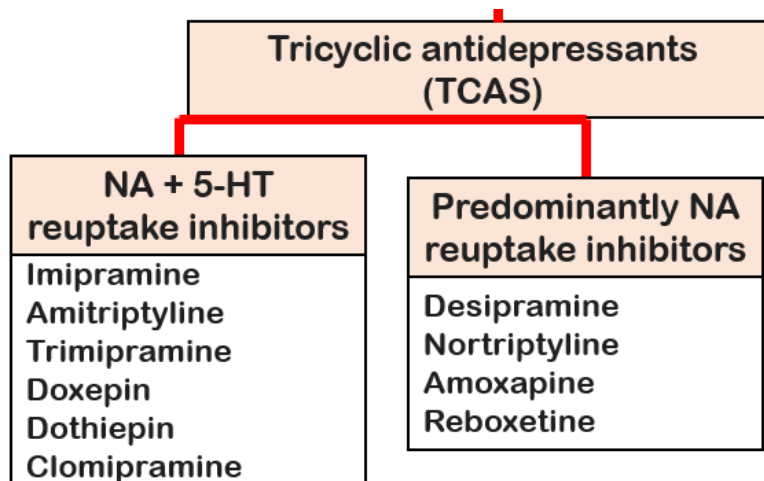
- Efficacious antidepressant, comparable to TCAs
- Moclobemide has emerged as a well tolerated alternative to TCAs for mild to moderate depression and for social phobia

# TRICYCLIC ANTIDEPRESSANTS (TCAS)

## Introduction

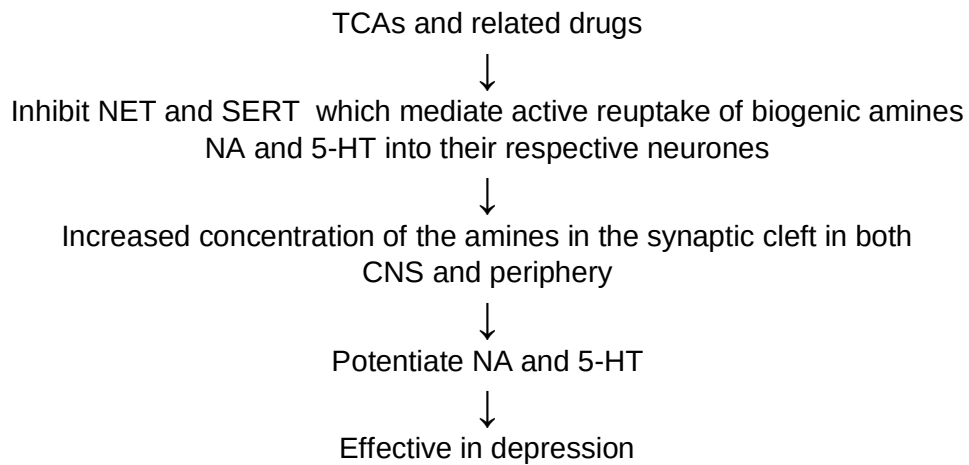


## Classification



- Imipramine is the prototype

## MOA

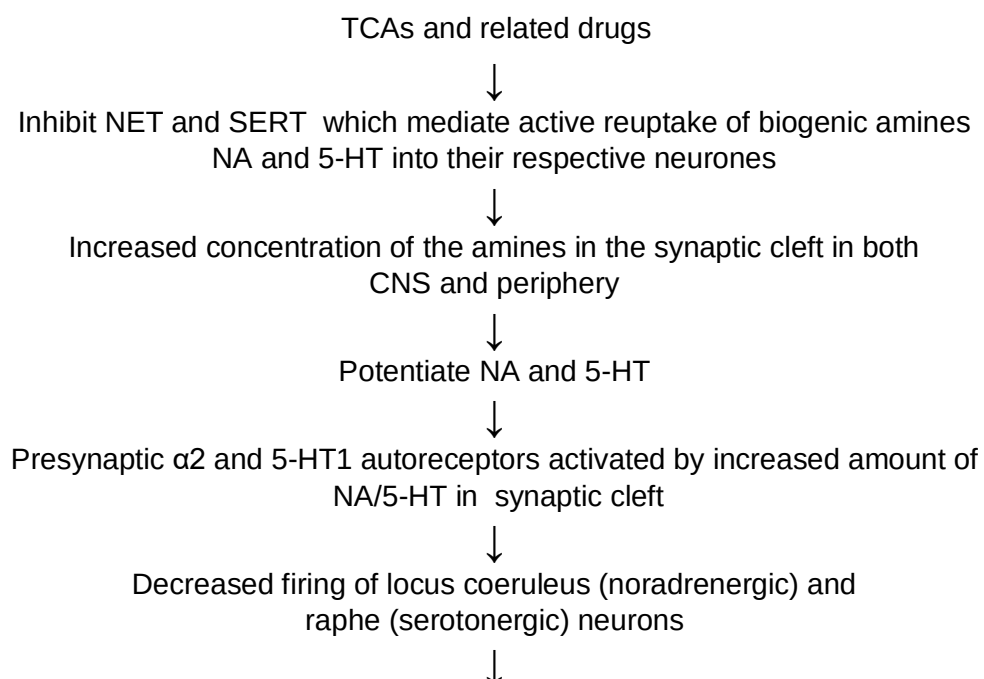


- Most of the compounds do not inhibit DA uptake, except bupropion
- It has been proposed that TCAs indirectly facilitate dopaminergic transmission in forebrain that may add to the mood elevating action.

## Remember

1. Inhibition of NA and 5-HT uptake is associated with antidepressant action.
  2. Inhibition of DA uptake correlates with stimulant action; but is not primarily involved in antidepressant action.
- In addition to uptake blockade have direct effects on adrenergic, cholinergic, serotonergic and histaminergic receptors (interact with a variety of receptors viz. muscarinic,  $\alpha$  adrenergic, histamine H<sub>1</sub>, 5-HT<sub>1</sub>, 5-HT<sub>2</sub> and occasionally dopamine D<sub>2</sub>)
  - **TCAs are referred to as 'first generation antidepressants'**

## Uptake blockade occurs quickly but antidepressant action develops after weeks



After long-term administration → antidepressants desensitise the presynaptic  $\alpha_2$ , 5-HT<sub>1A</sub>, 5-HT<sub>1D</sub> autoreceptors



Net effect is enhanced nor-adrenergic and serotonergic transmission

## Pharmacological Actions

1. CNS
2. ANS
3. CVS

### 1. CNS

#### In normal individuals

- It induces a peculiar clumsy feeling, tiredness, light-headedness, sleepiness
- Difficulty in concentrating and thinking
- Unsteady gait.
- These effects tend to provoke anxiety.
- There is no mood elevation or euphoria
- Effects are rather unpleasant

#### In depressed patients

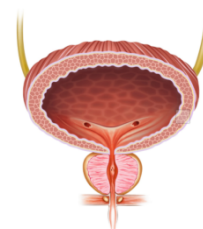
- After 2–3 weeks of continuous treatment, the mood is gradually elevated
- Patients become more communicative and start taking interest in self and surroundings.
- Thus, TCAs are not euphorics but only antidepressants
- In depressed patients who have preponderance of REM sleep, this phase is suppressed and awakenings during night are reduced.
- Thus TCA are also sedatives
- The TCAs lower seizure threshold and produce convulsions in overdose



### 2. ANS

#### In normal individuals

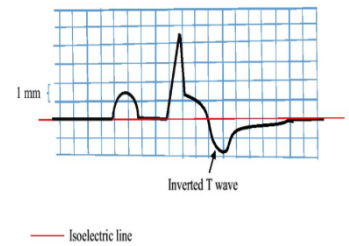
- Most TCAs are potent anticholinergics → cause dry mouth, blurring of vision, constipation and urinary hesitancy as side effect.
- Weak  $\alpha_1$  adrenergic blocking action
- Slight H<sub>1</sub> antihistaminic action





### 3. CVS

- Tachycardia and cardiac arrhythmias: due to anticholinergic and NA potentiating actions.
- Postural hypotension: due to inhibition of cardiovascular reflexes and  $\alpha_1$  blockade
- ECG changes : T wave suppression or inversion is the most consistent change.



### Adverse effects

1. Anticholinergic → Dry mouth, bad taste, urinary retention, blurred vision, palpitation, constipation
2. Sedation, mental confusion, weakness.
3. Increased appetite → weight gain
4. Sweating and tremor
5. Decreased seizure threshold → clomipramine, maprotiline & bupropion
6. Postural hypotension → Maximum by amitriptyline
7. Cardiac arrhythmia → Maximum by amitriptyline and dosulpin.
8. Some patients receiving any antidepressant may abruptly 'switch over' to a dysphoric agitated state or to mania. Most likely, these are cases of bipolar depression, the other pole being unmasked by the antidepressant.

### Remember

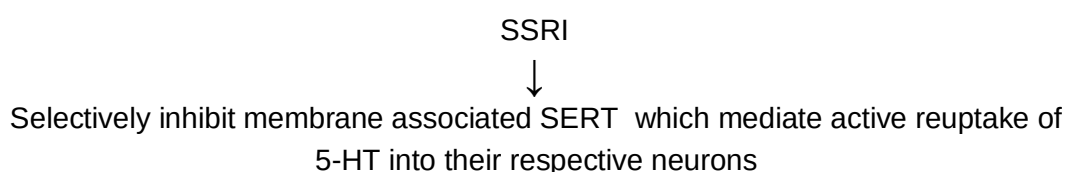
- **Bupropion** → also inhibits dopamine uptake (no other antidepressant inhibits DA reuptake)
- **Amoxapine** → unique in that it blocks D2 receptors in addition to inhibition of NA reuptake → Mixed antidepressant and neuroleptic action → can produce extrapyramidal side effects due to D2 blockade
- **Reboxetine** → it is selective NA reuptake inhibitor with little effect on 5-HT uptake. It is safer than old TCAs.

## SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

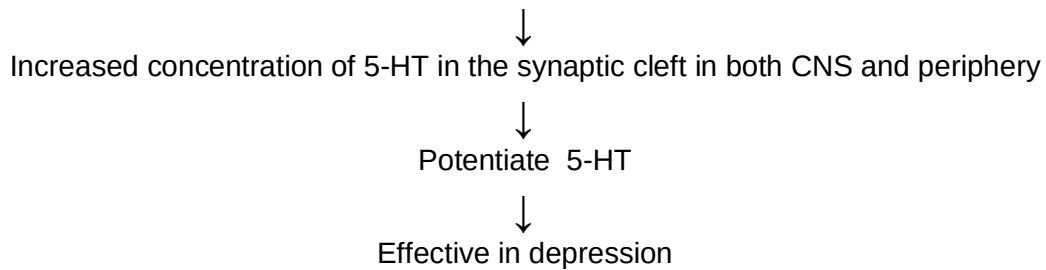
### Classification

- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline
- Citalopram
- Escitalopram
- Dapoxetine

### MOA







- No effects on adrenergic, cholinergic, serotonergic and histaminergic receptors
- **SSRI are referred as → 'Second generation antidepressants'**

### Advantages over TCA

1. SSRIs produce little or no sedation
2. Do not interfere with cognitive and psychomotor function
3. Do not produce anticholinergic side effects.
4. Devoid of  $\alpha$  adrenergic blocking action—postural hypotension does not occur, making them suitable for elderly patients.
5. No seizure precipitating propensity
6. Do not inhibit cardiac conduction—overdose arrhythmias are not a problem.

### Interactions

- When any serotonergic drug (e.g. MAOIs, tramadol, pethidine) is taken by a patient receiving SSRIs → Serotonin syndrome → agitation, restlessness, rigidity, hyperthermia, delirium, sweating, twitchings, convulsion

### Adverse effect

- Nausea (most common) (due to 5-HT<sub>3</sub> receptor stimulation)
- Diarrhea (activation of 5-HT<sub>4</sub> receptors on enteric plexus neurones)
- Interfere with ejaculation and orgasm
- Increased incidence of epistaxis & ecchymosis → Impairment of platelet function.

### Remember

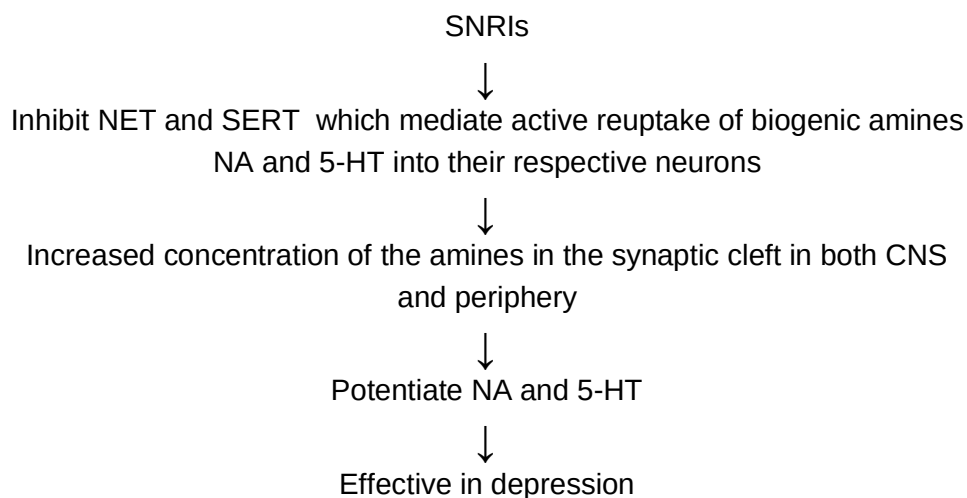
- **Fluoxetine and sertraline** → prodrugs
- **Fluoxetine and sertraline** → metabolize to active product
- **Fluvoxamine, paroxetine and citalopram** → do not form active metabolite.
- **Fluoxetine** → longest acting
- **Fluvoxamine** → shortest acting.
- **Eccitalopram** → active S (+) enantiomer of citalopram - effective at half the dose with fewer s
- **Paroxetine** → teratogenic potential

## SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS (SNRIs)

### Classification

- Venlafaxine
- Duloxetine

### MOA



- SNRIs have high selectivity for noradrenergic reuptake inhibitor over serotonin reuptake inhibition.
- No effects on adrenergic, cholinergic, serotonergic and histaminergic receptors
- SNRIs are referred to as → 'Second generation antidepressants'

### TCAs versus SNRIs

- TCAs → non-selective, i.e. TCAs interact with cholinergic, adrenergic (NA, 5-HT), and histaminergic system; and also have sedative effect.
- SNRIs → selective for adrenergic system (NA, 5-HT) with no effect on cholinergic and histaminergic system → therefore, these drugs are also called selective serotonin and norepinephrine reuptake inhibitor (SSNRIs).

### Adverse effects

- Nausea
- Sweating
- Anxiety
- Insomnia
- Dizziness
- Impotence
- Rise in BP
- Withdrawal reactions on discontinuation

## Remember

- **Venlafaxine** → faster acting (other faster acting antidepressants are bupropion and mirtazapine).
- **Venlafaxine** → raises the BP (all other antidepressants cause hypotension)
- **Duloxetine** → indicated in treatment of neuropathic pain (diabetic neuropathy), urinary incontinence in women (because it increases urethral tone), panic attack.

## ATYPICAL ANTIDEPRESSANTS

### Mianserine

- Blocks presynaptic  $\alpha_2$  receptors → increases NA release and turnover in brain.
- Cause sedation, seizures, blood dyscrasia (bone marrow suppression) and liver dysfunction.

### Tianeptine

- Increases the uptake of serotonin (Action opposite to SSRI).
- Neither sedative nor stimulant.

### Amineptine

- Enhances serotonin uptake.

### Trazodone

- Prominent  $\alpha$ -blocking and weak 5-HT antagonistic action.
- Only antidepressant which causes bradycardia (all others cause tachycardia).
- Mild anxiolytic action.
- Causes sedation, priapism (painful penile erection) and postural hypotension.

### Mirtazapine

- Blocks  $\alpha_2$  auto-receptors (on NA neurones) and heteroreceptors (on 5HT-neurons), enhancing both NA and 5-HT release.
- Augmented NA further increases firing of serotonergic raphe neurones via receptors.
- Selective enhancement of antidepressive 5-HT<sub>1</sub> receptors action is achieved by concurrent blockade of 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors which are held responsible for some of the adverse effects of high serotonergic tone.
- Accordingly, it has been labelled as norenergic and specific serotonergic antidepressant (NaSSA).

### Bupropion

- Inhibits DA and NA uptake.
- Metabolised to amphetamine like compound.
- Only antidepressant which has excitatory action (all others have sedative action) → can cause insomnia and can precipitate seizure.
- Used in nicotine withdrawal for smoking cessation.

## Nefazodone

- Selectively blocks 5-HT reuptake and 5-HT<sub>1</sub> receptors.
- Shortest acting antidepressant.

## Atomoxetine

- Inhibits NA uptake selectively.
- Used in attention deficit hyperactivity disorder (ADHD).

## REMEMBER

### Duration of action

- **Protriptyline** → longest acting TCA.
- **Fluoxetine** → longest acting SSRI.
- **Mirtazapine** → longest acting atypical antidepressant.

### Potency

- **Paroxetine** → most potent SSRI
- **Desipramine** → most potent blockers of NA reuptake
- **Mirtazapine** → least potent blocker of NA reuptake

### Selectivity

- **Escitalopram** → most selective 5-HT reuptake inhibitor (SSRI)
- **Bupropion** → most selective DA reuptake inhibitor.
- **Oxaprotiline** → most selective NA reuptake inhibitor.
- **Nefazodone** → maximum antihistaminic activity
- **Amitriptyline** → maximum anticholinergic activity.
- **Doxepin** → maximum deblocking activity.
- **Venlafaxine** → minimum antihistaminic, anticholinergic and deblocking activity.

## Uses of Antidepressants

1. Endogenous (major) depression
2. Obsessive-compulsive and phobic states
3. Anxiety disorders
4. Neuropathic pain
5. Attention deficit-hyperactivity disorder (ADHD) in children
6. Premature ejaculation
7. Enuresis
8. Migraine

### 1. Endogenous (major) depression

- SSRIs are currently used as first choice for their better tolerability, safety and may be higher efficacy as well.
- SNRIs and newer atypical agents also offer some advantages.

- The only antidepressants clearly shown to be effective in juvenile depression are fluoxetine and sertraline.
- TCAs are mostly used as alternatives in non-responsive cases or in those not tolerating the second generation antidepressants.
- Moclobemide is a well tolerated option for mild to moderate depression, especially suited for elderly and cardiac patients.

## 2. Obsessive-compulsive and phobic states

- SSRIs, particularly fluoxetine, are the drugs of choice
  - a) OCD
  - b) Panic disorder
  - c) Social phobia
  - d) Compulsive eating in bulimia
  - e) Help patients with body dysmorphic disorder
  - f) Compulsive buying and kleptomania,
  - g) Premenstrual dysphoric disorder
  - h) PTSD

## 3. Anxiety disorders

- SSRIs exert a delayed but sustained beneficial effect in many patients of generalized anxiety disorder
- May be used along with a short course of BZDs to cover exacerbations.

## 4. Neuropathic pain

- Amitriptyline afford considerable relief in diabetic and some other types of chronic pain.
- Duloxetine, a SNRI, is now a first line drug for diabetic neuropathy, fibromyalgia, etc

## 5. Attention deficit-hyperactivity disorder (ADHD) in children

- Atomoxetine is a NA reuptake inhibitor unrelated to both TCAs as well as amphetamine, which is used specifically in ADHD

## 6. Premature ejaculation

- It refers to repeated occurrences of ejaculation before or shortly after penetration, or with minimal sexual stimulation.
- It is a very common sexual complaint, which is often interpreted as sexual weakness;
- Can cause considerable distress and dissatisfaction in the patient as well as in his partner.
  - a. Primary treatment of premature ejaculation is counselling and behavioural therapy, but this can be supplemented by drugs.
  - b. Dapoxetine is a SSRI which has been specifically introduced for this purpose. It acts rapidly; 60 mg taken 1 hour before intercourse

## 7. Enuresis

- Children above 5 years, imipramine 25 mg at bedtime is effective,

## 8. Migraine

- Amitriptyline has some prophylactic value, especially in patients with mixed headaches.

## ANTIANXIETY DRUGS

### Introduction

- Anxiety is an emotional state, unpleasant in nature, associated with uneasiness, discomfort and concern or fear about some defined or undefined future threat.
- Some degree of anxiety is a part of normal life.
- Treatment is needed when it is disproportionate to the situation and excessive.



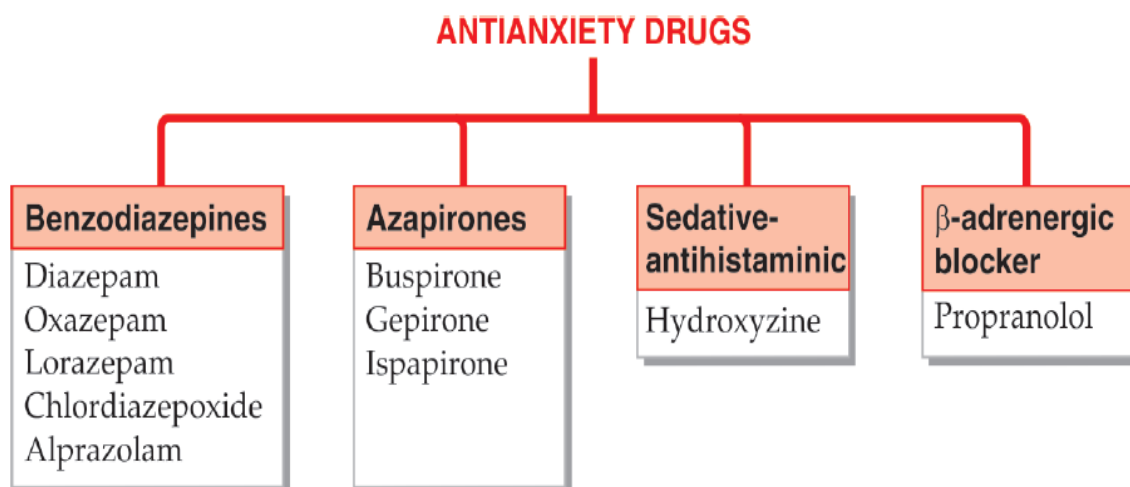
### Anxiolytic drugs versus Antipsychotics drugs

- Anxiolytic drugs differ from antipsychotics drugs as →
  - Have no therapeutic effect to control thought disorder of schizophrenia.
  - Do not produce extrapyramidal side effects.
  - Have anticonvulsant property.
  - Produce physical dependence and carry abuse liability.

### Pathogenesis of anxiety

- It is due to →
  1. Reduction in GABAergic activity
  2. Increase in serotonergic activity

### Classification



## BENZODIAZEPINES

### Introduction

- Most commonly used anxiety drugs.
- Important antianxiety BZDS are
  - Diazepam
  - Chlordiazepoxide

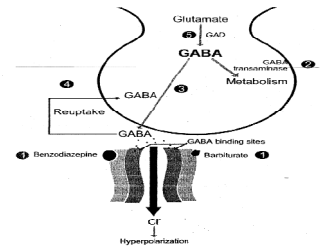
- Oxazepam
- Lorazepam
- Alprazolam
- Oxazepam and lorazepam → safe in elderly and in liver disease

## MOA

- **GABA** → Inhibitory neurotransmitter
- **Glutamate** → Excitatory neurotransmitter

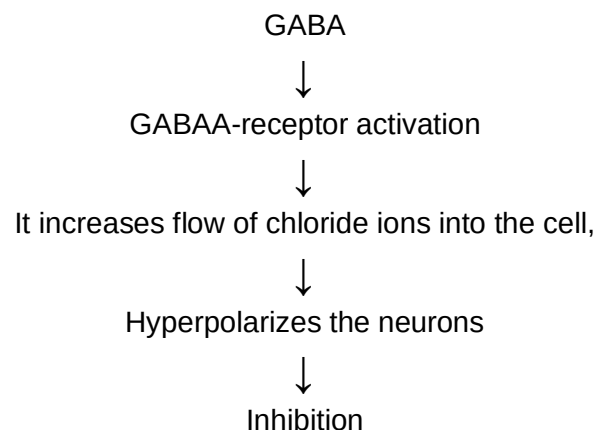
## GABA (gamma amino butyric acid)

- GABA (gamma amino butyric acid) is an inhibitory neurotransmitter in CNS
- GABA is synthesized from glutamate by GAD (glutamic acid decarboxylase).
- GABA is removed mainly by neuronal uptake and partly by deamination catalyzed by GABA transaminase.
- It acts on two different types of receptors namely GABA<sub>A</sub> and GABA<sub>B</sub>

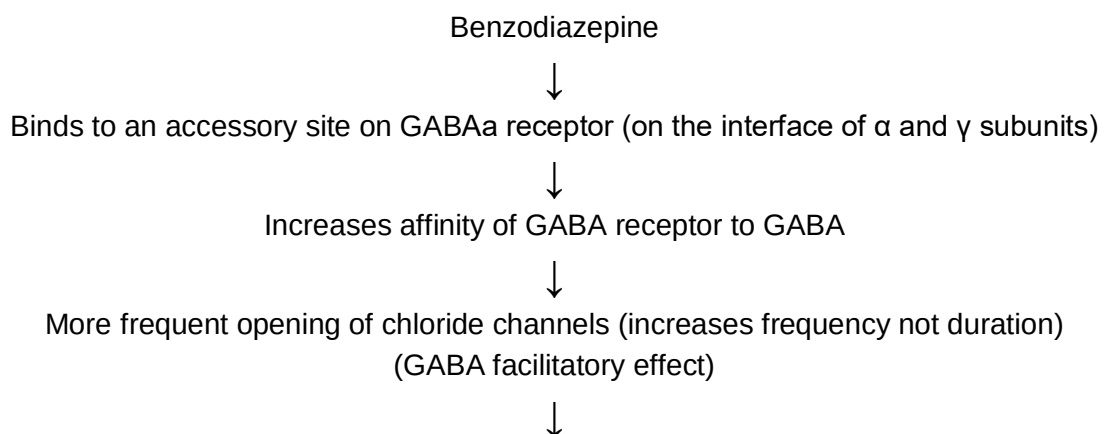


## GABA<sub>A</sub> receptor

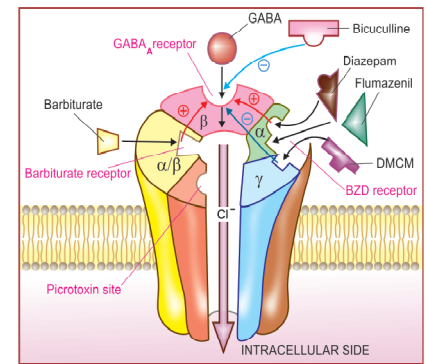
- GABA<sub>A</sub> receptor is an ionotropic receptor, directly coupled to chloride channels
- Ionotropic GABA<sub>A</sub> receptor has a pentameric structure consisting of 2 $\alpha$ , 2 $\beta$  and 1 $\gamma$  subunits.



## Benzodiazepine → GABA facilitatory effect only



Cl enters in the cells  
 ↓  
 Hyperpolarization  
 ↓  
 Inhibition



## Remember

- **Alprazolam**
  - Some mood elevating action in mild depression
  - Particularly useful in anxiety associated with depression.
  - It causes less sedation (drowsiness)

## Adverse Effects

- Tiredness, somnolence, ataxia, headache, vertigo, dizziness and impaired judgment.
- Prolonged effects and hangover.
- Tolerance.
- Dependence.
- Use for more than two weeks need gradual tapering.

## BZDs most widely used antianxiety drug

- Because →
  1. Little effect on other body systems
  2. Lower dependence producing liability than barbiturates and other sedatives;
  3. Withdrawal syndrome is milder and delayed due to their long half lives
  4. Relatively safe even in gross overdose

## AZAPIRONES

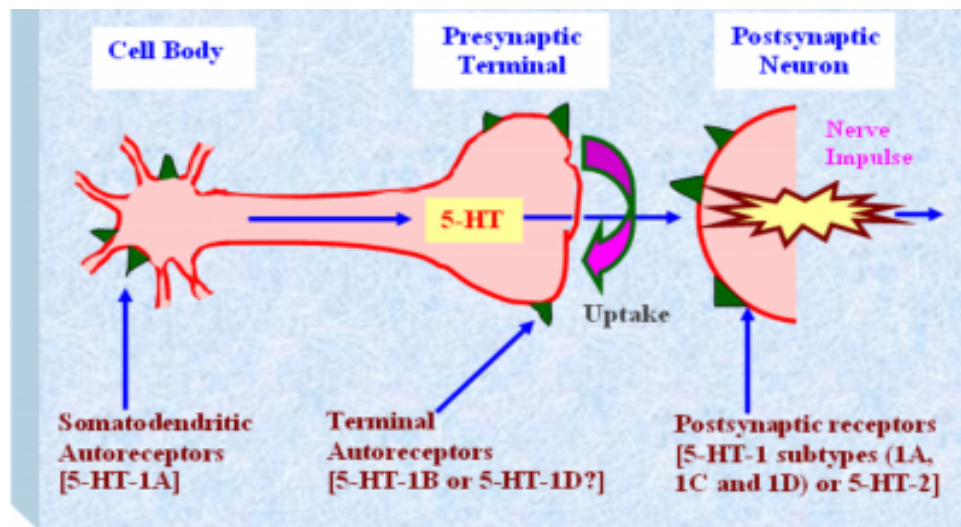
### Introduction

- Non-sedative, non-habit forming anxiolytics.

### MOA

Azapirones  
 ↓  
 Partial agonist at presynaptic 5HT<sub>1A</sub> receptors and  
 Antagonistic action at postsynaptic 5-HT<sub>1A</sub> receptors  
 ↓  
 Reduces activity of dorsal raphe serotonergic neurones





## Azapirones versus BZDS

- Does not produce sedation or tolerance or dependence.
- Has no muscle relaxant or anticonvulsant activity.
- Do not act through GABAergic activity.

## β BLOCKERS

### Introduction

- Many symptoms of anxiety (palpitation, rise in BP, shaking, tremor, gastrointestinal hurrying, etc.) are due to sympathetic overactivity
- These symptoms reinforce anxiety

### Uses

- Do not affect the psychological symptoms such as worry, tension and fear
- Valuable in acutely stressful situations (examination fear, unaccustomed public appearance, etc.).
- Used for performance/situational anxiety or as adjuvant to BZDs.

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## GENERAL ANAESTHETICS

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### Anaesthesia

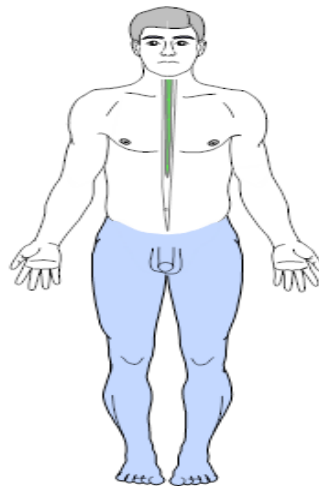
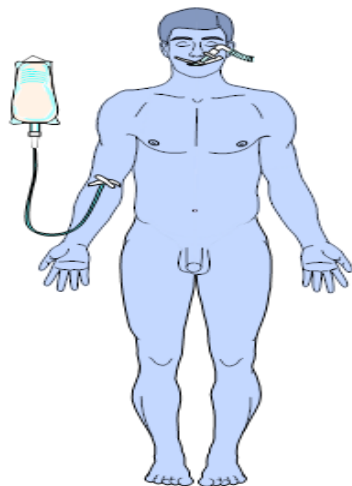
- Anaesthesia is reversible loss of response to a noxious stimuli.

### Types

1. **General anaesthesia** → if associated with loss of consciousness
2. **Local anaesthesia** → consciousness is maintained

|  | General anaesthesia | Local anaesthesia |
|--|---------------------|-------------------|
|--|---------------------|-------------------|

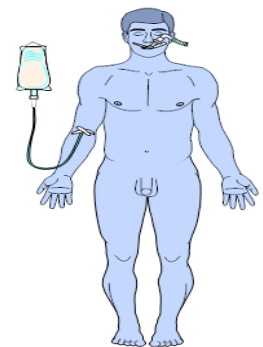
|                                   |               |                    |
|-----------------------------------|---------------|--------------------|
| 1. Site of action                 | CNS           | Peripheral nerves  |
| 2. Area of body involved          | Whole body    | Restricted area    |
| 3. Consciousness                  | Lost          | Unaltered          |
| 4. Care of vital functions        | Essential     | Usually not needed |
| 5. Poor health patient            | Risky         | Safer              |
| 6. Use in non-cooperative patient | Possible      | Not possible       |
| 7. Major surgery                  | Preferred     | Cannot be used     |
| 8. Minor surgery                  | Not preferred | Preferred          |



## GENERAL ANAESTHETICS

### Definition

- General anaesthetics (GAs) are drugs which produce reversible loss of all sensation and consciousness.



### Cardinal features of general anaesthesia

- Loss of all sensation → especially pain
- Muscle relaxation and Immobility
- Sleep (unconsciousness)
- Amnesia
- Abolition of somatic and autonomic reflexes

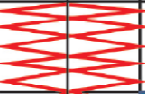
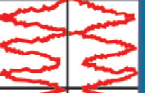
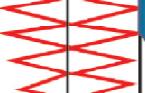
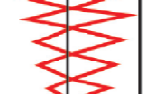
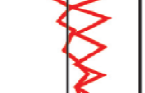
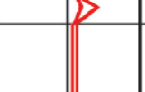


### Effect of GA on CNS

- GAs cause** → irregular descending depression of the CNS
- In Brain** →
  - Higher functions are lost first and progressively lower area of brain are involved.
  - Vital centers located in the medulla are paralyzed last as depth of anaesthesia increases.
- In spinal cord** → lower segments are affected earlier than upper segment

## STAGES OF ANAESTHESIA

- Guedel described 4 stages of ether anaesthesia dividing the IIIrd stage into 4 planes.
  - Stages 1
  - Stages 2
  - Stages 3 →
    - Plane 1
    - Plane 2
    - Plane 2
    - Plane 2
  - Stages 4

| STAGE                       | Respiration                                                                       |                                                                                     | Ocular movem.    | Pupil size                                                                          | Reflexes                                                                            |                                                                                     |                                                                                     |                                                                                      | SK.mus. tone                                                                          | B. P.                                                                                 | H. R.                                                                                 | USES                             |
|-----------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------|
|                             | Thor.                                                                             | Abd.                                                                                |                  |                                                                                     | EYE LID                                                                             | PHARYNGEAL                                                                          | CORNEAL                                                                             | LIGHT                                                                                |                                                                                       |                                                                                       |                                                                                       |                                  |
| I<br>ANALGESIA              |  |                                                                                     | NORMAL           |    |    |    |    |    |    |    |    | Labour, Incisions and Minor ops. |
| II<br>DELIRIUM              |  |                                                                                     | ROVING EYE BALLS |    |    |    |    |    |    |    |    | NIL                              |
| SURGICAL ANAESTHESIA<br>III | 1                                                                                 |   | ROVING EYE BALLS |   |   |   |   |   |   |   |   | Most of the surgical operations  |
|                             | 2                                                                                 |  |                  |  |  |  |  |  |  |  |  |                                  |
|                             | 3                                                                                 |  | FIXED EYES       |  |  |  |  |  |  |  |  | Occasionally reached now         |
|                             | 4                                                                                 |  |                  |  |  |  |  |  |  |  |  | Never attempted                  |
| IV<br>MEDULLARY PARALYSIS   |                                                                                   |                                                                                     |                  |  |  |  |  |  |  |  |  |                                  |

| Stage       | Respirations             | Eyeballs | Pupils            | Muscle Tone          | Loss of Reflexes                          |
|-------------|--------------------------|----------|-------------------|----------------------|-------------------------------------------|
| 1.          | Regular                  | Normal   | Normal            | Normal               | Relief from pain                          |
| 2.          | Irregular                | Roving   | Partially dilated | Increased, tense     | Loss of eyelash reflex                    |
| 3. Plane- 1 | Regular                  | Fixed    | Normal            | Increasingly relaxed | Loss of eyelid reflex                     |
| 3. Plane- 2 |                          | Fixed    | Start dilating    |                      | Loss of corneal reflex                    |
| 3. Plane- 3 | Regular, hypoventilation | Fixed    | 3/4 dilated       |                      | Loss of Swallowing and laryngeal reflexes |
| 3. Plane- 4 | Irregular, hypopnea      | Fixed    | fully dilated     |                      | Loss of carinal reflex                    |
| 4.          | Apnea                    | Fixed    | Dilated, fixed    | Flaccid              |                                           |

## Stage 1 → Stage of analgesia

- From beginning of anaesthetic inhalation to the loss of consciousness
- There's relief from pain.
- Though some minor operations can be carried out during this stage → it is rather difficult to maintain



## Stage 2 → Stage of delirium or excitement

- From the loss of consciousness to beginning of regular respiration.
- Roving eye ball (maximum movement of eye)
- Pupil is partially dilated
- Apparent excitement is seen → patient may shout, struggle and hold his breath; muscle tone increases, jaws are tightly closed, breathing is jerky
- Swallowing, highest risk of laryngospasm
- Vomiting, involuntary micturition or defecation may occur.
- Heart rate and BP may rise
- Eye lash reflex is lost → First reflex to be lost
- No stimulus should be applied or operative procedure carried out during this stage.

## Stage 3 (stage of surgical anaesthesia)

- From beginning of regular respiration to cessation of spontaneous breathing.
- Most surgeries are done in this stage
- It is divided into 4 planes

### Plane 1

- From beginning of regular respiration to cessation of eye movement.
- This plane ends when eye ball become fixed
- Pupil size is normal
- Eye lid reflex is lost.

### Plane 2

- From cessation of eye movement to respiratory Paresis.
- Eye ball is fixed.
- Pupil starts dilating
- Loss of corneal reflex.

### Plane 3

- From respiratory paresis to respiratory paralysis.
- Pupil 3/4 dilated.
- Swallowing reflex and laryngeal reflexes are lost.

## Plane 4

- Intercostal paralysis → there is only abdominal respiration.
- Pupil is fully dilated.
- Carinal reflex (Cough reflex) is lost → Last reflex to be lost

## Remember

- As anaesthesia passes to deeper planes, progressively →
  1. Muscle tone decreases
  2. BP falls
  3. HR increases with weak pulse
  4. Respiration decreases in depth

## Stage 4 (stage of medullary paralysis)

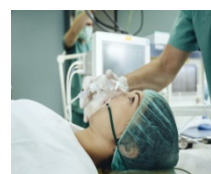
- Respiratory arrest and apnea.
- Pupil is fully dilated & fixed.

## Properties of an ideal anaesthetic

- A. For the patient
- B. For the surgeon
- C. For the anaesthetist

### A. For the patient

- It should be pleasant, nonirritating
- Should not cause nausea or vomiting
- Induction and recovery should be fast with no after effects.



### B. For the surgeon

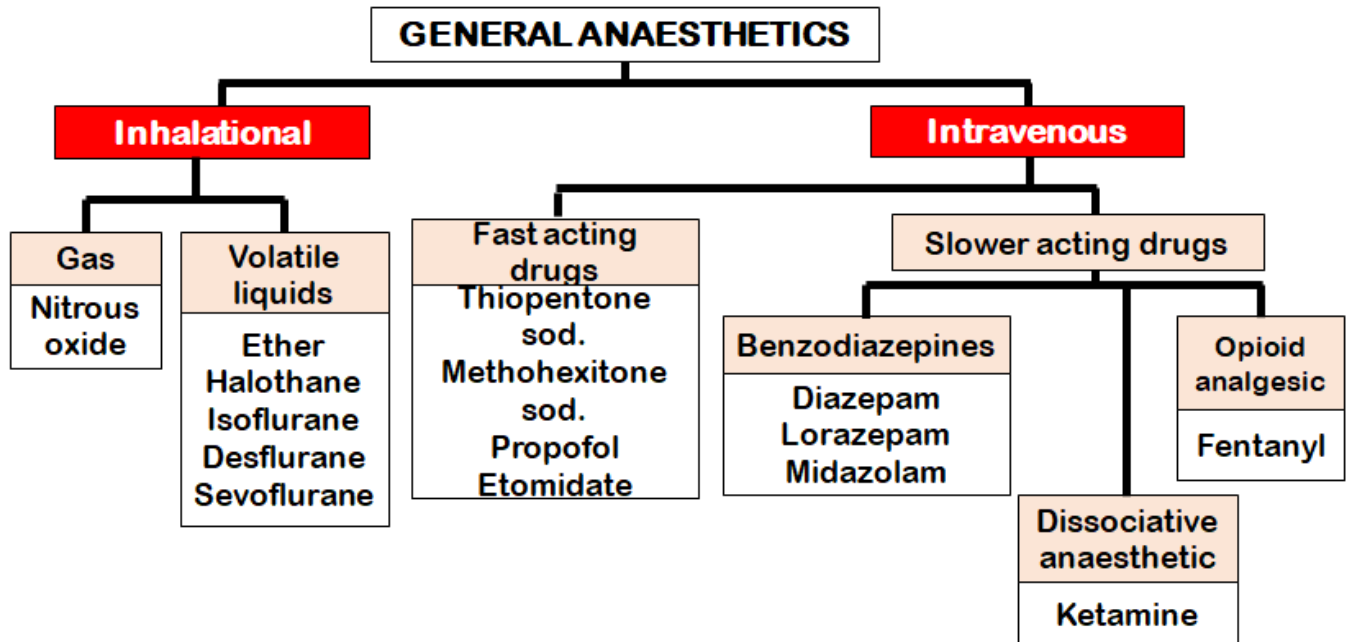
1. It should provide adequate analgesia, immobility and muscle relaxation.
2. It should be noninflammable and nonexplosive so that cautery may be used.

### C. For the anaesthetist

1. Margin of safety should be wide → no fall in BP.
2. Heart, liver and other organs should not be affected.
3. It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.
4. Rapid adjustments in depth of anaesthesia should be possible.
5. It should be cheap, stable and easily stored.



## Classification



## Remember

- In modern practice of balanced anaesthesia these modalities are achieved by using combination of inhaled and IV drugs.
- In usual situations →
  - Intravenous anaesthetics** → used for induction of anaesthesia
  - Inhalational agents** → used for maintenance.

## INHALATIONAL ANAESTHETICS

### Introduction

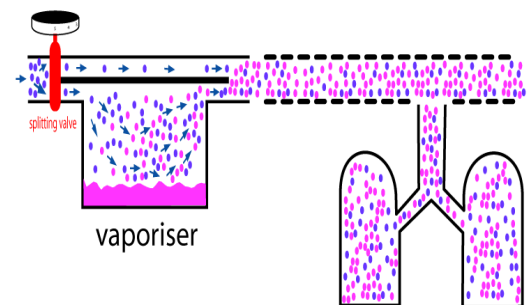
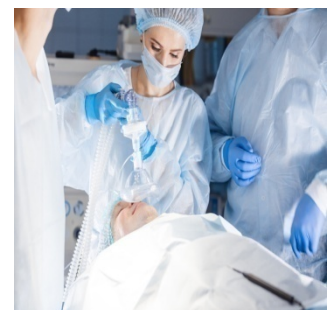
- Inhalational anaesthetics are gases or volatile agents that possess anaesthetic qualities
- Administered by breathing through an anaesthetic mask or ET tube connected to an anaesthetic machine

Volatile anaesthetic agent is put in vaporizer of anaesthetic machine

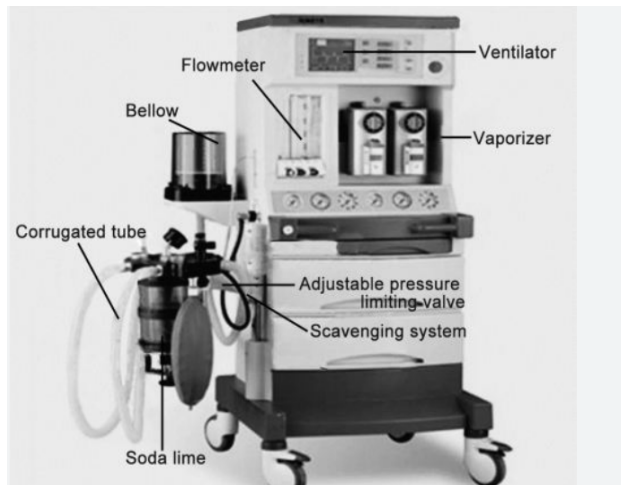
↓  
Gas mixture of O<sub>2</sub>, N<sub>2</sub>O & air (acts as a carrier for volatile anaesthetic agent) is passed through vaporizer

↓  
Volatile anaesthetic evaporates to mix with this gas mixture

↓  
Finally this gas mixture is delivered to patients by passing through breathing circuit





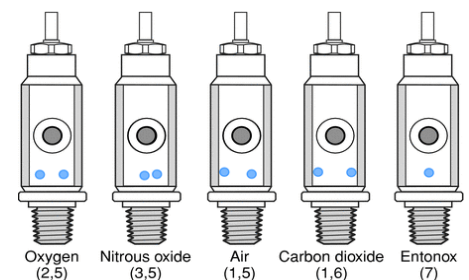


## Colour Coding of Cylinders

|                  |                                 |
|------------------|---------------------------------|
| N <sub>2</sub> O | Blue                            |
| Cyclopropane     | Orange                          |
| Air              | Grey body with white shoulders  |
| O <sub>2</sub>   | Black body with white shoulders |
| CO <sub>2</sub>  | Grey                            |
| Helium           | Brown                           |
| Entonox          | Blue body with white shoulders  |

## Pin Index Safety System (PISS)

- Pin Index Safety System (PISS) is a safety feature used in anesthesia machines to prevent connecting the wrong gas cylinder to the wrong gas inlet.
- This system can be seen on an anesthesia machines

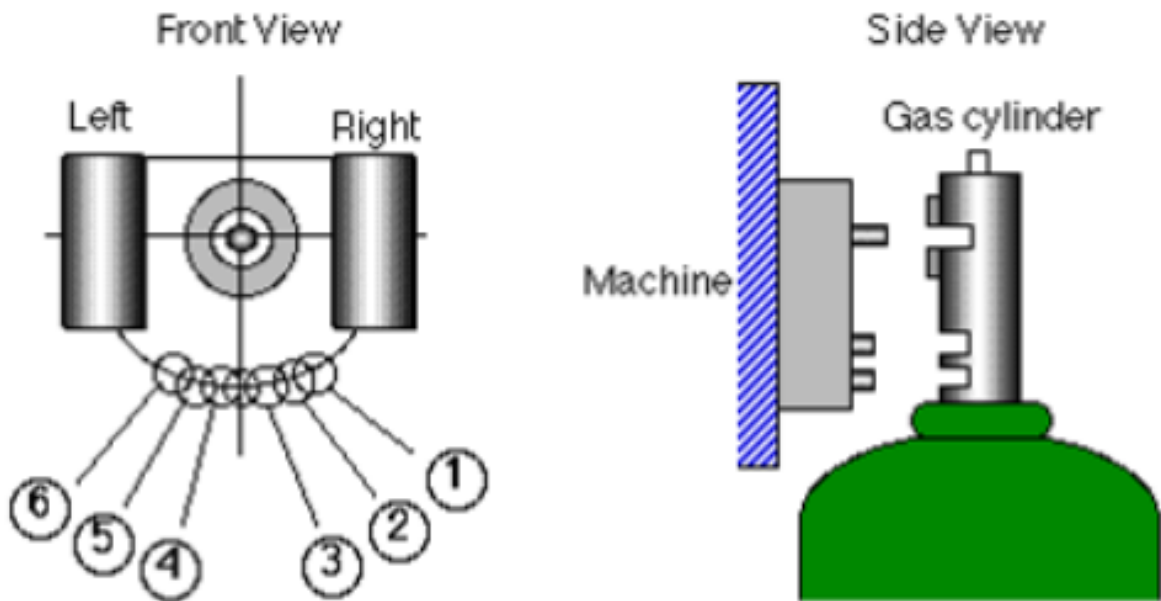


## Need

- Different gases like oxygen, nitrous oxide and air → stored in cylinders.
- If you accidentally connect the wrong gas to the wrong port → it can be dangerous for the patient.
- PISS helps avoid such mix-ups.

## Mechanism

- Gas cylinder valve has 6 hole positions
- Arranged in a circle
- Numbered from 1 to 6.
- Only 2 are drilled for each gas.
- Only 2 of these 6 positions are used for each gas.
- Anesthesia machine or yoke has 2 fixed metal pins in positions that match a specific gas.
- The combination of these 2 hole positions is unique for each gas.
- The pins and holes must match — so only the correct gas cylinder can fit on its respective port.
- This ensures no wrong gas can be connected.

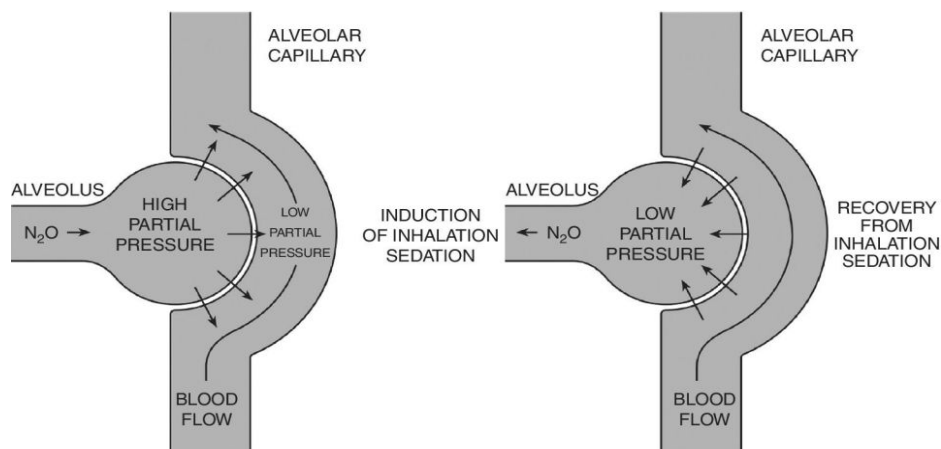


## Pin Index System

|                         |     |
|-------------------------|-----|
| Air                     | 1,5 |
| O <sub>2</sub>          | 2,5 |
| N <sub>2</sub> O        | 3,5 |
| CO <sub>2</sub> (>7.5%) | 1,6 |
| CO <sub>2</sub> (<7.5%) | 2,6 |
| Cyclopropane            | 3,6 |
| Entonox                 | 7   |

## Pharmacokinetics of Inhalational Anaesthetics

- Transfer of the anaesthetic between lung and brain depends on a series of tension gradients which may be summarized as—





## Potency of volatile anaesthetics

- A. Minimal alveolar concentration (MAC)
- B. Oil: gas partition coefficient

### A. Minimal alveolar concentration (MAC)

- Minimum Alveolar Concentration that prevents movements in 50% of patients in response to surgical stimulation
- OR
- Concentration that produces irritability in 50% of patients exposed to a noxious stimulus
    - At 1 MAC = 50% response
    - At 1.3 MAC = 99% response
    - Higher the MAC → less potent is the agent.

**Methoxyflurane**  
↓  
Minimum MAC  
↓  
**Most potent**

**N2O**  
↓  
Maximum MAC  
↓  
**Least potent**

### B. Oil: gas partition coefficient

- Measures → lipid solubility of the agent.
- Higher the lipid solubility → more is the potency.

**Methoxyflurane**  
↓  
Maximum Oil : gas  
partition coefficient  
↓  
Most lipid soluble  
↓  
**Most potent**

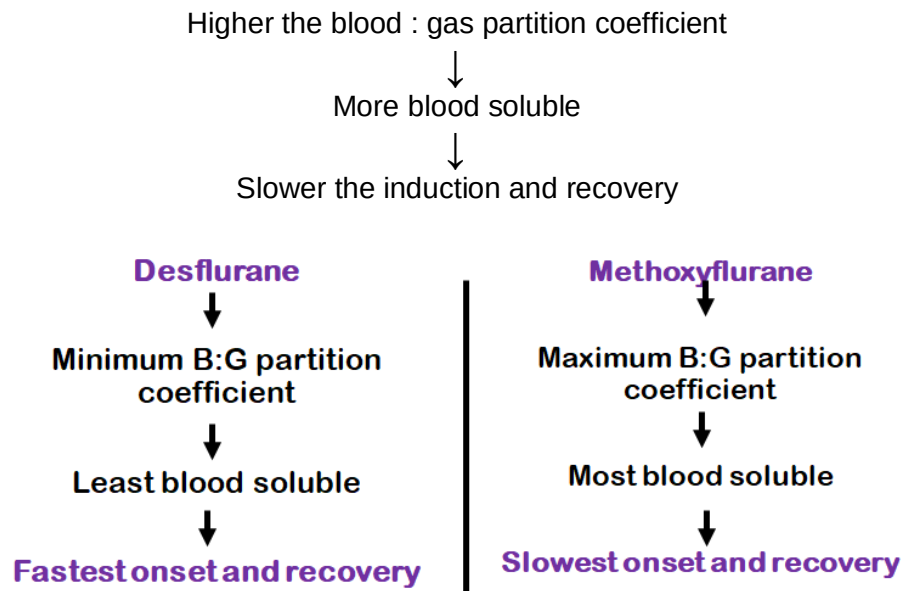
**N2O**  
↓  
Minimum Oil : gas  
partition coefficient  
↓  
Least lipid soluble  
↓  
**Least potent**

## Speed of onset and recovery

- A. Blood : gas partition coefficient

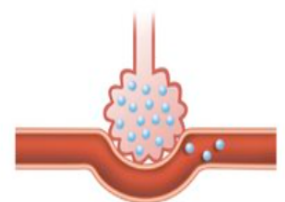
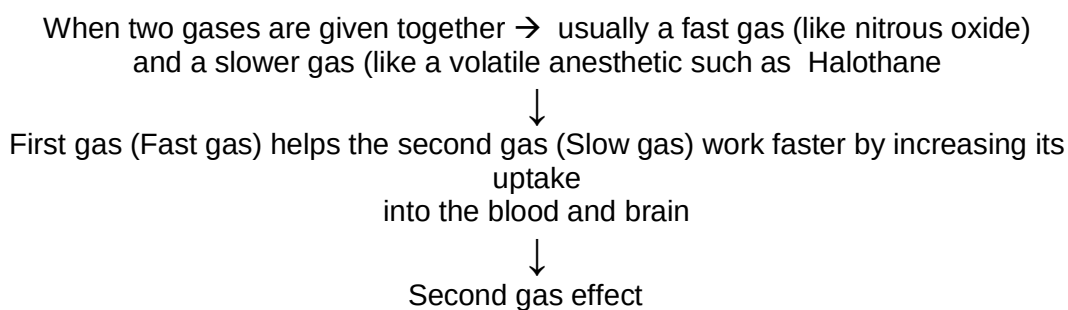
## Blood : gas partition coefficient

- Measures** → blood solubility of agent → determines the speed of onset and recovery.

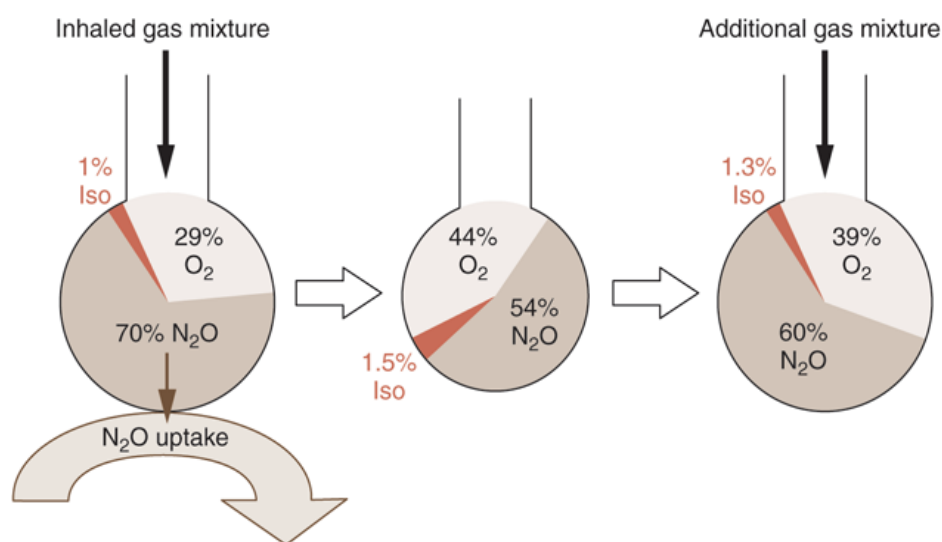
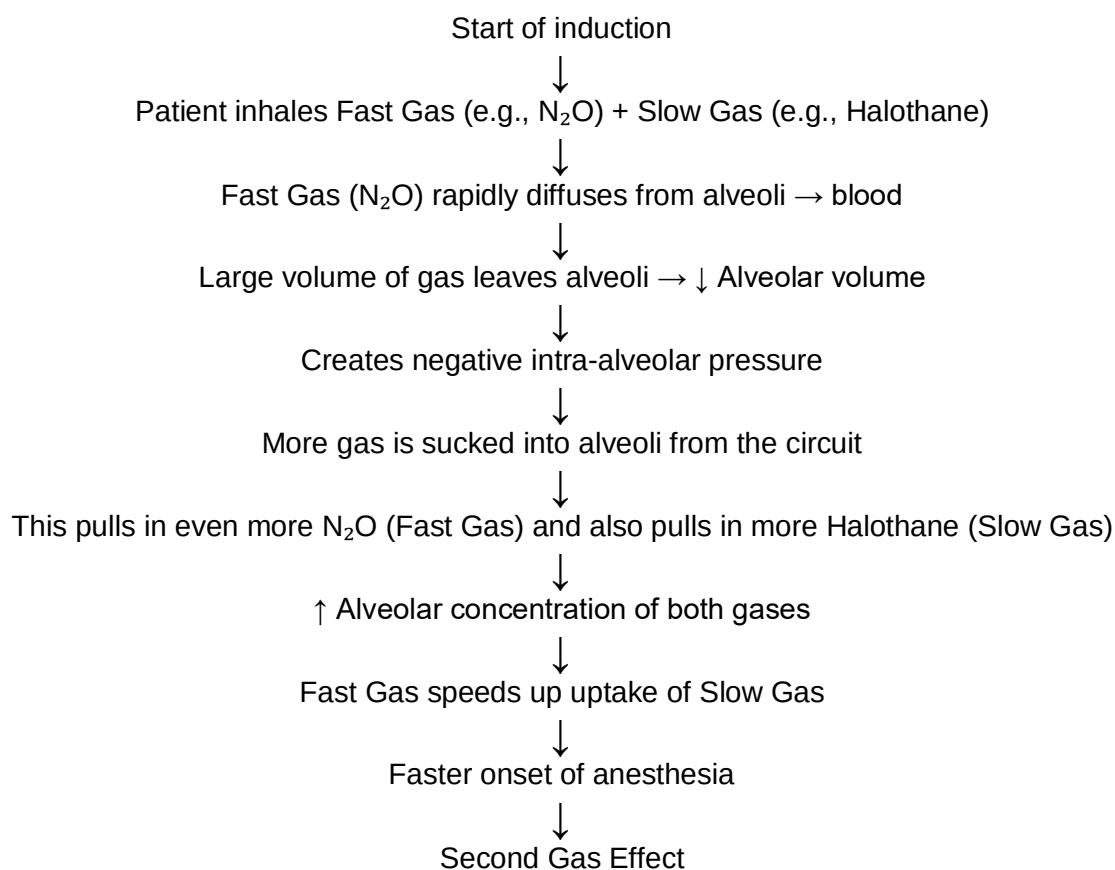


| Anaesthetic    | MAC (% atm) | Blood gas partition coefficient |
|----------------|-------------|---------------------------------|
| Halothane      | 0.74        | 2.3                             |
| Enflurane      | 1.68        | 1.8                             |
| Isoflurane     | 1.15        | 1.4                             |
| Desflurane     | 6.0         | 0.42                            |
| Sevoflurane    | 2.05        | 0.69                            |
| Cyclopropane   | 9.2         | 0.44                            |
| Nitrous oxide  | 104         | 0.47                            |
| Trilene        | 0.2         | 9                               |
| Ether          | 1.92        | 12                              |
| Chloroform     | 0.8         | 8                               |
| Methoxyflurane | 0.16        | 15                              |
| Xenon          | 70          | 0.115                           |

## Second gas effect

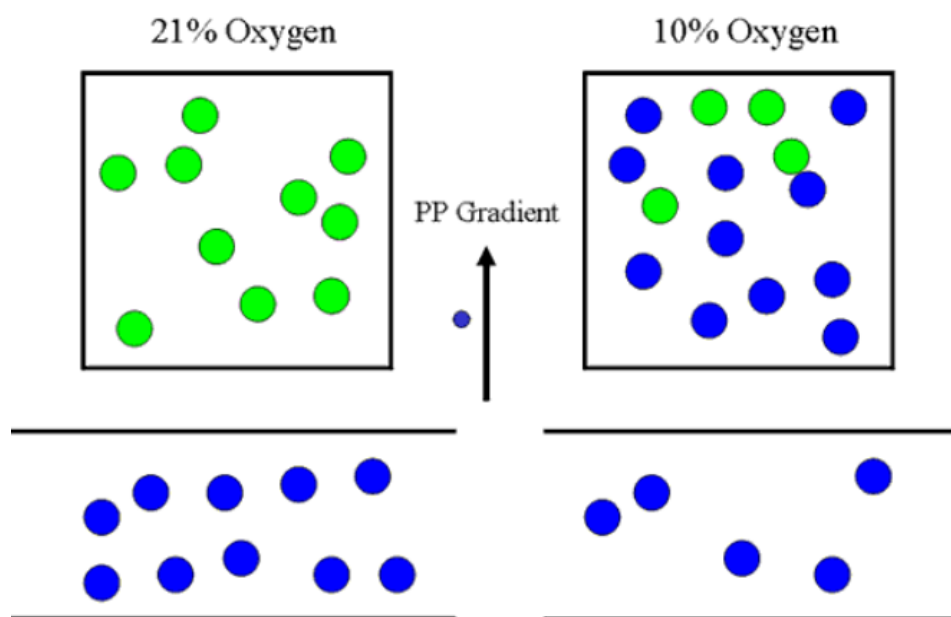
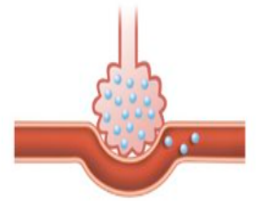


| Fast Gas                                                                                                                                 | Slow Gas                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Absorbed quickly from the lungs into the blood.</li> </ul>                                        | <ul style="list-style-type: none"> <li>Absorbed slowly into the blood.</li> </ul>                                                             |
| <ul style="list-style-type: none"> <li>Has low blood-gas solubility → doesn't dissolve much in blood → so reaches brain fast.</li> </ul> | <ul style="list-style-type: none"> <li>Has higher blood-gas solubility → dissolves in blood more → so takes longer to reach brain.</li> </ul> |
| <ul style="list-style-type: none"> <li>Acts quickly</li> </ul>                                                                           | <ul style="list-style-type: none"> <li>Acts slowly</li> </ul>                                                                                 |
| <ul style="list-style-type: none"> <li>e.g. N<sub>2</sub>O</li> </ul>                                                                    | <ul style="list-style-type: none"> <li>e.g. Sevoflurane, Isoflurane, Halothane</li> </ul>                                                     |



## Diffusion hypoxia

During recovery reverse occurs  
↓  
N<sub>2</sub>O having low blood solubility  
↓  
Rapidly diffuses into alveoli and dilutes the alveolar air  
↓  
Partial pressure of oxygen in alveoli is reduced.  
↓  
Resulting hypoxia  
↓  
Diffusion hypoxia (Fink effect)



- Diffusion hypoxia can be prevented by continuing 100% O<sub>2</sub> inhalation for a few minutes after discontinuing N<sub>2</sub>O, instead of straight away switching over to air

### Remember

- **Second gas effect** → during induction
- **Diffusion hypoxia** → during recovery

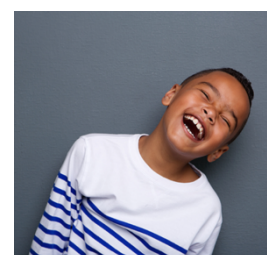
## INDIVIDUAL INHALATIONAL ANAESTHETICS

|                    | Gas              | Drugs for Peptic ulcer |                        |    |    |    |    |
|--------------------|------------------|------------------------|------------------------|----|----|----|----|
|                    |                  |                        | Florinated Anesthetics |    |    |    |    |
|                    | N <sub>2</sub> O | Ether                  | Halothane              | EF | IF | DF | SF |
| Properties         |                  |                        |                        |    |    |    |    |
| Uses               |                  |                        |                        |    |    |    |    |
| Adveese effects    |                  |                        |                        |    |    |    |    |
| Contraindic ations |                  |                        |                        |    |    |    |    |

## NITROUS OXIDE → N<sub>2</sub>O

### Properties

- Also called laughing gas
- Colourless, odourless, heavier than air
- Nonirritating and inflammable gas.
- MAC is 105% (least potent) → even pure N<sub>2</sub>O at 1 atmospheric pressure can not produce adequate anaesthesia.
- It has good analgesic but poor muscle relaxant activity
- It is supplied under pressure in blue coloured steel cyclinders.
- It has very low blood solubility → induction is quick and smooth with rapid recovery.
- Second gas effect and diffusion hypoxia occur with N<sub>2</sub>O
- N<sub>2</sub>O is generally used as a carrier and adjuvant to other anaesthetics → A mixture of 66% N<sub>2</sub>O + 33% O<sub>2</sub> + 0.2 - 2% another potent anaesthetic is employed for most of the surgical procedures.
- Entonox → mixture of 50% N<sub>2</sub>O and 50% O<sub>2</sub>.
- It has little effect on respiration, heart and BP → Safest anaesthetic

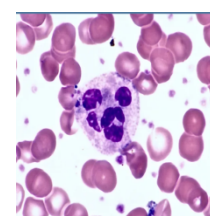


### Uses

- Used as a supplement to anaesthesia → because it is not a complete anaesthetic
- Used as a carrier gas for inhalational agents like halothane.

### Adverse effects

1. **Hematologic toxicity and neurotoxicity** → with long term administration.
  - Because of the interaction of N<sub>2</sub>O with vit B12.
  - Bone marrow changes are preventable by pretreating patients with large dose of folinic acid.
2. **Methemoglobinemia** → due to the presence of impurities like nitric oxide (NO) and nitrogen dioxide (NO<sub>2</sub>).



3. **Laryngospasm** → due to the presence of impurities like nitric oxide (NO) and nitrogen dioxide (NO<sub>2</sub>).

## Contraindication

- In air containing closed cavities → nitrous oxide exchanges with nitrogen
- 1 mole of nitrogen removed → 35 moles of N<sub>2</sub>O is replaced (N<sub>2</sub>O is 35 times more soluble than N<sub>2</sub>)
  1. **Pneumothorax , Pneumoperitoneum, Emphysema , volvulus , intestinal obstruction** → Increase in pressure & expansion can occur
  2. **Middle ear surgery** → tympanoplasties → graft may displace due to increased pressure.
  3. **Posterior fossa surgery and laproscopic surgery** → Air embolism may occur.
  4. **Pneumoencephalum** → Entry of N<sub>2</sub>O can significantly increase the ICT and once the pneumoencephalum has developed, N<sub>2</sub>O should not be used for 1 week

## ETHER (DIETHYL ETHER)

### Properties

- It is highly volatile liquid
- Produces irritating vapours which are highly inflammable and explosive → Cautery should not be used
- Potent anaesthetic with good analgesic and muscle relaxant property → Ether has maximum muscle relaxant property among anaesthetics.
- It is highly soluble in blood → Induction is prolonged and unpleasant with marked postoperative nausea and vomiting.
- BP and respiration are well maintained because of reflex stimulation and high sympathetic tone
- It does not sensitive the heart to Adr.



### Uses

- Very cheap
- Very safe → does not produce any cardiac or respiratory depression, so can be used at remote places (like wars and disasters) and with less experienced hands
- Ether is the only complete anaesthetic agent → has all properties of anaesthesia, i.e., narcosis, analgesia, muscle relaxation.

### Adverse effect

- Not used now a days as it is highly inflammable & explosive
- One of the most emetogenic of all the inhalational agent
- Irritant → Increases respiratory & salivary secretion



## Contraindications

- Cause hyperglycemia → Contraindicated in diabetic.



## FLURINATED ANAESTHETICS

- Fluorine atoms are added to some agents to make them non-inflammable.
- Fluorinated anaesthetics are →
  1. Halothane
  2. Desflurane
  3. Sevoflurane
  4. Enflurane
  5. Methoxyflurane
- Note: All fluorinated agents has flurane as suffix in there name, except halothane.

## 1. HALOTHANE

### Properties

- Volatile liquid with sweet odour
- Nonirritating and noninflammable
- Halothane is decomposed by light → therefore 0.01% thymol is added to stabilize it.
- It is stable when stored in amber colour bottles.
- Halothane is absorbed by rubber of anaesthetic circuit and polyvinylchloride of ET-tube
- It also corrodes metal in breathing circuit & vaporizers
- It is a potent anaesthetic (MAC-0.74%) but is a poor analgesic and poor muscle relaxants.
- Recovery is smooth and reasonably quick.
- Halothane is absorbed by rubber of anaesthetic circuit and polyvinylchloride of ET-tube
- It also corrodes metal in breathing circuit & vaporizers
- It is a potent anaesthetic (MAC-0.74%) but is a poor analgesic and poor muscle relaxants.



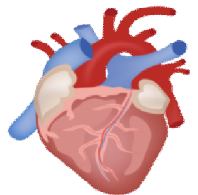
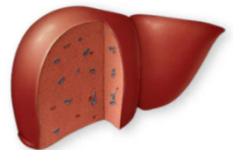
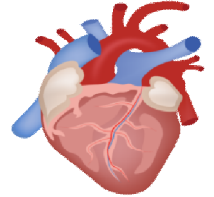
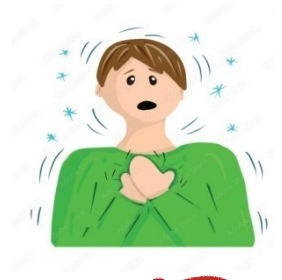
### Uses

1. **Dilates bronchi** → inhalational agent of choice in asthmatics  
(Intravenous anaesthetic of choice in asthmatics is ketamine)
2. **Causes Uterine relaxation** → agent of choice for assisting external or internal version during late pregnancy.



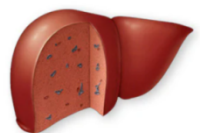
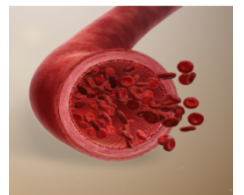
## Adverse effects

1. **Halothane shakes** → Halothane causes post anaesthetic shivering → Maximum propensity amongst inhalational agents.
2. **Sensitize heart to arrhythmogenic action of adrenaline** → Epinephrine should be avoided in doses above 1.5 µg/kg.
3. **Halothane hepatitis** →
  - Halothane causes hepatitis called as halothane hepatitis in which there is centrilobular necrosis
  - Clinically there is increased SGOT, SGPT, bilirubin (jaundice)
  - A metabolite of halothane → trifluoroacetic acid acts as an antigen and induces autoimmunity which is responsible for hepatitis



## Contraindications

1. Halothane causes maximum direct depression of myocardial contractility by reducing intracellular calcium → **Contraindicated in severe cardiac disease**
2. It causes fall in BP & CO (due to myocardial depression) → **Contraindicated in hypovolemia.**
3. Halothane causes direct hepatotoxicity (hepatitis, hepatic necrosis) → **Contraindicated in patients with acute hepatic disease & Jaundice**
4. **Contraindicated during labour** → Tocolytic → Post partum hemorrhage (PPH)



## Halothane Mnemonic

### HALOTHANE CCC

|           |   |                                                                    |
|-----------|---|--------------------------------------------------------------------|
| <b>H</b>  | - | <b>H</b> yperthermia [malignant hyperthermia]                      |
| <b>A</b>  | - | <b>A</b> rrhythmias (sensitize heart to adrenaline)                |
| <b>L</b>  | - | <b>L</b> iver toxic                                                |
| <b>O</b>  | - | <b>O</b> rthostatic hypotension                                    |
| <b>T</b>  | - | <b>T</b> ocolytic                                                  |
| <b>H</b>  | - | <b>H</b> eat [inhibits heart; decreases cardiac output]            |
| <b>A</b>  | - | <b>A</b> sthma [bronchodilator]                                    |
| <b>NE</b> | - | <b>N</b> on-Explosive                                              |
| <b>C</b>  | - | <b>C</b> hills [post-anaesthetic shivering]                        |
| <b>C</b>  | - | <b>C</b> atecholamines [sensitizes heart to arrhythmogenic action] |
| <b>C</b>  | - | <b>C</b> hildren [safe in children]                                |



## 2. ENFLURANE

### Properties

- Faster acting substitute of halothane.
- It is a halogenated ether.

### Uses

- Largely replaced by safer, more stable agents like Sevoflurane and Isoflurane in modern practice.
- Used in combination with IV agents like thiopental or opioids.

### Adverse effects

- Cause maximum respiratory depression.
- Enflurane can induce seizure-like EEG activity → Not used in epilepsy
- It causes uterine relaxation, which may lead to uterine atony and bleeding → Avoid in obstetrics

### Contraindications

- Because of its propensity to provoke seizures, it has been superseded by isoflurane → **contraindicated in epilepsy**



## 3. ISOFLURANE

### Properties

- Isomer of enflurane with similar properties but more potent.

### Uses

1. BP falls due to vasodilation, while cardiac output is maintained → inhalation anaesthetic of choice in Cardiac surgery (intravenous anaesthetic of choice for cardiac surgery is etomidate)
2. It does not sensitize the heart to Adr → Safe in Pheochromocytoma.
3. Isoflurane causes minimum increase in ICT → Preferred agent in increased ICT
4. It does not provoke seizures → preferred in neurosurgery.
5. Uterine and skeletal muscle relaxant action is similar to halothane → can be used for assisting version as an alternative to halothane.
6. Volatile agent of choice in liver disease as it has least effect on hepatic blood flow
7. Used for day care surgery (also sevoflurane and desflurane).

### Adverse effects

1. Cause coronary steal phenomenon
2. Causes significant respiratory depression.

## 4. DESFLURANE

### Properties

- Newer fluorinated congener of isoflurane
- Fastest acting inhalation anaesthetic with minimum blood: gas partition coefficient 0.42
- Less potent than isoflurane → higher concentration has to be used for induction
- Highly volatile → a thermostatically heated special vaporizer is used to deliver a precise concentration of pure desflurane vapour in carrier gas (N<sub>2</sub>O + O<sub>2</sub>) mixture.
- Among all inhalational agents → desflurane causes maximum global warming and green house effect

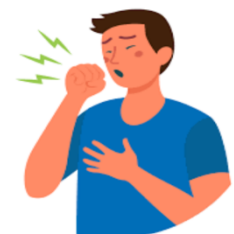
### Uses

- Safe anaesthetic for geriatric patients as its cardiovascular effects are similar to isoflurane but without coronary steal
- Do not provoke seizures
- Not arrhythmogenic
- Do not have liver and kidney toxicity.



### Adverse effects

- Induce coughing and laryngospasm because of pungent odour → Unsuitable for induction.



## 5. SEVOFLURANE

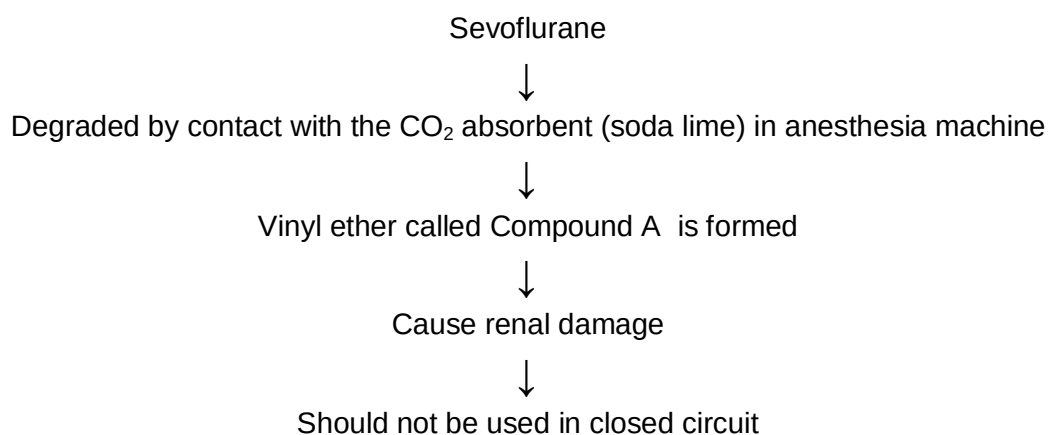
### Properties

- Fluorinated isopropyl methyl ether
- (Enflurane, desflurane & isoflurane are ethyl-methyl ether).
- More potent than desflurane but less potent than isoflurane.

### Uses

- Inhalational agent of choice for induction in adults as well as children
- (Amongst the intravenous agent propofol & ketamine can be used for induction as well as maintenance).

## Adverse effects



## Remember

Inhalational anaesthetics that can precipitate seizures

- S** - Sevoflurane
- E** - Enflurane (Maximum)
- I** - Isoflurane
- ZURE**

| Agent         | Induction    |                        | Heart rate | BP  | Ventilation |
|---------------|--------------|------------------------|------------|-----|-------------|
|               | Onset        | Smoothness             |            |     |             |
| Nitrous oxide | Fast         | Not used for induction | 0          | 0   | ↓           |
| Ether         | Slow         | Highly irritable       | ↑          | ↑   | ↑           |
| Halothane     | Intermediate | Very smooth            | ↓          | ↓↓  | ↓           |
| Enflurane     | Intermediate | Slightly irritable     | ↓          | ↓↓  | ↓           |
| Isoflurane    | Intermediate | Slightly irritable     | ↑ (reflex) | ↓↓↓ | ↓           |
| Desflurane    | Fastest      | Slightly irritable     | ↑          | ↓↓  | ↓           |
| Sevoflurane   | Fast         | Very smooth            | ↓          | ↓   | ↓           |

## INTRAVENOUS ANAESTHETICS

|                   | Thiopentone sod | Methohexitone | Propofol | Etomidate | Ketamine |
|-------------------|-----------------|---------------|----------|-----------|----------|
| Properties        |                 |               |          |           |          |
| Uses              |                 |               |          |           |          |
| Adveese effects   |                 |               |          |           |          |
| Contraindications |                 |               |          |           |          |

## THIOPENTONE SOD.

### Properties

- Ultra short acting barbiturate
- Most commonly used intravenous inducing agent.
- Used as a 2.5% solution.
- Sulphur is added to pentobarbitone to increase the lipid solubility.
  - Due to high lipid solubility, it is very fast acting drug.
  - Action of this drug terminates very quickly due to redistribution (although half life is longer)

### Uses

- Agent of choice for cerebral protection → decreases cerebral oxygen consumption, decreases intra-cranial tension and decreases cerebral metabolic rate
- Possesses anticonvulsant action

### Adverse effects

- Causes peripheral vasodilatation and also depresses CVS → Hypotension.
- Instead of producing analgesic effect → it can produce hyperalgesia at subanaesthetic doses.

On accidental injection of thiopentone in arteries



Thrombosis and vasoconstriction



Progress to ischemia and gangrene

- This condition is treated by leaving needle in situ (needle should not be withdrawn)
  1. Dilution of injected thiopentone with saline
  2. Immediate heparinization
  3. papaverine injection to relieve spasm.
  4. Vasodilators, steroids, lignocaine and urokinase can also be employed.

### Contraindication

- Acute intermittent porphyria

## METHOHEXITONE

### Properties

- Ultra short acting barbiturate.
- 3 times more potent than thiopentone.

## Uses

- Agent of choice for electroconvulsive therapy.

## Adverse effects

- Induces seizures

# PROPOFOL

## Properties

- Opaque, white milky fluid
- Indicated when rapid return to preoperative mental status is required.
- Rapid onset and recovery.
- Less severe hangover → so a rapid discharge from recovery room is possible.
- Rapid clearance even after multiple doses or infusion owing to rapid metabolism hence can be used as infusion or frequent administration.
- Antiemetic effect.



## Uses

- IV anaesthetic of choice for →
  - Day care surgery.
  - For total intravenous anaesthesia (TIVA)
  - Sedation in ICU.
  - In patients with malignant hyperthermia.

## Mnemonic

Propofol is the intravenous anaesthetic of choice for:

- D** - Day care surgery  
**I** - Total Intravenous anaesthesia (TIVA)  
**S** - Sedation in ICU  
**H** - Malignant **H**yperthermia

## Adverse effects

1. Pain on injection (reduced by mixing with lignocaine)
2. Proconvulsant tendency
3. Potential to produce hypotension, respiratory depression and increase in histamine release (like thiopental).
4. Prolonged, high dose infusion can lead to potentially fatal complication → Propofol infusion syndrome.



## ETOMIDATE

### Properties

- Onset: Rapid
- Duration: Short

### Uses

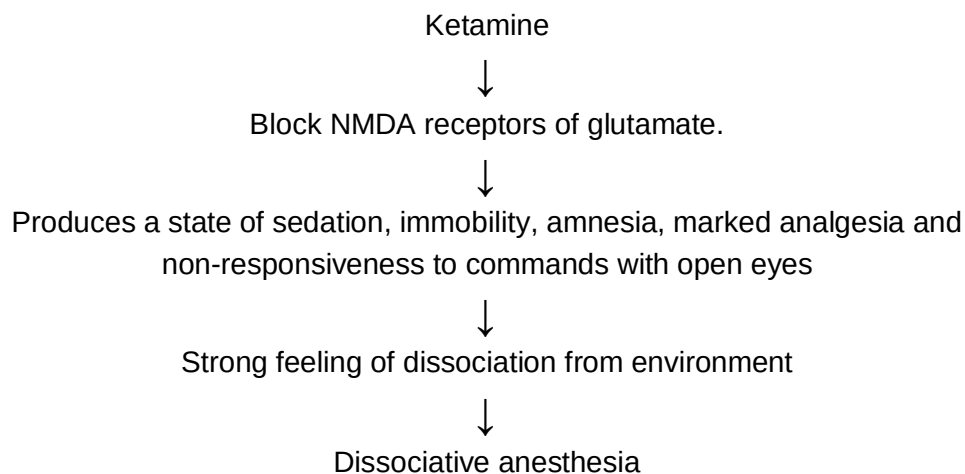
- It does not interfere with cardiovascular functions → Agent of choice for aneurysm surgeries and cardiac disease.
- Causes minimal respiratory depression.

### Adverse effects

1. Maximum incidence of nausea and vomiting
2. Produce myoclonus.
3. Injection of etomidate is painful → result in thrombophlebitis.
4. Adrenocortical suppression
5. Vitamin C deficiency

## KETAMINE

### Properties



- Good analgesic efficacy
- No pain on injection
- No excitatory behavior
- Laryngeal spasm is retained
- Muscle tone is maintained so patient is able to maintain airways
- Less respiratory depression
- Potent bronchodilator due to indirect sympathetic activity
- Increase BP, heart rate, and COP due to sympathetic activity (reduction in catecholamine uptake) → useful in patients with risk of hypotension

## Uses

- Ketamine is preferred for induction of anesthesia in
  - Pediatric age group
  - A Patients with risk of hypotension (shock) and
  - Bronchospasm (asthma)
  - A Patient with full stomach (emergency)

## Adverse effects

- Increases oxygen consumption** → not ideal for patients with risk of MI
- Increases cerebral blood flow** → an increases risk of postoperative hallucinations and night mares → Emergence delirium

## Contraindication

- Increases all pressures** → BP, intracranial and intraocular pressure → contraindicated to a patient of →
  - Hypertension
  - M.I.
  - Head injury
  - Eye injury
  - psychiatric manifestations

## Mnemonic

|          |                                                                                                                |
|----------|----------------------------------------------------------------------------------------------------------------|
| <b>K</b> | <b>K</b> ids (IV anaesthetic of choice in children)                                                            |
| <b>E</b> | <b>E</b> mergence reaction [hallu-inations, illusions, vivid dreams etc. seen while recovery from anaesthesia] |
| <b>T</b> | <b>T</b> halamocortical junction [site of action, responsible for dissociative anaesthe-sia]                   |
| <b>A</b> | <b>A</b> nalgesic [maximum among anaesthetics]                                                                 |
| <b>M</b> | <b>M</b> eals [can be given in full stomach]                                                                   |
| <b>I</b> | <b>I</b> ncreases all pressures [BP, IOP, ICT]                                                                 |
| <b>N</b> | <b>N</b> MDA antagonist                                                                                        |
| <b>E</b> | <b>E</b> xcellent for asthmatics.                                                                              |

| Agent        | Cardiovascular system |               | Central nervous system              |     |                     | Respiratory system |                            |
|--------------|-----------------------|---------------|-------------------------------------|-----|---------------------|--------------------|----------------------------|
|              | Heart rate            | Mean arterial | O <sub>2</sub> of consumption brain | ICT | Cerebral blood flow | Venti-lation       | Bronchial muscles          |
| Thiopentone  | ↑ (reflex)            | ↓↓            | ↓↓↓                                 | ↓↓↓ | ↓↓↓                 | ↓↓                 | Constriction (tachycardia) |
| Methohexital | ↑                     | ↓↓            | ↓↓↓                                 | ↓↓↓ | ↓↓↓                 | ↓↓                 | Constriction               |
| Propofol     | 0                     | ↓↓↓           | ↓↓↓                                 | ↓↓↓ | ↓↓↓                 | ↓↓                 | 0                          |
| Etomidate    | 0                     | ↓             | ↓↓                                  | ↓↓  | ↓↓                  | ↓                  | 0                          |
| Ketamine     | ↑↑                    | ↑↑            | ↑↑                                  | ↑↑  | ↓↓↓                 | ↑                  | Dilatation                 |

## Remember

### IV anaesthetic inducing agent causing pain on injection

- Propofol (++)
- Thiopentone (+/ 0) → Minimum pain
- Methohexitone (+)
- Etomidate (+++) → Maximum pain

### IV anaesthetic inducing agent not causing pain on injection

- Ketamine

## Complications of General Anaesthesia

### A. During anaesthesia

#### 1. Respiratory system →

- Respiratory depression and hypercarbia.
- Aspiration of gastric contents: acid pneumonitis.
- Laryngospasm and asphyxia.

#### 2. CVS →

- Cardiac arrhythmias
- Asystole
- Fall in BP

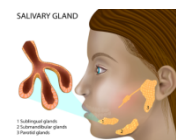
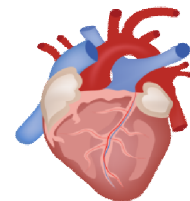
#### 3. CNS →

- Awareness → dreadful perception and recall of events during surgery → due to use of light anaesthesia + analgesics and muscle relaxants.
- Delirium, convulsions and other excitatory effects with i.v. anaesthetics → suppressed by opioids.

#### 4. Glands →

- Salivation, respiratory secretions → Less problematic now as nonirritant anaesthetic are mostly used.

#### 5. Fire and explosion → rare now due to use of non-inflammable anaesthetics.



### B. After anaesthesia

#### 1. Respiratory system →

- Pneumonia
- Atelectasis.

#### 2. GIT →

- Nausea and vomiting.

#### 3. CNS →

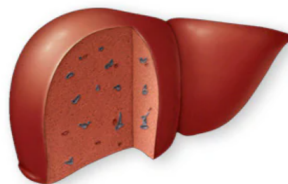
- Persisting sedation: impaired psychomotor function.
- Nerve palsies—due to faulty positioning.



- Emergence delirium.
- Cognitive defects: prolonged excess cognitive decline has been observed in some patients, especially the elderly, who have undergone general anaesthesia, particularly of long duration.

#### 4. Organ toxicities →

- Liver damage
- Kidney damage



## REMEMBER

### Drugs Useful for Day Care Surgery

Mnemonic →

|          |   |                               |
|----------|---|-------------------------------|
| Dr       | – | Desflurane                    |
| Manmohan | – | Midazolam (Benzodiaz-epine)   |
| Singh    | – | Sevoflurane                   |
| Is       | – | Isoflurane                    |
| A        | – | Alfentanil                    |
| Prime    | – | Propofol                      |
| Minister | – | Mivacurium (Muscle relax-ant) |

| DRUG OF CHOICE                     |                |
|------------------------------------|----------------|
| Condition                          | Drug of choice |
| Day care:                          | Propofol       |
| Ischemic heart disease:            | Etomidate      |
| Congenital heart disease           |                |
| - Left to right shunt:             | Isoflurane     |
| - Right to left shunt:             | Ketamine       |
| CHF:                               | Ketamine       |
| Shock:                             | Ketamine       |
| To produce deliberate hypotension: | Isoflurane     |
| Asthma and COPD:                   | Ketamine       |
| Epilepsy:                          | Thiopentone    |
| For electroconvulsive therapy:     | Methohexitone  |
| Thyrotoxicosis:                    | Thiopentone    |
| Cardiac surgery:                   | Isoflurane     |
| Neurosurgery:                      | Isoflurane     |

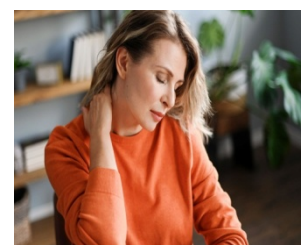
| DRUG OF CHOICE                         |                                          |
|----------------------------------------|------------------------------------------|
| Condition                              | Drug of choice                           |
| • Neurolept analgesia                  | Droperidol + Fentanyl                    |
| • Neurolept anaesthesia                | Droperidol + Fentanyl + N <sub>2</sub> O |
| • GA for internal version              | Halothane                                |
| • GA for asthma                        |                                          |
| - Inducing agent                       | Ketamine                                 |
| - Inhalational                         | Halothane                                |
| • GA to produce controlled hypotension | Isoflurane                               |
| • GA for cardiac surgery               |                                          |
| - Inducing agent                       | Etomidate                                |
| - Inhalational                         | Isoflurane                               |

| DRUG OF CHOICE                                          |                              |
|---------------------------------------------------------|------------------------------|
| Condition                                               | Drug of choice               |
| • Day care surgery                                      | Propofol                     |
| • Total Intravenous Anaesthesia                         | Propofol                     |
| • GA for malignant hyperthermia                         | Propofol                     |
| • GA in patients with shock                             | Ketamine                     |
| • LA in patients with malignant hyperthermia            | Procaine                     |
| • Intravenous Regional Anaesthesia (IVRA; Bier's block) | Prilocaine                   |
| • Malignant hyperthermia                                | Dantrolene                   |
| • Malignant Neuroleptic Syndrome                        | Danrolene                    |
| • MR in patients with asthma                            | Vecuronium                   |
| • MR in liver and kidney disease                        | Atracurium or Cis-atracurium |
| • MR for endotracheal intubation                        | Succinylcholine              |

## OPIOID ANALGESICS AND ANTAGONISTS

### Algesia (Pain)

- An ill-defined, unpleasant bodily sensation → usually evoked by an external or internal noxious stimulus.
- Pain is a warning signal
  - Primarily protective in nature



- Causes discomfort and suffering
  - Sometimes unbearable and incapacitating.
- It is the most important symptom that brings the patient to physician.
  - Excessive pain may produce other effects → sinking sensation, apprehension, sweating, nausea, palpitation, rise or fall in BP, tachypnoea.



## Analgesic

- A drug that selectively relieves pain by acting in CNS or on peripheral pain mechanisms, without significantly altering consciousness.



## Remember

- Analgesics relieve pain as a symptom, without affecting its cause.
- They are used when the noxious stimulus (evoking pain) cannot be removed or as adjuvants to more etiological approach to pain.

## Types of Analgesics

2 types →

1. Opioid/ Narcotic/ Morphine-like analgesics.
2. Nonopioid/ Non-narcotic/ Aspirin-like/ Antipyretic or Antiinflammatory analgesics → NSAIDS

| NSAIDS Versus Opioids                          |                                              |
|------------------------------------------------|----------------------------------------------|
| Nonsteroidal Anti inflammatory Drugs (Aspirin) | Opioids (Example-Morphine, Methadone)        |
| Weaker Analgesic                               | Strong Analgesic                             |
| Acts Peripherally                              | Acts both Spinal and Supraspinal (emotional) |
| Do not depress CNS                             | Depress CNS (sedation)                       |
| No abuse liability                             | High abuse potential                         |
| No dependence                                  | Can Cause Physical and Mental Dependence     |

## OPIOID ANALGESICS

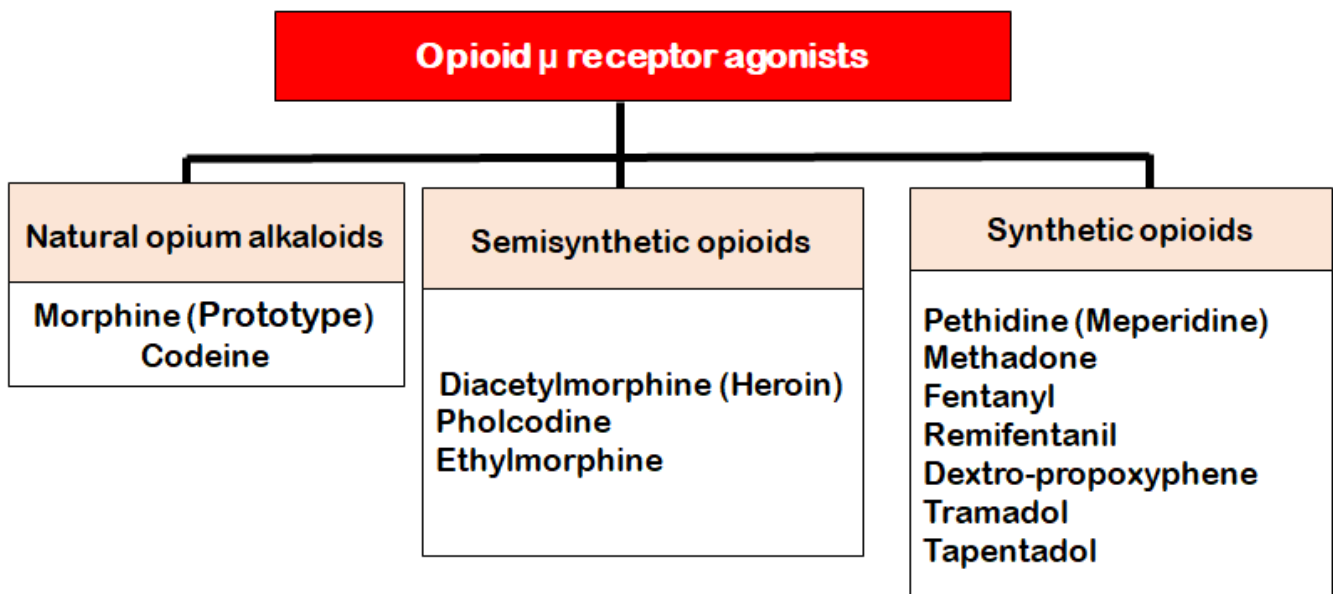
| OPIOID ANALGESICS                          |  |
|--------------------------------------------|--|
| Introduction                               |  |
| Classification                             |  |
| MOA                                        |  |
| Pharmacological Actions                    |  |
| Pharmacokinetics                           |  |
| Uses                                       |  |
| Adverse effects                            |  |
| Opioid Toxicity / Acute morphine poisoning |  |
| Contraindications                          |  |

### Introduction

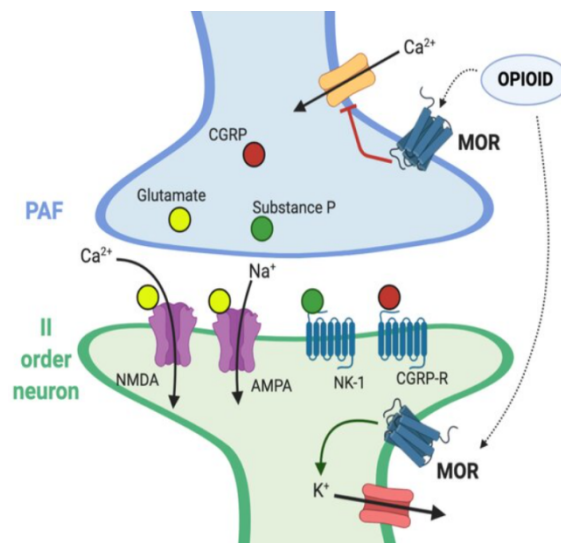
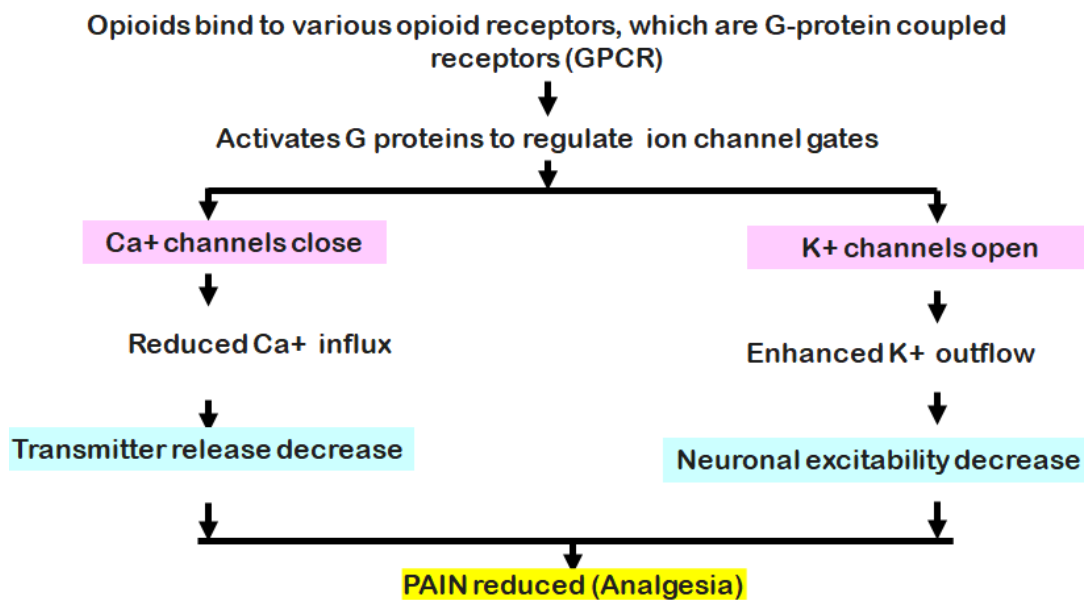
- Obtained from Opium
- A dark brown, resinous material obtained from poppy (*Papaver somniferum*) capsule.
- Contains 2 types of alkaloids→
  - i. Phenanthrene derivatives
  - ii. Benzoisoquinoline derivatives
- **Phenanthrene derivatives**
  - Morphine (10% in opium)
  - Codeine (0.5% in opium)
  - Thebaine (0.2% in opium)
- **Benzoisoquinoline derivatives**
  - Papaverine (1%)
  - Noscapine (6%)



## Classification



## MOA



## Pharmacological Actions

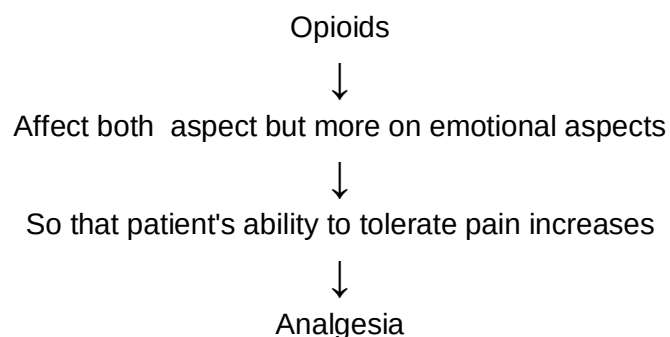
1. CNS
2. CVS
3. GIT
4. Biliary tract
5. Urinary tract
6. Uterus
7. Lung
8. Skin
9. Tolerance
10. Drug dependence

### 1. CNS

- a) Analgesia
- b) Sedation
- c) Euphoria
- d) Respiratory depression
- e) Miosis
- f) Suppression of Cough
- g) Nausea and vomiting
- h) Muscle rigidity
- i) Convulsions
- j) Increased ICT

#### a) Analgesia

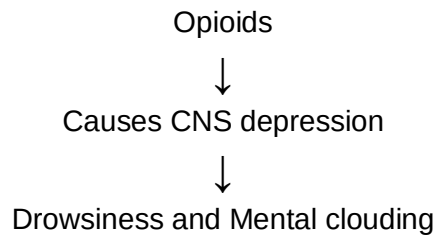
- Pain has two components →
  - i. Specific sensation component.
  - ii. Emotional or affective component → original sensation of pain is enhanced by previous experience of pain.



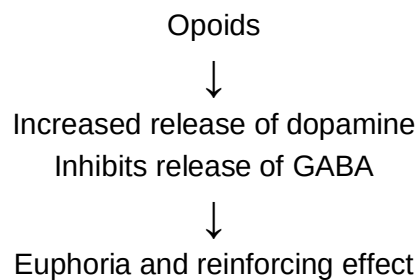
- Affective responses to pain → such as anxiety, fear, panic and suffering are changed.
- Continuous dull pain is better relieved than sharp intermittent pain.

- Visceral pain is better affected than superficial pain
- Nociceptive pain responds better but neuropathic pain responds poorly.

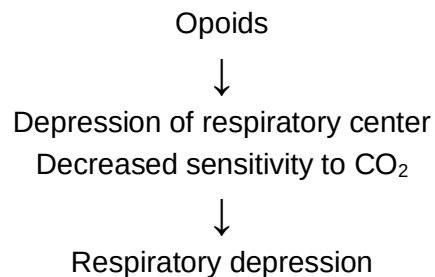
## b) Sedation



## c) Euphoria

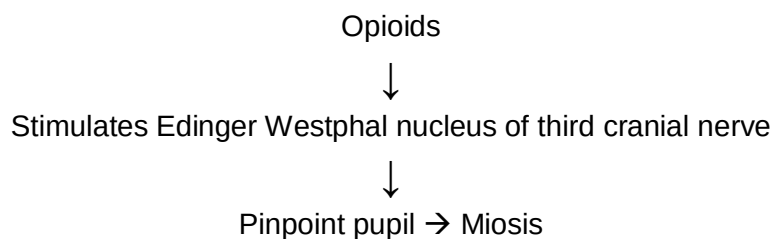


## d) Respiratory depression

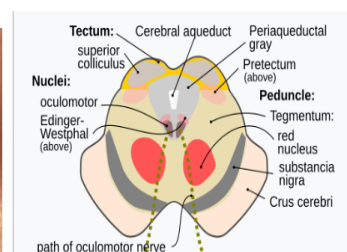
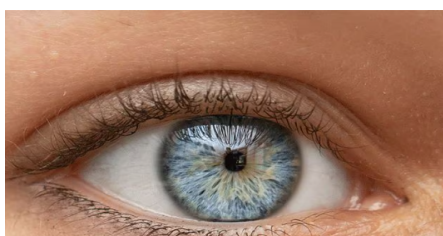


- Death in poisoning is always due to respiratory failure.

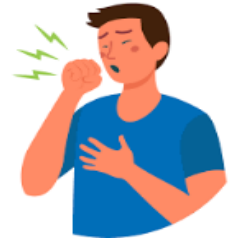
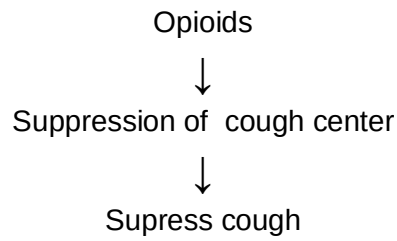
## e) Miosis



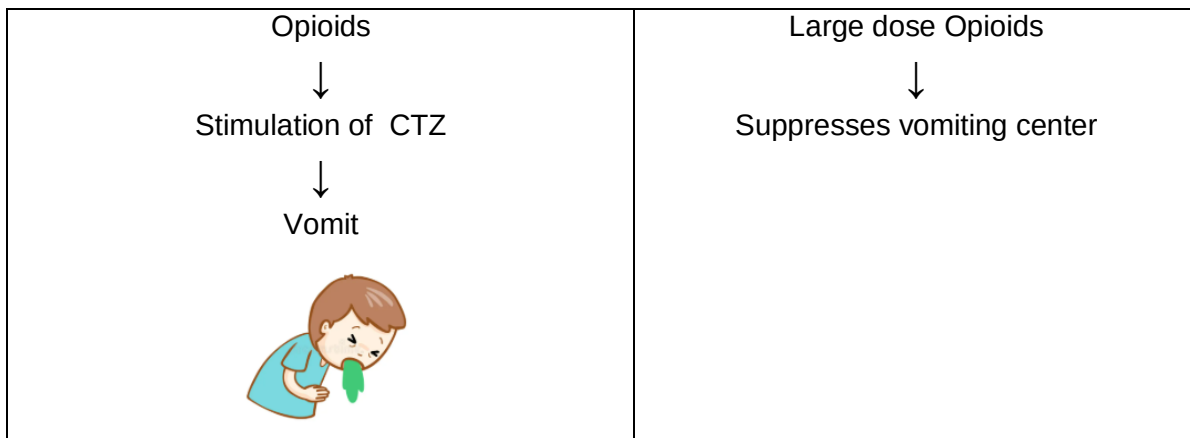
- Tolerance does not develop to miosis.



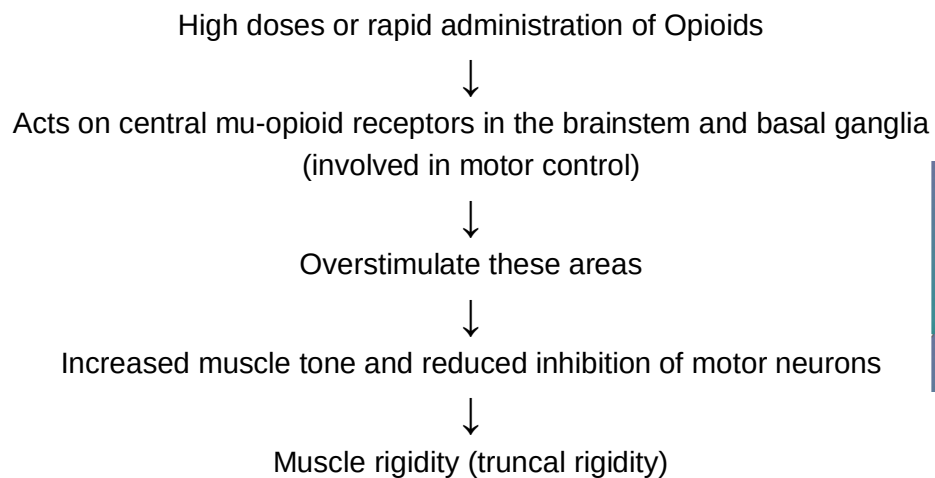
## f) Suppression of Cough



## g) Nausea and Vomiting



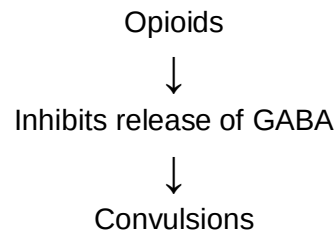
## h) Muscle rigidity (truncal rigidity)



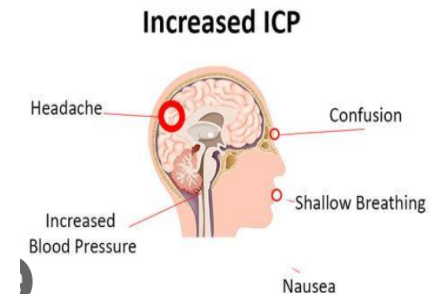
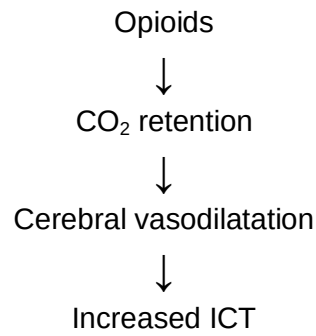
- Adversely affect ventilation.
- More common with highly lipid soluble drugs such as fentanyl and its analog.
- Reduced by → avoiding rapid i/v administration and by concomitant use of a NM blocker



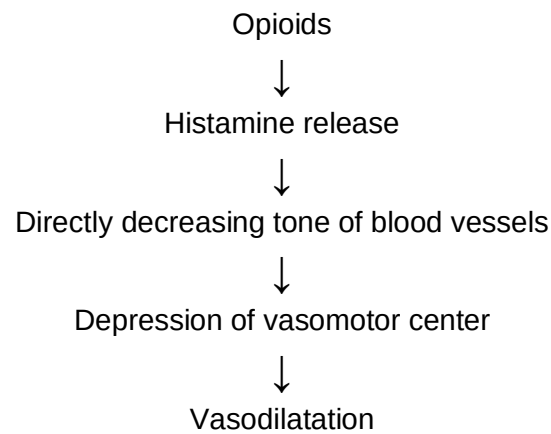
## i) Convulsions



## j) Increased ICT



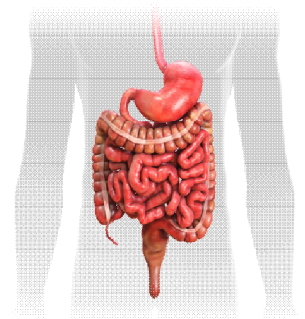
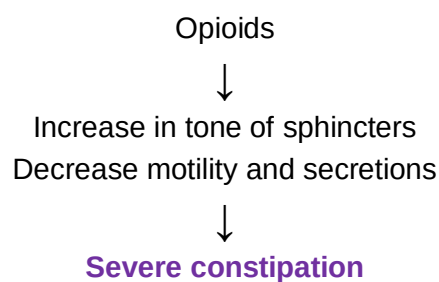
## 2. CVS



**Venodilatation → Postural hypotension**

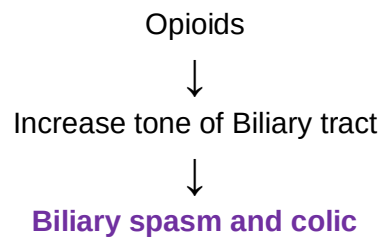
**Shift blood from pulmonary to systemic circuit → relieves pulmonary congestion and edema**

## 3. GIT

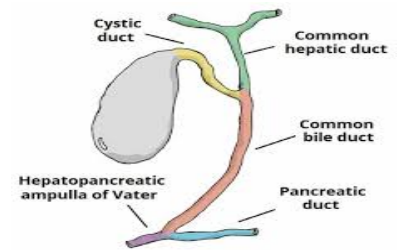


- Tolerant does not develop.

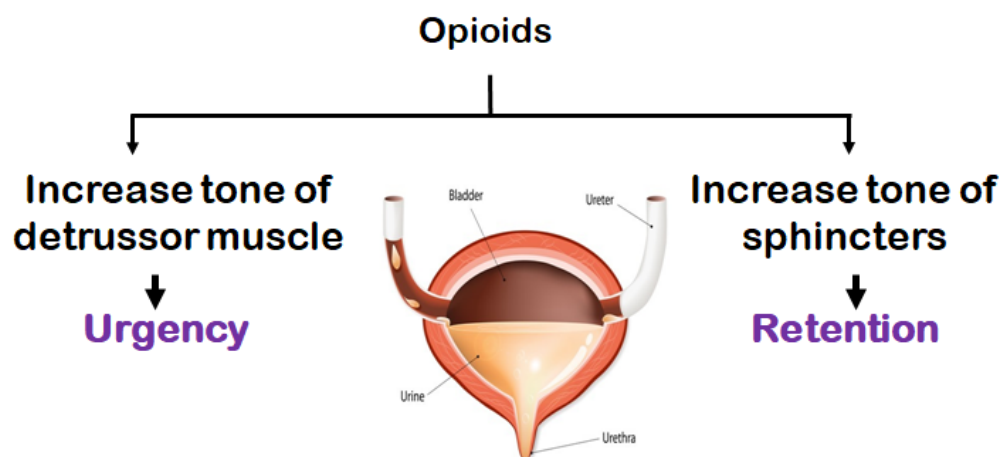
## 4. Biliary tract



- Relieved by atropine and nitroglycerine

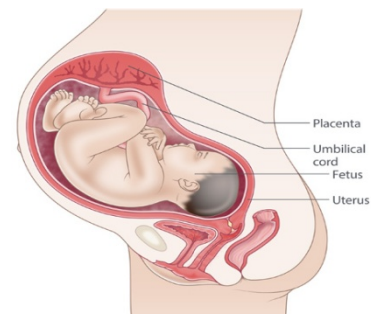


## 5. Urinary tract

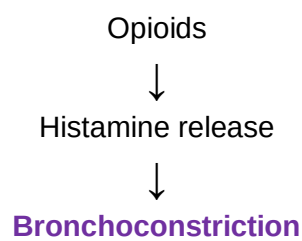


## 6. Uterus

- It prolongs labor.
- Causes respiratory depression in neonate



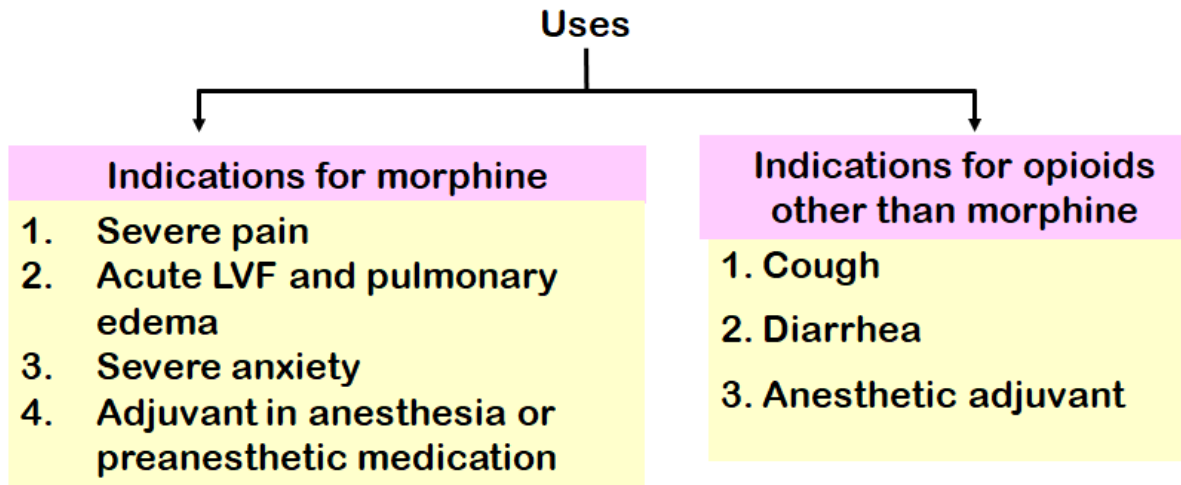
## 7. Lung





## Uses

- A. Indications for morphine
- B. Indications for opioids other than morphine



### A) Indications for morphine

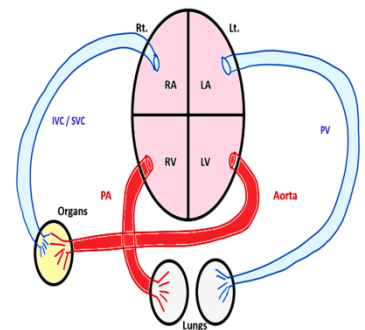
#### 1. Severe pain / analgesia

- Severe pain such as →
  - Myocardial infarction
  - Burn, fracture
  - Embolism
  - Pleurisy
  - Biliary colic
  - Renal colic
  - Refractory severe pain
  - Pain of terminal illnesses like malignancy.



#### 2. Acute LVF and pulmonary edema

- Morphine injected i.v. affords dramatic relief by →
  - (a) Reducing preload on heart due to vasodilatation and peripheral pooling of blood.
  - (b) Shift blood from pulmonary to systemic circuit → relieves pulmonary congestion and edema.
  - (c) Allays air hunger and dyspnoea by depressing respiratory centre.
  - (d) Cuts down sympathetic stimulation by calming patient → reduces cardiac work.



#### 3. Severe anxiety

- Severe anxiety with distressing conditions like hematemesis.



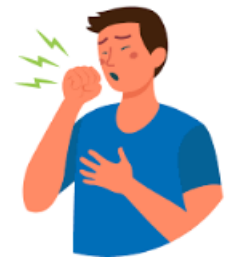
#### 4. Adjuvant in anesthesia or preanesthetic medication



### B) Indications for opioids other than morphine

#### 1. Cough

- Opioids used →
  - Codein
  - Oxymorphone
  - Hydromorphone
  - Hydrocodone
  - Dextromethorphan



#### 2. Diarrhea

- Opioids used →
  - Diphenoxylate
  - Loperamide



### Adverse Effects

#### Mnemonic

|          |                                        |
|----------|----------------------------------------|
| <b>M</b> | <b>Miosis (pin point pupil)</b>        |
| <b>O</b> | <b>Orthostatic hypotension</b>         |
| <b>R</b> | <b>Respiratory depression</b>          |
| <b>P</b> | <b>Physical dependency</b>             |
| <b>H</b> | <b>Histamine release , Hypothermia</b> |
| <b>I</b> | <b>Itching, Increase ICT</b>           |
| <b>N</b> | <b>Nausea, Vomiting</b>                |
| <b>E</b> | <b>Euphoria</b>                        |
| <b>S</b> | <b>Sedation</b>                        |
| <b>G</b> | <b>GIT → constipation</b>              |
| <b>U</b> | <b>Urinary retention</b>               |
| <b>T</b> | <b>Tolerance</b>                       |

### Physical Dependence

- Opioids are worst drug to cause physical dependence.
- Even first dose may initiate it.
- Morphine produces pronounced psychological and physical dependence
- Abuse liability is rated high.

- To get a 'rush' or to maintain a state of dreamy indifference → addict constantly increases the dose.
- Withdrawal of an opioid leads to a rebound phenomenon that manifests with the symptoms in opposite directions to the action of morphine

## Symptoms of withdrawal

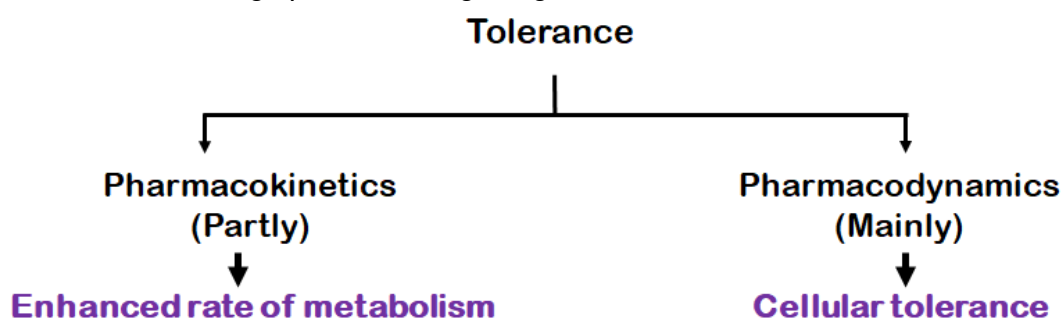
- Restlessness
- Irritability
- Mydriasis
- Hyperventilation
- Tachycardia
- Hypertension
- Hyperpyrexia
- Diarrhea

## Management of opioid dependence

1. Substitution therapy with a long acting opioid → methadone → maintains the dependent stage for a long period.
  - Dose of methadone is then gradually reduced.
  - Then methadone is discontinued
2. When methadone is discontinued → clonidine is given for 7-10 days.
  - Opioid inhibits locus caeruleus, which contains adrenergic neurons so withdrawal increases activity of noradrenaline and that is suppressed by clonidine.

## Tolerance

- High degree of tolerance can be developed to morphine and related opioids if the drug is used repeatedly.
- Tolerance is exhibited to most actions, except constipating and miotic actions.
- Addicts tolerate morphine in grams: lethal dose is markedly increased.
- Cross tolerance among opioids is of high degree.



## Opioid Toxicity / Acute morphine poisoning

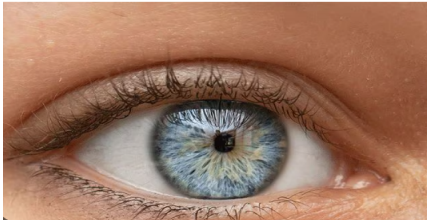
- It may be accidental, suicidal or seen in drug abusers.
- In nontolerant adult → 50 mg of morphine i.m. produces serious toxicity.
- Human lethal dose → 250 mg





## Symptoms

- Triad →
  1. Pinpoint pupil / Miosis
  2. Respiratory depression
  3. Coma
- Death is due to respiratory failure.



## Treatment of acute poisoning

- A. Death is due to resGeneral treatment
- B. Specific antidote

### General treatment

1. **Respiratory support** → positive pressure
2. **Maintenance of BP** → i.v. fluids, vasoconstrictors
3. **Gastric lavage** → with pot. permanganate to remove unabsorbed drug.
  - Lavage is indicated even when morphine has been injected.
  - Being a basic drug it is partitioned to acid gastric juice → ionizes there and does not diffuse back into blood

### Specific antidote

**Naloxone** → specific antagonist of choice because

1. Acts rapidly
  2. Does not have any agonistic action
  3. Does not per se depress respiration
- Naloxone 0.4–0.8 mg i.v. repeated every 2–3 min till respiration picks up
  - Due to short duration of action, naloxone should be repeated every 1–4 hours, according to the response.

## Contraindications

- Mnemonic → **A<sub>2</sub>BCD H<sub>3</sub> PR<sub>2</sub>ST**
- 1. Acute **A**bdomen → analgesic effect masks diagnosis; also spasmogenic and constipating effect that further worsen the problem.
- 2. **A**lcoholic intoxication.
- 3. **B**ronchial asthma → potent release of histamine → bronchoconstriction.
- 4. Acute ulcerative **C**olitis and infective diarrhea → decrease motility, in absence of specific drug, carries risk of toxic dilatation of colon.
- 5. Acute **D**iverticular disease of colon → risk of rupture.
- 6. **H**ypersensitivity reactions
- 7. Impaired **H**epatic functions

8. Acute **h**ead injury → 2 reasons
  - Potential risk of increase in ICT and respiratory depression.
  - Mental clouding, miosis and vomiting that interfere with the prognostic evaluation of patient.
9. **P**rostatic enlargement → urinary retention by morphine
10. Low **R**espiratory reserve → emphysema, cor pulmonale, kyphoscoliosis and severe obesity
11. Impaired **R**enal functions
12. Hypovolemic **S**hock → vasodilatation and fall in B.P. further complicate the clinical situation.
13. Hypo**t**hyroidism → decrease metabolism so increases effect of opioids.

## INDIVIDUAL COMPOUNDS

|                          | Codeine | Pethidine<br>(Meperidine) | Fentanyl | Tramadol |
|--------------------------|---------|---------------------------|----------|----------|
| Introduction             |         |                           |          |          |
| Comparison with Morphine |         |                           |          |          |
| Uses                     |         |                           |          |          |
| Adverse effects          |         |                           |          |          |

## CODEINE

### Introduction

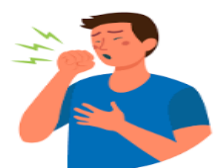
- It is methyl-morphine
- Occurs naturally in opium
- Partly converted in the body to morphine.

### Codeine versus Morphine

1. Weak analgesic → having 1 /10th potency than that of morphine →
  - About 10% is metabolized to morphine → responsible for analgesic effect.
  - Codeine itself has a low affinity for opioid receptor.
  - Better oral absorption due to less first-pass metabolism in liver.
2. Less risk of respiratory depression
3. Less dependence.
4. Less Nausea and vomiting

### Uses

- It is metGood antitussive effect

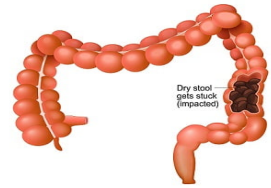




## Adverse effects

- Constipation → major adverse effect.

Constipation



## PETHIDINE (MEPERIDINE)

### Introduction

- Pethidine was synthesized as an atropine substitute in 1939 and has some actions like it.
- Though chemically unrelated to morphine, it interacts with  $\mu$  opioid receptors and its actions are blocked by naloxone.

### Pethidine versus Morphine

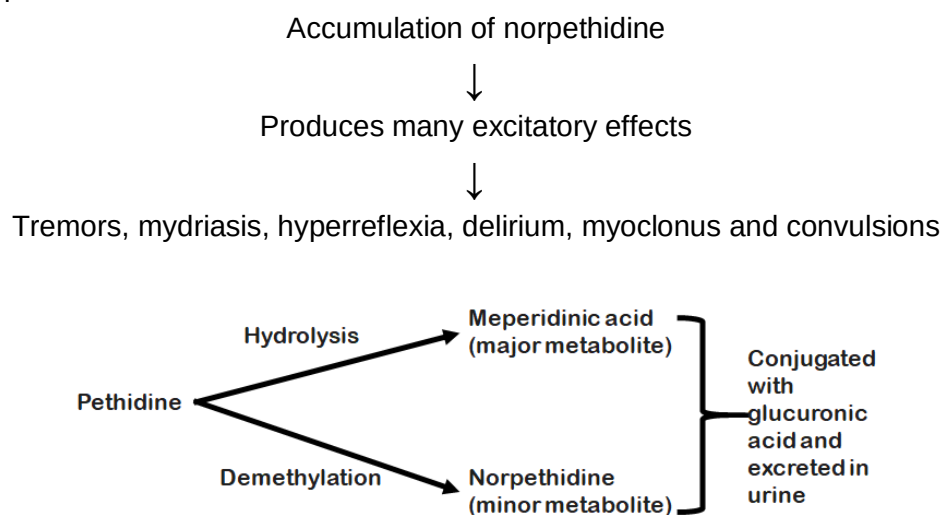
1. Dose to dose 1/10th in analgesic potency → But analgesic efficacy approaches near to morphine and is greater than codeine.
2. Does not effectively suppress cough
3. Spasmodic action on smooth muscles is less marked → miosis, constipation and urinary retention are less prominent.
4. Equally sedative and euphoriant
5. Similar abuse potential.
6. Degree of respiratory depression seen at equianalgesic doses is equivalent to that with morphine.
7. Tachycardia (due to antimuscarinic action) occurs instead of bradycardia.
8. Less histamine release → safer in asthmatics.
9. Local anaesthetic action → corneal anaesthesia is seen after systemic doses

### Uses

1. As an analgesic (substitute of morphine)
2. In preanaesthetic medication
3. To control shivering during recovery from anaesthesia or that attending i.v. infusions.
4. Preferred opioid analgesic during labour because at equianalgesic doses neonatal respiratory depression is less marked, but still significant.

### Adverse effects

1. Some atropinic effects → dry mouth, blurred vision, tachycardia
2. Overdose of pethidine



## FENTANYL

### Introduction

- $\mu$  receptor agonist

### Fentanyl versus Morphine

1. Much more potent than morphine as analgesic.
2. Rapid achievement of peak analgesic effect
3. No release of histamine
4. Relative cardiovascular stability
5. Minimum effect on intracranial pressure if ventilation is controlled
6. Muscle rigidity is more common

### Uses

- Fentanyl has been used with droperidol for neurolept analgesia → mild sedation, stage of apathy, and mental detachment

### Adverse effects

1. Muscle rigidity → more common → can be reduced by avoiding bolus administration and can be managed by a NM blocker.
2. Higher doses may produce seizures.

## TRAMADOL

### Introduction

- Centrally acting analgesic
- Atypical opioid which relieves pain by opioid as well as additional mechanisms.
- Affinity for  $\mu$  opioid receptor is low, while that for  $\kappa$  and  $\delta$  is very low.

### Tramadol versus Morphine

1. Causes less respiratory depression, sedation, constipation, urinary retention and rise in intrabiliary pressure than morphine.
2. Inhibits reuptake of NA and 5-HT, increases 5-HT release → activates monoaminergic spinal inhibition of pain → Tramadol should not be given to patients taking SSRI therapy because of risk of 'serotonin syndrome'
3. Its analgesic action is only partially reversed by opioid antagonist naloxone.

### Uses

- Indicated for →
  - Mild-to-moderate short-lasting pain due to diagnostic procedures, injury, surgery
  - Chronic pain including cancer pain
  - Not effective in severe pain.

## Adverse effect

1. Dizziness, Nausea
2. Sleepiness
3. Dry mouth
4. Sweating
5. Lowering of seizure threshold

## PURE OPIOID ANTAGONISTS

### Classification

- **Pure opioid antagonists** →
  - Naloxone
  - Naltrexone
  - Nalmefene

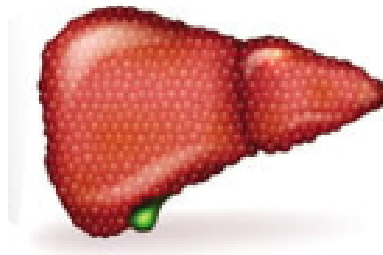
### Naloxone

- Orally absorbed
- Almost completely metabolized in liver before reaching systemic circulation → so used parenterally.
- Effect persists for a short period only, just 1-2 hours only.



### Naltrexone

- Effective orally
- Longer duration of action for about 24-48 hours.
- With excessive doses there is risk of hepatotoxicity.



### Nalmefene

- Greater oral bioavailability
- Longer duration of action
- Lack of risk of hepatotoxicity
- Relatively pure  $\mu$  receptor antagonist.

### Uses

- Opioid induced toxicities
- Diagnosis of opioid addict
- Treatment of compulsive users
- Conditions with excess of endogenous opioid activities like:

- Septic shock
- Cerebral ischemia
- Stroke
- Spinal cord damage
- Obesity
- Stress-induced eating disorders





# Drugs acting on Kidney

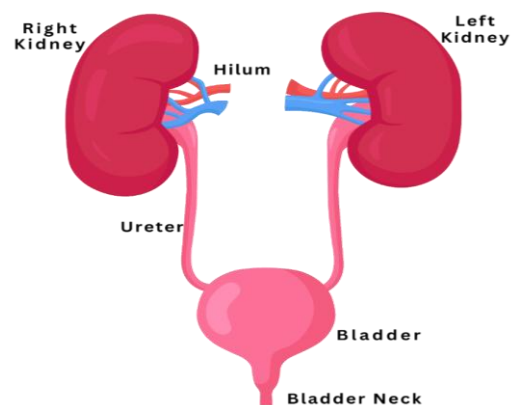
CHAPTER

11

## NORMAL ANATOMY AND HISTOLOGY OF KIDNEY

### Normal kidney → Anatomy

- Bean-shaped paired organs
- Surrounded by a thin fibrous capsule
- Hilum of kidney → situated at midpoint on medial aspect → artery, vein, lymphatics and ureter are located

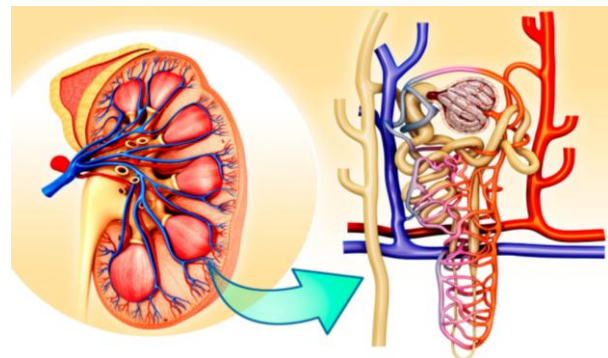


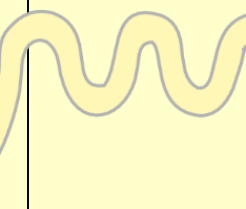
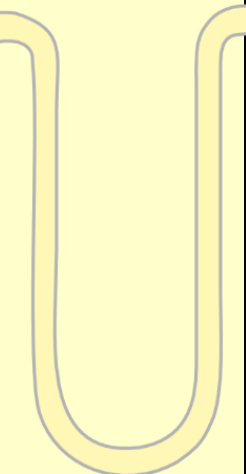
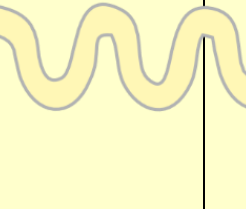
### Nephron

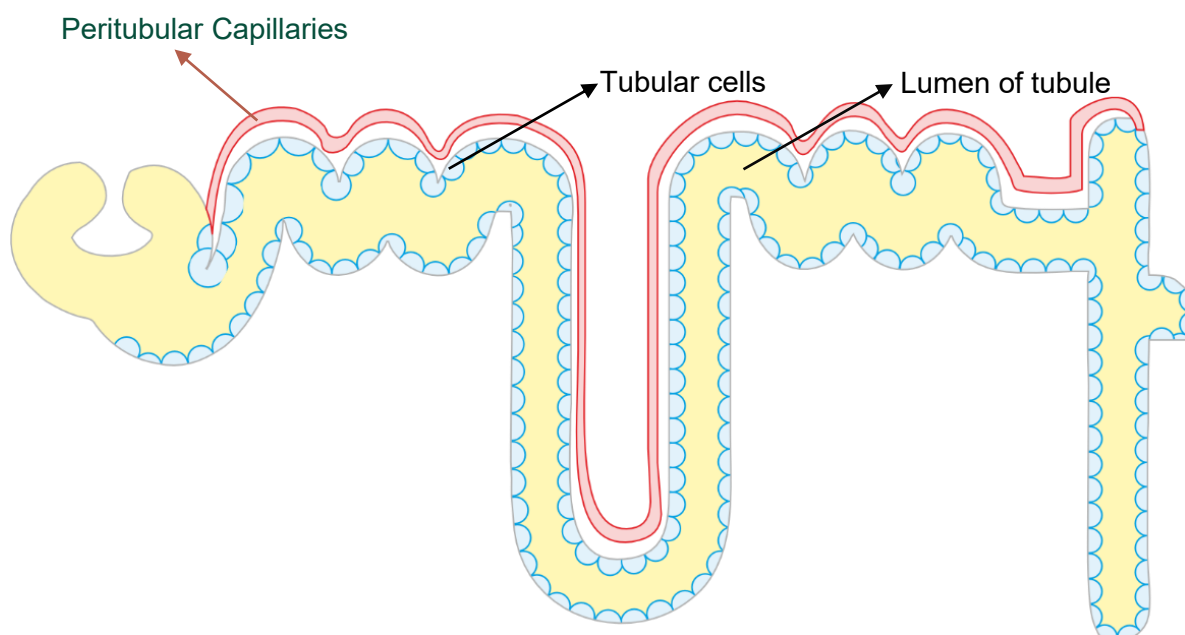
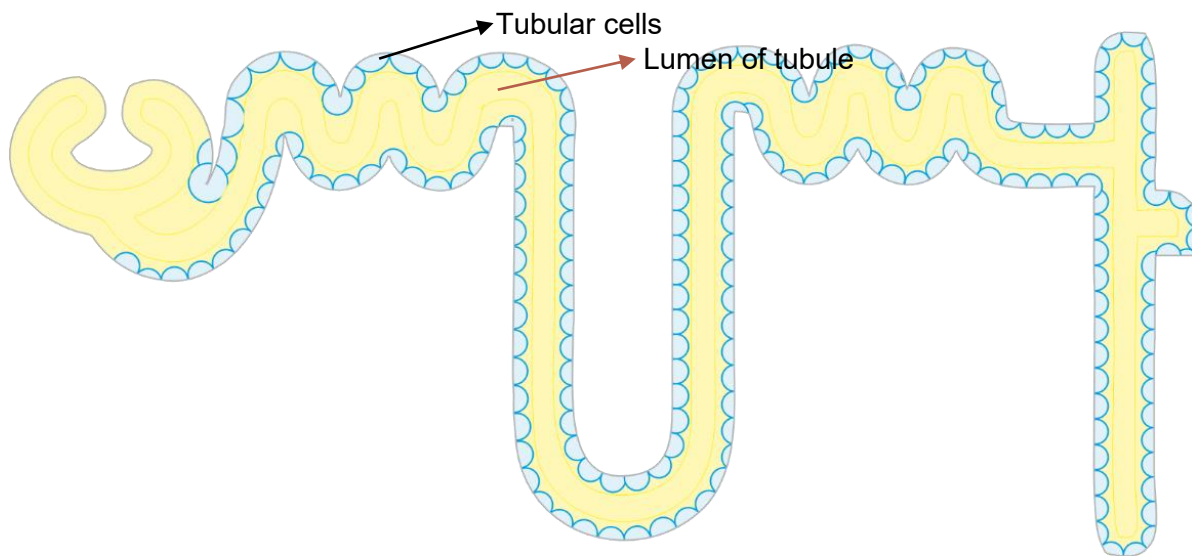
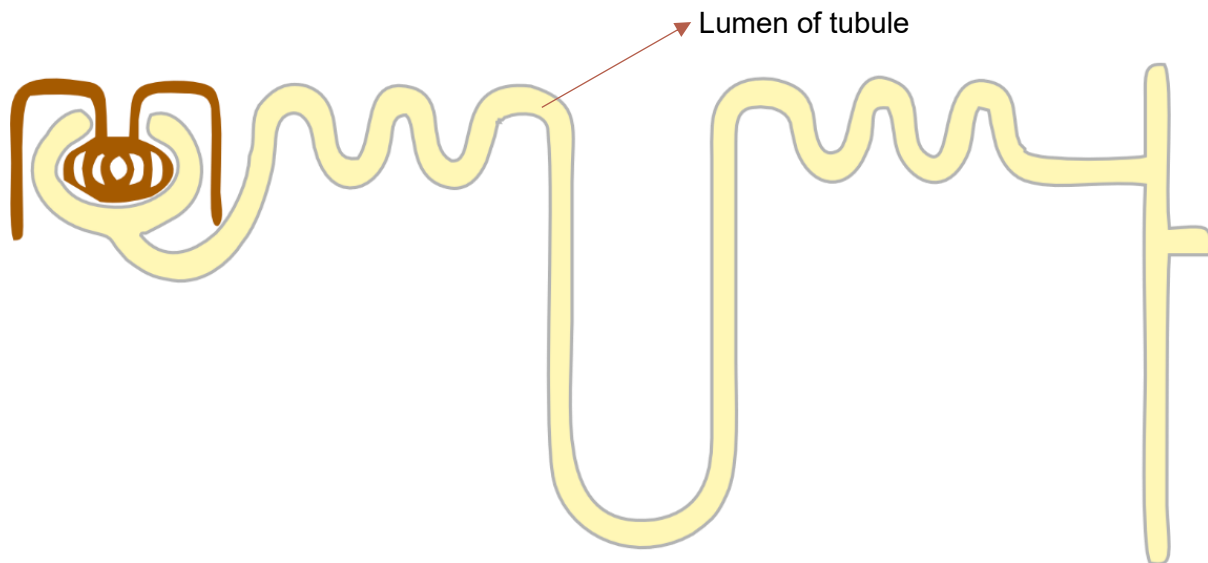
- Parenchyma is composed of approx one million microstructures called nephrons

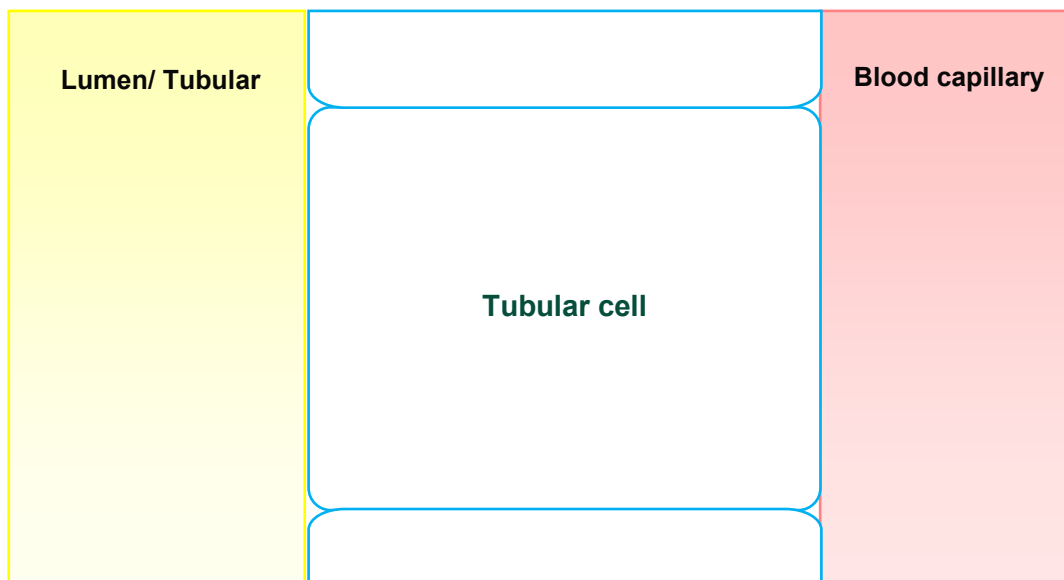
### Structure of Nephron

- 5 major parts →
  1. Glomerular capsule (glomerulus and Bowman's capsule)
  2. Proximal convoluted tubule (PCT)
  3. Loop of Henle
  4. Distal convoluted tubule (DCT)
  5. Collecting ducts



| Bowman's Capsule                                                                    | Proximal Tubule                                                                     | Loop of Henle                                                                       | Distal Tubule                                                                        | Collecting Duct                                                                       |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
|  |  |  |  |  |



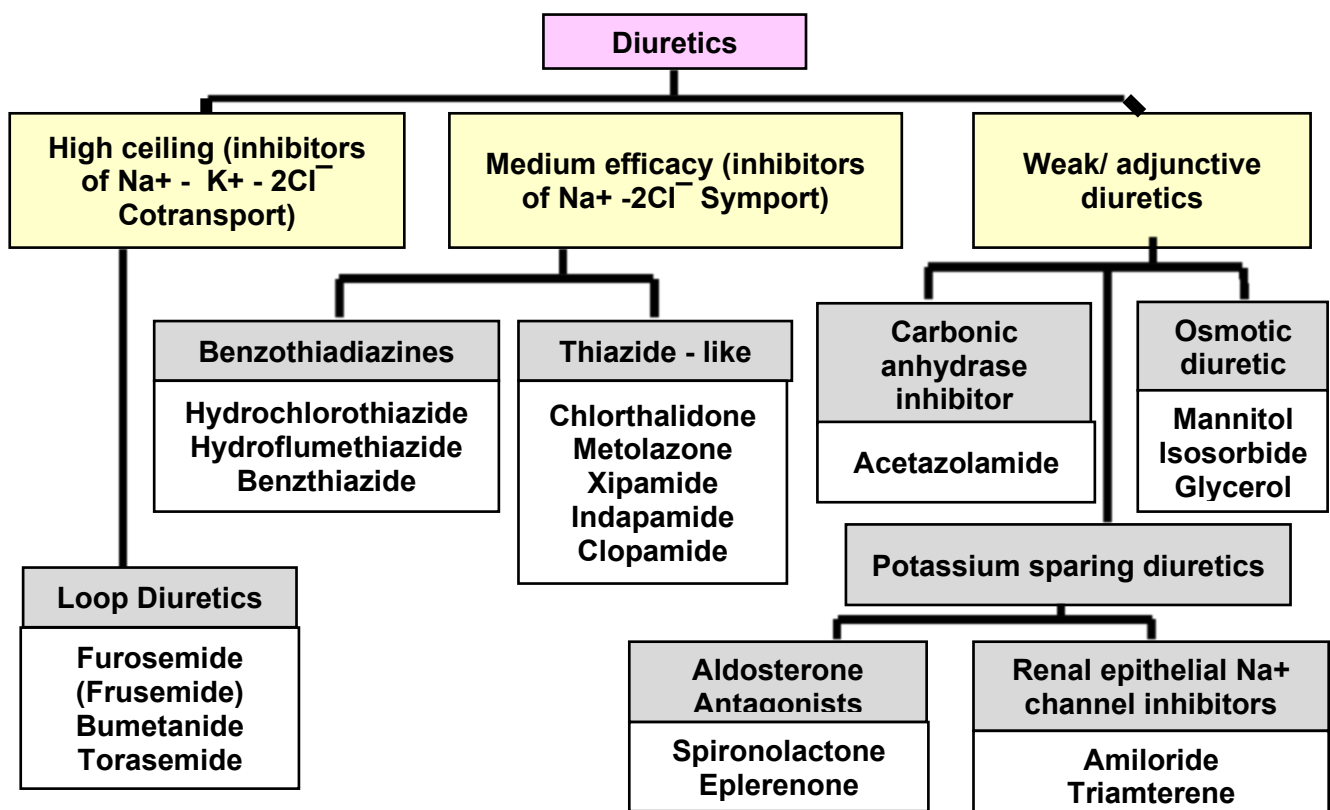


## DIURETICS

### Definition

- **Diuretics** → Drugs which cause a net loss of  $\text{Na}^+$  and water in urine.  
(Exception- Osmotic diuretics (Mannitol) don't cause natriuresis but produce diuresis)
- **Natriuresis** → increased Sodium ( $\text{Na}^+$ ) excretion
- **Kaliuresis** → Increased Potassium ( $\text{K}^+$ ) excretion

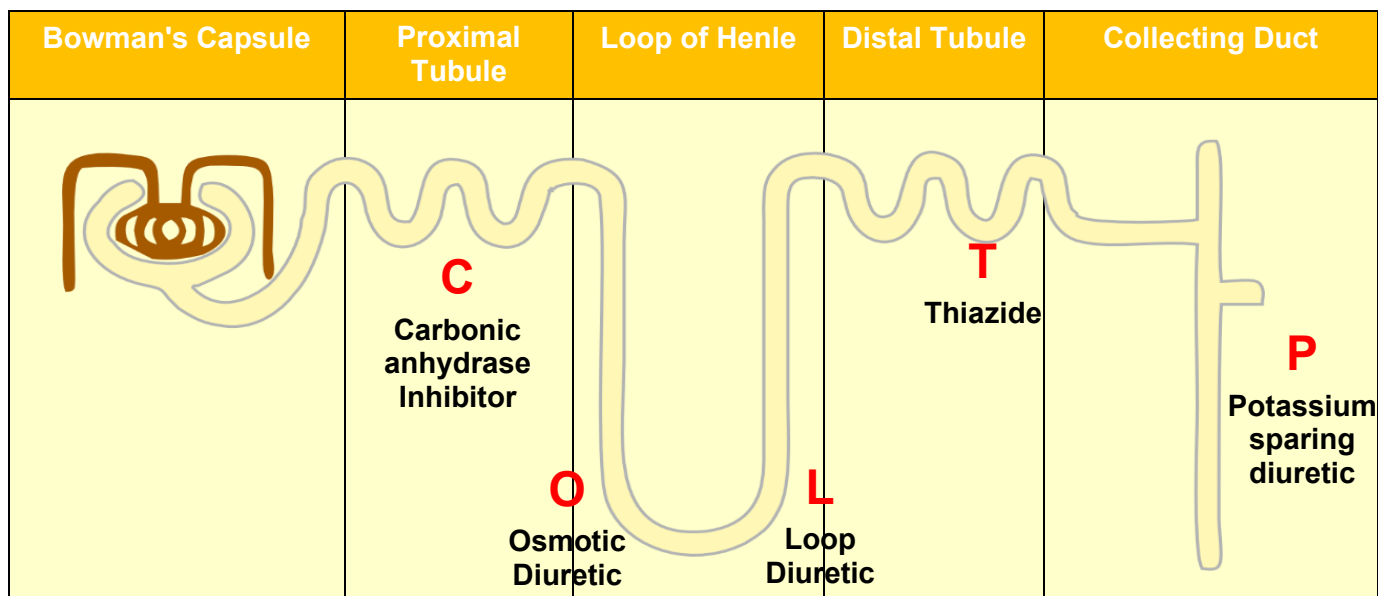
### Classification



## Site of Action

Mnemonic → **COLT Pee**

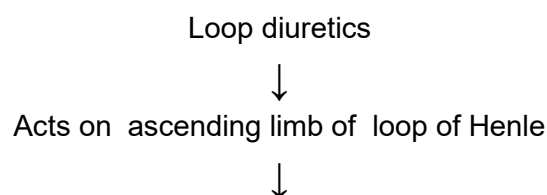
- **C**arbonic anhydrase inhibitors → at PCT
- **O**smotic diuretics → at Loop of Henle
- **L**oop diuretics → at ascending limb of Loop of Henle
- **T**hiazides → at DCT
- **P**otassium-sparing diuretics → at collecting tubules



|                  | Loop Diuretics | Thiazides | Carbonic Anhydrase Inhibitor | Potassium Sparing Diuretics | Osmotic Diuretics |
|------------------|----------------|-----------|------------------------------|-----------------------------|-------------------|
| Introduction     |                |           |                              |                             |                   |
| Drugs            |                |           |                              |                             |                   |
| Site of action   |                |           |                              |                             |                   |
| MOA              |                |           |                              |                             |                   |
| Pharmacokinetics |                |           |                              |                             |                   |
| Uses             |                |           |                              |                             |                   |
| Adverse effect   |                |           |                              |                             |                   |

## HIGH CEILING DIURETICS / LOOP DIURETICS / LASIX

### Introduction





So called Loop diuretics

Loop diuretics



Progressive increase in dose is matched by increasing diuresis

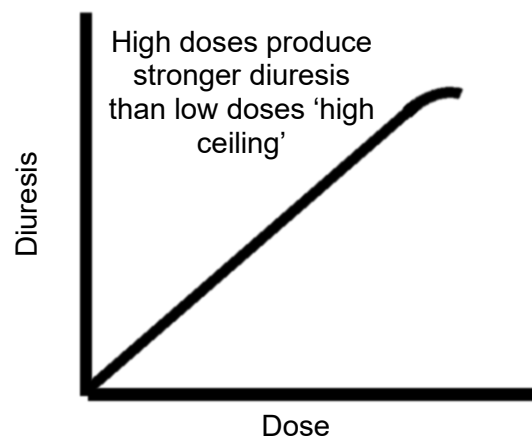


High ceiling effect



So called high ceiling diuretics

## Loop diuretics



## Drugs

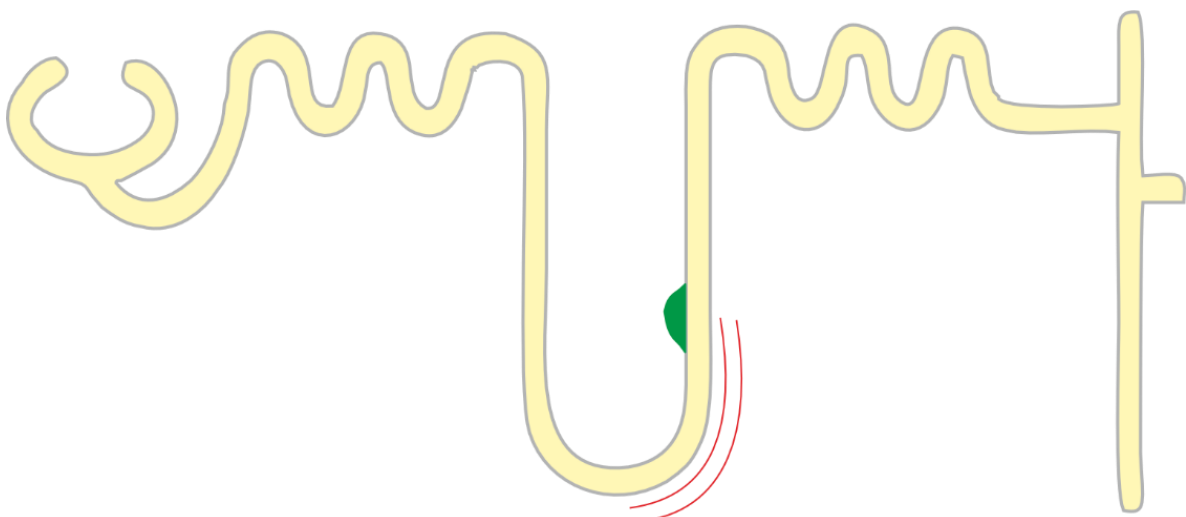
- Furosamide
- Bumetanide
- Torasemide

Historical importance

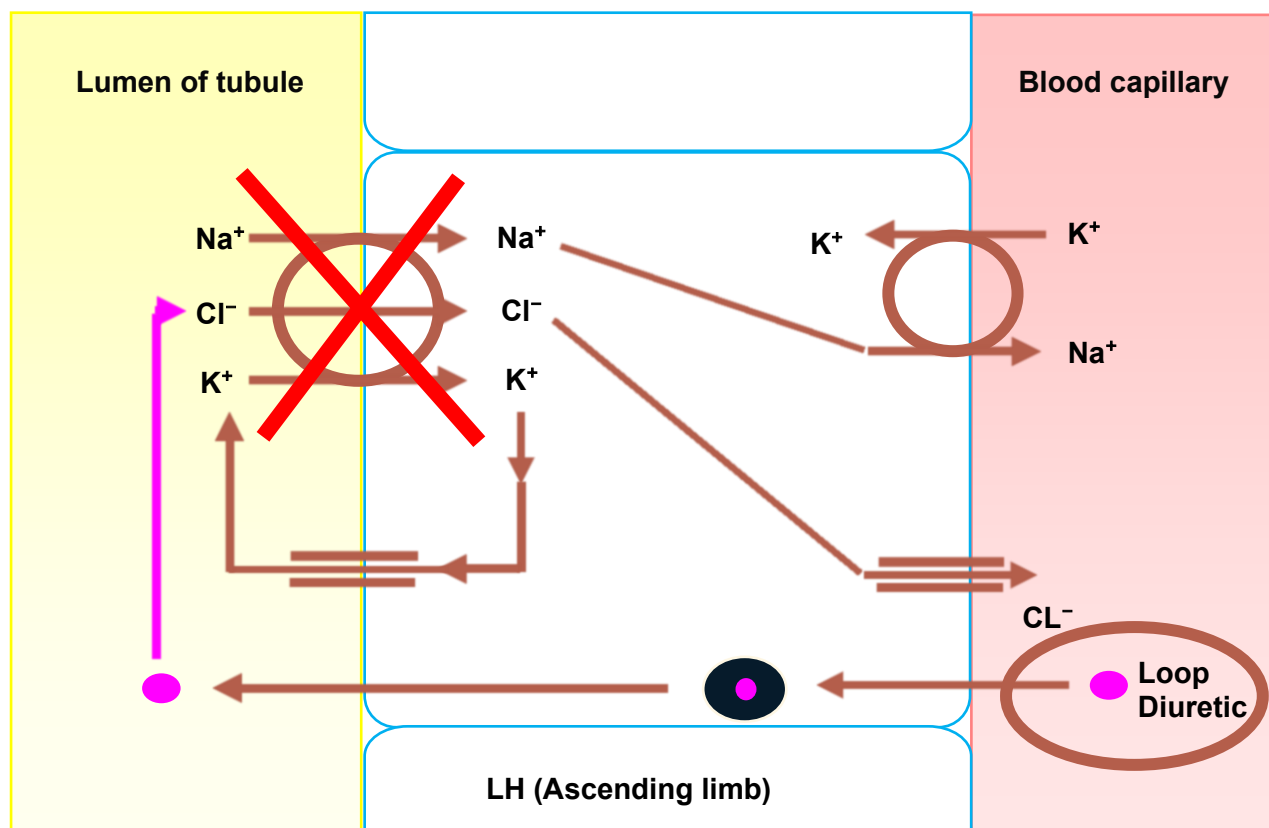
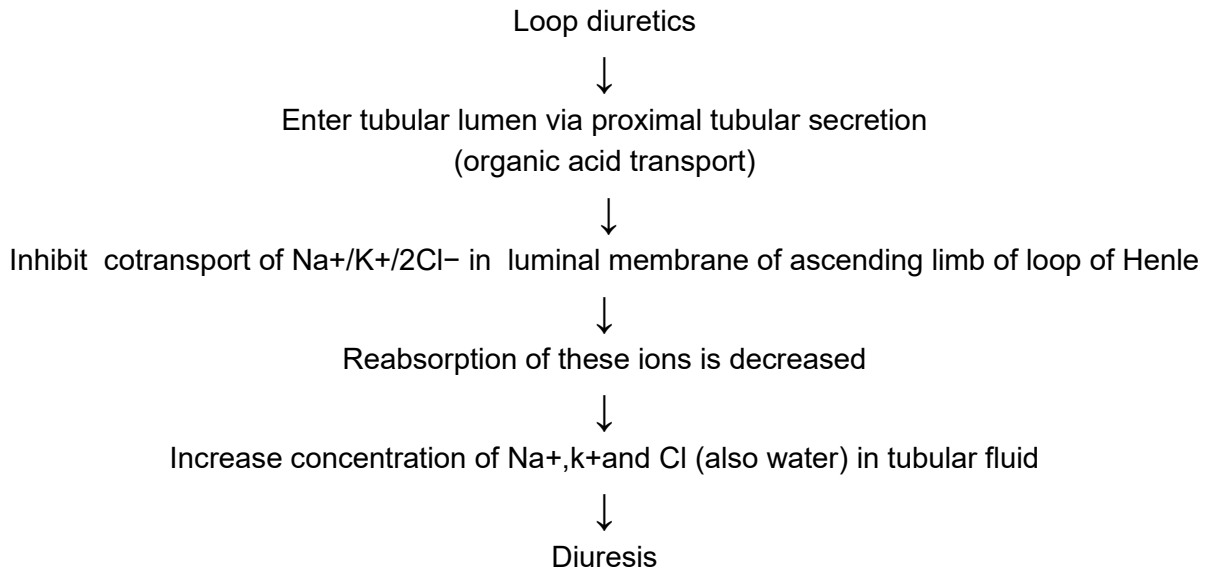
- Ethacrynic acid → most ototoxic loop diuretic
- Organomercurials (mersalyl)

## Site of Action

- Acts on → ascending limb of loop of Henle



## MOA



## Pharmacokinetics

- **Furosamide** →
  - Bioavailability 65%
  - $t_{1/2}$  30–60 min.
  - After oral administration effect is achieved in 20–30 min and lasts 4–6 h.
  - After i.v. administration effect begins in 3–5 min and lasts 2 h.

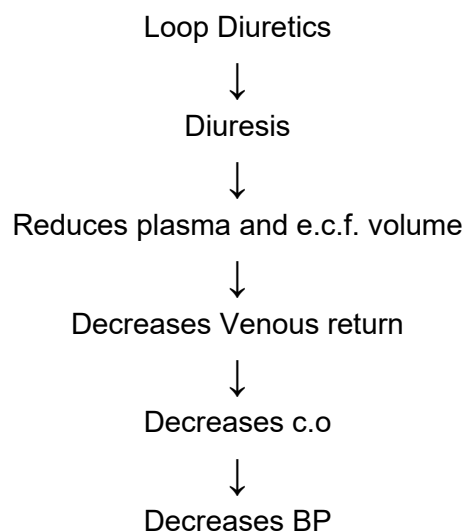
## Uses

### Mnemonic → HEAMTT

1. **H**ypertension
2. **E**dema
3. **CHF** → decreases preload as well as afterload
4. Hypercalcaemia of **M**alignancy
5. Chemical in **T**oxication (to increase urine flow)
6. Blood **T**ransfusion

## 1. Hypertension

- Indication →
  - Only in presence of renal insufficiency
  - In resistant cases
  - Hypertensive emergencies
- Otherwise thiazides are preferred



### Remember

- Here fall in BP is entirely dependent on reduction in plasma volume and c.o.
- Vasodilatation does not occur in High ceiling diuretics because of their brief duration of action.

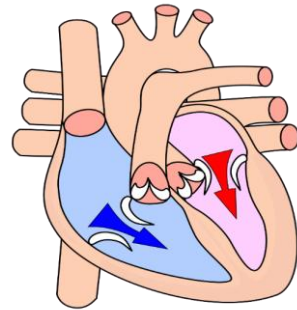
## 2. Edema

- Irrespective of etiology of edema → cardiac, hepatic or renal, Acute pulmonary edema
- Cerebral edema → Though osmotic diuretics are primarily used, furosemide may be combined to improve efficacy.

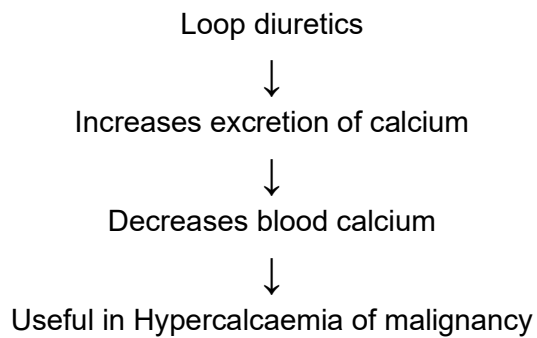


### 3. CHF

- Decreases preload as well as afterload



### 4. Hypercalcaemia of malignancy



### 5. Chemical intoxication

- To increase urine flow



### 6. Blood Transfusion

- In severe anaemia → to prevent vascular overload.



## Adverse Effects

### Mnemonic → Hypo PMNHC

1. Hypokalemia → Because they increase  $\text{Na}^+$  in filtrate arriving at DCT → more  $\text{K}^+$  is exchanged for  $\text{Na}^+$  → continual loss of  $\text{K}^+$  → hypokalemia.
2. Hypomagnesemia
3. Dilutional hyponatremia
4. Dehydration
5. Hypocalcemia

### Mnemonic → Hyper GLU

6. Hyperglycemia → causes hypokalemia which results in decreased insulin release.



7. Hyperlipidemia



8. Hyperuricemia (Gout) → uric acid excretion decreased bcoz it competes with uric acid in proximal tubular secretion.



9. Not safe in pregnancy (all diuretics)



10. Sulphonamide hypersensitivity



11. Ototoxicity- hearing loss



## Summary → Adverse effects

### Hypo PMNHC

1. Potassium
2. Mg
3. Na
4. H<sub>2</sub>O
5. Calcium

### Hyper GLU

6. Glycemia
7. Lipidemia
8. Uricemia (Gout)
9. Not safe in pregnancy (all diuretics)
10. Sulphonamide hypersensitivity
11. Ototoxicity- hearing loss

### Bumetanide

- Similar to furosemide in all respects, but is 40 times more potent.
- Induces very rapid diuresis

- Highly effective in pulmonary edema
- Bumetanide may act in some cases not responding to furosemide, and may be tolerated by patients allergic to furosemide.
- Hyperuricaemia, K<sup>+</sup> loss, glucose intolerance and ototoxicity are less marked, but it may rarely cause myopathy.



### Torasemide (Torsemide)

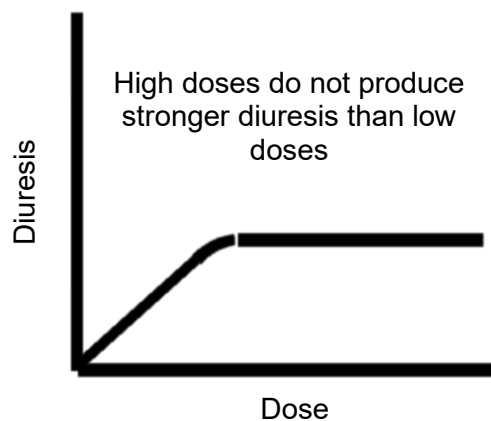
- Properties similar to furosemide, but 3 times more potent
- Longest acting.
- Elimination  $t_{1/2}$  (3.5 hours) and duration of action (4–8 hours) are longer.
- Torasemide has been used in edema and in hypertension

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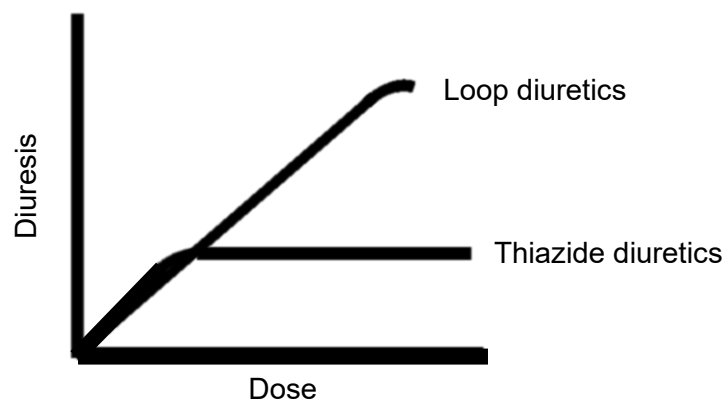
## MEDIUM EFFICACY DIURETICS / THIAZIDES DIURETICS

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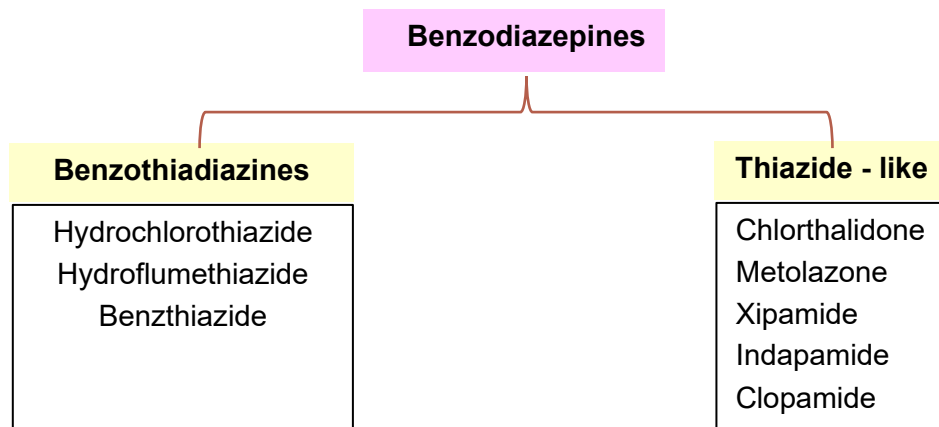
### Introduction



### Comparison of loop and thiazide diuretics

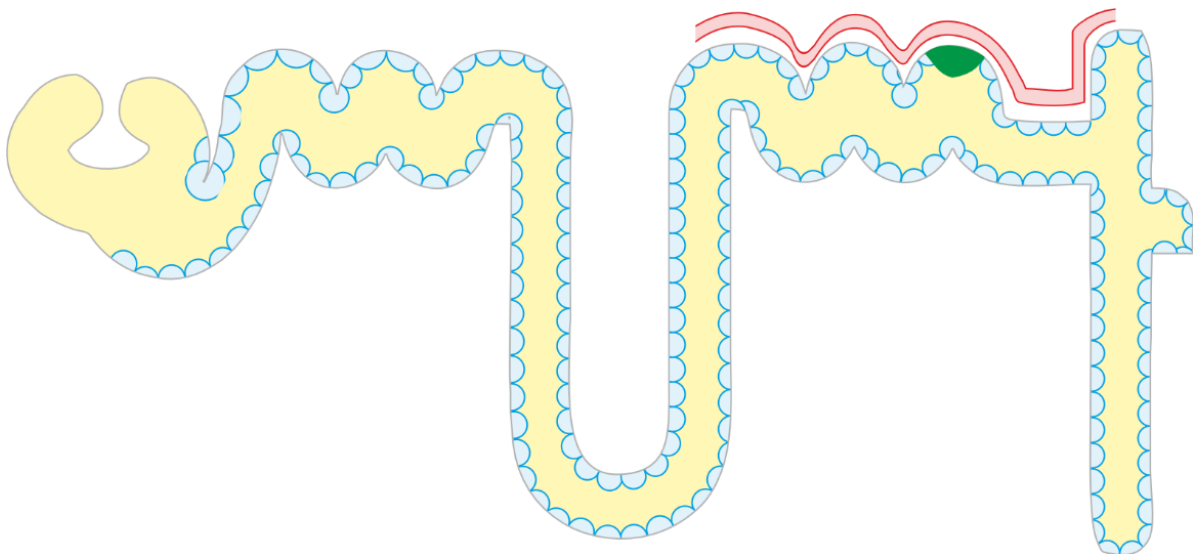


## Drugs

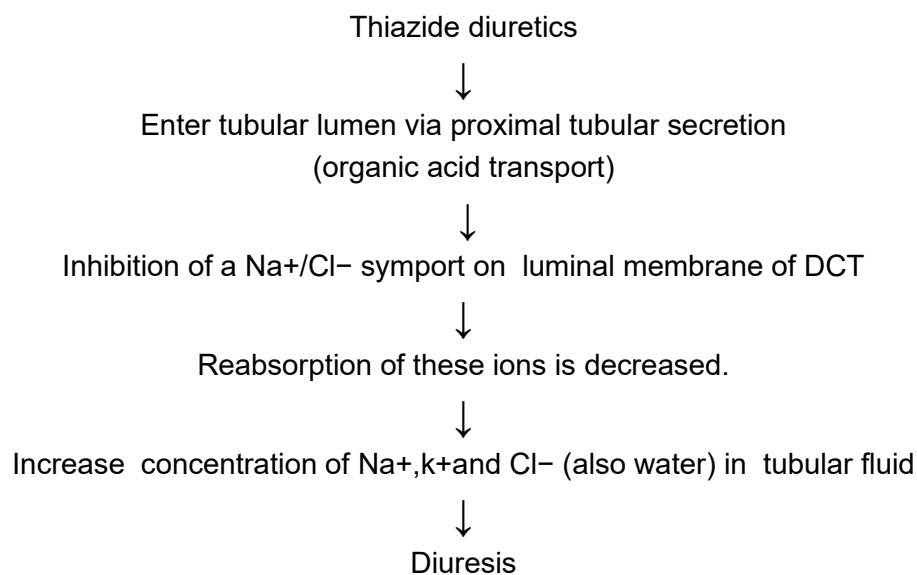


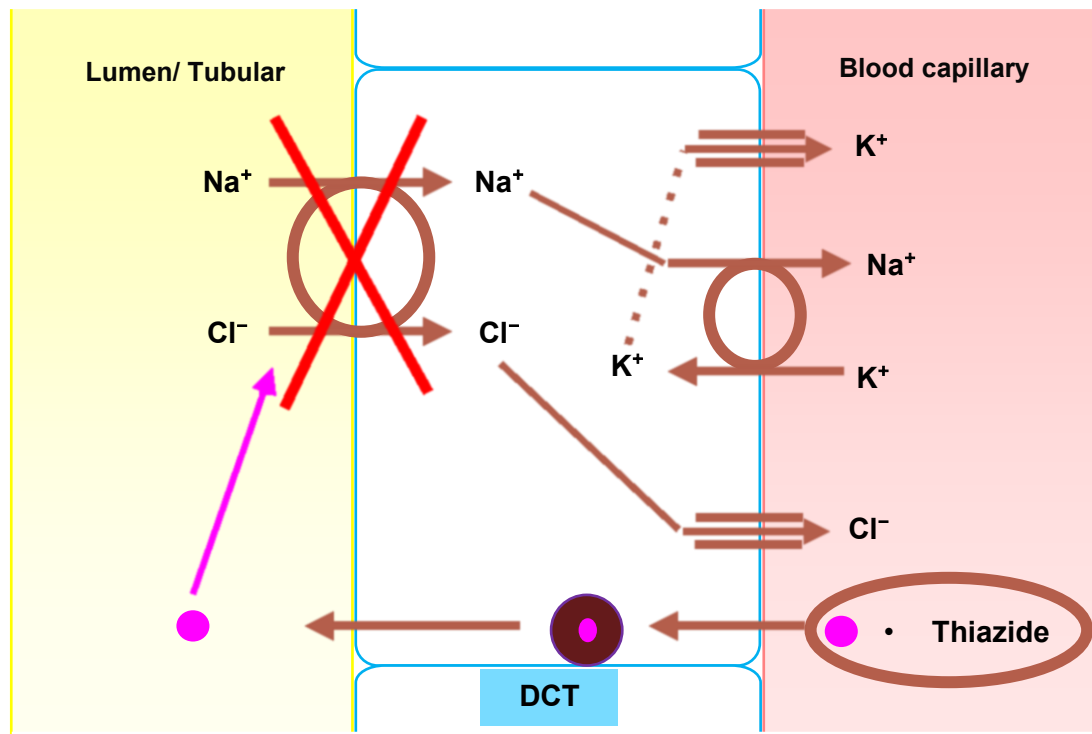
## Site of Action

- Acts on → Distal convoluted tubule (DCT)



## MOA





## Pharmacokinetics

### Hydrochlorothiazide →

- Orally administered
- Poor absorption
- Onset of action in ~ 1 hour
- Wide range of T<sub>1/2</sub> amongst different thiazides, longer than loop diuretics

## Uses

### Mnemonic → HEARD

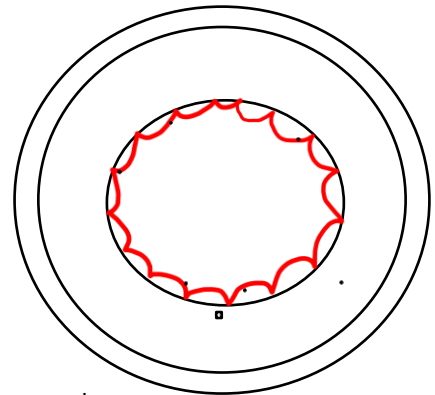
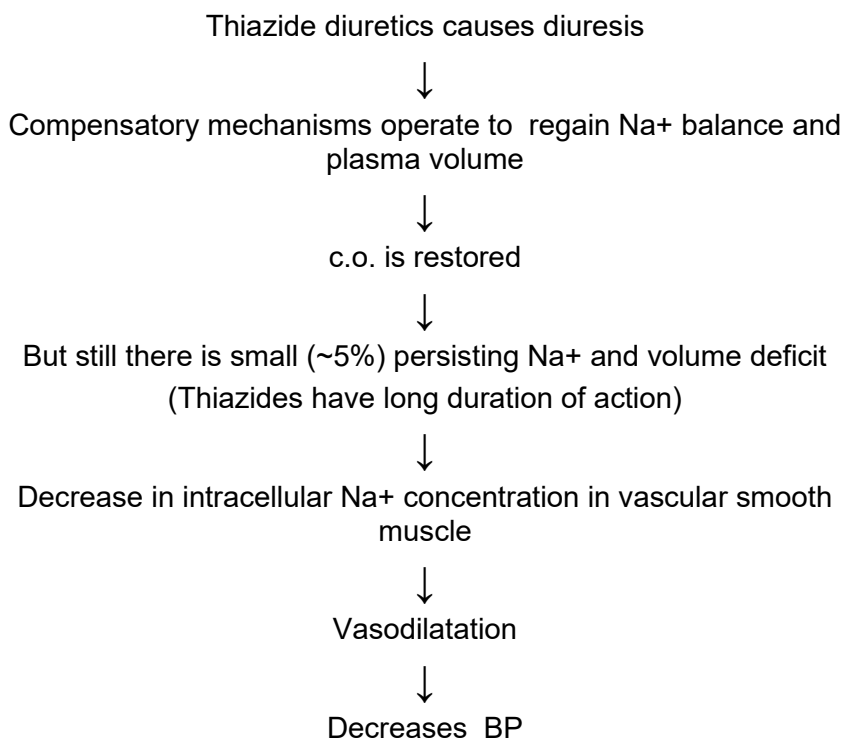
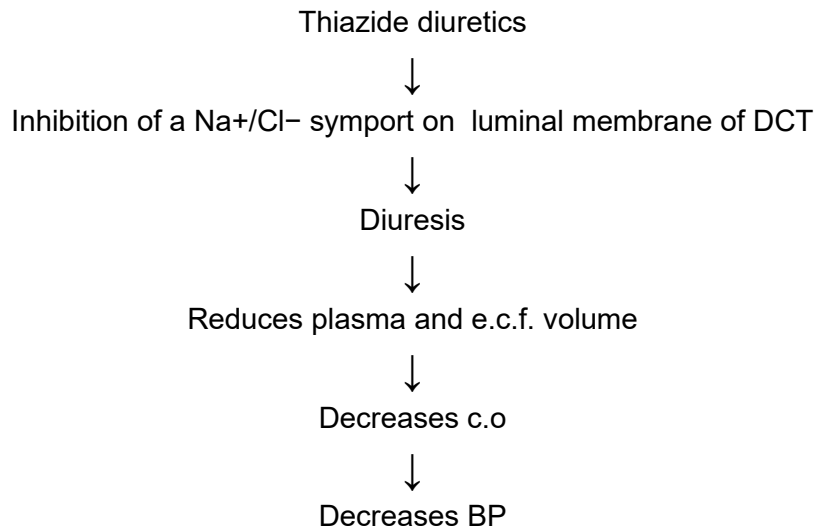
1. **H**ypertension
2. **E**dema
3. **CHF** → decreases preload as well as afterload
4. Hypercalciuria with **R**enal calcium stones
5. **D**iabetes insipidus

### 1. Hypertension

- Thiazides are one of the first line drugs
- Causes fall in BP by 2 MOA →
  - (a) Reduces plasma and Decreases CO
  - (b) Vasodilatation







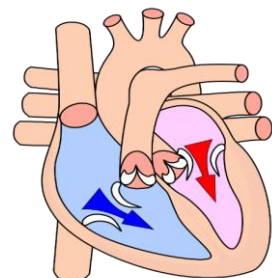
## 2. Edema

- For mobilization of edema fluid high ceiling diuretics are preferred, but thiazides may be considered for maintenance.
- Act best in cardiac edema
- Less effective in hepatic or renal edema.

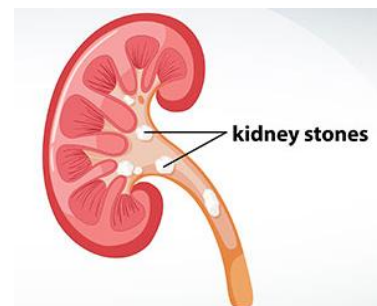
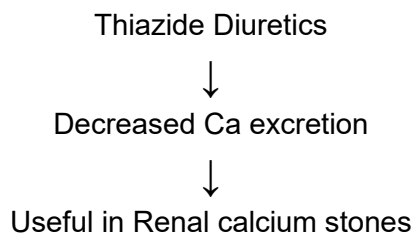


## 3. CHF

- Decreases preload as well as afterload



#### 4. Hypercalciuria with Renal calcium stones



#### 5. Diabetes insipidus

- They reduce urine volume in Chronic renal failure



#### Remember

- Thiazides are less efficacious diuretics than loop diuretics, but have more effective antihypertensive action than loop diuretics.
- Thiazides with added K<sup>+</sup> sparing diuretic is the first choice treatment for essential hypertension.
- Furosemide (loop diuretic) is preferred over thiazide only when hypertension is complicated by CRF or CHF.

#### Adverse Effects

##### Mnemonic → Hypo PMNH

1. Hypokalemia → Because they increase Na<sup>+</sup> in filtrate arriving at DCT → more K<sup>+</sup> is exchanged for Na<sup>+</sup> → continual loss of K<sup>+</sup> → hypokalemia.
2. Hypomagnesemia
3. Dilutional hyponatremia
4. Dehydration → acute saline depletion Hyperuricemia

##### Mnemonic → Hyper GLUC

5. Hyperglycemia
6. Hyperlipidemia
7. Hyperuricemia (Gout)



8. Hypercalcaemia → Thiazide increases parathormone regulated reabsorption of  $\text{Ca}^{2+}$  in DCT Not safe in pregnancy (all diuretics)



9. Not safe in pregnancy (all diuretics)



10. Sulphonamide hypersensitivity



11. Renal insufficiency



## Summary → Adverse effects

### Hypo PMNH

1. Potassium
2. Mg
3. Na
4.  $\text{H}_2\text{O}$

### Hyper GLUC

5. Glycemia
6. Lipidemia
7. Uricemia (Gout)
8. Calcium

9. Not safe in pregnancy (all diuretics)
10. Sulphonamide hypersensitivity
11. Renal insufficiency

## Compare → Adverse effects

| Loop diuretics                                                                                                                                                  | Thiazides                                                                                                                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Hypo PMNHC</b> <ul style="list-style-type: none"> <li>Potassium</li> <li>Mg</li> <li>Na</li> <li><math>\text{H}_2\text{O}</math></li> <li>Calcium</li> </ul> | <b>Hypo PMNH</b> <ul style="list-style-type: none"> <li>Potassium</li> <li>Mg</li> <li>Na</li> <li><math>\text{H}_2\text{O}</math></li> </ul> |

|                                                                                                                               |                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Hyper GLU</b> <ul style="list-style-type: none"> <li>• Glycemia</li> <li>• Lipidemia</li> <li>• Uricemia (Gout)</li> </ul> | <b>Hyper GLUC</b> <ul style="list-style-type: none"> <li>• Glycemia</li> <li>• Lipidemia</li> <li>• Uricemia (gout)</li> <li>• Calcium</li> </ul> |
|-------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|

## Remember

- Longest acting thiazide → **Chlorthalidone**
- Most potent thiazides → **Trichlormethiazide**
- Least potent thiazide → **Chlorthalidone**
- Only thiazide which is effective in severe renal failure → **Metolazone**
- 100% bioavailability → **Bendroflumethiazide**

## WEAK EFFICACY DIURETICS

### Types

3 Types →

1. Carbonic Anhydrase Inhibitors
2. Potassium Sparing Diuretics
3. Osmotic Diuretics

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## CARBONIC ANHYDRASE INHIBITORS

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### Introduction

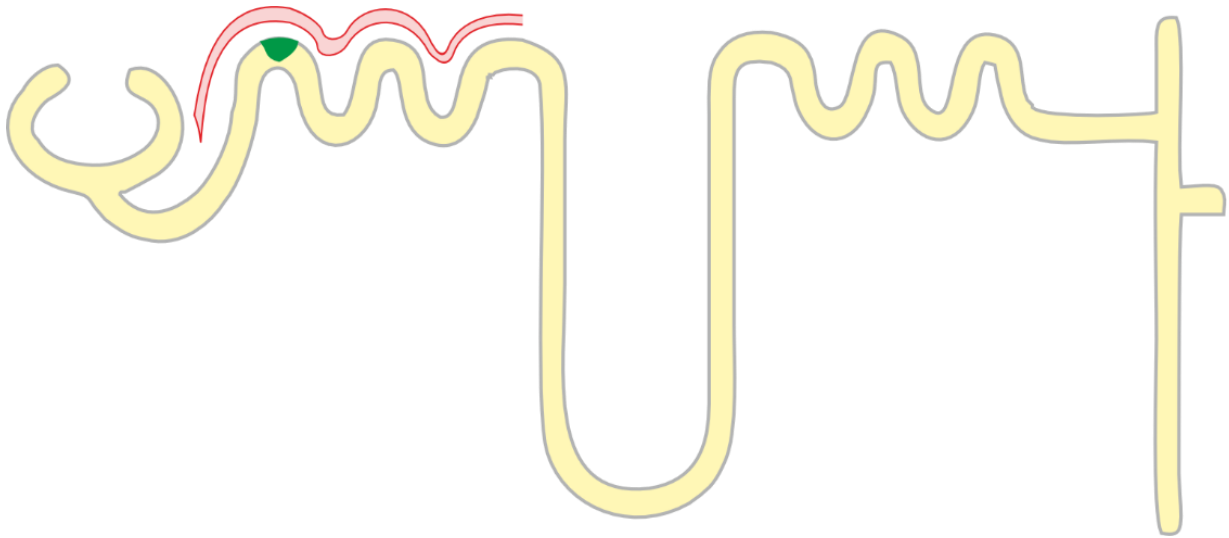
- Carbonic Anhydrase Inhibitors are Weak Efficacy Diuretics

### Drugs

- Acetazolamide
- Dichlorphenamide
- Methazolamide
- Brinzolamide
- Dorzolamide

### Site of Action

- Acts on → PCT

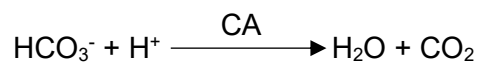


## MOA

- Carbonic anhydrase enzyme is present in brush border as well as PCT cell
- Carbonic Anhydrase Inhibitors → Noncompetitively but reversibly inhibits Carbonic anhydrase enzyme

## Normally

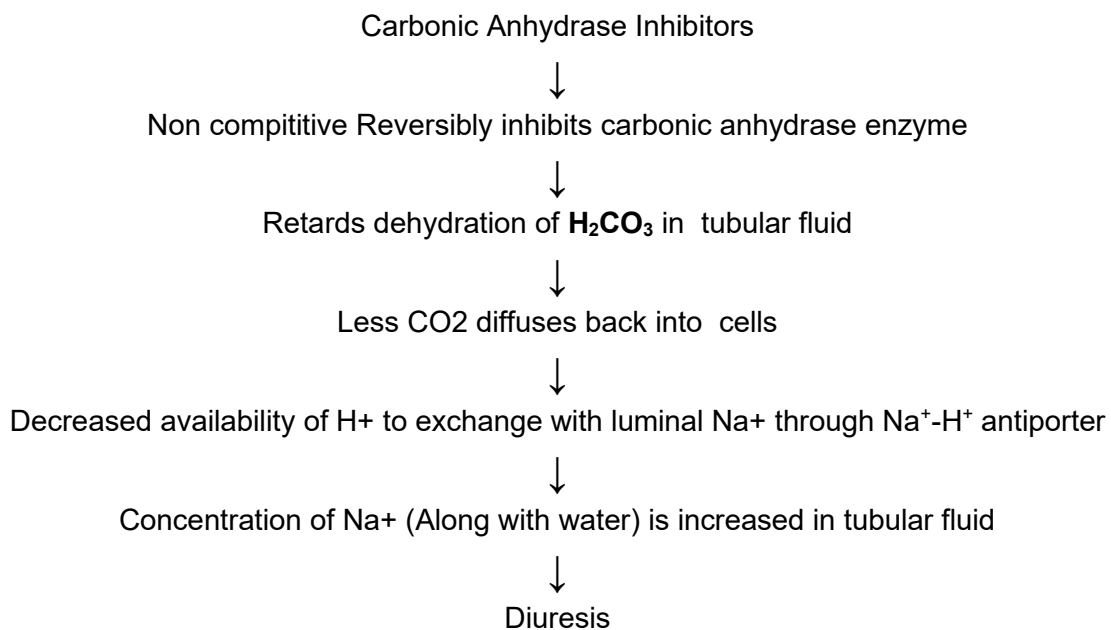
- In tubular lumen →

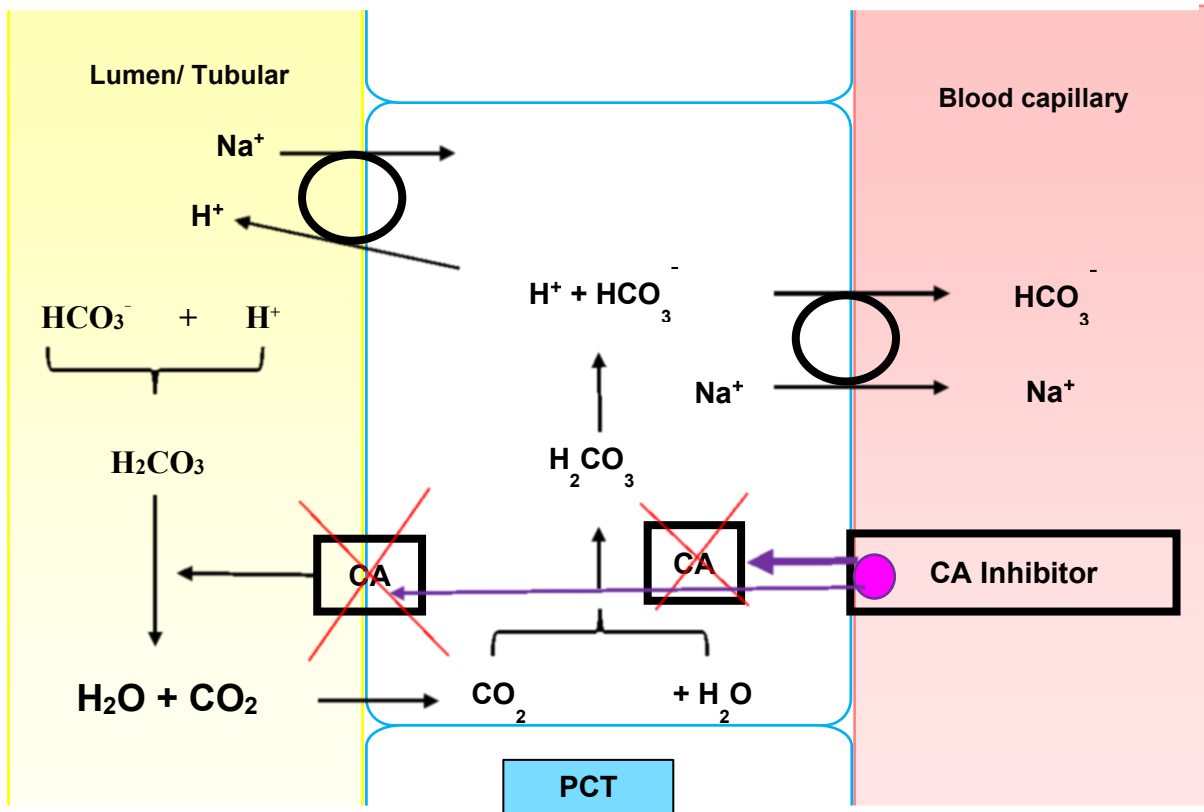


- CO<sub>2</sub> diffuses into cell



- H<sup>+</sup> now available again for countertransport with Na<sup>+</sup> through the Na<sup>+</sup>-H<sup>+</sup> antiporter.
- Na<sup>+</sup> and HCO<sub>3</sub><sup>-</sup> now transported into peritubular capillary





## Remember

Carbonic Anhydrase Inhibitors causes→

- **Urine** → alkaline and rich in  $\text{HCO}_3^-$
- **Blood** → Acidosis

Continued action of acetazolamide

↓  
Depletes body  $\text{HCO}_3^-$

↓  
Causes acidosis

↓  
Less  $\text{HCO}_3^-$  is filtered at glomerulus

↓  
Self-limiting diuretic action

## Other Actions

1. **Eye** → Lowering of intraocular tension due to decreased formation of aqueous humour
2. **Stomach** → Decreased gastric  $\text{HCl}$  and pancreatic  $\text{NaHCO}_3$  secretion
3. **Brain** → Raised level of  $\text{CO}_2$  in brain and lowering of pH → sedation and elevation of seizure threshold.

## Pharmacokinetics

- **Acetazolamide** →
  - Well absorbed orally
  - Excreted unchanged in urine.
  - Action of a single dose lasts 8-12 hours.

## Uses

**Mnemonic** → **GAMAPE**

1. **G**laucoma
2. To **A**lkalise urine → for urinary tract infection
3. Acute **M**ountain sickness → due lowering of brain pH.
4. Metabolic **A**lkalosis
5. **P**eriodic paralysis
6. **E**pilepsy → as adjuvant in absence seizures when primary drugs are not fully effective



glaucoma



UTI



Acute Mountain sickness



Metabolic Alkalosis



Periodic paralysis



Epilepsy

## Remember

- Because of self-limiting action, production of acidosis and hypokalaemia, acetazolamide is not used as diuretic.

## Adverse effects

1. Hypokalaemia
2. Acidosis
3. Drowsiness, paresthesias, fatigue
4. Abdominal discomfort.
5. Hypersensitivity reactions → fever, rashes.
6. Contraindicated in liver disease: may precipitate hepatic coma by interfering with urinary elimination of NH<sub>3</sub> (due to alkaline urine).

### Remember

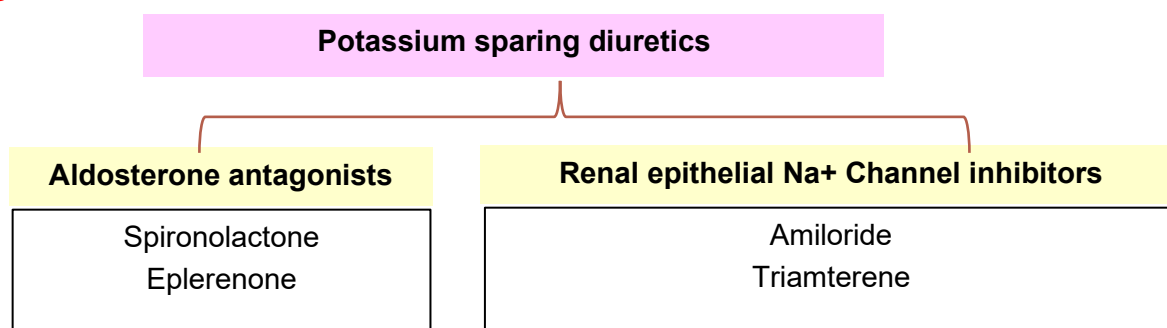
- Hypokalaemia → For same degree of natriuresis CA inhibitors cause the most marked kaliuresis
- Potency of producing hypokalaemia →  
CAI > Thiazides > Loop

## POTASSIUM SPARING DIURETICS

### Introduction

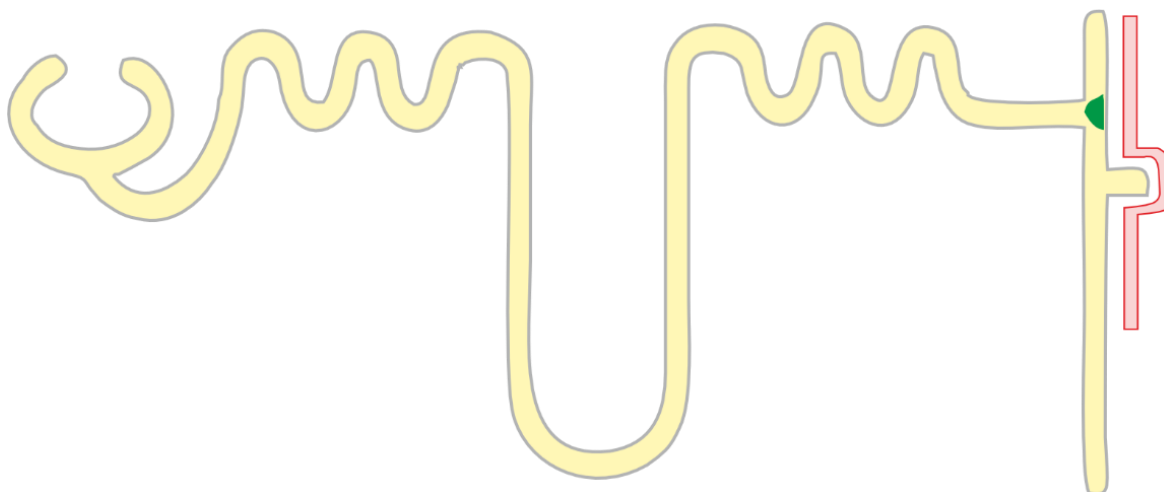
- They conserve K<sup>+</sup> while inducing mild natriuresis and diuresis so called 'potassium sparing diuretics'

### Drugs



### Site of Action

Acts on → CD



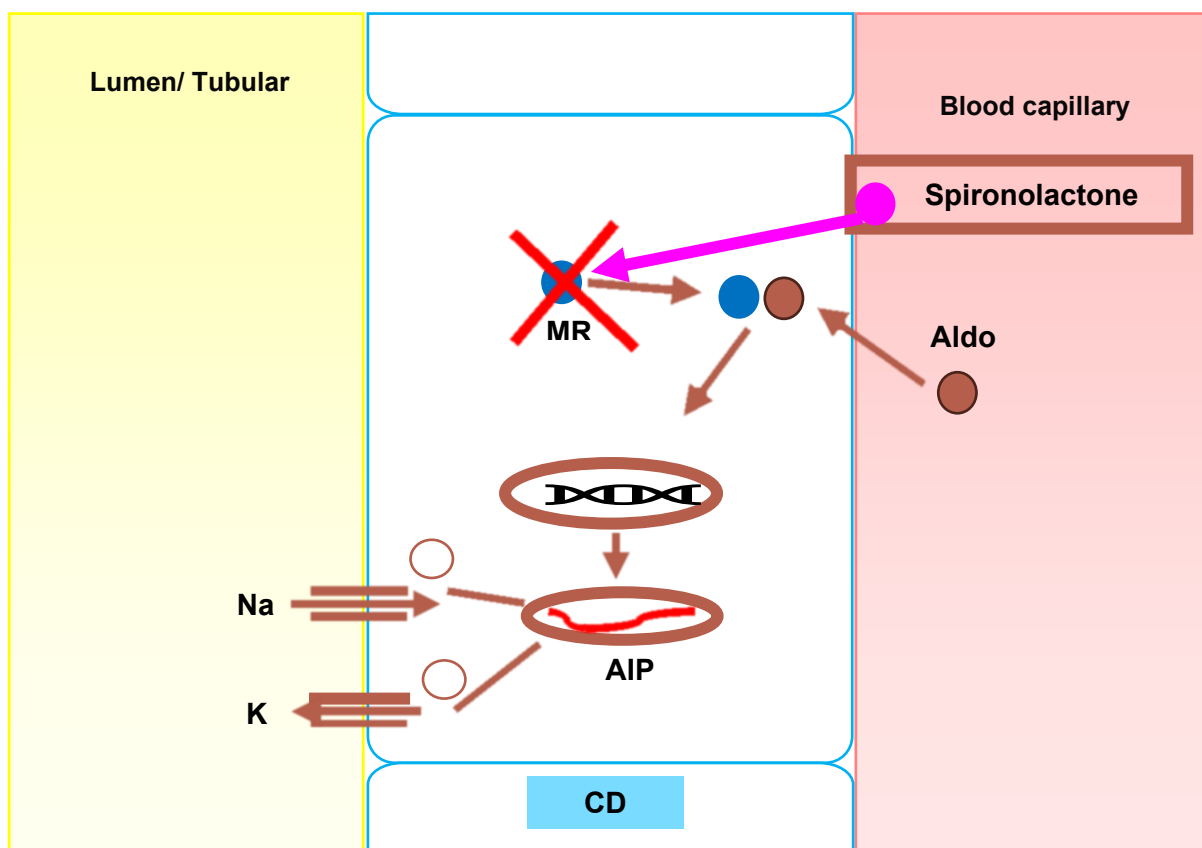
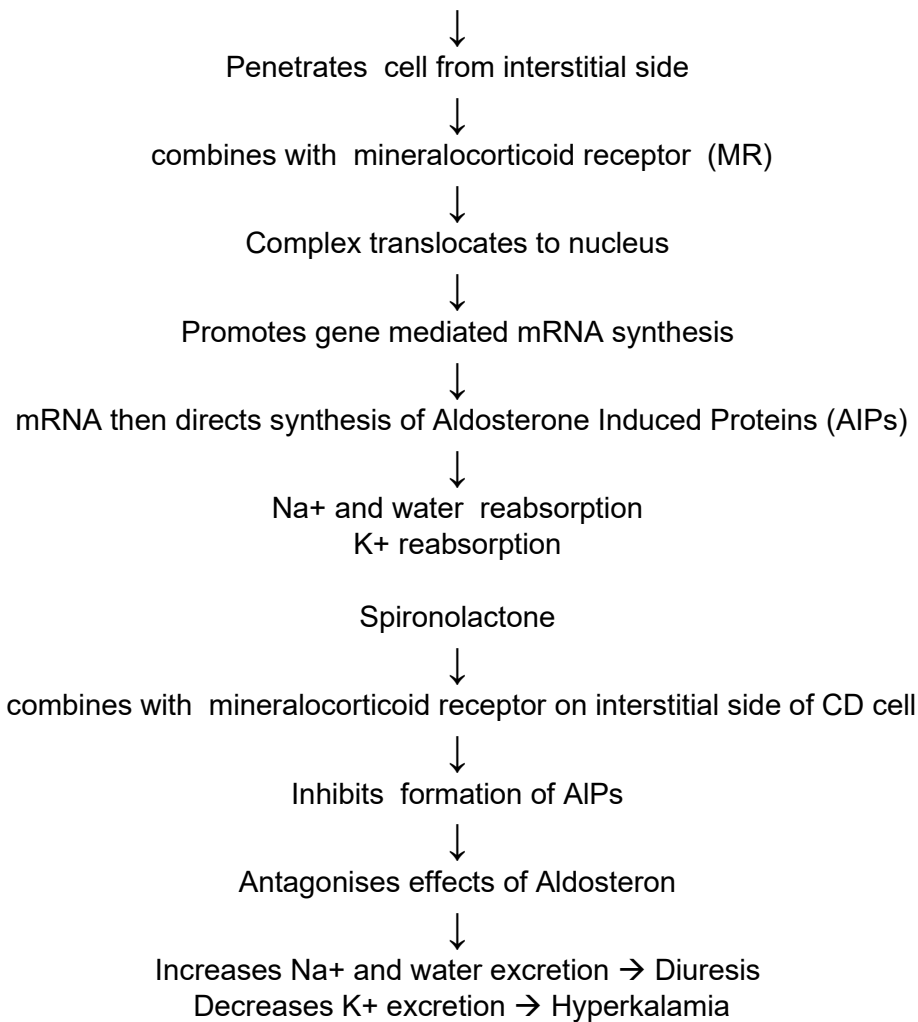
### MOA

- Aldosterone antagonist (Spironolactone)
- Renal epithelial Na<sup>+</sup> channel blockers (Amiloride)

#### A) MOA of Aldosterone antagonist (Spironolactone)

Normally  
↓  
Aldosterone acts on late CD cells

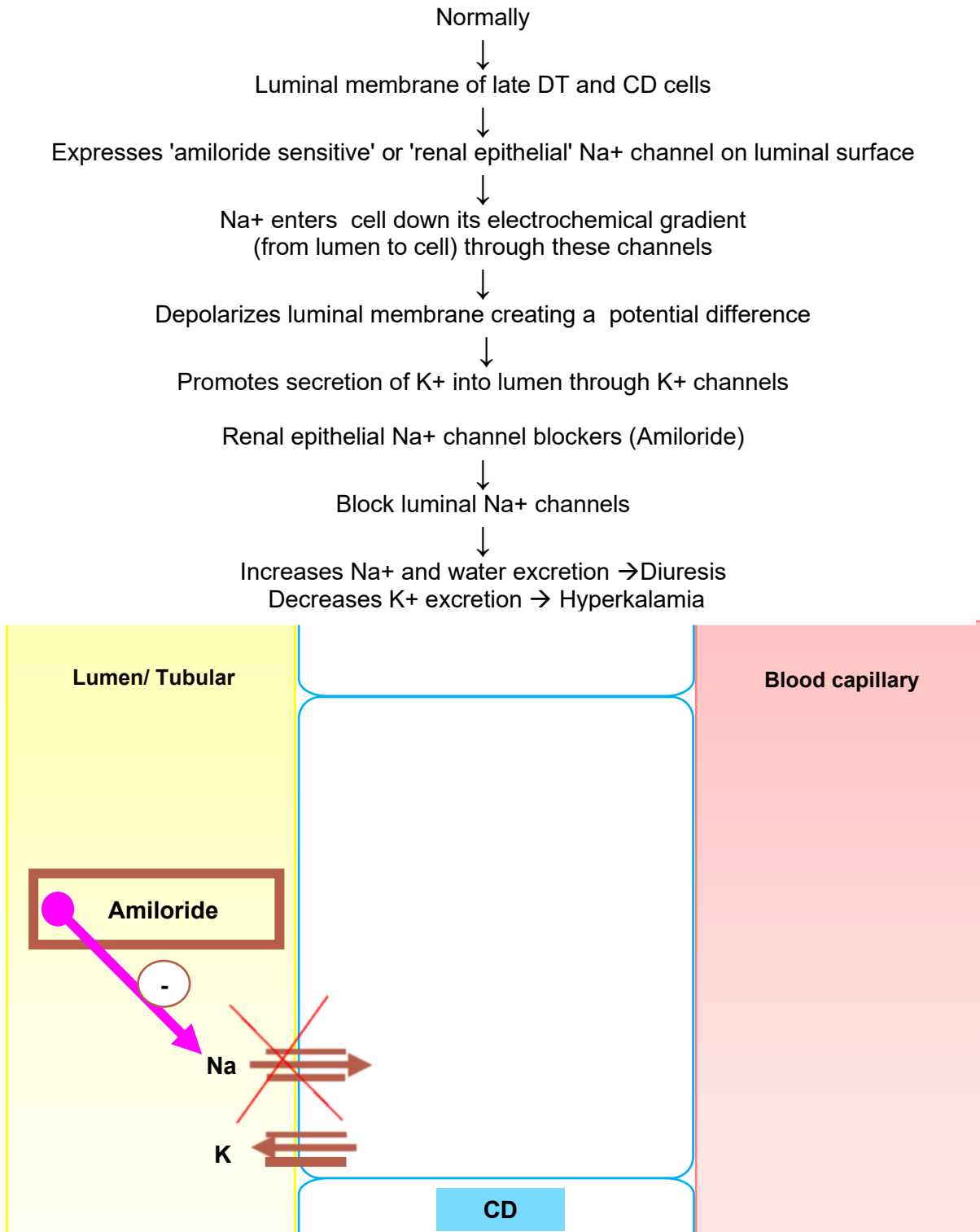




## Remember

- All diuretics act from luminal (tubular) surface of tubular cells, except for aldosterone antagonists which act on interstitial surface.
- Therefore, aldosterone antagonists do not require access to tubular lumen while other diuretics need access to tubular lumen.
- It has no effect on  $\text{Na}^+$  and  $\text{K}^+$  transport in the absence of aldosterone

## B) MOA of Renal epithelial $\text{Na}^+$ channel blockers (Amiloride)



## Pharmacokinetics

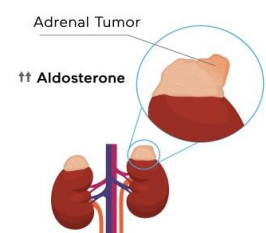
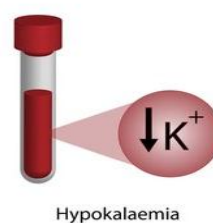
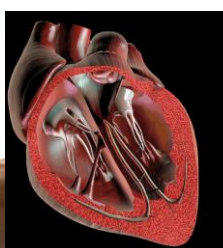
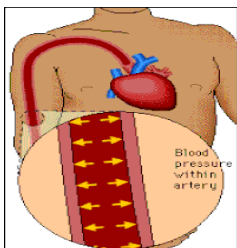
- **Spironolactone**
  - Given orally microfine powder tab.
  - Bioavailability 75%
  - Converted to active metabolite canrenone
  - Onset of action is very slow (steroid receptors)
- **Triamterene**
  - Absorbed orally
  - $t_{1/2}$  is 4 hours
  - Effect of a single dose lasts 6-8 hours
- **Amiloride**
  - 10 times more potent than triamterene.
  - $T_{1/2}$  (10-20 hours) and duration of action are longer than triamterene.

## Uses

Mnemonic → **HEAPC**

1. **H**ypertension
  - Used only in conjunction with a thiazide diuretic to prevent  $K^+$  loss
2. **E**dema → more useful in cirrhotic and nephrotic syndrome
  - Spironolactone → DOC for initial management of edema of liver cirrhosis
  - Breaks resistance to thiazides or frusemide in refractory edema
3. **C**HF
4. Hypokalaemia (**P**otassium) → To counteract  $K$  loss due to thiazides, frusemide
5. Primary Hyperaldosteronism (**C**onn's syndrome)

Mnemonic → Potassium sparing Diuretic  Uses  **HEAPC**



## Adverse Effects

### 1. Hyperkalemia risk

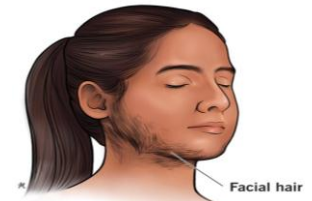
- In CRF patients
- Patients taking ACEI (Enalapril) or ARB (Losartan)
- KCl supplement

### 2. Antiandrogen

- Gynaecomastia, Impotence in males
- Hirsutism, menstrual irregularities in female



Hirsutism



Facial hair

---

## OSMOTIC DIURETICS

---

### Introduction

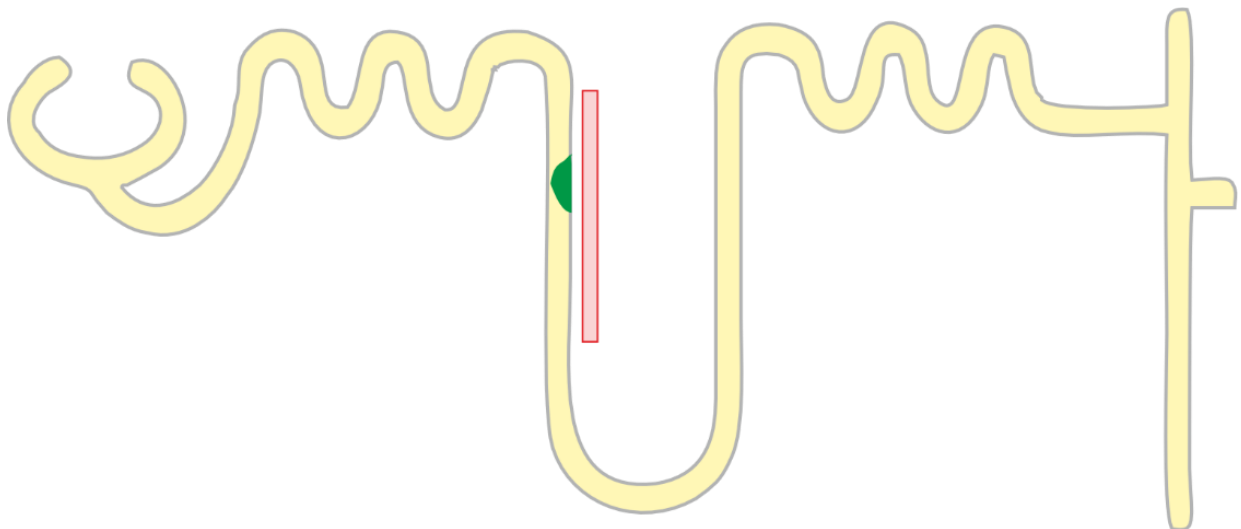
- Do not interact with receptors or directly block renal transport
- Activity dependent on development of Osmotic pressure

### Drugs

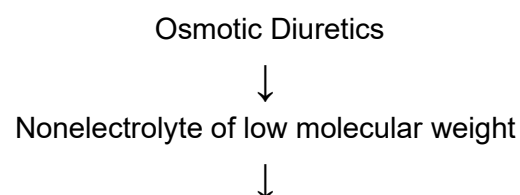
- Mannitol
- Isosorbide
- Glycerol

### Site of action

- Acts on → loop of Henley

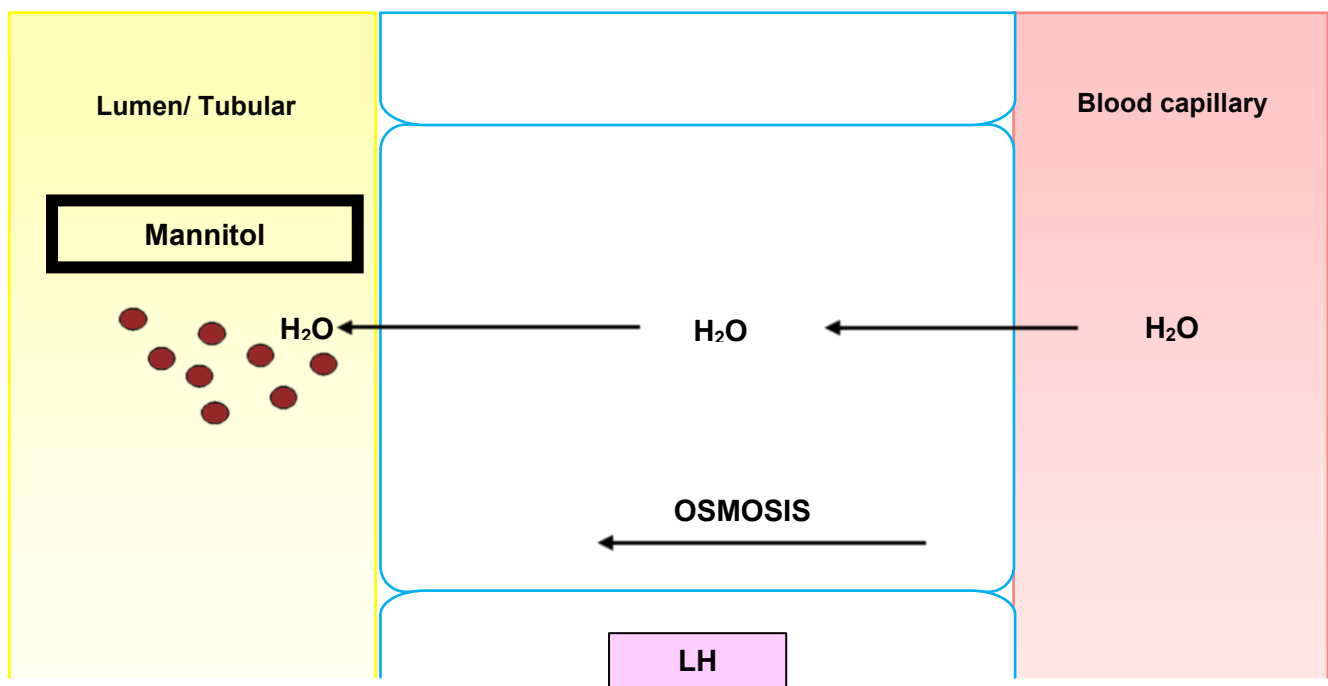


### MOA



Pharmacologically inert  
 Not metabolized in body  
 Freely filtered at glomerulus  
 Not reabsorbed  
 Raise osmolarity of tubular fluid

↓  
 Prevents passive reabsorption of H<sub>2</sub>O  
 ↓  
 Diuresis



## Uses

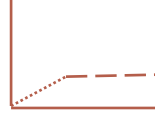
Mnemonic → **BEK DD**

1. **B**rain → To lower intracranial tension → Before brain surgery and Cerebral edema
2. **E**ye → To lower intraocular tension → Acute glaucoma and Before intraocular surgeries
3. **K**idney → ARF → Treatment & prevention, To maintain GFR during major surgeries, trauma
4. To counteract low plasma osmolality after **D**ialysis
5. **D**rug poisoning → forced diuresis (barbiturate poisoning)

## Adverse Effects

1. Acute Intravascular volume expansion
  - Before diuresis starts it exerts osmotic effect in the blood
  - Contraindicated in → pulmonary edema, Cardiac edema (CHF) and intracranial hemorrhage
2. Results in large water loss, smaller electrolyte loss → can result in hypernatremia ☐ Headache , Nausea

## MASTERCHART

|                | LOOP DIURETICS                                                                    | THIAZIDES                                                                         | CARBONIC ANHYDRASE INHIBITOR                                                      | POTASSIUM SPARING DIURETICS                                                         | OSMOTIC DIURETICS |
|----------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|
| Drugs          | Furosamide                                                                        | Hydrochlor thiazide                                                               | Acetazolamide                                                                     | Spironolactone<br>-Amiloride                                                        | Mannitol          |
| Introduction   |  |  |  |  |                   |
| Site of Action | LH (asc. Limb)                                                                    | DCT                                                                               | PCT                                                                               | • CD                                                                                | • LH              |
| MOA            | ⊖ Na – K – 2 Cl                                                                   | ⊖ Na – Cl                                                                         | ⊖ CA enzyme                                                                       | • ⊖ MR rec<br>• ⊖ Renal epi. NA channel                                             | • Osmosis         |
| Uses           | HEAMTT                                                                            | HEARD                                                                             | GAMAPE                                                                            | HEAPC                                                                               | BEKDD             |
| Adverse effect | H↓ PMNHC<br>H↑ GLU                                                                | H↓ PMNH<br>H↑ GLUC                                                                | • H↓K<br>• Hepatic loma<br>• Acidosis<br>• Alkalosis                              | • H↑K<br>• Antiandrogen                                                             | Vol. ↑<br>Na ↑    |

## ANTIDIURETICS

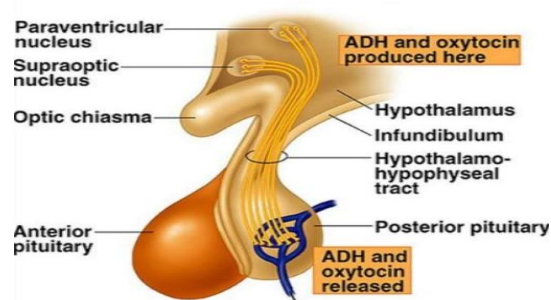
### Introduction

- These are drugs that reduce urine volume
- Also called 'Anti-aquaretics' because they inhibit water excretion without affecting salt excretion
- Primary indication is diabetes insipidus (DI)



### Antidiuretic Hormone - ADH (Arginine Vasopressin-AVP)

- **Synthesized** → in hypothalamic nerve cell bodies along with its binding protein neurophysin
- **Transported** → down the axons to nerve endings in posterior Pituitary
- **Secreted** → by posterior pituitary along with oxytocin
  - 8-arginine-vasopressin (Vasopressin) → human ADH



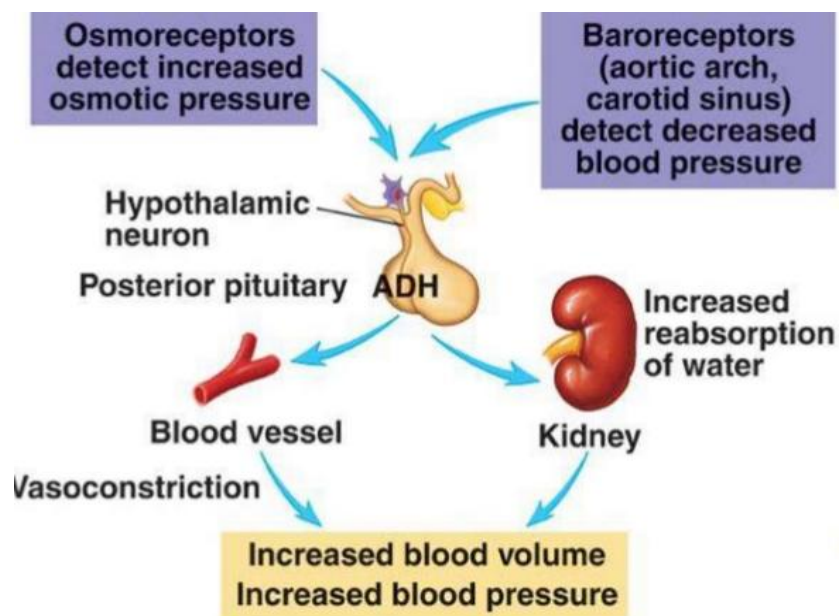
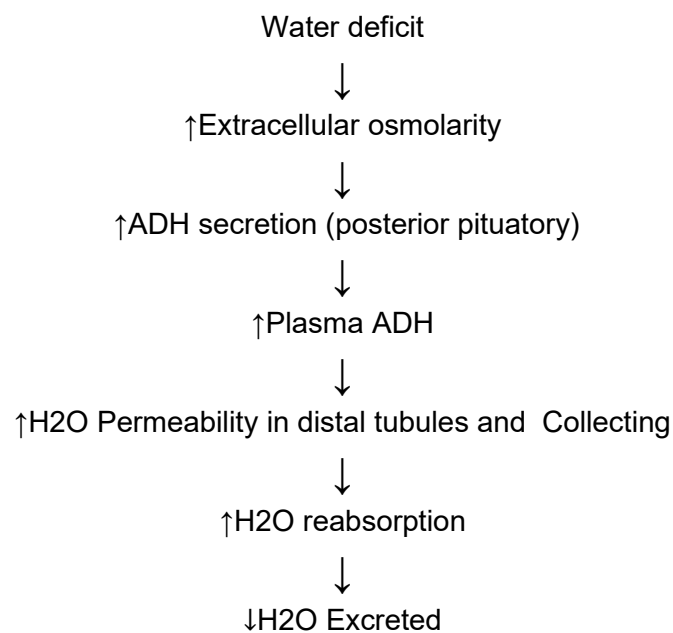
- 8-lysine-vasopressin (lypressin) → found in swine and has been synthetically prepared

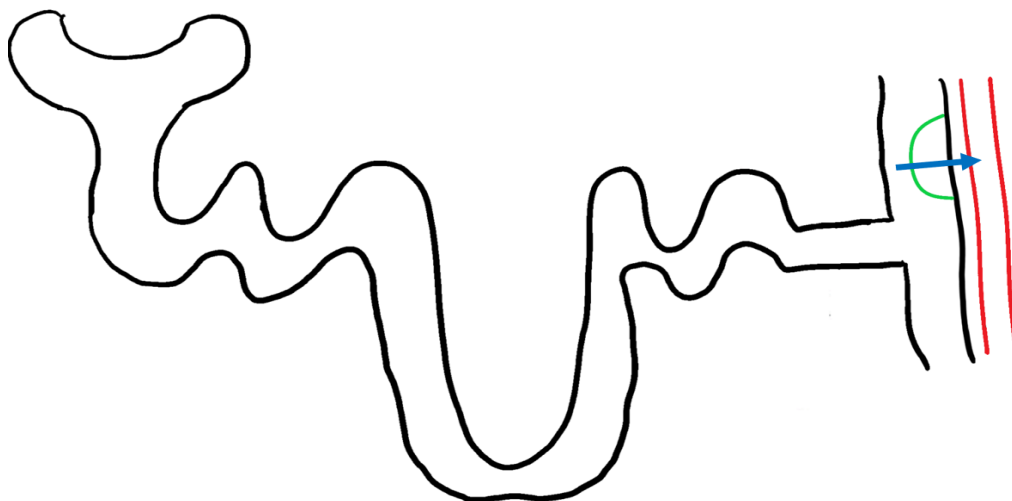
## Regulation of ADH secretion

- ADH secretion depends upon volume of body fluid and osmolarity of body fluid

## Potent stimulants for ADH secretion

- 2 main physiological stimuli for ADH release →
  - Rise in plasma osmolarity
  - Contraction of ECF volume



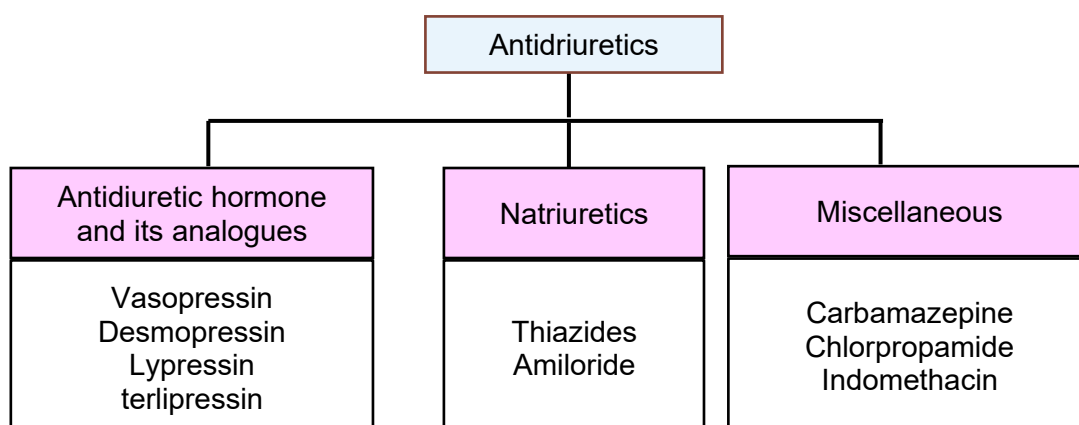


## ADH (Vasopressin) receptors

- G protein coupled cell membrane receptors;
  1. V1a
  2. V1b (V3 ) subtypes
  3. V2

| V1a                                                                                                                                           | V2                                                                                                              | V1b / V3                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Blood vessels (VC)</li> <li>• GIT</li> <li>• Uterus</li> <li>• Liver</li> <li>• Platelets</li> </ul> | <ul style="list-style-type: none"> <li>• Kidney</li> <li>• Blood vessels (VD)</li> <li>• Endothelium</li> </ul> | <ul style="list-style-type: none"> <li>• Anterior pituitary</li> </ul> |

## Classification





|                          | ADH And Its Analogues | Natriuretics |
|--------------------------|-----------------------|--------------|
| <b>Drugs</b>             |                       |              |
| <b>MOA</b>               |                       |              |
| <b>Pharmacokinetics</b>  |                       |              |
| <b>Uses</b>              |                       |              |
| <b>Adverse effect</b>    |                       |              |
| <b>Contraindications</b> |                       |              |

## ADH AND ITS ANALOGUES

### Drugs

Antidiuretic hormone and its analogues

Vasopressin  
Desmopressin  
Lypressin  
Terlipressin

### MOA

- A) MOA (V2)
- B) MOA (V1)

### A) MOA (V2)

1. Kidney (V2)
2. Blood Vessels (V2)
3. Vascular endothelium (V2)

### 1. Kidney

#### Rapid actions

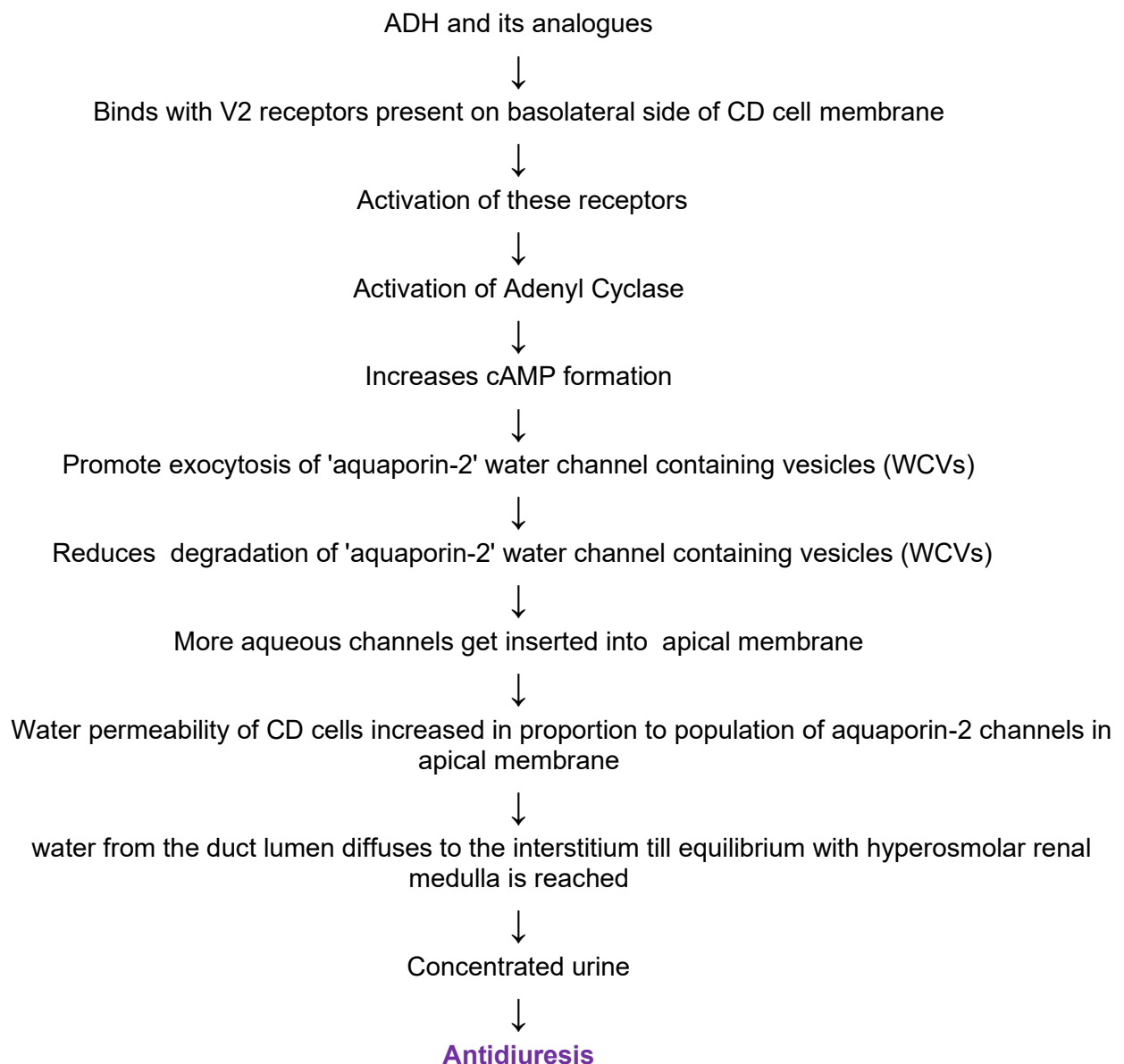
1. Translocation of water channel containing vesicles (WCVs) and exocytotic insertion into the apical membrane and Inhibition of endocytotic removal of aquaporin 2 channels from the apical membrane of principal cells of collecting ducts → the primary action responsible for antidiuresis
2. Activation of vasopressin regulated urea transporter (VRUT) at apical membrane of collecting ducts in the inner medulla.

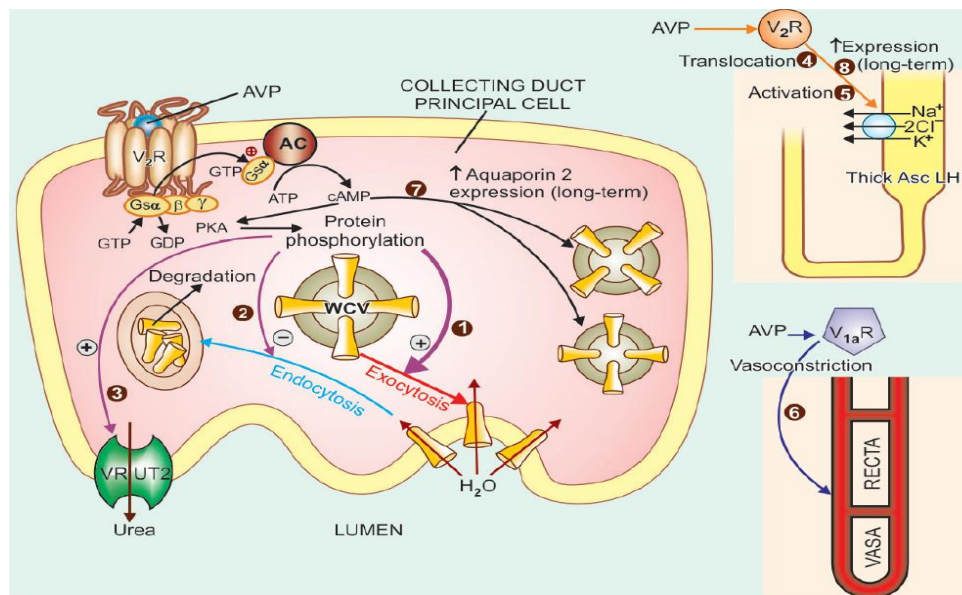
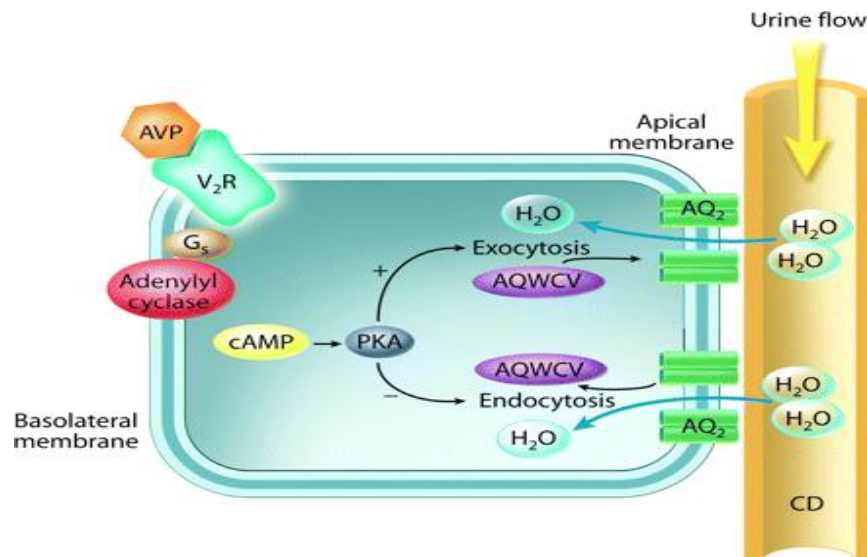
3. Translocation and Activation of  $\text{Na}^+\text{K}^+\text{2Cl}^-$  cotransporter to the luminal membrane of cells in thick ascending limb of loop of Henle (AsclH).
4. Via receptor ( $\text{V}_{12}\text{R}$ ) mediated vasoconstriction of vasa recta

### Long-term actions

1. Gene mediated increased expression of aquaporin 2 channels in collecting duct cells.
2. Gene mediated increased expression of  $\text{Na}^+\text{K}^+\text{2Cl}^-$  cotransporter in AsclH cells.

### Rapid Actions





### ADH and its analogues

↓

Activation of V2 receptors basolateral side of CD cell

↓

Stimulating a vasopressin regulated urea transporter (VRUT or UT-1)

↓

Increases urea permeability of terminal part of CDs in inner medulla

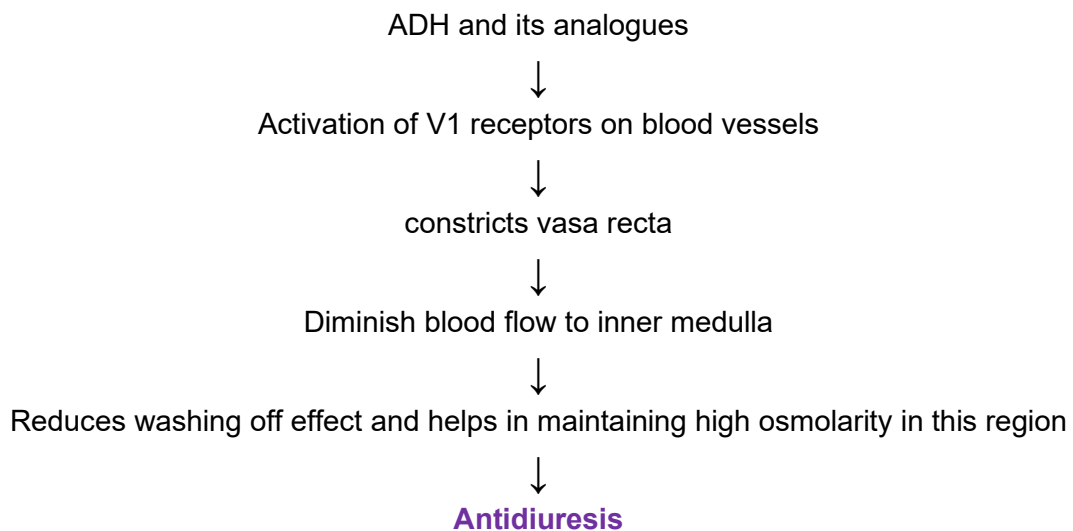
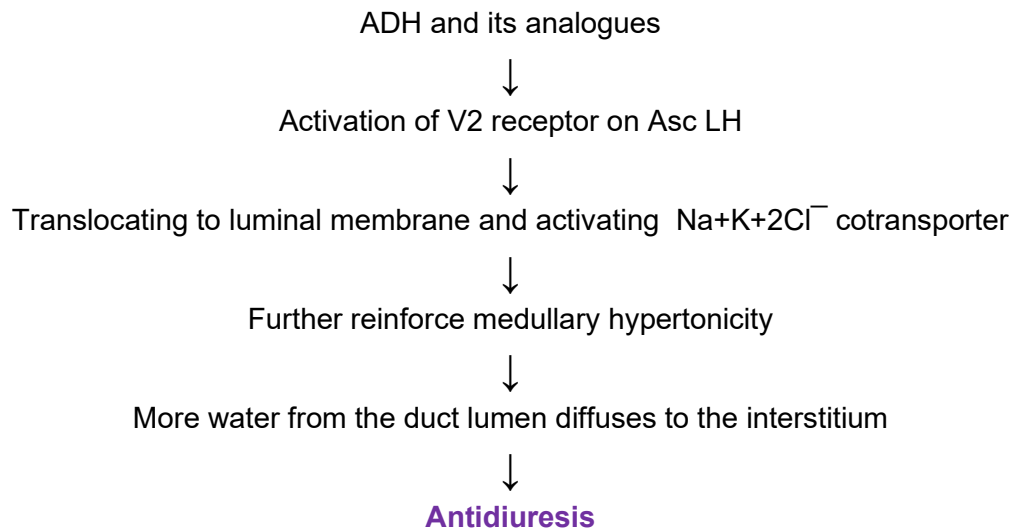
↓

Augments medullary hypertonicity

↓

More water from duct lumen diffuses to interstitium

**Antidiuresis**



## Long-term Actions

1. Gene mediated increased expression of aquaporin 2 channels in collecting duct cells.
2. Gene mediated increased expression of  $\text{Na}^+\text{K}^+\text{2Cl}^-$  cotransporter in AscLH cells.

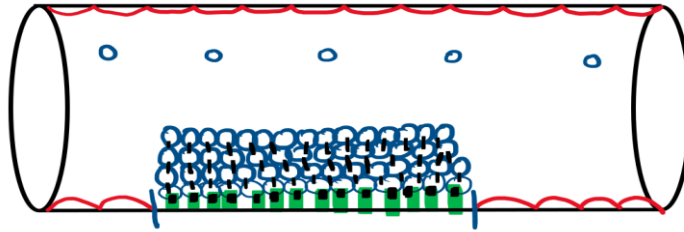
## 2. Blood Vessels (V2)

- V2 receptors
  - Causes vasodilatation
  - It is due to endothelium dependent NO production.



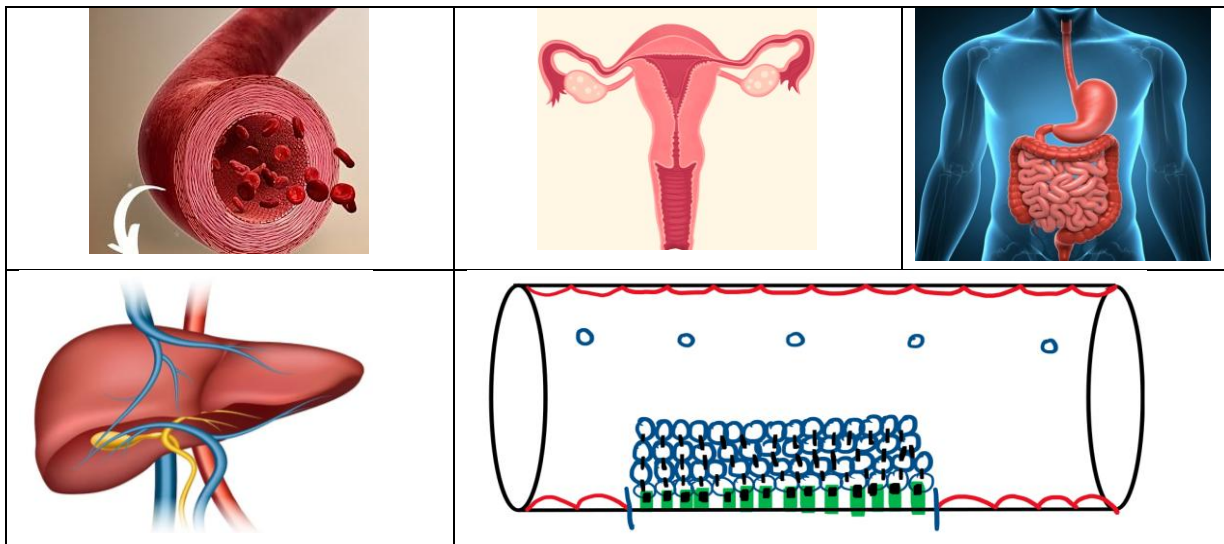
### 3. Vascular endothelium (V2)

- Releases coagulation factor VIII and von Willebrand's factor → platelet aggregation



### B) MOA → V1

- Blood vessels (V1)** → Vasoconstriction
- GIT (V1)** → Increased peristalsis in gut (especially large bowel), evacuation and expulsion of gases may occur.
- Uterus (V1)** → contracted by AVP acting on oxytocin receptors.
- Liver(V1)** → hepatic glycogenolysis
- Platelet (V1)** → platelet aggregation



### Pharmacokinetics

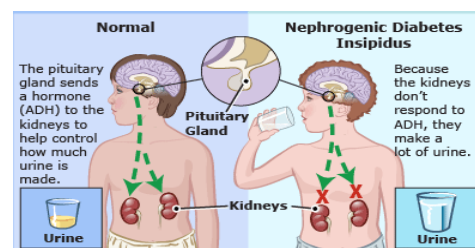
- Vasopressin (AVP)**
  - 8-arginine-vasopressin (AVP)
  - AVP is inactive orally because it is destroyed by trypsin.
  - Administered by any parenteral route or by intranasal application
  - T<sub>1/2</sub> 20 min

| Lypressin            | Terlipressin                     | Desmopressin (dDAVP) |
|----------------------|----------------------------------|----------------------|
| 8-lysine vasopressin | Synthetic prodrug of vasopressin | Synthetic peptide    |

|                                               |                                             |                                                                                            |
|-----------------------------------------------|---------------------------------------------|--------------------------------------------------------------------------------------------|
| Less potent than AVP                          | Bleeding esophageal varices                 | Selective V <sub>2</sub> agonist                                                           |
| V <sub>1</sub> and V <sub>2</sub> activity    | Less severe adverse effects than lyspressin | 12 times more potent than AVP                                                              |
| Longer duration of action 4-6 hrs             |                                             | Negligible vasoconstrictor activity                                                        |
| Substitute for AVP for V <sub>1</sub> actions |                                             | Longer duration of action 8-12 hrs                                                         |
|                                               |                                             | Preparation of choice for all V <sub>2</sub> mediated actions                              |
|                                               |                                             | Intranasal route preferred (bioavailability 10-20%) oral (1-2%; avoids nasal side effects) |

## Uses

- **Based on V<sub>2</sub> Actions:**
  1. Diabetes Insipidus (Neurogenic)
  2. Bedwetting in children and nocturia in adults
  3. Renal Concentration Test
  4. Hemophilia, von Willebrand's Disease



- **Based on V<sub>1</sub> Actions:**
  1. Bleeding Esophageal Varices
  2. Before abdominal radiography



## Adverse effects

1. **Kidney** → Fluid retention and hyponatraemia may develop.
2. **CVS** → increase cardiac afterload and precipitate angina by constricting coronary vessels.
3. **GIT** → abdominal cramps, pallor, urge to defecate,
4. **Uterus** → backache in females (due to uterine contraction).

## Contraindications

1. Ischaemic heart disease
2. Hypertension
3. Psychogenic polydipsia

## NATRIURETICS

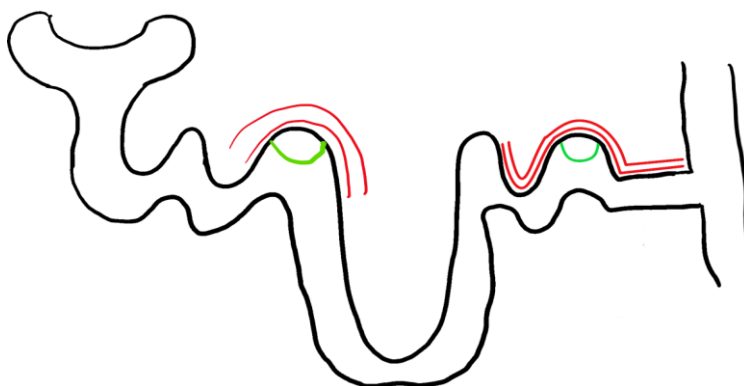
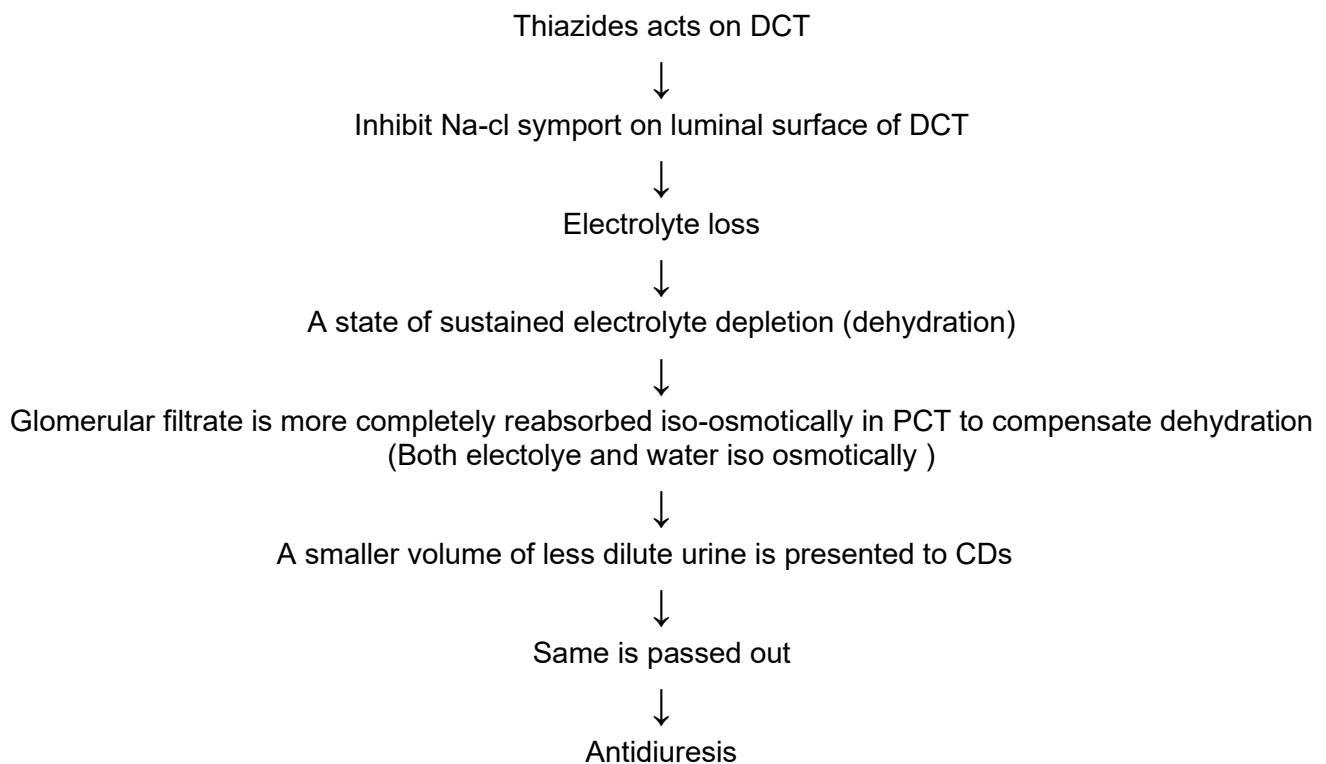
### Drugs

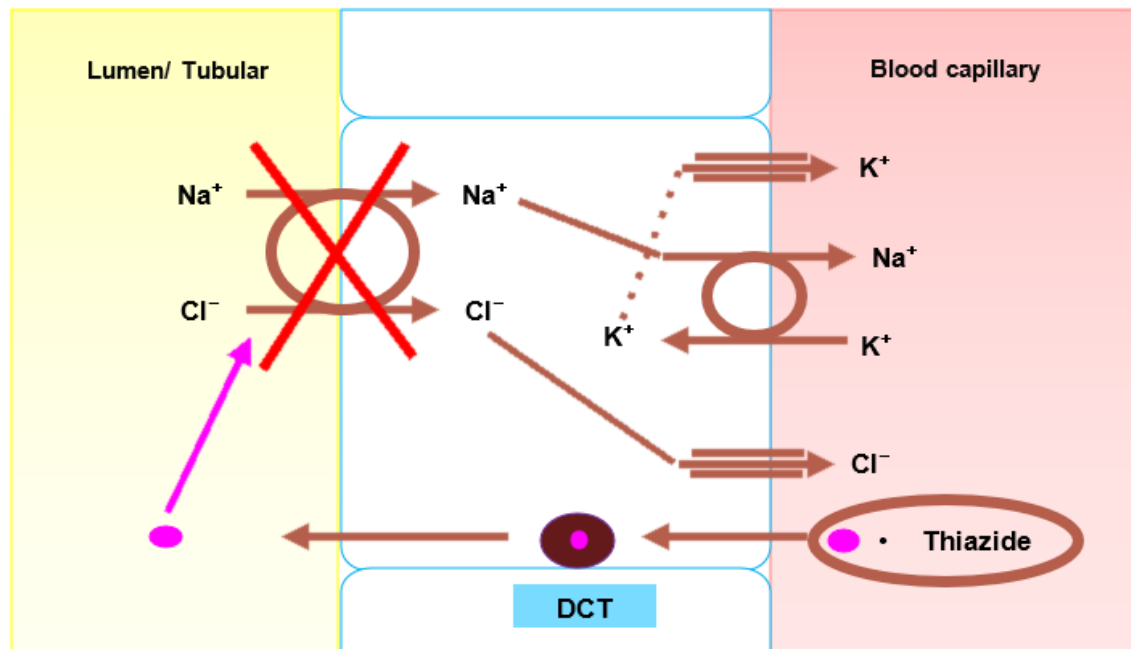
- Thiazide

### THIAZIDES

- Diuretic thiazides paradoxically exert an antidiuretic effect in DI.
- Effective in both pituitary origin as well as renal DI.
- They are especially valuable for renal DI in which AVP is ineffective.
- Their efficacy is low

### MOA of Thiazide





## Uses

- **Amiloride** → DOC for lithium induced nephrogenic DI (Lithium can cause nephrogenic DI)





# Antimicrobial Drugs

CHAPTER

12

## CONTENT

- General Considerations
- Tetracyclines, Chloramphenicol, Aminoglycoside Antibiotics, Macrolides
- Sulfonamides, Cotrimoxazole and Quinolones
- Beta-Lactam Antibiotics
- Antitubercular Drugs
- Antileprotic Drugs
- Antimalarial Drugs
- Antifungal Drugs
- Antiviral Drugs (Non-retroviral)
- Antiviral Drugs (Anti-retrovirus)
- Antiamoebic Drugs
- Anthelmintic Drugs

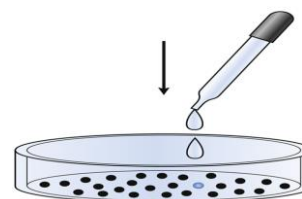
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## GENERAL CONSIDERATIONS

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## ANTIMICROBIAL AGENTS

- Agents that kill or inhibit growth of microorganisms



## CLASSIFICATION

- A) Chemical structure
- B) Type of organisms against which primarily active
- C) Spectrum of activity
- D) Mechanism of action
- E) Type of action
- F) Antibiotics obtained from

## A) Chemical structure

1. **Sulfonamides** : Sulfadiazine and others, Sulfones—Dapsone (DDS), Paraaminosalicylic acid (PAS).
2. **Diaminopyrimidines**: Trimethoprim, Pyrimethamine.
3. **Quinolones**: Nalidixic acid, Norfloxacin, Ciprofloxacin, Prulifloxacin, etc.
4.  **$\beta$ -Lactam antibiotics**: Penicillins, Cephalosporins, Monobactams, Carbapenems.
5. **Tetracyclines**: Oxytetracycline, Doxycycline, etc.
6. **Nitrobenzene derivative**: Chloramphenicol.
7. **Aminoglycosides**: Streptomycin, Gentamicin, Amikacin, Neomycin, etc.
8. **Macrolide antibiotics**: Erythromycin, Clarithromycin, Azithromycin, etc.
9. **Lincosamide antibiotics**: Lincomycin, Clindamycin
10. **Glycopeptide antibiotics**: Vancomycin, Teicoplanin
11. **Oxazolidinone**: Linezolid.
12. **Polypeptide antibiotics**: Polymyxin-B, Colistin, Bacitracin, Tyrothricin.
13. **Nitrofurantoin derivatives**: Nitrofurantoin, Furazolidone.
14. **Nitroimidazoles**: Metronidazole, Tinidazole, etc.
15. **Nicotinic acid derivatives**: Isoniazid, Pyrazinamide, Ethionamide.
16. **Polyene antibiotics**: Nystatin, Amphotericin- B, Hamycin.
17. **Azole derivatives**: Miconazole, Clotrimazole, Ketoconazole, Fluconazole.
18. **Others**: Rifampin, Spectinomycin, Sod. fusidate, Cycloserine, Viomycin, Ethambutol, Thiacetazone, Clofazimine, Griseofulvin.

## B) Type of organisms against which primarily active

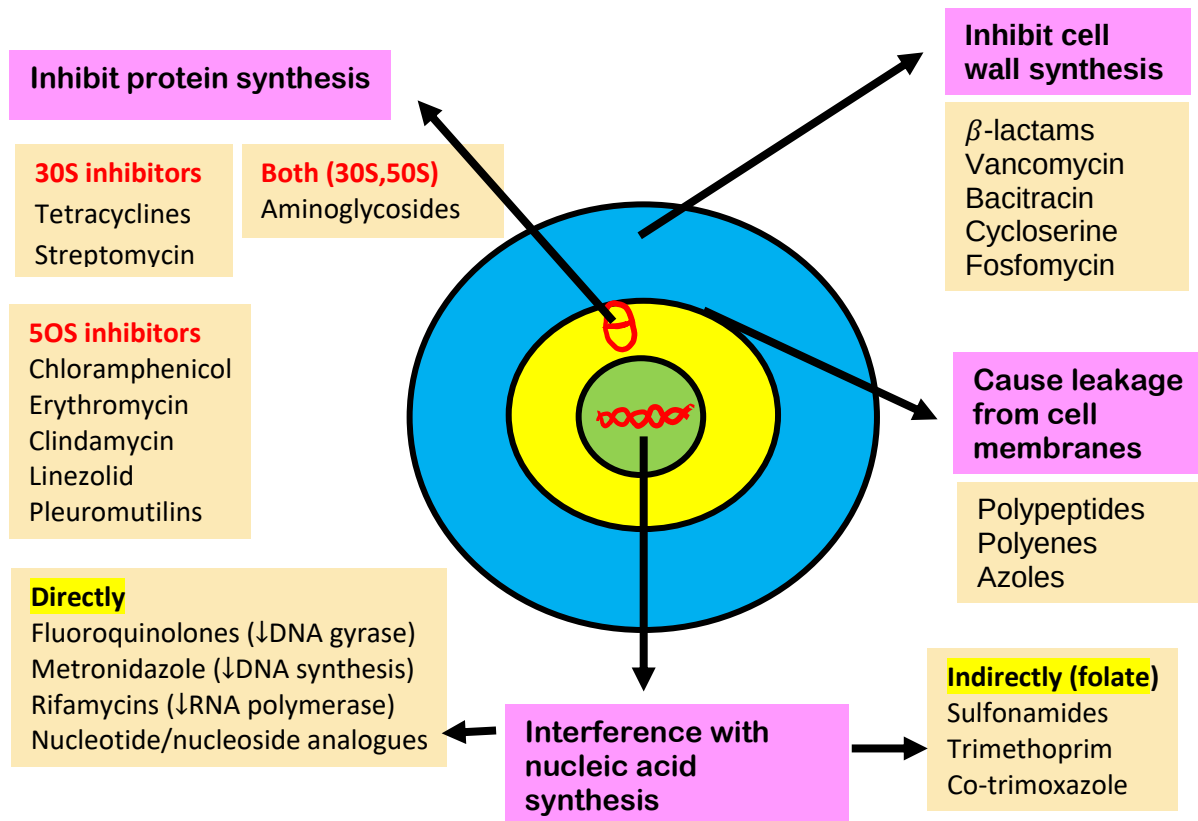
1. **Antibacterial** → Acts on bacteria
2. **Antifungal** → Acts on fungus
3. **Antiviral** → Acts on virus
4. **Antiprotozoal** → Acts on protozoa
5. **Anthelmintic** → Acts on helminths

## C) Spectrum of activity

1. **Narrow spectrum**
  - Penicillin G
  - Streptomycin
  - Erythromycin
2. **Broad spectrum**
  - Tetracyclines
  - Chloramphenicol

## D) Mechanism of action

- Inhibit cell wall synthesis
- Cause leakage from cell membranes
- Inhibit protein synthesis
- Interference with nucleic acid synthesis



### a) Inhibit cell wall synthesis

- β-lactam antibiotics (penicillin, cephalosporins, monobactam, carbapenems)
- Vancomycin
- Bacitracin
- Cycloserine
- Fosfomycin

- All antibiotic inhibiting cell wall synthesis are bactericidal

### b) Cause leakage from cell membranes

- Polypeptides → Polymyxins, Colistin, Bacitracin
- Polyenes → Amphotericin B, Nystatin, Hamycin
- Azoles → ketoconazole, fluconazole, itraconazole

- All antimicrobials that act on cell membrane are bactericidal

### c) Inhibit protein synthesis:

#### 1. Based on the steps of translation on which drug act:

- Freeze initiation: Aminoglycosides.

- Inhibit elongation: Tetracyclines, puromycin, chloramphenicol.
- Inhibit translocation: Clindamycin, erythromycin
- Causing premature termination: Puromycin

## 2. Based on ribosome on which they act:

- 30 S ribosome: Tetracycline, streptomycin.
- 50 S ribosome: Chloramphenicol, erythromycin, clindamycin, Linezolid, pleuromutilins (retapamulin).
- Both 30S and 50S ribosomes: Aminoglycosides (except streptomycin).
- All protein synthesis inhibitors are bacteriostatic except aminoglycosides and streptogramins which are bactericidal

## d) Interference with nucleic acid synthesis

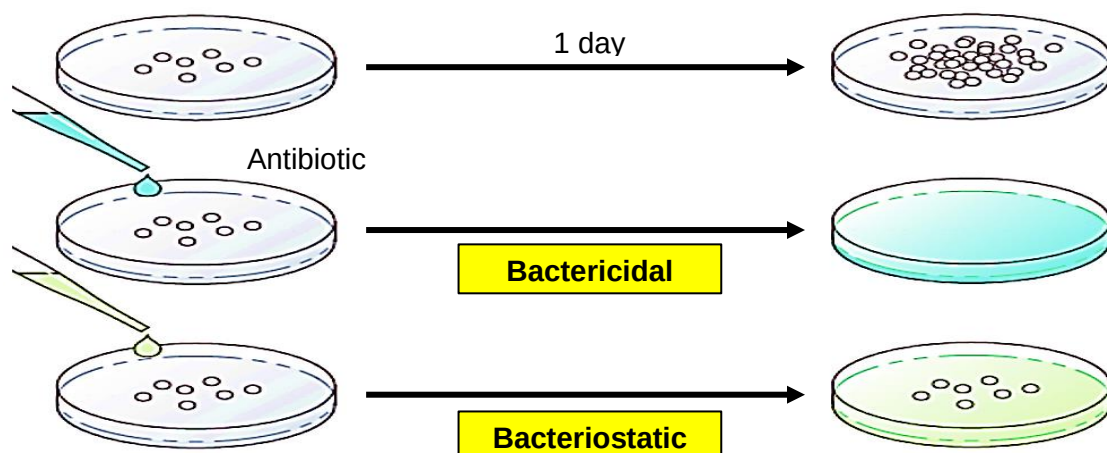
### 1. Drugs directly affecting nucleic acids (RNA or DNA)

- DNA gyrase inhibitors → Quinolones (nalidixic acid and fluoroquinolones) and novobiocin.
- Drugs destroying DNA → Metronidazole, nitrofurantoin.
- DNA dependent RNA polymerase inhibitors □ Rifampicin
- Nucleotide/nucleoside analogues □ get incorporated into DNA or RNA and lead to formation of faulty nucleic acid that may be unstable or nonfunctional. Drugs are □ Acyclovir, Zidovudin, Idoxuridine.

### 2. Drugs acting indirectly by affecting intermediary metabolism □ so that tetrahydrofolate can not be synthesized, which is essential for the synthesis of DNA.

- Inhibits folate synthase → sulphonamide
- Inhibits dihydrofolate reductase → Trimethoprim

## E) Type of action



| Bacteriostatic                                                                                                                                                                                                             | Bactericidal                                                                                                                                                                                                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Protein synthesis inhibitors</b> <ul style="list-style-type: none"> <li>• Tetracyclines</li> <li>• Tigecycline</li> <li>• Chloramphenicol</li> <li>• Lincosamides</li> <li>• Macrolides</li> <li>• Linezolid</li> </ul> | <b>Protein synthesis inhibitors</b> <ul style="list-style-type: none"> <li>• Aminoglycosides</li> <li>• Streptogramins</li> </ul>                                                                                        |
| <b>Drugs affecting DNA</b> <ul style="list-style-type: none"> <li>• Nitrofurantoin</li> <li>• Novobiocin</li> </ul>                                                                                                        | <b>Drugs affecting DNA</b> <ul style="list-style-type: none"> <li>• Quinolones</li> <li>• Metronidazole</li> </ul>                                                                                                       |
| <b>Drugs affecting metabolism</b> <ul style="list-style-type: none"> <li>• Sulfonamides</li> <li>• PAS</li> <li>• Trimethoprim</li> <li>• Ethambutol</li> <li>• Dapsone</li> </ul>                                         | <b>Polypeptide antibiotics</b> <ul style="list-style-type: none"> <li>• Polymixin B</li> <li>• Colistin</li> <li>• Amphotericin B</li> </ul>                                                                             |
|                                                                                                                                                                                                                            | <b>Cell wall synthesis inhibitors</b> <ul style="list-style-type: none"> <li>• Fosfomycin</li> <li>• Bacitracin</li> <li>• Penicillins</li> <li>• Cycloserine</li> <li>• Vancomycin</li> <li>• Cephalosporins</li> </ul> |
|                                                                                                                                                                                                                            | <b>First line ATT drugs (except Ethambutol)</b> <ul style="list-style-type: none"> <li>• Rifampicin</li> <li>• Pyrazinamide</li> <li>• Isoniazid</li> <li>• Streptomycin (aminoglycoside)</li> </ul>                     |

## F) Antibiotics are obtained from:

### 1. Fungi

- Penicillin
- Griseofulvin
- Cephalosporin

### 2. Bacteria

- Polymyxin B
- Tyrothricin
- Colistin
- Aztreonam
- Bacitracin

### 3. Actinomycetes

- Aminoglycosides
- Macrolides
- Tetracyclines
- Polyenes
- Chloramphenicol

## Potency of antimicrobial drug

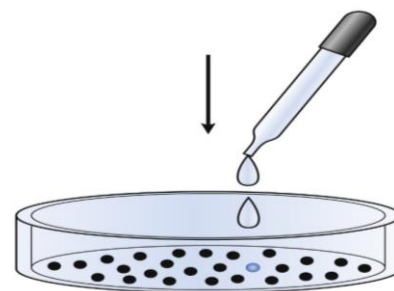
Measured by →

### 1. Minimum inhibitory concentration (MIC)

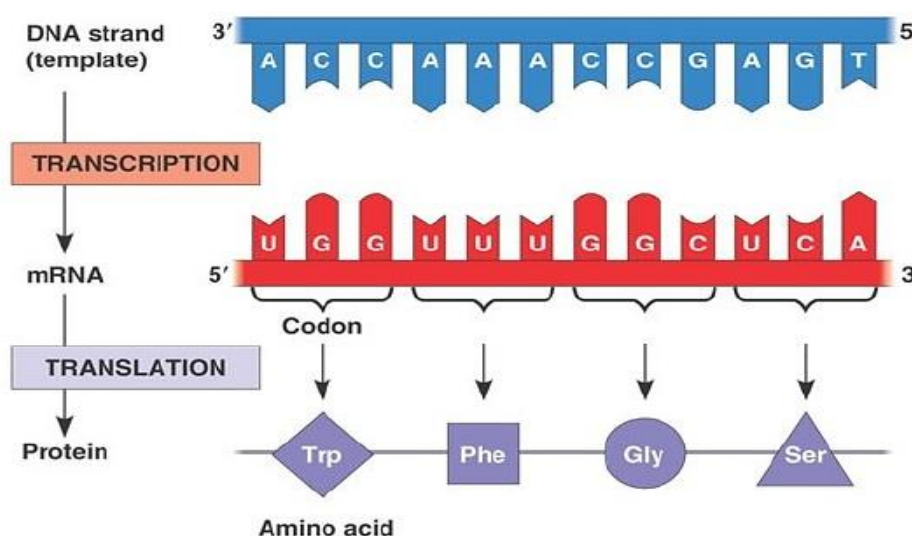
- Lowest concentration of antibiotic which prevents visible growth of a bacterium

### 2. Maximum bactericidal concentration (MBC)

- Concentration of an antibiotic which kills 99.9% of bacteria.

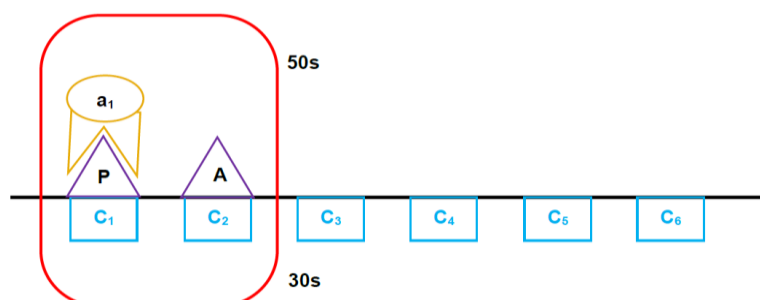


## TETRACYCLINES, CHLORAMPHENICOL, AMINOGLYCOSIDE ANTIBIOTICS, MACROLIDES

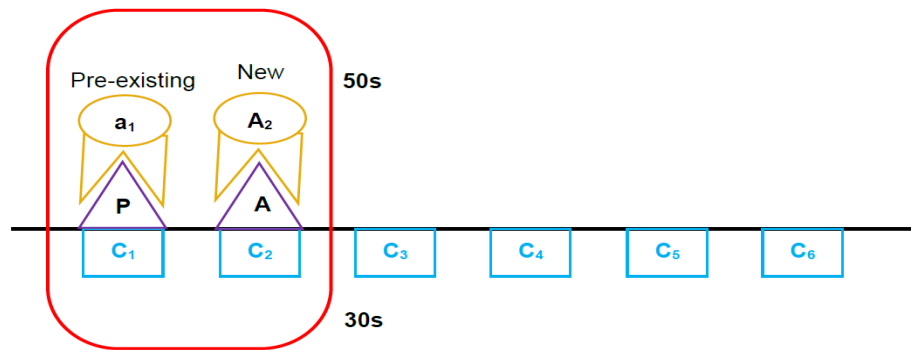


## STEPS OF TRANSLATION

### 1. Initiation

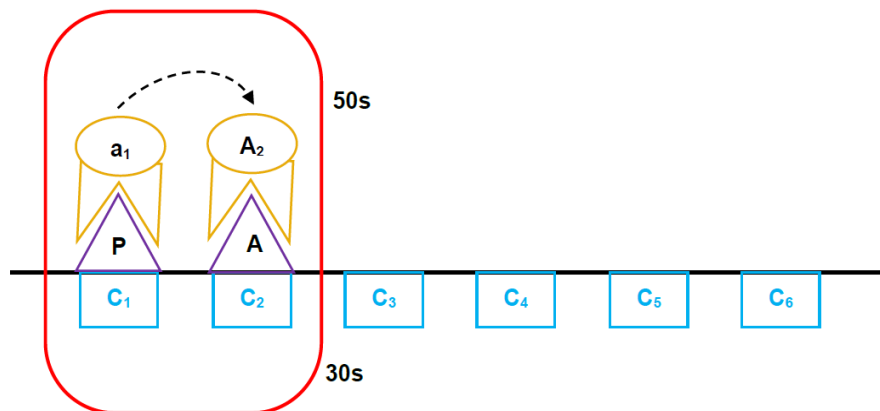


## 2. Attachment of new aminoacyl tRNA on A site

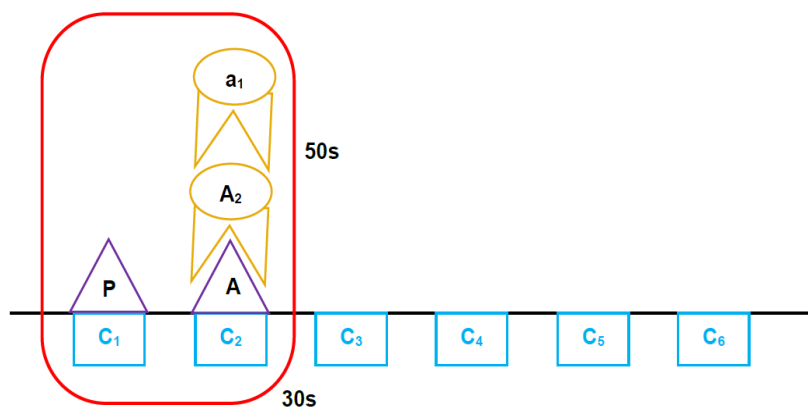


## 3. Peptide bond formation

- Between the newly attached aminoacid and the nascent peptide chain

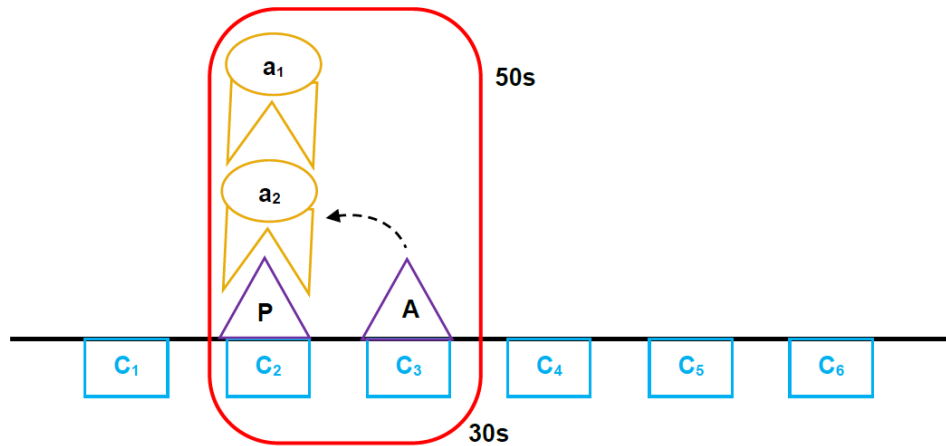


## Transfer of peptide chain from P site



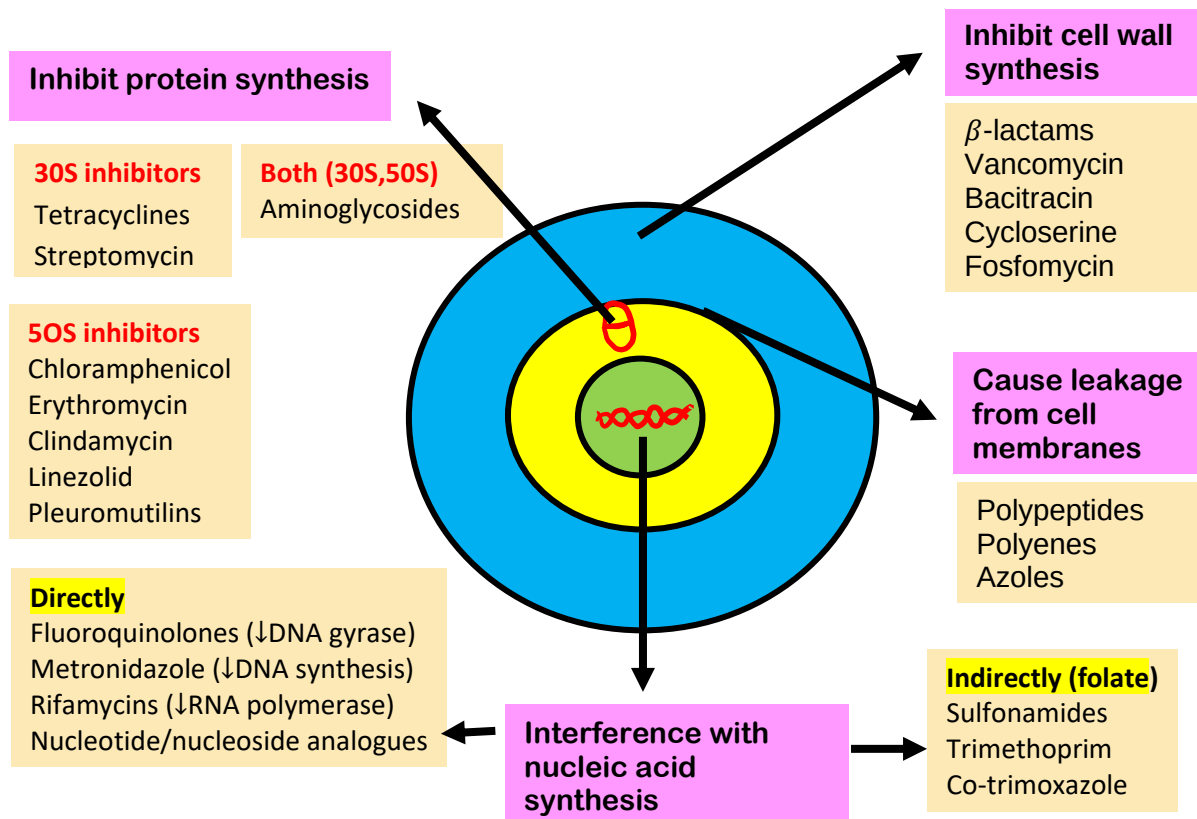
## 4. Translocation

- Ribosome move along the mRNA to expose the next codon.
- Translocation of the elongated peptide chain back from 'A' site to 'P' site

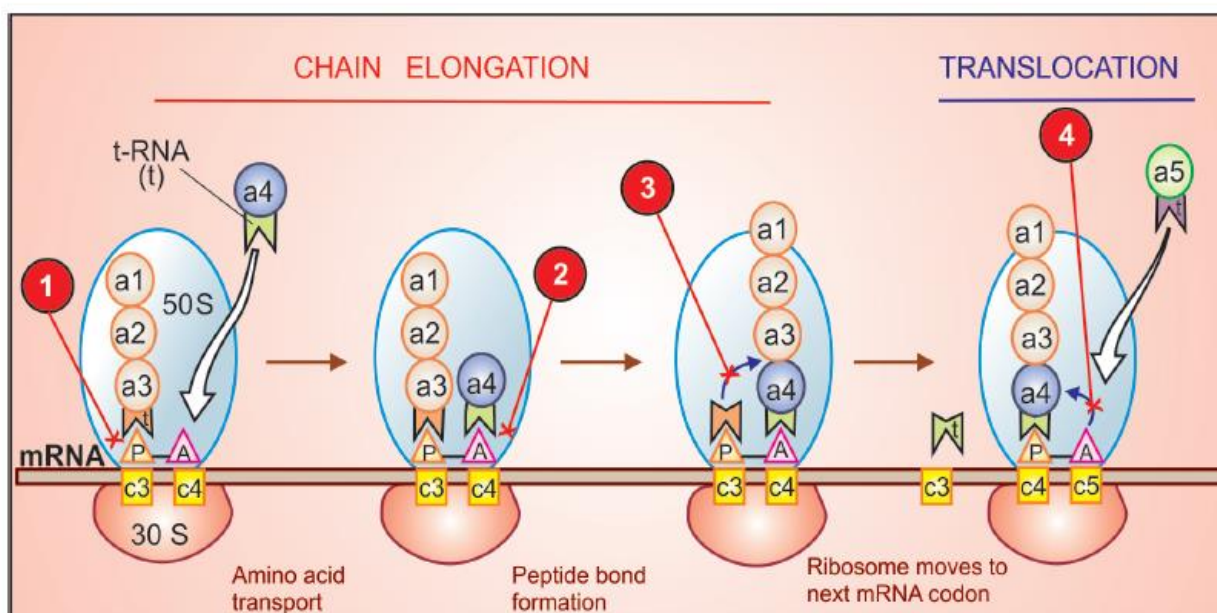


## PROTEIN SYNTHESIS INHIBITORS

1. Tetracyclines
2. Chloramphenicol
3. Aminoglycoside
4. Macrolide Antibiotics (Erythromycin)





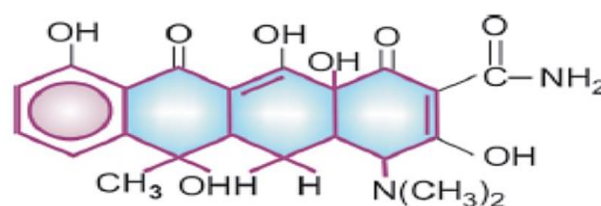


|                 | Tetracyclin | Chloramphenicol | Aminoglycosides | Erythromycin |
|-----------------|-------------|-----------------|-----------------|--------------|
| Introduction    |             |                 |                 |              |
| Classification  |             |                 |                 |              |
| Spectrum        |             |                 |                 |              |
| MOA             |             |                 |                 |              |
| Resistance      |             |                 |                 |              |
| Adverse effects |             |                 |                 |              |
| Uses            |             |                 |                 |              |

## TETRACYCLINES

### Introduction

- Have nucleus of four cyclic rings



### Classification

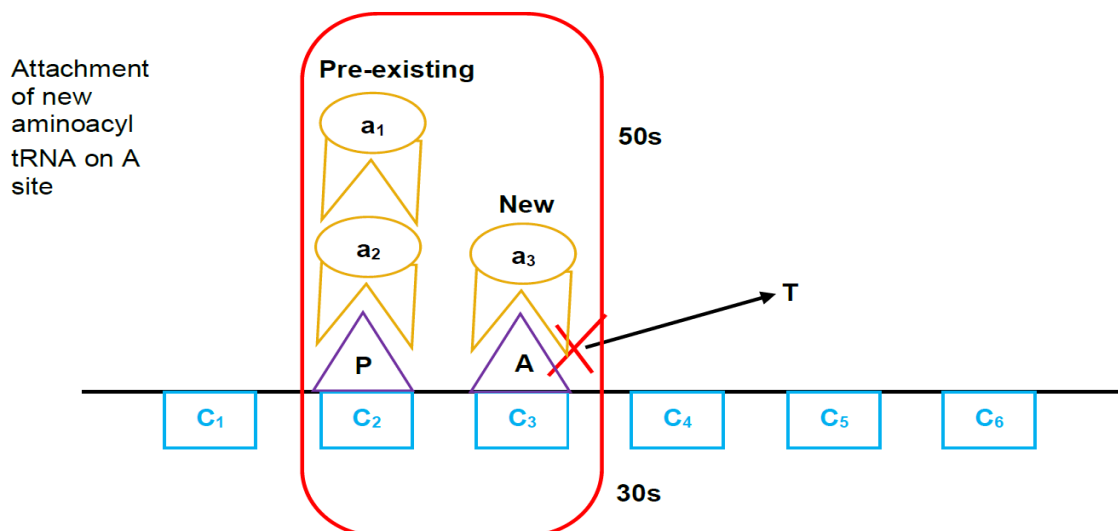
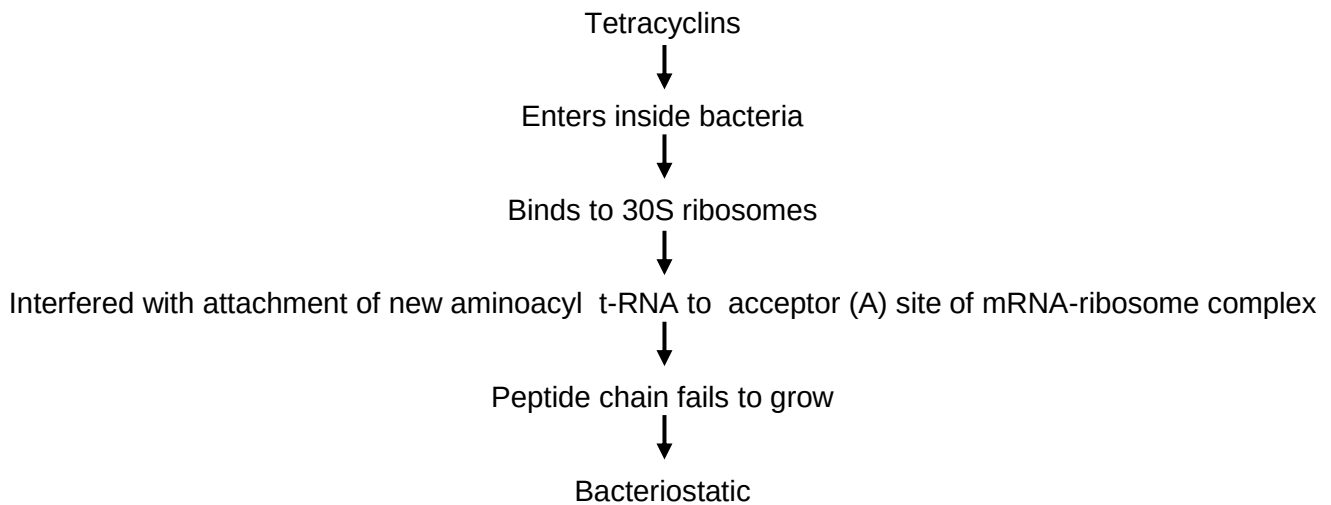
- Group I:** Tetracycline, chlortetracycline, oxytetracycline
- Group II:** Demeclocycline, lymecycline
- Group III:** Doxycycline, minocycline

### Spectrum

- All gram positive and gram negative Cocci
- All gram positive and gram negative Bacilli

## Mechanism of action

- Inhibit protein synthesis



## Resistance

1. Reduced accumulation due to decrease influx or increase efflux
2. Decrease access to the ribosome due to ribosomal protective proteins.
3. Elaboration of tetracycline inactivating enzymes

## Adverse Effects

Mnemonic → **L.K. ADVanI is P.T. Teacher**

- **L** - Liver damage
- **K** - Kidney damage
- **A** - Antianabolic effect
- **D** - Diabetes insipidus
- **V** - Vestibular toxicity
- **I** - Intracranial pressure raised

- **P**- **P**hototoxicity
- **T**- **T**eeth and bones
- **T**- **T**eratogenic

### 1. Liver damage

- Fatty infiltration of liver and jaundice occasionally.

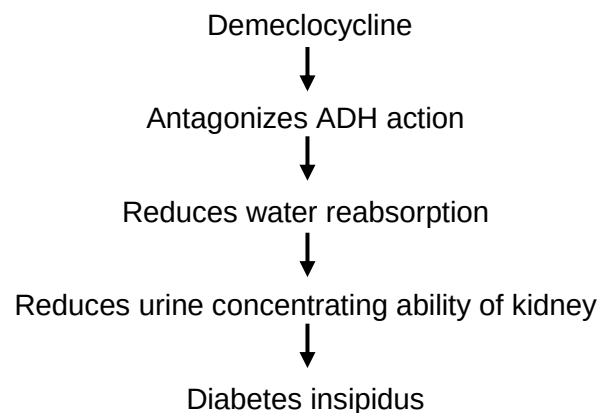
### 2. Kidney damage

- All tetracyclines, except doxycycline, accumulate and enhance renal failure.
- A reversible Fanconi syndrome like condition is produced by outdated tetracyclines.
- Caused by degraded products → epitetracycline, anhydrotetracycline and epianhydrotetracycline which damage proximal tubules.
- Doxycycline can be used in renal failure

### 3. Antianabolic effect

- Tetracyclines reduce protein synthesis and have an overall catabolic effect.
- They induce negative nitrogen balance and can increase blood urea.

### 4. Diabetes insipidus



### 5. Vestibular toxicity

- Minocycline → cause ataxia, vertigo and nystagmus → subside when drug is discontinued.

### 6. Intracranial pressure raised

- Raised IOT

### 7. Phototoxicity

- A sunburn-like reaction on exposed parts (specially Demeclocycline and Doxycycline)



## 8. Teeth and bones

- Tetracyclines have chelating property.
- Calcium-tetracycline chelate gets deposited in developing teeth and bone.
- Tetracyclines given between 3 months and 6 years of age affect crown of permanent anterior dentition.



## Uses

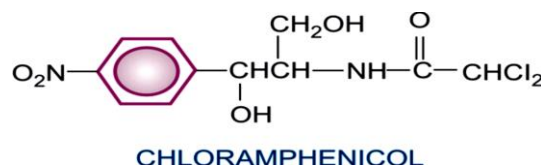
Mnemonic → **VACUM The BedRoom**

- **V**ibrio cholera
- **A**cne
- **C**hlamydia → LGV
- **U**reaplasma urealyticum
- **M**ycoplasma pneumoniae
- **T**ularemia / Plague
- **B**orrelia burgdorferi (Relapsing fever)
- **R**ickettsia

## CHLORAMPHENICOL

### Introduction

- Nitrobenzene moiety → responsible for antibacterial activity

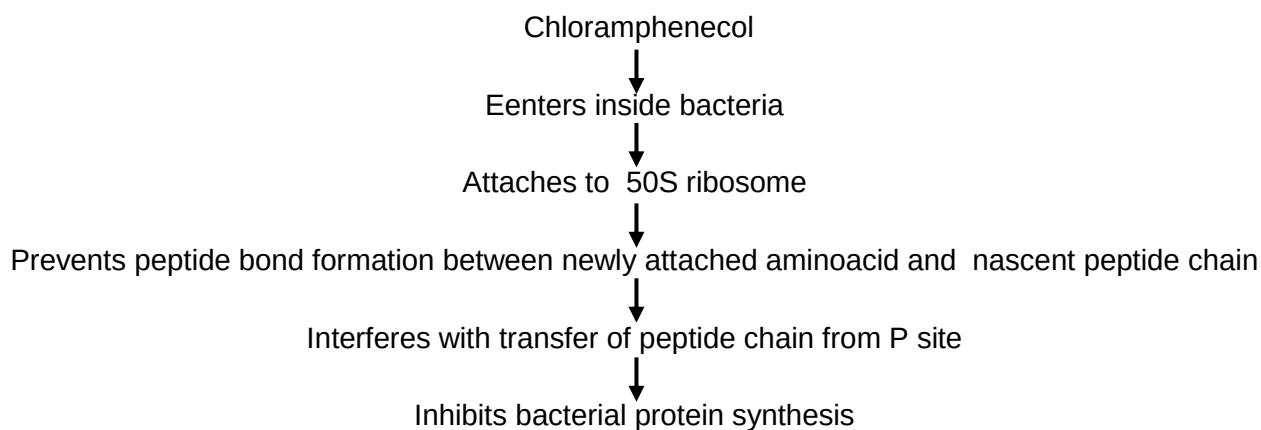


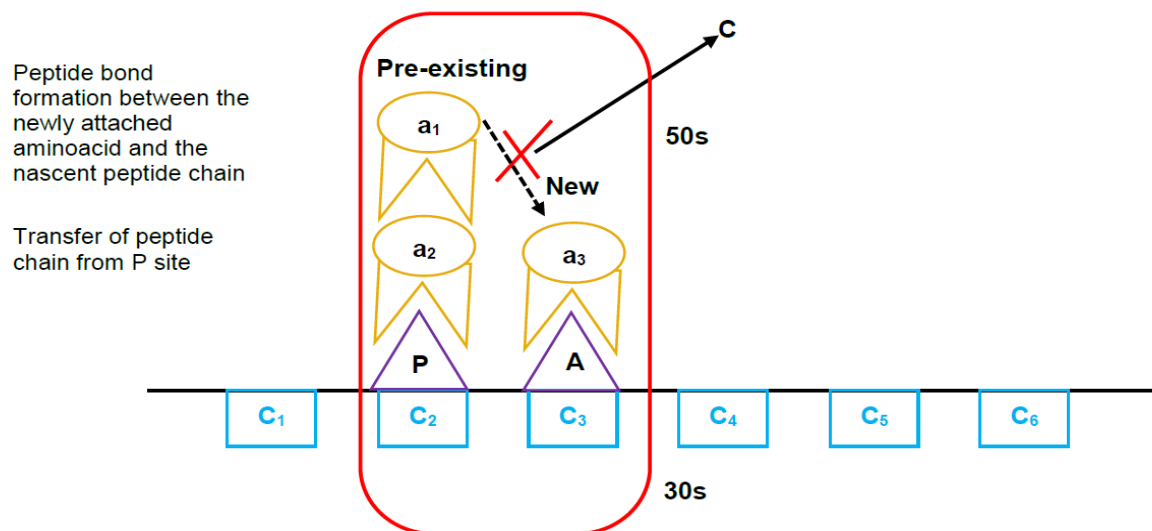
### Spectrum

1. All gram positive and gram negative Cocci
2. All gram positive and gram negative Bacilli
3. Spirochetes, including T. pallidum and Borrelia
4. Rickettsiae (typhus, etc.) and chlamydiae
5. Mycoplasma and Actinomyces
6. Protozoa like Entamoeba histolytica and Plasmodia

### Mechanism of action

- Inhibit protein synthesis



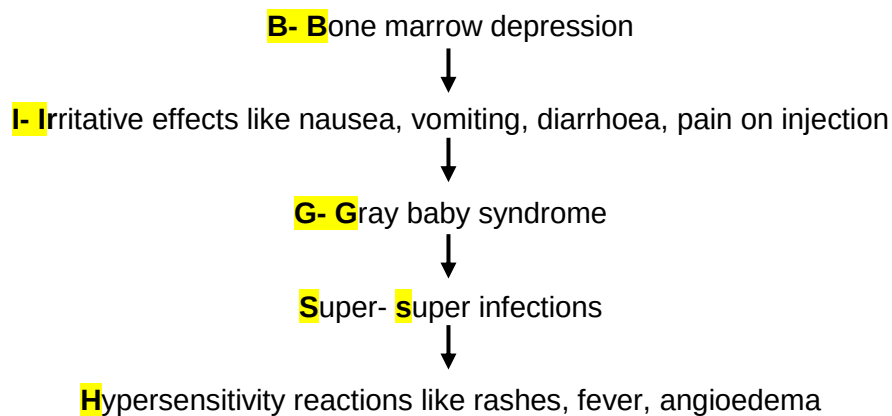


## Resistance

1. Due to a specific acetyl transferase produced by the organism, which inactivates chloramphenicol.
2. There may be decreased permeability in cell
3. Ribosomal insensitivity.

## Adverse effects

Mnemonic → **BIG Super Hypersensitivity**



### 1. Bone marrow depression

- Of all drugs, chloramphenicol is most important cause of aplastic anaemia, agranulocytosis, thrombocytopenia or pancytopenia.

## Types

### a) Non-dose related idiosyncratic reaction:

- Rare (1 in 40,000), unpredictable, but serious, fatal
- Genetic basis
- More common after repeated courses.
- Aplastic anaemia → most common manifestation.

### b) Dose and duration of therapy related myelosuppression:

- A direct toxic effect, predictable
- Due to inhibition of mitochondrial enzyme synthesis in erythropoietic cells.
- Reversible without long-term sequelae.

## 2. Irritative effects

- Nausea
- Vomiting
- Diarrhoea
- Pain on injection

## 3. Gray baby syndrome

- Occurred when high doses (~100 mg/kg) given prophylactically to premature neonates
- It occurs because of inability of newborn to adequately metabolize and excrete chloramphenicol.
- At higher concentration → chloramphenicol blocks electron transport in liver, myocardium and skeletal muscle
- Baby stopped feeding, vomited, became hypotonic and hypothermic, abdomen distended, respiration became irregular, an ashen gray cyanosis developed in many, followed by cardiovascular collapse and death.

## 4. Superinfections

- Similar to tetracyclines, but less common

## 5. Hypersensitivity reactions

- Rashes
- Fever
- Atrophic glossitis
- Angioedema

## Uses

- Clinical use of chloramphenicol for systemic infections is now highly restricted due to fear of fatal toxicity
- Because of risk of serious (though rare) bone marrow aplasia:
  - (a) Never use chloramphenicol for minor infections or those of undefined etiology.
  - (b) Do not use chloramphenicol for infections treatable by other safer antimicrobials.
  - (c) Avoid repeated courses.
  - (d) Daily dose not to exceed 2–3 g; duration of therapy to be < 2 weeks, total dose in a course < 28 g
  - (e) Regular blood counts (especially reticulocyte count) may detect dose-related bone marrow toxicity but not the idiosyncratic type.
  - (f) Combined formulation of chloramphenicol with any drug meant for internal use is banned in India

- Highly restricted due to fear of fatal toxicity

**Mnemonic** → **BARE TB**

- **B** - **B**acterial meningitis/Pyogenic meningitis
- **A** - **A**naerobic infections
- **R** - **R**ickettsia infection
- **E** - **E**ar & Eye infection(conjunctivitis, endophthalmitis)
- **T** - **T**yphoid
- **B** - **B**rucellosis

## AMINOGLYCOSIDES

### Introduction

- Have amino groups linked glycosidically to two or more aminosugar

### Classification

#### Systemic aminoglycosides (TANGSS KP)

- Tobramycin
- Amikacin
- Netilmicin
- Gentamicin
- Sisomicin
- Streptomycin
- Kanamycin
- Paromomycin

#### Topical aminoglycosides (NF)

- Neomycin
- Framycetin

### Spectrum

- Gram negative aerobic Bacilli

### Mechanism of Action

- Inhibit protein synthesis

Transport of aminoglycoside through bacterial cell wall and cytoplasmic membrane (transport mechanism)



Binds to ribosomes 30S subunit, 50 subunit, 30S-50S interface



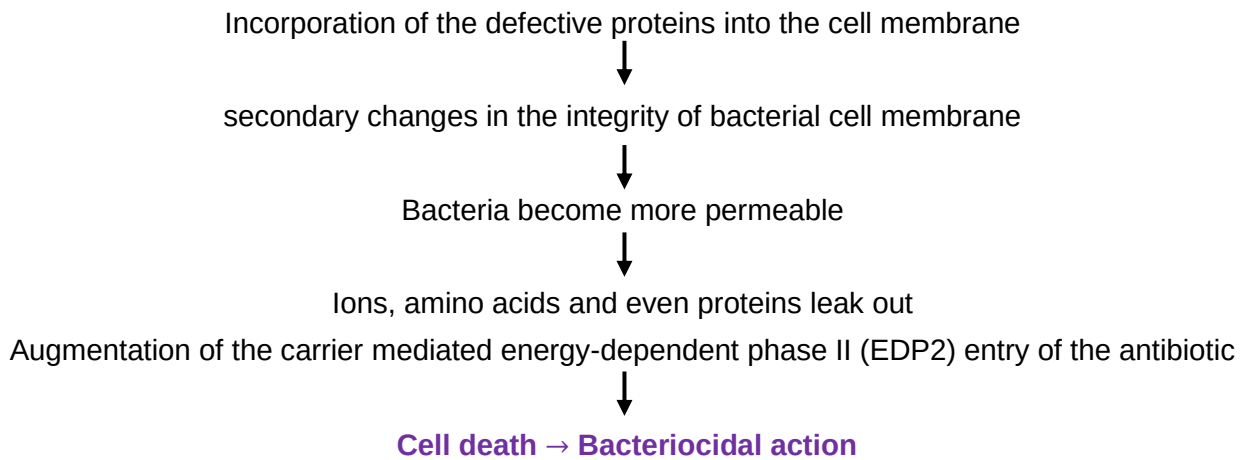
Freeze initiation of protein synthesis  
Prevent polysome formation



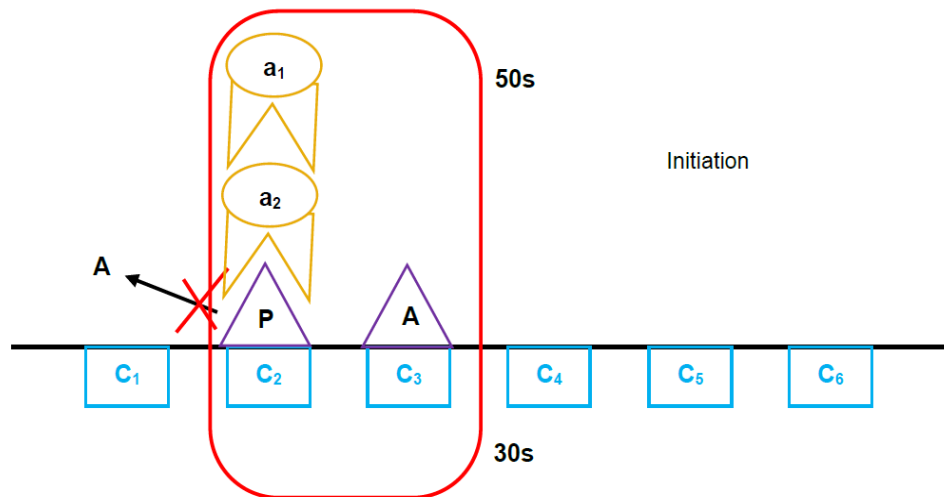
Distortion of mRNA codon recognition resulting in misreading of code



**Inhibit protein synthesis → Bacteriostatic action**



## INITIATION



## Resistance

1. Inability to reach to the site of action → the transport mechanism is defective
2. Reduced affinity for ribosome → change of an amino acid at a particular position significantly changes the picture. Replacement of lysine by asparagine makes it resistant and by glutamine makes it dependent on streptomycin.
3. Inactivation by adenylating, acetylating or phosphorylating enzymes produced by the organisms.

## Adverse effects

Mnemonic → **ONN HT**

- **O**totoxicity
- **N**ephrotoxicity
- **N**euromuscular blockade
- **H**ypersensitivity reactions
- **T**eratogenic

### 1. Ototoxicity

- Vestibular and cochlear → both components involved.



- Accumulation of drug in endo/ perilymph of inner ear alters ionic balance → progressive destruction of sensory cells.
- Earlier changes are reversible but later on they become irreversible since cell regeneration do not occur after loss of sensory cells.

#### a) Cochlear damage

- Starts from base and spreads to apex
- Affect outer hair cells of basal turn of cochlea
- Hearing loss affects high frequency sound first, then progressively encompasses lower frequencies.
- No regeneration of sensory cells occurs → auditory nerve fibres degenerate in a retrograde manner → deafness is permanent.
- Tinnitus appears first followed by progressive hearing loss.
- On stopping drug → tinnitus disappears in 4–10 days, but frequency loss persists.

#### b) Vestibular damage

- Headache → first to appear, followed by nausea, vomiting, dizziness, nystagmus, vertigo and ataxia.
- When drug is stopped at this stage → it passes into a chronic phase lasting 6 to 10 weeks in which patient is asymptomatic while in bed and has difficulty only during walking.
- Compensation by visual and proprioceptive positioning and recovery occurs over 1–2 years.

### Remember

- **Vestibular symptoms** → headache, nausea, vomiting, nystagmus, vertigo, and ataxia
- **Cochlear symptoms** → tinnitus, sensation of pressure or fullness in ears and deafness
- **Concurrent use of ototoxic drugs** → furosemide, cisplatin, vancomycin, amphotericin B → enhance ototoxicity.

## 2. Nephrotoxicity

- Drugs binds with phospholipid in brush border leading to acute tubular necrosis.
- Inability to concentrate urine.
- Protein and casts appear in urine.
- Toxicity is related to total amount of drug received by patient.
- Toxicity is reversible with timely discontinuation of drug and use of calcium which inhibits uptake and binding to renal tubular cells.
- Nephrotoxicity → increased by →
  - Advanced age
  - Liver disease
  - Hypokalemia
  - Septic shock
  - Concurrent use of nephrotoxic drugs (amphotericin B, cisplatin, cyclosporine)
  - Prolonged therapy

| Systemically Used Aminoglycoside | Ototoxicity (Vestibular) | Ototoxicity (Cochlear) | Nephrotoxicity |
|----------------------------------|--------------------------|------------------------|----------------|
| 1. Streptomycin                  | ++                       | ±                      | +              |
| 2. Gentamicin                    | ++                       | +                      | ++             |
| 3. Kanamycin                     | +                        | ++                     | ++             |
| 4. Tobramycin                    | ±                        | +                      | ++             |
| 5. Amikacin                      | +                        | ++                     | ++             |
| 6. Sisomicin                     | ++                       | +                      | ++             |
| 7. Netilmicin                    | ±                        | +                      | ++             |

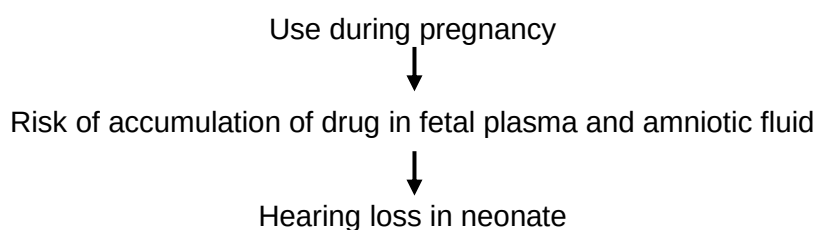
### 3. Neuromuscular blockade

- All aminoglycosides reduce ACh release from motor nerve endings.
- Interfere with mobilization of centrally located synaptic vesicles to fuse with terminal membrane
- Lead to acute muscle paralysis or apnea
- Myasthenic weakness is accentuated by these drugs

### 4. Hypersensitivity reactions

- Rare but there may be rashes

### 5. Teratogenic



### Uses

- **For gram negative infections** → UTI, meningitis, pneumonia, peritonitis, burn, osteomyelitis, sepsis — gentamicin, sisomicin, tobramycin, amikacin and netilmicin.
- **For tuberculosis** → streptomycin, kanamycin, amikacin, netilmicin.
- **For intestinal amoebiasis and tape worm** → paramomycin.
- **For topical application** → for infected wound, ulcers, burn, external ear infections, conjunctivitis → neomycin, framycetin

### Dosing Regimens

- Because of low safety margin → daily dose of systemically administered aminoglycosides □ precisely calculated accordingly to body weight and level of renal function.
- For an average adult with normal renal function (CLcr >70 ml/min), the usual doses are:

|                                                   |   |                        |
|---------------------------------------------------|---|------------------------|
| Gentamicin / tobramycin<br>sisomicin / netilmicin | → | 3 – 5 mg / kg / day    |
| Streptomycin / kanamycin<br>/ amikacin            | → | 7.5 – 15 mg / kg / day |

- Considering short  $t_{1/2}$  (2-4 hr) of aminoglycosides → daily doses are conventionally divided into 3 equal parts and injected i.m. (or i.v. slowly over 60 min) every 8 hours

| Guideline for dose adjustment of gentamicin in renal insufficiency |                   |
|--------------------------------------------------------------------|-------------------|
| CLcr (ml/min)                                                      | % of daily dose   |
| 70                                                                 | 70% daily         |
| 50                                                                 | 50% daily         |
| 30                                                                 | 30% daily         |
| 20-30                                                              | 80% alternate day |
| 10-20                                                              | 60% alternate day |
| <10                                                                | 40% alternate day |

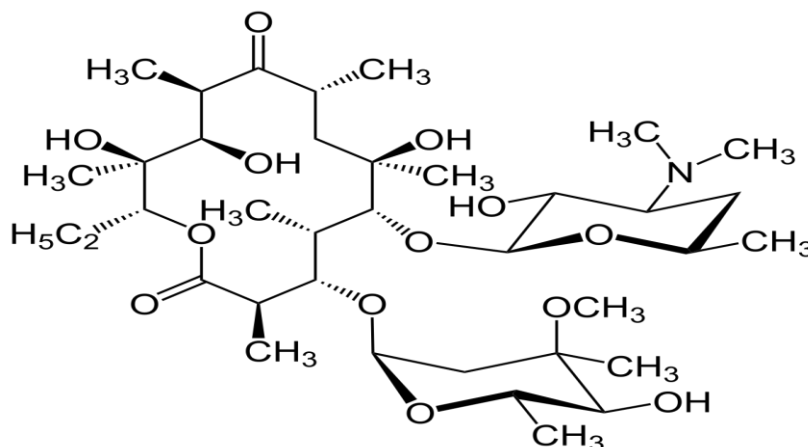
### Remember

- Gentamycin** → most commonly used of all the aminoglycosides.
- Tobramycin** → maximally active aminoglycoside against pseudomonas.
- Spectinomycin** → MOA similar to aminoglycosides (but it is not an aminoglycoside) and it is used to treat gonorrhea in patients allergic to penicillin.
- Amikacin** → widest spectrum as it has resistance to aminoglycoside inactivating enzyme

## MACROLIDE ANTIBIOTICS

### Introduction

- Have a macrocyclic lactone ring with attached sugars



## Classification

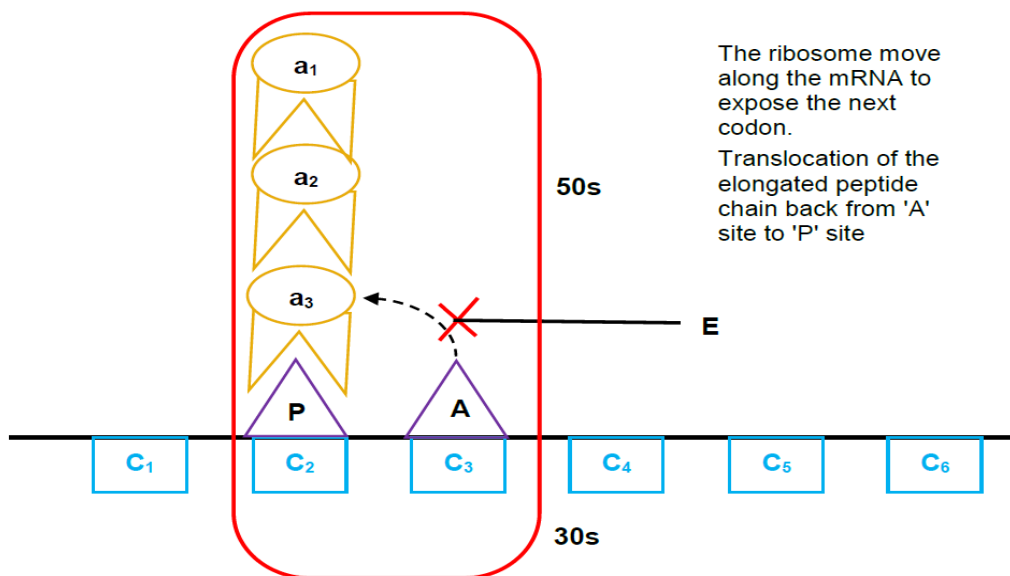
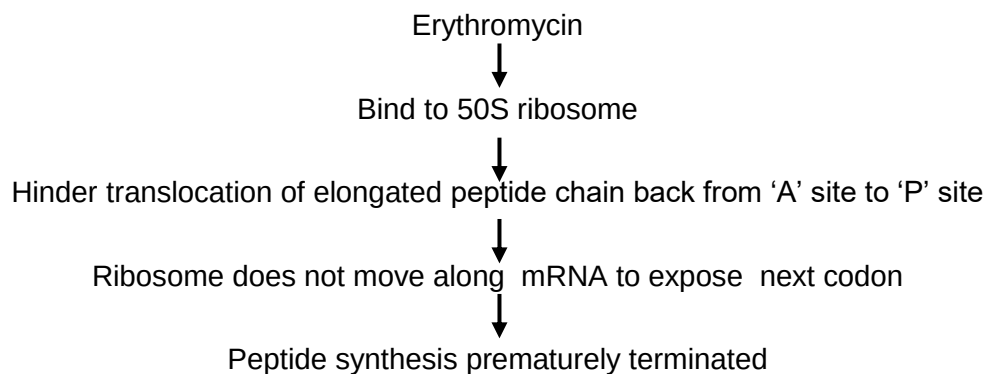
1. Erythromycin
  2. Roxithromycin
  3. Clarithromycin
  4. Azithromycin
  5. Spiramycin
- Immunosuppressant drug tacrolimus is also a macrolides

## Spectrum

- All bacterias except Gram negative Bacilli

## Mechanism of action

- Inhibit protein synthesis



## Resistance

1. Reduced permeability or increase efflux of the drug
2. Modification of the target → methylase produced by organism leads to methylation of y RNA receptor that prevents the drug attachment.(plasmid mediated)
3. Production of esterase that hydrolyze the drug.

## Pharmacokinetics

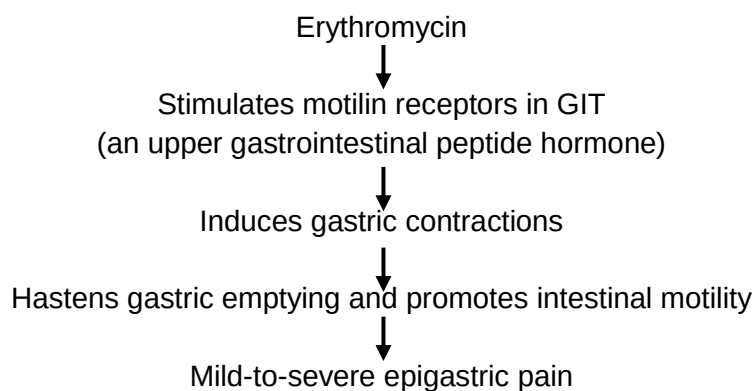
- **Erythromycin** →
  - Acid labile
  - To protect it from gastric acid → given as enteric coated tablets, from which absorption is incomplete
  - Food delays absorption by retarding gastric emptying.
  - Undergoes enterohepatic circulation and is excreted in bile.

## Adverse effects

Mnemonic → **MACRO**

- **M** - **M**otilin receptor agonists
- **A** - **A**llergy
- **C** - **C**holestasis
- **R** - **R**eversible
- **O** - **O**totoxicity

### 1. Motilin Receptor Agonist



- Tolerance quickly develops to this action
- Undesirable alteration of bacterial flora limit use of erythromycin as a prokinetic agent.

### 2. Allergy

- Rashes
- Fever

### 3. Cholestatic hepatitis

- Occur with erythromycin
- Starts 10-20 days after therapy
- Characterized by → nausea, vomiting, abdominal cramps, jaundice, and fever.
- Pain often mimics pain of acute cholecystitis.
- Incidence higher in pregnant women
- Symptoms disappear with in few days of stoppage of therapy.

### 4. Reversible Ototoxicity

- Very high doses of erythromycin → reversible hearing impairment.

## Uses

Mnemonic → **CLAW**

- **C** - **C**hancroid, **C**orynebacterium, **C**ampylobacter
- **L** - **L**egionella infections
- **A** - **A**typical pneumonia
- **W** - **W**hooping cough by Bordetella pertussis

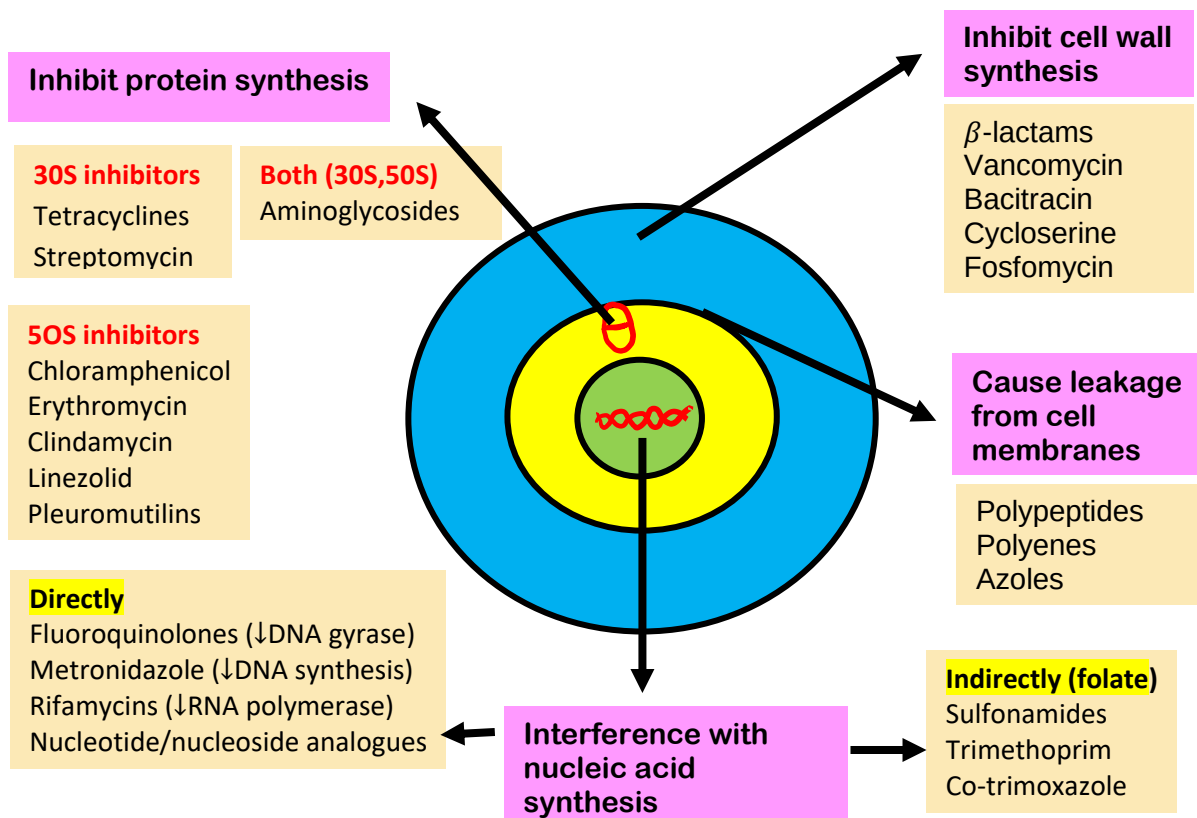
## Remember

- **Spiramycin** → another macrolide antibiotic □ used for toxoplasma infection during pregnancy.
- **Clarithromycin** → used for infection with MAC and peptic ulcer caused by H. Pylori.
- **Erythromycin and other macrolide antibiotics** → Maternal and infant use → risks factors for infantile hypertrophic pyloric stenosis (IHPS)
- **Ketolides (Telithromycin)** → resembles macrolides in MOA and spectrum of activity.

## SULFONAMIDES, COTRIMOXAZOLE AND QUINOLONES

### ANTIBIOTICS THAT DIRECTLY INTERFERE WITH NUCLEIC ACID SYNTHESIS

- Sulfonamides
- Trimethoprim
- Quinolones

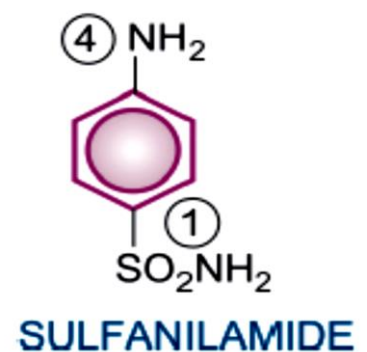


|                 | Sulfonamides | Trimethoprim | Quinolones |
|-----------------|--------------|--------------|------------|
| Introduction    |              |              |            |
| Classification  |              |              |            |
| Spectrum        |              |              |            |
| MOA             |              |              |            |
| Resistance      |              |              |            |
| Adverse effects |              |              |            |
| Uses            |              |              |            |

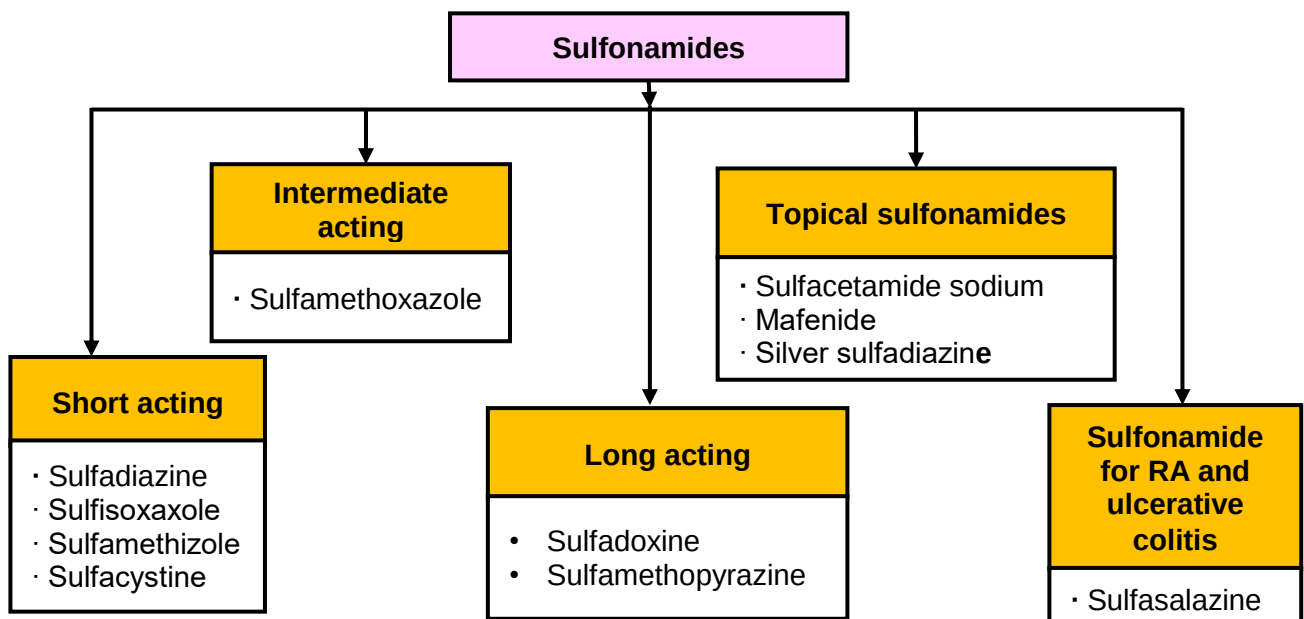
## SULFONAMIDES

### Introduction

- Sulfonamides are synthetic antimicrobials having a sulfamino group,  $-SO_2NH_2$
- A large number of sulfonamides were produced and used extensively in the subsequent years
- Current utility is limited (except in combination with trimethoprim or pyrimethamine) because of →
  - Rapid emergence of bacterial resistance
  - Availability of many safer and more effective antibiotics



### Classification



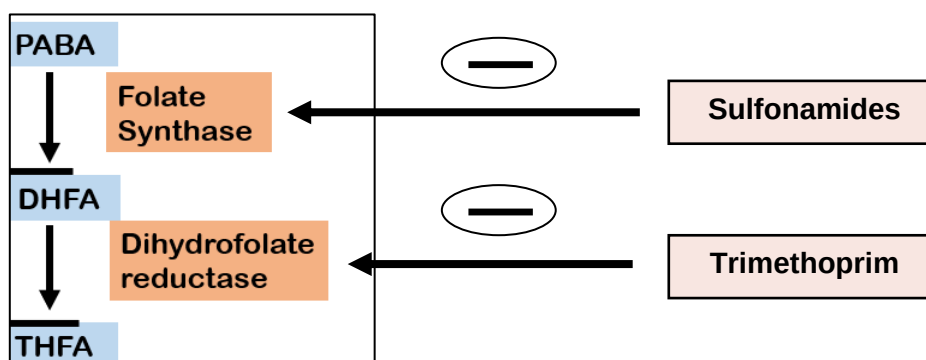
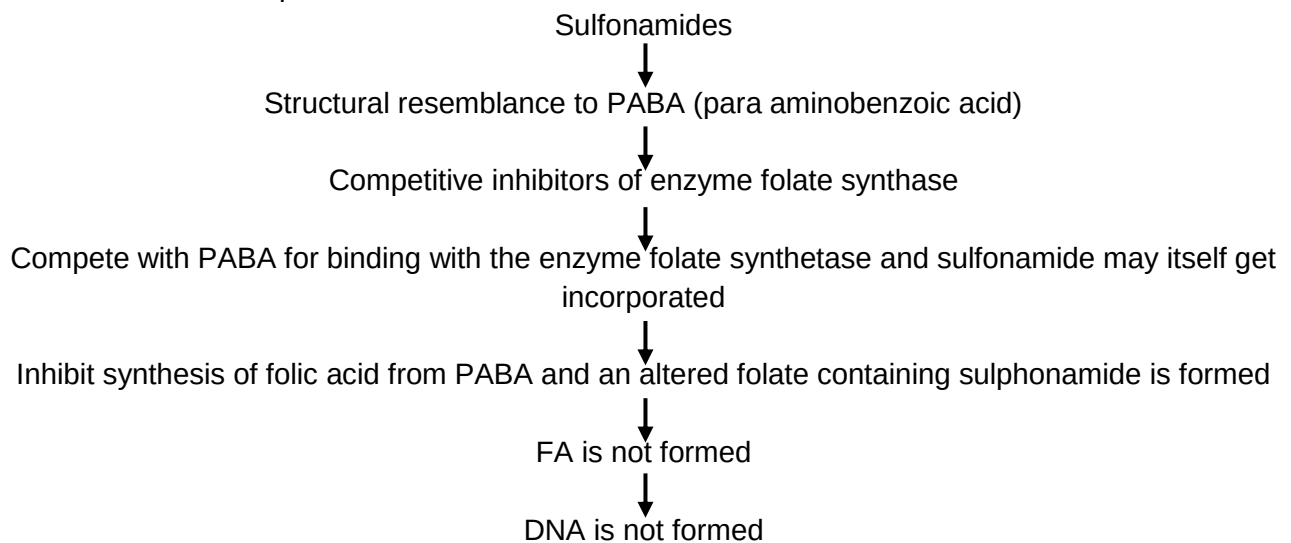
## Spectrum

- Sulfonamides are primarily bacteriostatic against many gram-positive and gram-negative bacteria

| More sensitive                                                                                                                                                                            | Less sensitive                                                                                                                                                                                                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Strepto. pyogenes</li> <li>Haemophilus influenzae</li> <li>H. ducreyi</li> <li>Calymmatobacterium granulomatis</li> <li>Vibrio cholerae</li> </ul> | <ul style="list-style-type: none"> <li>Staph. aureus</li> <li>Gonococci</li> <li>Meningococci</li> <li>Mneumococci</li> <li>Escherichia coli</li> <li>Shigella</li> <li>Chlamydiae</li> <li>Actinomyces</li> <li>Nocardia</li> <li>Toxoplasma</li> </ul> |

## MOA

- Many bacteria synthesize their own folic acid (FA) from p-aminobenzoic acid (PABA)
- PABA is taken up from medium.





## Resistance

1. Their folate synthase enzyme has low affinity for sulfonamides
2. Produce increased amounts of PABA
3. Adopt an alternative pathway in folate metabolism
  - When an organism is resistant to one sulfonamide → it is resistant to them all.
  - No cross resistance between sulfonamides and other AMAs has been noted.
  - Development of resistance limited clinical usefulness of Sulfonamides

## Adverse Effects

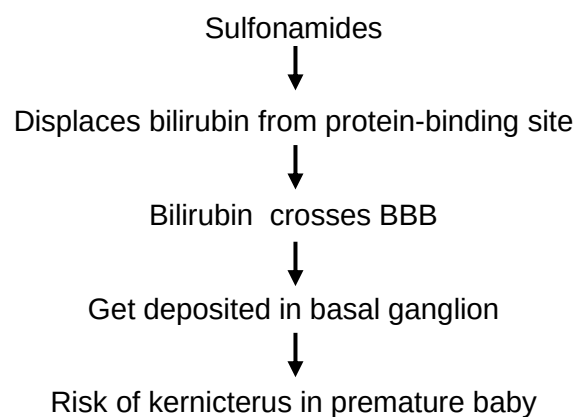
Mnemonic → **ABC HHH**

- **A** - **A**plastic anemia
- **B** - **B**ilirubin displacement (kernicterus)
- **C** - **C**rystalluria
- **H** - **H**epatitis
- **H** - **H**emolysis in G-6-PD deficiency
- **H** - **H**ypersensitivity (MC side effect)

### 1. Aplastic anemia

- Rare

### 2. Bilirubin displacement (kernicterus)



### 3. Crystalluria

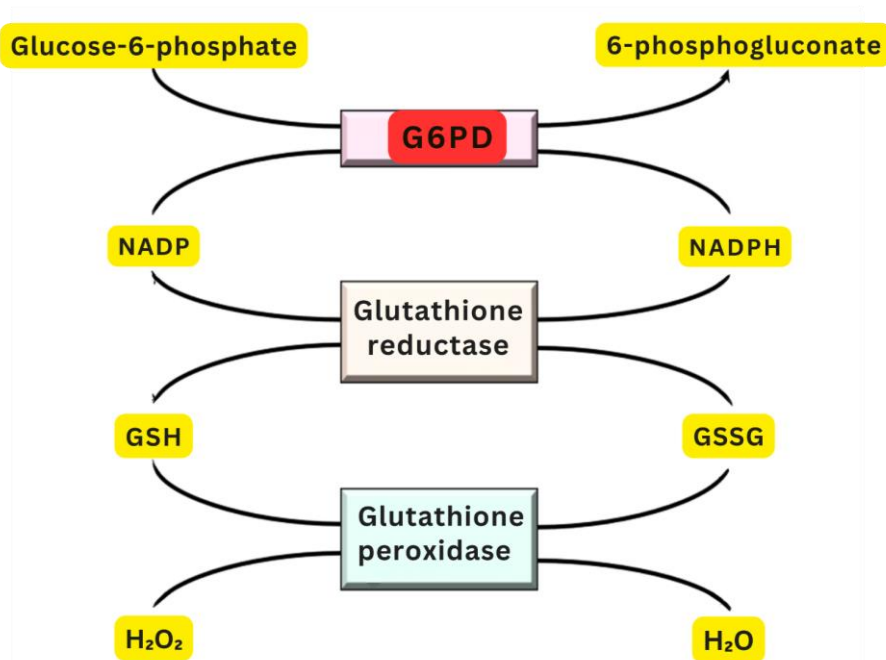
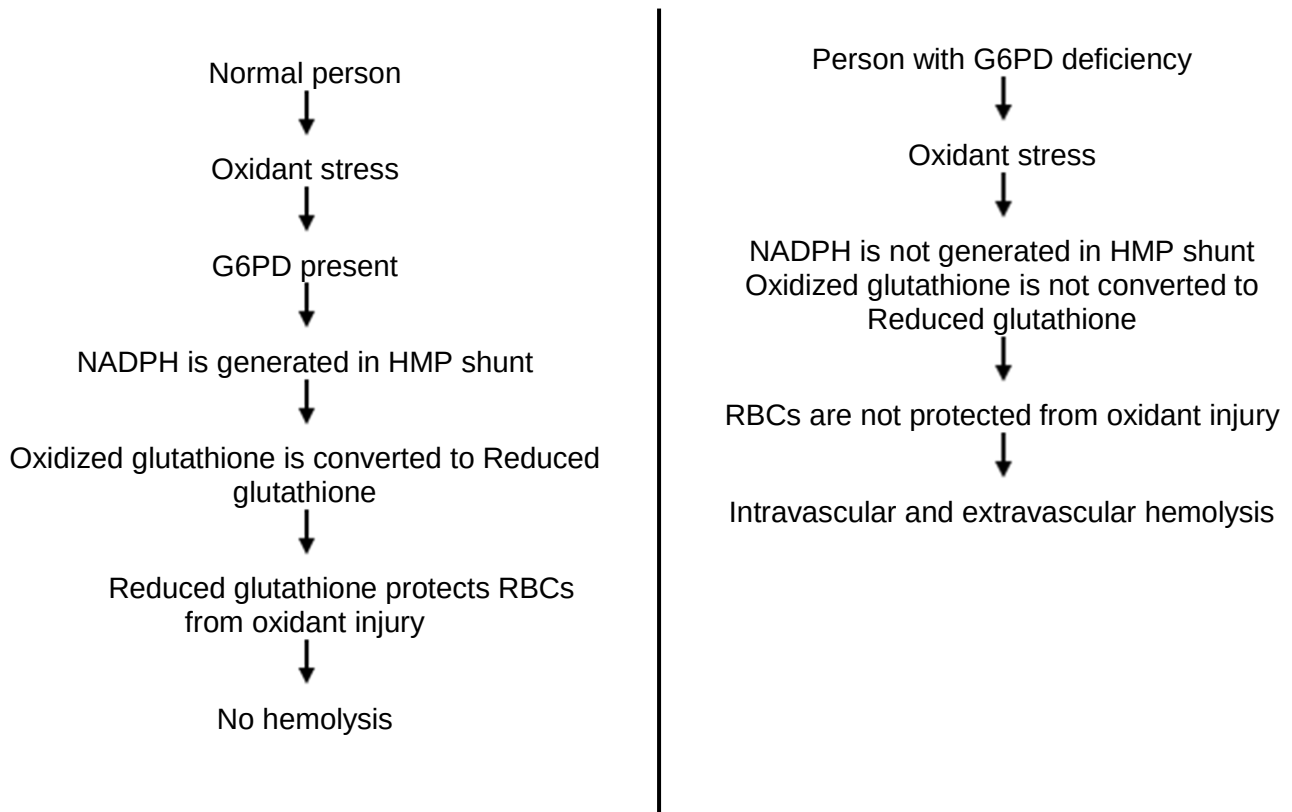
- Due to Precipitation in urine
- Precipitation in urine can be minimized by →
  - Taking plenty of fluids
  - Alkalinizing the urine in which sulfonamides and their acetylated derivatives are more soluble

### 4. Hepatitis

- Rare
- Unrelated to dose

## 5. Hemolysis in patients with G6PD deficiency

- Normally RBCs are protected from oxidant injury by reduced glutathione
- Reduced glutathione is generated from oxidized glutathione and reducing equivalent for this reaction is provided by NADPH.
- NADPH is generated in HMP shunt by enzyme Glucose-6-phosphate dehydrogenase
- Sulfonamide is a pro-oxidant drug.
- Other pro-oxidant drugs are aspirin, nitrofurantoin, primaquine, chloroquine, sulfortes, vitamin K3; etc.



## 6. Hypersensitivity reactions

- Sulfonamides have potential to produce almost all type of allergic reactions.
- **Mild reactions** →
  - Skin rashes
  - bronchospasm
  - Arthralgia
- **Severe life threatening reactions** →
  - Stevens-Johnson's syndrome (severe, potentially fatal form of erythema multiformis with fever, malaise, ulceration of mucous membrane of mouth and genitalia)
  - Toxic epidermal necrosis (TEN).

## Uses

- In combination with trimethoprim
- In combination with pyrimethamine

## In combination with trimethoprim

- **Mnemonic** → **SEPTRAN**
  - **S** - **S**TD's (Chancroid, LGV)
  - **E** - **E**nteritis (E.coli, Shigella)
  - **P** - **P**C , **P**J
  - **T** - **T**yphoid (Bacterial diarrhoeas and dysentery)
  - **R** - **R**TI
  - **A** - **A**cute uncomplicated UTI
  - **N** - **N**ocardia

## In combination with pyrimethamine

- **Mnemonic** → **MT**
  - **M** - Resistant **M**alaria
  - **T** - **T**oxoplasmosis

# TRIMETHOPRIM

## Introduction

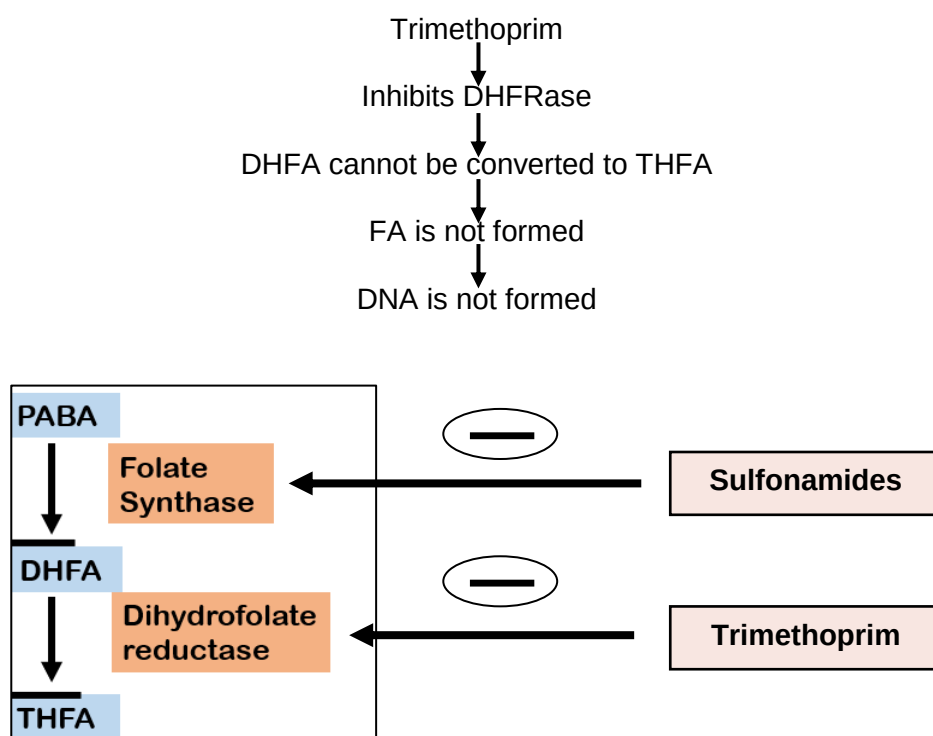
- Fixed dose combination of trimethoprim and sulfamethoxazole is called cotrimoxazole (SEPTRAN)
- It is a combination of sulfamethoxazole and trimethoprim in a ratio of 5:1 to provide a blood level in ratio of 20:1.
- This occurs because trimethoprim has a larger volume of distribution than Sulfamethoxazole and attains lower plasma concentration
- Sulfamethoxazole was selected for combining with trimethoprim because Both have nearly the same  $t_{1/2}$  (~ 10 hr)

## Spectrum

- Antibacterial spectra of trimethoprim and sulfonamides overlap considerably.
- Additional organisms covered by the combination □
  - *Salmonella typhi*
  - *Serratia*
  - *Klebsiella*
  - *Enterobacter*
  - *Yersinia enterocolitica*
  - *Pneumocystis jiroveci*
  - Sulfonamide-resistant strains of *Staph. aureus*, *Strep. pyogenes*, *Shigella*, enteropathogenic *E. coli*, *H. influenzae*, gonococci and meningococci.

## MOA

- Many bacteria synthesize their own folic acid (FA) from p-aminobenzoic acid (PABA)
- PABA is taken up from medium.



## Advantages of Combination

1. Combination is synergistic in nature, since the two different sequential steps are blocked by the combination of these two drugs.
2. Individual drug is bacteriostatic but the combination becomes Bacteriocidal
3. Bacteriocidal activity is due to sequential blockade at two steps in DNA synthesis (sulfamethoxazole inhibits folate synthase and trimethoprim inhibits DHFRase).
4. Resistance to combination has been slow to develop compared to either drug alone

## Resistance

- Bacteria are capable of acquiring resistance to trimethoprim mostly through plasmid mediated acquisition of a DHFRase having lower affinity for the inhibitor.
- Resistance to combination has been slow to develop compared to either drug alone

## Adverse Effects

Mnemonic → **Bus → New Mumbai To Kolkata**

- **B**us → **B**one marrow toxicity → Pancytopenia
- **N**ew → **N**ausea, vomiting
- **M**umbai → **M**egaloblastic Anemia → Due to folate deficiency
- **T**o → **T**eratogenic → Neonatal haemolysis, Methaemoglobinaemia
- **K**olkata → Hyper**K**alemia (due to amiloride like action, amiloride is a Potassium sparing diuretic).

## Uses

- In combination with trimethoprim

Mnemonic → **SEPTRAN**

- **S** - **S**TD's (Chancroid, LGV)
- **E** - **E**nteritis (E.coli, Shigella)
- **P** - **P**C, **P**J
- **T** - **T**yphoid (Bacterial diarrhoeas and dysentery)
- **R** - **R**TI
- **A** - **A**cute uncomplicated UTI
- **N** - **N**ocardia

## Remember

- **Trimethoprim** → crosses blood brain barrier and placenta, while sulfamethoxazole has poor entry.
- **Trimethoprim** → more rapidly absorbed than Sulfamethoxazole (It does not affect absorption of Sulphamethoxazole)
- **Trimethoprim** → 40 % plasma protein bound, Sulphamethoxazole is 60% plasma protein bound.

# QUINOLONES

## Introduction

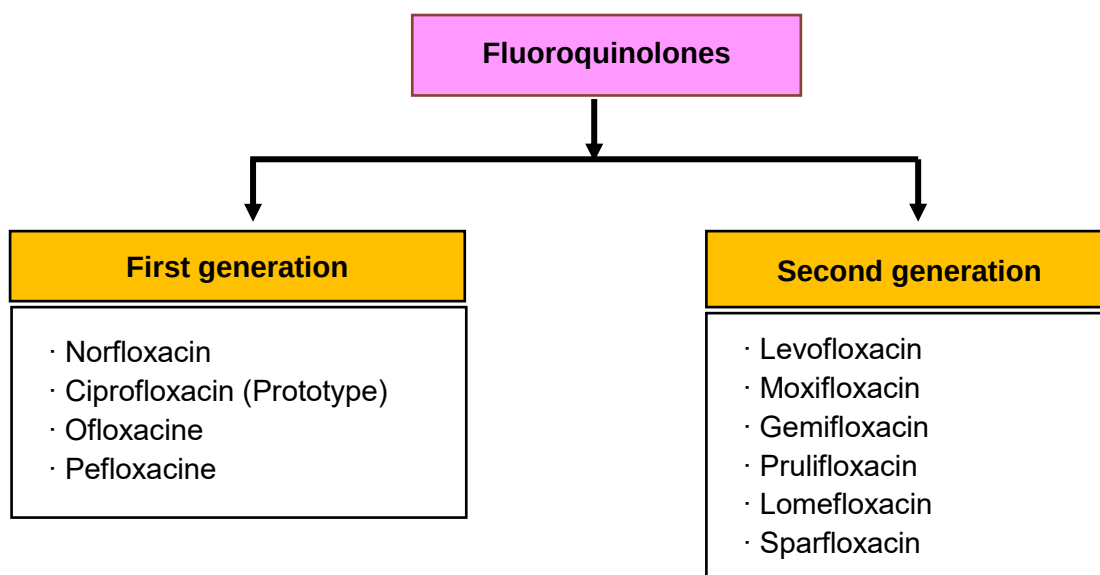
- Synthetic antimicrobials having a quinolone structure
- First member → Nalidixic acid



- A breakthrough was achieved by fluorination of quinolone structure at position 6 and introduction of a piperazine substitution at position 7 resulting in derivatives called fluoroquinolones
- Fluoroquinolones are quinolone antimicrobials having one or more fluorine substitutions
- Fluoroquinolones have
  1. High potency
  2. Expanded spectrum
  3. Slow development of resistance
  4. Better tissue penetration and good tolerability



## Classification

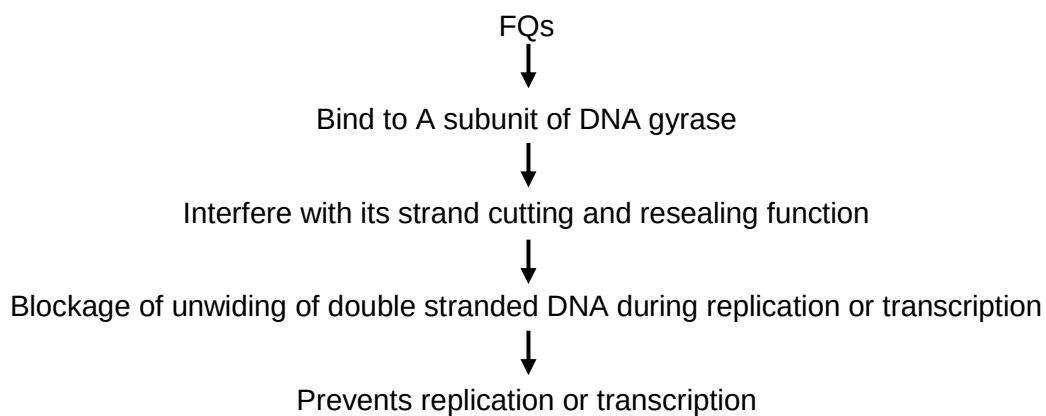
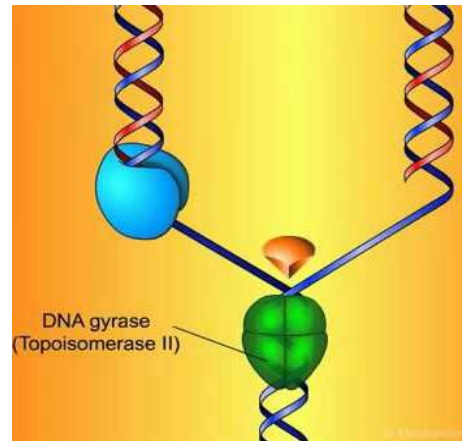
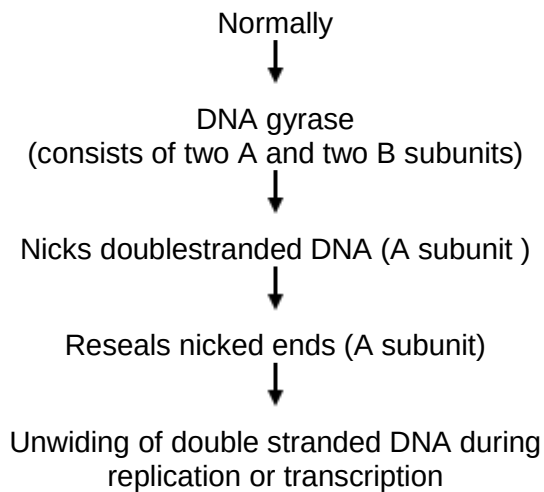


## Spectrum

- **Nalidixic acid** → Narrow spectrum → Gram-negative activity especially coliforms: E. coli, Proteus, Klebsiella, Enterobacter, Shigella
- **First generation** → Narrow spectrum → Gram negative activity with limited or no activity on gram positive.
- **Second generation** → Broad spectrum → Gram negative, Gram positive, Anaerobic activity

## MOA

- FQs inhibit →
  - **Bacterial DNA gyrase** → in gram negative bacteria
  - **Topoisomerase IV** → in gram positive bacteria



- In place of DNA gyrase or topoisomerase IV, the mammalian cells possess an enzyme topoisomerase II (that also removes positive supercoils)
- FQs has very low affinity for topoisomerase II → hence the low toxicity to host cells

## Resistance

1. Due to chromosomal mutation producing a DNA gyrase or topoisomerase IV with reduced affinity for FQs
2. Due to reduced permeability/increased efflux of these drugs across bacterial membranes

## Pharmacokinetics

- **Ciprofloxacin** →
  - Rapidly absorbed orally, but food delays absorption.
  - High tissue penetrability → concentration in lung, sputum, muscle, bone, prostate and phagocytes exceeds that in plasma; but CSF and aqueous levels are lower.
  - Less active at acidic pH

## Adverse effects

### 1. GIT

- Most common
- Nausea, vomiting,
- Abdominal disturbances, Diarrhea.

## 2. CNS

- Due to GABA antagonistic action.)
- Headaches, dizziness, sleep disorders, mood changes and seizures.
- Inhibit binding of GABA to receptors so may precipitate seizures.

## 3. Bone, soft tissue

- There may be tendonitis with risk of tendon rupture
- Contraindicated in children.

## 4. Phototoxicity → by lomefloxacin (maximum), sparfloxacin and pefloxacin

## 5. prolong QT interval (Torsades de pointes) → Sparfloxacin, gatifloxacin and moxifloxacin can

## 6. Teratogenicity → contraindicated in pregnancy

## Uses

### Mnemonic → 4G SPECTRUM CT

- **4G** : **G**onorrhoea, **G**astroenteritis, **G**ynaecological infections, **G**ram -ve Infections
- **S** : **S**epsis
- **P** : **P**rophylaxis
- **E** : **E**nterocolitis
- **C** : **C**hancroid
- **T** : **T**yphoid
- **R** : **R**TI
- **U** : **U**TI
- **M** : **M**eningitis
- **C** : **C**onjunctivitis
- **T** : **T**uberculosis

## Remember

- Most potent first generation → **Ciprofloxacin**
- Least potent FQ → **Norfloxacin**
- Highest oral bioavailability (~ 100%) → **Levofloxacin**
- Least oral bioavailability → **Norfloxacin**
- Highest incidence of phototoxicity → **Lomefloxacin > Sparfloxacin > Pefloxacin**
- Maximum plasma protein binding → **Sparfloxacin**
- Highest first pass metabolism → **Pefloxacin**
- Longest acting FQ → **Sparfloxacin**
- Attains high CSF concentration → **Preferred for meningeal infections → Pefloxacin**
- Most potent FQ against tuberculosis → **Moxifloxacin**
- Unique amongst FQs in that it has strong activity against gram (+)ve bacteria → **Moxifloxacin**
- FQs does not require dose reduction in renal pathology → **trovafloxacin, pefloxacin, moxifloxacin and grepofloxacin.**
- Fluoroquinolones that are primarily excreted by kidney and require dose adjustment in renal failure → **ciprofloxacin, lomefloxacin, ofloxacin, gatifloxacin, cinafloxacin, levofloxacin, and norfloxacin.**

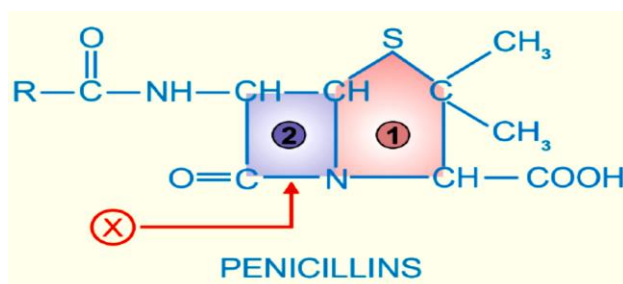


- **Sparfloxacin** → 50% renal and 50% fecal excretion
- Following FQs have been withdrawn from the market because of their rare but potentially fatal side effects →
  - **Temafloxacin** → Immune hemolytic anemia
  - **Grepafloxacin** → Cardiotoxicity
  - **Trovafloxacin** → Hepatotoxicity
  - **Clinafloxacin** → Phototoxicity
  - **Gatifloxacin** → recently been banned in India because of risk of severe hyperglycemia in elderly

## BETA LACTAMS

### Introduction

- These are antibiotics having a  $\beta$ -lactam ring



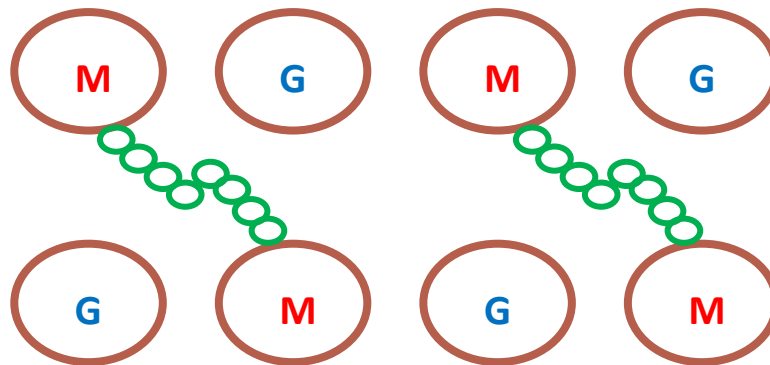
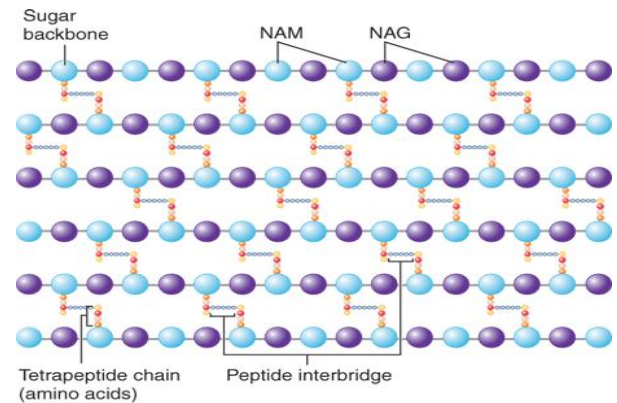
### Classification

1. Penicillins
2. Cephalosporins
3. Monobactam
4. Carbapenems

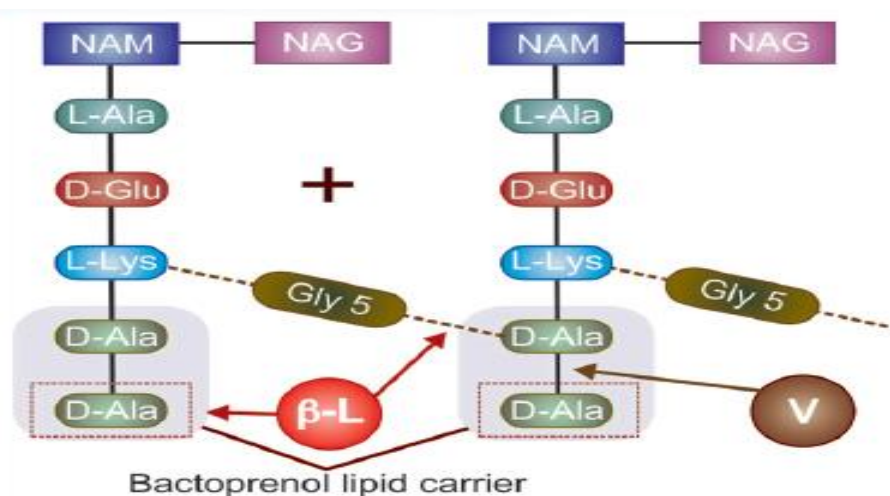
|                  | Penicillin | Cephalosporin | Monobactam | Carbapenam |
|------------------|------------|---------------|------------|------------|
| MOA              |            |               |            |            |
| Resistance       |            |               |            |            |
| Introduction     |            |               |            |            |
| Classification   |            |               |            |            |
| Pharmacokinetics |            |               |            |            |
| Spectrum         |            |               |            |            |
| Adverse effects  |            |               |            |            |
| Uses             |            |               |            |            |

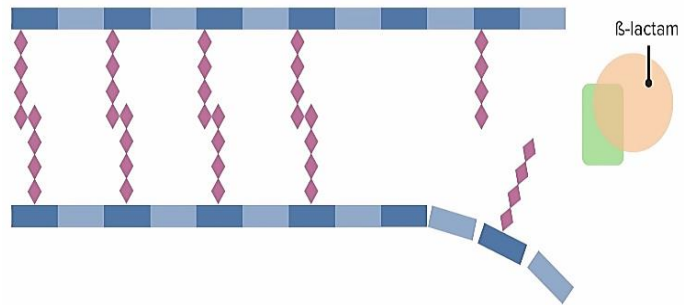
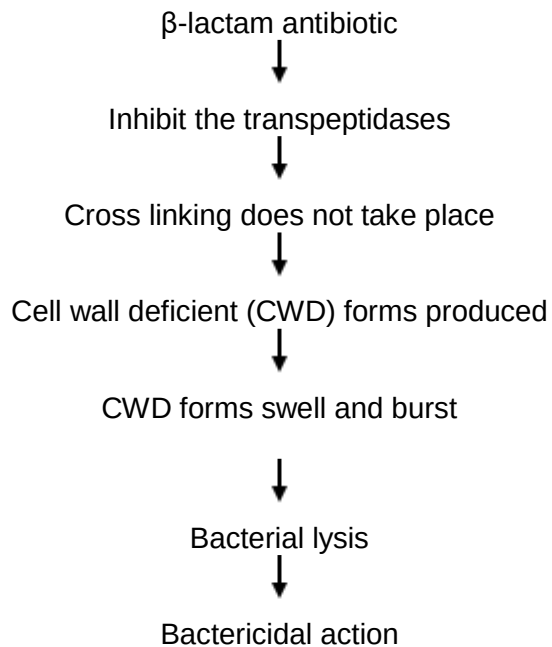
## MOA

- Interfere with synthesis of bacterial cell wall
- Cell wall consist of→
- Peptidoglycan → Polymer of →
  - UDP-N-acetylmuramic acid (NAM)→ pentapeptide
  - UDP-N-acetyl glucosamine (NAG)



Normally  
 ↓  
 UDP- NAM and UDP- NAG  
 ↓  
 Peptidoglycan residues linked together forming long strands and UDP is split off  
 ↓  
 Final step is cleavage of terminal D-alanine of peptide chains by transpeptidases  
 ↓  
 Energy so released is utilized for establishment of cross linkages  
 ↓  
 This cross linking provides stability and rigidity to cell wall



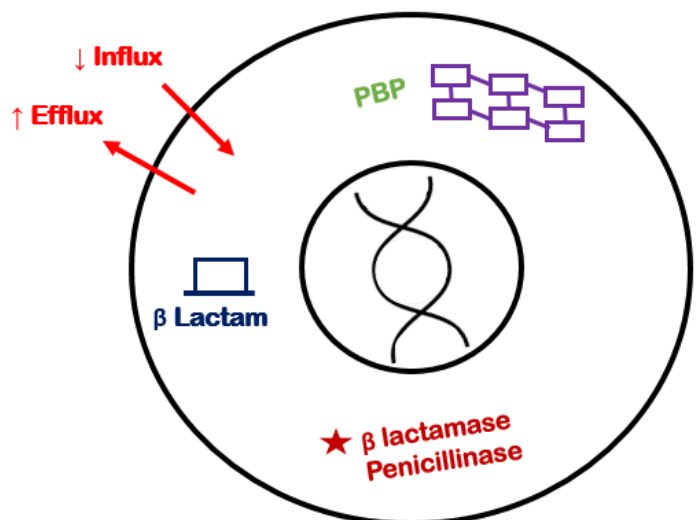


- Bactericidal
- Active against multiplying organisms only
- Penicillin → higher susceptibility for gram-positive bacteria
  1. In gram-positive bacteria □ cell wall consists of thick layer of peptidoglycan and extensively cross linked
  2. In gram-negative bacteria □ cell wall consists of thin layer of peptidoglycan with little cross linking
- Peptidoglycan cell wall is unique to bacteria.
- No such substance is synthesized (particularly, D-alanine is not utilized) by higher animals.
- This is why penicillin is nontoxic to man

## Resistance

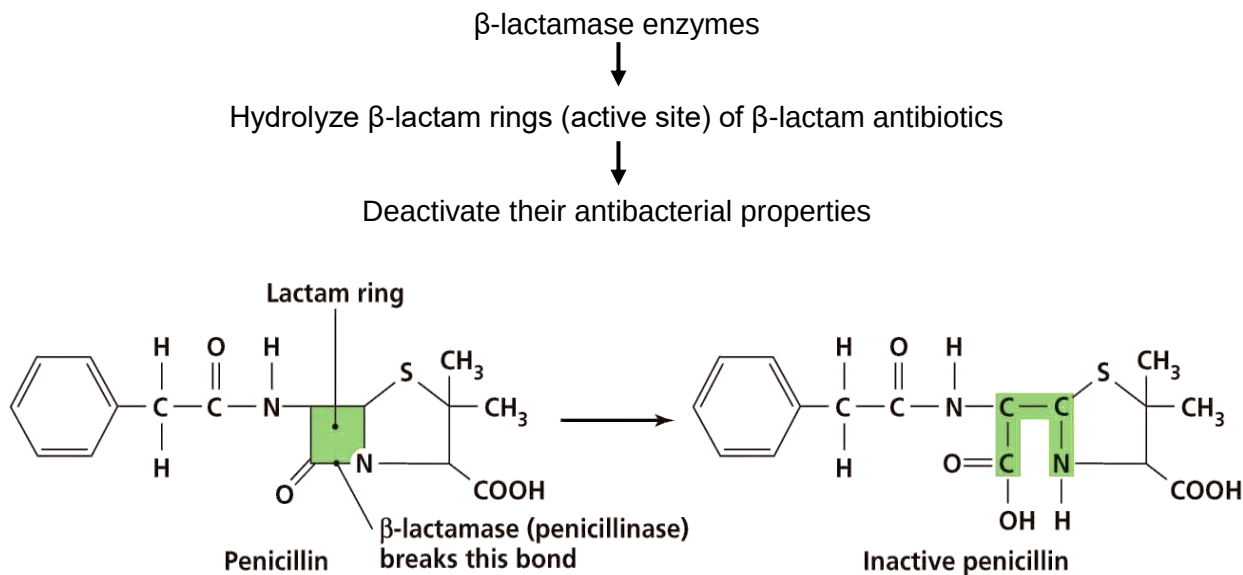
### 4. Mechanisms →

1. **Decrease Influx** → Decreased Permeability across the Cell Wall → by modifying their cell membrane porin channels
2. **Increased Efflux** → Efflux Pumps → expulsion of the drugs from the cell, soon after their entry → preventing intracellular accumulation of drugs



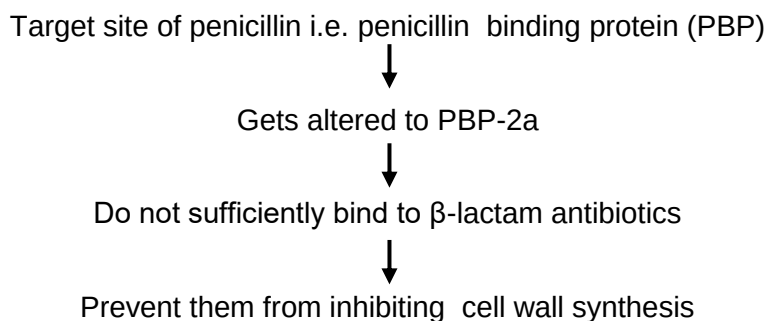
### 3. By Enzymatic Inactivation → Eg . $\beta$ -lactamase, penicillinase

Most common mechanism



- a) Plasmid encoded beta lactamase (produced by E.coli and gonococci)
- b) Chromosomal encoded beta lactamase (produced by pseudomonas and enterobacter)

### 4. Altered PBPs → that lacks the binding affinity for penicillin → MRSA



### Remember

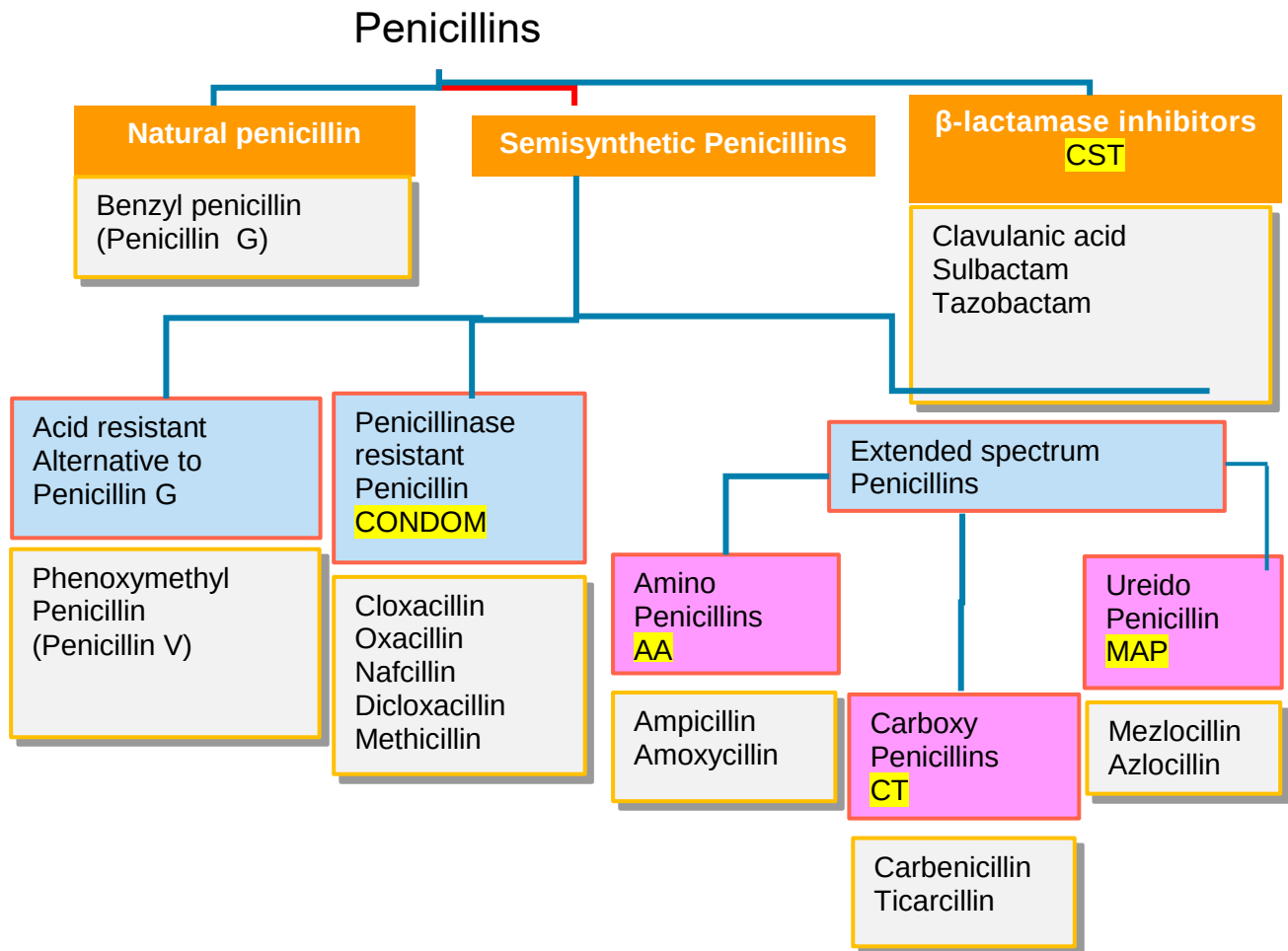
- **In gram-positive bacteria**
  - Penicillinase is found in large quantity
  - Penicillinase is inducible
  - Methicillin is an important inducer
- **In gram-negative bacteria**
  - Penicillinase is found in small quantity
  - Penicillinase is mostly a constitutive enzyme.

## PENICILLINS

### Introduction

- Penicillin was first antibiotic to be used.
- Credit for discovery of penicillin goes to Alexander Fleming
- Natural penicillin is obtained from a fungus □ *Penicillium notatum* and *Penicillium chrysogenum*.

## Classification



|                  | Natural | Semisynthetic  |                         |                   | β Lactamase Inhibitors |
|------------------|---------|----------------|-------------------------|-------------------|------------------------|
|                  |         | Acid Resistant | Penicillinase Resistant | Extended spectrum |                        |
| Drugs            |         |                |                         |                   |                        |
| Introduction     |         |                |                         |                   |                        |
| Pharmacokinetics |         |                |                         |                   |                        |
| Spectrum         |         |                |                         |                   |                        |
| Adverse effects  |         |                |                         |                   |                        |
| USES             |         |                |                         |                   |                        |

## NATURAL PENICILLIN

### Drugs

- Benzyl penicillin (Penicillin G)

### Introduction

- Limitations in its clinical use→
  1. **Not effective orally** → because of breakdown by acid in stomach
  2. **Susceptibility to penicillinase** → Penicillinase hydrolyze  $\beta$ -lactam rings (active site)→ Deactivate their antibacterial properties
  3. **Narrow spectrum of activity** → covering mainly gram positive bacteria.

### Pharmacokinetics

- Absorption of sod. PnG from i.m. site is rapid and complete
- Peak plasma level is attained in 30 min.
- About 60% is plasma protein bound.
- Plasma  $t_{1/2}$  of PnG in healthy adult  $\square$  30 min

### Spectrum

- PnG is a narrow spectrum antibiotic → activity is limited primarily to gram-positive bacteria

### Adverse effects

Mnemonic → **HIJ**

1. **H**ypersensitivity reactions
2. Local **I**rritancy
3. **J**arisch-Herxheimer reaction

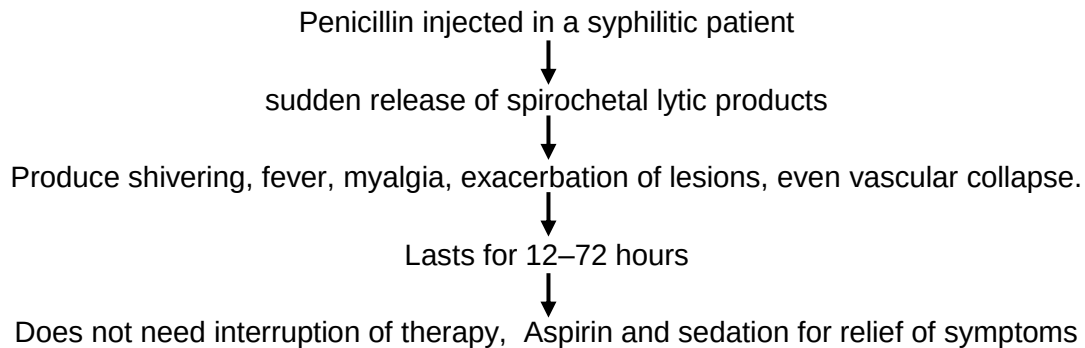
### 1. Hypersensitivity reactions

- **PnG** →
  - Most common drug implicated in drug allergy, because of which it has practically vanished from use in general practice.
  - Most common drugs responsible for anaphylactic shock.
    - Frequent manifestations of penicillin allergy  $\square$  rash, itching, urticaria and fever.
    - Anaphylaxis is rare (1 to 4 per 10,000 patients), but may be fatal
    - If a person is severely allergic to any penicillin, no  $\beta$  - lactam (except monobactams) should be administered to that person.
    - Intra-dermal skin testing can be used to prevent severe allergic reactions.
    - If a patient is allergic to penicillin, it is best to use an alternative antibiotic.
    - Hyposensitization by the injection of increasing amounts of penicillin intradermally at hourly intervals may be tried only if there is no other choice

## 2. Local irritancy

- Pain at IM injection site
- Nausea on oral ingestion
- Thrombophlebitis of injected vein are dose related expressions of irritancy.
- Intrathecal injection of PnG is no longer recommended because it has caused arachnoiditis and degenerative changes in spinal cord.

## 3. Jarisch-Herxheimer reaction



## Uses

- A. Theuraptic Uses
- B. Prophylactic uses

### A. Theuraptic Uses

- **Mnemonic → LAST MAN DP**
  - **L** - **L**eptospira
  - **A** - **A**ctinomyces
  - **S** - **S**treptococcus, **S**taphylococcus (non-penicillinase-producing)
  - **T** - **T**reponema, **T**etanus
  - **M** - **M**eningococcus
  - **AN** - **A**nthrax, **A**ctinomycosis
  - **D** - **D**iphtheria
  - **P** - **P**neumococcus

### B. Prophylactic uses

**Mnemonic → RAB**

1. **R**heumatic fever → Benzathine penicillin 1.2 MU every 4 weeks till 18 years of age or 5 years after an attack, whichever is more
2. **A**granulocytosis patients → Dental extractions, endoscopies, catheterization, etc. cause bacteremia which in patients with valvular defects can cause endocarditis.
3. **B**acterial endocarditis → Dental extractions, endoscopies, catheterization, etc. cause bacteremia which in patients with valvular defects can cause endocarditis.

## SEMISYNTHETIC PENICILLINS

### Aim

- To overcome the shortcomings of PnG
  1. Poor oral efficacy due to acid susceptibility
  2. Susceptibility to penicillinase.
  3. Narrow spectrum of activity

### Types

**3 Types** →

1. Acid resistant Alternative to Penicillin G
2. Penicillinase resistant Penicillin
3. Extended spectrum Penicillins

## ACID RESISTANT ALTERNATIVE TO PENICILLIN

### Drugs

- Phenoxyethyl Penicillin (Penicillin V)

### Introduction

- It differs from PnG only in that it is acid stable.

### Remember

- Acid-resistant penicillins → **Mnemonic** → **VODKA**
  - **V** - Penicillin V
  - **O** - Oxacillin
  - **D** - Dicloxacillin
  - **K** - Cloxacillin
  - **A** - Amoxycillin and Ampicillin

### Pharmacokinetics

- Oral absorption is better
- Peak blood level is reached in 1 hour
- Plasma  $t_{1/2}$  is 30–60 min.

### Spectrum

- The antibacterial spectrum of penicillin V is identical to PnG, but it is about 1/5 as active against Neisseria, other gram negative bacteria and anaerobes

### Adverse effects

- Same as that of Natural Penicillin
- Mnemonic → **HIJ**
  1. **H**ypersensitivity reactions



2. Local Irritancy
3. Jarisch-Herxheimer reaction

## Uses

- It cannot be depended upon for more serious infections
- It is used only for →
- Mnemonic → **OP<sub>2</sub>RS**
  - Otitis media
  - Pharyngitis (Streptococcal)
  - Pneumococcal infections (less serious)
  - Rheumatic fever Prophylaxis
  - Sinusitis

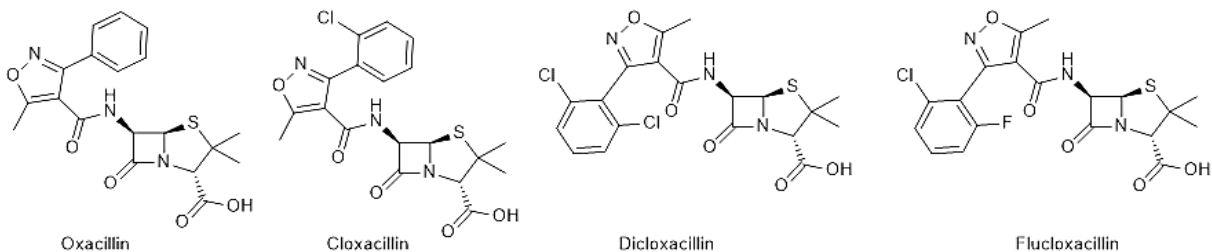
## PENICILLINASE RESISTANT PENICILLIN

### Drugs

- Mnemonic → **CONDM**
  - Cloxacillin
  - Oxacillin
  - Nafcillin
  - Dicloxacillin
  - Methicillin

### Introduction

- Have side chains that protect the  $\beta$ -lactam ring from attack by penicillinase



### Methicillin

- Highly penicillinase resistant ie. resistant to  $\beta$ -lactamases
- But it is not acid resistant → must be injected

### MRSA

- MRSA have emerged in many areas.
- MRSA have altered PBPs which do not bind penicillins.
- These are insensitive to all penicillinase-resistant penicillins
- All MRSA → multidrug resistance
- DOC → vancomycin, linezolid and teichoplanin

## Spectrum

- Penicillinase producing Staphylococci except MRSA

## Adverse effects

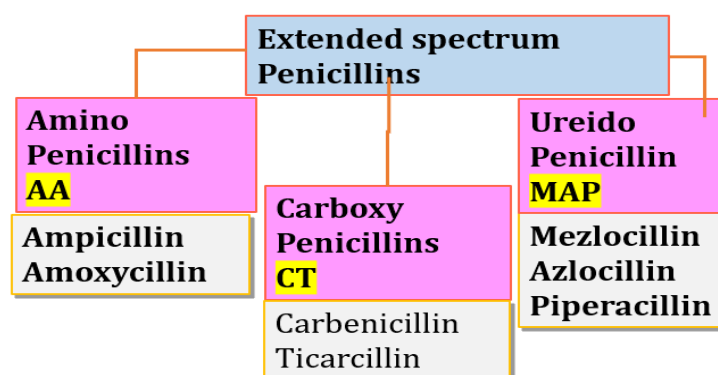
- **Mnemonic** → **HAI**
  1. **H**aematuria
  2. **A**lbuminuria
  3. **I**nterstitial nephritis (Reversible)

## Uses

- DOC → Penicillinase producing Staphylococci except MRSA

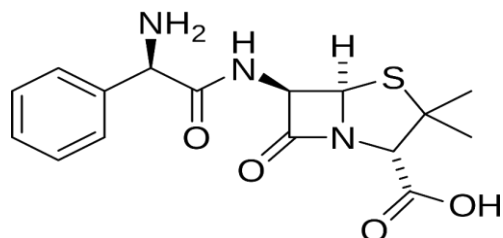
## EXTENDED SPECTRUM PENICILLINS

### Drugs



### 1. Aminopenicillins

- This group has an amino substitution in side chain
- Ampicillin is prototype →
  - Acid stable
  - Not resistant to penicillinase or  $\beta$ -lactamases



### Spectrum

- It is active against all organisms sensitive to PnG.
- In addition, many gram-negative bacilli → e.g. H. influenzae, E. coli, Proteus, Salmonella, Shigella and Helicobacter pylori are inhibited.

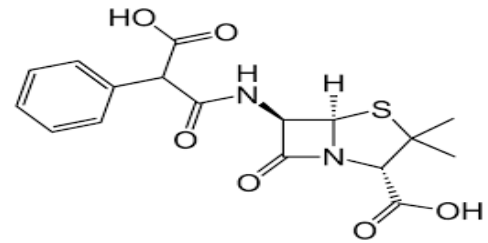
### Adverse effects

1. **Diarrhoea** → after oral administration. Ampicillin is incompletely absorbed → unabsorbed drug irritates the lower intestines as well as causes marked alteration of bacterial flora

2. **Rashes and hypersensitivity** → produces a high incidence of rashes, especially in patients with AIDS, EB virus infections or lymphatic leukaemia.

## 2. Carboxypenicillins

- This group has an carboxy substitution in the side chain
- Carbenicillin is prototype →
  - It is not acid resistant (inactive orally)
  - It is not penicillinase-resistant



### Spectrum

- Active against *Pseudomonas aeruginosa* and *Proteus* which are not inhibited by PnG or aminopenicillins.

### Adverse effects

1. High doses causes bleeding by interfering with platelet function.
2. Used as sodium salt → At higher doses, enough Na may be administered to cause fluid retention and CHF in patients with borderline renal or cardiac function

## 3. Ureidopenicillins

- Piperacillin is prototype

### Spectrum

- 8 times more active for *pseudomonas* than carbenicillin.
- Activity against *Klebsiella*, many *Enterobacteriaceae* and some *Bacteroides*.

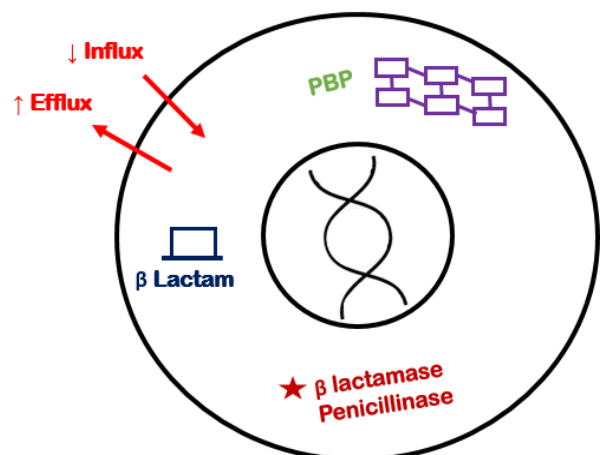
## β LACTAMASE INHIBITORS

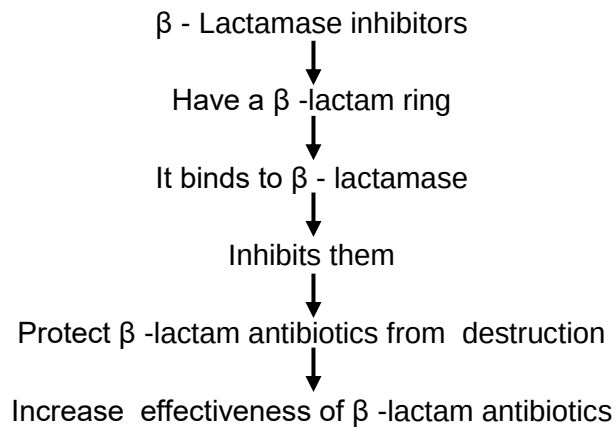
### Drugs

1. Clavulanic acid (combined with amoxicillin)
2. Sulbactam (combined with ampicillin)
3. Tazobactam (combined with piperacillin)

### MOA

β-lactamase enzyme produced by various organisms  
 ↓  
 Hydrolysis of β-lactam ring of penicillins (β-lactam antibiotics)  
 ↓  
 Reduces their effectiveness





## Remember

- β-lactamase inhibitors themselves are not antibacterial
- But augment the activity of penicillins against β-lactamase producing organisms

## Clavulanic acid

- Obtained from *Streptomyces clavuligerus*
- Has a β-lactam ring but no antibacterial activity of its own.
- Inhibits a wide variety (class II to class V) of β-lactamases (but not class I cephalosporinase) produced by both gram-positive and gram-negative bacteria
- These drugs are more active against plasmid encoded beta lactamase (produced by *E.coli* and gonococci) than chromosomal encoded beta lactamase (produced by *pseudomonas* and *enterobacter*).
- Clavulanic acid is a 'progressive' inhibitor → binding with β-lactamase is reversible initially, but becomes covalent later → inhibition increasing with time.
- Called a 'suicide' inhibitor → it gets inactivated after binding to the enzyme.
- Clavulanic acid + amoxicillin = Coamoxiclav (AUGMENTIN)

## Uses

- Clavulanic acid (combined with amoxicillin) □
  - Skin and soft tissue infections
  - Intra-abdominal sepsis
  - Gynaecological sepsis
  - Hospital acquired infections
  - PPNG Gonorrhoea
  - Urinary, biliary infections
  - Respiratory tract infections

## Sulbactam

- Semisynthetic β-lactamase inhibitor
- Also a progressive inhibitor
- Highly active against class II to V but poorly active against class I β-lactamase.
- Does not inhibit chromosomal β-lactamases, while clavulanic acid can inhibit some of them.
- Oral absorption of sulbactam is inconsistent □ preferably given parenterally.
- It has been combined with ampicillin for use against β-lactamase producing resistant strains

## Uses

- Sulbactam (combined with ampicillin) →
  - Skin and soft tissue infections
  - Intra-abdominal sepsis
  - Gynaecological sepsis
  - Hospital acquired infections
  - PPNG Gonorrhoea
  - Mixed aerobic-anaerobic infections

## Tazobactam

- Its pharmacokinetics matches with piperacillin with which it has been combined
- It does not inhibit inducible chromosomal  $\beta$ -lactamase produced by Enterobacteriaceae.

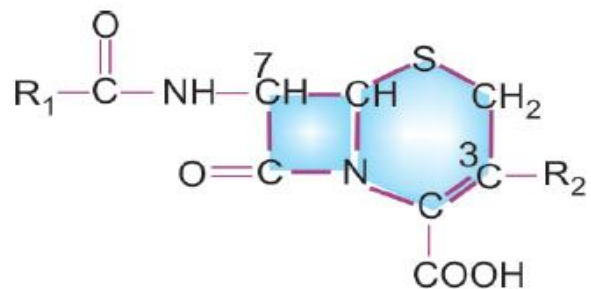
## Uses

- Tazobactam (combined with piperacillin) →
  - Severe infections like peritonitis
  - Pelvic / Urinary / Respiratory infections caused by  $\beta$ -lactamase producing bacilli.

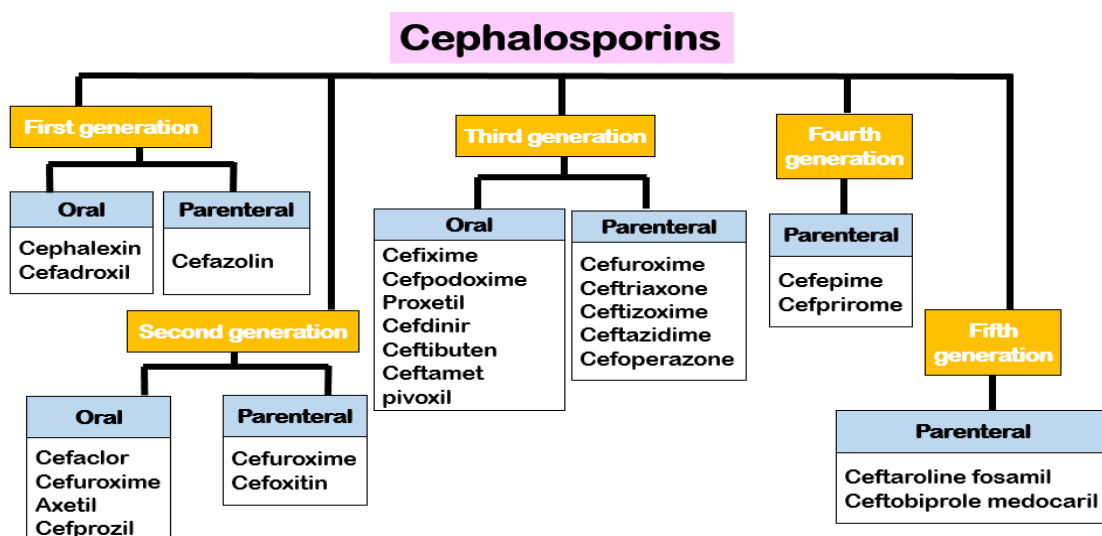
# CEPHALOSPORINS

## Introduction

- Cephalosporins are  $\beta$  lactam
- Bactericidal antibiotics
- Obtained from a fungus Cephalosporium
- Consists of a  $\beta$ -lactam ring fused to a dihydrothiazine ring, (7-aminocephalosporanic acid).
- By addition of different side chains at →
  1. Position 7 of  $\beta$ -lactam ring (altering spectrum of activity)
  2. Position 3 of dihydrothiazine ring (affecting pharmacokinetics)



## Classification



| 1st Generation<br>"FA/PHA"                                                           | 2nd Generation<br>"Everything<br>Else"                                                   | 3rd Generation<br>"ONE/TEN/IME"                                                                   | 4th<br>Generation<br>"PI" | 5th Generation<br>"ROL"         |
|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------|---------------------------------|
| CEFAZOLIN<br>CEFADROXIL<br>CEPHALEXIN<br><br>CEPHALOTHIN<br>CEPHAPIRIN<br>CEPHRADINE | CEFOXITIN<br>CEFOTETAN<br>CEFMETAZOLE<br>CEFPROZIL<br><br><br><br>CEFACLOR<br>CEFUROXIME | CEFTRIAZONE<br>CEFTIBUTEN<br>CEFOTAXIME<br>CEFTAZIDIME<br>CEFPODOXIME<br>CEFIXIME<br><br>CEFDINIR | CEFEPIME<br><br>CEFPIROME | CEFTAROLINE<br><br>CEFTOBIPROLE |

## Spectrum

| Generation | Gram Negatives | Gram Positives | $\beta$ -Lactamase<br>Stability |
|------------|----------------|----------------|---------------------------------|
| 1st        | +              | +++            | +/-                             |
| 2nd        | ++             | ++             | +                               |
| 3rd        | +++            | +              | ++                              |
| 4th        | +++            | ++             | ++                              |
| 5th        | +++            | +++            | ++++                            |

## Adverse effects

- Mnemonic → **DDT HAPeNS**

- D** – **D**iarrhea
- D** – **D**isulfiram like reaction with alcohol
- T** – **T**hrombophlebitis , Thrombocytopenia (bleeding)
- H** – **H**ypoprothrombinemia → bleeding
- A** – **A**llergy (hypersensitivity)
- P** – **P**ain (severe with i.m.)
- N** – **N**ephrotoxicity, Neutropenia
- S** – **S**uper infections with fungi

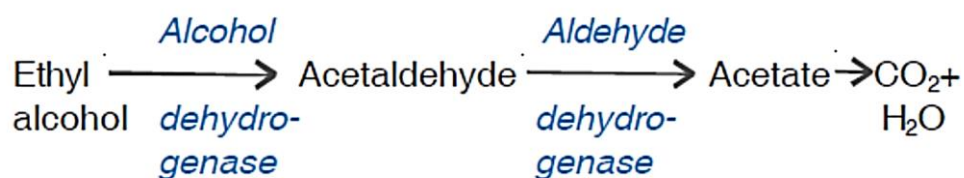
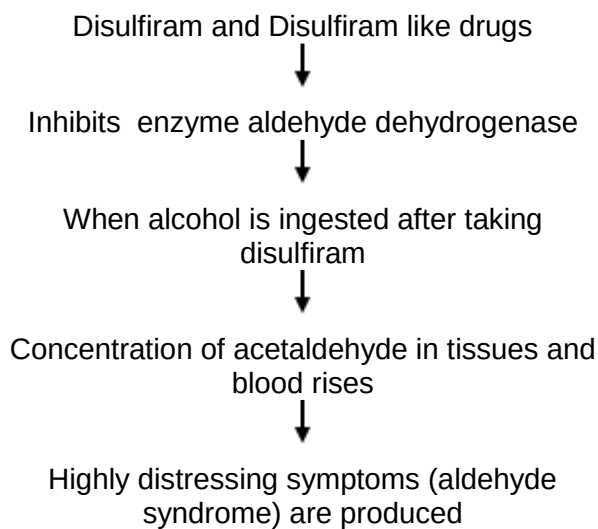
## 1. Diarrhoea

- Due to alteration of gut ecology or irritative effect
- More common with orally administered compounds like cephalexin, cefixime and parenteral cefoperazone, which is largely excreted in bile.



## 2. Disulfiram-like interaction

- A disulfiram-like interaction with alcohol has been reported with cefoperazone.
- Cefamandole, cefoperazone, moxalactam and cefotetan can cause disulfiram like reaction with alcohol.



## Drugs Causing Disulfiram Like Reaction

- **Mnemonic → Sorry Pluto Can't Go to Mars**
  - **S**orry - **S**ulfonyleureas (1st generation - like chlorpropamide)
  - **P**luto - **P**rocarbazine (Anticancer drugs)
  - **C**an't - **C**ephalosporins (Cefotetan, Cefoperazone)
  - **G**o - **G**riseofulvin
  - **M**ars - **M**etronidazole

### 3. Bleeding

- Occurs with cephalosporins having a methylthiotetrazole or similar substitution at position 3 (cefoperazone, ceftriaxone).
  - Ceftriaxone
  - Cefoperazone
  - Moxalactam
  - Cefamandole
- This is due to hypoprothrombinaemia caused by the same mechanism as warfarin and is more common in patients with cancer, intra-abdominal infection or renal failure

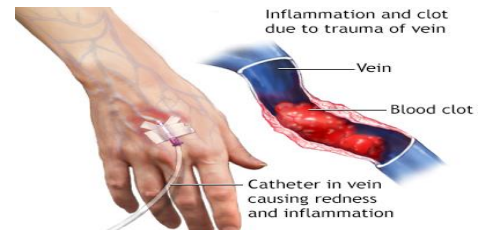


### 4. Hypersensitivity reactions

- Most common side effect.
- Cross allergy between penicillins and cephalosporine in 5-10% of cases.

### 5. Pain

- After IM injection occurs with many cephalosporins
- Thrombophlebitis of injected vein can occur.



### 6. Nephrotoxicity

- Highest with cephaloridine
- Increased by concurrent use of a loop diuretics
- Safe in renal failure → as these are excreted primarily in bile.
  - Cefoperazone
  - Ceftriaxone
  - Cefoperamide



### 7. Neutropenia and thrombocytopenia

- Caused by ceftazidim

### 8. Superinfection

- Most common organisms are Candida and pseudomonas
- Less common are staphylococci, proteus.

### Uses

- DOC in →**
  - Surgical prophylaxis: Cefazolin
  - Melioidosis (Burkholderia pseudomalleri): Ceftazidime
  - Gonorrhea, salmonellosis (including typhoid), E. coli sepsis, Proteus, Serratia, Haemophilus and empirical therapy for bacterial meningitis: Ceftriaxone



4. Pseudomonal CNS infection: Ceftazidime or Cefepime or Meropenem (For GU and GI infections – Fluoroquinolones and Aminoglycosides)
5. Bacteroides → Metronidazole (Cefoxitin is an alternative along with clindamycin and chloramphenicol)

### Remember

- **Most cephalosporine** → excreted by kidney mainly by tubular secretion
- **Ceftriaxone and cefoperazone** → excreted mainly in bile
- **Ceftriaxone** → achieves high concentration in bile and, as the calcium salt, may precipitate to cause symptoms resembling cholelithiasis (Biliary pseudolithiasis).

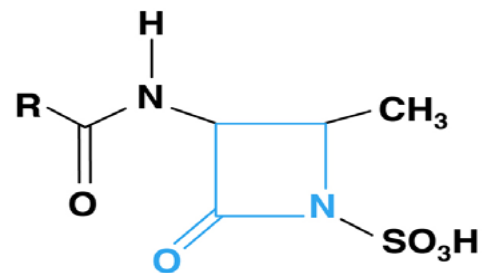
## MONOBACTAM

### Classification

- Aztreonam

### Introduction

- Aztreonam
  - Novel  $\beta$ -lactam antibiotic in which other ring is missing (hence monobactam)
  - Resistant to gram-negative  $\beta$ -lactamases.
  - Lack of cross sensitivity with other  $\beta$ -lactam antibiotics except ceftazidime
  - Only beta lactam antibiotic that can be used in patients having severe allergy to penicillins or cephalosporins (as it is not cross allergenic).



### Spectrum

- Active against  $\beta$ -lactamase producing gram negative bacilli including pseudomonas
- No activity against gram positive organisms or anaerobes
- So it is a  $\beta$ -lactam antibiotic with a spectrum resembling aminoglycosides

### Adverse effects

1. Hypersensitivity
2. Rise in serum aminotransferases

### Uses

- Hospital acquired infections originating from urinary, biliary, gastrointestinal and female genital tracts.

## CARBAPENEMS

### Introduction

- Carbapenems are B-lactamase resistant

- These are the only B-lactams which are reliably efficacious against ESBL (extended spectrum B-lactamase) producing organisms and are thus drug of choice for ESBL- producing bacteria.

## Classification

1. Imipenem
2. Doripenem
3. Meropenem
4. Ertapenem

## Pharmacokinetics

- Imipenem is rapidly inactivated by renal dehydropeptidase I, so it is combined with cilastatin, an inhibitor of this enzyme

## Spectrum

- Widest spectrum of activity including ☐
  - Gram positive cocci
  - Gram negative bacilli
  - Anaerobes

## Adverse effects

1. Seizures → Imipenem has propensity to induce seizures at higher doses and in predisposed patients.
2. Diarrhoea, vomiting
3. Hypersensitivity → Skin rashes



## Uses

1. Hospital-acquired respiratory, urinary, abdominal, pelvic, skin and soft tissue infections
2. Infections in neutropenic, cancer and AIDS patients.

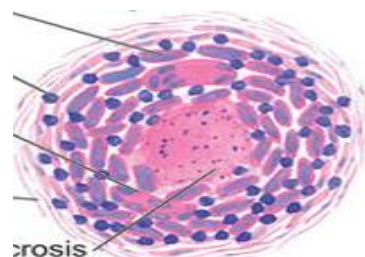
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## ANTITUBERCULAR DRUGS

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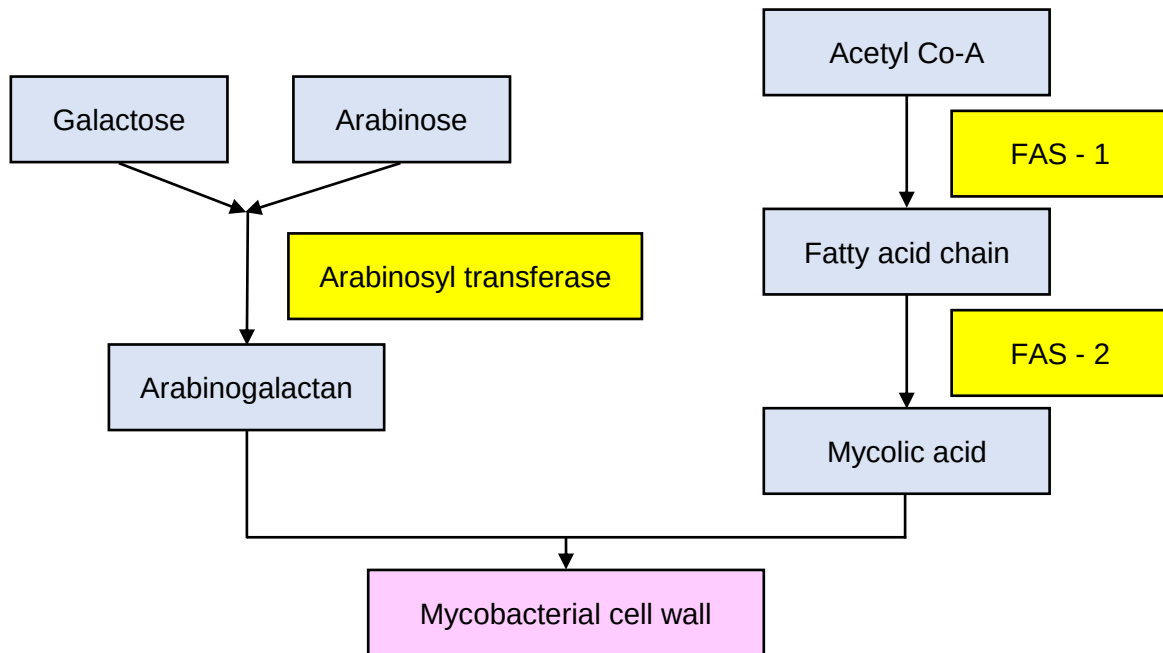
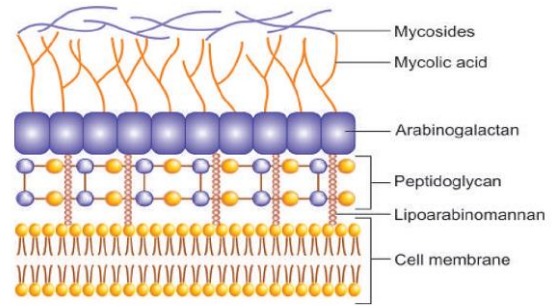
### Tuberculosis

- It's a chronic bacterial infection caused by Mycobacterium tuberculosis
- Mycobacterium tuberculosis is an acid-fast bacillus



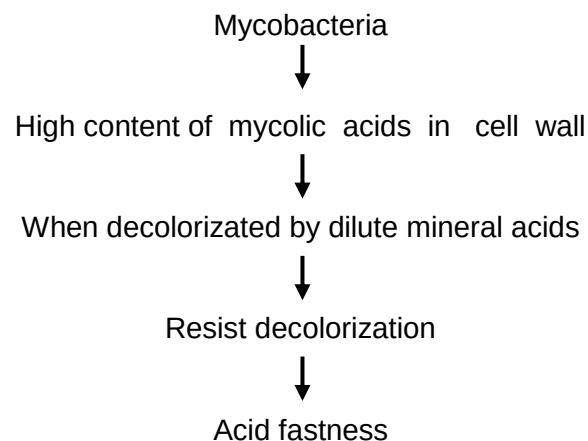
## Mycobacterium tuberculosis Cell wall

- **Peptidoglycan layer** → shape and rigidity of cell
- **Arabinogalactan layer**
- **Mycolic acid layer** → responsible for acid fastness



## Acid fastness

- Unique property of Mycobacteria is 'acid-fast'

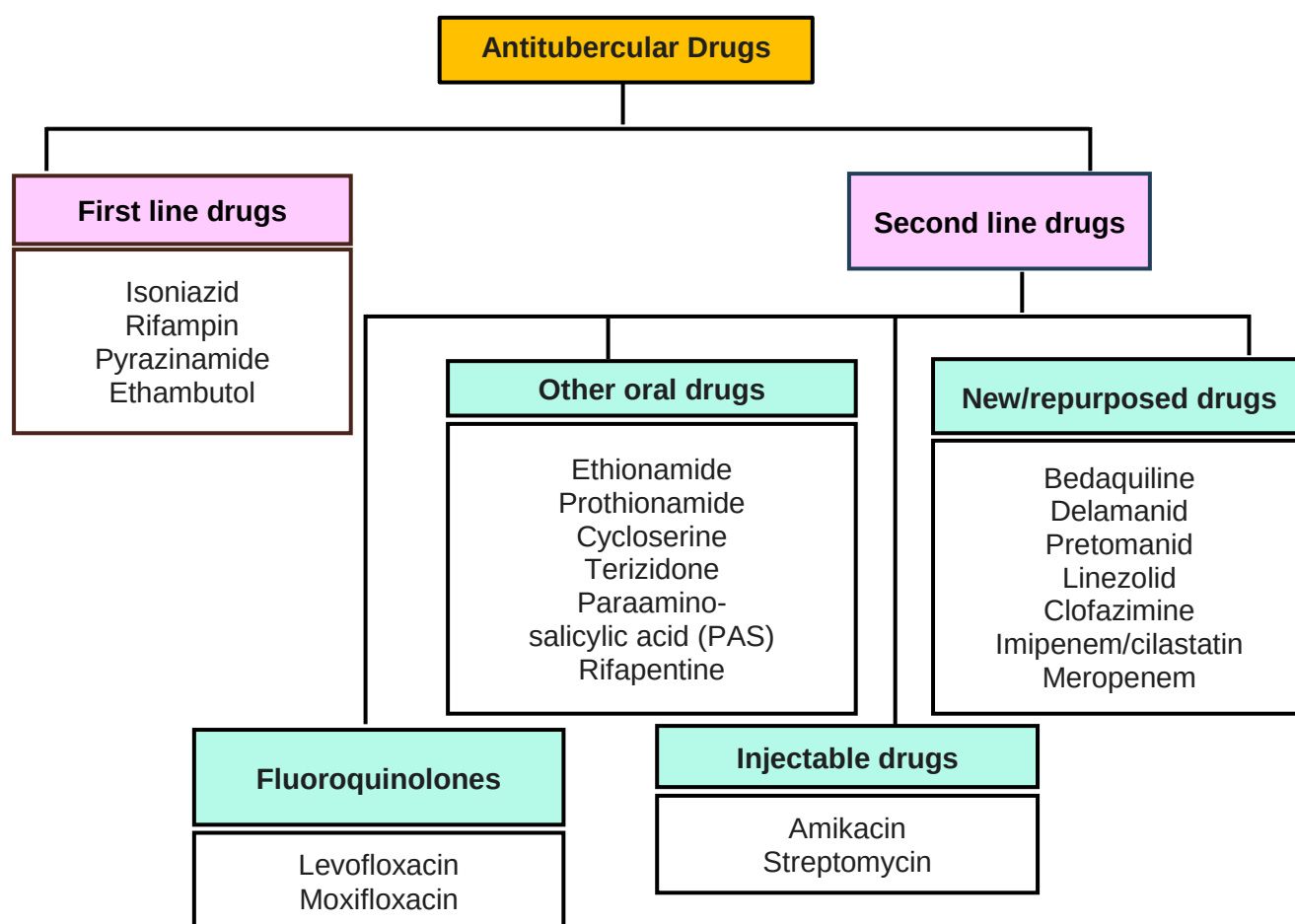


- Used as an important identification feature in diagnostic laboratories.

## ANTI-TB DRUGS

### Classification

| First line                                    | Second line                                  |
|-----------------------------------------------|----------------------------------------------|
| These drugs have high antitubercular efficacy | These drugs have low antitubercular efficacy |
| Low toxicity                                  | Higher toxicity                              |
| Used routinely                                | Used as reserve drugs                        |



## FIRST LINE DRUGS

- Isoniazid (H)
- Rifampin (R)
- Pyrazinamide (Z)
- Ethambutol (E)

**MOA**

| Drug             | MOA                         | Bactericidal/<br>Bacteristatic |
|------------------|-----------------------------|--------------------------------|
| Isoniazid (H)    | Inhibit cell wall synthesis | Cidal                          |
| Rifampicin (R)   | Inhibit RNA synthesis       | Cidal                          |
| Pyrazinamide (Z) | Inhibit cell wall synthesis | Cidal                          |
| Ethambutol (E)   | Inhibit cell wall synthesis | Static                         |

| Drug             | Bactericidal/<br>Bacteristatic | Hepatotoxicity | Bacteria<br>Inhibited |
|------------------|--------------------------------|----------------|-----------------------|
| Isoniazid (H)    | Cidal                          | +              | Both                  |
| Rifampicin (R)   | Cidal                          | +              | Both                  |
| Pyrazinamide (Z) | Cidal                          | ++++           | Intra                 |
| Ethambutol (E)   | Static                         | -              | Both                  |

|                  | H | R | Z | E |
|------------------|---|---|---|---|
| Introduction     |   |   |   |   |
| MOA              |   |   |   |   |
| Resistance       |   |   |   |   |
| Pharmacokinetics |   |   |   |   |
| Adverse Effects  |   |   |   |   |

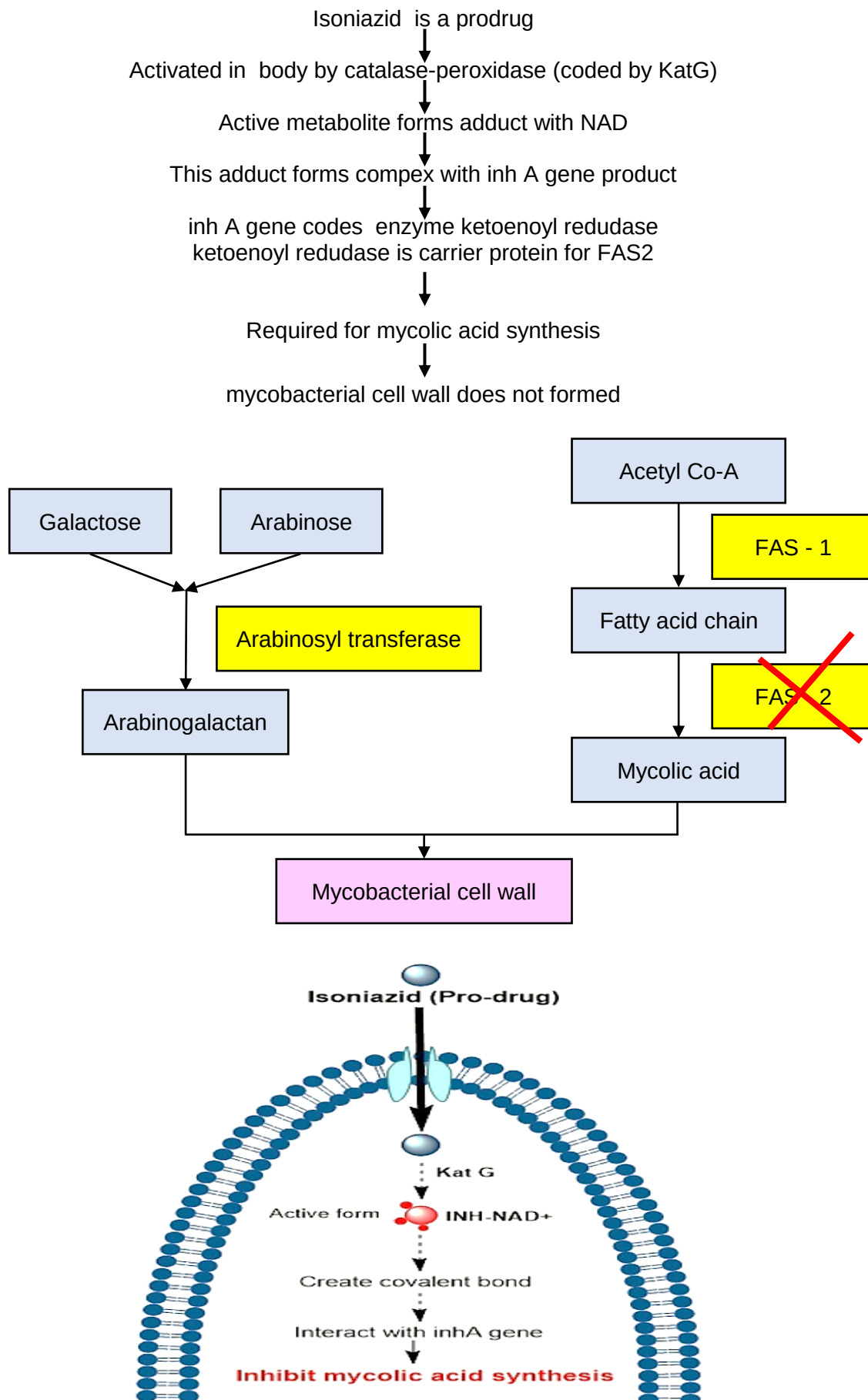
**ISONIAZID****Introduction**

- Single most important drug used in tuberculosis
- Bacteriostatic against resting and bactericidal against rapidly multiplying organisms.
- Effective against intra- as well as extra-cellular mycobacteria.
- Action is most marked against rapidly multiplying bacilli (less effective against slow multipliers).
- DOC → for TB
- DOC → for prophylaxis of tuberculosis
- Anti-tubercular drug which make the patient non-infectious earliest
- Most important drug in intensive phase.

**MOA**

- Primary mechanism of action of INH → inhibition of synthesis of mycolic acids □ which are unique fatty acid components of mycobacterial cell wall.

- High selectivity of INH for mycobacteria (it is not active against any other microorganism).



## Resistance

- Due to mutation in **Kat G (gene for catalase-peroxidase)** → high level resistance
- Due to mutation in **inhA** → Low level resistance

## Pharmacokinetics

1. It is widely distributed in body and has maximum CSF penetration.
2. It is extensively metabolized in liver → most important pathway being N-acetylation by NAT2.
  - Acetylated metabolite is excreted in urine.
  - Rate of INH acetylation shows genetic variation.
    - Fast acetylators → (30–40% of Indians)  $t_{1/2}$  of INH 1 hr.
    - Slow acetylators → (60–70% of Indians)  $t_{1/2}$  of INH 3 hr.
  - Isoniazid induced peripheral neuritis is more common in slow acetylators.

## Adverse effects

1. Peripheral neuritis
2. Hemolysis in patients with deficiency of G6PD
3. Hepatitis
4. Hypersensitivity reactions

### 1. Peripheral neuritis

- Due to interference with production of active coenzyme Pyridoxal phosphate from pyridoxine (Vitamin B6)
- Transient memory loss
- Prophylactic pyridoxine must be given to diabetics, chronic alcoholics, malnourished, pregnant, lactating and HIV infected patients, but routine use is not mandatory.



### 2. Hemolysis in patients with deficiency of G6PD

Pro-oxidant drugs produces free radicals (which damages RBCs)

↓  
For removal of free radical Glutathion is oxidized

↓  
For reduction of oxidized glutathione NADPH is required

↓  
G6PD is required for regeneration of NADPH

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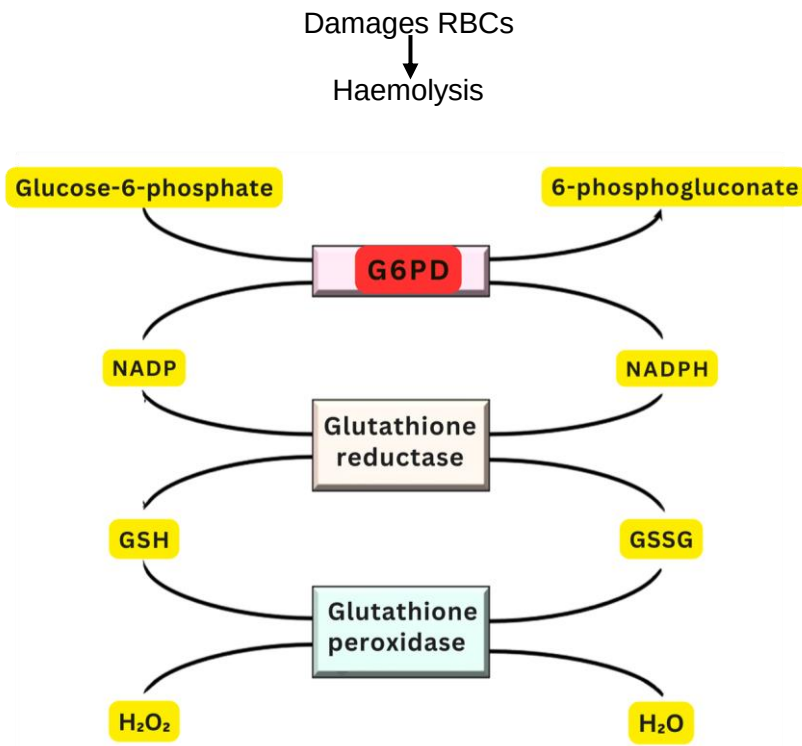
In a patient with deficiency of G6PD

↓  
Prooxidant drug is given

↓  
Produces free radicals

↓  
(which cannot be removed because regeneration of NADPH is not there which is required for reduction of oxidized glutathione)





### 3. Hepatitis

- INH hepatotoxicity is due to dose-related damage to liver cells, but is reversible on stopping the drug

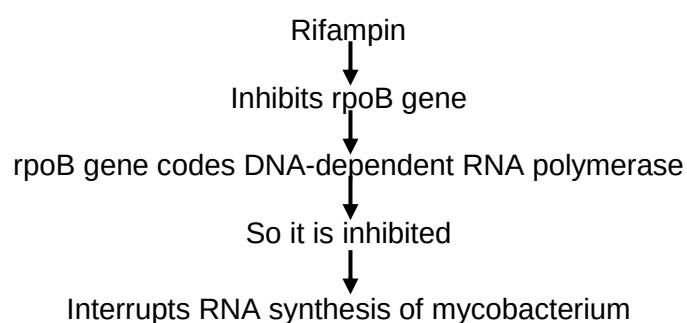


## RIFAMPIN

### Introduction

- Semi synthetic derivative of antibiotic rifamycin-B.
- It is broad spectrum, effective against ☐ Streptococci, Staphylococci, Meningococci, H. influenza, Legionella, Mycobacterium tuberculosis and leprae.
- Rifampin is bactericidal
- Action is most marked against slow and intermittent multipliers
- Both extra- and intracellular organisms are affected
- Rifampicin is the most potent sterilising antitubercular drug ☐ fastest to kill all bacilli in the lesion.

### MOA





## Resistance

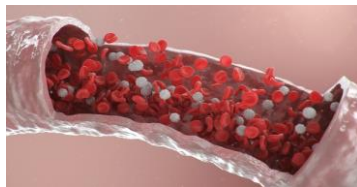
- Due to mutation in rpoB gene reducing its affinity for the drug
- In India it is estimated to be 2%

## Pharmacokinetics

1. It is well absorbed orally, (bioavailability → 70%) □ but food decreases absorption → rifampin is to be taken in empty stomach
2. Though it crosses meninges, it is largely pumped out from CNS by P-glycoprotein.
3. It is metabolized in liver to an active deacetylated metabolite which is excreted mainly in bile → enterohepatic circulation
4. Rifampin is a potent enzyme inducer so it is required to adjust the doses of various other drugs metabolized by microsomal enzymes.

## Adverse effects

1. Urine and secretions may become orange-red → but this is harmless.
2. Flu like syndrome with fever, chills, and myalgia
3. Blood dyscrasias
4. Hepatitis: chronic alcoholics and patient with old age or chronic liver disease are more prone for it.
5. Rashes, fever, nausea, and vomiting.



## Other uses of rifampin

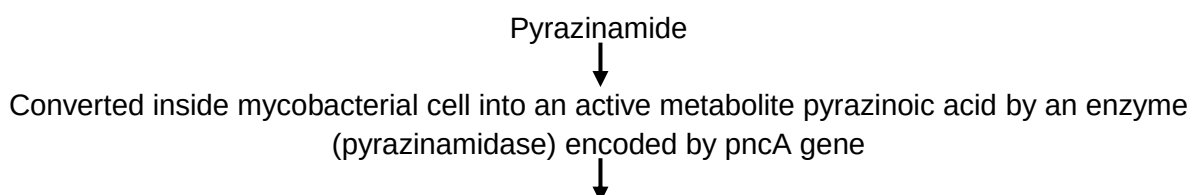
1. Leprosy
2. Prophylaxis of Meningococcal and H. influenzae meningitis and carrier state.
3. Second/third choice drug for → MRSA, diphtheroids and Legionella infections.
4. Combination of doxycycline and rifampin → first line therapy of brucellosis.

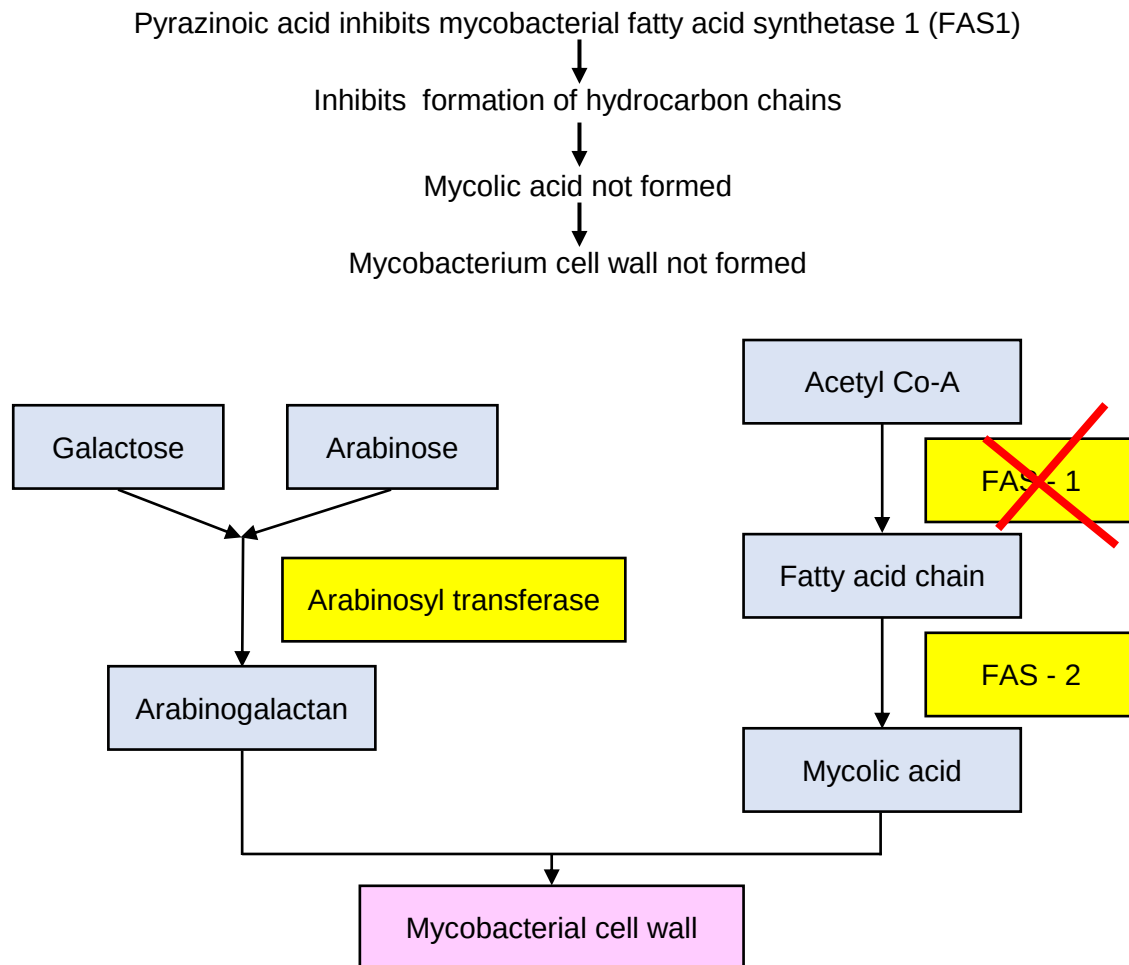
## PYRAZINAMIDE

### Introduction

- Weakly tuberculocidal and more active in acidic medium
- Bactericidal at low pH so well effective against intracellular organisms residing in macrophages.
- Effective only against intracellular bacteria

### MOA





## Resistance

- Due to mutation in the *pncA* gene

## Pharmacokinetics

1. Good penetration in CSF → highly useful in meningeal TB
2. Extensively metabolized in liver and excreted in urine

## Adverse effects

1. Arthralgia
2. Hepatic damage → Pyrazinamide is most hepatotoxic antitubercular drug
3. Decrease urate excretion → Hyperuricaemia (Gout can occur)
4. Anorexia, nausea, vomiting, dysuria.

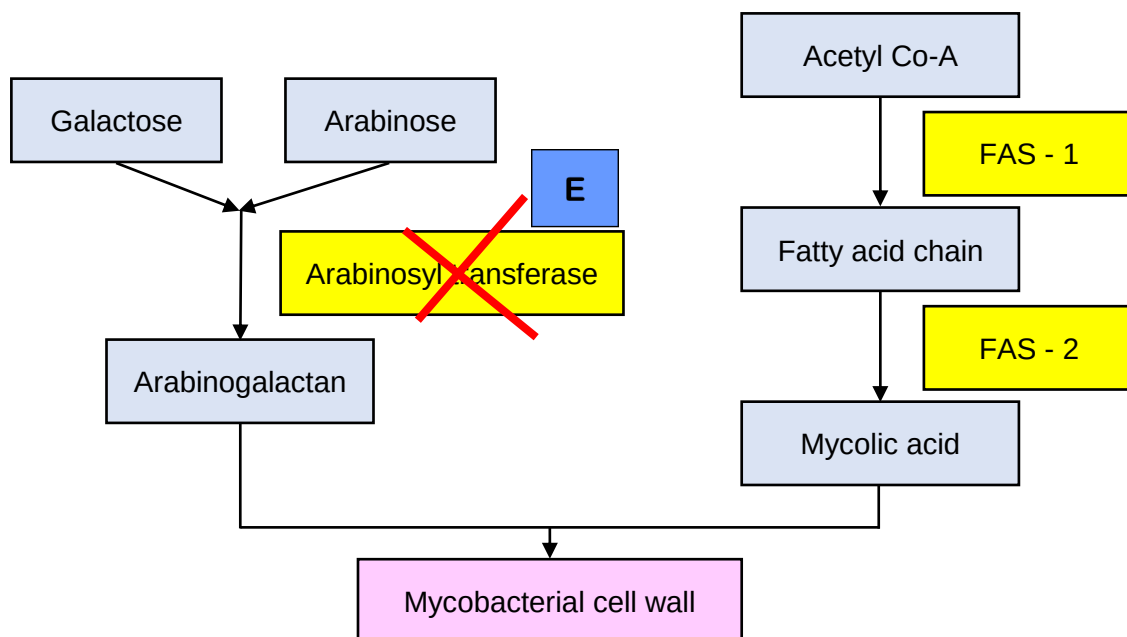
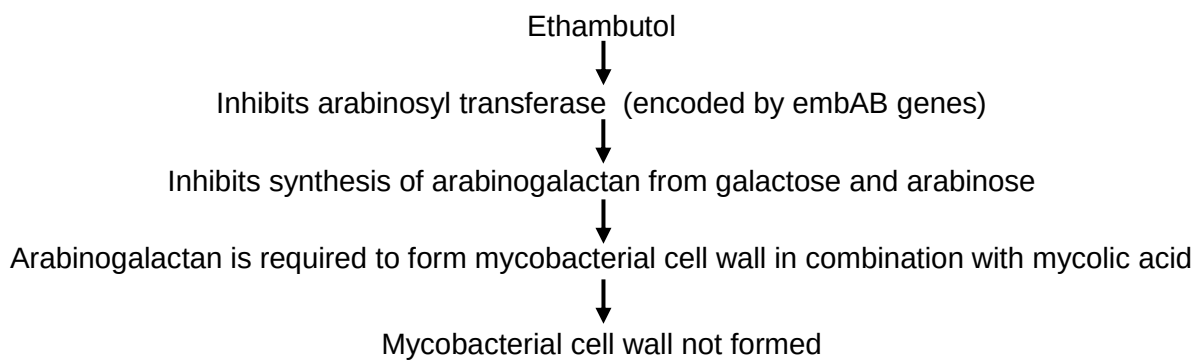


# ETHAMBUTOL

## Introduction

- Specific against tubercular bacilli
- Bacteriostatic effect
- Fast multiplying bacilli are more susceptible
- One of the least toxic antitubercular drug

## MOA



## Resistance

- Mutation in embB gene

## Pharmacokinetics

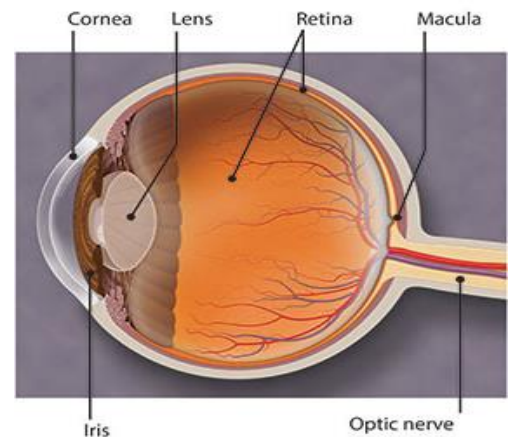
1. About 3/4 of an oral dose of E is absorbed.
2. Penetrates meninges incompletely and is temporarily stored in RBCs.

3. Ethambutol is excreted mainly by kidney → dose of ethambutol should be reduced in impaired renal function as it accumulates in renal failure
  - Ethambutol is not hepatotoxic
  - Ethambutol accumulates in renal failure, and the dose should be reduced by half if creatinine clearance is less than 10 mL/min.

## Adverse effects

### 1. Optic neuritis/ Retrobulbar neuritis

- Decrease visual acuity and loss of ability to differentiate red from green, hence it may produce green vision.
- The incidence of ocular toxicity is directly proportional to dose and intensity is proportional to duration.
- Periodic test of visual acuity and color discrimination gives the early indication of the toxicity and timely stoppage reverses the features.
- With early recognition and stoppage of the drug, visual toxicity is largely reversible.



2. CNS: Headache, dizziness, confusion, disorientation, hallucination, arthralgia.

3. Increases blood urate because of decrease renal excretion, in about 50% patients.

4. Rashes, drug fever, GI upset and pruritus.

## SECOND LINE DRUGS

## STREPTOMYCIN

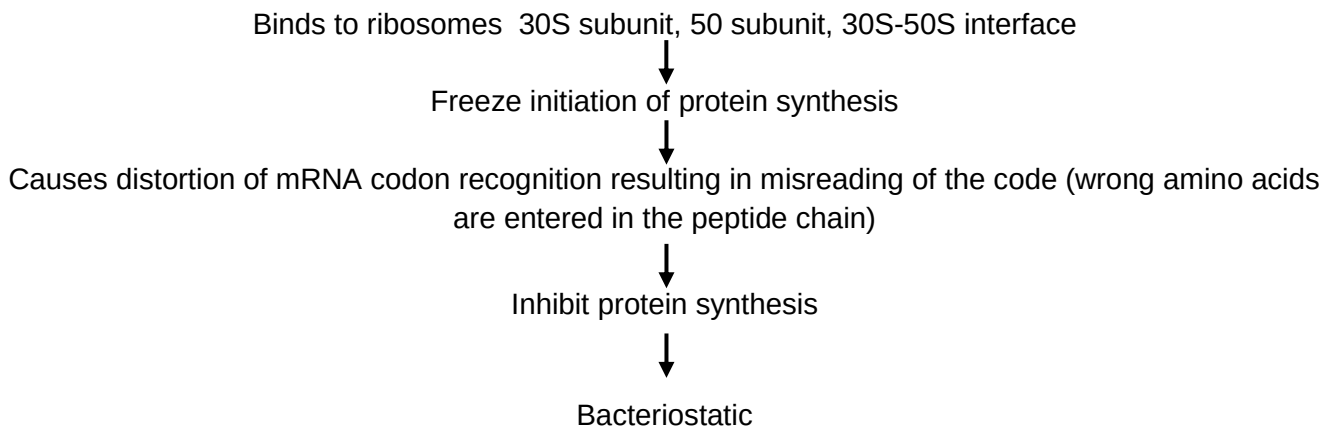
### Introduction

- Initially First antitubercular drug
- Now shift to second line drug in view of toxicity and less effectiveness
- It is tuberculocidal, but less effective than INH or rifampin
- Acts only on extracellular bacilli
- In tuberculosis at any moment, 90% bacilli are intracellular hence streptomycin is less effective.

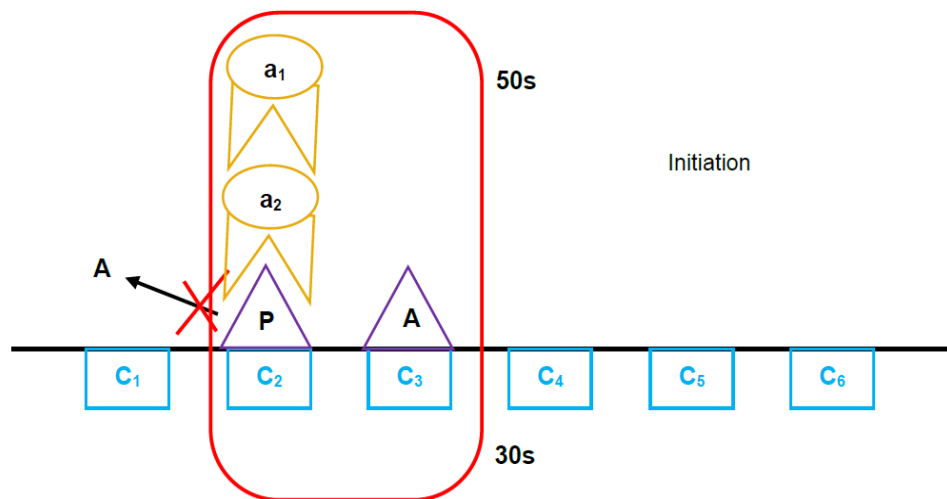
### MOA

Transport of aminoglycoside through bacterial cell wall and cytoplasmic membrane (transport mechanism)





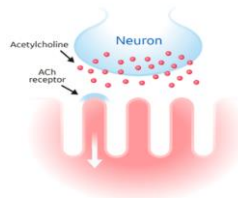
## INITIATION



## Adverse effects

Mnemonic → **ONN HT**

- **O**totoxicity
- **N**ephrotoxicity
- **N**euromuscular blockade
- **H**ypersensitivity reactions
- **T**eratogenic



| Drug               | Group                          | Mechanism                          | Major adverse effects                                        |
|--------------------|--------------------------------|------------------------------------|--------------------------------------------------------------|
| <b>Ethionamide</b> | Isoniazid                      | Inhibits synthesis of mycolic acid | Gastric irritation, neurological symptoms & hepatic toxicity |
| <b>Cycloserine</b> | Structural analog of D-alanine | Inhibit cell wall synthesis        | Neuropsychiatric symptoms                                    |
| <b>Capreomycin</b> | Polypeptide                    | Alter cell membrane permeability   | Ototoxicity & nephrotoxicity,                                |
| <b>Kanamycin</b>   | Aminoglycoside                 | Inhibiting protein synthesis       | Ototoxicity, nephrotoxicity, NM blockade                     |

|                     |                          |                                                   |                                                     |
|---------------------|--------------------------|---------------------------------------------------|-----------------------------------------------------|
| <b>Amikacin</b>     | Aminoglycoside           | Inhibiting protein synthesis                      | Ototoxicity, nephrotoxicity, NM blockade            |
| <b>Thiacetazone</b> | Thiosemicarbazone        |                                                   | Agranulocytosis, hepatotoxic, ototoxicity           |
| <b>PAS</b>          | Synthetic analog of PABA | Like sulfonamide inhibits formation of folic acid | Hepatic toxicity, Blood dyscrasias, sodium overload |

## MANAGEMENT OF TUBERCULOSIS

### Short course chemotherapy

- WHO introduced 6-8 month multidrug 'short course' regimens in 1995 under the DOTS programme.



### Supervised Therapy

- **DOTS** → Directly Observed Therapy - short course, as per RNTCP (Revised National Tuberculosis Control Programme, India).
- **In DOT** → a health worker or trained person watches the patient swallow each medicine in the intensive phase and at least first of three doses in continuation phase



### Phases

#### 1. Intensive phase →

- Under direct supervision
- With 4–5 drugs
- Lasting 2–3 months
- Aimed to rapidly kill the bacilli, bringing about sputum conversion and afford fast symptomatic relief.

#### 2. Continuation phase →

- At least first dose of every week is directly observed.
- With 2–3 drugs
- Lasting 4–5 months
- During this remaining bacilli are eliminated so that relapse does not occur.
- NTEP have brought out their latest guidelines in 2021, in which extensive use of drug – sensitivity testing has been incorporated to effectively treat DR-TB.
- Dose of all first line drugs was standardized on body weight basis.

## Definitions

1. Drug-sensitive TB (DS-TB)
2. Multidrug resistant TB (MDR-TB)
3. Extensive drug resistant TB (XDR-TB)
4. Rifampin resistant TB (RR-TB)
5. Isoniazid (H) mono-resistant TB

### 1. Drug-sensitive TB (DS-TB)

- Patient's bacilli are susceptible to all 4 first line anti-TB drugs (ATDs).
- All new TB patients who have never taken any ATD or have taken them for less than one month are presumed to have drug-sensitive TB.

### 2. Multidrug resistant TB (MDR-TB)

- Patient's bacilli are resistant to both R and H with or without resistance to any number of other 1st line drugs.

### 3. Extensive drug resistant TB (XDR-TB)

- A MDR-TB case whose bacilli are additionally resistant to a FQ and one or more second. line ATD.

### 4. Rifampin resistant TB (RR-TB)

- Patient's bacilli are resistant to R but not to H, with or without resistance to other first line ATDs.
- These patients are to be treated as if they have MDR-TB.

### 5. Isoniazid (H) mono-resistant TB

- Bacilli are resistant only to INH.
- As described earlier the INH resistance could be low level due to *InhA* mutation, or high level due to both *InhA* and *KatG* mutation.

## TREATMENT GUIDELINES

### Drug-Sensitive TB

- Treatment regimen for new patients or previously treated patients of pulmonary TB presumed to be drug sensitive

| Type of patient           | Intensive phase     | Continuation Phase | Total duration |
|---------------------------|---------------------|--------------------|----------------|
| New or previously treated | 2 <sup>€</sup> HRZE | 4 HRE              | 6 <sup>€</sup> |

- Daily dose of 1st line antitubercular drugs on body weight basis

| Drug                | Daily dose (mg/kg) |
|---------------------|--------------------|
| 1. Isoniazid (H)    | 5 (4-6)            |
| 2. Rifampin (R)     | 10 (8-12)          |
| 3. Pyrazinamide (Z) | 25 (20-30)         |
| 4. Ethambutol (E)   | 15 (15-20)         |

- Daily dose of 1st line oral antituberculars drugs as number of fixed dose combination (FDC) tablets

| Body weight category | Intensive phase | Continuation phase |
|----------------------|-----------------|--------------------|
|                      | HRZE            | HRE                |
| 25-39 kg             | 2               | 2                  |
| 40-54 kg             | 3               | 3                  |
| 55-69 kg             | 4               | 4                  |
| ≥ 70 kg              | 5               | 5                  |

- Interisive phase: each tablet contains** →  
H (75 mg) + R (150 mg) + Z (400 mg) + E (275 mg)
- Continuation phase: each tablet contains** →  
H (75 mg)+ R (150 mg) + E (275 mg).

## Multidrug-Resistant (MDR) & Extensive Drug-Resistant (XDR) TB

- MDR-TB has a more rapid course with worse outcomes.
- Its treatment requires complex multiple second line drug containing regimens which are longer in duration, more expensive and more toxic.
- Grouping of anti-TB drugs for designing longer MDR-TB regimen (According to NTEP guidelines 2021)

| Group A                                  | Group B                         | Group C                                                                     |
|------------------------------------------|---------------------------------|-----------------------------------------------------------------------------|
| Include all three unless contraindicated | Include one or both if possible | Add to complete 5 drug regimen when Group A and B medicines cannot be used. |
| 1. Levofloxacin (Lfx)                    | 1. Clofazimine (Cfz)            | 1. Ethambutol (E)                                                           |



|                      |                                         |                                                     |
|----------------------|-----------------------------------------|-----------------------------------------------------|
| 2. Bedaquiline (Bdq) | 2. Cycloserine (Cs) or Terizidone (Trd) | 2. Delamanid (Dim)                                  |
| 3. Linezolid (Lzd)   |                                         | 3. Pyrazinamide (Z)                                 |
|                      |                                         | 4. Imipenem-cilastatin (Ipm-Clm) or Meropenem (Mpm) |
|                      |                                         | 5. Amikacin (Am) or Streptomycin (S)                |
|                      |                                         | 6. Ethionamide (Eto) or Prothionamide (Pto)         |
|                      |                                         | 7 p-Aminosalicylic acid (PAS)                       |

### 3 Regimens

1. Shorter oral bedaquiline-containing MDR/RR-TB regimen
2. Longer oral M/XDR-TB regimen
3. Bedaquiline, pretomanid and linezolid (BPaL) regimen

#### 1. Shorter oral bedaquiline-containing MDR/RR-TB regimen

- This regimen of 9-11 month duration is recommended for eligible patients with confirmed MDR/RR-TB who have not been exposed to 2nd line drugs at all, or exposed for less than one month, and in whom.
  - **0 - 4 Month (IP)** → Bdq, Lfx, Cfz, Z, E, H<sup>h</sup>, ETO (7 drugs for 4 month)
  - **5 – 6 month** → Bdq, Lfx, Cfz, Z, E (5 drugs for 2 months)
  - **7 – 9 months** (CP) → Lfx, Cfz, Z, E (4 drugs for 3 months)

#### Exclusion criteria

Patients of MDR/RR-TB are not started on the shorter Bdq-containing regimen if the following are found:

- H resistance is detected with both Kat G and InhA mutation.
- FQ resistance is detected
- Intolerance to or risk of toxicity with Bdq (QT prolongation) or with any other drug in the regimen.
- Extensive pulmonary TB with bilateral cavities, etc.
- Severe form of extrapulmonary (EP) TB.
- Pregnant and lactating women.
- Children below 5 years of age.

#### 2. Longer oral M/XDR-TB regimen

- This regimen of 18-20 month duration is recommended for MDR/RR-TB patients who are excluded from the above described shorter regimen, and for XDR-TB patients.
- There is no separate IP and CP in this regimen.
  - **0 - 6 Months** → Lfx, Bdq, Lzd, Cfz, Cs (5 drugs for 6 month)
  - **7 – 18 months** → Lfx, Lzd, Cfz, Cs (4 drugs for 12 months)
- For XDR-TB patients the total duration of longer regimen is 20 months.

#### 3. Bedaquiline, pretomanid and linezolid (BPaL) regimen

- This is a new short (6-9 month) regimen, still under investigation in India

- Bdq 400 mg daily for 2 weeks - followed by 200 mg 3 times per week for next 24 weeks +
- Linezolid 1200 mg daily for 24 weeks +
- Pretomanid 200 mg / day for 26 weeks

### Rifampin Resistant TB (RR-TB)

- A case of RR-TB is treated as MDR-TB.
- Because the bacilli are sensitive to H □ this first line drug is added to the MDR-regimen
- RR-TB cases are treated with the shorter oral Bdq containing regimen described above.

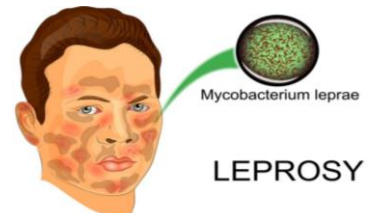
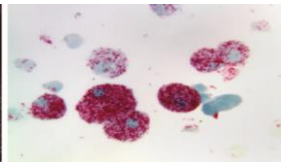
### Isoniazid (H) mono/poly drug resistant-T

- Bacilli are R sensitive, but resistant to H alone or to H+E or Z or both.
- Lfx, R, E, Z for 6-9 months.

## ANTILEPROTIC DRUGS

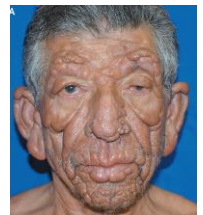
### Leprosy (Hansen's Disease)

- Chronic granulomatous infection caused by *Mycobacterium leprae*
- It attacks superficial tissues like skin and peripheral nerves.
- Organisms grow very slowly.
- It can't be cultured in artificial media but grows in footpads of armadillos or mouse.



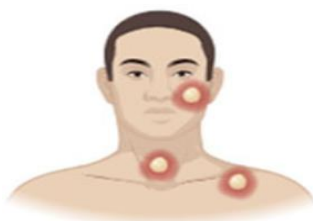
### Clinical features

- **Leprosy** → chronic granulomatous disease
- **Sites** → Primarily involving cooler parts of body → skin, peripheral nerves, upper respiratory tract, eyes, and testes
- **IP** → long incubation period → 5–7 years



#### 1. Paucibacillary (PB) leprosy

- a) 1 to 5 skin lesions
- b) No nerve involvement
- c) Slit-skin smear negative for lepra bacilli



#### 2. Multibacillary (MB) leprosy

- (a) >5 skin lesions
- (b) Nerve involvement (neuritis)
- (c) Slit-skin smear positive for lepra bacilli

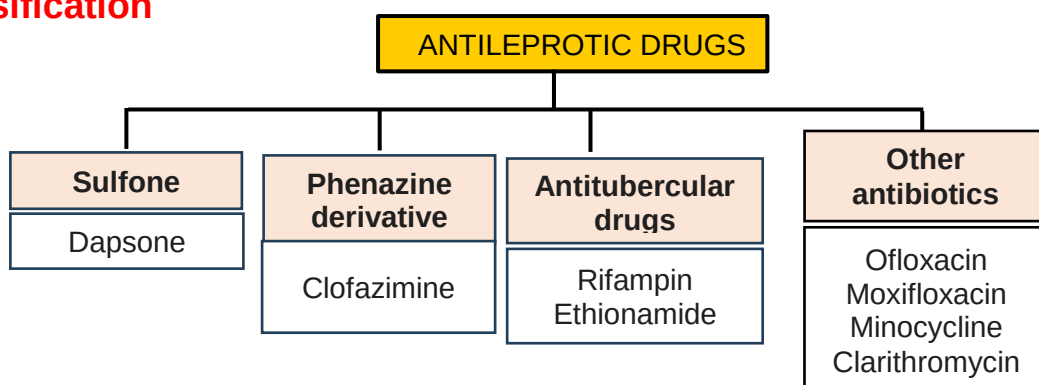


## Classification of Leprosy

| Ridley – Jopling Classification (1966) |
|----------------------------------------|
| Lepromatous leprosy (LL)               |
| Borderline Lepromatous leprosy (BL)    |
| Borderline leprosy (BB)                |
| Borderline tuberculoid leprosy (BT)    |
| Tuberculoid leprosy (TT)               |

## ANTILEPROTIC DRUGS

### Classification



|                         | Dapsone (DDS) | Clofazimine | Rifampin |
|-------------------------|---------------|-------------|----------|
| <b>Introduction</b>     |               |             |          |
| <b>MOA</b>              |               |             |          |
| <b>Resistance</b>       |               |             |          |
| <b>Pharmacokinetics</b> |               |             |          |
| <b>Adverse Effects</b>  |               |             |          |

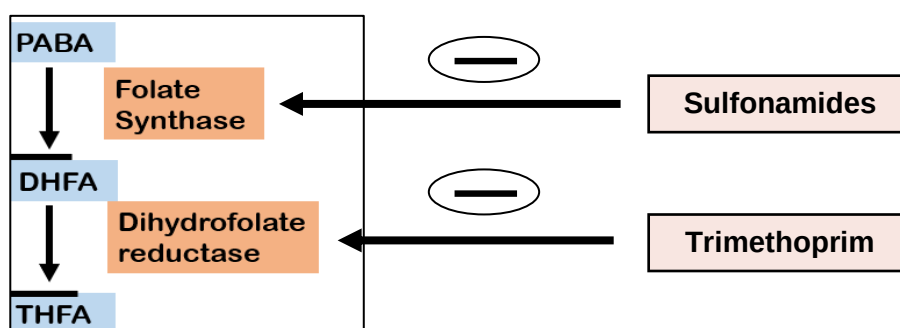
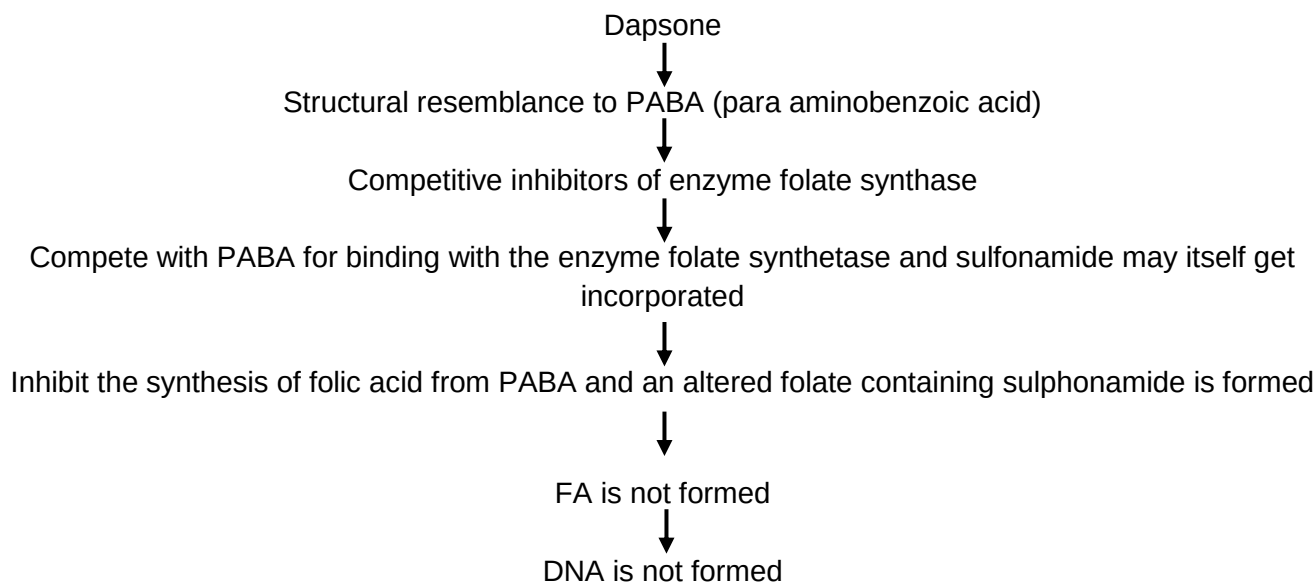
## DAPSONE (DDS)

### Introduction

- It is diamino diphenyl sulfone (DDS)
- Simplest, oldest, cheapest, most active and most commonly used Antileprotic drug
- All other sulfones have become obsolete.

### MOA

- Same as sulfonamides



## Resistance

1. Produce increased amounts of PABA
2. Their folate synthase enzyme has low affinity for sulfonamides
3. Adopt an alternative pathway in folate metabolism.

## Resistance types

- **Primary resistance** → When dapsone resistance is encountered in an untreated patient, it is called 'primary', and indicates that the infection was contacted from a patient harbouring resistant bacilli.
- **Secondary resistance** → Resistance which develops during monotherapy in an individual patient with dapsone is called 'secondary' due to selective propagation of resistant bacilli over time.

## Persistence

- Persisters are drug sensitive bacilli which become dormant, hide in some tissues and are not affected by any drug.
- They may stage a comeback after the drug is withdrawn.

## Pharmacokinetics

- It undergoes enterohepatic circulation
- It is metabolized by acetylation

## Adverse effects

1. Hemolysis, in patients with G6PD deficiency → MC
2. Methemoglobinemia → 2nd MC
3. Neurotoxicity and psychosis
4. Sulfone syndrome →
  - After 5-6 weeks of treatment in malnourished patients there may be exacerbation of lepromatous leprosy (similar to Jarisch Herxheimer reaction, seen in syphilis with penicillin).
  - Characterized by → fever, malaise, exfoliative dermatitis, jaundice, lymphadenopathy, methemoglobinemia and anemia.
  - Treatment → stop dapsone and instituting corticosteroid therapy along with supportive measures.
5. Nausea, vomiting, anorexia
6. Allergic reactions

## Other uses of Dapsone

- In combination with pyrimethamine, dapsone can be used for
  1. Chloroquine-resistant malaria,
  2. Toxoplasmosis
  3. P. jirovecii infection.

## CLOFAZIMINE

### Introduction

- It's a dye
- Weak bactericidal

### MOA

1. Interference with template function of DNA in M.leprae
2. Alteration of membrane structure and its transport function.
3. Disruption of mitochondrial electron transport chain
- Due to its anti-inflammatory action it is also used in lepra reaction

### Remember

- When used alone, the clinical response to clofazimine is slower than that to dapsone, and resistance develops in 1–3 years
- Clofazimine is used as a component of multidrug therapy (MDT) of leprosy.

## Adverse effects

### 1. Ichthyosis of skin

- Reddish-black discolouration of skin on exposed parts.
- Discolouration of hair and body secretions
- Dryness of skin and itching



2. GI symptoms → Nausea, anorexia, abdominal pain, weight loss and enteritis with intermittent loose stools

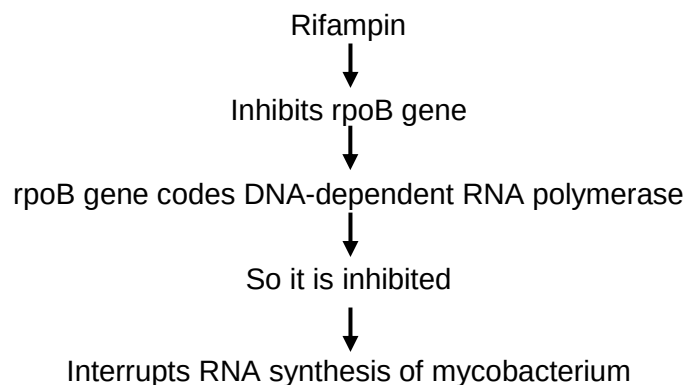
## RIFAMPIN (R)

### Introduction

- This important tuberculocidal drug is also the most potent cidal drug for *M. leprae*
- Upto 99.99% *M. leprae* are killed in 3–7 days by 600 mg/day dose.
- Rifampicin is most active and fastest acting antileprotic drug

### Remember

- It is not satisfactory if used alone
- Some bacilli persist even after prolonged treatment and resistance develops.
- Rifampin has been included in the MDT of leprosy whereby it shortens duration of treatment and no resistance develops
- Rifampin remains effective in leprosy even if given once a month.



### Resistance

- Due to mutation in *rpoB* gene reducing its affinity for the drug
- In India it is estimated to be 2%

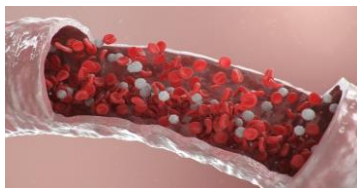
### Pharmacokinetics

1. It is well absorbed orally, (bioavailability → 70%) → but food decreases absorption → rifampin is to be taken in empty stomach
2. Though it crosses meninges, it is largely pumped out from CNS by P-glycoprotein.
3. It is metabolized in liver to an active deacetylated metabolite which is excreted mainly in bile → enterohepatic circulation
4. Rifampin is a potent enzyme inducer so it is required to adjust the doses of various other drugs metabolized by microsomal enzymes.

### Adverse effects

1. Urine and secretions may become orange-red → but this is harmless.

2. Flu like syndrome with fever, chills, and myalgia
3. Blood dyscrasias
4. Hepatitis: chronic alcoholics and patient with old age or chronic liver disease are more prone for it.
5. Rashes, fever, nausea, and vomiting.



## MANAGEMENT OF LEPROSY

- In India → National Leprosy Control Programme was launched in 1955
- It was changed to → National Leprosy Eradication Programme (NLEP) in 1982.
- India introduced multidrug therapy (MDT) for leprosy through NLEP in 1982 and achieved elimination of leprosy as a public health problem
- (prevalence rate < 1 case per 10,000 population) in Dec. 2005, though some states still had >1 case per 10,000.

### Conventional Monotherapy

- Conventionally → all forms of leprosy had been treated with dapsone alone 100–200 mg daily, 5 days a week
- Duration of treatment depending on the type:
  - **TT** → 4 to 5 years,
  - **LL** → 8 to 12 years or lifelong.
- Emergence of dapsone resistance since 1964 → threatened efficacy of monotherapy
- Monotherapy is no longer given



### Multidrug therapy (MDT) of leprosy

- This was implemented under the NLEP in 1982
  1. To deal with dapsone resistant strains of *M. leprae*
  2. To shorten the duration of treatment

| Multidrug therapy (MDT) of leprosy |                                                                  |                                |
|------------------------------------|------------------------------------------------------------------|--------------------------------|
|                                    | Multibacillary                                                   | Paucibacillary                 |
| Rifampin                           | 600 mg once a month supervised                                   | 600 mg once a month supervised |
| Dapsone                            | 100 mg daily self administered                                   | 100 mg daily self administered |
| Clofazimine                        | 300 mg once a month supervised and 50 mg daily self administered | -                              |
| Duration                           | 12 months                                                        | 6 months                       |

| Child dose  |                                        |
|-------------|----------------------------------------|
| Rifampin    | : 10 mg/kg once monthly                |
| Clofazimine | : 1 mg/kg daily + 6 mg/kg once monthly |
| Dapsone     | : 2 mg/kg daily                        |

## Advantages

1. Effective in cases with primary dapsone resistance.
2. Prevents emergence of dapsone resistance
3. Affords quick symptom relief
4. MBL cases noncontagious within few days.
5. Reduces total duration of therapy.

## Alternative regimens

- Indications →
  - Rifampin-resistance
  - When it is impossible/inadvisable to employ standard MDT regimen

## When Rifampin resistance or it cannot be used due to side effects

- Clofazimine 50 mg +
- Any two of ofloxacin 400 mg/minocycline 100 mg/clarithromycin 500 mg daily for 6 month
  - ↓
- Clofazimine 50 mg +
- Any one of ofloxacin 400 mg/minocycline 100 mg daily for additional 18 months.

## When Clofazimine resistance or it cannot be used due to side effects

- Intermittent ROM
  1. Rifampin 600 mg
  2. Ofloxacin 400 mg
  3. Minocycline 100 mg
- Given once a month for →
  - 3–6 month for PBL
  - 12 or 24 month for MBL cases without any drug in between.

## Four drug regimen

1. Rifampin 600 mg
  2. Sparfloxacin 200 mg
  3. Clarithromycin 500 mg
  4. Minocycline 100 mg
- Daily for 12 weeks
  - Yielded equivalent clinical improvement in MBL cases to standard 12 month MDT.



## Intermittent RMMx

1. Rifampin 600 mg
  2. Moxifloxacin 400 mg
  3. Minocycline 200 mg
- Administered once a month
    - 6 doses given for PBL
    - 12 doses given for MBL cases
  - Have produced rapid and marked clinical response

## Reactions in leprosy

1. Type II lepra reaction → Erythema nodosum leprosum
2. Type I lepra reaction → Reversal reaction

| Characters               | Lepra reaction type I                                                                                                                            | Lepra reaction type II                                           |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| <b>Hyper-sensitivity</b> | Type IV (delayed hypersensitivity)                                                                                                               | Type III (immune complex-mediated)                               |
| <b>Seen with</b>         | Borderline leprosy                                                                                                                               | Lepromatous variety (BL, LL)                                     |
| <b>Manifests as</b>      | Inflammation of previous lesions, new skin lesions and neuritis                                                                                  | Crops of painful erythematous papules which become nodular (ENL) |
| <b>Progresses as</b>     | If occurs before treatment → progresses towards LL (downgrading reaction). If occurs after treatment → progresses towards TT (reversal reaction) | Usually occurs following the start of chemotherapy               |
| <b>T-helper response</b> | T1 predominates → ↑ IFN-γ and IL-2                                                                                                               | T2 predominates → ↑ IL-6, IL-8. TNF-α plays a central role       |
| <b>Other organs</b>      | Usually not affected                                                                                                                             | Eyes, testes, and kidney are affected                            |
| <b>Treatment</b>         | Glucocorticoid                                                                                                                                   | Glucocorticoid, thalidomide, clofazimine, and antipyretics       |

### 1. Type II lepra reaction/ Erythema nodosum leprosum

- Occurs in LL
- Usually coincides with institution chemotherapy and/ or intercurrent infection.
- It is a Jarish Herxheimer (Arthus) type of reaction due to release of antigens from the killed bacilli

## Symptoms

- Lepra reaction is of abrupt onset
  - May be mild, severe or life-threatening, i.e. erythema nodosum leprosum (ENL)
1. Existing lesions enlarge, become red, swollen and painful;
  2. several new lesions may appear.
  3. Malaise, fever and other constitutional symptoms



## Treatment

1. Temporary discontinuation of dapsone is recommended only in severe cases.
2. Clofazimine (200 mg daily) is effective in controlling the reaction (except the severe one) because of its antiinflammatory property.
3. For severe reaction, prednisolone 40–60 mg/day is started immediately and continued till the reaction subsides. The dose is then tapered over 2–3 months.
4. Thalidomide

## 2. Type I lepra reaction Reversal reaction

- Seen in TT and BL
- Due to improvement in host immunity.
- It is a manifestation of delayed hypersensitivity to *M. leprae* antigens.

## Symptoms

- Cutaneous ulceration
- Multiple nerve involvement with swollen, painful and tender nerves, occur suddenly even after completion of therapy.



## Treatment

- Treated with clofazimine or corticosteroids in same way as ENL, but thalidomide is ineffective.

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# ANTIMALARIAL DRUGS

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## Introduction

- Malarial parasites infecting humans belong to four species of Genus Plasmodium:
  1. *P. vivax*
  2. *P. falciparum*
  3. *P. malariae*
  4. *P. ovale*

## MOT

1. Bite of infected mosquito (Female anopheles mosquito )
2. Blood transfusion
3. Transplacental transmission



## Life Cycle

2 Hosts →

- **Definitive host** → Female anopheles mosquito
- **Intermediate host** → Man

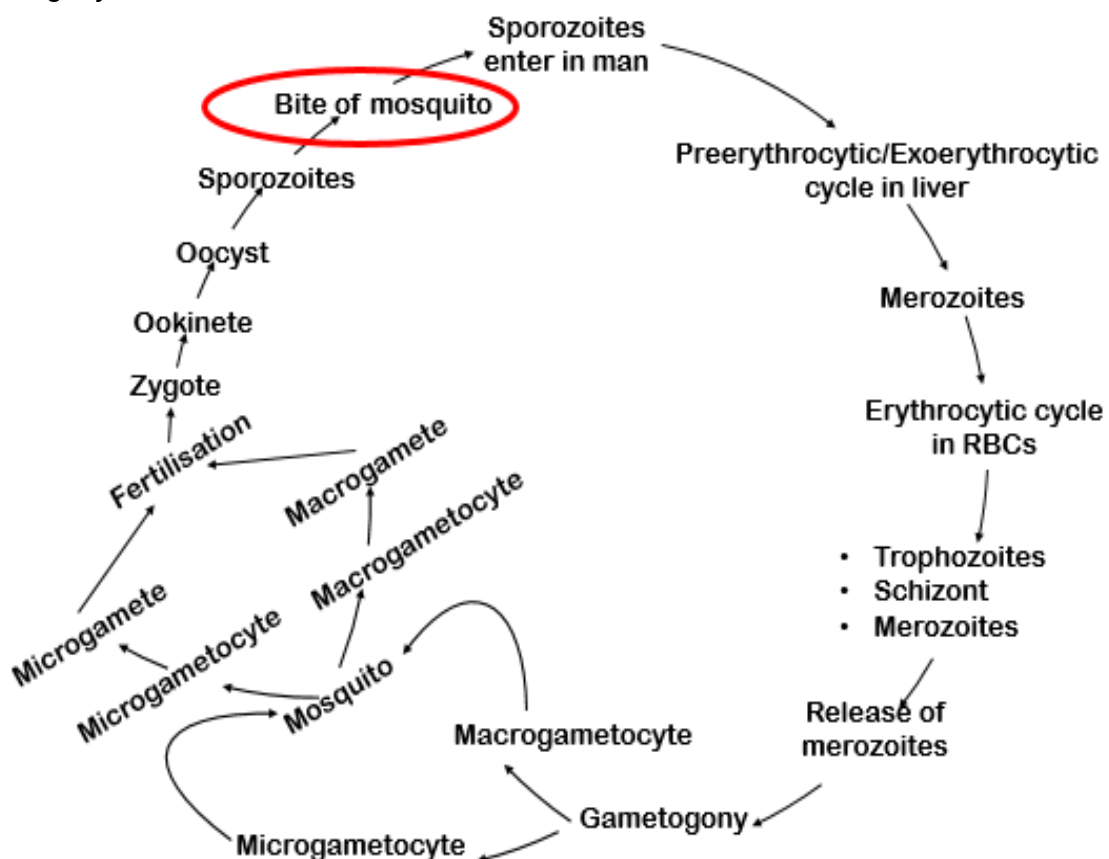
## Stages

### A. Asexual cycle (Man)

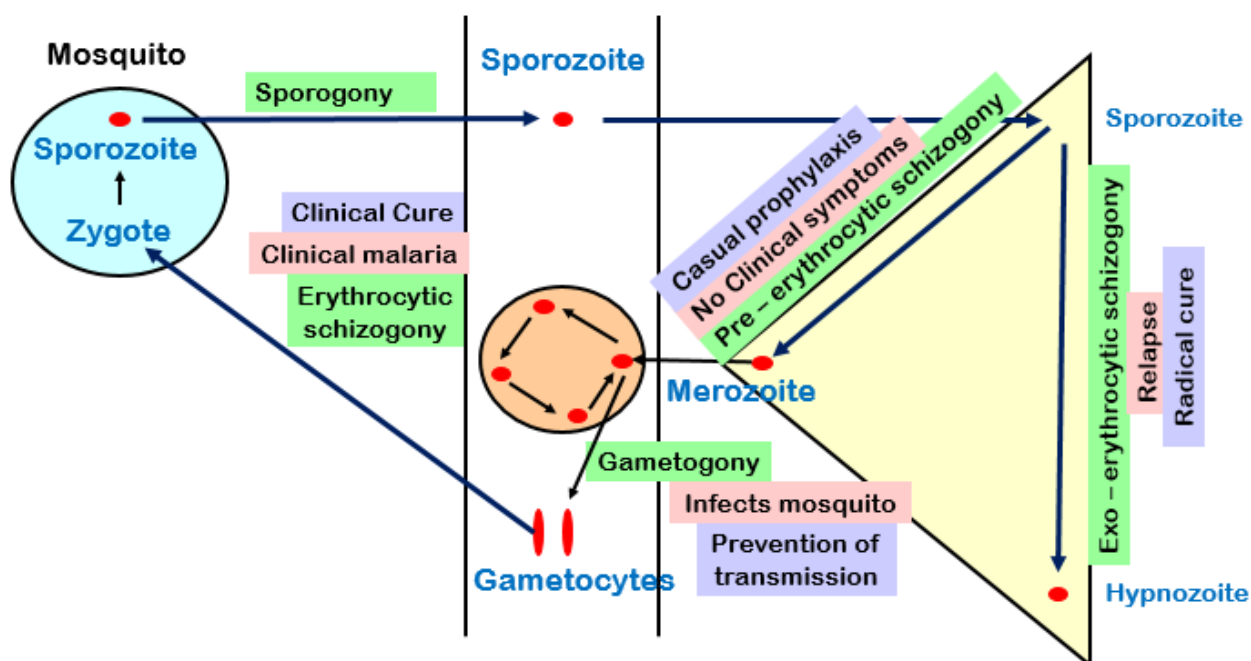
1. Pre-erythrocytic schizogony (Liver)
2. Exo-erythrocytic schizogony (Liver)
3. Erythrocytic schizogony (RBC)
4. Gametogony (RBC)

### B. Sexual cycle (Mosquito)

- Sporogony



- **Inside the liver**
  - Pre erythrocytic schizogony → No clinical symptom
  - Exo erythrocytic schizogony → Cause of relapse
- **Inside RBCs**
  - Erythrocytic schizogony → Cause of clinical malaria
  - Gametogony → Infects mosquito



| Stages                      | Site | Mechanism | Importance |
|-----------------------------|------|-----------|------------|
| Pre-erythrocytic schizogony |      |           |            |
| Exo-erythrocytic schizogony |      |           |            |
| Erythrocytic schizogony     |      |           |            |
| Gametogony                  |      |           |            |
| Sporogony                   |      |           |            |

## Objectives And Use of Antimalarial Drugs

1. To prevent clinical attack of malaria → Casual Prophylactic
2. To treat clinical attack of malaria → Clinical cure
3. To completely eradicate the parasite from the patient's body → Radical cure
4. To cutdown human-to-mosquito transmission → Prevention of transmission

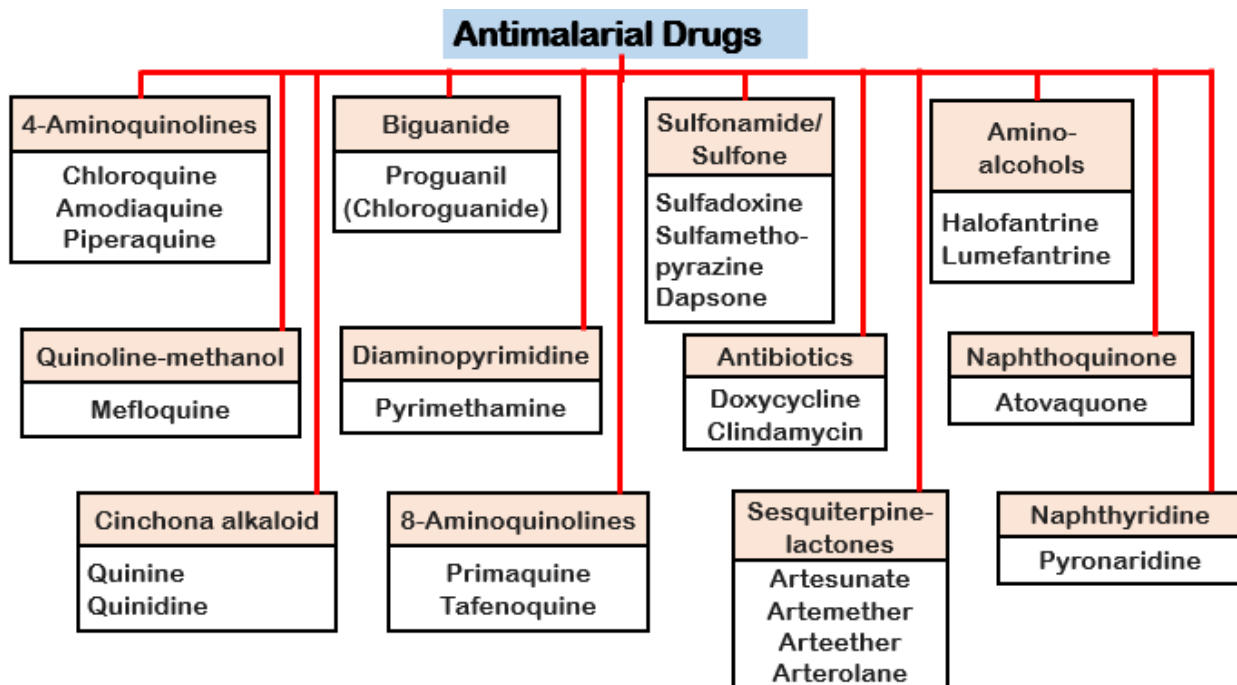
| Stage             | Clinical Use               |
|-------------------|----------------------------|
| Pre- Erythrocytic | Causal prophylaxis         |
| Erythrocytic      | Clinical cure              |
| Exo- Erythrocytic | Radical cure               |
| Gametocytic       | Prevention of transmission |

# ANTIMALARIAL DRUGS

## Classification

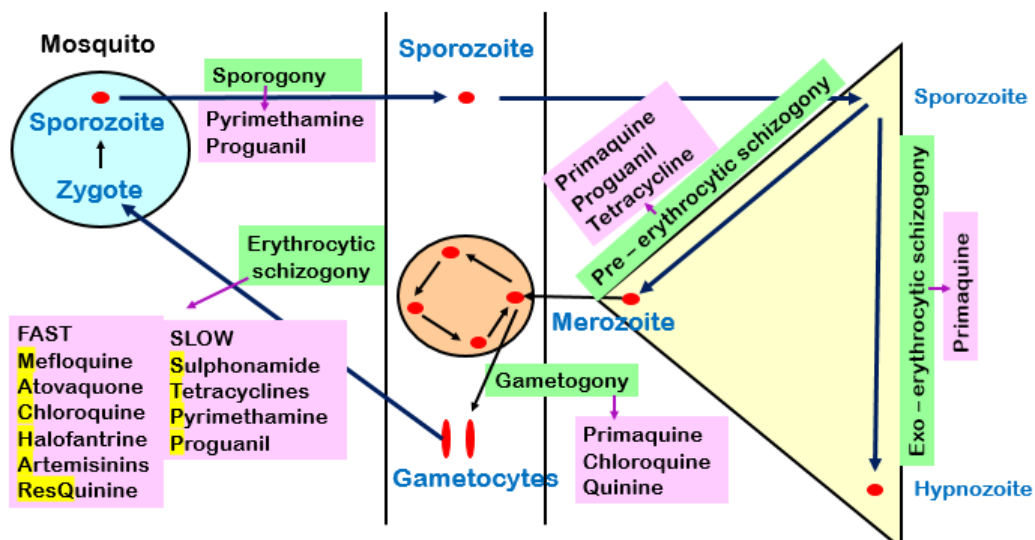
- Based on Chemical structure
- Based on MOA

## Based on Chemical structure



## Based on MOA

- A. Tissue schizonticides
  - a) Primary tissue schizonticides
  - b) Secondary tissue schizonticides
- B. Blood schizonticides
- C. Gametocytocides
- D. Sporontocides



## A. Tissue schizonticides

- **Act on** → primary tissue forms, i.e. forms in liver.
  - a) **Primary tissue schizonticides** → Tissue schizonticides for causal prophylaxis
  - b) **Secondary tissue schizonticides** → Tissue schizonticides for preventing relapse

### a) Primary tissue schizonticides

- **Act on** → Pre-erythrocytic schizogony
- **Drugs acting on this stage** → prevent infection of RBC
- **Used for** → prevention of Clinical attack of malaria → causal prophylaxis
- **Drugs** →
  1. Proguanil & Tetracycline → for falciparum.
  2. Primaquine → for all species

### b) Secondary tissue schizonticides

- **Act on** → Exoerythrocytic schizogony
- **Drugs acting on this stage** → prevent relapse
- **Used for** → Radical cure
- **Drugs** → Primaquine is the only drug which acts on exoerythrocytic schizogony
- **Remember** → Exoerythrocytic schizogony is absent in P.falciparum, so it does not require radical cure.

## B. Blood schizonticides

- **Act on** → Erythrocytic schizogony
- **Drugs acting on this phase** → Prevent and treat clinical attack
- **Used for** → Clinical cure
- **Drugs** →
  1. Fast acting → Mefloquine, Atovaquone, Chloroquine (Amadioquine), Halofantrine (lumefantrine), Artemisinin, Quinine
  2. Slow acting → Sulfonamides, Tetracyclines, Pyrimethamine, Proguanil

### Mnemonic

#### FAST acting

**M** - Mefloquine  
**A** - Atovaquone  
**C** - Chloroquine  
**H** - Halofantrine  
**A** - Artemisinins  
**R** - ResQ - Quinine

#### SLOW acting

**S** - some - Sulphonamide  
**T** - Tiny - Tetracyclines  
**P** - Pest - Pyrimethamine  
**P** - Persist - Proguanil

## C. Gametocytocides

- **Act on** → Gametogony
- **Drugs acting on this phase** → Prevents development of Gametocytes in Man

- **Used to** → Prevents transmission from Man to Mosquito  
(These drugs are of no benefit to the patient being treated)
- **Drugs** →
  1. Primaquine & Artemisinins → for all species
  2. Chloroquine & Quinine → for P vivax

#### D. Sporontocides

- **Act on** → Sporogony
- **Drugs acting on this phase** → prevent development of oocysts in mosquito
- **Used to** → Prevents transmission from mosquito to Man
- **Drugs** → Proguanil and Pyrimethamine.

| Classification                  | Acts on                     | Drugs acting on this phase prevents | Use                               | Drugs                           |
|---------------------------------|-----------------------------|-------------------------------------|-----------------------------------|---------------------------------|
| Primary tissue schizonticides   | Pre-erythrocytic Schizogony | RBC infection                       | Causal Prophylaxis                | All → P<br>Fal → P,T            |
| Secondary tissue schizonticides | Exo-erythrocytic Schizogony | Relapse                             | Radical Cure                      | P                               |
| Blood schizonticides            | Erythrocytic Schizogony     | Clinical attack                     | Clinical Cure                     | Fast → MACHARESQ<br>slow → STPP |
| Gametocytocides                 | Gametogony                  | Dev. of Gametes in Man              | Transmission from Man to Mosquito | All → P,A<br>vivax → C,Q        |
| Sporontocides                   | Sporogony                   | Dev. of oocyst in Mosquito          | Transmission from Mosquito to Man | P,P                             |

| DRUG |               | PRE-ERYTHRO. |      | ERYTHROCYTIC PHASE |       |          | HYPNO-ZOITE | GAMETES | RESISTANCE | TOXICITY GRADING |
|------|---------------|--------------|------|--------------------|-------|----------|-------------|---------|------------|------------------|
|      |               | Fal.         | Viv. | Activity           | Onset | Duration |             |         |            |                  |
| 1.   | Chloroquine   | -            | -    | +                  | Fast  | Long     | -           | -       | Slow       | +                |
| 2.   | Mefloquine    | -            | -    | +                  | Int   | Long     | -           | -       | Minor      | ++               |
| 3.   | Quinine       | -            | -    | +                  | Int   | Short    | -           | -       | Minor      | +++              |
| 4.   | Proguanil     | +            | -    | +                  | Int   | Short    | -           | *       | Rapid      | ±                |
| 5.   | Pyrimethamine | -            | -    | +                  | Slow  | Long     | -           | -       | Rapid      | +                |
| 6.   | Primaquine    | +            | +    | -                  | -     | -        | +           | +       | Minor      | ++               |
| 7.   | Sulfonamides  | -            | -    | ±                  | Slow  | Long     | -           | -       | Minor      | ±±               |

|     |               |   |   |   |         |       |   |   |     |    |
|-----|---------------|---|---|---|---------|-------|---|---|-----|----|
| 8.  | Tetracyclines | - | - | + | Slow    | Short | - | - | Nil | ++ |
| 9.  | Clindamycin   | - | - | + | Slow    | Short | - | - | Nil | ++ |
| 10. | Artemisinin   | - | - | + | Fastest | Short | - | + | Nil | ++ |
| 11. | Lumefantrine  | - | - | + | Int     | Long  | - | - | Nil | ++ |

## INDIVIDUAL DRUGS

|                         | Chloroquine | Mefloquine | Quinine | Proguanil |
|-------------------------|-------------|------------|---------|-----------|
| <b>Introduction</b>     |             |            |         |           |
| <b>MOA</b>              |             |            |         |           |
| <b>Resistance</b>       |             |            |         |           |
| <b>Pharmacokinetics</b> |             |            |         |           |
| <b>Interactions</b>     |             |            |         |           |
| <b>Adverse effects</b>  |             |            |         |           |
| <b>Uses</b>             |             |            |         |           |

|                         | Pyrimethamine | Primaquine | Halofantrine | Artemisinin Derivatives |
|-------------------------|---------------|------------|--------------|-------------------------|
| <b>Introduction</b>     |               |            |              |                         |
| <b>MOA</b>              |               |            |              |                         |
| <b>Resistance</b>       |               |            |              |                         |
| <b>Pharmacokinetics</b> |               |            |              |                         |
| <b>Interactions</b>     |               |            |              |                         |
| <b>Adverse effects</b>  |               |            |              |                         |
| <b>Uses</b>             |               |            |              |                         |

## CHLOROQUINE

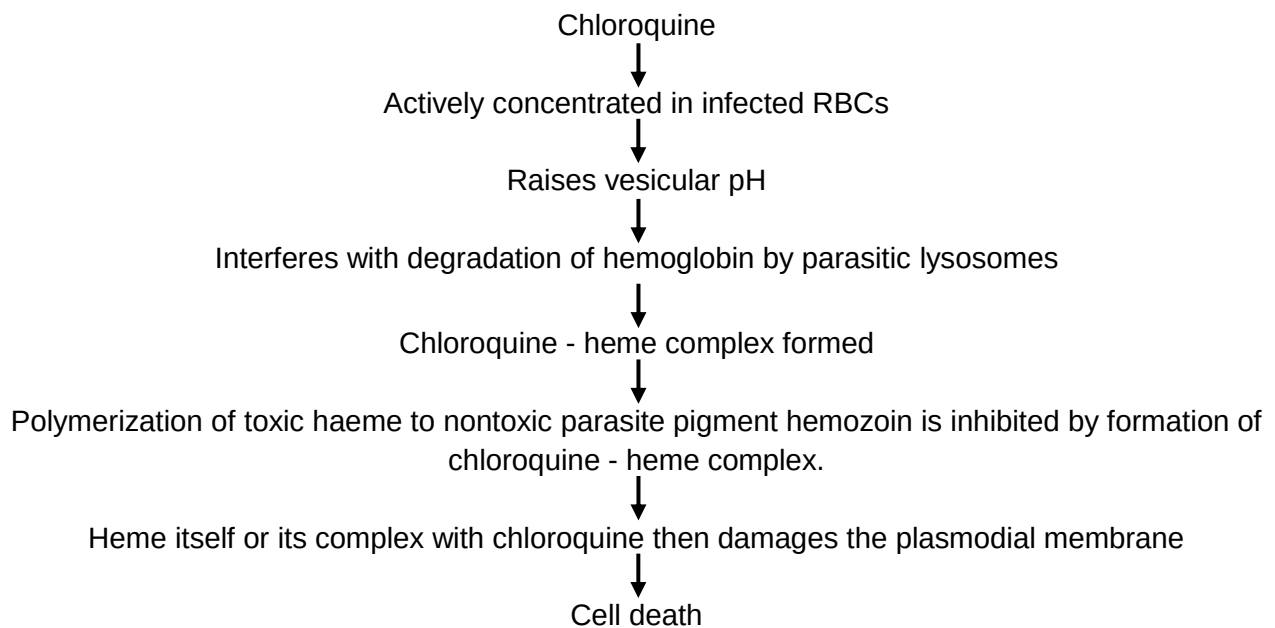
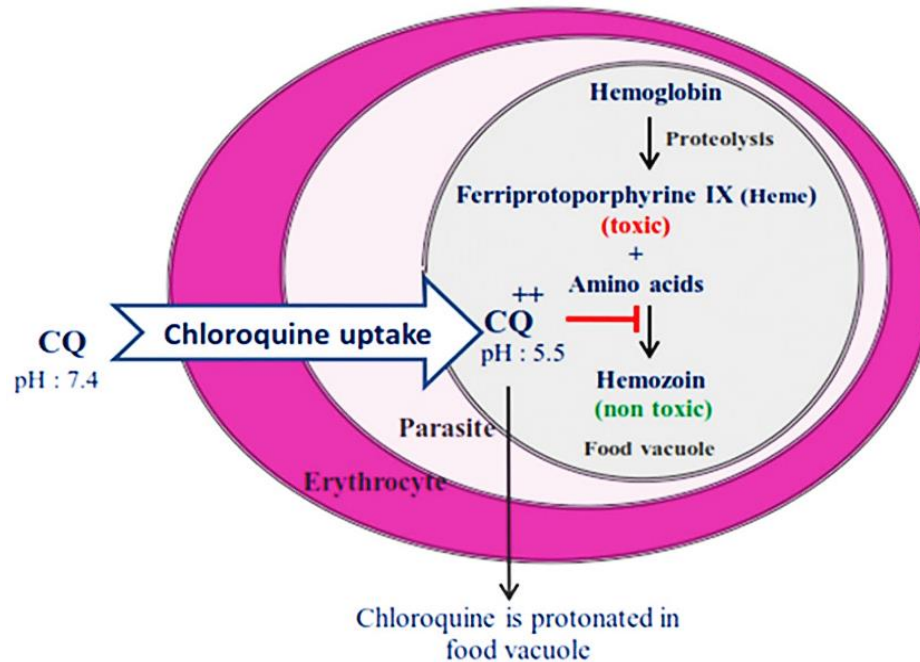
### Introduction

- It is a rapidly acting erythrocytic schizontocide against all species of plasmodia
- Controls most clinical attacks in 1–2 days with disappearance of parasites from peripheral blood
- No effect on pre and exo-erythrocytic stage □ Does not prevent relapses in vivax and ovale malaria.
- No gametocidal activity



## MOA

- Plasmodia derive nutrition by digesting haemoglobin in their acidic vacuoles.



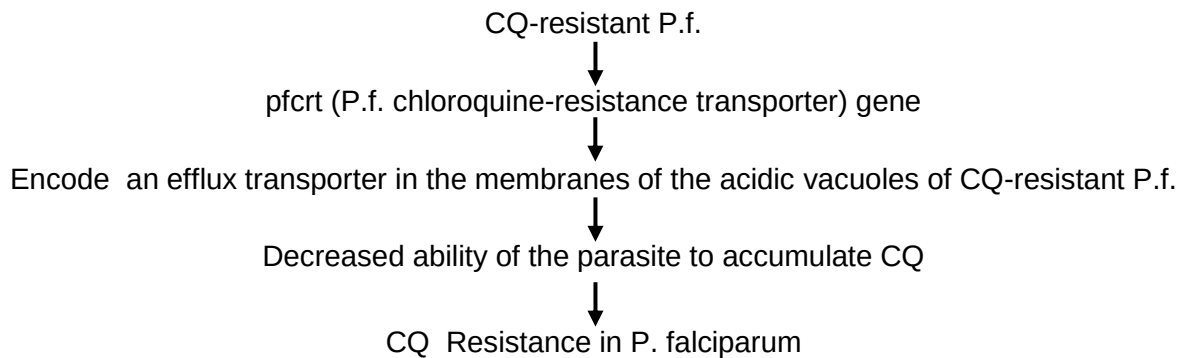
## Drugs act in same manner

- Quinine
- Mefloquine
- Lumefontrine

## Resistance

- Chloroquine-resistance among *P. vivax* has been slow in developing, but *P. falciparum* has acquired significant resistance

- Due to spread of CQ-resistant P.f. to most parts of India, the NVBDCP has switched over to ACT as the first line treatment of P.f. cases countrywide

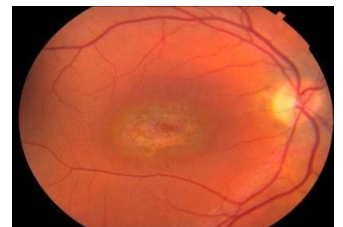


## Other actions

- Chloroquine is also active against
  1. Entamoeba histolytica
  2. Giardia lamblia

## Pharmacokinetics

- **High affinity for melanin and nuclear chromatin** → gets tightly bound to these tissue constituents → concentrated in liver, spleen, kidney, lungs (several hundred-fold), skin, leucocytes and some other tissues.
- **Selective accumulation in retina** → responsible for ocular toxicity



## Adverse effects

Mnemonic → **GBS RANA**

- **G** → **G**IT irritation, Graying of hair
- **B** → **B**ull's eye maculopathy
- **S** → **S**kin rash and skin lesions □ Lichenoid eruption, Photoallergy
- **R** → **R**enal damage
- **A** → **A**uditory damage
- **N** → **N**europathies
- **A** → **A**ttacks of porphyria

## Uses

Mnemonic → **RED LIP Mahatma Gandhi**

- **R**heumatoid arthritis
- **E**xtraintestinal amoebiasis
- **D**iscoid lupus erythematosus
- **L**epa reaction
- **I**nfectious mononucleosis

- **P**hotogenic reactions
- **M**alaria
- **G**iardiasis

## MEFLOQUINE

### Introduction

- Like chloroquine it is also a rapidly acting erythrocytic schizontocide
- No effect on pre and exo-erythrocytic stage.

### MOA

- Same as chloroquine.
- Recent evidence suggests that the site of action of MQ is in parasitic cytosol rather than in the acidic vacuole

### Resistance

- Enhanced translation of pfmdr1 gene, though Pfcrt mutation
- pfmdr gene encoded P-glycoprotein is an energy-dependent ABC transporter

### Interactions

- **Halofantrine or Quinine or CQ** → given to patients who have received MQ cause → QTc lengthening → cardiac arrests are reported.

### Adverse effects

- GIT → Bitter taste, dizziness, nausea, vomiting, diarrhoea, abdominal pain
- CVS → Sinus bradycardia
- CNS → Neuropsychiatric reaction
- Rare events → hematological, hepatic and cutaneous toxicity.

### Uses

- **Malaria** →
  - Malaria chemoprophylaxis
  - To treat uncomplicated plasmodium falciparum (both chloroquine sensitive and resistant)
  - Chloroquine resistant P. vivax malaria.

## QUININE

### Introduction

- Levo rotatory alkaloid obtained from cinchona bark
- d-isomer quinidine is used as an antiarrhythmic.
- Quinine is an erythrocytic schizontocide for all species of plasmodium



### MOA

- Similar to chloroquine.

## Other actions

- **Local irritant** → on i.v. injection pain & local necrosis of muscles and venous thrombosis.
- **Heart** → Cardiodepressant, antiarrhythmic, hypotensive action (rapid i.v. injection can cause marked fall in BP and collapse), directly decreases myocardial contractility
- **GIT** → Increases gastric secretion, nausea, vomiting, epigastric discomfort
- **Pancreas** → Decreases blood sugar due to release of insulin.
- **Ear and Eye** → Affects hearing and vision at higher doses.
- **Anaesthetic, weak analgesic, antipyretic**

## Adverse effects

### 1. Cinchonism

- A large single dose or higher therapeutic doses taken for a few days produce a syndrome called 'cinchonism'.
- It consists of →
  - Ringing in ears
  - Nausea
  - Vomiting (due to both gastric irritation and CTZ stimulation), Headache, mental confusion, vertigo
  - Difficulty in hearing and visual defects (due to direct neurotoxicity, constriction of retinal and auditory vessels),
  - Diarrhoea
  - Flushing and marked perspiration
  - It subsides completely if the drug is stopped.

### 2. Hypotension

### 3. Cardiac arrhythmias

**4. Hypoglycemia** → To prevent hypoglycemia, iv infusion of quinine should be given in 5% dextrose.

### 5. Hypersensitivity reaction

## Uses

1. **Malaria** → Quinine is used orally for uncomplicated CQ-resistant malaria, and i.v. for complicated/cerebral malaria
2. **Nocturnal muscle cramp**

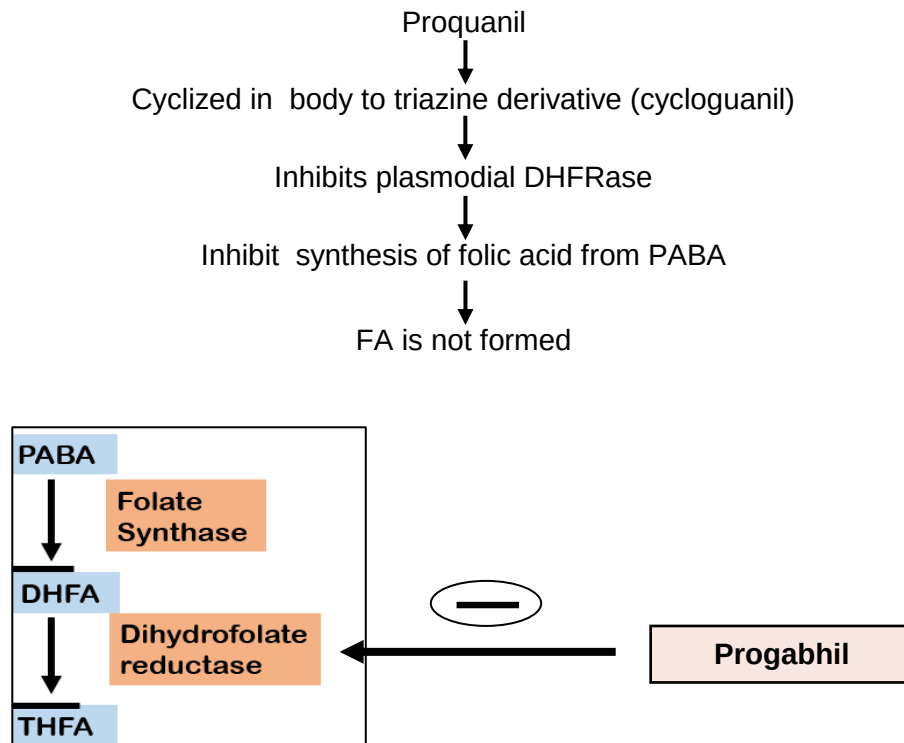


## PROGUANIL

### Introduction

- Slow acting erythrocytic schizonticide
- Also inhibits pre-erythrocytic stage of *P. falciparum*.

### MOA



- Other dihydrofolate reductase inhibitor, used in malaria → Pyrimethamine.
- Plasmodicidal action is markedly enhanced by combination with sulfonamides because there is inhibition of sequential steps in folate synthesis.

### Adverse effects

- Stomatitis
- Hematuria
- Transient hair loss
- Rashes

### Uses

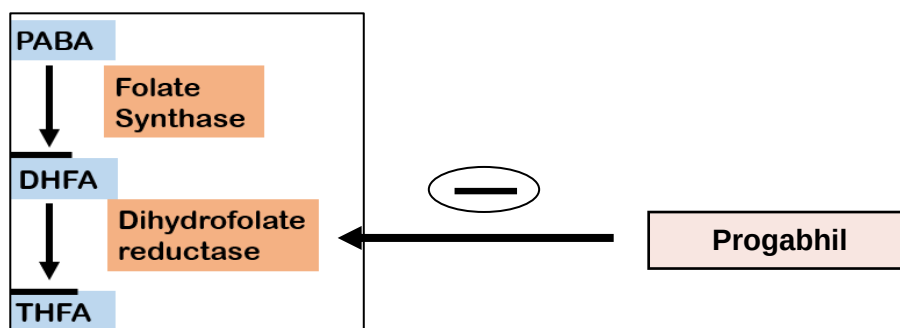
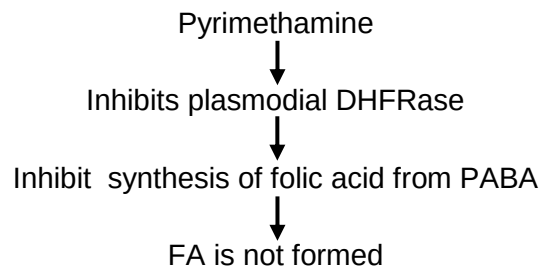
- Hardly used now in Malaria because of →
  - Slow response
  - Rapid resistance
- Malaria → Currently used in combination of Atovaquone to potentiate its action

## PYRIMETHAMINE

### Introduction

- Slow acting erythrocytic schizonticide and Sporozoicide
- Prevents transmission from mosquito to Man
- No action on pre and exoerythrocytic stage.

### MOA



- Other dihydrofolate reductase inhibitor, used in malaria → Pyrimethamine.
- Plasmodicidal action is markedly enhanced by combination with sulfonamides because there is inhibition of sequential steps in folate synthesis.

## Adverse effects

- Stomatitis
- Hematuria
- Transient hair loss
- Rashes

## Uses

- Hardly used now in Malaria because of
  - Slow response
  - Rapid resistance
- Malaria → Currently used in combination of Atovaquone to potentiate its action

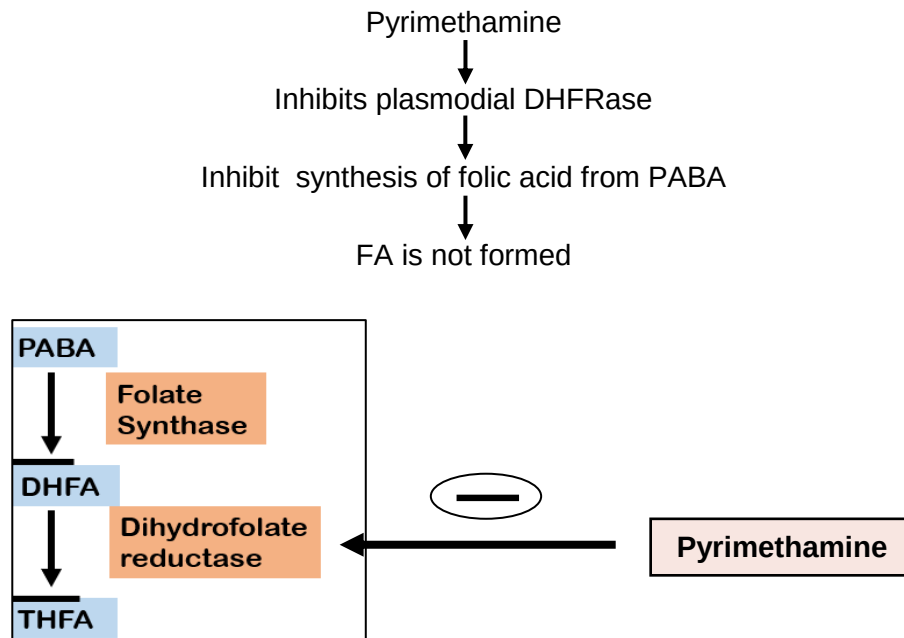
# PYRIMETHAMINE

## Introduction

- In contrast to other antimalarial drugs, it is a poor erythrocytic schizontocide has weak action on *P. vivax*, but blood forms of *P. falciparum* are totally insensitive.
- Active on → pre-erythrocytic, Exo-erythrocytic stage and Gametogony
- Primaquine → only antimalarial which is active on exoerythrocytic stage

## MOA

- MOA of primaquine is not known.



## Adverse effects

- Megaloblastic anemia and Granulocytopenia (due to folate deficiency)

## Uses

1. **Malaria** → Used in combination of Sulphonamide to treat Falciparum malaria
2. **Toxoplasma gondii**

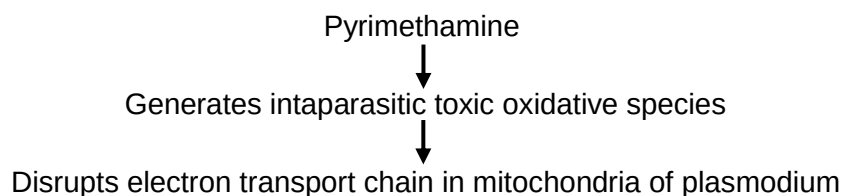
# PRIMAQUINE

## Introduction

- In contrast to other antimalarial drugs, it is a poor erythrocytic schizontocide has weak action on *P. vivax*, but blood forms of *P. falciparum* are totally insensitive.
- Active on → pre-erythrocytic, Exo-erythrocytic stage and Gametogony
- Primaquine → only antimalarial which is active on exoerythrocytic stage

## MOA

- MOA of primaquine is not known.



## Adverse effect

- Haemolytic anaemia in G-6-PD deficiency →
  - Due to oxidant property of primaquine.
  - It should be avoided in pregnancy as fetus with G6PD deficiency may develop hemolytic anemia

## Uses

- **Malaria** →
  - For radical cure of Malaria
  - To kill gametes and cut down transmission

# HALOFANTRINE

## Introduction

- Rapidly acting erythrocytic schizontocide
- Halofantrine is effective against chloroquine resistant *P. falciparum* and *P. vivax*.

## MOA

- Not understood

## Pharmacokinetics

- Its absorption from GIT is variable, incomplete and substantially increased by taking the drug with food.
- Halofantrine can cause prolonged QT interval, so it should not be used with →
  1. Food → increases absorption, toxicity may occur.
  2. Other drugs causing prolonged QT interval, e.g. cisapride, mefloquine, astemizole, terfenadine etc.
  3. Patients with cardiac disease having prolonged QT interval.
  4. Drugs causing electrolyte imbalance, e.g. diuretics.

## Adverse effects

- Prolongation of QT interval
- Ventricular arrhythmias

## Uses

- **Malaria** →
  - Mainly used for multidrug resistant *falciparum* malaria
  - It should not be used for prophylaxis.

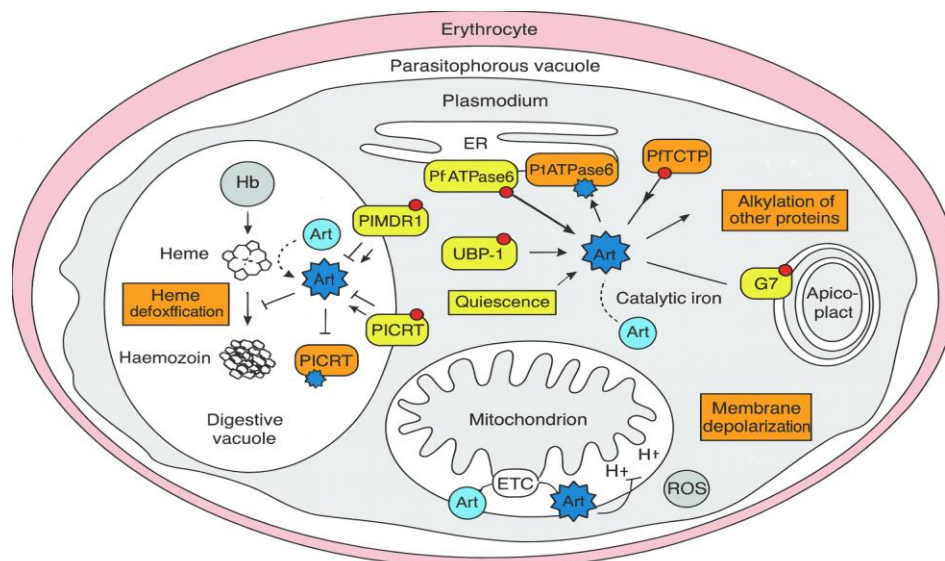
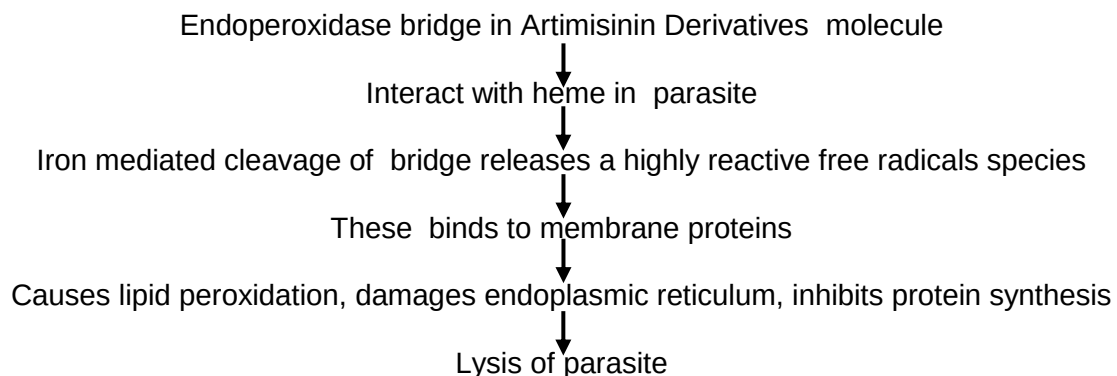


# ARTIMISININ DERIVATIVES

## Introduction

- Artemisinin is active principle of plant *Artemisia annua*
- Fastest acting erythrocytic schizontocide.
- Active against *P. falciparum* resistant to all other antimalarial drugs as well as sensitive strains and other malarial species.
- **Artesunate**
  - Its sodium salt is water-soluble
  - Administered by oral, i.m. or i.v. routes.
  - In addition, rectal route has been tried.
- **Artemether**
  - It is lipid-soluble
  - Administered orally or i.m., but not i.v
- **$\alpha/\beta$  Arteether**
  - This compound developed in India
  - Available for i.m. administration only to adults for complicated malaria.
- **Dihydroartemisinin and Arterolane**  
Available for oral use only

## MOA



## Adverse effects

1. **GIT** → nausea, vomiting and diarrhea
2. **CNS** → Irreversible neurotoxicity
3. **Teratogenic** → avoided in pregnancy if possible because teratogenicity has been seen in animal studies.

## Uses

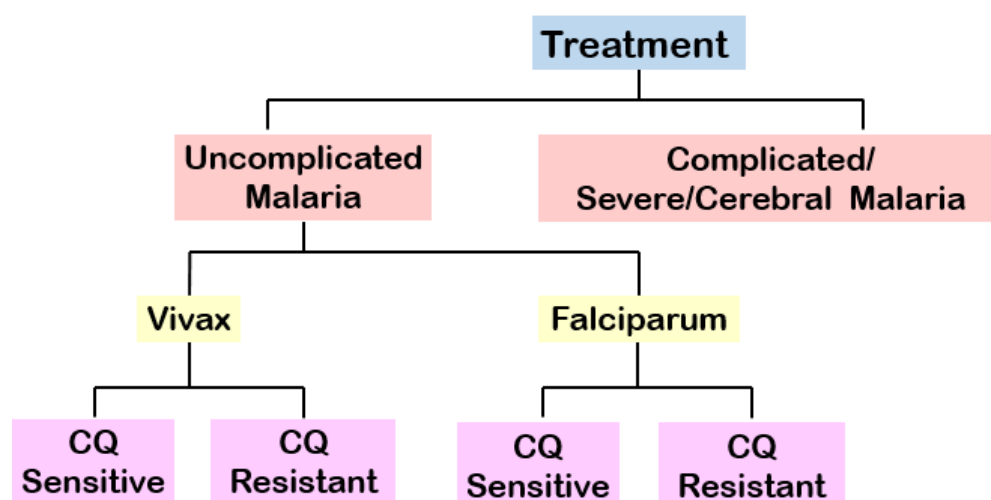
- **Malaria** →
  - Uncomplicated falciparum malaria
  - Severe complicated falciparum malaria

## Artemisinin-based combination therapy (ACT)

- WHO has recommended that all cases of acute uncomplicated falciparum malaria should be treated only by combining one of the artemisinin compounds with another effective erythrocytic schizonticide.

| WHO recommended ACTS                   |
|----------------------------------------|
| • Artemether-Lumefantrine              |
| • Artesunate-Mefloquine                |
| • Artesunate-Amodiaquine               |
| • Dihydroartemisinin-Piperaquine       |
| • Artesunate-Sulfadoxine-Pyrimethamine |
| • Arterolane - Piperaquine             |

## TREATMENT OF MALARIA



## A) Uncomplicated Malaria

|                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------|
| <b>1. Vivax CQ sensitive</b>                                                                                             |
| Chloroquine x 3 days + Primaquine x 14 days                                                                              |
| <b>2. Vivax CQ Resistant</b>                                                                                             |
| ACT x 7 days + Primaquine x 14 days<br>OR<br>Quinine x 7 days + Doxycycline/ Clindamycin x 7 days + Primaquine x 14 days |
| <b>3. Falcifarum CQ Sensitive</b>                                                                                        |
| Chloroquine x 3 days + Primaquine single dose. (on day 2)                                                                |
| <b>4. Falcifarum CQ resistant</b>                                                                                        |
| ACT x 7 days<br>OR<br>Quinine x 7 days + Doxycycline/ Clindamycin x 7 days + Primaquine single dose                      |

## B) Treatment of Complicated / Cerebral falciparum malaria

- Quinine x 7 days  
Or
- Artesunate x 7 days  
Or
- Artemether x 7 days  
Or
- Artether x 5 days

## Chemoprophylaxis

- **For short-term chemoprophylaxis (<6 weeks):**
  - Doxycycline → Drug should be started 2 days before travel and continued for 4 weeks after leaving the malaria endemic area.
- **Long-term chemoprophylaxis (>6 weeks):**
  - Mefloquine → Administered two weeks before, during and four weeks after leaving the area.

## Treatment of Malaria in Pregnancy

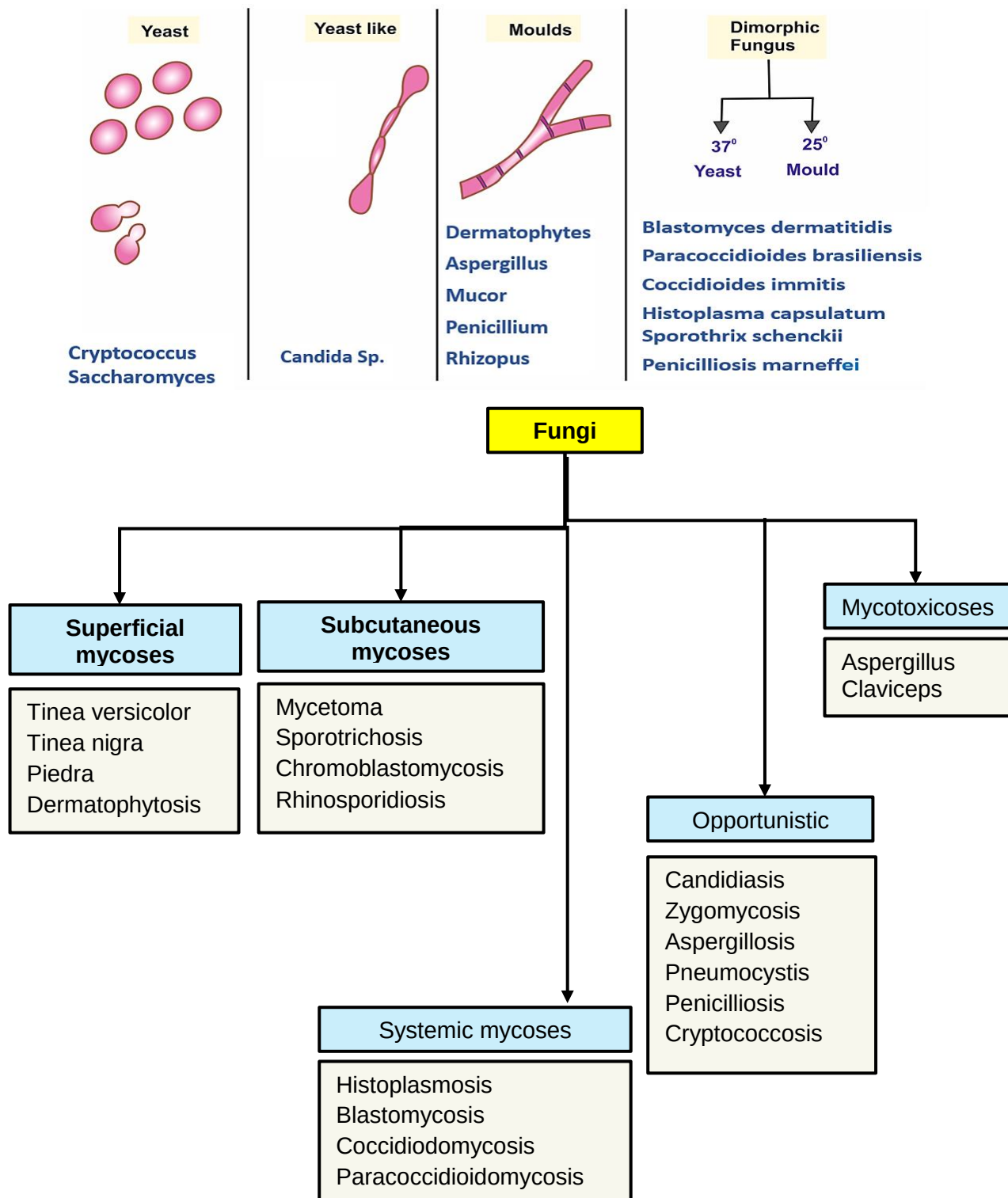
|                               | Pregnancy 1 <sup>st</sup> trimester          | Pregnancy 2 <sup>nd</sup> and 3 <sup>rd</sup> trimester  |
|-------------------------------|----------------------------------------------|----------------------------------------------------------|
| P. Vivax                      | Chloroquine (3 days)                         | Chloroquine (3 days)                                     |
| P. Falciparum                 | Quinine (3 days)                             | Artesunate (3 days) + Sulfadoxine/ pyrimethamine (1 day) |
| Severe or complicated malaria | Parenteral Quinine (Minimum 24 hours) + Oral | Parenteral artemisinin derivative                        |



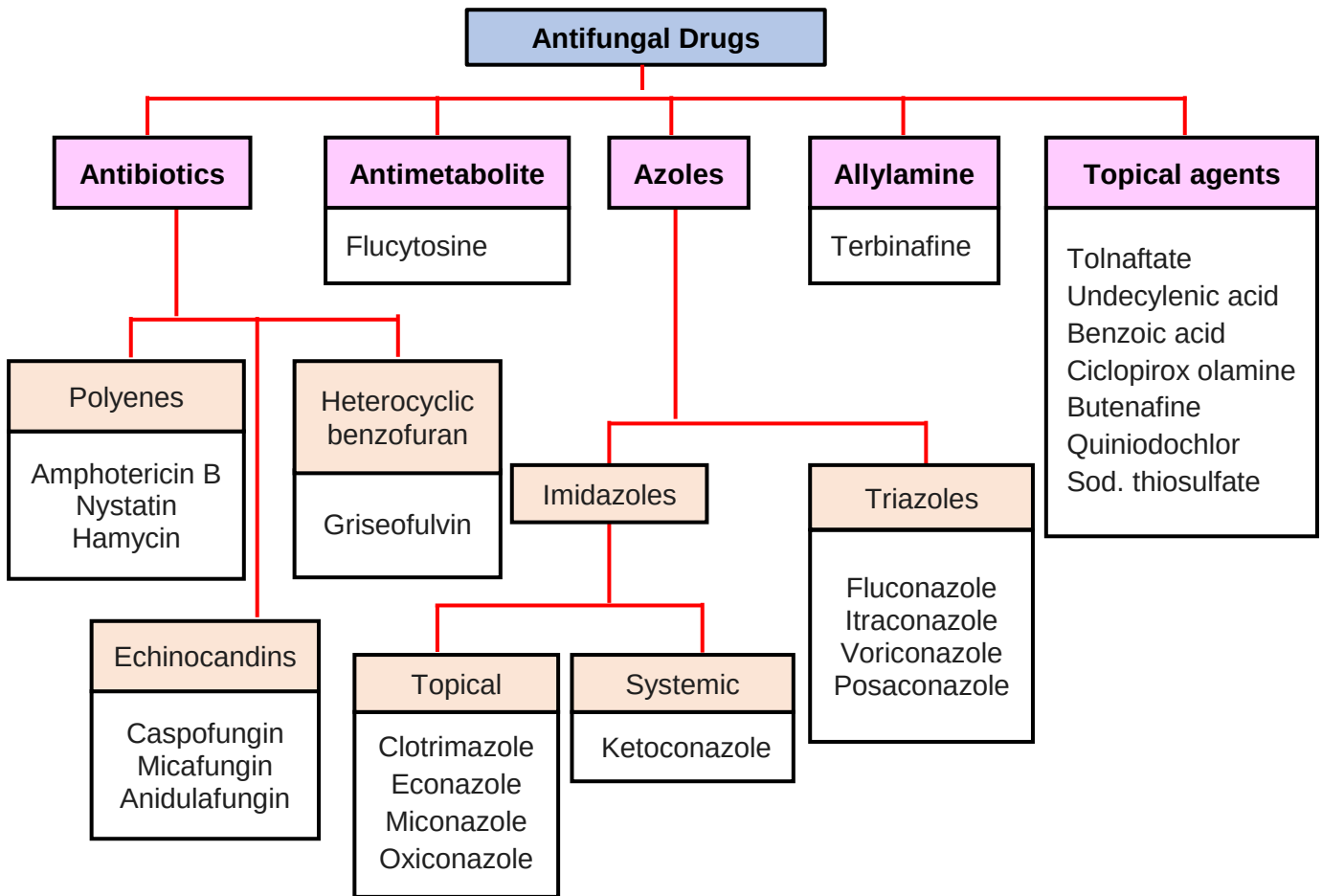
|  |                                          |                                                        |
|--|------------------------------------------|--------------------------------------------------------|
|  | quinine +<br>Clinadmycin (for 7<br>days) | (minimum 24<br>hours) followed by<br>oral ACT (3 days) |
|--|------------------------------------------|--------------------------------------------------------|

## ANTIFUNGAL DRUGS

### Classification of Fungi

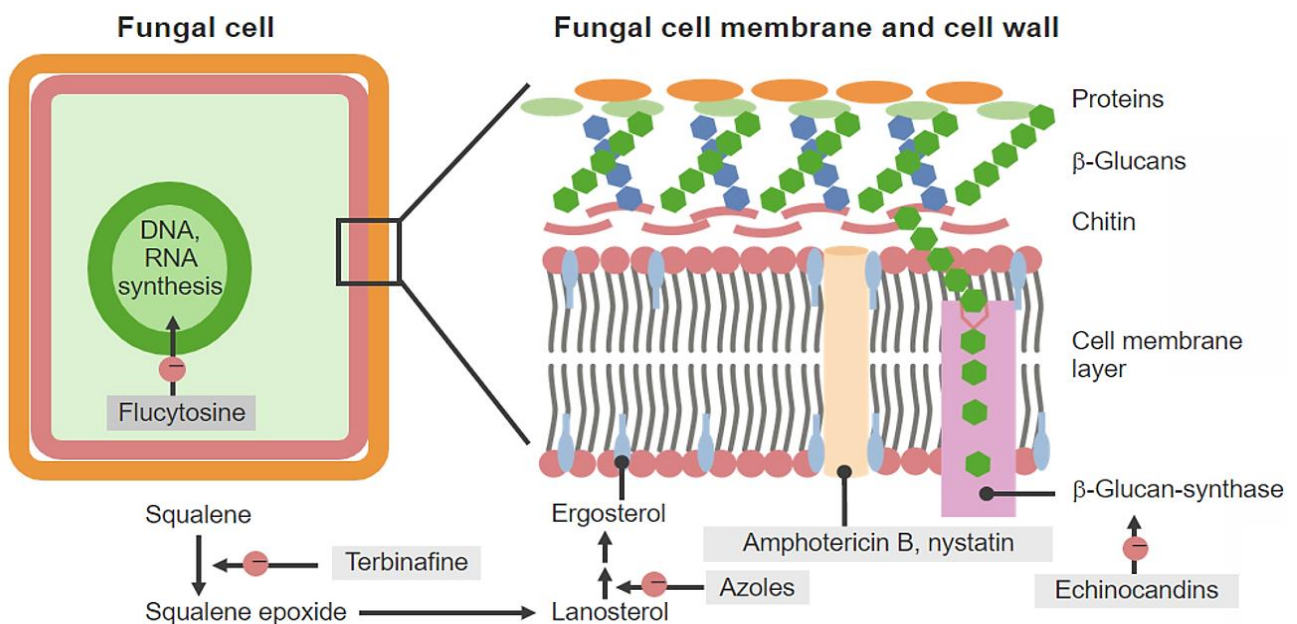


## Classification of Antifungal Drugs



## MOA

1. **Altering membrane permeability** → Polyenes, Azoles, Allylamines.
2. **Inhibit cell wall synthesis** → Caspofungins
3. **Interferes with mitosis (disrupts microtubules)** → Griseofulvin
4. **Inhibit nucleic acid synthesis (inhibit thymidylate synthase)** → Flucytosine (5-FC)



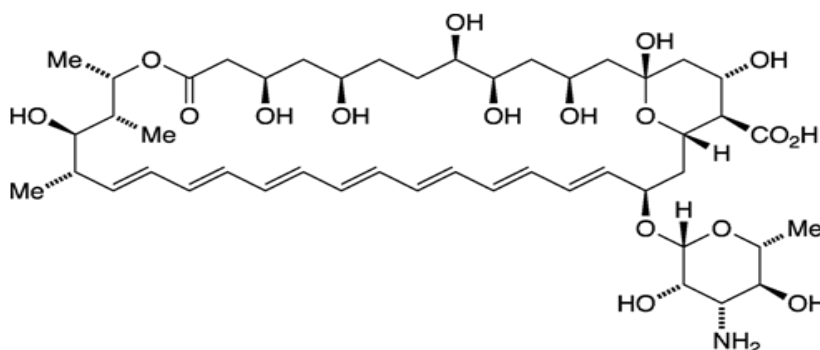
|                  | Antibiotics |               |                          | Antimetabolites |
|------------------|-------------|---------------|--------------------------|-----------------|
|                  | Polyenes    | Echinocandins | Heterocyclic benzofurans |                 |
| Introduction     |             |               |                          |                 |
| Drugs            |             |               |                          |                 |
| MOA              |             |               |                          |                 |
| Pharmacokinetics |             |               |                          |                 |
| Interactions     |             |               |                          |                 |
| Adverse effects  |             |               |                          |                 |
| Uses             |             |               |                          |                 |

|                  | Azoles     |           | Allylamines |
|------------------|------------|-----------|-------------|
|                  | Imidazoles | Triazoles |             |
| Introduction     |            |           |             |
| Drugs            |            |           |             |
| MOA              |            |           |             |
| Pharmacokinetics |            |           |             |
| Interactions     |            |           |             |
| Adverse effects  |            |           |             |
| Uses             |            |           |             |

## POLYENES

### Introduction

- Name polyene is derived from their highly double-bonded structure.
- Amphotericin B is the prototype



## Drugs

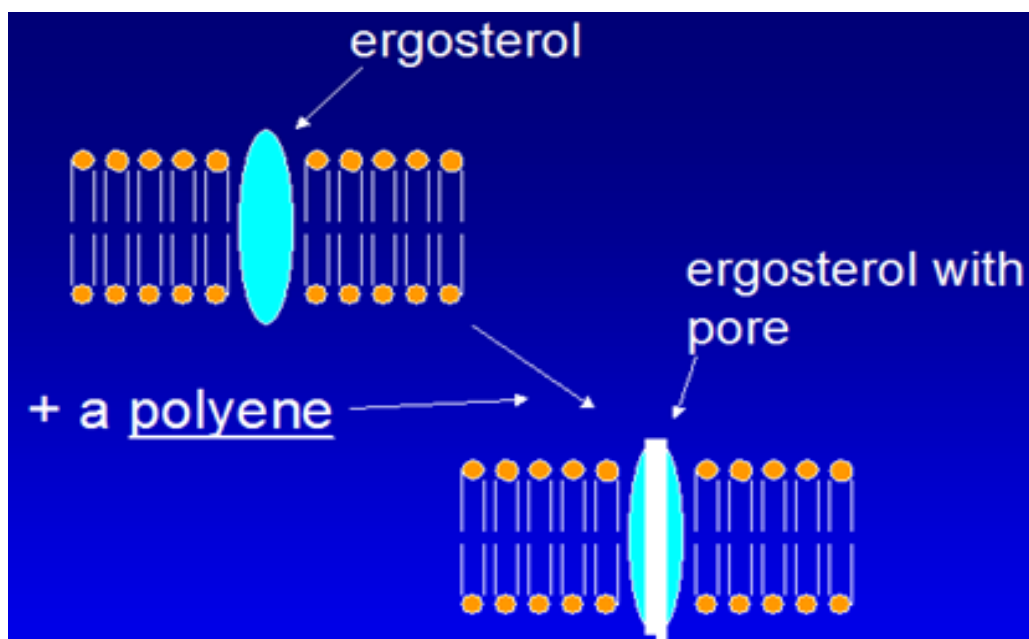
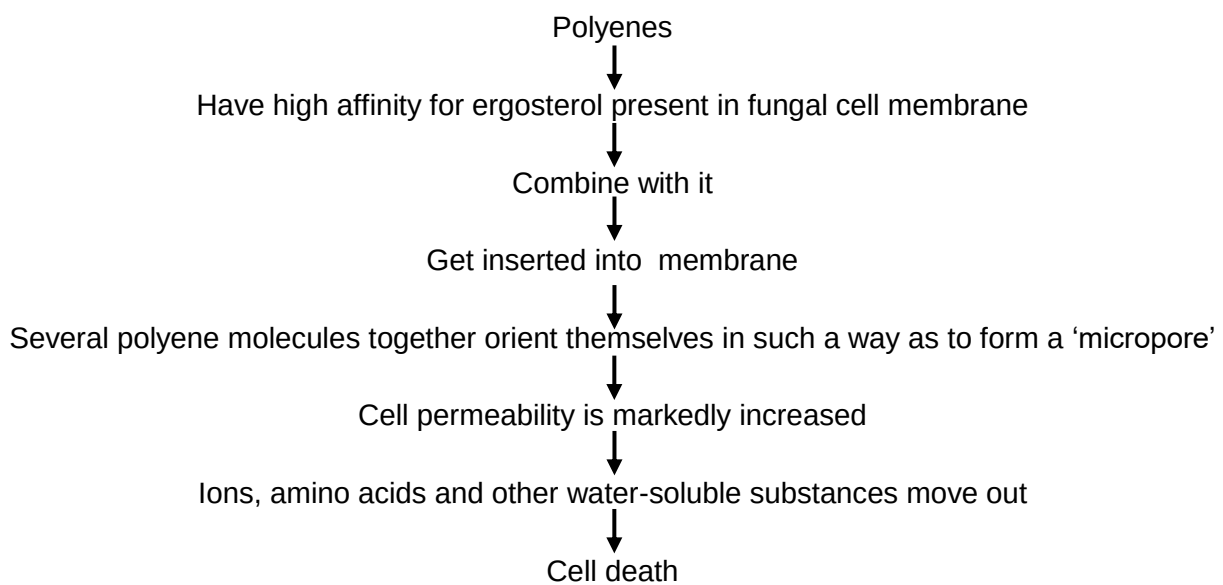
- Amphotericin B
- Nystatin
- Hamycin

## AMPHOTERICIN-B

### Introduction

- Obtained from *Streptomyces nodosus*

### MOA



- It is fungicidal at high and static at low concentrations

Cholesterol present in host cell membranes → closely resembles ergosterol

↓  
Polyenes bind to it as well, though with lesser affinity.

↓  
AMB is one of most toxic systemically used antibiotics

- Bacteria do not have sterols and are unaffected by polyenes

## Pharmacokinetics

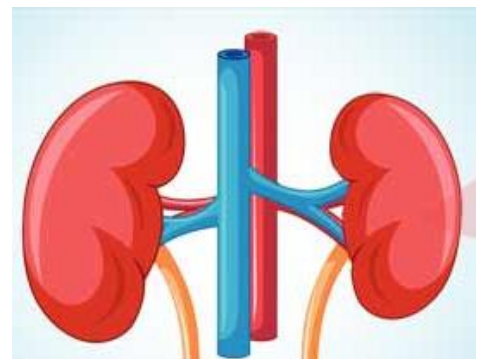
1. AMB is not absorbed orally; it can be given orally for intestinal candidiasis without systemic toxicity.
2. Administered i.v. as a suspension made with help of deoxycholate (DOC), it gets widely distributed in the body
3. It can also be used intrathecally for fungal meningitis
4. Topically for corneal ulcer (keratitis).

## Adverse effects

1. Infusion related acute reactions (most common)
2. Anemia
3. Hypokalemia
4. Phlebitis
5. Headache, anorexia, vomiting, fever with chills (prevented by hydrocortisone)

## Nephrotoxicity

- Most important dose limiting toxicity is nephrotoxicity
- Risk is in more than 80% cases
- Manifestations → azotemia, reduced g.f.r., acidosis, hypokalaemia and inability to concentrate urine.
- Reverses slowly and often incompletely after stoppage of therapy
- Concomitant use of other nephrotoxic drugs (aminoglycosides, cyclosporine, vancomycin) should be avoided



## Parameters to monitored

- Important parameters which should be monitored during AMB therapy →
  1. Serum creatinine
  2. Serum K
  3. Serum Mg

## Minimized by

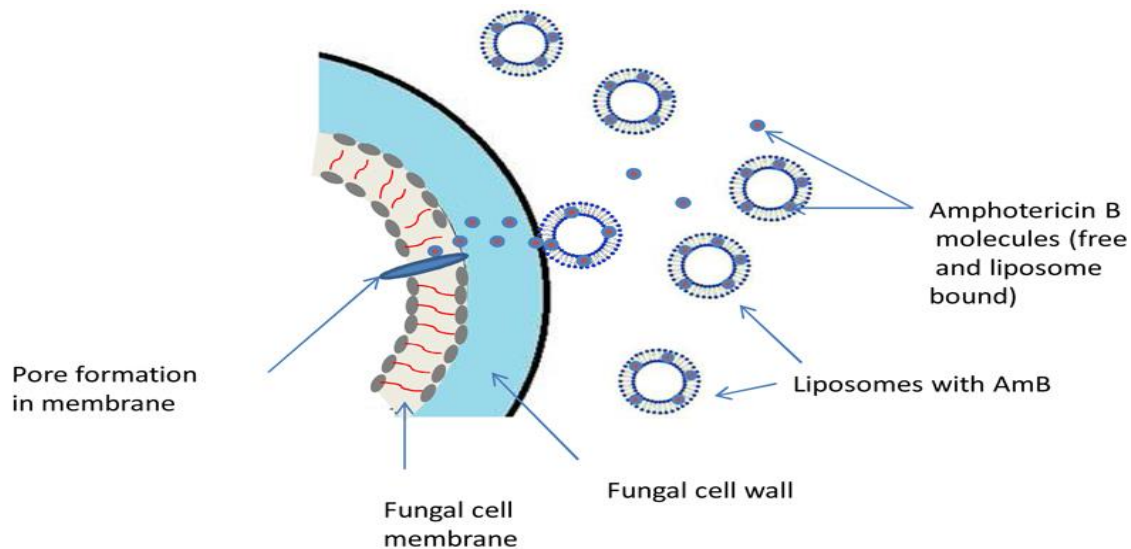
- Adequate hydration
- Pre and post infusion of mannitol
- Alternate day therapy
- Use of liposomal amphotericin-B → special lipid formulations that carries less risk of toxicity





## Liposomal amphotericin B (L-AMB)

- Produced to improve tolerability of i.v. infusion of AMB
- Reduce its toxicity
- Achieve targeted delivery
- It consists of 10% AMB incorporated in uniform sized (60–80 nM) unilamellar liposomes made up of lecithin and other biodegradable phospholipids
- Liposomal-AMB produces equivalent blood levels, has similar clinical efficacy with less acute reaction and renal toxicity than conventional preparation.
- Costlier than conventional AMB.



## Advantages

- Produce milder acute reaction on i.v. infusion.
- Can be used in patients not tolerating infusion of conventional AMB formulation.
- Lower nephrotoxicity.
- Causes minimal anaemia.

## Uses

- Most effective drug for various types of systemic mycoses
- Gold standard of antifungal therapy.
- Widest antifungal spectrum.

## DOC or 2nd DOC for most of fungal infections

- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Paracoccidioidomycosis
- Cryptococcal meningitis
- Mucormycosis
- Candidal endocarditis.
- Systemic aspergillosis

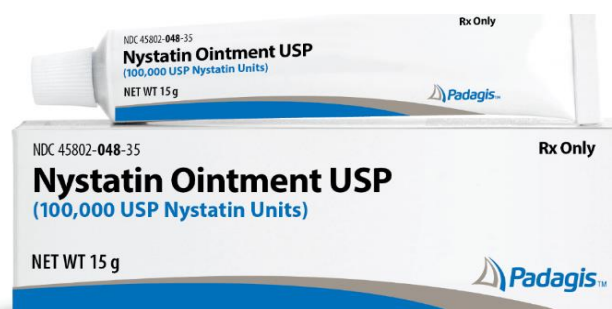
## Remember

- **Because of higher toxicity of AMB** → Azole antifungals are now preferred in conditions where their efficacy approaches that of AMB
- **In immunocompromised patients** → it's the first line drug

| Disease                                                    | Drugs                     |                       |
|------------------------------------------------------------|---------------------------|-----------------------|
|                                                            | 1st Choice                | 2nd Choice            |
| 1. Candidiasis<br>oral/vaginal /cutaneous<br>deep/invasive | FLU / NYS/CLO<br>AMB/VORI | ITR<br>FLU/CAS / POSA |
| 2. Cryptococcosis                                          | AMB ± 5-FC                | FLU                   |
| 3. Histoplasmosis                                          | ITR/AMB                   | FLU                   |
| 4. Coccidioidomycosis                                      | AMB/FLU                   | ITR/KTZ               |
| 5. Blastomycosis                                           | ITR/AMB                   | KTZ/FLU               |
| 6. Sporotrichosis<br>(disseminated)                        | AMB                       | ITR                   |
| 7. Paracoccidioidomycosis                                  | ITR/AMB                   | AMB                   |
| 8. Aspergillosis                                           | VORI/AMB                  | ITR/CAS/POSA          |
| 9. Mucormycosis                                            | AMB                       | POSA                  |
| 10. Chromomycosis                                          | ITR                       | TER/POSA              |

## NYSTATIN

- Obtained from → *S. noursei*
- Similar to AMB in antifungal action and other properties.
- Because of higher systemic toxicity → used only locally in superficial candidiasis.



## HAMYCIN

- Isolated from → *S. pimprina*
- Similar to nystatin
- Use is restricted to topical application for oral thrush, cutaneous candidiasis, monilial and trichomonas vaginitis and otomycosis by Aspergillus.

## ECHINOCANDINS

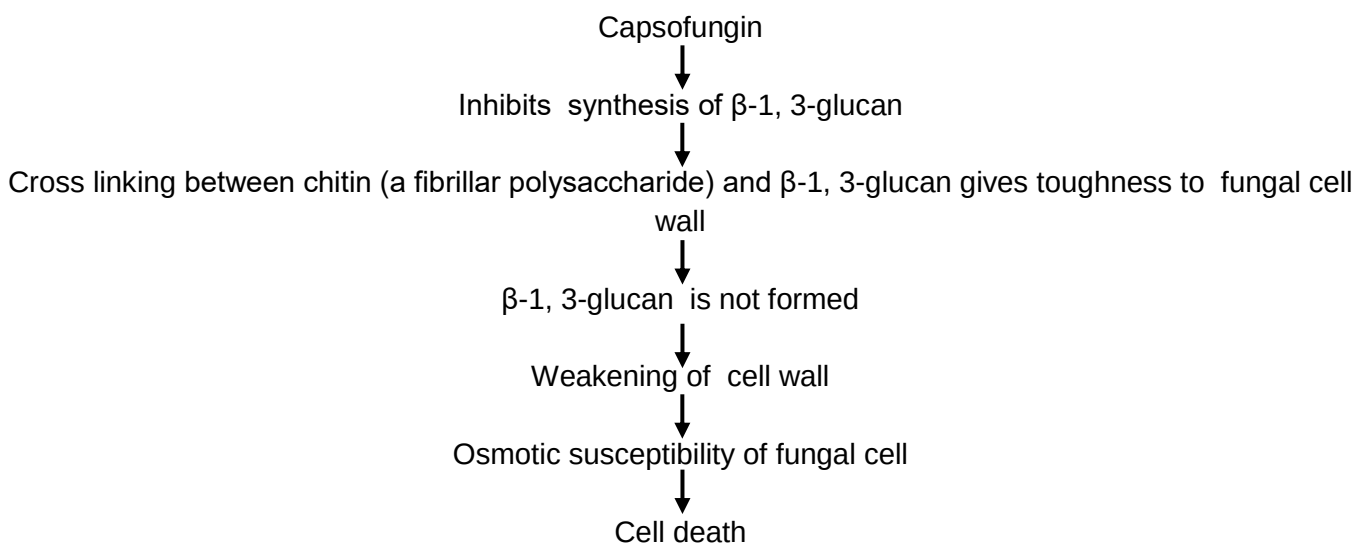
### Introduction

- Complex cyclic lipopeptide structure, which stand out due to their low toxicity compared to AMB.

### Drugs

- Caspofungin
- Micafungin
- Anidulafungin

## CASPOFUNGIN



### Pharmacokinetics

- Caspofungin is not absorbed orally → infused i.v.



### Adverse effects

- Acute febrile reaction some times attends the i.v. infusion of caspofungin
- Phlebitis of injected vein
- Joint pain
- Hypokalemia
- Vomiting
- Dyspnoea



## Uses

1. Deep and invasive candidiasis
2. Esophageal candidiasis
3. Salvage therapy of nonresponsive Invasive aspergillosis.

## Remember

- **Nikkomycins** → act by inhibiting synthesis of chitin component of cell wall.

# HETEROCYCLIC BENZOFURANS

## Drugs

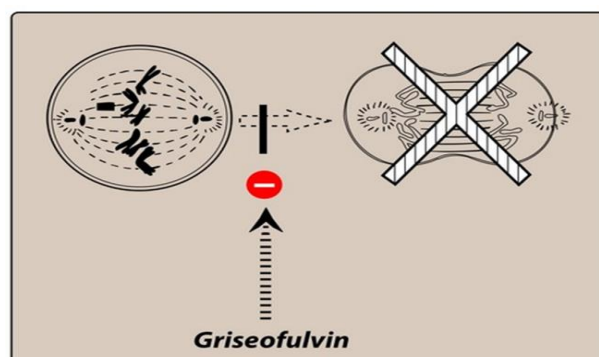
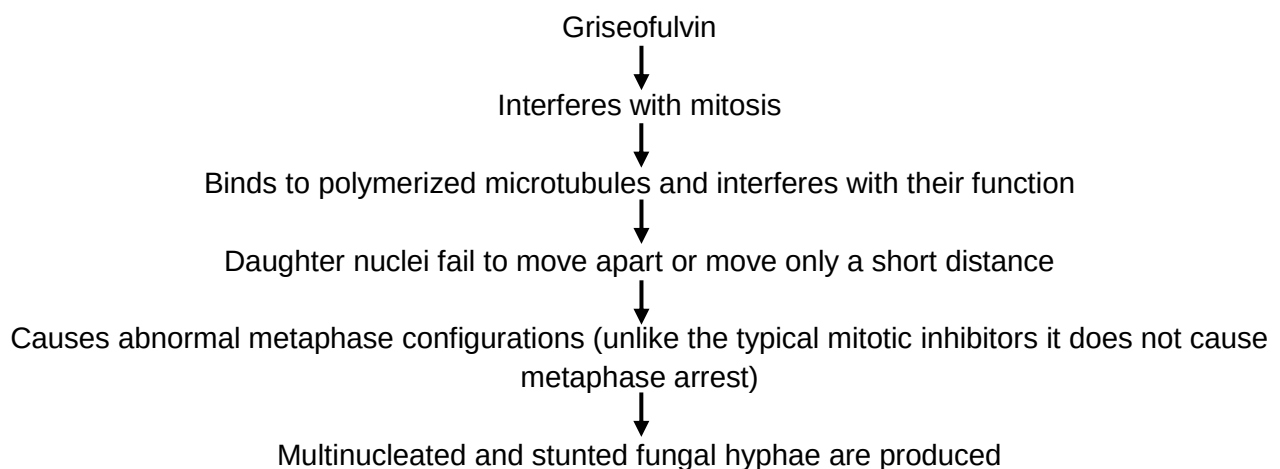
- Griseofulvin

# GRISEOFULVIN

## Introduction

- Extracted from → *Penicillium griseofulvum*.
- Narrow spectrum → Griseofulvin is fungistatic for most Dermatophytes → Epidermophyton, Trichophyton, Microsporum, etc., but not against *Candida* and other fungi causing deep mycosis.

## MOA



- It is fungistatic and not cidal

## Pharmacokinetics

- Plasma  $t_{1/2}$  of griseofulvin is 48 hours
- Absorption is improved by taking it with fat

## Interactions

1. Griseofulvin induces CYP450 enzymes
  - Hastens warfarin metabolism.
  - Efficacy of oral contraceptives may be lost.
2. Griseofulvin can cause intolerance to alcohol □ Disulfiram (antabuse) like reaction
3. Phenobarbitone reduces the oral absorption and induces the metabolism of Griseofulvin

## Adverse effects

- Neurological manifestations
- Hepatitis
- Blood dyscrasias
- Headache
- GI disturbances

## Uses

- Dermatophytoses of skin, Nail, hair (tinea infections) because it gets concentrated in keratin.
  - Griseofulvin is used orally only for dermatophytosis.
  - On getting deposited in skin through circulation, it prevents fungal invasion of keratin.
  - Because it is fungistatic and not cidal → newly formed keratin is not invaded by the fungus, but the fungus persists in already infected keratin, till it is shed off.
  - Thus duration of treatment is dependent upon the site of infection, thickness of infected keratin and its turnover rate.
  - It is ineffective topically



## Duration of therapy

- Scalp → 4 weeks
- Palm, soles → 6 to 8 weeks
- Finger nails → 6 to 8 months
- Toe nails → 10 to 12 months



## ANTIMETABOLITES

### Drugs

- Flucytosine (5-FC)

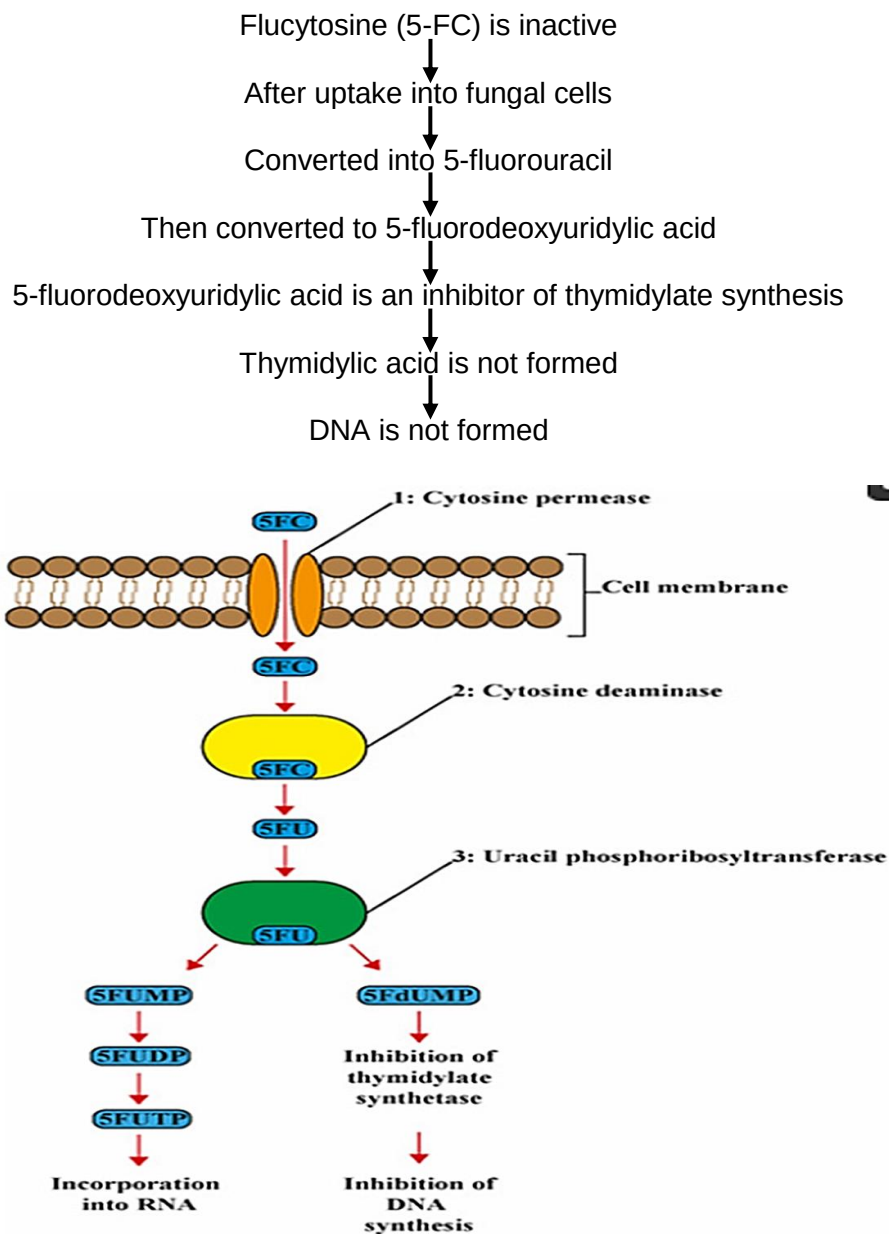
## FLUCYTOSINE (5-FC)

### Introduction

- Narrow spectrum → active against *Cryptococcus neoformans*, *Chromoblastomyces* and a few strains of *Candida*.
- Fungistatic

### MOA

- It is a pyrimidine antimetabolite



- Fungal selectivity of 5-FC depends on the fact that mammalian cells have low capacity to convert 5-FC into 5-fluorouracil
- 5-fluorouracil is a potent anticancer drug.

## Adverse effects

1. Dose-dependent bone marrow depression
2. Gastrointestinal disturbances → enteritis and diarrhoea.
3. Liver dysfunction is mild and reversible.

## Uses

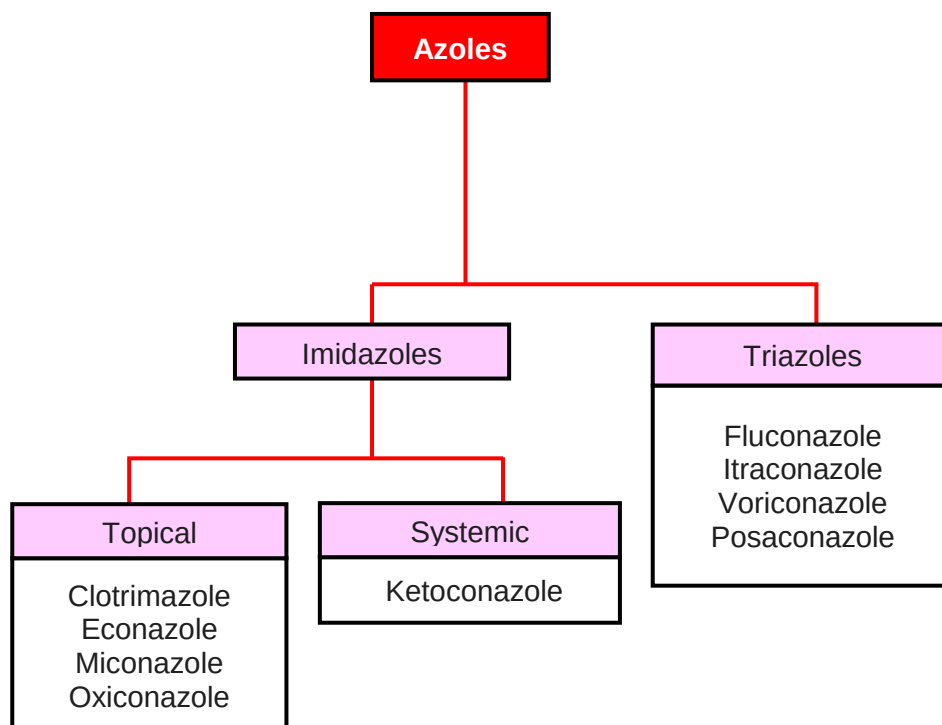
1. Chromoblastomycosis
2. Cryptococcosis (both meningeal and nonmeningeal) its synergistic action with AMB □ So, Amphotericin B makes holes in the cell membrane, and flucytosine enters and inhibits DNA synthesis
3. Therapy with 5-FC is generally limited to first 2 weeks of AMB regimen to avoid its bone marrow toxicity.

# AZOLES

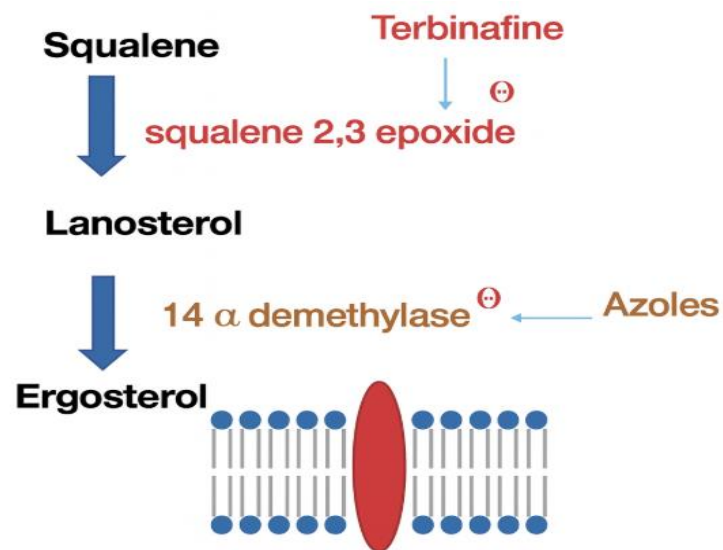
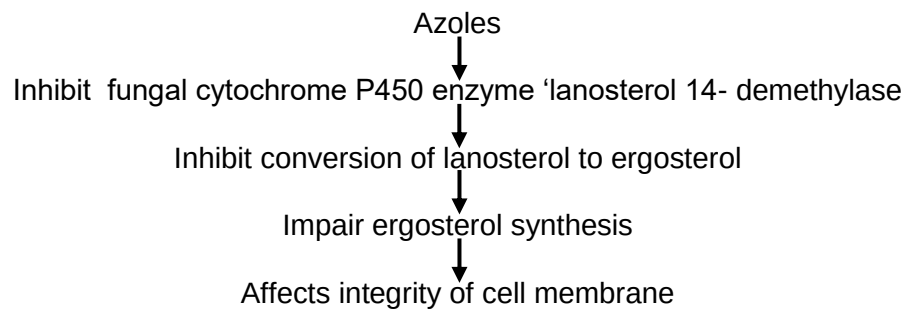
## Introduction

- Most extensively used antifungal drugs
- Broad spectrum antifungal activity covering → dermatophytes, Candida, other fungi involved in deep mycosis (except mucor), Nocardia and Leishmania.

## Drugs



## MOA



## Resistance

- Mutation of the gene encoding for fungal 14-demethylase enzyme

## IMIDAZOLES

- Clotrimazole and econazole:** For topical use only.
- Miconazole:** For topical as well as parenteral use.
- Ketoconazole:** For topical as well as oral use.

## KETOCONAZOLE (KTZ)

- First orally effective broad-spectrum antifungal drug
- Useful in both dermatophytosis and deep mycosis.

## Pharmacoinetics

- Oral absorption of KTZ is facilitated by gastric acidity because it is more soluble at lower pH.
- Penetration in CSF is poor → not effective in fungal meningitis.





## Interactions

- Ketoconazole inhibits CYP450 enzymes
- Raises the blood levels of several drugs including

|               |                           |
|---------------|---------------------------|
| Phenytoin     | Digoxin                   |
| Carbamazepine | Omeprazole                |
| Diazepam      | Cyclosporine              |
| Haloperidol   | Nifedipine and other DHPs |
| Warfarin      | HIV protease inhibitors   |
| Sulfonylureas | Statins                   |

- Dangerous interaction with terfenadine, astemizole and cisapride resulting in polymorphic ventricular tachycardia due to excessive rise in plasma levels of these drugs

## Adverse effects

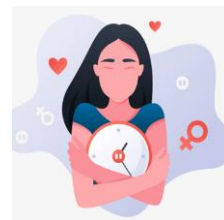
1. Nausea and vomiting
2. Hormonal effects
3. Others

### 1. Nausea and vomiting

- Most common side effects are nausea and vomiting
- Can be reduced by giving the drug with meals.

### 2. Hormonal effects

- Most important draw back of KTZ is its hormonal effects.
  - a. It decreases androgen production from testes, and displaces testosterone from protein binding sites
  - b. Suppression of estradiol synthesis
    - Men → Gynaecomastia, loss of hair and libido, and oligozoospermia
    - Women → Menstrual irregularities occur in some



### 3. Others

- Loss of appetite
- Headache
- Paresthesia
- Rashes
- Hair loss

## Contraindication

- Pregnant
- Nursing women



## Uses

- Orally administered KTZ is effective in dermatophytosis because it is concentrated in the stratum corneum
- Used as a lotion or shampoo, KTZ is quite effective in seborrhoea of scalp and dandruff
- Monilial vaginitis
- Systemic mycosis
- Dermal leishmaniasis and in kala azar.
- High-dose KTZ has been used in Cushing's syndrome to decrease corticosteroid production

## CLOTRIMAZOLE

- Penetrates superficial layers of the skin
- Effective in the topical treatment of →
  1. Tinea infections like ringworm
  2. Athletes' foot
  3. Otomycosis
  4. oral/cutaneous/ vaginal candidiasis

## ECONAZOLE

- Similar to clotrimazole
- Penetrates superficial layers of the skin
- Highly effective in □ dermatophytosis, otomycosis, oral thrush, but is inferior to clotrimazole in vaginitis.

## MICONAZOLE

- Topical imidazole
- Good penetrating power
- Highly efficacious drug for □ tinea, pityriasis versicolor, otomycosis, cutaneous and vulvovaginal candidiasis.

## OXICONAZOLE

- Newer topical imidazole
- Antifungal effective in  $\square$  tinea and other dermatophytic infection, as well as vaginal candidiasis.

## TRIAZOLES

### Drugs

| Triazoles                                                   |
|-------------------------------------------------------------|
| Fluconazole<br>Itraconazole<br>Voriconazole<br>Posaconazole |

## FLUCONAZOLE

- Oral bioavailability is not affected by food or gastric pH.

### Adverse effects

1. GIT : mostly nausea, vomiting, abdominal pain
2. Elevation of hepatic transaminase in AIDS patients.
3. Not recommended in pregnant and lactating mothers.

### Remember

- Unlike KTZ, it does not inhibit steroid synthesis in man
- So antiandrogenic and other endocrine side effects have not occurred

### Use

1. Candidiasis  $\rightarrow$  Vaginal, Oropharyngeal , Cutaneous, Disseminated
2. Cryptococcal / coccidioidal meningitis (good CSF penetration)
3. Tinea infections

## ITRACONAZOLE

- Broader spectrum of activity than KTZ or fluconazole  $\square$  includes some moulds like Aspergillus
- Steroid hormone synthesis inhibition is absent in itraconazole, and serious hepatotoxicity is rare

## VORICONAZOLE

- Widest spectrum.
- DOC for invasive aspergillosis.

- Specific side effects of voriconazole □ visual disturbances like blurred vision, photophobia & altered color perception.

## POSACONAZOLE

- Only azole which has shown efficacy in mucormycosis.
- Indicated for salvage therapy of this difficult to treat fungal infection.
- Because of its high cost and limited experience □ it is reserved for nonresponsive cases of aspergillosis and invasive candidiasis.

### Remember

- **Ketoconazole, itraconazole, voriconazole** → inhibit CYP3A4 → dangerous arrhythmias with terfenadine, astemizole and cisapride.
- **Fluconazole** → causes ventricular tachycardia with cisapride (relatively safe).
- **Fluconazole** → best penetration into CSF → Preferred azole for cryptococcal meningitis.
- **Voriconazole** → widest spectrum → DOC for invasive aspergillosis.
- **Posaconazole** → only azole active against mucormycosis

## ALLYLAMINES

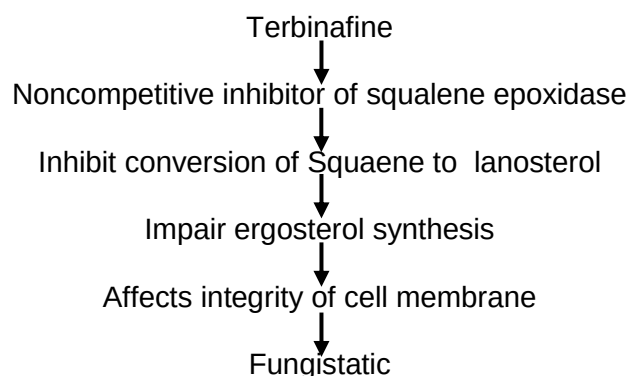
### Drugs

- Terbinafine

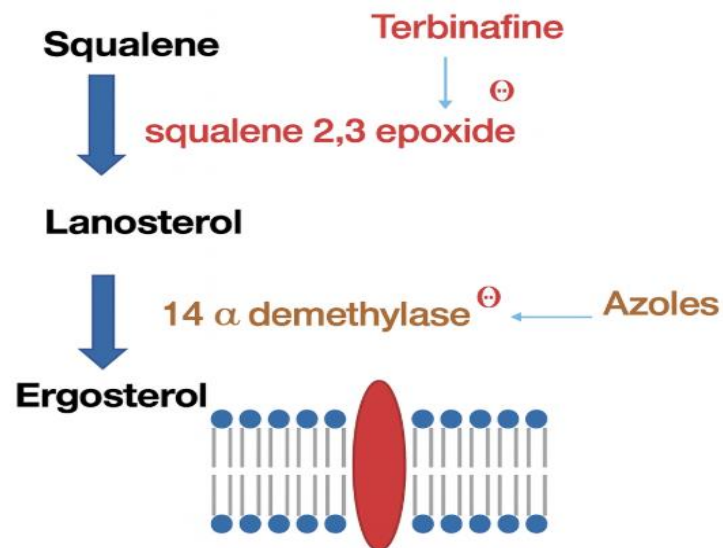
## TERBINAFINE

### Introduction

- Orally and topically active
- High affinity for keratin → concentrated in sebum, stratum corneum of skin and into nail plates.
- Active drug against dermatophytes and Candida



- Accumulation of squalene within fungal cells
- Fungicidal



- Mammalian enzyme is inhibited only by 1000-fold higher concentration of terbinafine.
- Terbinafine does not inhibit CYP450.

### Adverse effects

- Gastric upset
- Rashes
- Taste disturbance

### Uses

- Topically as 1% cream in → localized tinea pedis/ cruris/corporis and pityriasis versicolor
- Oral treatment → onychomycosis, tinea capitis and wide spread lesions.
- Efficacy in nail infection is 80%, which is higher than griseofulvin and itraconazole.

## TREATMENT OF FUNGAL INFECTIONS

- A. Treatment of systemic fungal infections
- B. Treatment of superficial fungal infections

### A. Treatment of systemic fungal infections

1. Amphotericin-B
2. Flucytosine
3. Triazoles
4. Ketoconazole
5. Allylamine (terbinafine)
6. Echinocandins (capsofungin, micafungin and anidulafungin) and nikkomycin

### B. Treatment of superficial fungal infections

#### a) Systemic drugs for superficial fungal infections

1. Griseofulvin
2. Allylamines (terbinafine, naftifine, butenafine)
3. Azoles (ketoconazole, fluconazole, itraconazole) Voriconazole is not used for this purpose.

## b) Topical drugs for superficial fungal infection

1. Polyenes (Nystatin, hamycin, natamycin)
2. Imidazoles (clotrimazole, econazole, miconazole, oxiconazole, ketoconazole)
3. Allylamines (terbinafine, butenafine, naftifine)
4. Tolnaftate, ciclopirox olamine, undecylenic acid, haloprogin, quiniodochlor, sodium thiosulfate and whitfields ointment (benzoic acid with salicylic acid)

## DRUGS OF CHOICE

### Amphotericin B is DOC

1. Disseminated candidiasis (voriconazole is alternative first line DOC)
2. Coccidioidomycosis
3. Cryptococcal meningitis
4. Mucormycosis,
5. Aspergillosis (voriconazole is preferred)
6. Disseminated sporotrichosis.

### Itraconazole is DOC

- Chromomycosis

### Voriconazole is DOC

1. Aspergillosis
2. Candida infection
3. Fusarium infection

| Disease                                                    | Drugs                     |                       |
|------------------------------------------------------------|---------------------------|-----------------------|
|                                                            | 1st Choice                | 2nd Choice            |
| 1. Candidiasis<br>oral/vaginal /cutaneous<br>deep/invasive | FLU / NYS/CLO<br>AMB/VORI | ITR<br>FLU/CAS / POSA |
| 2. Cryptococcosis                                          | AMB ± 5-FC                | FLU                   |
| 3. Histoplasmosis                                          | ITR/AMB                   | FLU                   |
| 4. Coccidioidomycosis                                      | AMB/FLU                   | ITR/KTZ               |
| 5. Blastomycosis                                           | ITR/AMB                   | KTZ/FLU               |
| 6. Sporotrichosis<br>(disseminated)                        | AMB                       | ITR                   |
| 7. Paracoccidioidomycosis                                  | ITR/AMB                   | AMB                   |
| 8. Aspergillosis                                           | VORI/AMB                  | ITR/CAS/POSA          |
| 9. Mucormycosis                                            | AMB                       | POSA                  |
| 10. Chromomycosis                                          | ITR                       | TER/POSA              |

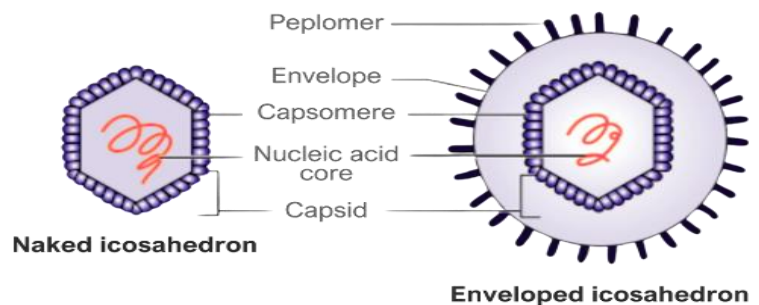
## ANTIVIRAL DRUGS

### Introduction

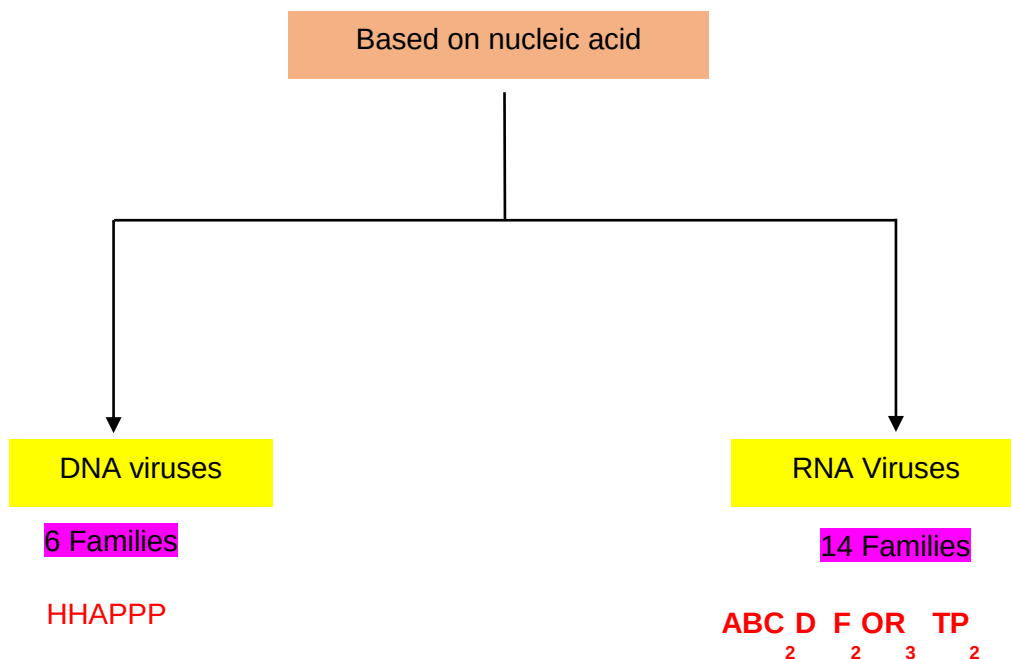
- **Viruses** →
  - Obligate intracellular organisms
  - Take nutrition from host cell
  - Direct host metabolic machinery to synthesize new virus particles.

### Morphology of virus

- **Nucleic acid core** → Genome
- **Capsid** → protein coat Surrounding Nucleic acid
- **Envelop** → Some viruses also have envelop



### Classification of Viruses



### DNA viruses → 6 families

Mnemonic → **HHAPPP**

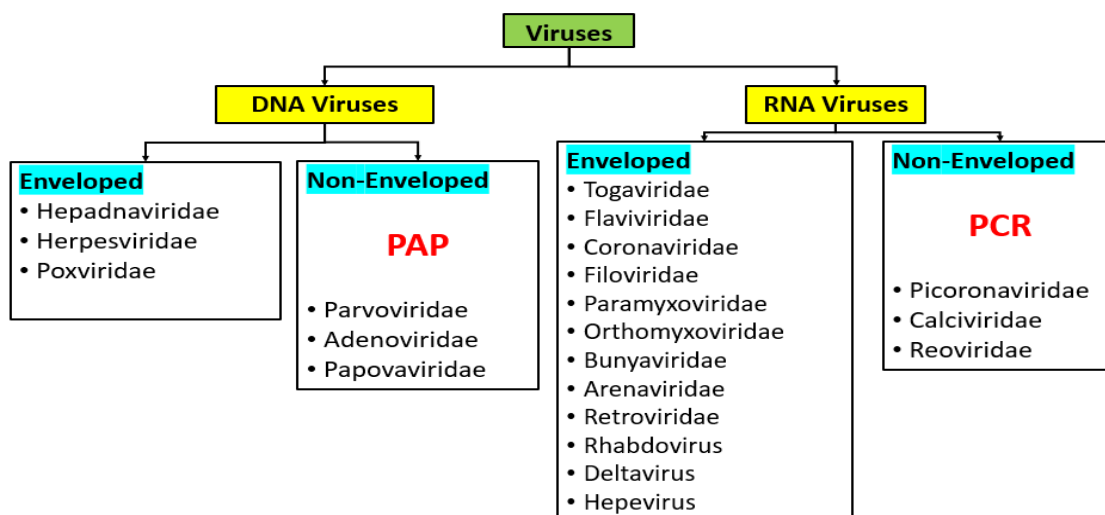
- **H**erpes → HSV-1, HSV-2, VZ, EBV, CMV, HHV – 6, HHV – 7, HHV - 8
- **H**epadna → HBV
- **A**deno → Adenovirus
- **P**ox → Variola, Molluscum contagiosum virus
- **P**arvo → Parvovirus B19
- **P**apova → Papilloma (HPV), Polymavirus (BK and JC virus)

## RNA viruses → 14 families

Mnemonic → **ABC<sub>2</sub>D F<sub>2</sub>OR<sub>3</sub> TP<sub>2</sub>**

- **A**rena → Lassa fever virus
- **B**unya → California encephalitis virus, hantavirus
- **C**alici → Norwalk virus, HEV
- **C**orona → Coronaviruses
- **D**eltav → HDV
- **F**ilo → Ebola, Marburg
- **F**lavi → Yellow fever, Dengue, West Nile virus, JE, KFD, Zika, HCV
- **O**rtomyxo → Influenza
- **R**eo → Rotavirus
- **R**habdo → Rabies
- **R**etro → HIV, HTLV
- **T**oga → Rubella, Chickengunya
- **P**aramyxo → Measles, Mumps, RSV, Parainfluenza, Nipah, Hendra
- **P**icorna → Poliov, Rhino, Cox sackie, HAV

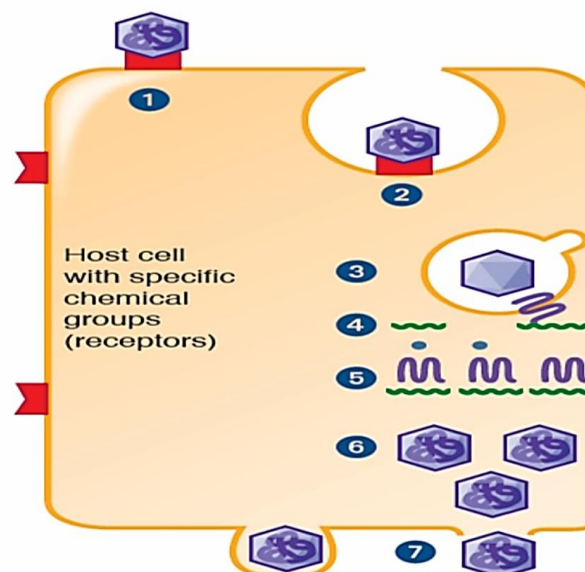
## Enveloped and Non enveloped (Nacked) Viruses



## Replication of Viruses

7 steps →

1. Attachment / Adsorption
2. Penetration
3. Uncoating
4. Biosynthesis
5. Assembly
6. Maturation
7. Release





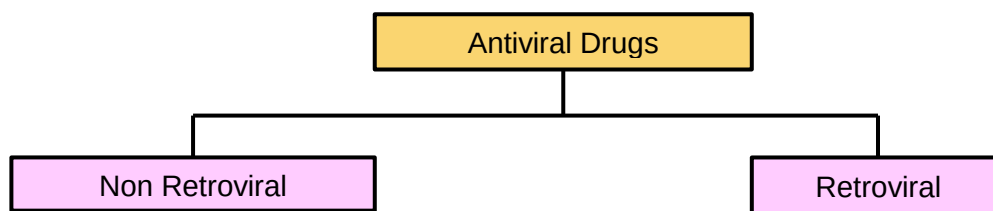
## Difficulties in Generating Effective Antiviral Drugs

- Lack of specific viral targets.
- Viruses replicate intracellularly.
- Asymptomatic during rapid growth phase
- Escape from Immune Surveillance.
- Persistence of Latent Reservoirs.
- Generation of Drug Resistance.

## Antiviral therapy based on

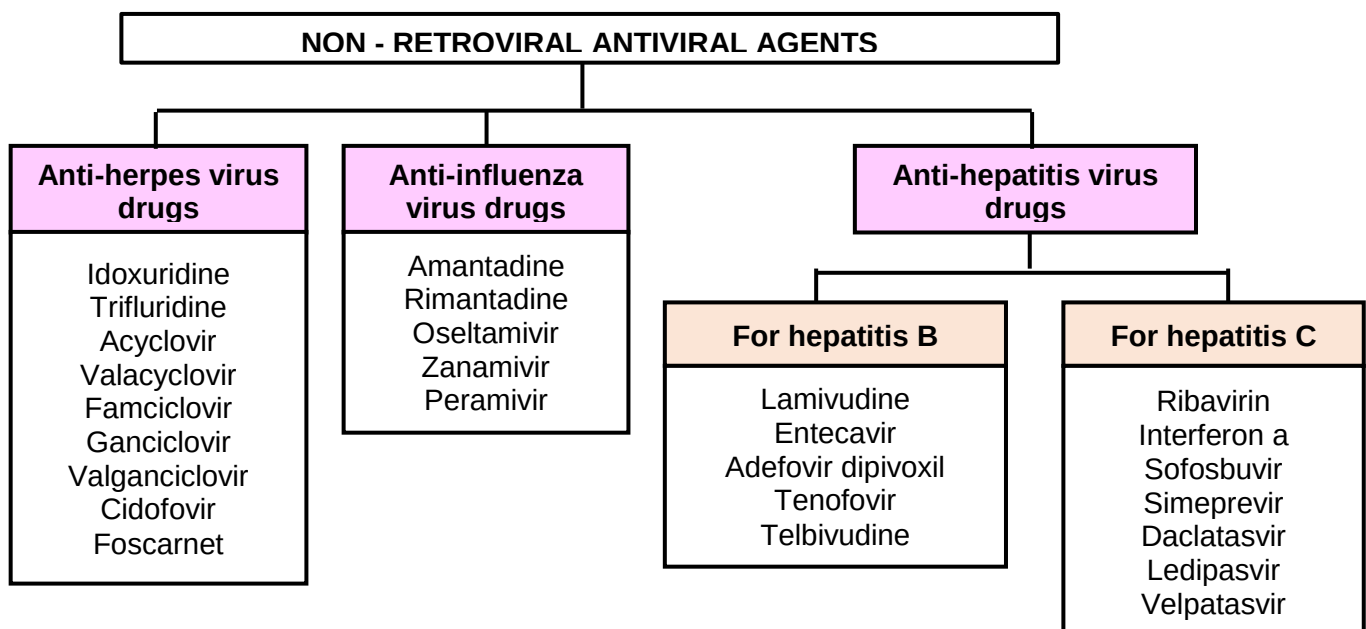
- Some Virus directed enzymes have been identified in the infected cell
- Some viruses have few enzymes of their own
- Drugs have been developed which target virus specific steps like cell penetration, uncoating, reverse transcription, virus assembly or maturation and release from host cell, etc

## Types



## NON - RETROVIRAL ANTIVIRAL AGENTS

### Classification



## ANTI - HERPES VIRUS DRUGS

### Herpes Classification

| Name               | Common name                             |
|--------------------|-----------------------------------------|
| Herpesvirus type 1 | HSV - 1                                 |
| Herpesvirus type 2 | HSV - 2                                 |
| Herpesvirus type 3 | Varicella Zoster virus                  |
| Herpesvirus type 4 | Epstein Barr virus                      |
| Herpesvirus type 5 | Cytomegalovirus                         |
| Herpesvirus type 6 | Human B cell lymphotropic virus         |
| Herpesvirus type 7 | R K virus                               |
| Herpesvirus type 8 | Kaposi's sarcoma-associated herpesvirus |

### Drugs

1. Idoxuridine
2. Trifluridine
3. Acyclovir
4. Valacyclovir
5. Famciclovir
6. Ganciclovir
7. Valganciclovir
8. Cidofovir
9. Foscarnet

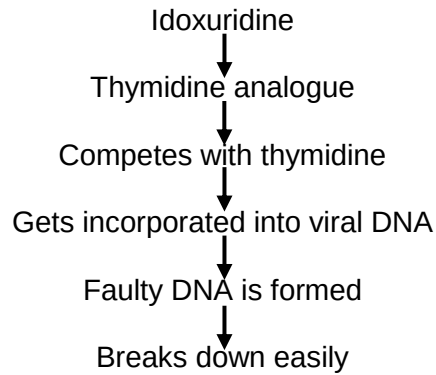
| Anti - Herpes Virus Drugs |             |           |              |             |             |           |
|---------------------------|-------------|-----------|--------------|-------------|-------------|-----------|
|                           | Idoxuridine | Acyclovir | Valacyclovir | Famciclovir | Ganciclovir | Cidofovir |
| Introduction              |             |           |              |             |             |           |
| MOA                       |             |           |              |             |             |           |
| Pharmacokinetics          |             |           |              |             |             |           |
| Uses                      |             |           |              |             |             |           |
| Adverse effects           |             |           |              |             |             |           |

## IDOXURIDINE

### Introduction

- Thymidine analogue.
- First pyrimidine antimetabolite to be used as antiviral drug.

## MOA



## Uses

- Topically used as eye drops for HSV keratoconjunctivitis.



## Adverse effects

1. Local irritation → Itching, Pain
2. Swelling of lids

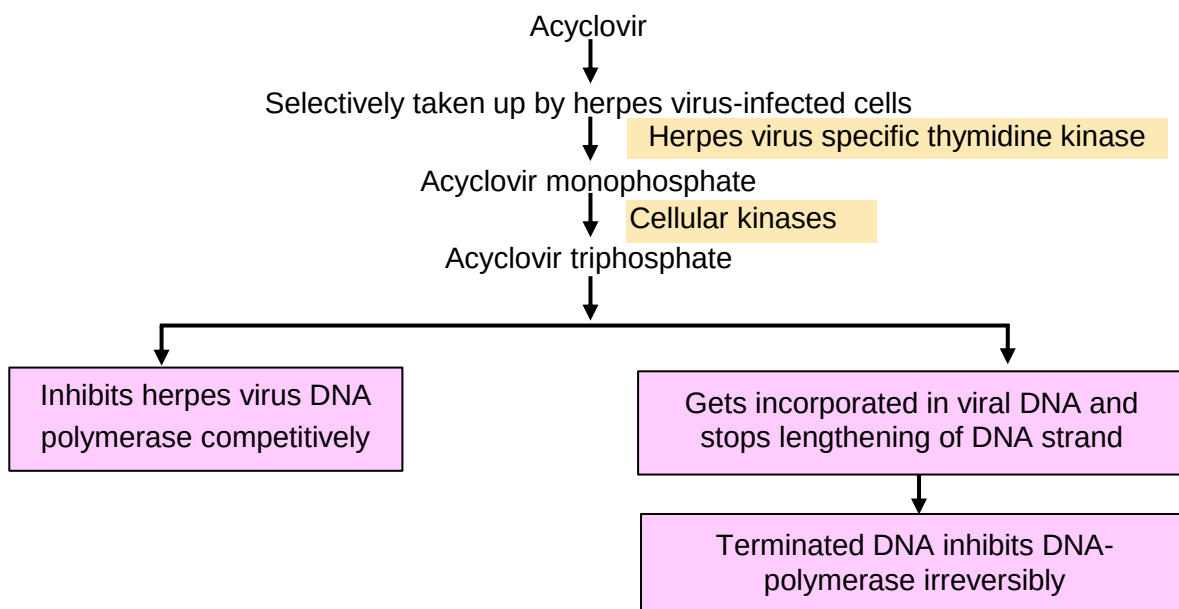


## ACYCLOVIR

### Introduction

- Purine nucleoside analogue

## MOA



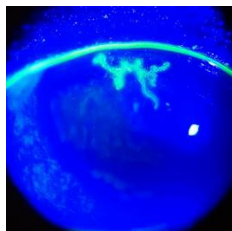
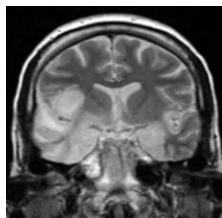
## Pharmacokinetics

- Available for oral, topical and i.v. administration.
- Highly potent antiherpes drug.
- High therapeutic index with low toxicity to host cells.
- Oral bioavailability is poor (20%)
- Poorly bound to plasma proteins □ widely distributed in body
- Freely crosses BBB
- Excreted in urine.

## Uses

- More effective against → HSV-1 > HSV-2 > VZV = EBV
- CMV is not affected

1. **Mucocutaneous HSV:** Acyclovir is used orally or topically in the treatment of stomatitis, herpes labialis and ulcers in mouth. It is used intravenously in immunocompromised patients.
2. **Herpetic encephalitis:** Intravenous acyclovir is the drug of choice for encephalitis caused by HSV.
3. **Herpes simplex keratitis:** Acyclovir is used topically in herpetic keratoconjunctivitis.



4. **Genital herpes:** Oral/intravenous/topical acyclovir is effective in genital herpes simplex infections. It is used for primary and recurrent infections; high doses of acyclovir are needed for recurrent infections. It reduces the frequency and severity of herpetic lesions.
5. **Chickenpox:** Acyclovir reduces the duration of illness if started early in patients at risk of severe illness and immunocompromised individuals.



6. **Herpes zoster:** Acyclovir (oral/topical/i.v.) and valacyclovir (oral) are effective.

## Adverse Effects

1. **GIT** → Nausea, vomiting, Diarrhoea
2. **CNS** → High doses → Headache, neurotoxicity with tremor, confusion, disorientation and convulsions.
3. **On topical use** → irritation and burning.

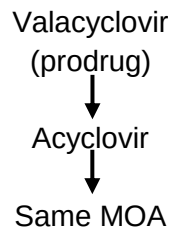


# VALACYCLOVIR

## Introduction

- Ester prodrug of Acyclovir

## MOA



## Pharmacokinetics

- Improved oral bioavailability (55-70%) due to active transport by peptide transporters in the intestine
- During passage through intestine and liver, it is completely converted to acyclovir in first passage by esterases.
- Higher plasma levels of Acyclovir are obtained improving clinical efficacy

## Uses

- DOC in herpes zoster



## Adverse effects

1. GIT → Nausea, vomiting, and abdominal pain
2. CNS → Headaches
3. Hypersensitivity → Itching, Rash

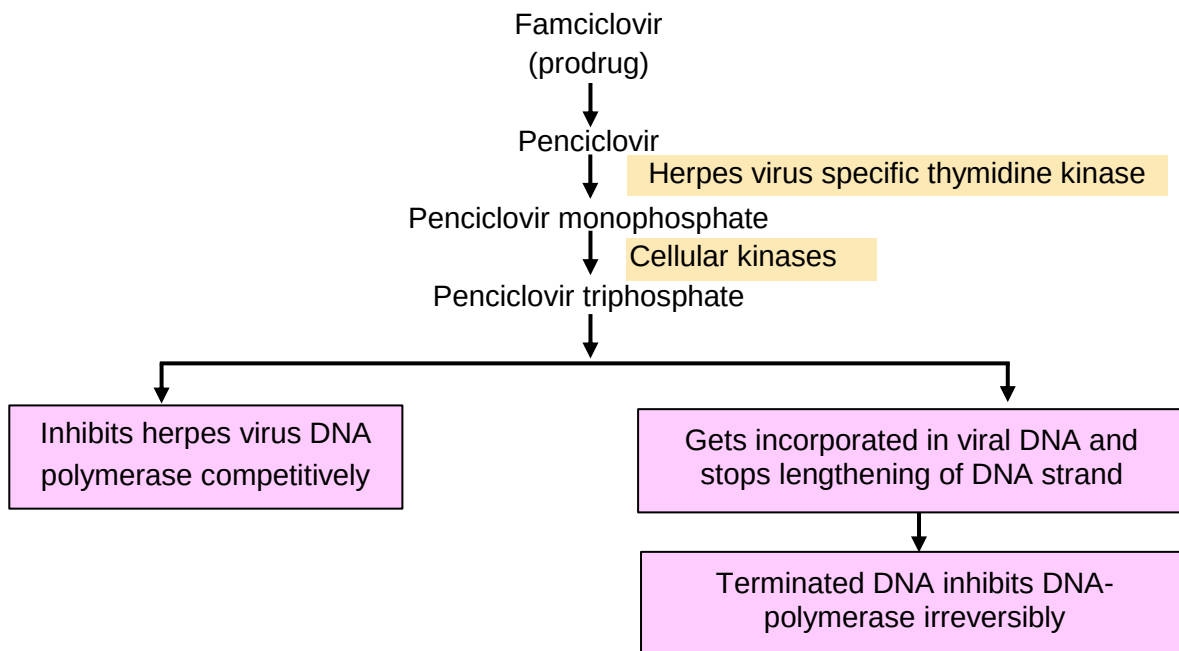


# FAMCICLOVIR

## Introduction

- Ester prodrug of a guanine nucleoside analogue Penciclovir

## MOA



## Pharmacokinetics

- Good oral bioavailability
- Prolonged intracellular  $t_{1/2}$  (> 8 hrs)

## Uses

- Alternative to acyclovir for →
  - Orolabial herpes
  - Genital herpes
  - Herpes zoster



## Adverse effects

1. **GIT** → Nausea, vomiting, abdominal pain, Diarrhoea
2. **CNS** → Headache, Mental confusion
3. **Hypersensitivity** → Itching, Rash

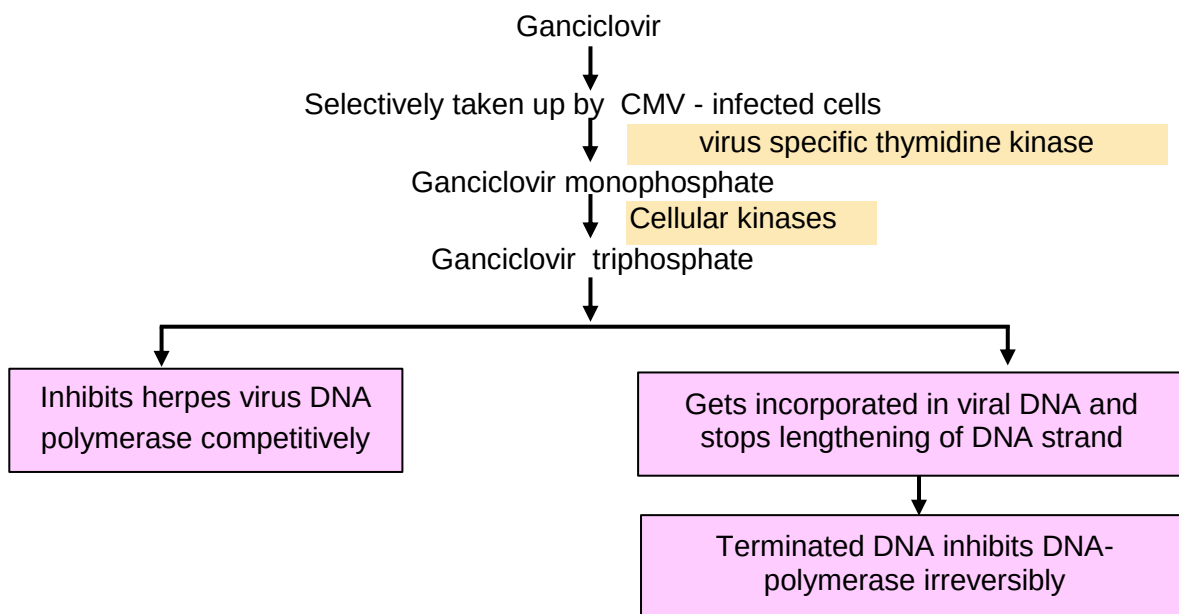


# GANCICLOVIR

## Introduction

- Analogue of acyclovir which is most active against CMV, but also inhibits other herpes viruses ie. H.simplex, H. zoster and EBV.

## MOA



## Pharmacokinetics

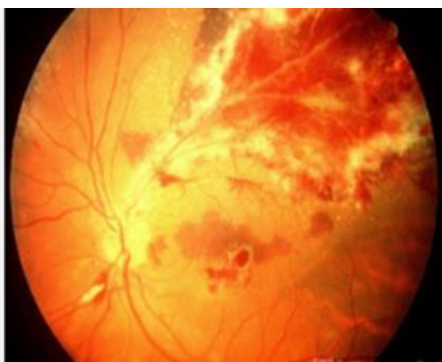
- Poor oral absorption
- Bioavailability low (<10%)

## Uses

- Prophylaxis and treatment of severe CMV infections (pneumonia/colitis/retinitis)** → in immunocompromised (AIDS, transplant recipient)



- CMV retinitis** → Systemic therapy can be supplemented by intravitreal injection of ganciclovir





## Adverse effects

1. **Bone marrow toxicity** → precursor cells in bone marrow are also quite sensitive to ganciclovir
2. **CNS** → Neuropsychiatric disturbances
3. **GIT** → Vomiting
4. **Hypersensitivity** → Rash, fever

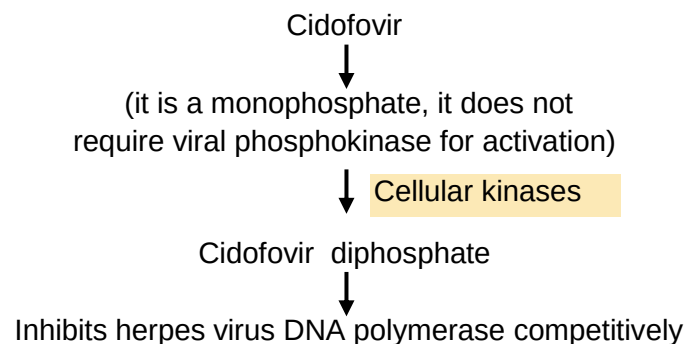


## CIDOFOVIR

### Introduction

- Monophosphate nucleotide analogue of cytidine
- Inhibits most DNA viruses → HSV, CMV, pox and adenoviruses.

### MOA



### Pharmacokinetics

- Very little cidofovir is absorbed orally → administered by i.v. infusion



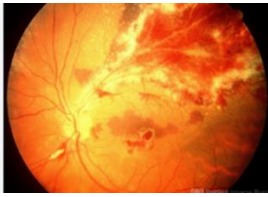
- Pre and post dose oral probenecid is given →
  - To inhibit its tubular secretion and improves its availability for entering into cells
  - To reduce nephrotoxicity





## Uses

1. **CMV retinitis** → in AIDS patients, particularly those who have failed ganciclovir therapy.
2. **Acyclovir-resistant mucocutaneous herpes simplex** → in immunosuppressed patients.
3. **Anogenital warts** → Topically



## Adverse effects

1. Renal → Kidney damage
2. Eye → Uveitis
3. GIT → Vomiting
4. Hypersensitivity → Rash, fever



## ANTI-INFLUENZA VIRUS DRUGS

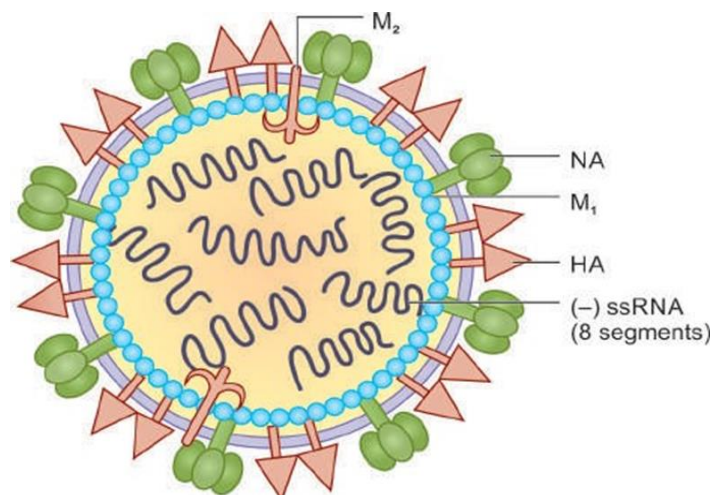
### Influenza

4 genera →

1. Influenza A
2. Influenza B
3. Influenza C
4. Influenza D

### Morphology

- Eight-segmented RNA
- Genetic reassortment is commonly seen



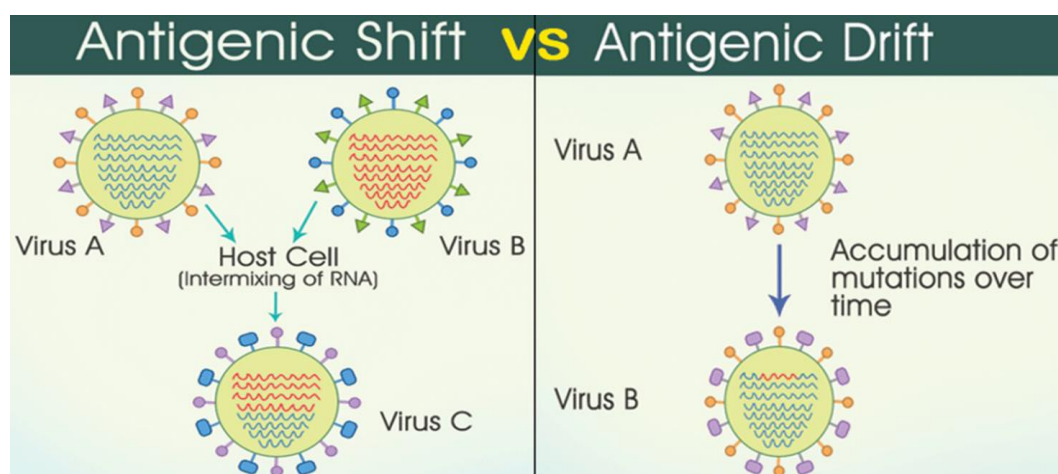
| Haemagglutinin                       | Neuraminidase                    |
|--------------------------------------|----------------------------------|
| Responsible for hemagglutination     | Responsible for elution          |
| Fifteen distinct subtypes → H1 - H15 | Nine different subtypes → N1- N9 |

### Antigenic shift

- Abrupt, drastic, discontinuous variation
- Resulting in a novel virus strain unrelated antigenically to predecessor strains.
- Accounts for the periodical Pandemics of influenza.
- Occurs only in type-A viruses

### Antigenic drift

- Gradual sequential change occurring regularly at frequent intervals.
- Here new antigens, though different from the previous antigens, are yet related to them.
- Accounts for the periodical epidemics of influenza.
- Occurs both in type-A and type -B viruses



## ANTI-INFLUENZA VIRUS DRUGS

### Drugs

- Amantadine
- Rimantadine
- Oseltamivir
- Zanamivir
- Peramivir

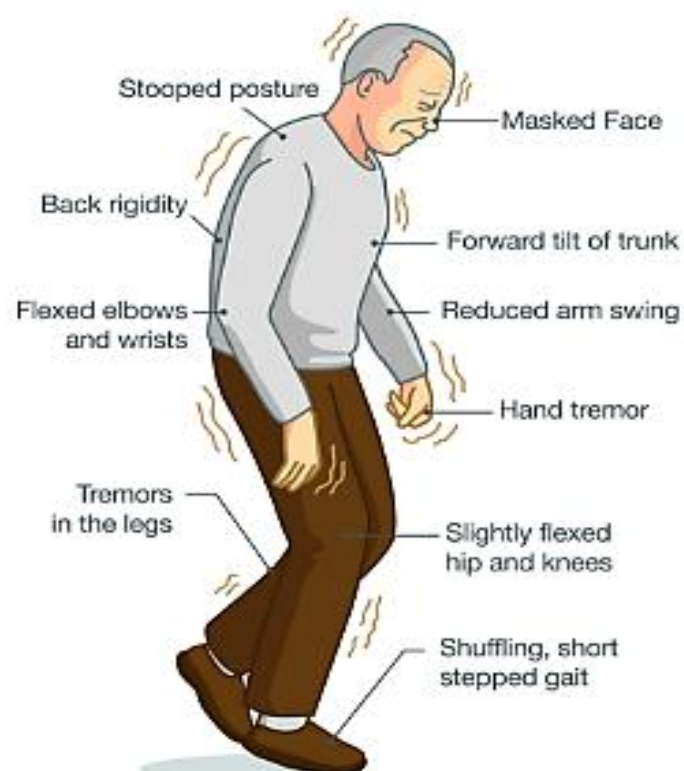
| Anti - Influenza Virus Drugs |            |             |             |           |           |
|------------------------------|------------|-------------|-------------|-----------|-----------|
|                              | Amantadine | Rimantadine | Oseltamivir | Zanamivir | Peramivir |
| Introduction                 |            |             |             |           |           |

|                  |  |  |  |  |  |
|------------------|--|--|--|--|--|
| MOA              |  |  |  |  |  |
| Pharmacokinetics |  |  |  |  |  |
| Uses             |  |  |  |  |  |
| Adverse effects  |  |  |  |  |  |

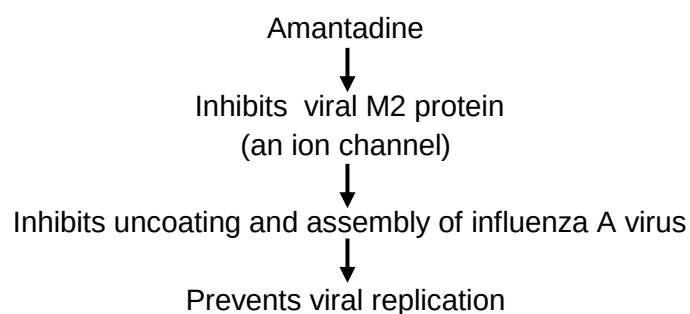
## AMANTADINE

### Introduction

- Antiviral drug that has antiparkinsonian effect as well
- Inhibits Influenza A virus, but not influenza B or H5N1 and H1N1 strains of influenza A



### MOA



### Pharmacokinetics

- Administered orally
- Well absorbed from GI tract
- Excreted unchanged in urine

## Uses

1. Prophylaxis and treatment of influenza A virus infection (Currently seldom used)
2. For Parkinsonism



## Adverse Effects

1. **CNS** → Insomnia, Headache, Confusion, Hallucinations
2. **CVS** → Hypotension
3. **GIT** → Anorexia, Nausea, Epigastric discomfort



## Contraindication

- Pregnancy → because of teratogenic effect.



## RIMANTADINE

### Introduction

- Methyl derivative of amantadine

### MOA

- MOA similar to that of amantadine

## Pharmacokinetics

- More potent
- Longer duration of action.
- Better tolerated , Fewer adverse effects

## Uses

- Same as that of amantadine

## Adverse effects

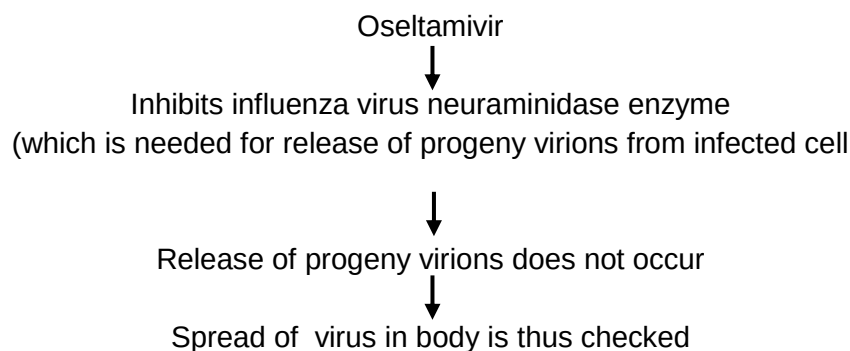
- Same as that of amantadine

# OSELTAMIVIR

## Introduction

- Most commonly used anti-influenza virus drug now
- Sialic acid analogue with broad spectrum activity covering ☐
  - Influenza A (amantadine sensitive as well as resistant)
  - H5N1 (bird flu)
  - H1N1 (swine flu)
  - Influenza B

## MOA



## Pharmacokinetics

- Oseltamivir is an ester prodrug that is rapidly and nearly completely hydrolysed during absorption in intestine and by liver esterases to the active form oseltamivir Carboxylate
- Oral bioavailability of ~ 80%.

## Uses

- Treatment and prevention of →
  1. Influenza A (avian influenza or bird flu and swine flu)
  2. Influenza B virus infections.
- Started within 48 hours of symptom onset → it reduces severity, duration and complications of illness.
- Early initiation of therapy is critical because viral replication is maximal during first 2 days of symptom onset.





## Adverse effects

1. **CNS** → Headache, weakness, sadness, insomnia
2. **GIT** → Nausea, Abdominal pain, diarrhoea,
3. **Hypersensitivity** → Skin reactions



## ZANAMIVIR

### MOA

- Similar as Oseltamivir

### Pharmacokinetics

- Administered by inhalation as a powder due to very low oral bioavailability.



### Uses

- Reserved for →
  1. Oseltamivir-resistant cases
  2. When Oseltamivir cannot be given
  3. For severely immunocompromised patients.

## Adverse effects

1. **Lungs** → Bronchospasm



2. **CNS** → Headache, Dizziness



## Contraindication

- Patients with airway disease.



## PERAMIVIR

### Introduction

- New single dose i.v. treatment for influenza in adults approved by the US-FDA in 2014.
- Active against human influenza A and B, as well as bird flu (H5N1), swine flu (H1N1) and those resistant to oseltamivir.

### MOA

- Similar as Oseltamivir.

### Pharmacokinetics

- Oral bioavailability of peramivir is very low (<3%) □ Given as single dose IV



### Uses

1. Severely ill influenza patients
2. Those unable to tolerate other drugs
3. For oseltamivir resistant cases

### Adverse effects

1. **GIT** → Nausea, Abdominal pain, diarrhoea,
2. **Hypersensitivity** → Skin reactions



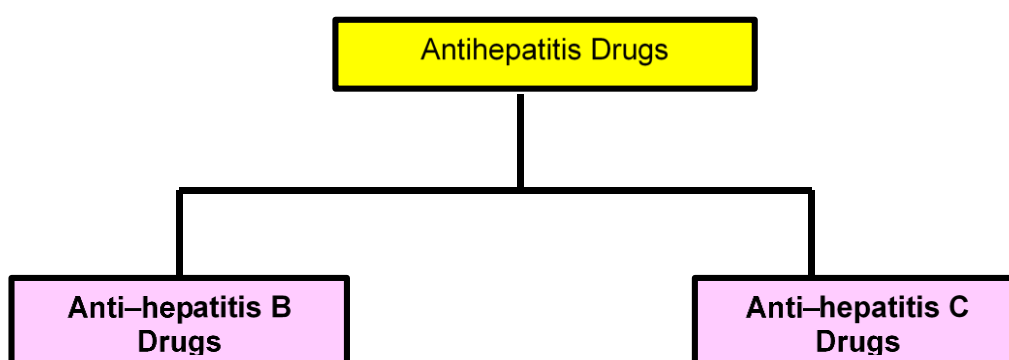
## ANTI-HEPATITIS DRUGS

| Properties  | HAV                  | HBV             | HCV            | HDV         | HEV         |
|-------------|----------------------|-----------------|----------------|-------------|-------------|
| Common name | Infectious hepatitis | Serum hepatitis | Non A non B or | Delta agent | Non A non B |

|            |                                 |                                   |                                            |                                         |                               |
|------------|---------------------------------|-----------------------------------|--------------------------------------------|-----------------------------------------|-------------------------------|
|            |                                 |                                   | post-transfusion hepatitis                 |                                         | enteric transmitted hepatitis |
| Genome     | ssRNA                           | dsDNA                             | ssRNA                                      | ssRNA                                   | ssRNA                         |
| Family     | Enterovirus-72 (Picornaviridae) | Hepadnaviridae                    | Flaviviridae                               | Deltavirus                              | Hepeviridae                   |
| Envelope   | No                              | Yes (HBsAg)                       | Yes                                        | Yes (HBsAg)                             | No                            |
| Route      | Feco-oral                       | Blood (MC)<br>Sexual,<br>Vertical | Blood (MC)<br>Sexual(+/-)<br>Vertical(+/-) | Blood (MC)<br>Sexual(++)<br>Vertical(+) | Feco-oral                     |
| I.P (days) | 15–45,<br>(Average 30)          | 30–180,<br>(Average 60–90)        | 15–160,<br>(Average 50)                    | 30–180,<br>(Average 60–90)              | 14–60,<br>(Average 40)        |

| Properties        | HAV         | HBV                | HCV            | HDV              | HEV                                      |
|-------------------|-------------|--------------------|----------------|------------------|------------------------------------------|
| Acute Hepatitis   | Yes         | Yes                | Yes            | Yes              | Yes                                      |
| Fulminant disease | Rare (0.1%) | Rare (0.1–1%)      | Rare (0.1%)    | Frequent (5–20%) | Usually rare (1–2%)<br>Pregnancy- 20–40% |
| Chronicity        | None        | Occasional (1–10%) | Common (85%)   | Common           | None                                     |
| Carrier           | None        | Yes (0.1–30%)      | Yes (1.5–3.2%) | Variable         | None                                     |
| Oncogenic         | No          | Yes (neonate)      | Yes            | +/-              | No                                       |
| Cirrhosis         | No          | Yes                | Yes            | Yes              | No                                       |

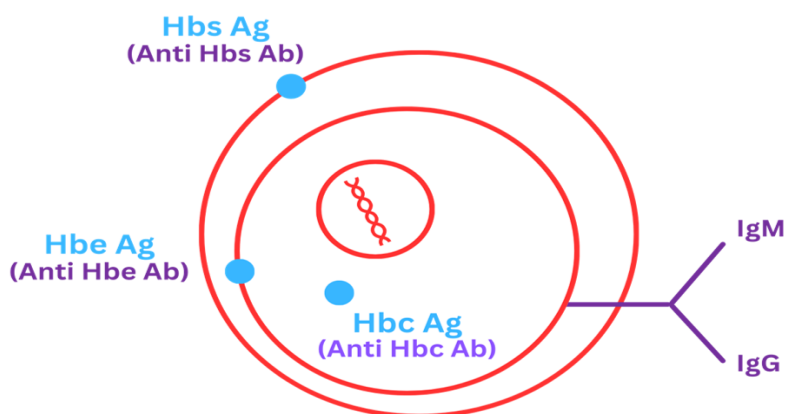
## Types





## ANTI-HEPATITIS DRUGS

### Hepatitis B virus (Serum Hepatitis)



### Aim of treatment

- Hepatitis B virus cannot be eradicated from body
- Treatment is aimed as →
  1. Suppression of virus and its inflammatory and hepatocyte damaging response
  2. Improvement of liver function
  3. Reduce of risk for development of cirrhosis and hepatic carcinoma.
    - Combination therapy of HBV has not proven superior
    - Drugs are generally used sequentially

### Drugs

- Lamivudine
- Entecavir
- Adefovir dipivoxil
- Tenofovir disoproxil fumarate
- Telbivudine

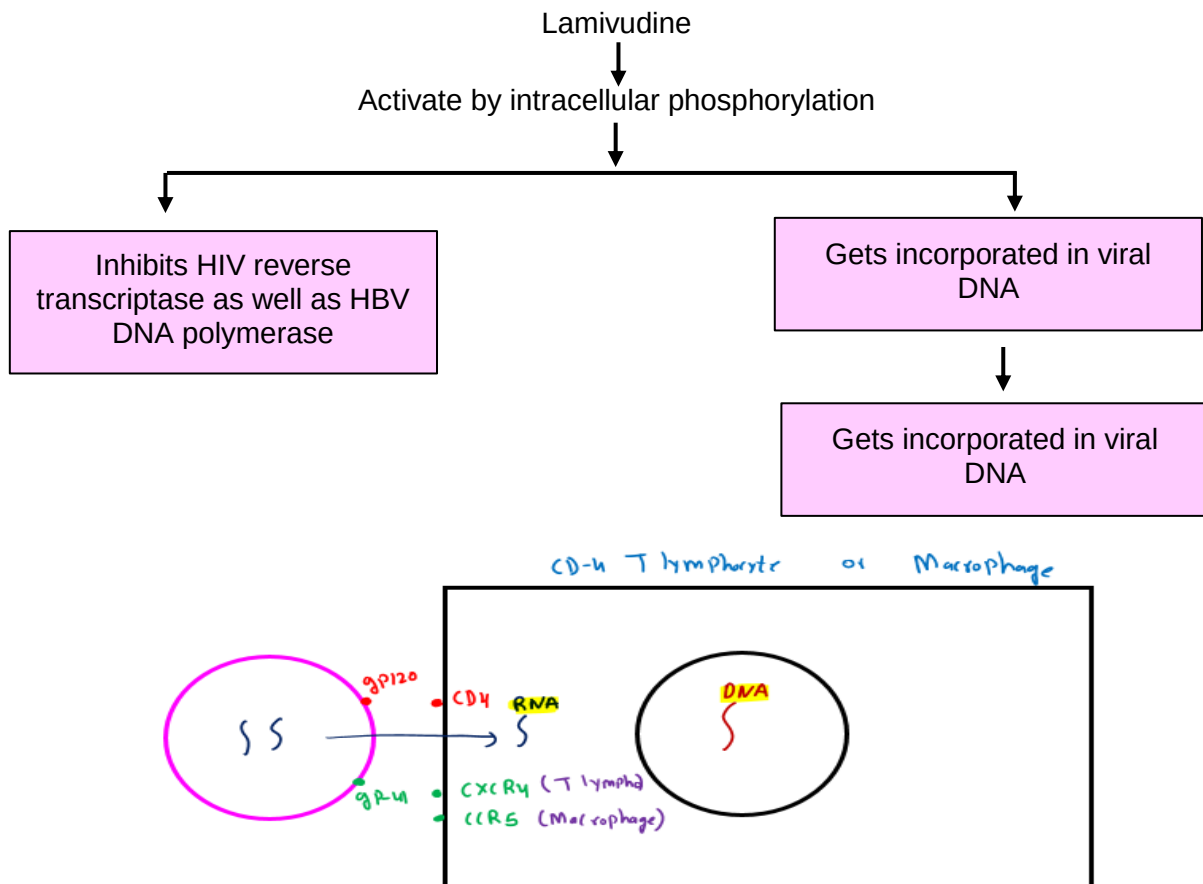
| Anti-hepatitis B Drugs |            |           |                    |                               |             |
|------------------------|------------|-----------|--------------------|-------------------------------|-------------|
|                        | Lamivudine | Entecavir | Adefovir dipivoxil | Tenofovir disoproxil fumarate | Telbivudine |
| Introduction           |            |           |                    |                               |             |
| MOA                    |            |           |                    |                               |             |
| Pharmacokinetics       |            |           |                    |                               |             |
| Uses                   |            |           |                    |                               |             |
| Adverse effects        |            |           |                    |                               |             |

# LAMIVUDINE

## Introduction

- Deoxycytidine analogue
- Active against HBV as well as HIV

## MOA



## Pharmacokinetics

- Oral bioavailability is high
- Mainly excreted unchanged in urine □ it can be employed in patients with hepatic insufficiency.

## Uses

1. HIV
2. Chronic hepatitis B

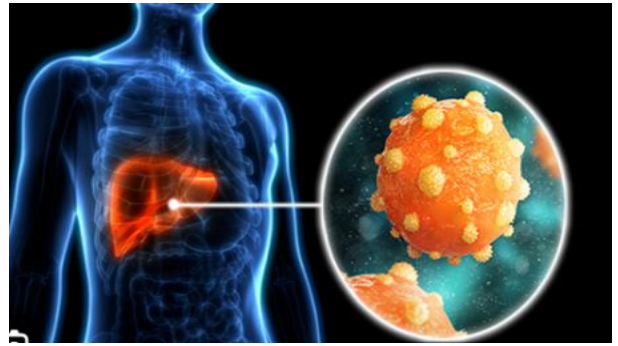
### 1. HIV

- It is an essential component of most first line triple drug WHO and NACO regimens.
- Used in combination with other anti-HIV drugs
- Synergises with most other NRTIs



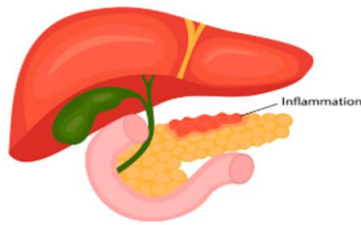
## 2. Chronic hepatitis B

- Lower doses are required than for HIV → due to longer intracellular  $t_{1/2}$  of lamivudine in HBV infected cells than in HIV infected cells.
- HBV-DNA titre is markedly reduced
- Biochemical as well as histological indices of liver function improve.
- Lamivudine-resistance develops in upto 70% patients within 1–5 years → it is no longer a 1st line drug for chronic hepatitis B.



### Adverse effects

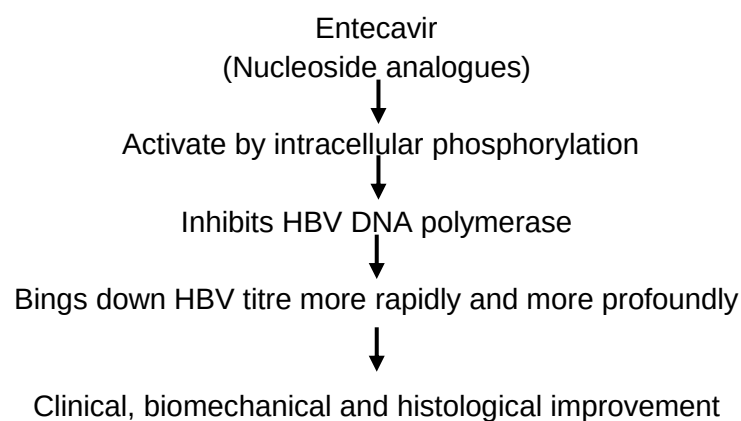
1. **Pancreas** → Pancreatitis
2. **CNS** → Neuropathy (rare)
3. **GIT** → nausea, anorexia, abdominal pain.



## ENTECAVIR

### Introduction

- Newer guanosine nucleoside analogue



- Weak anti-HIV activity as well

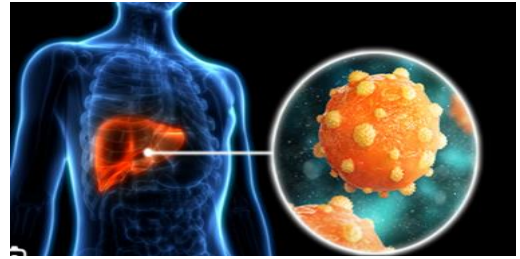
### Pharmacokinetics

- Completely absorbed after oral dosing
- Food decreases bioavailability□ it should be taken in empty stomach.



## Uses

- Currently most active and 1st line option for treating chronic hepatitis B.

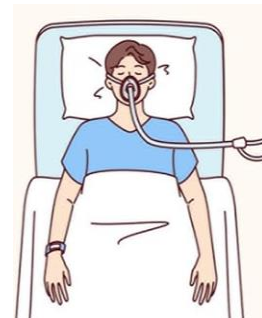


## Adverse effects

1. GIT → Dyspepsia, nausea, Diarrhoea



2. Metabolism → Lactic acidosis in patients with decompensated cirrhosis of liver.

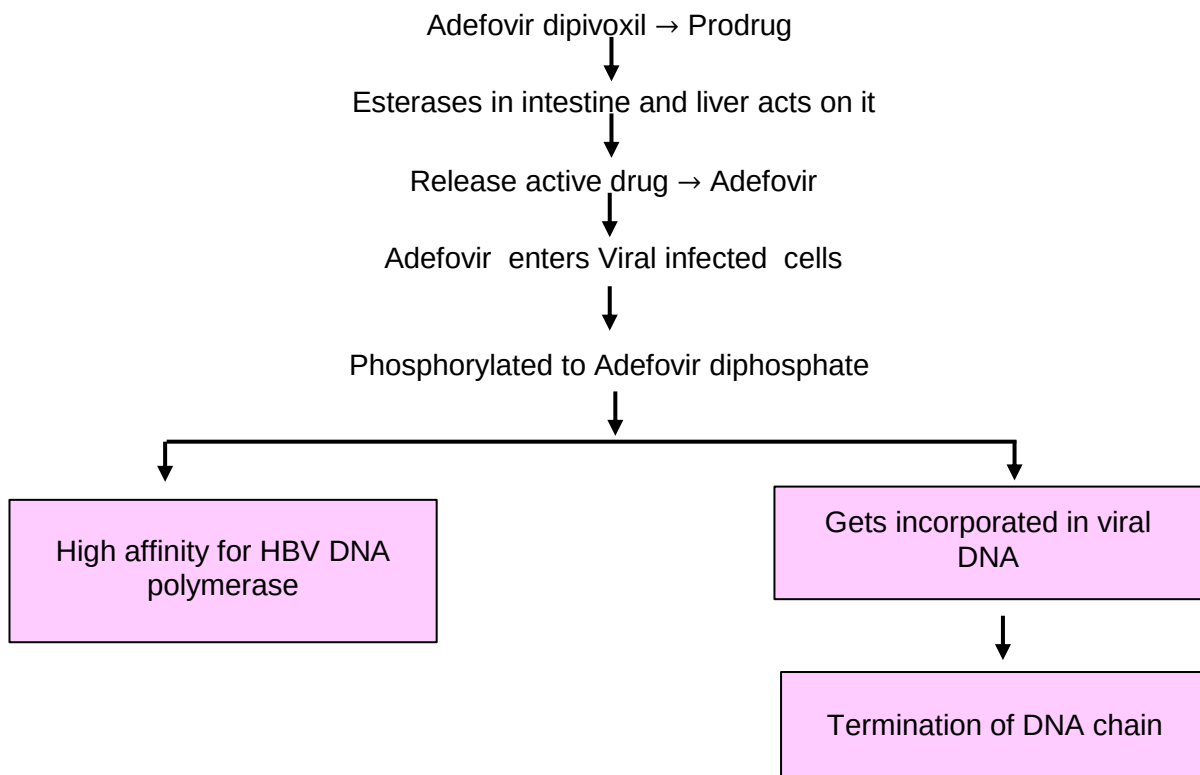


## ADEFOVIR DIPIVOXIL

### Introduction

- Monophosphate analogue of AMP

### MOA



## Pharmacokinetics

- Oral bioavailability of ~60%

## Uses

1. Chronic hepatitis B including lamivudine-resistant cases
2. Those having concurrent HIV infection
  - It is least active nucleotide analogue against HBV → not a first line drug.
  - Adefovir resistance occurs in about 30% patients.



## Adverse effects

1. **Renal** → Nephrotoxicity → at higher doses and in those with preexisting renal insufficiency.
2. **Respiratory system** → Sore throat, flu syndrome
3. **GIT** → Abdominal pain

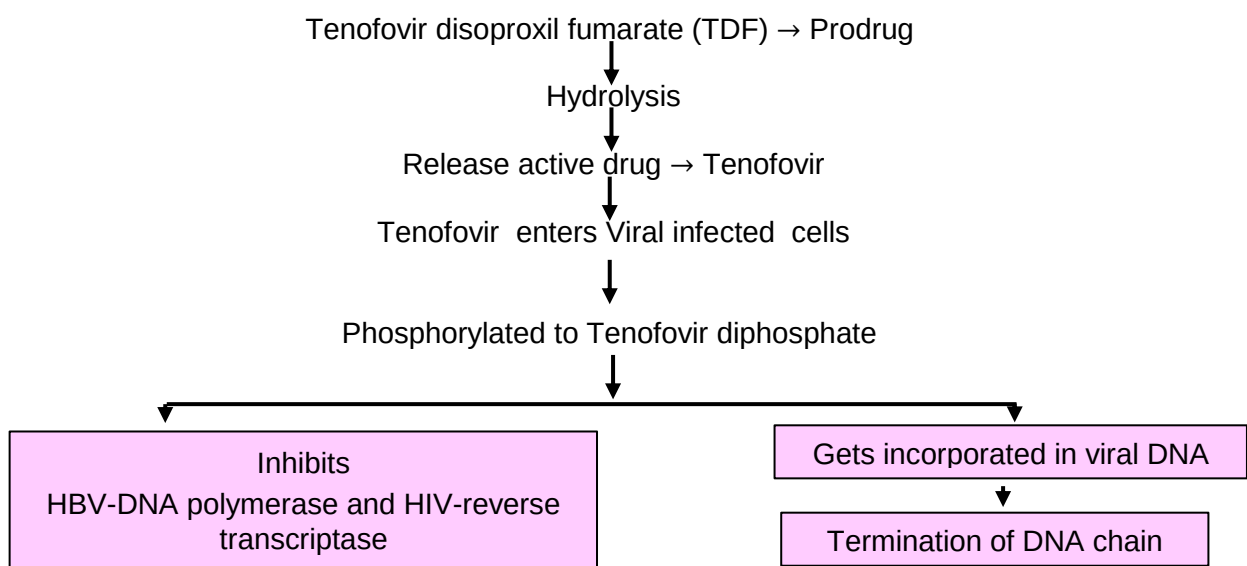


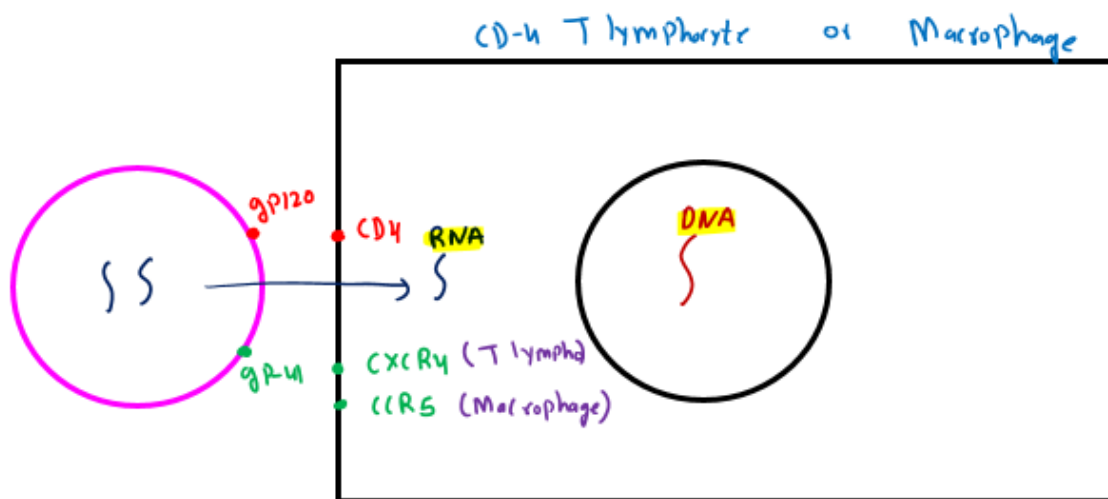
## TENOFOVIR DISOPROXIL FUMARATE

### Introduction

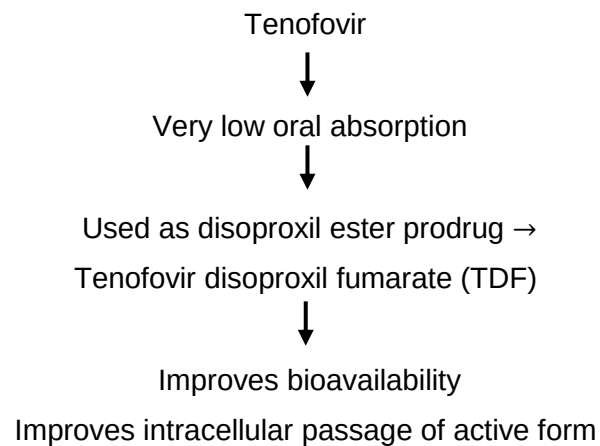
- Monophosphate nucleotide related to AMP
- Active against HBV as well as HIV.

### MOA



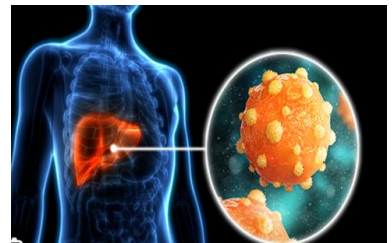


## Pharmacokinetics



## Uses

- Due to its high efficacy, good tolerability and low risk of resistance → tenofovir is one of the first line drugs for chronic hepatitis due to HBV.
- Produced good clinical and virological response in chronic hepatitis B
- A response rate of > 90% has been reported among HBe antigen negative patients.



## Adverse effects

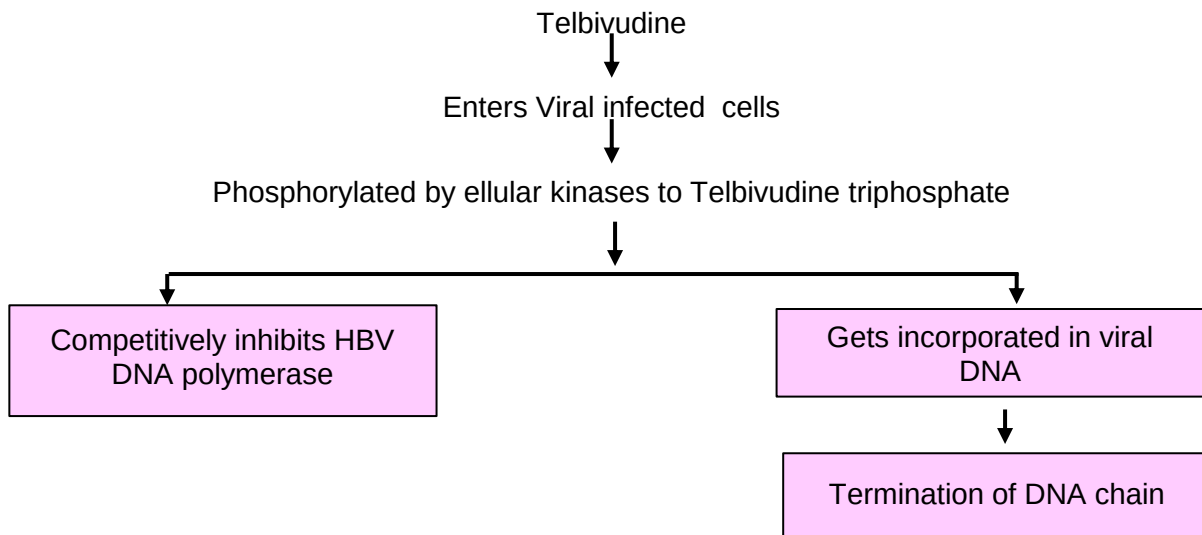
1. Renal → Acute renal injury or chronic renal disease
2. GIT → nausea, flatulence, abdominal discomfort, loose motions



# TELIVUDINE

## Introduction

- Newer anti-HBV drug
- Thymidine nucleoside analogue.



## Pharmacokinetics

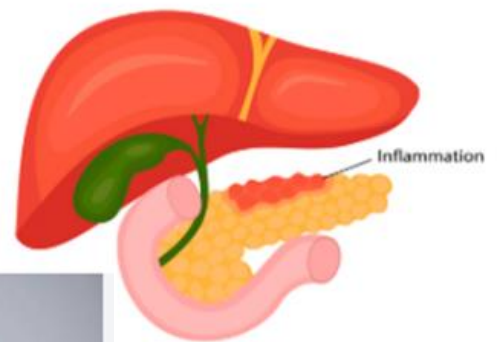
- Absorbed orally well
- Its bioavailability is not affected by food.

## Uses

- It not a first line drug for chronic hepatitis B because resistance often develops resulting in return of viraemia.

## Adverse effects

- GIT → abdominal pain, diarrhoea
- CNS → Headache, dizziness
- Pancreas → Serum amylase rise

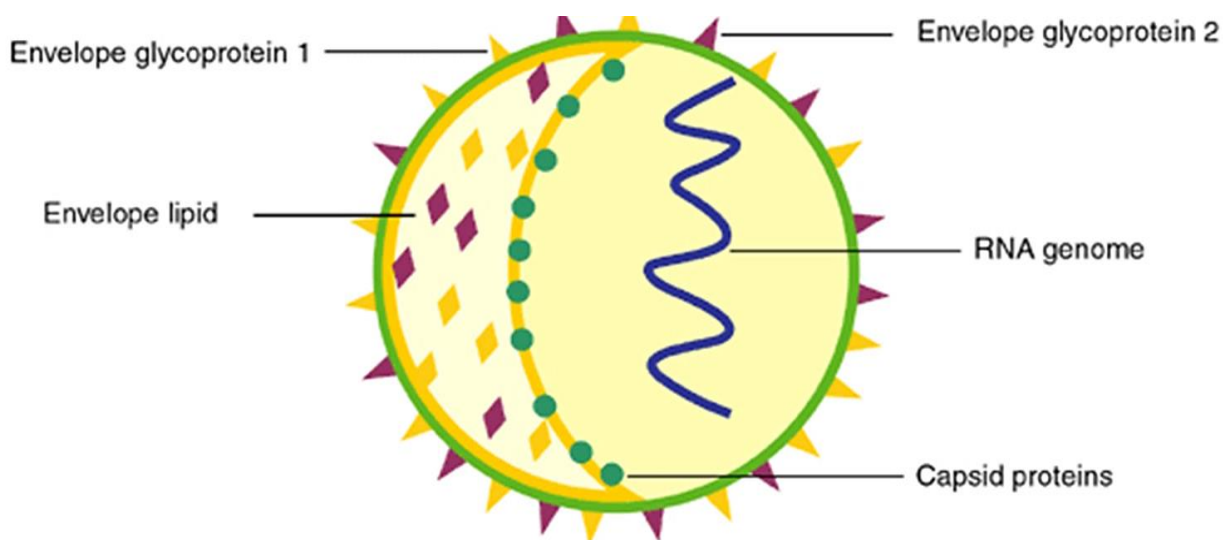




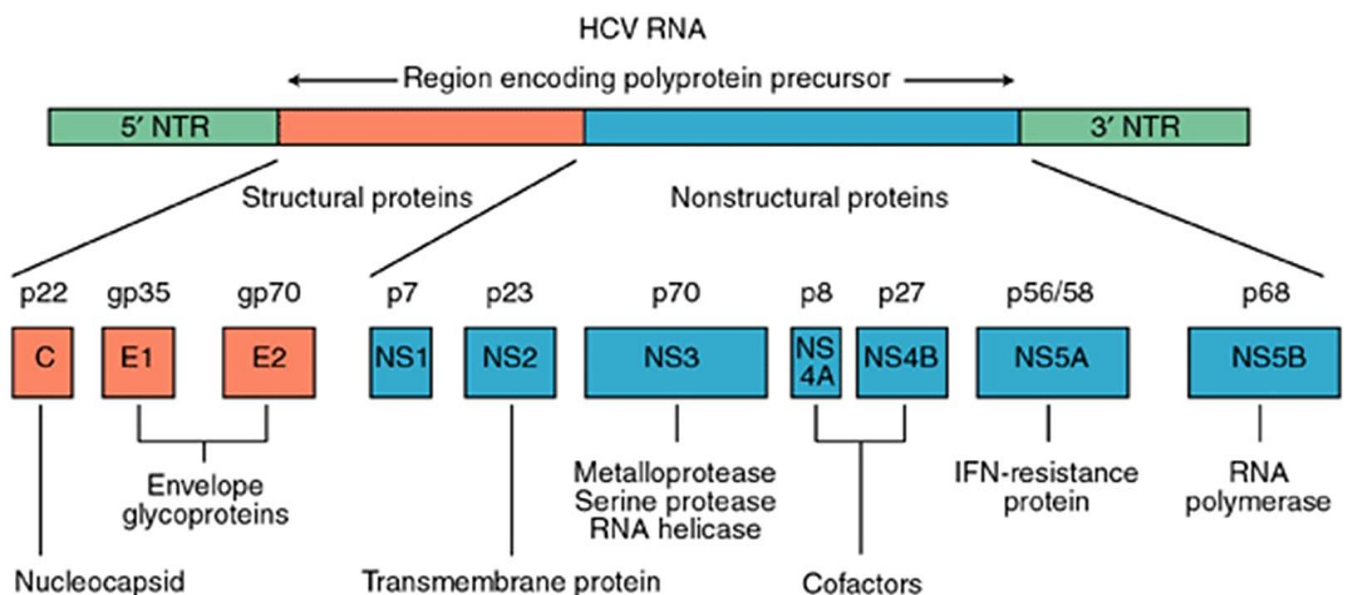
## ANTI-HEPATITIS C DRUGS

### Hepatitis C Morphology

- Family Flaviviridae, genus Hepacivirus.
- Enveloped
- Nucleic acid → It contains a positive sense ssRNA
- Proteins → HCV possesses:
  - 3 structural proteins: The nucleocapsid core protein C; two envelope glycoproteins (E1 and E2)
  - 6 nonstructural (NS) proteins: NS2, NS3, NS4A, NS4B, NS5A, and NS5B
  - 1 p7 membrane protein: functions as an ion channel; was earlier considered as NS1.



### b Proteins encoded by the HCV genome





## Aim of treatment for chronic hepatitis C

1. To attain sustained viral response (SVR) → undetectable HCV-RNA in blood for at least 6 months after completion of therapy.
2. If this is achieved, only ~5% patients relapse.
  - Conventionally standard therapy for HCV infection → Oral ribavirin combined with injected PegINFα
  - Several novel direct acting oral antiviral drugs have been developed over the past 5–10 years which have revolutionized the treatment of hepatitis C.

## Drugs

1. Ribavirin
2. Interferons
3. Sofosbuvir
4. Simeprevir
5. Daclatasvir and ledipasvir

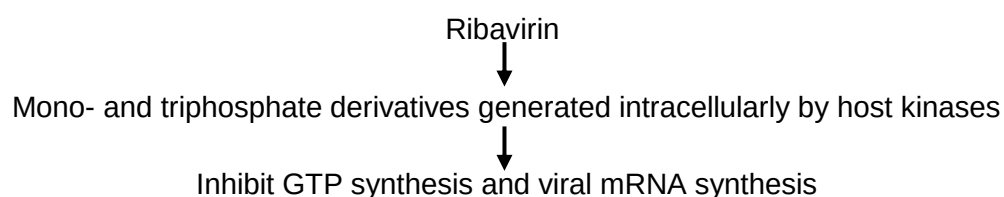
| Anti-hepatitis C Drugs  |           |              |            |            |                           |
|-------------------------|-----------|--------------|------------|------------|---------------------------|
|                         | Ribavirin | Interferon α | Sofosbuvir | Simeprevir | Daclatasvir<br>Ledipasvir |
| <b>Introduction</b>     |           |              |            |            |                           |
| <b>MOA</b>              |           |              |            |            |                           |
| <b>Pharmacokinetics</b> |           |              |            |            |                           |
| <b>Uses</b>             |           |              |            |            |                           |
| <b>Adverse effects</b>  |           |              |            |            |                           |

## RIBAVIRIN

### Introduction

- Synthetic purine nucleoside analogue
- Wide range of antiviral activity.

### MOA



### Pharmacokinetics

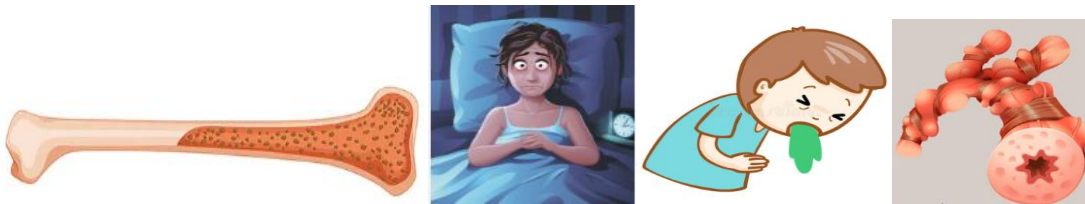
- Administered by → oral, aerosol or i.v. routes.
- Metabolized in liver
- Excreted in urine

## Uses

- Ribavirin is effective against a wide range of RNA and DNA viruses.
  - Chronic hepatitis C infection □ traditionally combined with injected peginterferon for 6–12 months
  - Influenza
  - Parainfluenza
  - Measles
  - Adenovirus
  - RSV bronchiolitis → Nebulized ribavirin is used

## Adverse Effects

1. **Hematology** → Dose-dependent haemolytic anaemia, bone marrow depression
2. **CNS** → Insomnia
3. **GIT** → Nausea
4. **Aerosol** → irritation of mucosae and bronchospasm.



## Contraindication

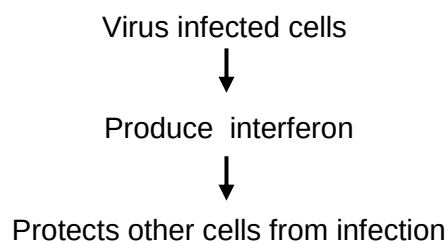
- **Pregnancy and child-bearing age group** → because of its teratogenic, mutagenic, embryotoxic and gonadotoxic effects.



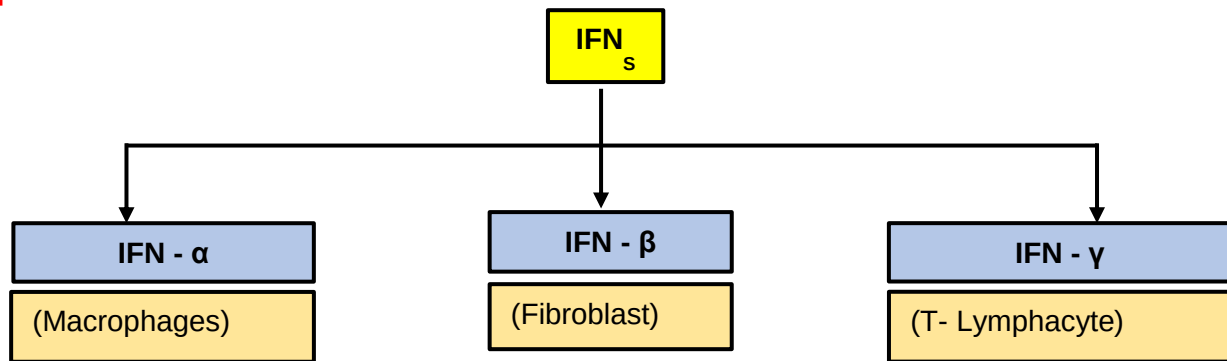
## INTERFERON $\alpha$

### Introduction

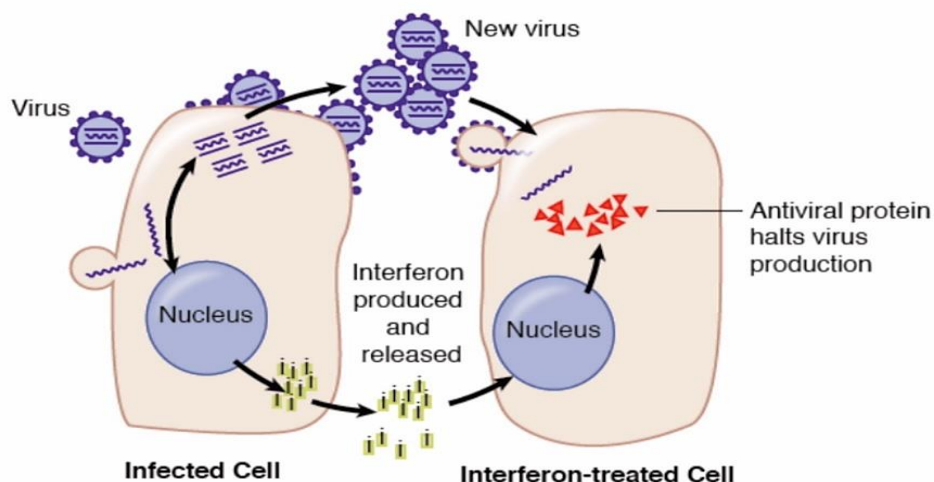
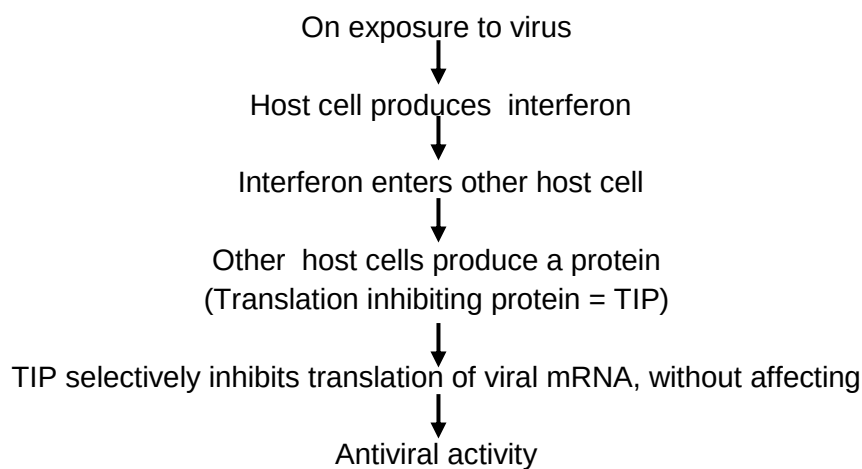
- Discovered by Isaacs and Lindenmann
- Low molecular weight glycoprotein cytokines produced by host cells in response to viral infections and some other inducers.



## Types



- **Only IFNα2A and IFNα2B** → produced by recombinant technology are available and are clinically used.



## Pharmacokinetics

- **Administered by** → i.m. and s.c. routes or locally into lesion.
- **Peginterferon (polyethylene glycol complexed)** →
  - Absorbed more slowly
  - Exerts more sustained effects → permitting weekly administration
  - Improving clinical efficacy.
- **PegIFN has replaced IFN** → except for consideration of cost.

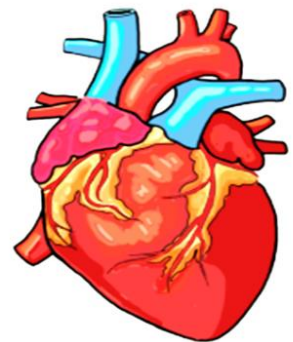
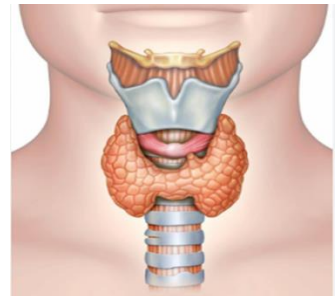


## Uses

1. Chronic hepatitis B
2. Chronic hepatitis C
3. AIDS-related Kaposi's sarcoma
4. Condyloma acuminata
5. H. simplex, H. zoster and CMV
6. Chronic myeloid leukaemia, follicular lymphoma, cutaneous T-cell lymphoma and multiple myeloma.

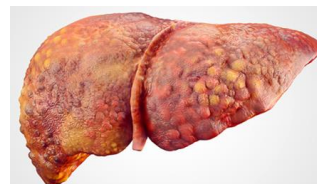
## Adverse effects

1. **Flu-like symptoms** → fatigue, aches and pains, malaise, fever, dizziness, anorexia, nausea, taste and visual disturbances
2. **Neurotoxicity** → numbness, neuropathy, altered behaviour, mental depression, tremor, sleepiness, rarely convulsions.
3. **Myelosuppression** → dose dependent neutropenia, thrombocytopenia.
4. **Thyroid dysfunction** → hypo as well as hyper
5. **CVS** → Hypotension, transient arrhythmias



## Contraindications

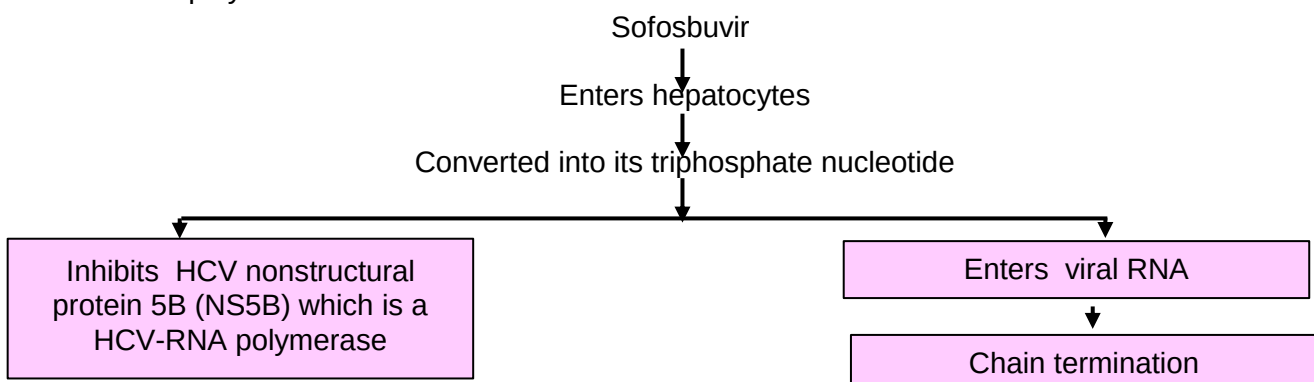
1. Pregnancy
2. Decompensated cirrhotics
3. Autoimmune disease patients.



## SOFOSBUVIR

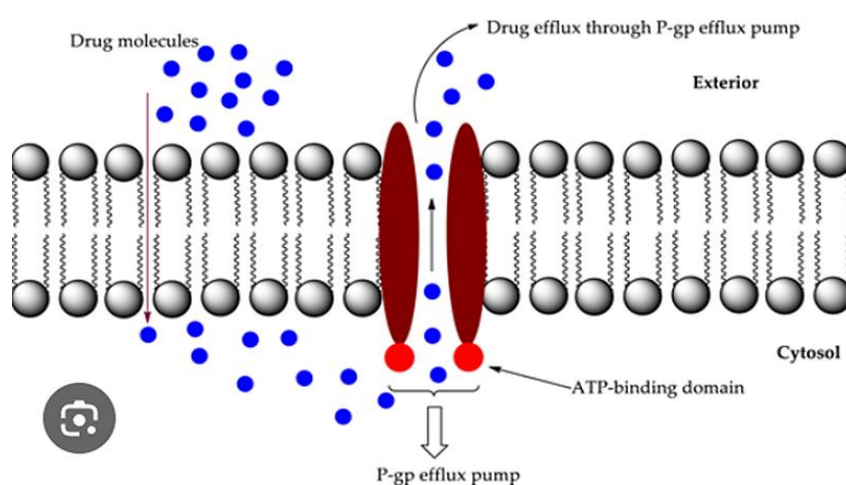
### Introduction

- Uridine analogue prodrug
- NS5B polymerase inhibitor



## Pharmacokinetics

- Oral bioavailability of sofosbuvir is ~80%
- It is a substrate for Pgp efflux transporter → should not be used with Pgp inducers like phenytoin, rifampin, etc. and in patients with severe renal impairment.

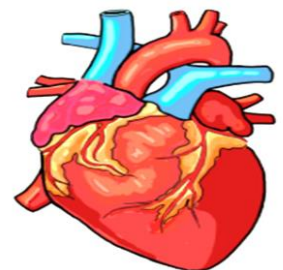


## Uses

- Active against all (1–6) HCV genotypes, especially genotype 1
- Always used in combination, either with one of the NS5A inhibitors or with simeprevir, or with ribavirin ± PegINFα.
- Also used in decompensated liver disease

## Adverse effects

- GIT → abdominal pain
- MSK → fatigue, joint pain
- CVS → Severe bradycardia and arrest has occurred in patients taking amiodarone.

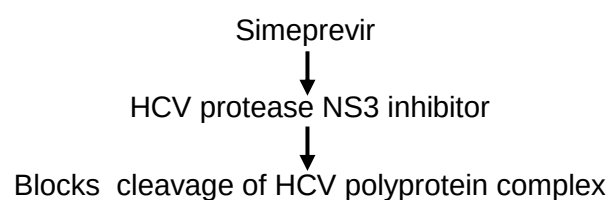


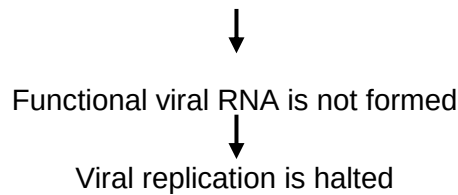
## SIMEPREVIR

### Introduction

- HCV protease NS3 inhibitor

### MOA





## Pharmacokinetics

- Orally active
- Should be taken with food to increase absorption
- Simeprevir is metabolized by CYP3A4



## Uses

- Active against HCV genotype 1 and 4
- Recommended for use along with sofosbuvir or with ribavirin + PegINFα.

## Adverse effects

- **GIT** → nausea
- **Skin** → rashes and photosensitivity.

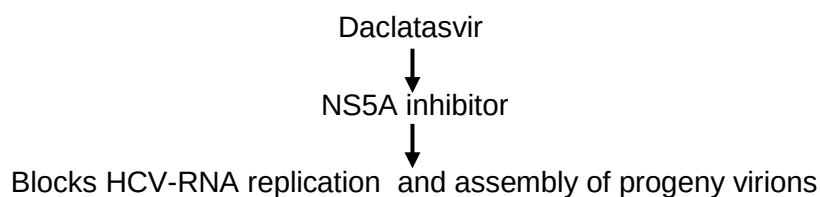


# DACLATASVIR & LEDIPASVIR

## Introduction

- NS5A inhibitors
- NS5A is a multifunctional protein that serves essential role in the replication of HCV

## MOA



## Pharmacokinetics

- Metabolized by CYP3A
- It is a substrate for efflux transporter Pgp.

## Uses

- Active against all genotypes of HCV
- In patients with HIV coinfection or with advanced liver disease, it can be employed regardless of the HCV genotype



## Adverse effects

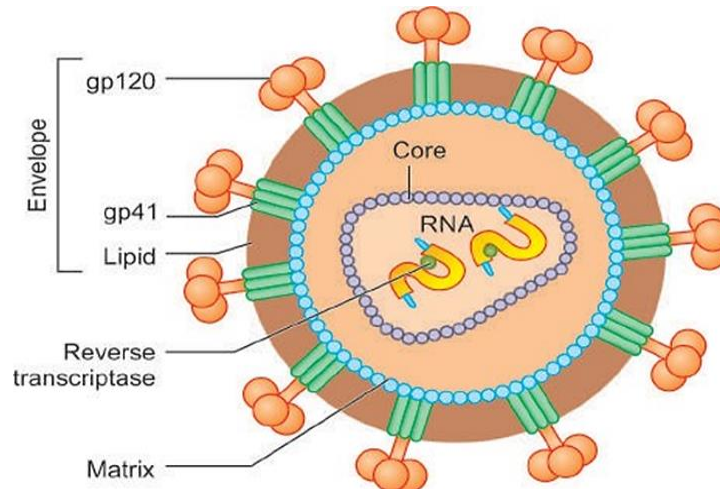
1. **Hairs** → Alopecia
2. **GIT** → Abdominal pain
3. **Hypersensitivity** → Allergy



## ANTIRETROVIRAL DRUGS

### HIV Virus → Morphology

- A. Envelope
- B. Nucleocapsid
- C. HIV Genes and Antigens



#### A. Envelope

- **Lipoprotein**
  - **Lipid part:** host cell membrane derived
  - **Protein part:** 2 components:
    - a) **GP 120** → main receptor of HIV that binds to CD4 molecules on host cell to initiate the infection
    - b) **GP 41** → fusion protein

#### B. Nucleocapsid

- Capsid is icosahedral in symmetry
- Inner core encloses:
  - **RNA** → 2 identical copies of single-stranded positive sense linear RNA
  - **Viral enzymes** →
    - Reverse transcriptase
    - Integrase
    - Proteases

#### C. HIV Genes and Antigens

- **3 structural genes** → gag, pol, and env
- **6 non-structural or regulatory genes** →
  - Essential regulatory genes: tat, nef and rev
  - Accessory regulatory genes: vif, vpr and vpu

## Mode of transmission

| Route of transmission | Risk of transmission (Worldwide, %) | % of total transmission |
|-----------------------|-------------------------------------|-------------------------|
| Sexual intercourse    | 0.1-1                               | 75                      |
| Blood transfusion     | >90                                 | 5                       |
| Percutaneous          | 0.5-1.0                             | 10                      |
| Parent to child       | 13-40                               | 10                      |



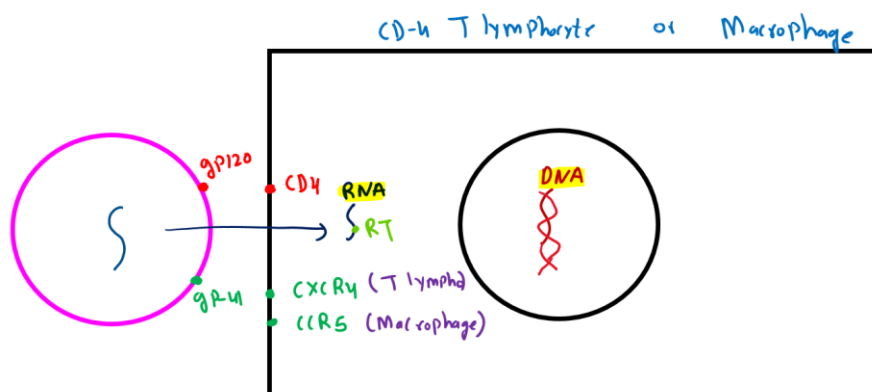
## Receptor Attachment

**Main receptor** →

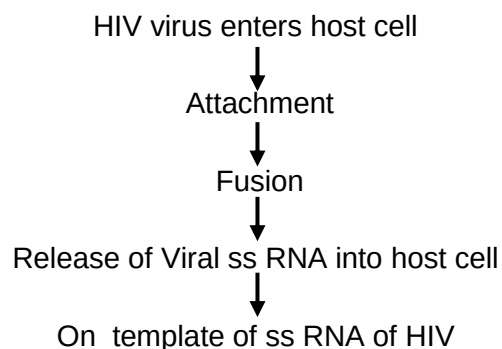
- Entry
- Binding of gp120 to the CD4 receptor

**Co-receptor** →

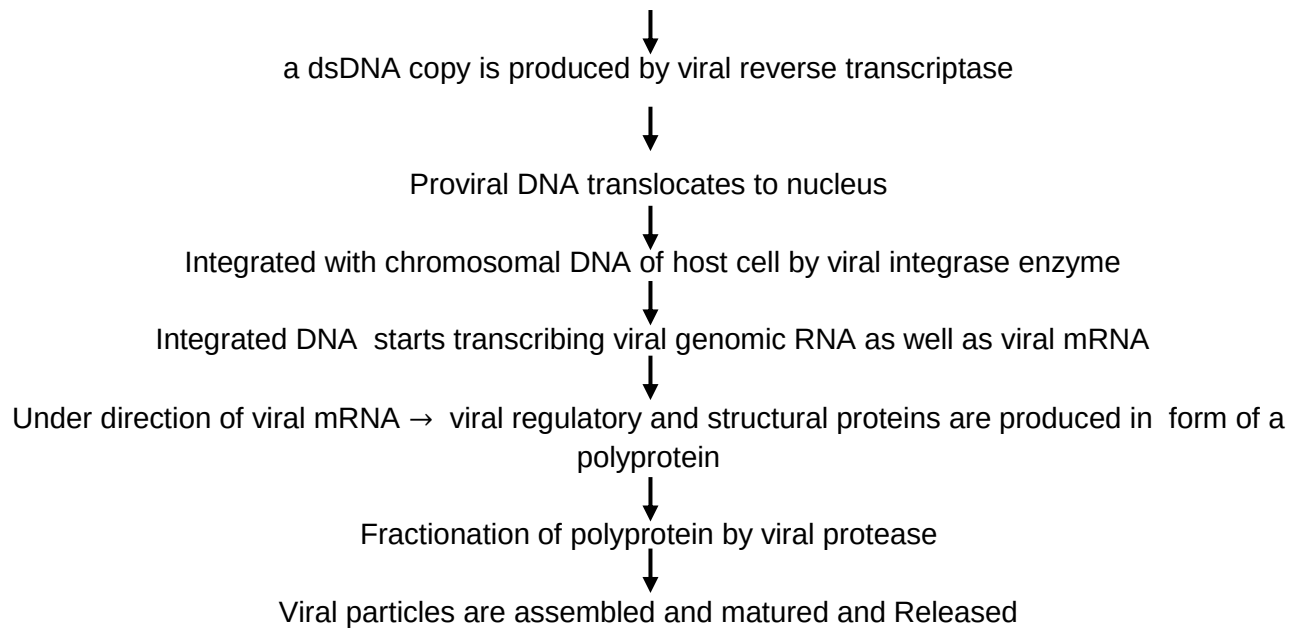
- Fusion
- Binding of gp 41 to →
  - CXCR4 → on T lymphocytes
  - CCR5 → on macrophage



## Life cycle





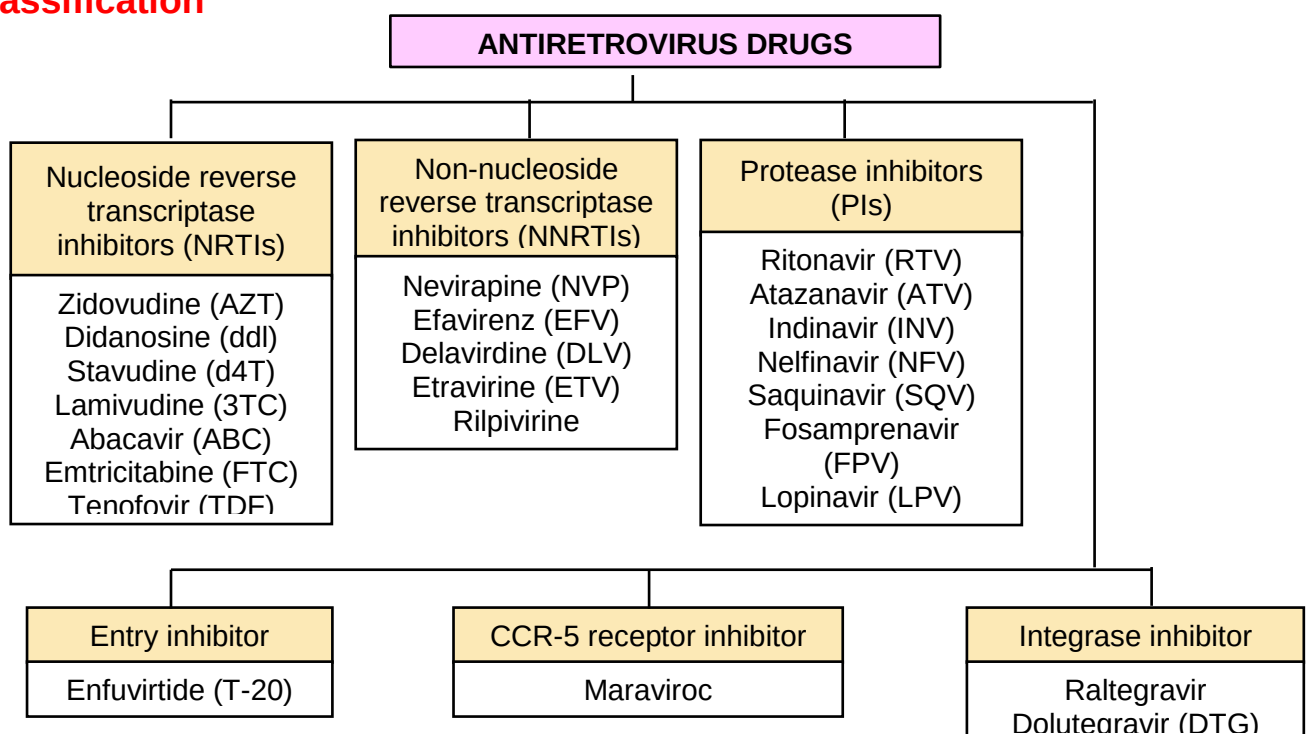


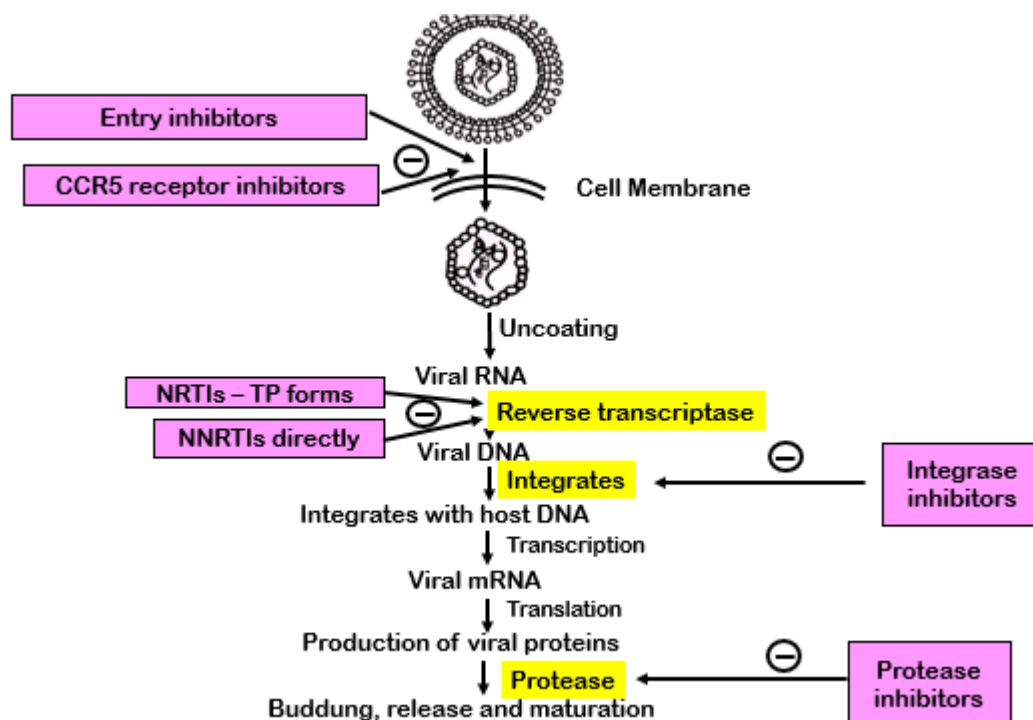
## ANTIRETROVIRAL DRUGS

### Introduction

- Drugs active against HIV
- Useful in →
  - Prolonging and improving quality of life
  - Postponing complications of AIDS or AIDS-related complex (ARC)
  - But do not cure the infection.
- Because HIV genome integrates with host DNA → Eradication of virus from body of victim appears impossible at present.

### Classification





| Antiretrovirus Drugs |       |        |                     |                     |                 |                          |
|----------------------|-------|--------|---------------------|---------------------|-----------------|--------------------------|
|                      | NRTIs | NNRTIs | Protease inhibitors | Integrase inhibitor | Entry inhibitor | CCR-5 receptor inhibitor |
| Introduction         |       |        |                     |                     |                 |                          |
| Drugs                |       |        |                     |                     |                 |                          |
| MOA                  |       |        |                     |                     |                 |                          |
| Pharmaco kinetics    |       |        |                     |                     |                 |                          |
| Uses                 |       |        |                     |                     |                 |                          |
| Adverse effects      |       |        |                     |                     |                 |                          |
| Interactions         |       |        |                     |                     |                 |                          |

## NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS)

### Introduction

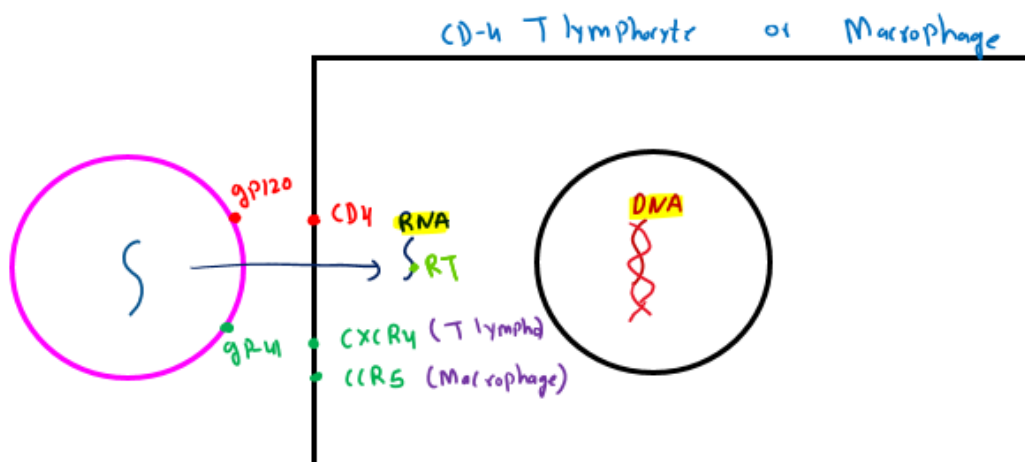
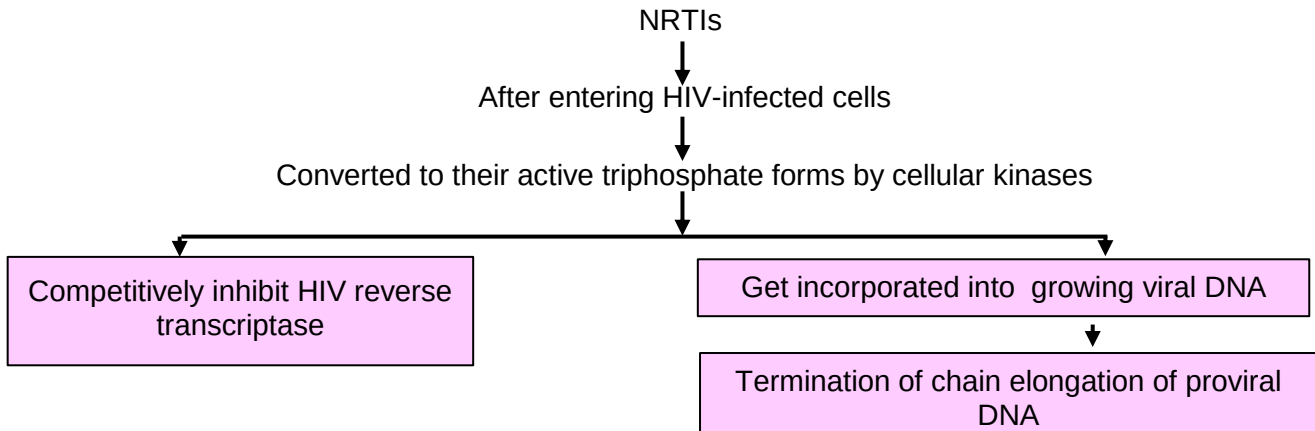
- Effective against both HIV-1 and HIV-2

### Drugs

- Zidovudine (AZT) → Prototype

- Didanosine (ddl)
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Tenofovir (TDF)
- Emtricitabine (FTC)

## MOA



## ZIDOVUDINE (AZIDOTHYMIDINE)

### Introduction

- Prototype drug of NRTIs.
- A thymidine analogue
- First antiretroviral drug approved for treatment of HIV infection.
- Effective against HIV-1 and HIV-2.
- Protects uninfected cells from HIV, but has no effect on HIV-infected cells.

### Pharmacokinetics

- Orally effective.
- Well absorbed from the GI tract

- Metabolized in liver by glucuronide conjugation
- Excreted in urine.
- Crosses placental and BBB and is also secreted in milk.

## Uses

- Zidovudine is used in HIV infected patients only in combination with at least 2 other ARV drugs.
- No longer included in the preferred 1st line WHO (2016) regimen, but is a component of one alternative regimen.

## Adverse Effects

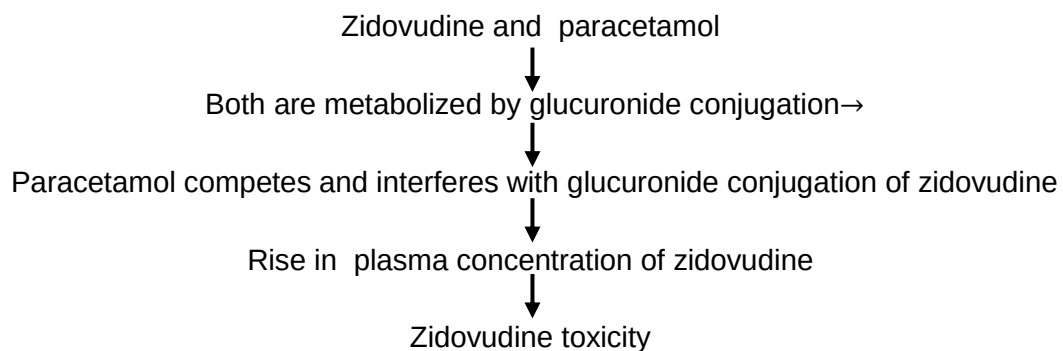
1. Hematology → Bone marrow suppression, Anaemia , Neutropenia
2. GIT → Nausea, vomiting, Abdominal discomfort
3. CNS → Headache, Insomnia
4. Liver → Hepatotoxicity
5. MSK → Myopathy with fatigue and lactic acidosis



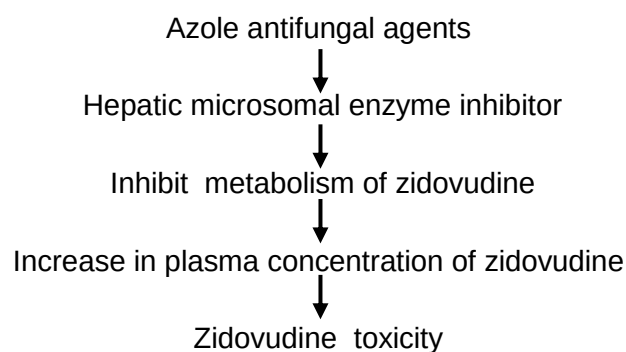
## Drug Interactions

1. Zidovudine and Paracetamol
2. Zidovudine and Azoles
3. Zidovudine and Stavudine

### 1. Zidovudine and paracetamol



### 2. Zidovudine and Azoles



### 3. Zidovudine and stavudine

- Both Compete for intracellular phosphorylation.

## DIDANOSINE (DDI)

- Purine nucleoside analogue
- MOA → Same as AZT
- In contrast to AZT → it does not cause myelosuppression.
- Major dose-related toxicity → Irreversible peripheral (stocking and glove) neuropathy



## STAVUDINE (D4T)

- Thymidine analogue
- MOA → Same as AZT
- Because of long term serious metabolic complications like lipodystrophy, lactic acidosis and peripheral neuropathy → stavudine is no longer employed in WHO as well as NACO regimens, except in exceptional circumstances.



## LAMIVUDINE (3TC)

- Deoxycytidine analogue
- Active against → HBV as well as HIV
- MOA → Inhibits HIV reverse transcriptase as well as HBV DNA polymerase
  - HIV → Essential component of most first line triple drug WHO and NACO regimens.
  - Chronic Hepatitis B → No longer a 1st line drug for chronic hepatitis B because of high Resistance

Adverse effects □ Pancreatitis and Neuropathy (rare)



## ABACAVIR (ABC)

- Guanosine analogue
- MOA → Intracellular conversion to carbovir triphosphate → gets incorporated in proviral DNA → terminates chain elongation.
- Component of preferred 1st line WHO regimen for children.
- Adverse effects → Hypersensitivity reactions → rashes, fever, abdominal pain, bowel upset, flu-like respiratory (Because of massive release of  $\text{TNF}\alpha$ )



## TENOFOVIR (TDF)

- Only nucleotide (not nucleoside) analogue of adenosine that is a commonly used anti-HIV drug.
- Also active against HBV
- It is included in preferred 1st line WHO regimen for adults and adolescents.
- Tenofovir containing regimens have been found less toxic as other first line regimens.
- Adverse effects → Renal toxicity



## NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS)

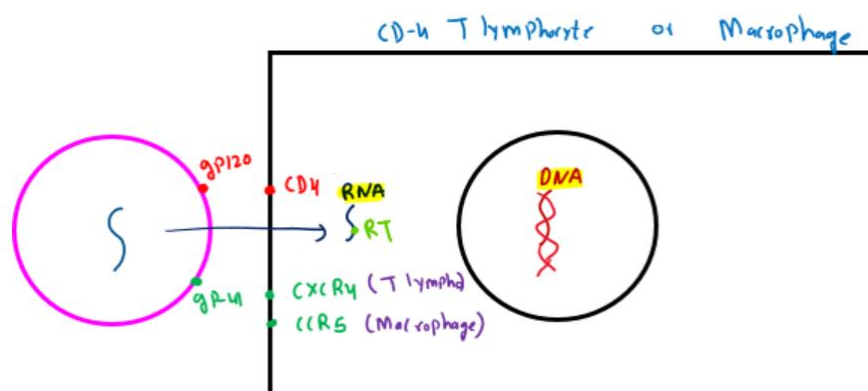
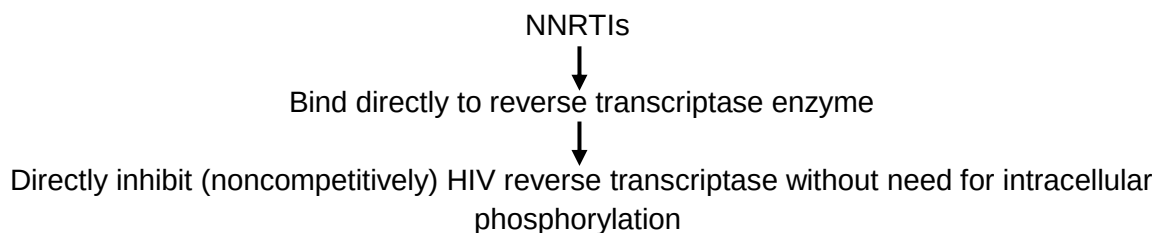
### Introduction

- NNRTIs are highly active against HIV-1 but have no effect on HIV-2.
- There is no cross-resistance with the NRTIs.
- Used in combination with NRTIs in treatment of AIDS.

### Drugs

- Nevirapine (NVP)
- Efavirenz (EFV)
- Etravirine (ETV)
- Delavirdine (DLV)
- Rilpivirine

### MOA



## NEVIRAPINE (NVP)

### Pharmacokinetics

- Oral absorption ~ 50%,
- Extensively metabolized  $\square$  mainly by CYP3A4 and to a lesser extent by CYP2B6

### Uses

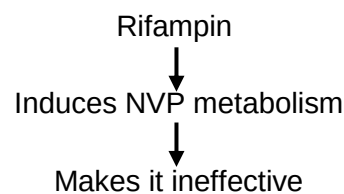
- Either NVP or EFV is included in first line triple drug regimen used by NACO, but the WHO (2016) regimen prefers EFV and advocates NPV as an alternative

### Adverse effects

1. **Hypersensitivity**  $\rightarrow$  Rashes  $\rightarrow$  commonest adverse effect
2. **Liver**  $\rightarrow$  Hepatotoxic
3. **GIT**  $\rightarrow$  Nausea



### Interactions

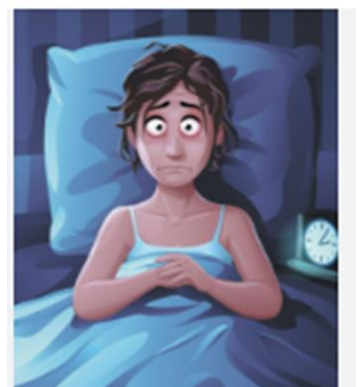


- Rifampin has little effect on EFV levels.
- If a patient being treated with NVP develops TB and is put on rifampin  $\square$  NVP should be replaced by EFV.

## EFAVIRENZ (EFV)

### Adverse effects

1. CNS  $\rightarrow$  Dizziness, insomnia and neuropsychiatric symptoms.
2. Endocrine  $\rightarrow$  Gynaecomastia
3. Hypersensitivity  $\rightarrow$  rashes



## ETRAVIRINE

- Second generation NNRTI which is active against HIV-1 mutants that are resistant to other NNRTIs.
- Indicated in adults and children >6 yr who have already been treated and are resistant / intolerant to other NNRTIs.
- Completely metabolized by → CYP3A4, CYP2C9 and CYP2C19

### Uses

- Etravirine is approved for use only in combination with a NRTI + one of PIs but not with fosamprenavir/r or atazanavir/r.

### Adverse effects

- Skin rashes
- Nausea



## PROTEASE INHIBITORS

### Introduction

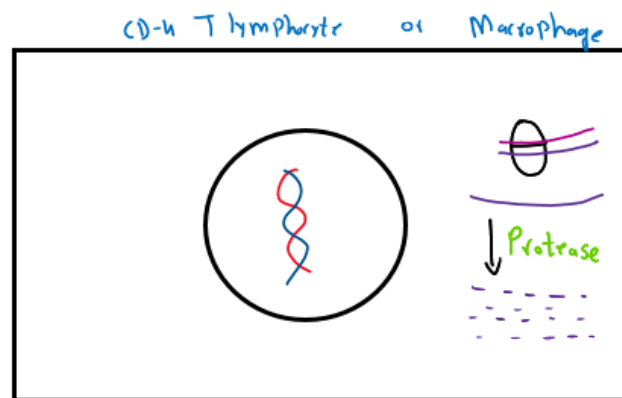
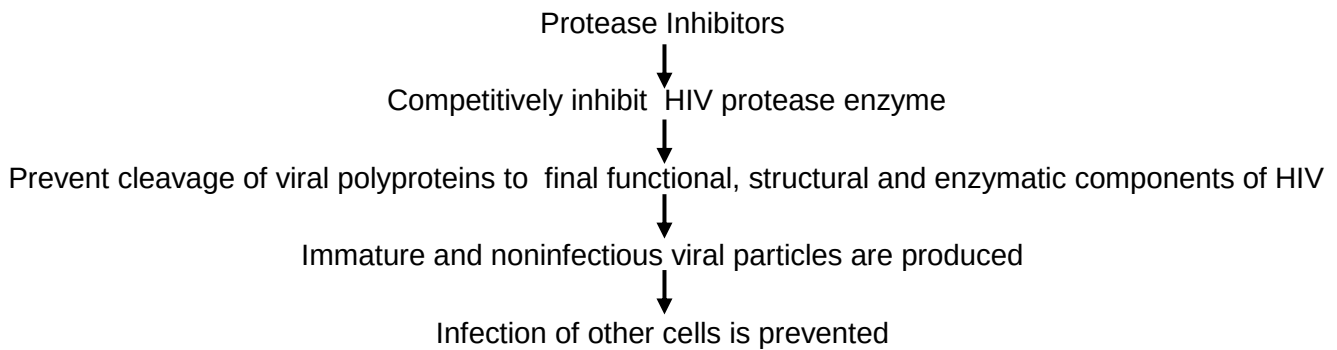
- Do not need intracellular activation by phosphorylation.
- Cross-resistance is common among PIs □ but there is no cross-resistance with reverse transcriptase inhibitors.
- PIs are used orally with reverse transcriptase inhibitors in patients with AIDS.
- Extensively metabolized in liver.

### Drugs

- Ritonavir (RTV)
- Atazanavir (ATV)
- Indinavir (INV)
- Nelfinavir (NFV)
- Saquinavir (SQV)
- Fosamprenavir (FPV)
- Lopinavir (LPV)
- Darunavir (DRV)



## MOA



- Because they act at a late step of viral cycle □ effective in both newly as well as chronically infected cells.

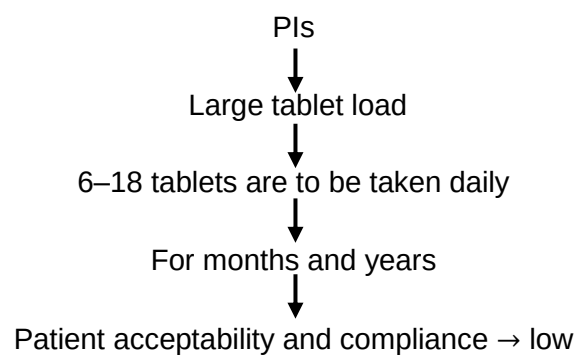
## Pharmacokinetics

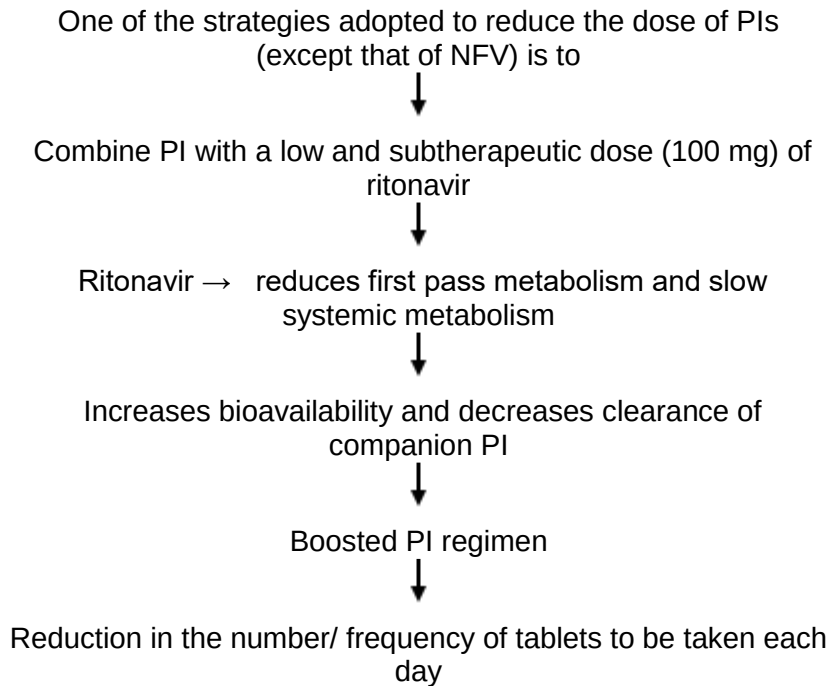
- Oral bioavailability → variable (IDV and RTV ~65%, NFV >20%, SQV 15%)
- Extensively metabolized mainly by CYP3A4, except NFV which is mainly a substrate of CYP2C19.
- All PIs → potent inhibitors of CYP3A4

## Uses

- Not used as monotherapy because resistance develops over months
- Combination of NRTIs with PIs is more effective than either drug given alone
- Current recommendation □ use a PI in combination with either two NRTIs or one NRTI + one NNRTI.

## Boosted PI regimen





## Adverse effects

1. **GIT** → Nausea, vomiting, Diarrhoea (Most common)
2. **CNS** → asthenia, headache, dizziness, facial tingling, numbness
3. **Metabolism** → Lipodystrophy (abdominal obesity, buffalo hump with wasting of limbs and face), dyslipidaemia (raised triglycerides and cholesterol)
4. **Endocrine** → Insulin resistance occurs and diabetes may be exacerbated.
5. **Urinary tract** → Indinavir crystallises in urine → increases risk of urinary calculi.

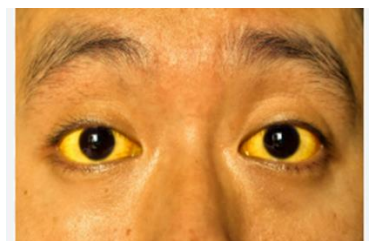


## Interactions

- Because different PIs inhibit as well as induce specific CYP isoenzymes to different extents → drug interactions with them are common and unpredictable.

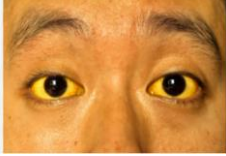
## ATAZANAVIR (ATV)

- Jaundice occurs in some patients without liver damage due to inhibition of hepatic glucuronyl transferase.



## INDINAVIR (IDV)

- Excess fluids must be consumed to avoid nephrolithiasis.
- Hyperbilirubinaemia occurs.



## NELFINAVIR (NFV)

- Diarrhoea and flatulence



## NELFINAVIR (NFV)

- Potent PI
- Potent CYP3A4 inhibitor.

## NELFINAVIR (NFV)

- Photosensitivity can occur



## LOPINAVIR

- ECG abnormalities noted.

## DARUNAVIR

- Active against both HIV-1 and HIV-2
- Adverse reactions → Nausea, diarrhoea, rise in hepatic enzymes, rashes and allergic reactions, particularly in those with sulfonamide allergy



## FOSAMPRENAVIR

- Phosphorylated prodrug of amprenavir → Better oral bioavailability and better tolerability than the parent drug.
- Active against both HIV-1 and HIV-2
- Adverse effects → nausea, diarrhoea, fatigue and rashes, but lipid abnormalities are less marked.

## INTEGRASE INHIBITORS

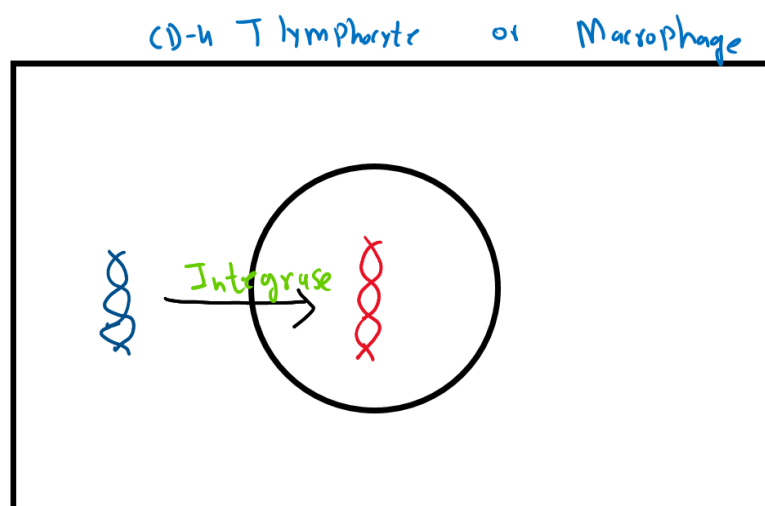
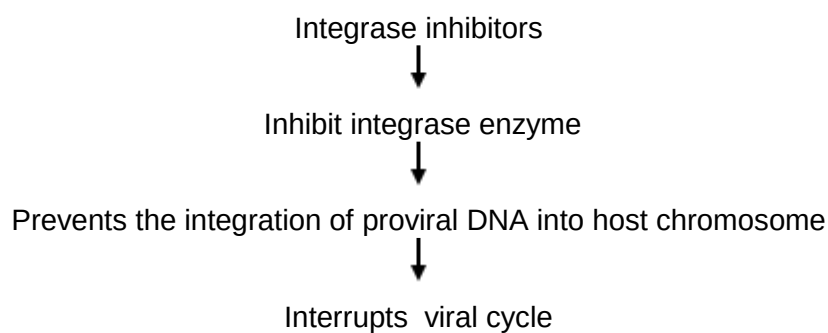
### Introduction

- Effective against both HIV-1 and HIV-2.
- No cross resistance with other classes of ARV drugs.

### Drugs

- Raltegravir
- Dolutegravir (DTG)

### MOA



### Pharmacokinetics

- Raltegravir, Dolutegravir □ glucuronide conjugated

## Uses

- Used along with 2 NRTIs as a 1st line regimen for treatment-naïve HIV patients if cost is not a consideration

## Adverse effects

- Raltegravir** → Myopathy is a potential toxicity
- Dolutegravir** → Hepatotoxicity is occasional.



## Interactions

- Rifampin** → induces metabolism of raltegravir and dolutegravir → dose needs to be doubled.
- Ca<sup>2+</sup> and Mg<sup>2+</sup> containing antacids and Ca<sup>2+</sup> or iron supplements** → should be avoided → because of their chelating property.

# ENTRY OR FUSION INHIBITORS

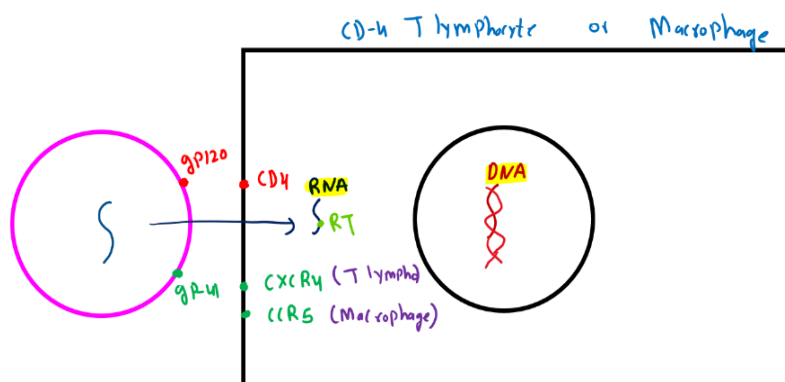
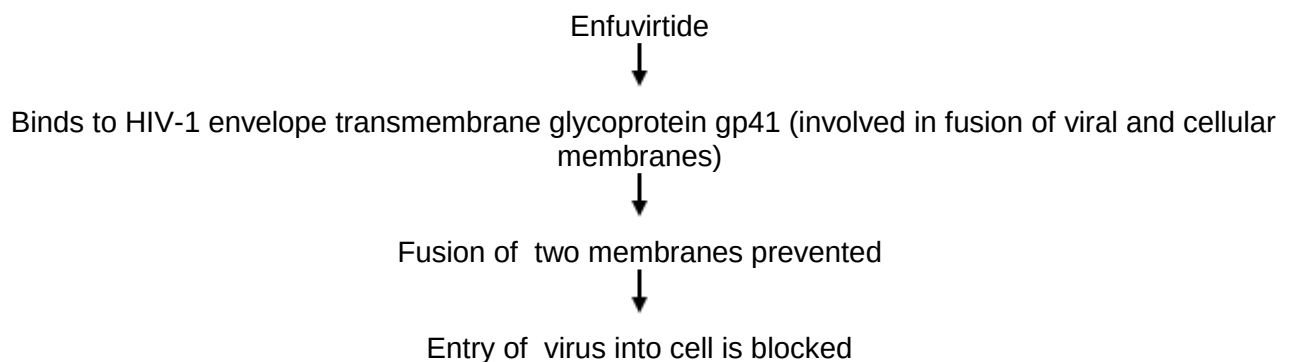
## Introduction

- Not active against HIV-2.
- No cross resistance with other classes of ARV drugs occurs.

## Drugs

- Enfuvirtide (T-20)

## MOA



## Pharmacokinatics

- Administered s.c. twice daily



## Uses

- As add-on drug to an optimized regimen in selected patients who have failed many earlier regimens or have multidrug resistant HIV
- For whom there is no other treatment option.

## Adverse effects

- Injections are painful** → local nodules/cysts

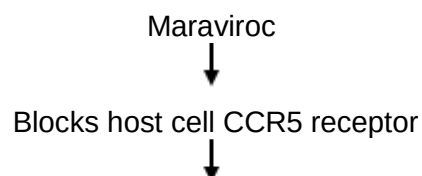


## CCR-5 RECEPTOR INHIBITOR

### Drugs

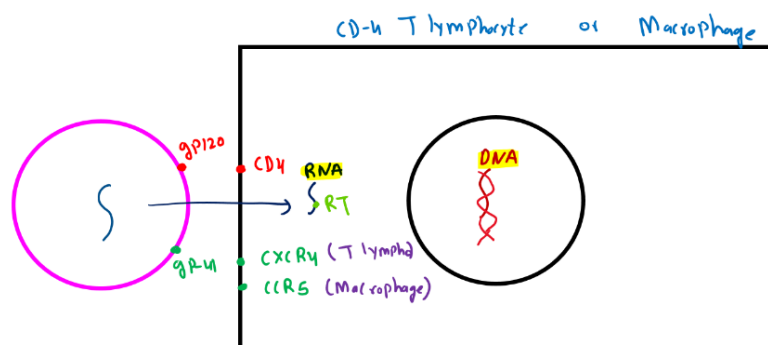
- Maraviroc

### MOA



Fusion of virus and subsequent entry of viral genome into cell is interfered

- It has no effect on HIV strains that are CXCR4 receptor tropic or dual CCR5/CXCR4 tropic.



## Pharmacokinetics

- Active orally
- No cross resistance with any other ARV drug

## Uses

- Added to optimized background therapy in patients who have already been treated with several regimens and who have CCR5-tropic HIV infection
- CCR5-tropism must be proven before using it.

## Adverse effects

1. **GIT** → Abdominal pain
2. **CVS** → Postural hypotension
3. **Hypersensitivity** → Rashes



# TREATMENT OF HIV INFECTION

## Introduction

- Retroviruses contain RNA-dependent DNA polymerase (reverse transcriptase) enzyme.
- They cause selective depletion of CD4 cells leading to a profound decrease in cell-mediated immunity.
- Infected person is prone to severe opportunistic infections, Kaposi sarcoma and lymphoid malignancies.

## Aim of anti-HIV therapy

- To cause maximal suppression of viral replication for the maximal period of time that is possible.

## Objectives of Antiretroviral Therapy

1. To suppress HIV replication and improve immune status of patient
2. To prevent emergence of drug-resistant virus
3. To prevent opportunistic infections

## Principles of Therapy

- In ART regimen, drugs with different mechanism of action should be used so that they produce synergistic effect.
- Use of drug combinations also prevents development of resistance.
- ART drugs are always used in combination of at least 3 drugs
- 3 drugs in the regimen should belong to at least 2 different classes
- It usually consists of a combination of → two NRTIs with a NNRTI/ Integrase inhibitor/ PI.
- For treatment-naïve patients → only PI sparing regimens (2 NRTI + NNRTI/Integrase inhibitor) chosen → more convenient with lower pill burden, simpler dosing schedules, more acceptable, better tolerated and no less metabolic complications.

- PI containing regimens (2 NRTI + PI or NRTI + NNRTI + PI) → reserved for advanced cases who have failed earlier regimens.
- Low dose ritonavir boosted PIs → preferred over higher dose single PI due to lower pill burden and better tolerability.
- In countries where cost is not a major constraint → integrase inhibitors (raltegravir and dolutegravir) used along with 2NRTIs as preferred regimen, because of high efficacy, better tolerability and convenience of dosing.
- Regimens have to be changed over time due to development of resistance.
- Life long therapy is required.



## Criteria for Anti-HIV Treatment

- National AIDS Control Organization (NACO) has adopted WHO 2016 guidelines for treatment of HIV infection.
- As per guidelines →
  1. ART should be started in all HIV-infected patients irrespective of CD4 count or clinical stage.
  2. Treatment is lifelong.
  3. Combination of antiretroviral drugs is used.

## FIRST-LINE ART REGIMEN IN ADULTS

- Two NRTIs + one NNRTI / Integrase inhibitor (INSTI)

| First-line antiretroviral regimens for adults and adolescents |  |
|---------------------------------------------------------------|--|
| Preferred regimens                                            |  |
| 1. Tenofovir + Lamivudine + Efavirenz                         |  |
| 2. Tenofovir + Emtricitabine + Efavirenz                      |  |
| Alternative regimens                                          |  |
| 1. Zidovudine + Lamivudine + Efavirenz                        |  |
| 2. Zidovudine + Lamivudine + Nevirapine                       |  |
| 3. Tenofovir + Lamivudine + Dolutegravir                      |  |
| 4. Tenofovir + Emtricitabine + Dolutegravir                   |  |
| 5. Tenofovir + Lamivudine + Nevirapine                        |  |
| 6. Tenofovir + Emtricitabine + Nevirapine                     |  |

## Monitoring

- Clinical efficacy of antiretrovirus drugs is monitored by →
  1. Plasma HIV-RNA assays
  2. CD4 lymphocyte count carried out at regular intervals.



## Optimum response to any regimen

1. Reduction of plasma HIV-RNA to undetectable levels (<50 copies/ $\mu$ L) within 6 months.
2. Restoration of CD4 cell count to near normal within 6 months.
3. Immune status improves and opportunistic infections become less common.

## Changing a failing regimen

An ART regimen is considered to have failed when:

1. Plasma HIV-RNA count is not rendered undetectable (<50 copies/ $\mu$ L) within 6 months therapy.
2. Repeated detection of virus in plasma after initial suppression to undetectable levels despite continuation of the drug regimen.
3. Clinical deterioration, fall in CD4 cell count, serious opportunistic infection while continuing drug therapy.

## SECOND-LINE ART REGIMEN IN ADULTS

- 2NRTIs + Boosted PI

| Choice of 2nd line ART regimens (NACO)                                                      |                                                                    |                                                                                                              |
|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| Failed 1st line regimen                                                                     | Second-line regimens                                               |                                                                                                              |
|                                                                                             | NRTI component                                                     | PI component                                                                                                 |
| 1. Zidovudine + Lamivudine + Nevirapine/Efavirenz<br>2. Tenofovir + Lamivudine + Nevirapine | Choices<br>1st: Tenofovir + Abacavir<br>2nd: Didanosine + Abacavir | Choices<br>1st: Atazanavir/r<br>2nd: Lopinavir/r<br>3rd: Saquinavir/r<br>4th: Indinavir/r<br>5th: Nelfinavir |

## Antiretroviral drug combinations to be avoided

- Components of a regimen should not have overlapping toxicities.

| Antiretroviral drug combinations to be avoided |                                                  |
|------------------------------------------------|--------------------------------------------------|
| 1. Zidovudine + stavudine:                     | Pharmacodynamic Antagonism                       |
| 2. Stavudine + didanosine:                     | Increased toxicity (neuropathy, lactic acidosis) |
| 3. Lamivudine + didanosine:                    | Clinically not Additive                          |
| 4. Tenofovir + didanosine:                     | Lower efficacy                                   |
| 5. Lamivudine + emtricitabine:                 | Similar drugs                                    |

## Pregnant Women

- ART should be started in all pregnant women with HIV irrespective of CD4 count and WHO clinical stage.
- A combination of →  
Tenofovir (300 mg) + lamivudine (300 mg)+ efavirenz (600 mg) is recommended in HIV-positive pregnant women.
- Treatment is lifelong.



## PROPHYLAXIS OF HIV INFECTION

- Pre-exposure prophylaxis (PrEP)
- Post-Exposure Prophylaxis (PEP)

### A. Pre-exposure prophylaxis (PrEP)

- Administration of antiretroviral drugs prior to exposure to HIV for preventing HIV infection.
- Key risk groups → Those at high risk of HIV infection include →
  - Men who have sex with men
  - Sex workers
  - Transgenders
  - IV drug abusers

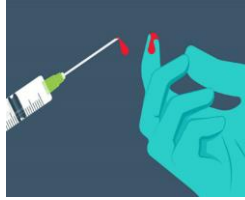


| Pre-exposure prophylaxis of HIV infection                     |
|---------------------------------------------------------------|
| Drug regimen                                                  |
| Tenofovir 300 mg daily<br>$\pm$<br>Emtricitabine 200 mg daily |

### B. Post-Exposure Prophylaxis (PEP)

- Use of antiretroviral drugs after exposure has occurred to prevent HIV infection is post-exposure prophylaxis.
- PEP should be initiated as early as possible, preferably within 72 hours of exposure.
- Individuals who have had exposure →
  - Sexual exposure
  - Needle-prick injury

- Exposure to blood
- Breast milk
- CSF, Pleural, pericardial fluid



| Post-exposure prophylaxis of HIV infection |                                                                 |
|--------------------------------------------|-----------------------------------------------------------------|
| For adults and adolescents                 |                                                                 |
| Preferred 2 NRTI:                          | Tenofovir (300 mg ) + Emtricitabine (200 mg) daily ±            |
| Preferred PI:                              | Lopinavir/r (400 + 100 mg) or Atazanavir/r (300 + 100 mg) daily |
| For children ≤ 10 years                    |                                                                 |
| Preferred 2 NRTI:                          | Zidovudine + Lamivudine                                         |
| Preferred PI:                              | Lopinavir/r                                                     |
| Duration of regimen:                       | 4 weeks                                                         |

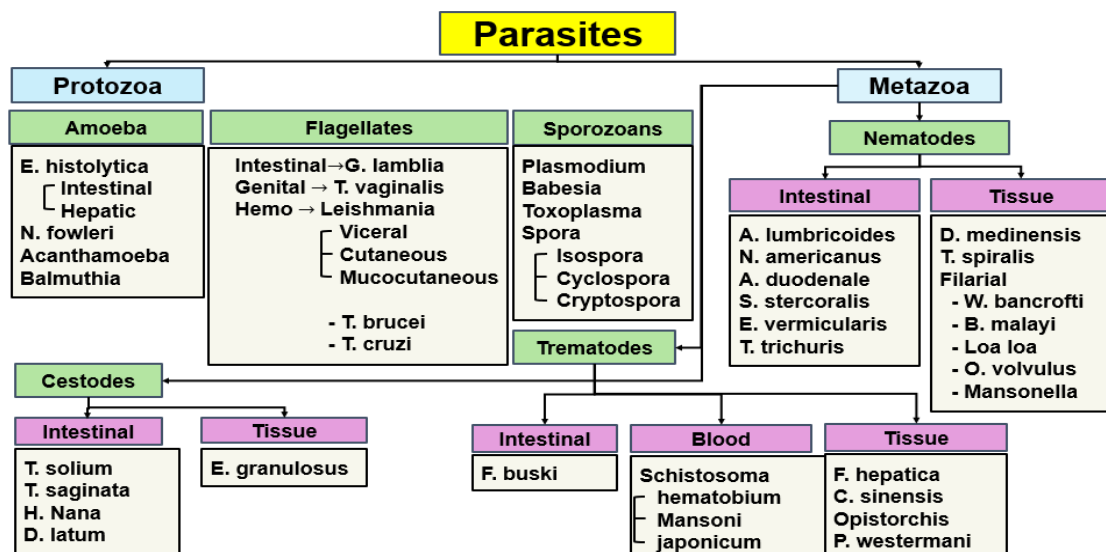
### Remember

- PEP is not required if exposure is to tears, urine or sweat, or source is HIV negative.

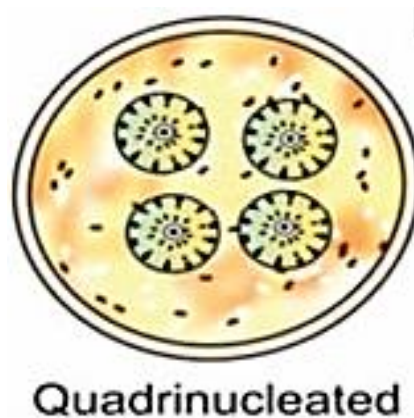
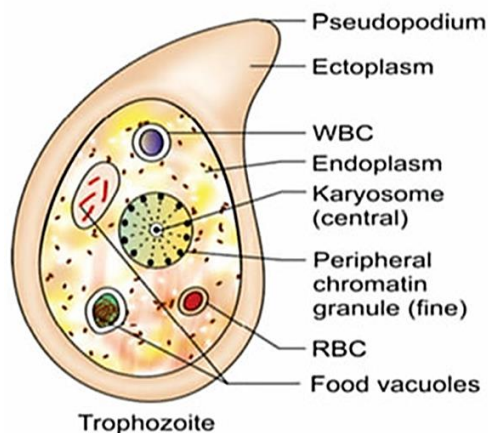


## ANTIAMOEBIC DRUGS

### Classification of Parasites



## Entamoeba Histolytica → Morphology



- **MOT** → Ingestion of water and food containing these cysts.
- **Infective form** → Quadrinucleate Cyst
- **Host** → 1
  - Definitive host → Man
  - Intermediate host → Nil



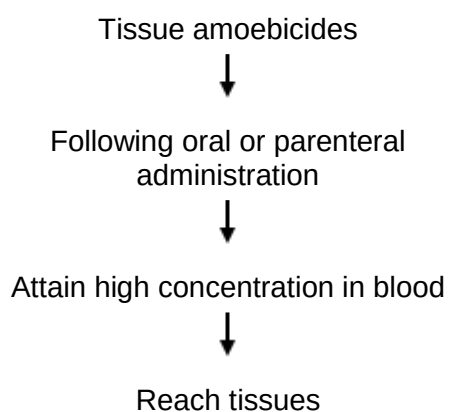
## ANTIAMOEBIC DRUGS

### Introduction

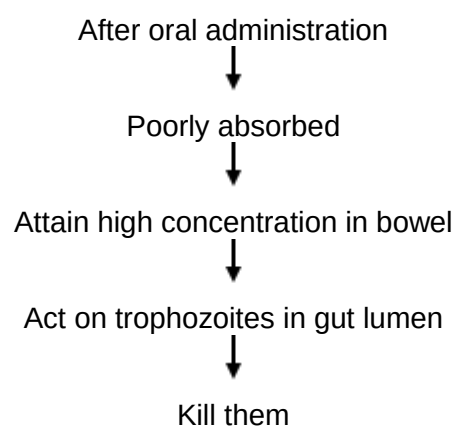
- Amoebiasis → a protozoal infection caused by *E. histolytica*, which is transmitted through faeco-oral route.
- Antiamoebic Drugs → drugs useful in infection caused by anaerobic protozoa *Entamoeba histolytica*.

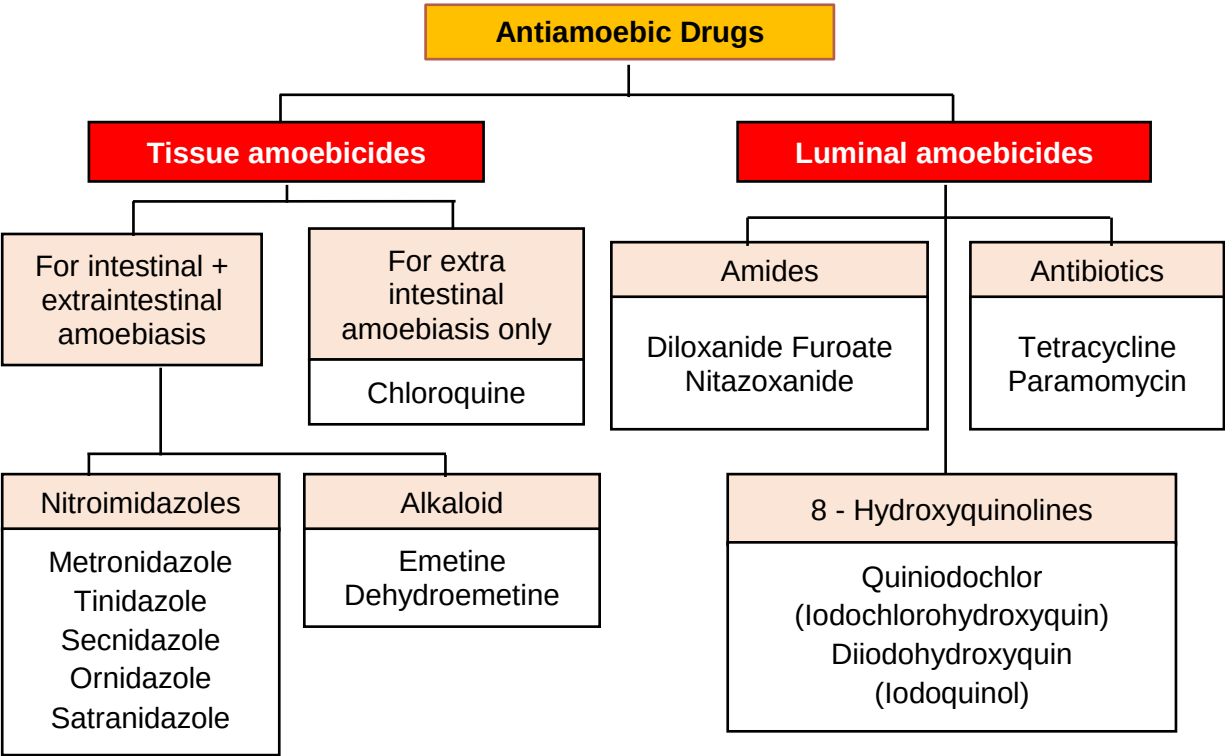
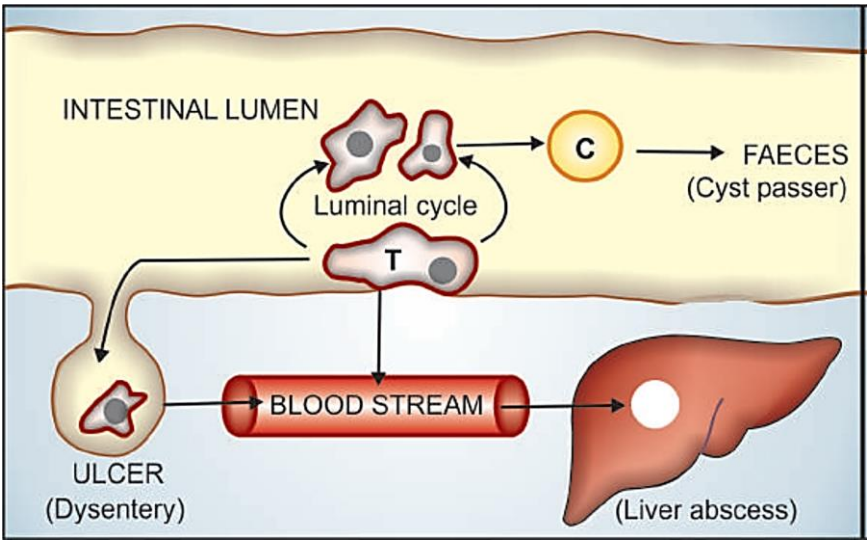
### Classification

#### Tissue amoebicides



#### Luminal amoebicides





| Antiamoebic Drugs        |                    |          |                   |                     |                        |             |
|--------------------------|--------------------|----------|-------------------|---------------------|------------------------|-------------|
|                          | Tissue amoebicides |          |                   | Luminal amoebicides |                        |             |
|                          | Nitroimidazoles    | Alkaloid | 4-Amino quinoline | Amides              | 8 – Hydroxy quinolines | Antibiotics |
| <b>Drugs</b>             |                    |          |                   |                     |                        |             |
| <b>MOA</b>               |                    |          |                   |                     |                        |             |
| <b>Pharmaco kinetics</b> |                    |          |                   |                     |                        |             |
| <b>Uses</b>              |                    |          |                   |                     |                        |             |
| <b>Adverse effects</b>   |                    |          |                   |                     |                        |             |
| <b>Interactions</b>      |                    |          |                   |                     |                        |             |

## NITROIMIDAZOLES

### Drugs

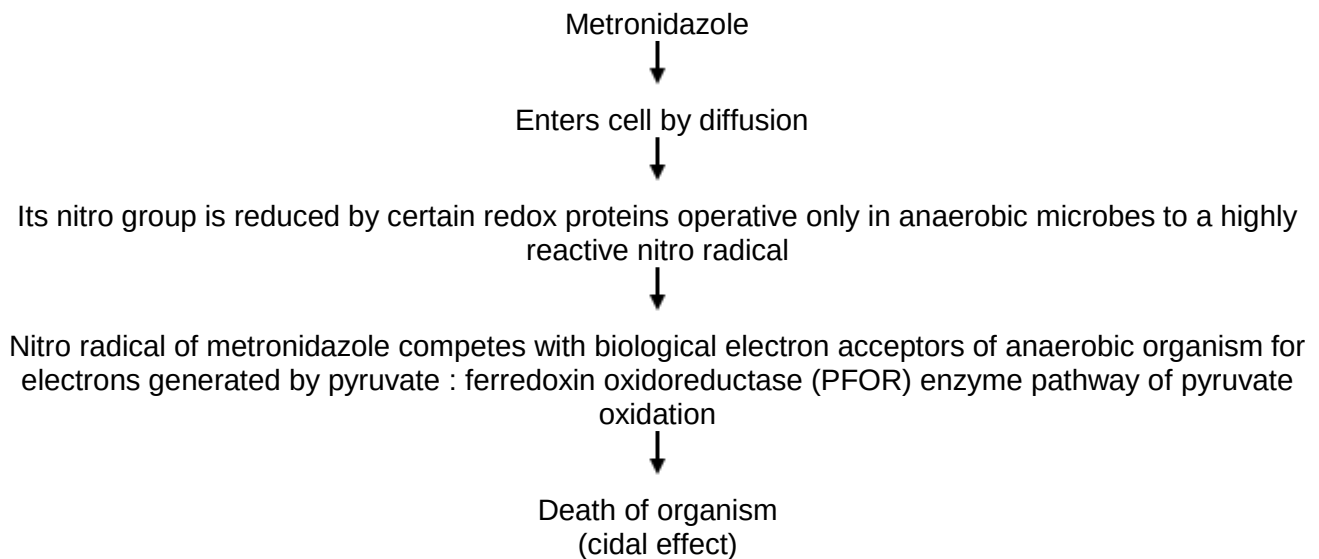
- Metronidazole (Prototype)
- Tinidazole
- Secnidazole
- Ornidazole
- Satranidazole

### Introduction

- Selective Broad spectrum cidal activity against anaerobic and microaerophilic microorganisms. →
  - **Anaerobic protozoa** → *E. histolytica*, *Giardia lamblia* and *Trichomonas vaginalis*.
  - **Anaerobic and microaerophilic bacteria** → *Bact. fragilis*, *Fusobacterium*, *Clostridium perfringens*, *Cl. difficile*, *Helicobacter pylori*, *Campylobacter*, peptococci, spirochetes and anaerobic Streptococci

### MOA

- **Metronidazole** → selectively toxic to anaerobic and microaerophilic microorganisms.



### Pharmacokinetics

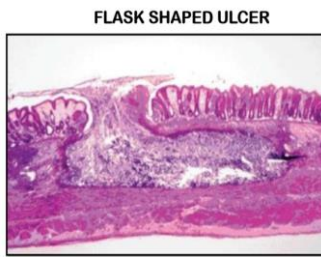
- Available for oral, i.v. and topical administration.
- Well absorbed in small intestine after oral administration
- Metabolized in liver
- Excreted mainly in urine.

### Uses

1. **Amoebiasis** → First-line agent for the treatment of both intestinal and extraintestinal amoebiasis except in asymptomatic carriers.
2. **Trichomonas vaginitis** → DOC. Both sexual partners should be treated simultaneously.
3. **Giardiasis** → very effective

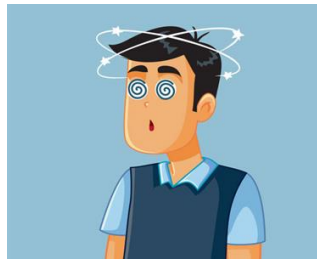


4. **Anaerobic infections** → Highly effective in most of anaerobic infections → pelvic inflammatory disease, lung abscess, intra-abdominal infection, etc., caused by *B. fragilis*, *Clostridium* and other anaerobic organisms.



## Adverse Effects

1. **GIT** → Anorexia, nausea, metallic taste, dry mouth, epigastric distress, abdominal cramps and occasionally vomiting.
2. **Allergic reactions** → skin rashes, urticaria, itching and flushing.
3. **CNS** → Dizziness, vertigo, confusion, irritability, headache, rarely convulsions, ataxia, Polyneuropathy (on prolonged therapy)
4. **Disulfiram-like reaction** → nausea, vomiting, abdominal cramps, headache, flushing □ occur if taken with alcohol → hence patient should be warned to avoid alcohol during treatment with metronidazole.



## Drug Interactions

1. **Metronidazole X Warfarin** → Metronidazole potentiates anticoagulant effect of warfarin and other oral coumarins by inhibiting their metabolism → prolongation of PT → reduction of warfarin dose may be needed.
2. **Metronidazole X Lithium** → Metronidazole may potentiate lithium toxicity by decreasing renal clearance of lithium.

## ALKALOID

### Drugs

- Emetine
- Dehydroemetine

### MOA

Emetine  
↓

Inhibit protein synthesis in amoebae by arresting intraribosomal translocation of tRNA-amino acid complex



Kills tissue trophozoites and have no effect on cysts

## Pharmacokinetics

- They are irritants, bitter in taste and nauseating → cannot be administered orally.
- Administered through i.m. route.

## Uses

- Highly toxic
- Used only when metronidazole is contraindicated or if the patient is not responding to metronidazole.
- DHE is less toxic than emetine → preferred to emetine.

## Adverse Effects

Mnemonic: **EMETINE**

1. **E**mesis (vomiting) – due to the stimulation of CTZ
2. **M**uscle weakness and stiffness.
3. **E**CG changes → T-wave inversion, prolongation of PR interval.
4. **T**achycardia, hypotension, cardiac arrhythmias.
5. **I**tching and skin rashes.
6. **N**ausea
7. **E**czematoid lesions at the injection site.

## 4 - AMINO QUINOLINE

### Drugs

- Chloroquine

### Pharmacokinetics

- Administered orally.
- It is completely absorbed from the upper GI tract and gets concentrated in liver.

### Uses

- Kills trophozoites of *E. histolytica* and is highly concentrated in liver → used in hepatic amoebiasis only.
- Not effective in intestinal amoebiasis because it attains low concentration in gut wall and lumen.
- A luminal amoebicide has to be added to it when used for hepatic amoebiasis.

### Other Uses

Mnemonic

**RED LIP** Mahatma **G**andhi



- **R**heumatoid arthritis
- **E**xtraintestinal amoebiasis
- **D**iscoid lupus erythematosus
- **L**epa reaction
- **I**nfectious mononucleosis
- **P**hotogenic reactions
- **M**alaria
- **G**iardiasis

## Adverse effects

Mnemonic → **GBS RANA**

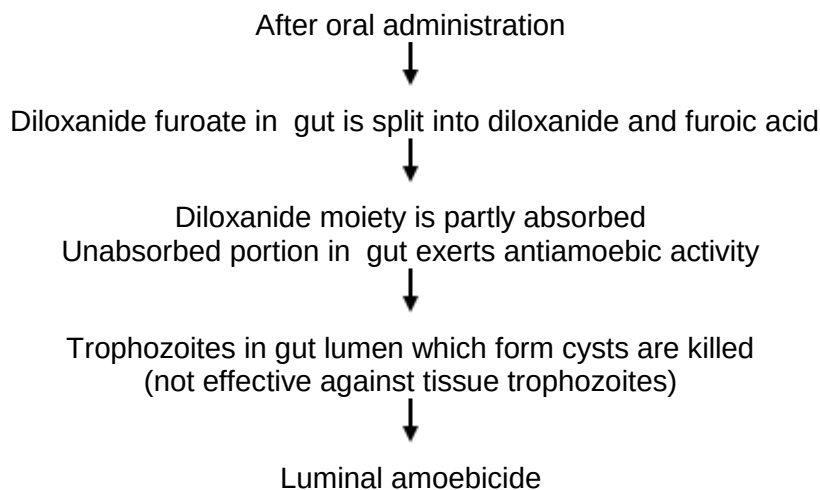
- **G** → GIT irritation, Graying of hair
- **B** → Bull's eye maculopathy
- **S** → Skin rash and skin lesions → Lichenoid eruption, Photoallergy
- **R** → Renal damage
- **A** → Auditory damage
- **N** → Neuropathies
- **A** → attacks of porphyria

## AMIDES

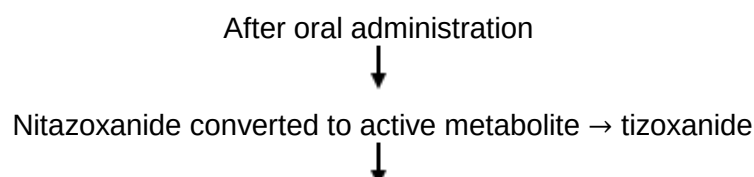
### Drugs

- Diloxanide Furoate
- Nitazoxanide

### MOA → Diloxanide Furoate



### MOA → Nitazoxanide



Trophozoites in gut lumen which form cysts are killed  
(not effective against tissue trophozoites)



Luminal amoebicide

## Uses

- DOC → for asymptomatic amoebic carriers.

## Adverse effects

- CNS → Headache
- GI disturbances

# 8 – HYDROXY QUINOLINES

## Drugs

- Quiniodochlor (Iodochlorohydroxyquin)
- Diiodohydroxyquin (Iodoquinol)
- Hydroxyquinolines were widely used as luminal amoebicides in the past for amoebiasis.
- They have been banned in various countries because of their toxicity □ subacute myeloptotic neuropathy (SMON).

# ANTIBIOTICS

- **Tetracyclines** →
  - They are luminal amoebicides.
  - Unabsorbed portion of older tetracyclines reaches colon and inhibits the bacterial flora, which are required for survival of *E. histolytica*.
- **Paromomycin** →
  - Paromomycin, an aminoglycoside, is a luminal amoebicide.
  - It is not absorbed from the GI tract following oral administration.
  - It alters the intestinal flora.
  - Adverse effects like nausea, vomiting and abdominal pain can occur.
  - Oral paromomycin is safe for use in pregnancy.
  - It is also useful in kala-azar.

| DOC of different forms of amoebic infection                                                                                                                                                                             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Acute Amoebic Dysentery                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>• Metronidazole 800 mg oral TDS × 7–10 days (in severe cases 500 mg slow i.v. 6 hourly till oral therapy can be instituted) or Tinidazole 2.0 g oral daily × 3–6 days</li> </ul> |
| +                                                                                                                                                                                                                       |

|                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Luminal amoebicide (Diloxanide furoate 500 mg TDS × 5–10 days)                                                                                                                                                                                                                                                                                                                   |
| <b>Mild intestinal amoebiasis/Asymptomatic cyst passers</b>                                                                                                                                                                                                                                                                                                                      |
| <ul style="list-style-type: none"> <li>• Metronidazole 400 mg oral TDS × 5–7 days or Tinidazole 2.0 g oral OD × 2–3 days</li> </ul> <p style="text-align: center;">+</p> <p style="text-align: center;">Luminal amoebicide (as above)</p>                                                                                                                                        |
| <b>Amoebic liver abscess</b>                                                                                                                                                                                                                                                                                                                                                     |
| <ul style="list-style-type: none"> <li>• Metronidazole 800 mg oral TDS × 10 days (in serious cases 500 mg slow i.v. infusion 6 hourly × 10 days) or Tinidazole 2.0 g oral daily × 3–6 days (severe cases: 800 mg i.v. daily × 6 days or till oral can be given)</li> </ul> <p style="text-align: center;">+</p> <p style="text-align: center;">Luminal amoebicide (as above)</p> |

## ANTHELMINTIC DRUGS

### Introduction

- Anthelmintics are drugs used in treatment of infestation with helminths in intestinal tract or tissues of body
- Anthelmintics that kill worms → vermicides
- Anthelmintics that help to expel worms → vermifuges

### Drugs

Mnemonic → **MANIPAL PD**

- **M**ebendazole
- **A**lbendazole
- **N**iclosamide
- **I**vermectin
- **P**yrantel pamoate
- **A**lbendazole
- **L**evamisole
- **P**raziquantel
- **D**iethylcarbamazine citrate

| Anthelmintic Drugs |             |             |                  |     |
|--------------------|-------------|-------------|------------------|-----|
|                    | Mebendazole | Albendazole | Pyrantel Pamoate | DEC |
| Introduction       |             |             |                  |     |
| MOA                |             |             |                  |     |

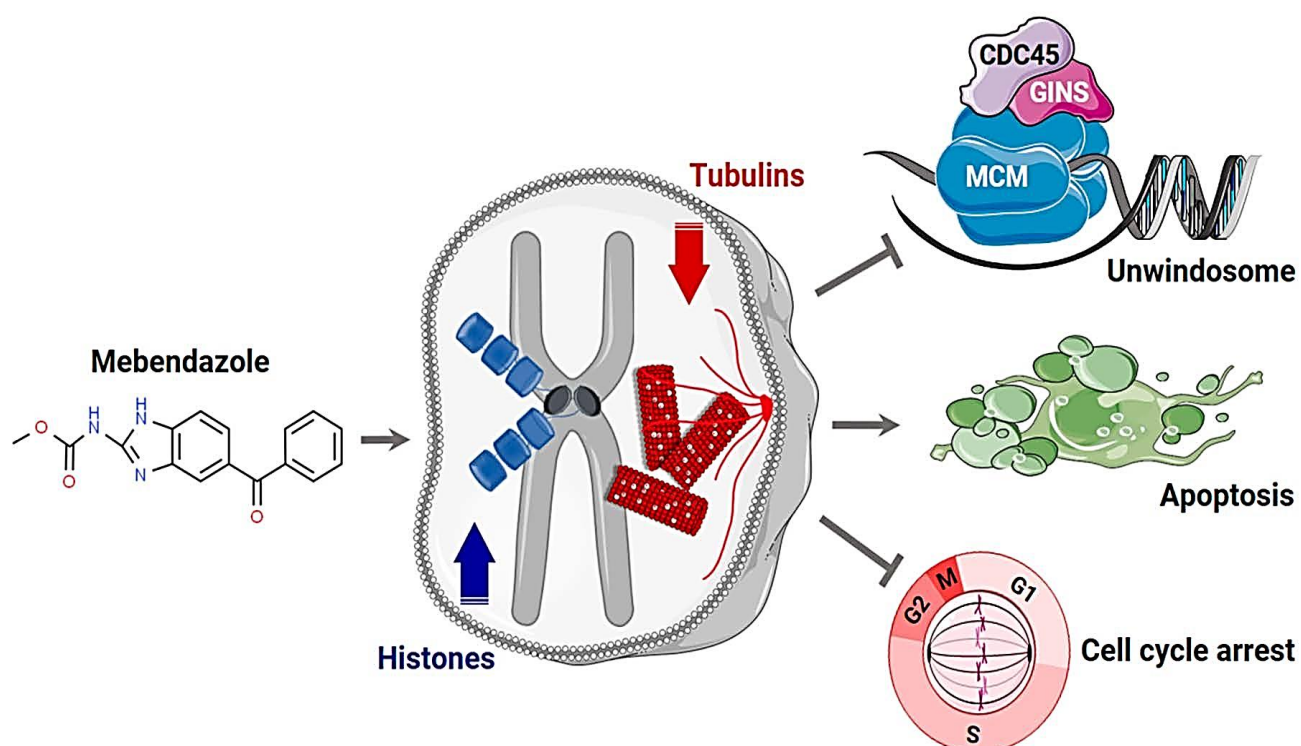
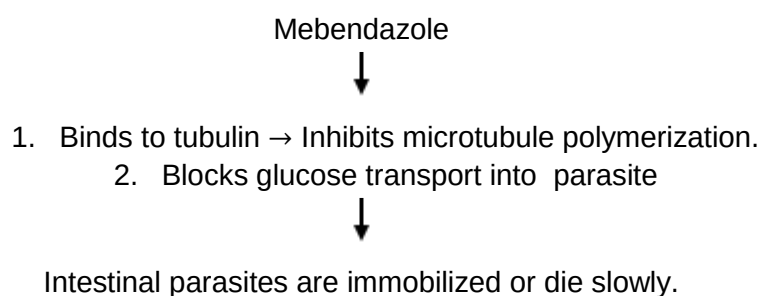
|                   |  |  |  |  |
|-------------------|--|--|--|--|
| Pharmaco kinetics |  |  |  |  |
| Uses              |  |  |  |  |
| Adverse effects   |  |  |  |  |

## MEBENDAZOLE

### Introduction

- Mebendazole is a benzimidazole
- Broad spectrum of anthelmintic activity.

### MOA



## Pharmacokinetics

- Administered orally
- Poorly absorbed from the GI tract
- Highly bound to plasma proteins
- Metabolized in liver.
- Most of oral dose is excreted in faeces.

## Uses

- Highly effective against intestinal nematodes ☐
  - Roundworm
  - Hookworm
  - Whipworm
  - Pinworm
  - Mixed worm infestations

## Adverse Effects

1. **GIT** → anorexia, nausea, vomiting, diarrhoea and abdominal discomfort.
2. **Skin** → rashes, itching, drug fever

## Contraindication

- Pregnancy
- Children younger than 1 year.



# ALBENDAZOLE

## Introduction

- It is also a benzimidazole
- Broad spectrum of anthelmintic activity.

## MOA

- Similar to that of mebendazole.

## Pharmacokinetics

- Given orally.
- Erratically absorbed → fatty food increases its absorption
- Metabolized in liver.
- Produces an active metabolite → albendazole sulphoxide → widely distributed into various tissues including hydatid cyst → So albendazole is preferred to mebendazole in the treatment of hydatid disease.

## Uses

1. Nematodes

2. Neurocysticercosis
3. Hydatid disease
4. Filariasis

### 1. Nematodes:

- Highly effective against intestinal nematodes – roundworm, hookworm, whipworm, pinworm and threadworm and also in mixed worm infestations.
- More effective than mebendazole in trichinosis.

### 2. Neurocysticercosis:

- Both albendazole and praziquantel are highly effective in neurocysticercosis. But albendazole is preferred to praziquantel because →
  - It is cheaper.
  - Duration of treatment is shorter.
  - Reaches high concentration in brain and CSF.
  - Less toxic and better tolerated.

**3. Hydatid disease** → In hydatid cyst, surgical resection is the treatment of choice, but albendazole is the drug of choice for medical therapy.

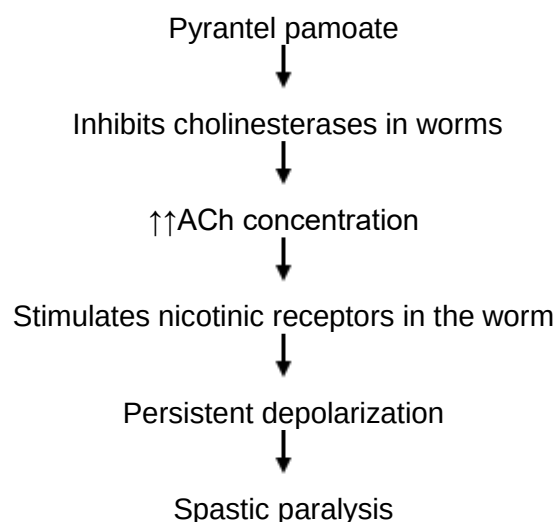
**4. Filariasis** → Single dose of (400 mg) albendazole is given with diethylcarbamazine citrate (DEC) or ivermectin in treatment of lymphatic filariasis. Albendazole has adjuvant value.

## Adverse Effects

- **GIT** → Nausea, vomiting, diarrhoea and epigastric distress.
- **CNS** → headache, dizziness
- **Liver** → hepatic dysfunction
  - Loss of hair
  - Neutropenia

## PYRANTEL PAMOATE

### MOA





Worms are expelled (vermifuge)

## Pharmacokinetics

- Pyrantel pamoate is given orally but absorbed poorly
- About 80%–90% of oral dose is excreted in faeces.

## Uses

- Highly effective for the treatment of →
  - Roundworm
  - Pinworm
  - Hookworm infestations
- Oxantel pamoate is effective in → Trichuriasis

## Adverse Effects

- **GIT** → Nausea, vomiting, Diarrhoea
- **CNS** → Headache, Dizziness
- **Skin** → rashes

# DEC

## Introduction

- DEC is available as citrate salt.
- It acts mainly on microfilariae but the adult worms are killed slowly only on long-term treatment.

## MOA

DEC



Damages microfilarial membrane structure

## Pharmacokinetics

- Well absorbed from the GI tract
- Metabolized in liver
- Excreted in urine.
- DEC is safe for use during pregnancy.

## Uses

1. **Filariasis**: DEC is DOC for treatment of filariasis due to *W. bancrofti* and *B. malayi*.
2. **Tropical eosinophilia**

## Adverse Effects

- **GIT** → anorexia, nausea, vomiting, headache and dizziness.
- **Parasite-induced reactions** → due to the release of proteins from dying parasites.

## Mazzotti reaction

- In onchocerciasis, DEC produces a severe reaction, which is termed Mazzotti reaction

- Characterized by ☐ severe itching, fever, skin rashes, nausea, vomiting, headache, joint pain, lymphadenitis, keratitis and uveitis.
- DEC is not recommended in onchocerciasis.
- In *W. bancrofti*, the reaction is usually mild.
- This can be minimized by administering H1-blockers.
- The reaction is treated with H1-blockers and glucocorticoids.

| Infestation and parasite                                                                                             | Drugs                                                              |
|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| <b>1. Nematodes</b>                                                                                                  |                                                                    |
| (a) Roundworm ( <i>Ascaris lumbricoides</i> )                                                                        | Mebendazole                                                        |
| (b) Hookworm ( <i>Ancylostoma duodenale</i> , <i>Necator americanus</i> )                                            | Pyrantel pamoate                                                   |
| (c) Pinworm ( <i>Enterobius vermicularis</i> )                                                                       |                                                                    |
| (d) Whipworm ( <i>Trichuris trichiura</i> )                                                                          | Albendazole , Mebendazole ,Oxantel pamoate                         |
| (e) Threadworm ( <i>Strongyloides stercoralis</i> )                                                                  | Ivermectin , Albendazole                                           |
| (f) Mixed worm infestation                                                                                           | Albendazole , Mebendazole ,Pyrantel pamoate                        |
| (g) Filariasis ( <i>Wuchereria bancrofti</i> , <i>Brugia malayi</i> ), onchocerciasis ( <i>Onchocerca volvulus</i> ) | Diethylcarbamazine (DEC) + albendazole<br>Ivermectin + albendazole |
| (h) Guinea worm ( <i>Dracunculus medinensis</i> )                                                                    | Metronidazole                                                      |

|                                                        |                             |
|--------------------------------------------------------|-----------------------------|
| <b>2. Trematodes</b>                                   |                             |
| (a) Blood flukes (schistosomes)                        | Praziquantel                |
| (b) Intestinal flukes                                  |                             |
| (c) Liver flukes                                       |                             |
| (d) Lung flukes                                        |                             |
| <b>3. Cestodes</b>                                     |                             |
| (a) <i>Taenia saginata</i> (beef tapeworm)             | Praziquantel<br>Niclosamide |
| (b) <i>Taenia solium</i> (pork tapeworm)               |                             |
| (c) <i>Diphyllobothrium latum</i> (fish tapeworm)      |                             |
| (d) <i>Hymenolepis nana</i> (dwarf tapeworm)           |                             |
| (e) Neurocysticercosis (caused by <i>T. solium</i> )   | Albendazole Praziquantel    |
| (f) Hydatid disease ( <i>Echinococcus granulosus</i> ) | Albendazole Mebendazole     |





# Hormones and Related Drugs

## CHAPTER 13

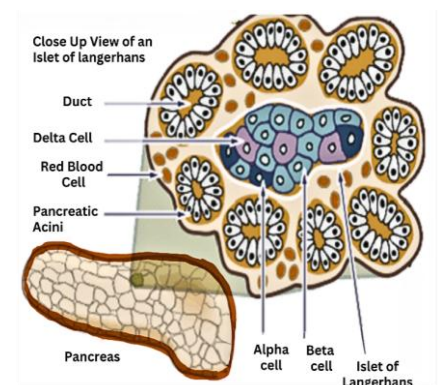
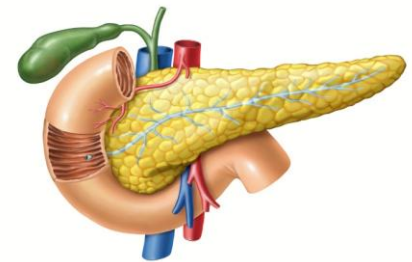
### CONTENT

- Antidiabetic Drugs
- Corticosteroids
- Thyroid Hormones and Thyroid Inhibitors
- Estrogens, Progestins
- Hormonal Contraceptives
- Uterine Stimulants and Relaxants
- Androgens and Related Drugs

### ANTIDIABETIC DRUGS

#### Pancreas

- Human pancreas, though anatomically a single organ, histologically and functionally, has 2 distinct parts →
  - **Exocrine part** → secretes enzymes
  - **Endocrine part** → secretes hormones
- Human pancreas, though anatomically a single organ, histologically and functionally, has 2 distinct parts →
  - **Exocrine part** → secretes enzymes
  - **Endocrine part** → secretes hormones



#### Endocrine pancreas

- Endocrine pancreas consists of microscopic collections of cells called islets of Langerhans
- Ultrastructurally and immunohistochemically → 4 major and 2 minor types of islet cells are distinguished

#### Major cell types

1. **Beta ( $\beta$ ) or B cells** → comprise about 70% of islet cells and secrete insulin (Glucose → Glycogen)

**2. Alpha ( $\alpha$ ) or A cells** → comprise 20% of islet cells and secrete glucagon (Glycogen → Glucose )

**3. Delta ( $\delta$ ) or D cells** → comprise 5-10% of islet cells and secrete somatostatin which suppresses both insulin and glucagon release.

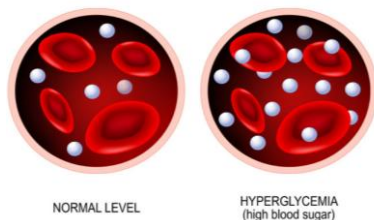
**4. Pancreatic polypeptide (PP) cells or F cells** → comprise 1-2% of islet cells and secrete pancreatic polypeptide having gastrointestinal effects.

| CELL                              | HORMONE SECRETED       |
|-----------------------------------|------------------------|
| Alpha ( $\alpha$ ) cell           | Glucagon               |
| Beta ( $\beta$ ) cell             | Insulin                |
| Delta ( $\delta$ ) cell           | Somatostatin           |
| Pancreatic polypeptide (PP) cells | Pancreatic polypeptide |

## DIABETES MELLITUS

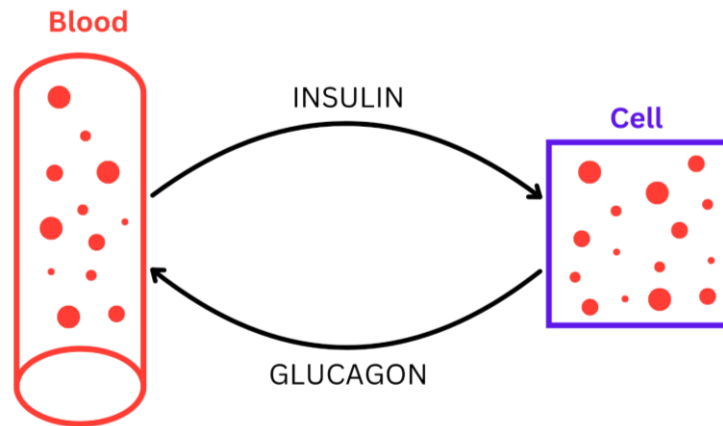
### Introduction

- Diabetes mellitus (DM) is a group of metabolic disorders sharing the common feature of hyperglycemia
- DM is diagnosed when blood glucose levels becomes too high

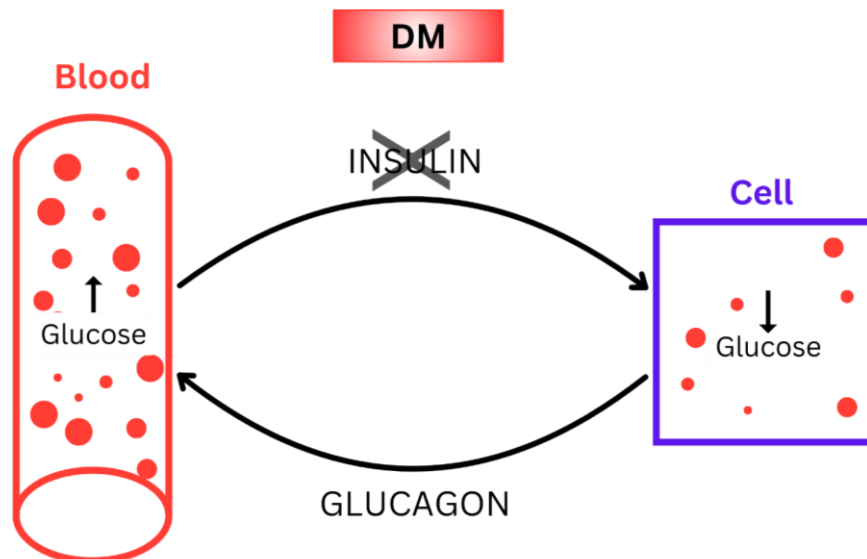
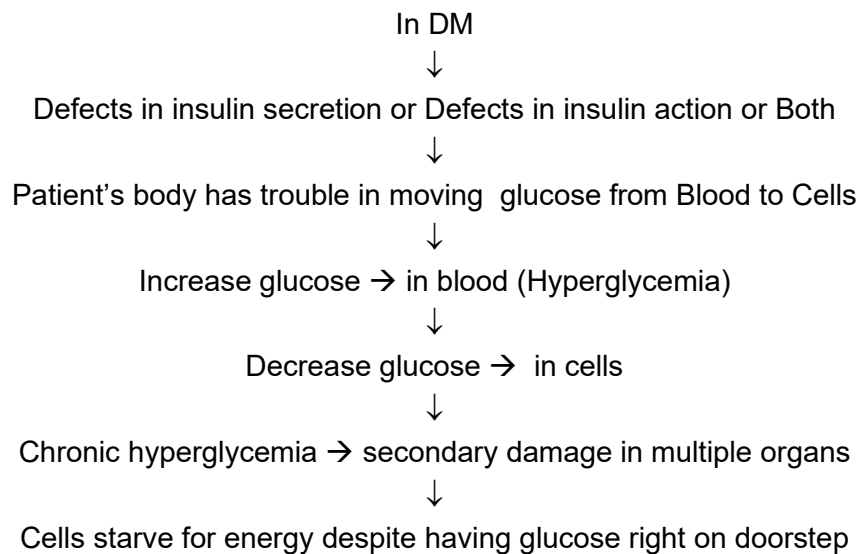


### Glucose Homeostasis

- In general body controls how much glucose is in the blood relative to how much is in the cell by 2 hormones →
  - Insulin** → Glucose → Glycogen
  - Glucagon** → Glycogen → Glucose



## Pathogenesis of DM



## Classification of Diabetes mellitus

### Type 1 DM →

- 10% cases of DM.
- Juvenile-onset diabetes → due to its occurrence in younger age
- Insulin-dependent DM (IDDM) → because these patients have absolute requirement for insulin replacement as treatment.

## Type 2 DM →

- 90% cases of DM.
- Maturity-onset diabetes
- Non-insulin dependent diabetes mellitus (NIDDM)

## INSULIN REGULATION

- In order to understand its pathogenesis of DM, it is essential to first recall physiology of normal insulin synthesis and secretion
  - Insulin synthesis
  - Insulin release
  - Insulin action

## Insulin Synthesis

Pre-proinsulin  
(single-chain 86-amino acid precursor polypeptide)

↓

Subsequent proteolysis removes amino terminal signal peptide, forming proinsulin

Proinsulin

↓

(α chain and β chain linked together by connecting segment called C-peptide)

↓

Further cleavage separates C-peptide

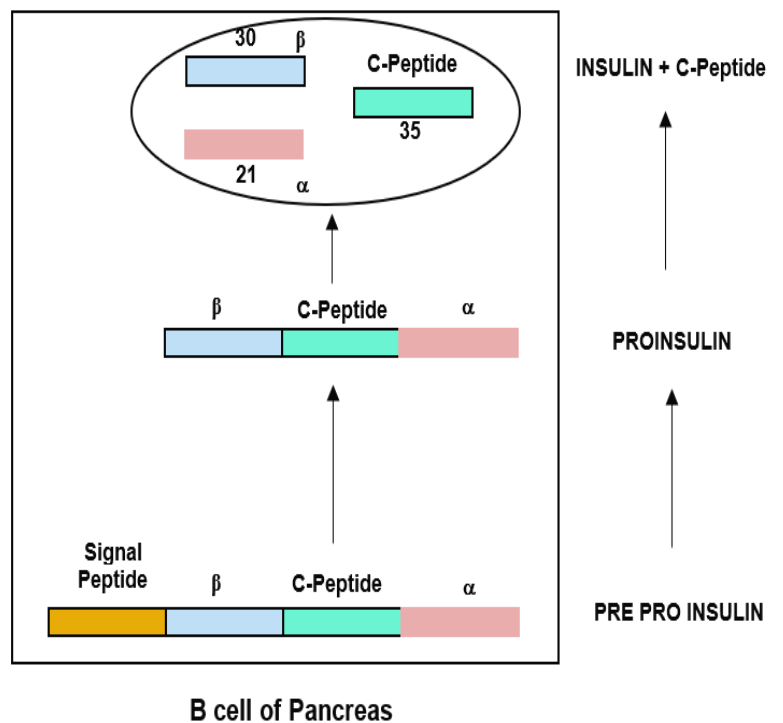
↓

Insulin is formed

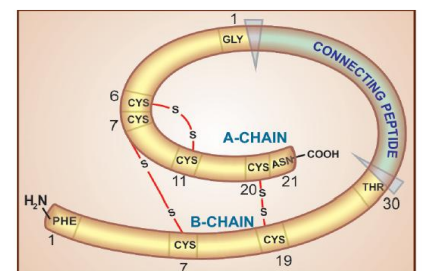
α chain (21 amino acids) and β chain (30 amino acids) are linked together

↓

Both insulin and C-peptide are then stored in secretory granules and secreted in equimolar quantities after physiologic stimulation

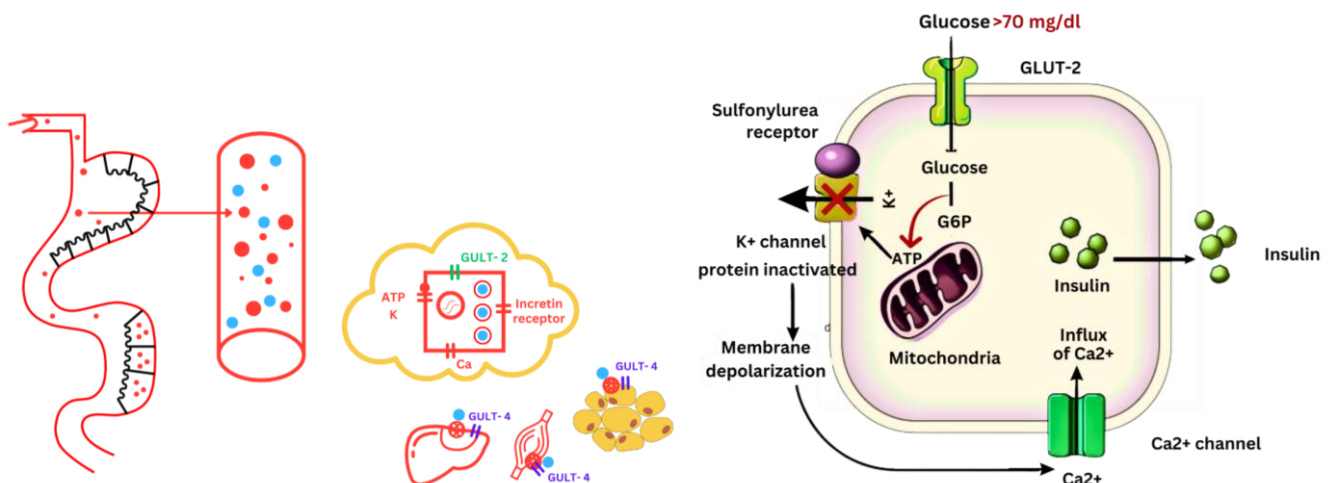
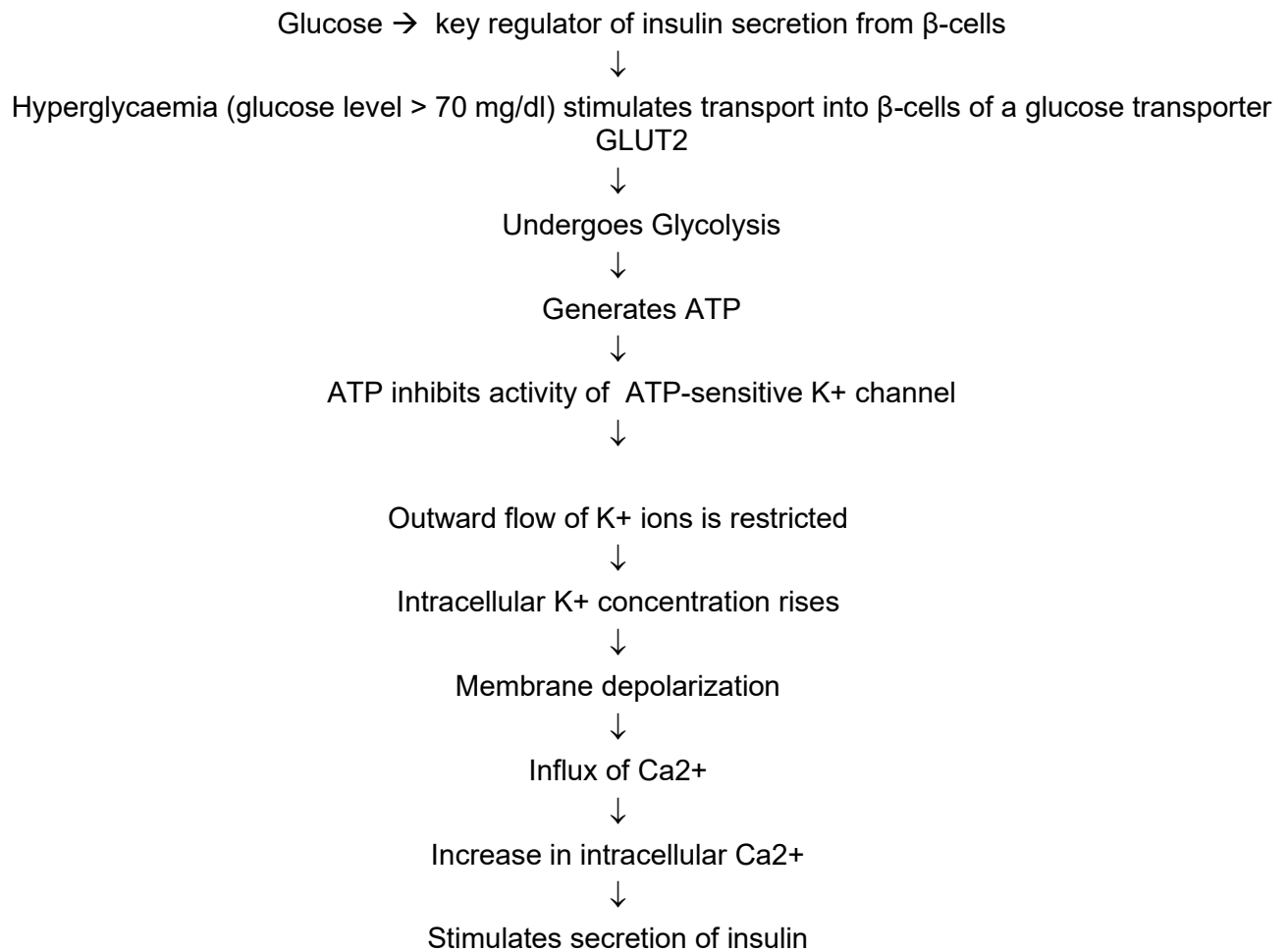


- **C-peptide** → used as a marker to distinguish endogenously synthesised and exogenously administered insulin.
- MW of insulin is 6000



## Insuline Release

- $\beta$  cells express an ATP-sensitive  $K^+$  channel on the membrane which comprises two subunits  
 →
  1. ATP-sensitive  $K^+$  channel
  2. Sulfonylurea receptor

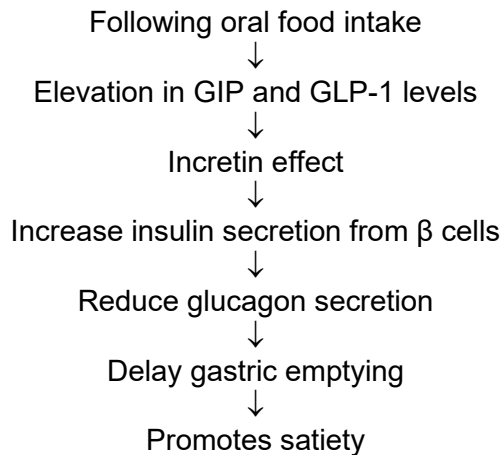


- **Initially** → from stored hormone within the  $\beta$ -cell granules. This is the phase of immediate release of insulin.
- **If secretory stimulus persists** → a delayed and protracted response follows that involves active synthesis of insulin

## Other hormones → Incretins

2 incretins have been identified:

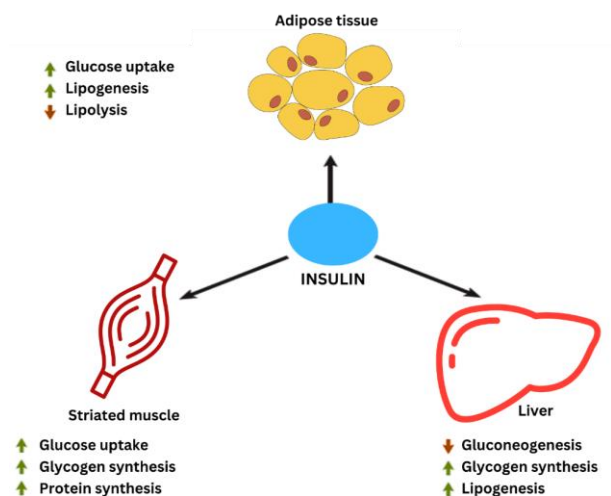
1. **Glucose-dependent insulintropic polypeptide (GIP)** → secreted by enteroendocrine “K cells” in proximal small bowel
2. **Glucagon-like peptide-1 (GLP-1)** → secreted by “L cells” in distal ileum and colon.



- **Once released** → circulating GIP and GLP-1 are degraded in circulation by a class of enzymes known as dipeptidyl peptidase (DPPs), especially DPP-4
- **Incretin effect** → blunted in patients with type 2 diabetes
- Efforts to restore incretin function can lead to improved glycemic control and loss of weight (through restoration of satiety).
- Development of two new classes of drugs for patients with type 2 diabetes:
  1. GLP-1 receptor agonists
  2. DPP-4 inhibitors

## Insulin Action

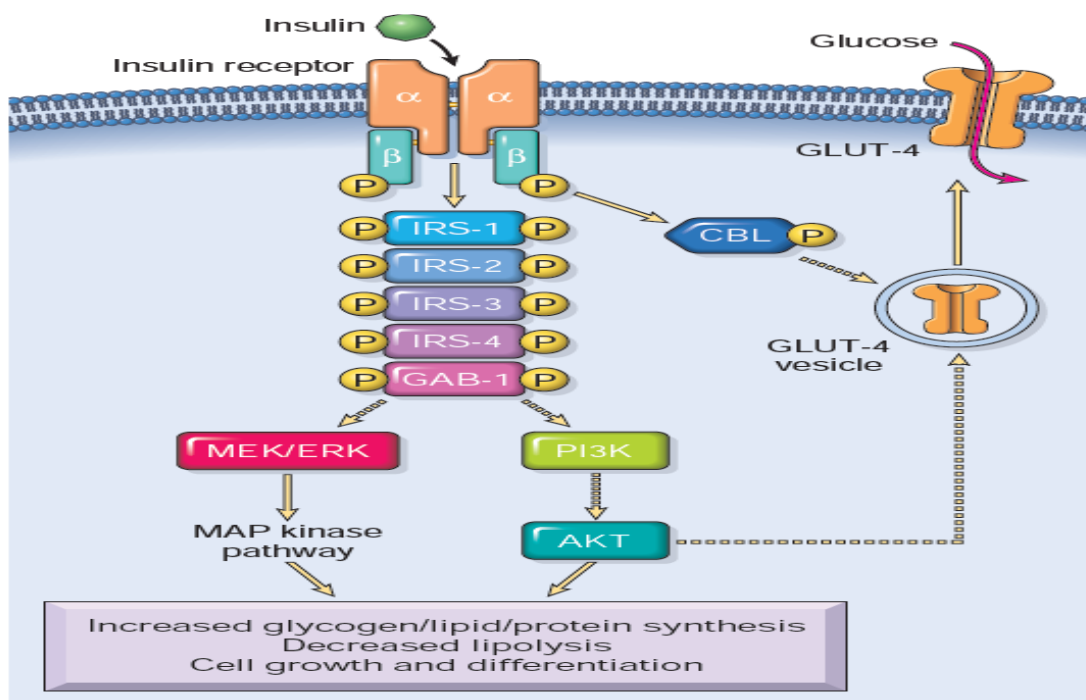
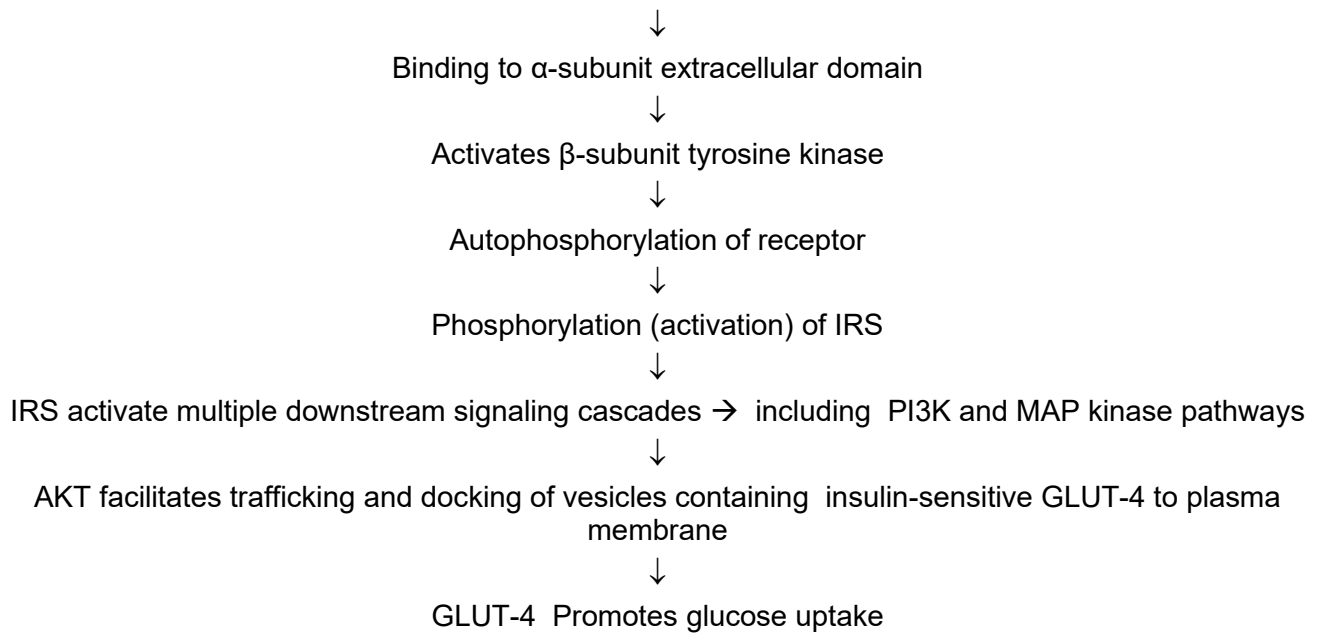
- Insulin from circulation binds to its receptor on target cells.
- Insulin receptor has intrinsic tyrosine kinase activity.
- Responsible for mitogenic and anabolic actions →
  1. Glycogen synthesis
  2. Protein synthesis
  3. Lipogenesis
  4. Glucose transport



## Insulin receptor

- Insulin receptor → tetrameric protein → two α- and two β-subunits
- β-subunit cytosolic domain possesses tyrosine kinase activity

Insulin

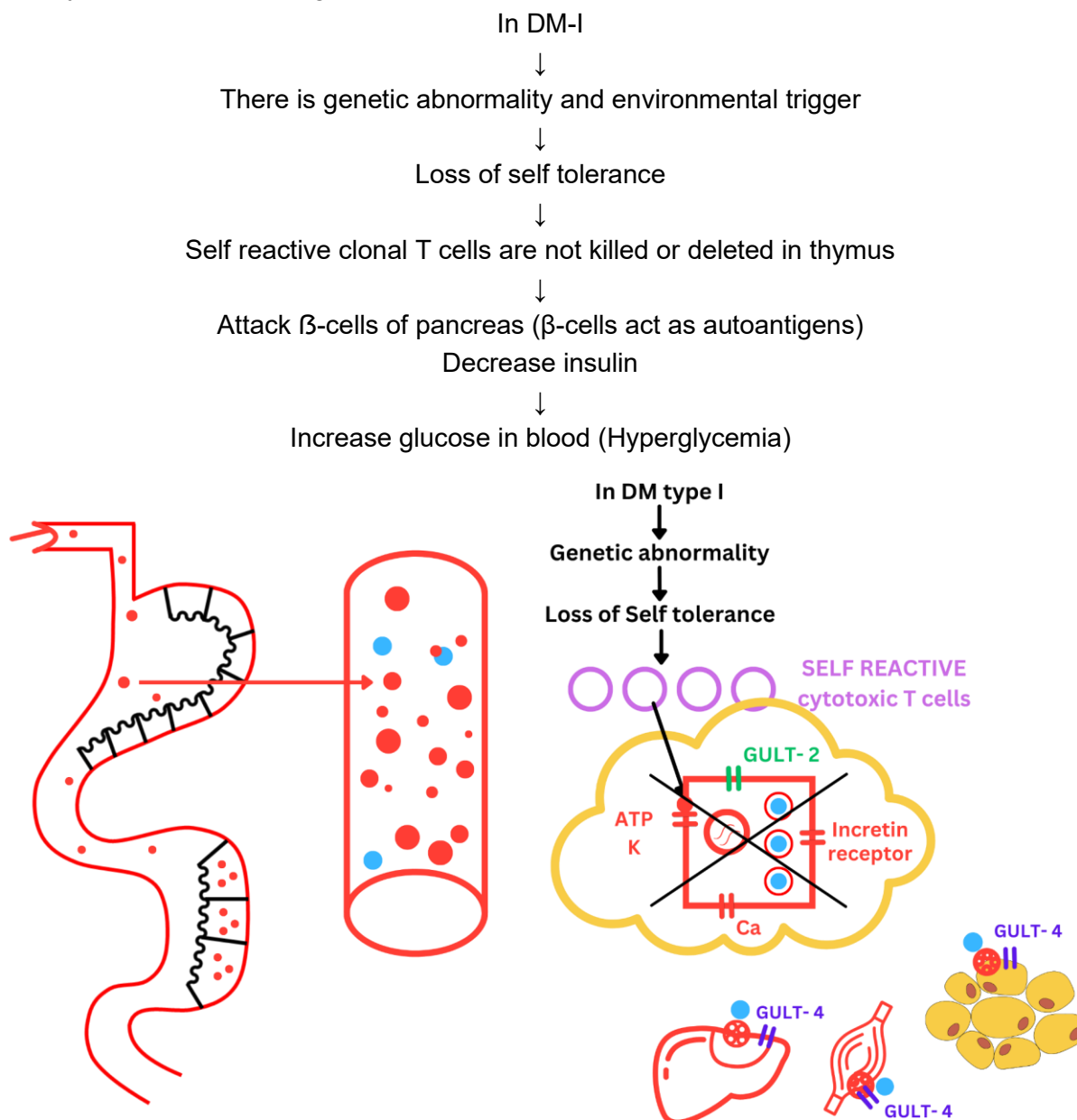


| Actions of insulin producing hypoglycaemia        |                                                                           |                                                            |
|---------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------|
| Liver                                             | Muscle                                                                    | Adipose tissue                                             |
| ▲ Increases glucose uptake and glycogen synthesis | ▲ Increases glucose uptake and utilization                                | ▲ Increases glucose uptake and storage as fat and glycogen |
| ▲ Inhibits glycogenolysis and glucose output      | ▲ Inhibits proteolysis and release of amino acids, pyruvate, lactate into | ▲ Inhibits lipolysis and release of FFA + glycerol         |

|                                                                     |                                                             |                                                   |
|---------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------|
| ▲ Inhibits gluconeogenesis from protein, pyruvate, FFA and glycerol | blood which form the substrate for gluconeogenesis in liver | which form substrate for gluconeogenesis in liver |
|---------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------|

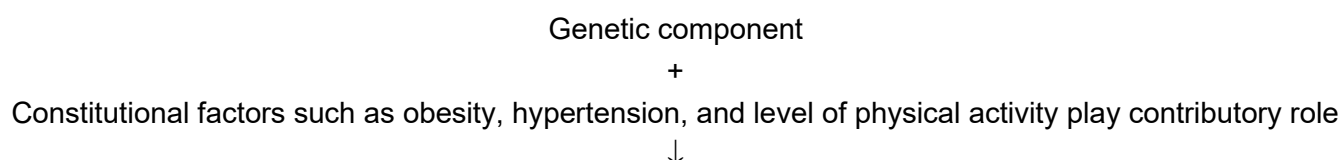
## Pathogenesis of Type 1 DM

- Body can not make enough INSULIN



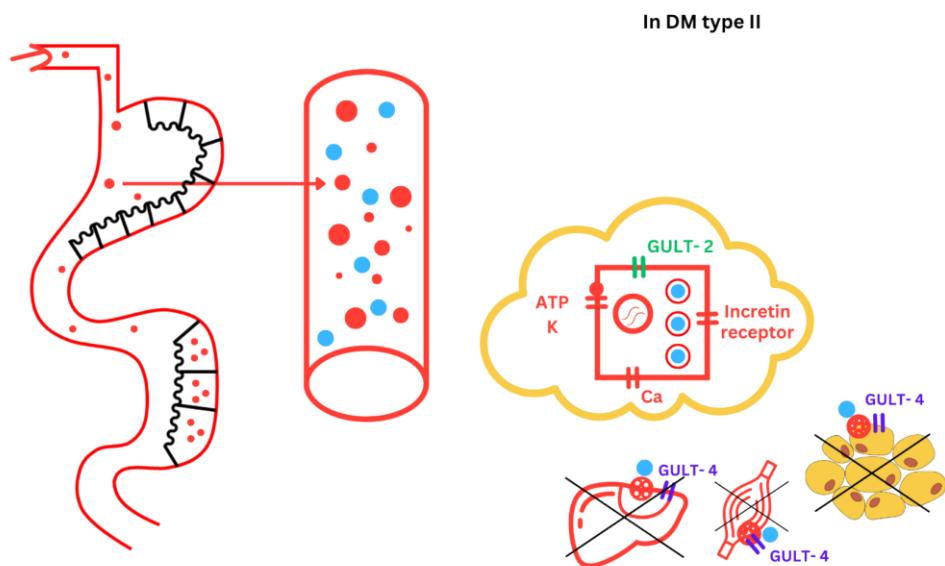
## Pathogenesis of Type 2 DM

- Type 2 diabetes is a complex disease that involves an interplay of genetic and environmental factors and a proinflammatory state.





Insulin resistance on target organ  
↓  
Hyperglycaemia



# ANTIDIABETIC DRUGS

- Insulin Preparations
- Oral Hypoglycaemic Drugs

# INSULIN PREPARATIONS

|                                      | Insulin |
|--------------------------------------|---------|
| Types                                |         |
| Routes                               |         |
| Sites                                |         |
| Factors affecting insulin absorption |         |
| Drug interactions                    |         |
| Adverse effect                       |         |
| Uses                                 |         |
| Regimens                             |         |
| Newer Insulin Delivery Devices       |         |

## Types

- A) Based on preparations
- B) Based on duration of action

### A) Based on preparations

- 4 types →
  1. Conventional
  2. Highly purified or Monocomponent (MC) insulins.
  3. Human insulins
  4. Insulin analogues

#### 1. Conventional insulin

- Produced from beef and pork pancreas.
  - **Beef insulin** → differs from human insulin by 3 amino acids
  - **Pork insulin** → differs from human insulin by 1 amino acid only
- Contain of other proteins (proinsulin, other polypeptides, pancreatic proteins) → potentially antigenic.
- No longer produced → totally replaced by highly purified pork/beef insulins/ recombinant human insulins/insulin analogues.

| Species | A-chain |         | B-chain |
|---------|---------|---------|---------|
|         | 8th AA  | 10th AA | 30th AA |
| Human   | THR     | ILEU    | THR     |
| Pork    | THR     | ILEU    | ALA     |
| Beef    | ALA     | VAL     | ALA     |



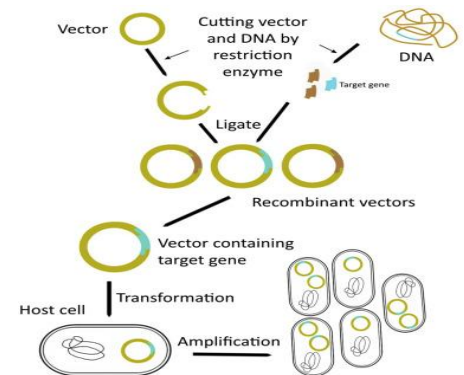
#### 2. Highly purified or monocomponent (MC) insulins

- Purified forms of conventional preparations to decrease immunogenicity

- Purification techniques →
  - Gel filtration
  - Ion-exchange chromatography
  - MC insulins →
  - More stable
  - Cause less insulin resistance or injection site lipodystrophy

### 3. Human insulin

- Produced by → Recombinant DNA technology in E. coli and in yeast.
- Features →
  - More rapid absorption
  - Earlier and more defined peak
  - Slightly shorter duration of action



### 4. Insulin analogues

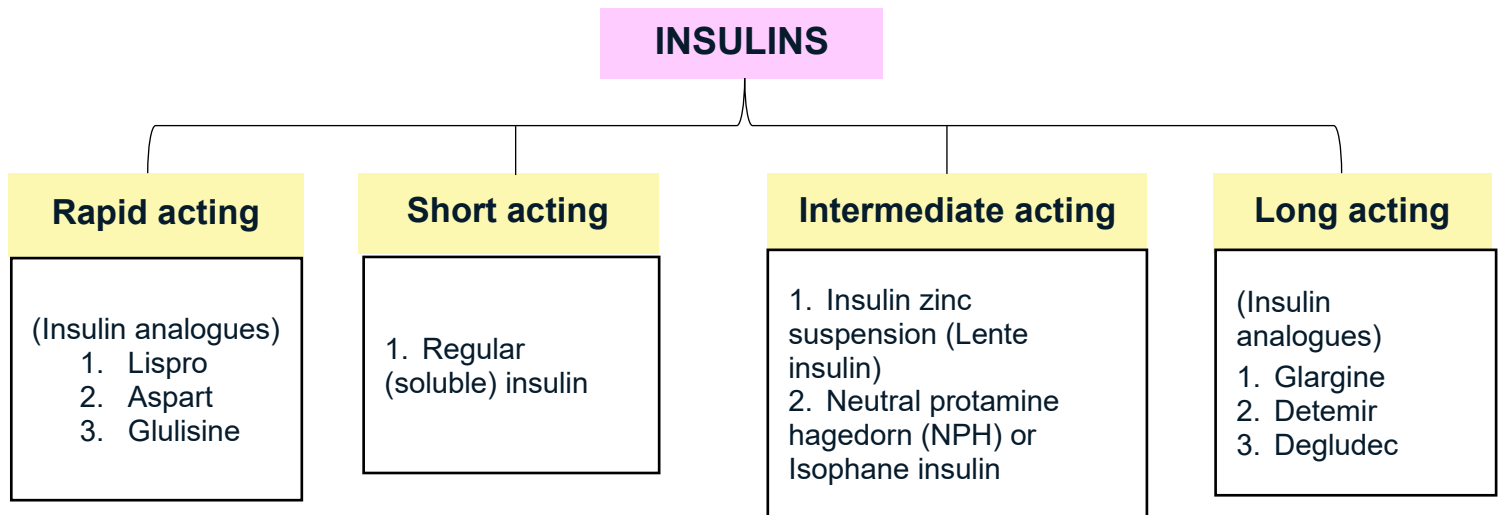
- They are having some chemical modification so do not aggregate in solution and remains monomeric. (Insulin aggregates into hexamers and then dissociate to monomers).
- With insulin analog there's less risk of hypoglycemia and achievement of better glycemic control as evidenced by hemoglobin HbA1c (glycosylated hemoglobin)

### Based on duration of action

- 4 types →
  1. Rapid acting
  2. Short acting
  3. Intermediate acting
  4. Long acting

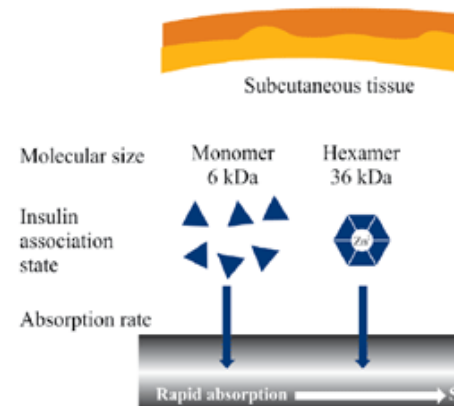
| Type                       | Insulin                           | Onset     | Duration    | Comment                                                                                             |
|----------------------------|-----------------------------------|-----------|-------------|-----------------------------------------------------------------------------------------------------|
| <b>Rapid Acting</b>        | <b>Lispro</b>                     | 15-20 min | 3-4 hours   | Present as monomers                                                                                 |
|                            | <b>Apart</b>                      | 15-20 min | 3-4 hours   | Most rapidly acting                                                                                 |
|                            | <b>Glulisine</b>                  | 15-20 min | 3-4 hours   |                                                                                                     |
| <b>Short Acting</b>        | <b>Regular (Crystalline zinc)</b> | 30-60 min | 5-8 hours   | Regular insulin can be given i.v.                                                                   |
| <b>Intermediate Acting</b> | <b>NPH or Isophane</b>            | 2 hours   | 16-18 hours |                                                                                                     |
|                            | <b>Lente</b>                      | 2 hours   | 16-20 hours |                                                                                                     |
| <b>Long Acting</b>         | <b>Glargine</b>                   | 4-6 hours | 15-24 hours | Supplied at pH = 4 cannot be mixed with any other insulin preparation → must be injected separately |

|  |                 |           |             |  |
|--|-----------------|-----------|-------------|--|
|  | <b>Detemir</b>  | 2-4 hours | 20-24 hours |  |
|  | <b>Degludec</b> | 2-4 hours | 24-40 hours |  |



## Short acting

- **Regular (soluble) insulin**
  - Neutral pH
  - Stabilized by a small amount of zinc.
  - Insulin molecules self aggregate to form hexamers around zinc ions.
  - Disadvantages → injected ½-1 hour before a meal.

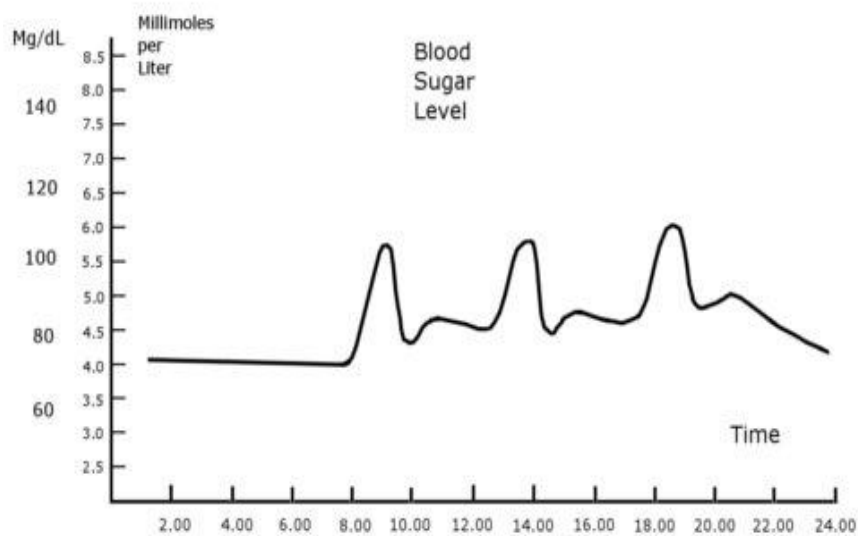


After s.c. injection  
↓  
Insulin monomers are released gradually by dilution  
↓  
Absorption occurs slowly  
↓  
Slow onset (0.5 to 1 hr.)

- Peak action is produced after → 2–3 hours
- Action continues upto → 6–8 hours

## Disadvantages

1. Injected ½-1 hour before a meal.
2. Not suitable for providing a low constant basal level of action in the interdigestive period

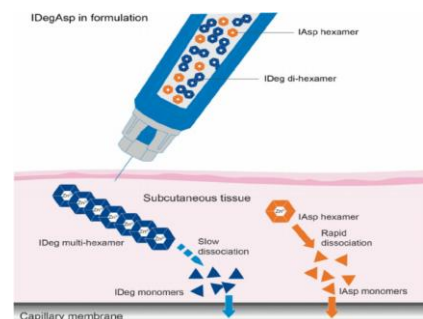


## Intermediate acting

- To overcome problems of Short insulin → some intermediate acting 'modified' or 'retard' preparations of insulin were soon developed.
- For obtaining Intermediate acting preparations, insulin is rendered insoluble either →
  1. By precipitating it with Excess zinc and increasing the particle size → Lente insulin (Insulin-zinc suspension)
  2. By complexing it with Protamine (a small molecular basic protein) → Isophane or NPH (Neutral Protamine Hagedorn) insulin

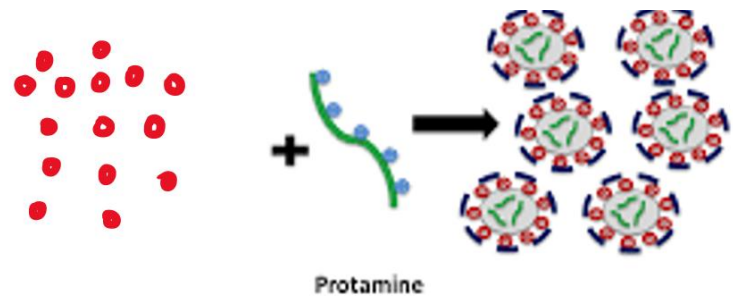
### 1. Lente insulin

- a) Large particles → crystalline → Ultralente → long-acting
- b) Smaller particles → amorphous → Semilente → short acting
- c) 7:3 ratio mixture is called 'Lente insulin' and is intermediate-acting.



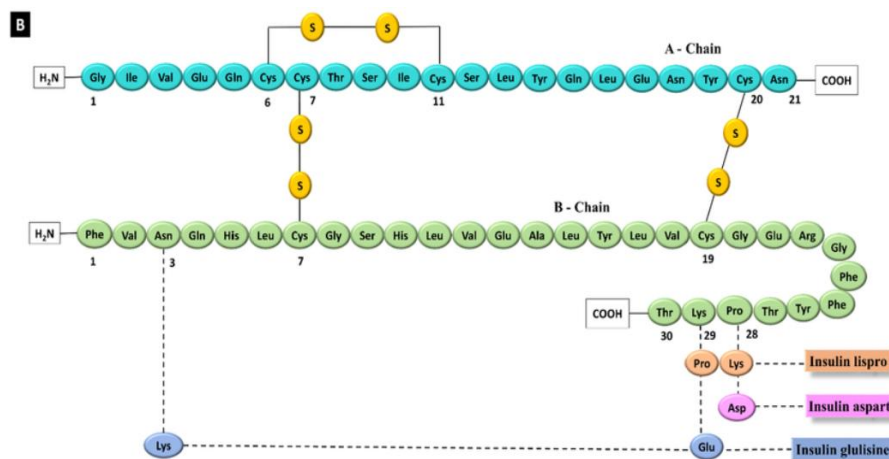
### 2. Isophane or NPH (Neutral Protamine Hagedorn) →

- Protamine is added in a quantity just sufficient to complex all insulin molecules
- On s.c. injection → complex dissociates slowly → intermediate duration of action.



## Rapid acting

1. **Insulin lispro** → Reversing proline and lysine at the carboxy terminus B 28 and B 29 positions
2. **Insulin aspart** → Proline at B 28 of human insulin is replaced by aspartic acid.
3. **Insulin glulisine** →
  - Lysine replacing asparagine at B 23
  - Glutamic acid replacing lysine at B 29.



## Long acting

### 1. Insulin glargine →

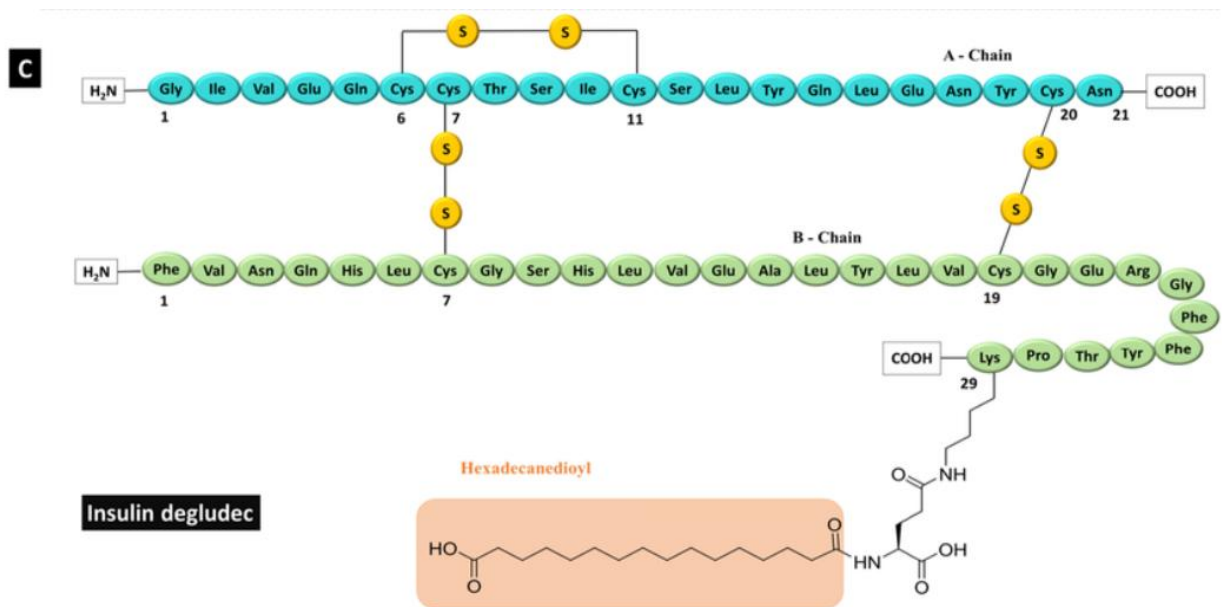
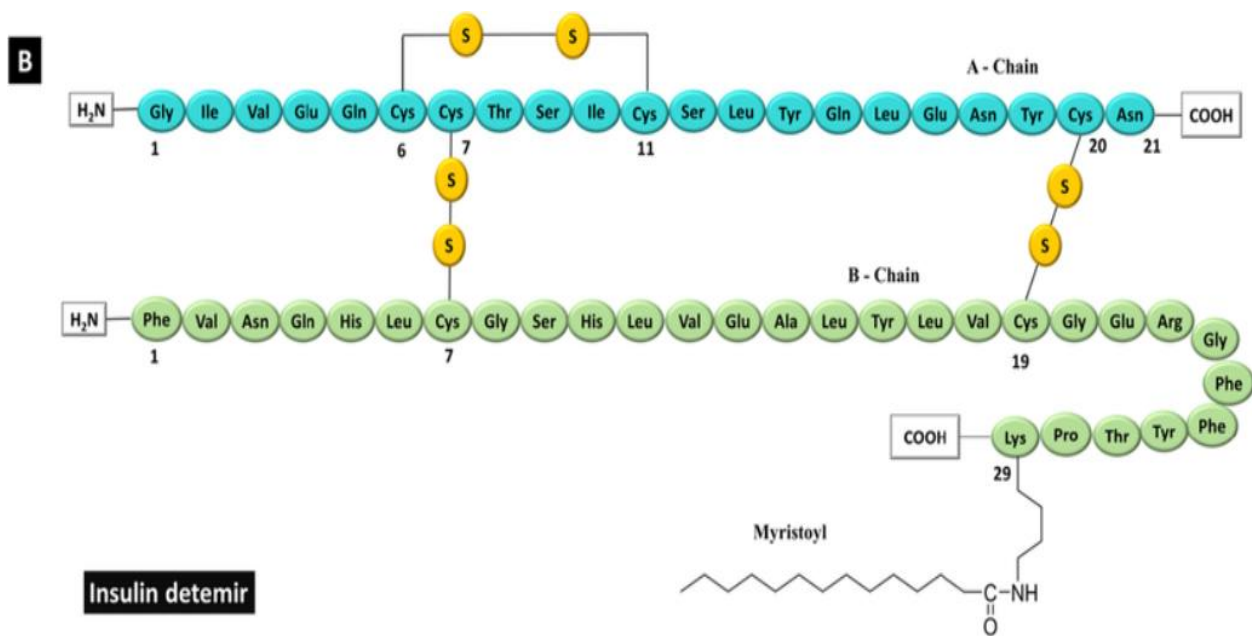
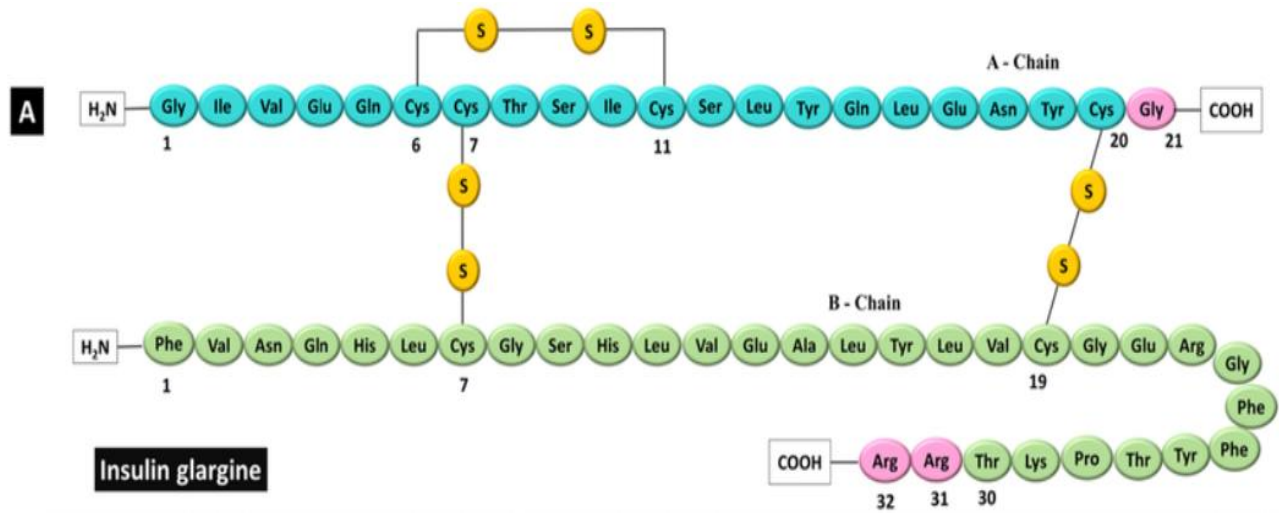
- 2 additional arginine residues at carboxy terminus of B chain
- Glycine replaces asparagine at A21.

### 2. Insulin detemir →

- Deletion of threonine at position B30
- Myristoyl (a fatty acid) radical is attached to amino group of lysine at B29 via an amide bond

### 3. Insulin degludec →

- Deletion of threonine at position B30
- Addition of a hexadecanedioic acid (a fatty acid) via a glutamic acid linker to lysine at B29



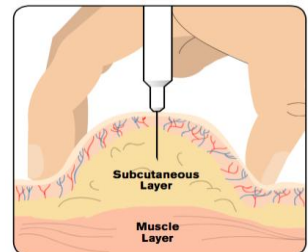
Remember



- Lispro, Glulisine and Aspart → all contain letter 's' → which means short acting.
- All insulin preparations are hexameric Except rapid acting insulins (Insulin lispro, insulin aspart, insulin glulisine), which are monomeric
- Insulin degludec → longest acting insulin and unlike insulin glargine, it can be mixed with other insulins too.
- All insulin preparations are supplied at neutral pH (7.2.-7.4) except glargine (supplied at pH 4.0) → Therefore, glargine cannot be mixed with any insulin.
- All insulin preparations contain buffer (phosphate or acetate) except regular, glulisine and glargine.

## Routes

1. All preparations can be given by → s.c. route.



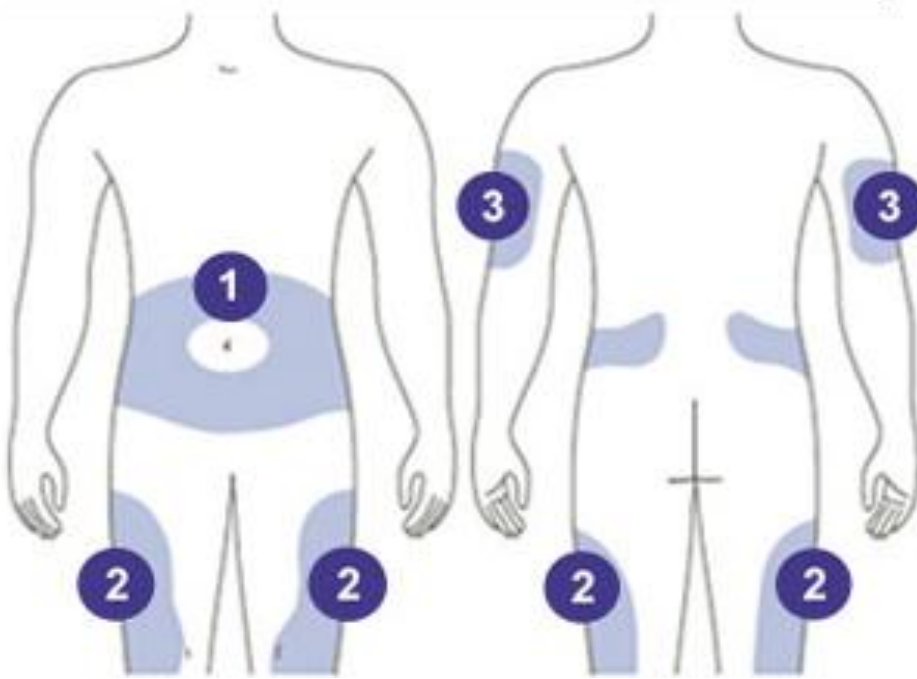
2. Only regular (crystalline zinc) insulin can be given → i.v. route.
- Inhalational insulin (exubera) → lung cancers and fibrosis → In June 2014, a new inhalational insulin (Afrezza) was approved by FDA for type-1 DM. It should not be used in patients with chronic lung diseases like asthma



## Sites







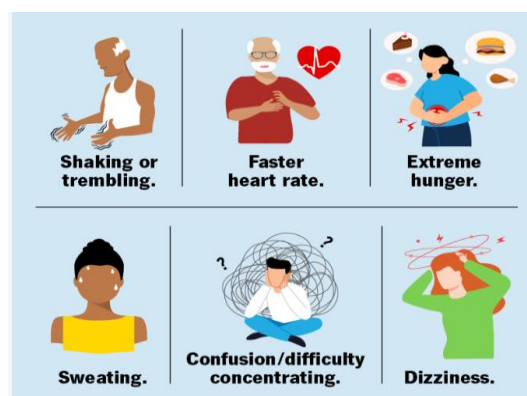
### Factors affecting insulin absorption

1. **Site of injection** → most rapid from abdomen followed by arm, buttock and thigh
2. **Type of insulin** → Fast with regular, aspart, lispro and glulisine
3. **Subcutaneous blood flow** → rate increases with massage, hot bath or exercise
4. **Depth of injection** → faster with i.m. than with s.c. route



### Drug interactions

- **Alcohol** → precipitate hypoglycaemia → by depleting hepatic glycogen.
- **Lithium, high dose aspirin and theophylline** → accentuate hypoglycaemia → by enhancing insulin secretion and peripheral glucose utilization
- **Thiazides, furosemide, corticosteroids, OCPs, salbutamol, nifedipine** → raise blood sugar and reduce effectiveness of insulin.



### Adverse effects

1. Hypoglycaemia
2. Local reactions
3. Allergy
4. Edema

## 1. Hypoglycaemia

- This is the most frequent and potentially the most serious reaction.
- Hypoglycaemia can occur in any diabetic
  - Following inadvertent injection of large dose
  - By missing a meal after injection
  - By performing vigorous exercise



### Symptoms

- Counter-regulatory sympathetic stimulation → sweating, anxiety, palpitation, tremor
- Neuroglucopenic symptoms → Due to deprivation of the brain of its essential nutrient glucose → dizziness, headache, behavioural changes, visual disturbances, hunger, fatigue, weakness, muscular incoordination and sometimes fall in BP, Coma



### Hypoglycaemic unawareness

- After longterm treatment → about 30% patients lose adrenergic symptoms.
- Diabetic neuropathy → abolish autonomic symptoms.

### Treatment

- Glucose → given orally or i.v. (for severe cases) → reverses symptoms rapidly.
- Glucagon → 0.5–1 mg i.v. or Adr 0.2 mg s.c. may be given as an expedient measure in patients who are not able to take sugar orally and injectable glucose is not available.



## 2. Local reactions

- Swelling, erythema and stinging occur at injected site, especially in beginning.
- Lipodystrophy of subcutaneous fat around injection site may occur if same site is injected repeatedly.



## 3. Allergy

- Due to contaminating proteins
- Very rare with human/ highly purified insulins.
- Rarely → Urticaria, angioedema and anaphylaxis



## 4. Edema

- Some patients develop short-lived dependent edema (due to Na<sup>+</sup> retention) when insulin therapy is started.



## Uses

- A) Diabetes mellitus
- B) Diabetic ketoacidosis (Diabetic coma)
- C) Hyperosmolar (nonketotic hyperglycaemic) coma

## A) Diabetes mellitus

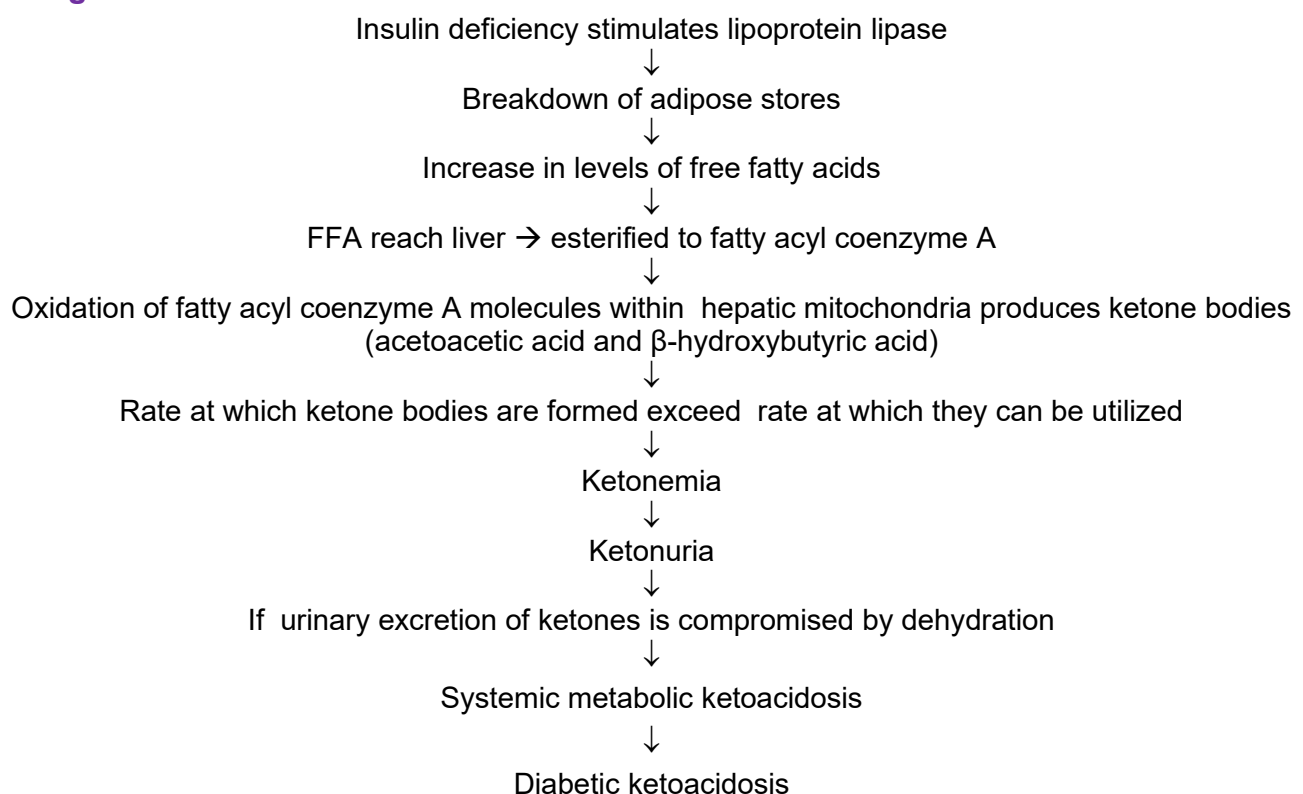
### Indications of insulin in DM

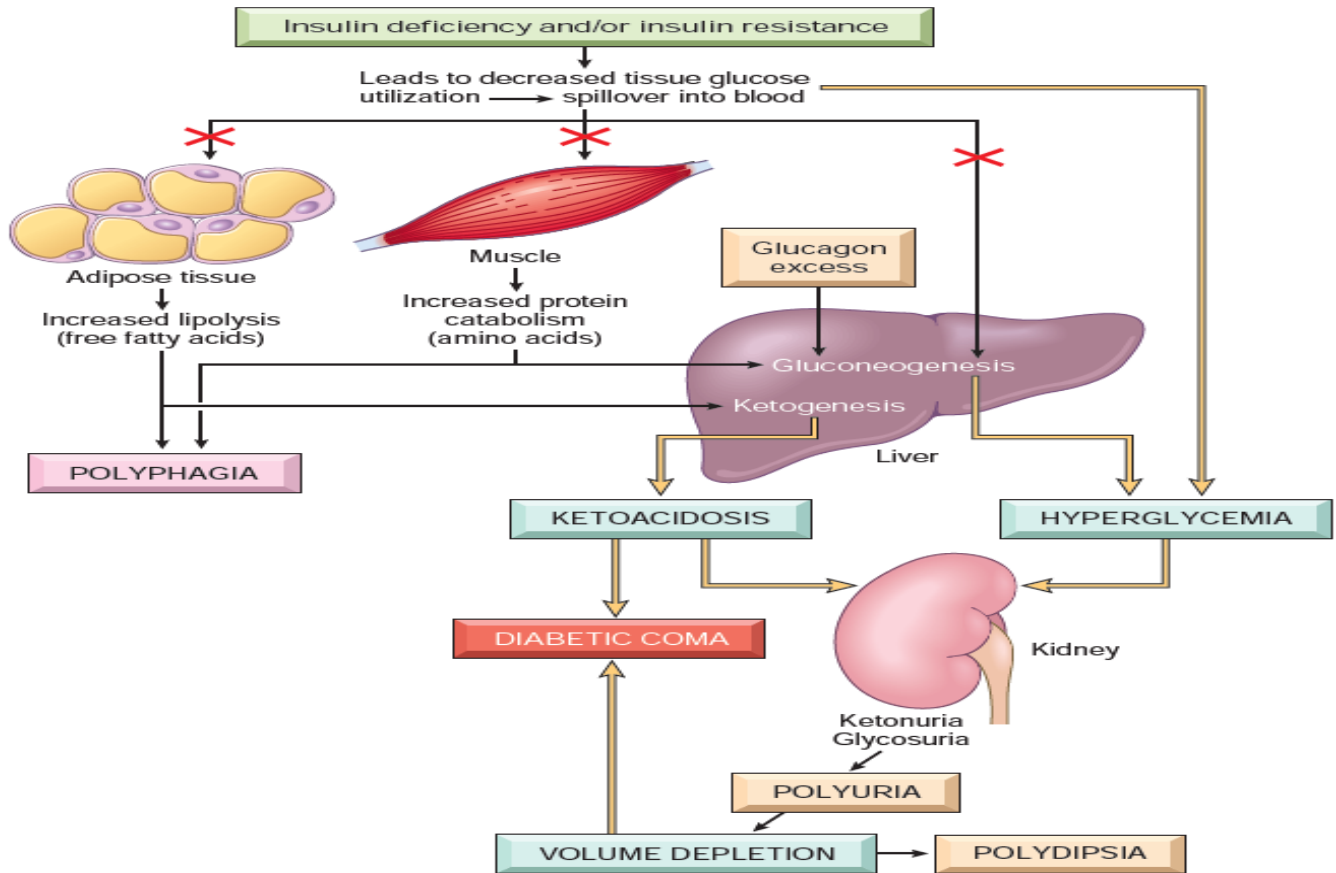
1. All cases of IDDM
2. NIDDM patients
  - Not controlled on OHA
  - In pregnancy
  - In complications like diabetic ketoacidosis and hyperosmolar coma (regular insulin i.v. is preferred).
  - To tide over stressful conditions like infections and surgery etc.
3. Acute hyperkalemia

## B) Diabetic ketoacidosis (Diabetic coma)

- Common in type 1 DM.

## Pathogenesis





## Clinical features

- Fatigue
- Nausea and vomiting
- Severe abdominal pain
- A characteristic fruity odor, and deep, labored breathing → Kussmaul breathing
- Persistence of ketotic state eventually leads to depression in cerebral consciousness and coma.

## Treatment

### 1. Insulin

- Regular insulin is used to rapidly correct metabolic abnormalities.
- A bolus dose of 0.1–0.2 U/kg i.v. is followed by 0.1 U/kg/hr infusion
- Rate is doubled if no significant fall in blood glucose occurs in 2 hr.
- Fall in blood glucose level by 10% per hour can be considered adequate response.

### 2. Intravenous fluids

- Vital to correct dehydration.
- Normal saline is infused i.v., initially at rate of 1 L/hr, reducing progressively to 0.5 L/4 hours depending on volume status

### 3. KCl

- When insulin therapy is instituted → ketosis subsides and K<sup>+</sup> is driven back intracellularly → dangerous hypokalemia can occur.
- After 4 hours it is appropriate to add 10–20 mEq/hr KCl to the i.v. fluid.

### 4. Sodium bicarbonate

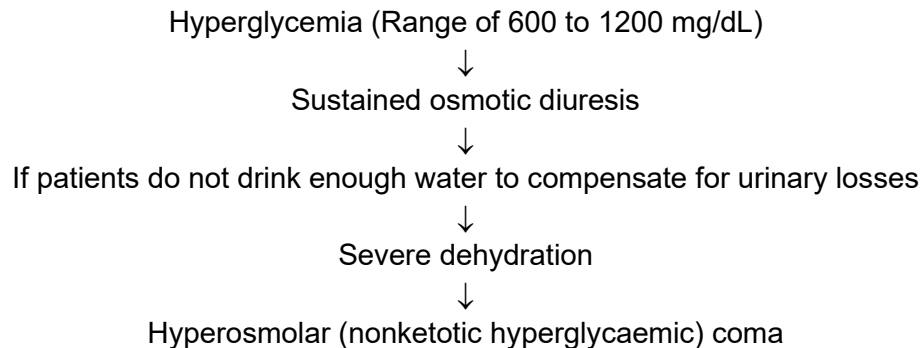
- Not routinely needed.
- Acidosis subsides as ketosis is controlled.

- If arterial blood pH is  $< 7.1 \rightarrow$  acidosis is not corrected spontaneously or hyperventilation is exhausting  $\rightarrow$  50 mEq of sod. bicarbonate is added to i.v. fluid.

### C) Hyperosmolar (nonketotic hyperglycaemic) coma

- Common in type 2 DM.

#### Pathogenesis

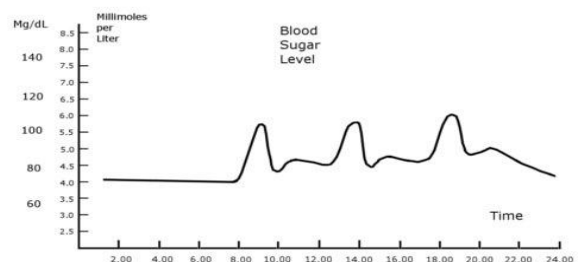


#### Treatment

- General principles of treatment are the same as for ketoacidotic coma  $\rightarrow$  except that faster fluid replacement is to be instituted and alkali is usually not required.
- Prophylactic heparin therapy  $\rightarrow$  These patients are prone to thrombosis (due to hyperviscosity and sluggish circulation)

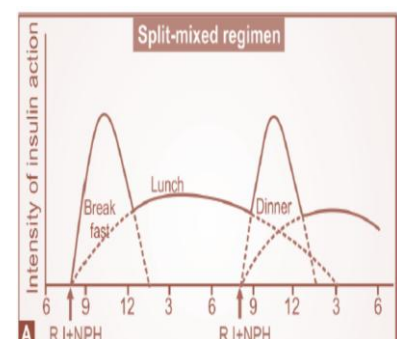
#### Regimens

1. Split-mixed regimen
2. Basal-bolus regimen



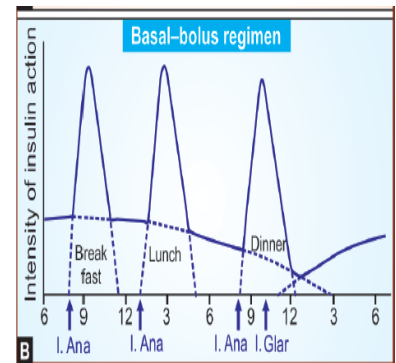
#### 1. Split-mixed regimen

- **Composition**  $\rightarrow$ 
  - Mixture of regular with lente isophane insulin.
  - Total daily dose of a 30:70 or 50:50 mixture of regular and NPH insulin is usually split into two (split-mixed regimen)
- **Schedule**  $\rightarrow$  Injected s.c. before breakfast and before dinner
- **Advantage**  $\rightarrow$  only two daily injections are required
- **Disadvantage**  $\rightarrow$  But post-lunch glycaemia may not be adequately covered



## 2. Basal-bolus regimen

- **Composition** →
  - A long-acting insulin (glargine) is injected once daily either before breakfast or before bed-time for basal coverage
  - Along with 2–3 meal-time injections of a rapid acting preparation (insulin lispro or aspart).
- **Schedule** → Needs 3–4 daily SC injections
- **Advantage** → Better control of blood glucose round a clock
- **Disadvantage** → Number of injections are more



## Newer Insulin Delivery Devices

1. **Insulin syringes** → Prefilled disposable syringes contain specific types or mixtures of regular and modified insulins.
2. **Pen devices** → Fountain pen like: use insulin cartridges for s.c. injection through a needle. Preset amounts (in 2 U increments) are propelled by pushing a plunger; convenient in carrying and injecting



### 3. Insulin pumps

- Portable infusion devices connected to a subcutaneously placed cannula provide 'continuous subcutaneous insulin infusion' (CSII).
- Only regular insulin or a fast acting insulin analogue is used.
- Pump can be programmed to deliver insulin at a low basal rate (approx. 1 U/hr) and premeal boluses (4-15 times the basal rate) to control post-prandial glycaemia.

## ORAL HYPOGLYCAEMIC DRUGS

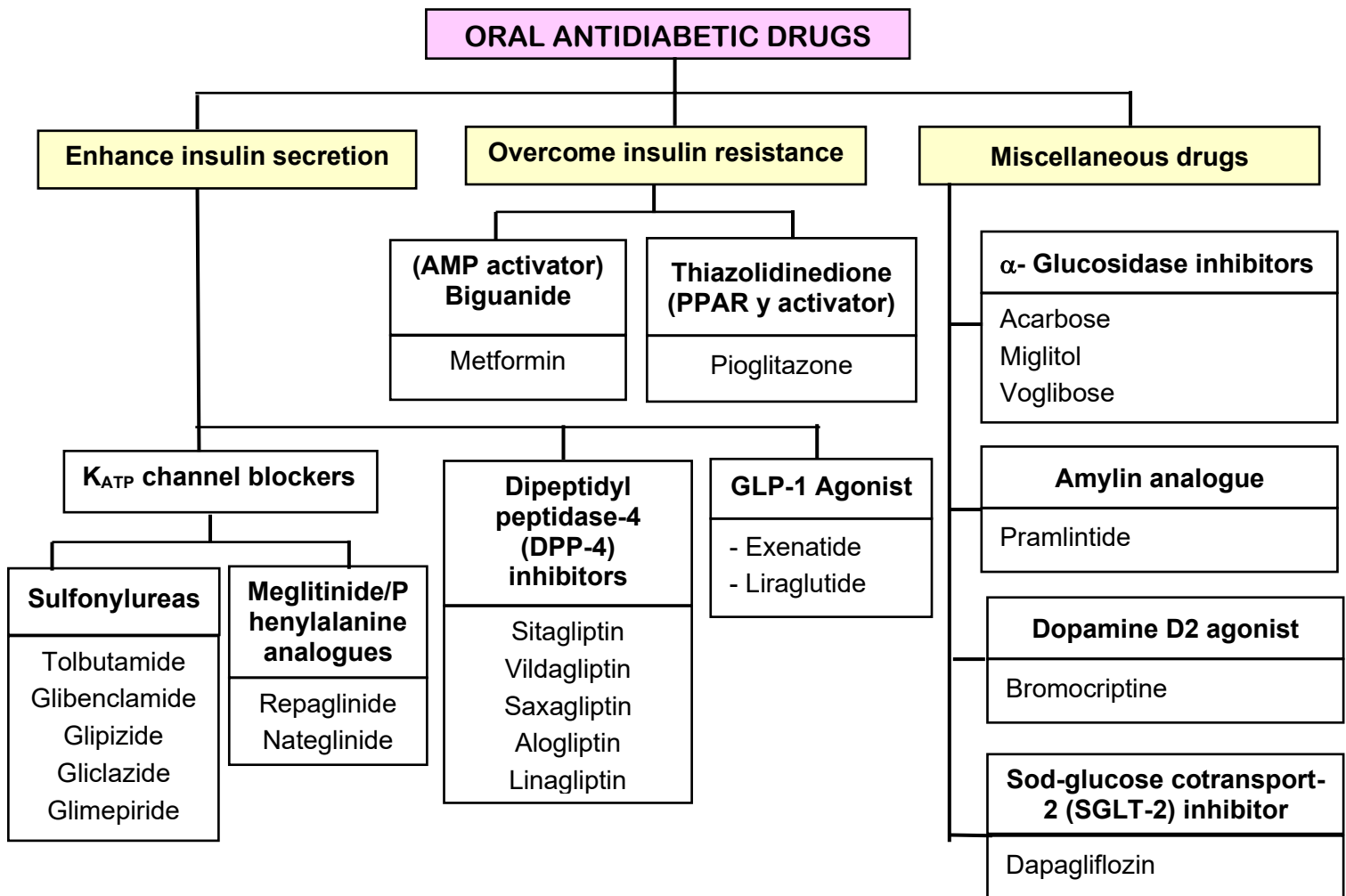
### Introduction

- These drugs lower blood glucose levels
- Effective orally.
- Chief draw back of insulin → it must be given by injection.





## Classification



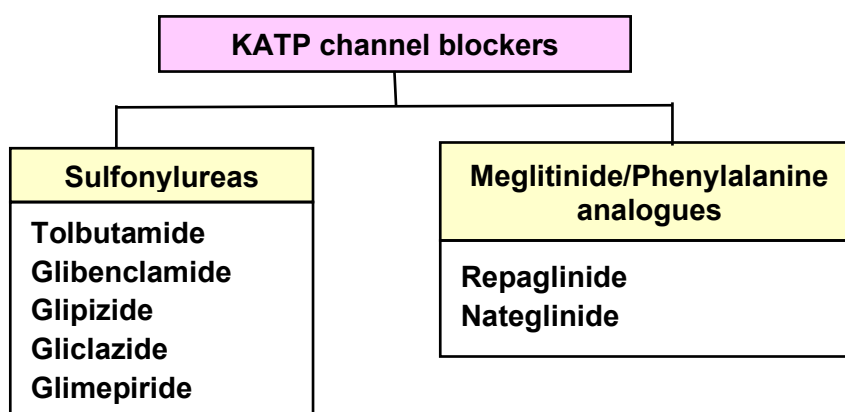
| Enhance insulin secretion |                                   |               |                  |
|---------------------------|-----------------------------------|---------------|------------------|
|                           | K <sub>ATP</sub> Channel blockers | GLP-1 Agonist | DPP-4 inhibitors |
| Introduction              |                                   |               |                  |
| Drugs                     |                                   |               |                  |
| MOA                       |                                   |               |                  |
| Uses                      |                                   |               |                  |
| Adverse effect            |                                   |               |                  |

| Overcome insulin resistance |            |                   |
|-----------------------------|------------|-------------------|
|                             | Biguanides | Thiazolidinedione |
| Introduction                |            |                   |
| Drugs                       |            |                   |
| MOA                         |            |                   |
| Uses                        |            |                   |
| Adverse effect              |            |                   |

| Miscellaneous drugs |                                  |                 |                     |                  |
|---------------------|----------------------------------|-----------------|---------------------|------------------|
|                     | $\alpha$ -Glucosidase inhibitors | Amylin analogue | Dopamine D2 agonist | SGLT-2 inhibitor |
| Introduction        |                                  |                 |                     |                  |
| Drugs               |                                  |                 |                     |                  |
| MOA                 |                                  |                 |                     |                  |
| Uses                |                                  |                 |                     |                  |
| Adverse effect      |                                  |                 |                     |                  |

## K<sup>+</sup>-ATP CHANNEL BLOCKERS

### Drugs





## MOA

Sulfonylureas (SU) and meglitinide analogues

↓  
Block ATP-sensitive K<sup>+</sup> channel (KATP)

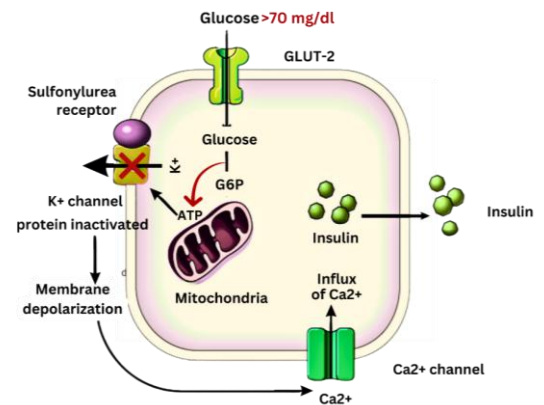
↓  
Outward flow of K<sup>+</sup> ions is restricted

↓  
Intracellular K<sup>+</sup> concentration rises

↓  
Membrane is partially depolarized

↓  
Augmenting Ca<sup>2+</sup> channel opening

↓  
Exocytotic release of insulin (insulinaemic action)



## Extrapancreatic action

After few months of administration

↓  
Insulinaemic action of Sus declines → probably due to down regulation of sulfonylurea receptors (SUR1) on  $\beta$  cells

↓  
In this phase → they increase in number of insulin receptors on target tissues (especially liver)

↓  
Sensitize target tissues to action of insulin

## Uses

- **Second-line therapy (after metformin)** → Used when HbA1c targets are not met with metformin alone.
- **Monotherapy** → In patients who cannot tolerate metformin (e.g. due to GI side effects or renal impairment with low GFR).
- **Add-on therapy** → Combined with insulin or other oral antidiabetics (e.g., metformin, DPP-4 inhibitors).

## Adverse effects

1. Hypoglycaemia → lower risk with meglitinide analogues
2. Nonspecific side effects
3. Hypersensitivity

### 1. Hypoglycaemia

- Commonest problem
- More common in elderly, liver and kidney disease patients
- Treatment of hypoglycaemic episode → to give glucose
- **Chlorpropamide** → Highest risk → due to its long action due to its long action.
- **Tolbutamide** → lowest risk → due to its low potency and short duration of action.



## 2. Nonspecific side effects

- Weight gain 1–3 kg
- Nausea, vomiting
- Flatulence, diarrhoea or constipation
- Headache
- Paresthesias



## 3. Hypersensitivity

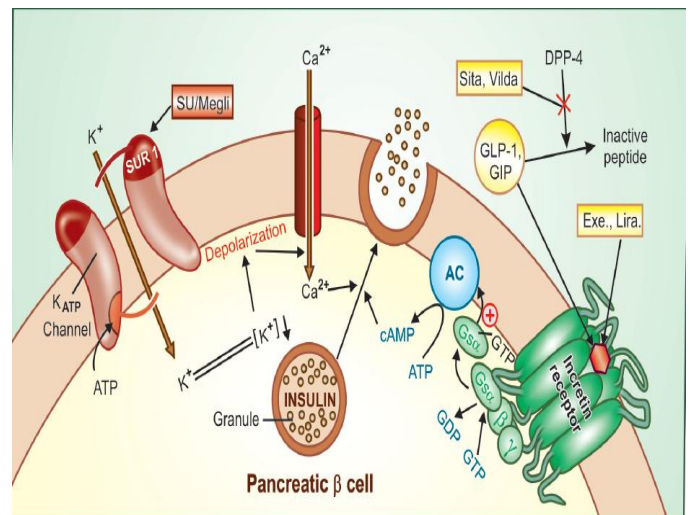
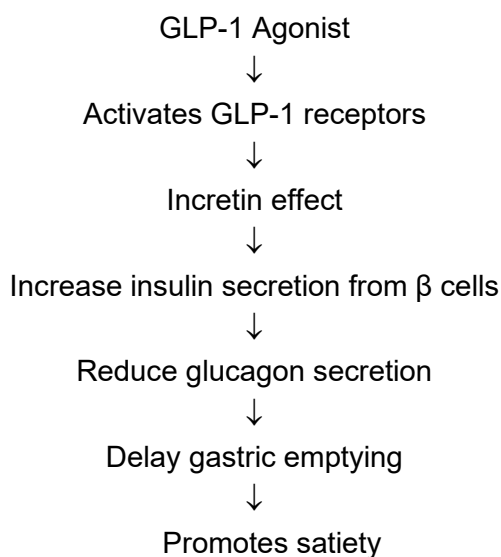
- Rashes
- Photosensitivity
- Purpura
- Flushing and a disulfiram-like reaction after alcohol

# GLP-1 AGONIST

## Drugs

- GLP-1 itself is not suitable for clinical use because of rapid degradation by enzyme dipeptidyl peptidase-4 (DPP-4)
  1. Exenatide
  2. Liraglutide

## MOA



## Exenatide

- Synthetic DPP-4 resistant analogue which activates GLP-1 receptors
- Being a peptide, it is inactive orally.
- After s.c. injection its plasma  $t_{1/2}$  is ~ 3 hours and duration of action 6–10 hours.

## Liraglutide

- Long-acting GLP-1 agonist

- Tight binding to plasma proteins extends  $t_{1/2}$  to > 12 hours and duration of action to > 24 hours.
- Injected s.c. once daily

## Uses

- As add-on drug to metformin/SU

## Adverse effect

- Nausea
- Hypoglycaemia → rare with exenatide/liraglutide monotherapy, but can occur when combined with SUs/metformin.

# GLP-1 AGONIST

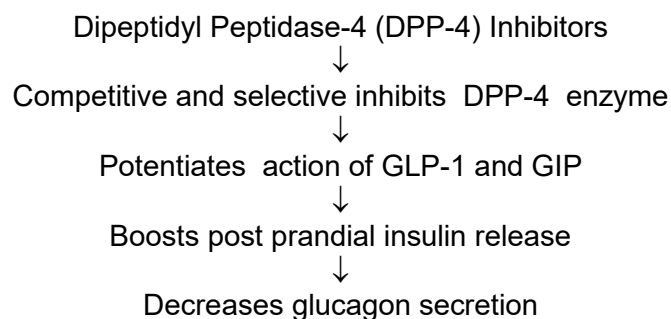
## Introduction

- Enzyme DPP-4 causes rapid degradation of endogenous GLP-1
- Orally active inhibitors of this enzyme act as indirectly acting insulin secretagogues.

## Drugs

- Sitagliptin
- Vildagliptin
- Saxagliptin
- Alogliptin
- Linagliptin

## MOA



## Uses

- As adjuvant drugs in type 2 diabetics not well controlled by metformin/SUs/pioglitazone or insulin.
- Sitagliptin monotherapy is recommended only when metformin cannot be used.
- Lower HbA1C to 0.5 - 0.8%

## Adverse effects

1. Nausea, loose stools, headache, rashes, allergic reactions and edema.
2. Nasopharyngitis and cough → Due to prevention of substance P degradation
3. URTI

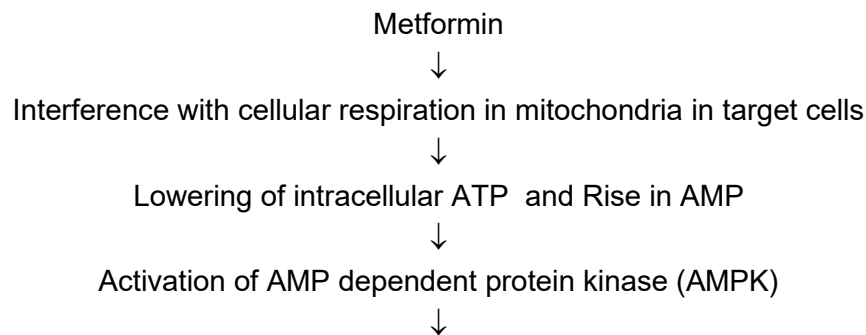


## BIGUANIDES

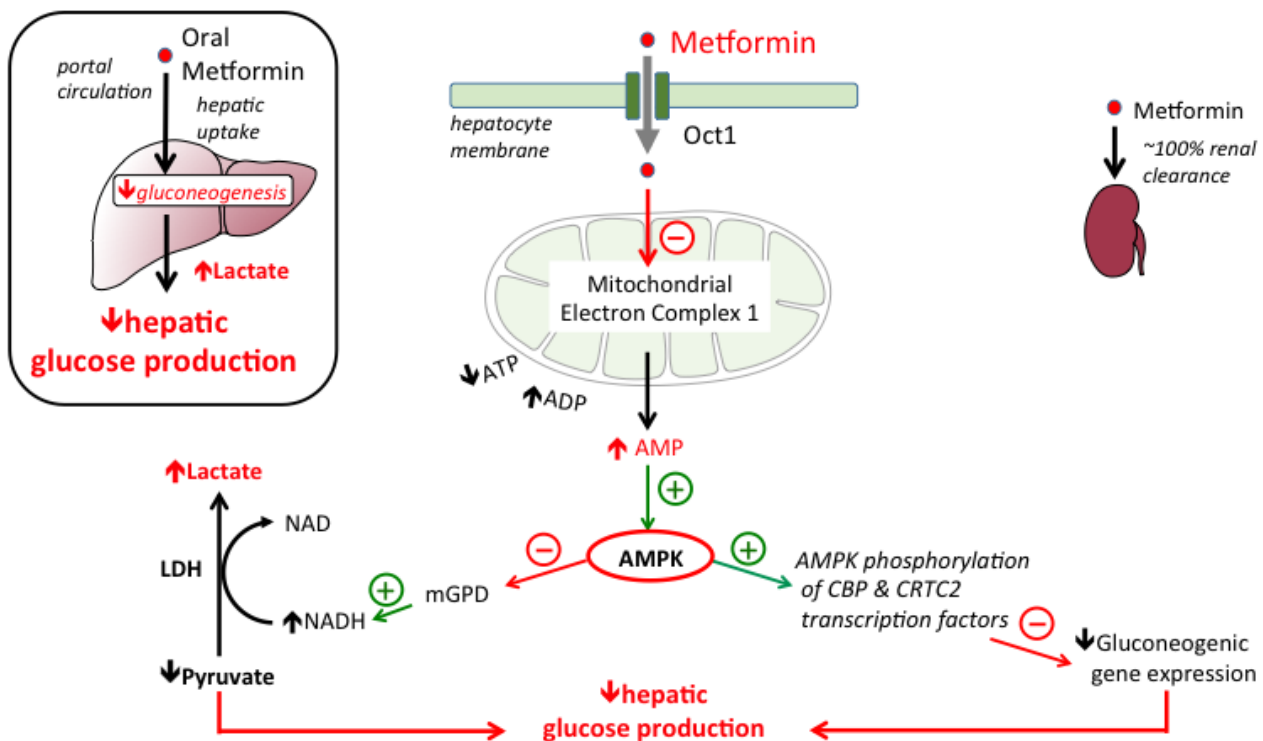
### Drugs

1. Metformin
2. Phenformin → higher risk of lactic acidosis → withdrawn and banned in India since 2003.

### MOA



1. Enhances insulin-mediated glucose uptake and disposal in skeletal muscle and fat.
2. Suppresses hepatic gluconeogenesis
3. Retards intestinal absorption of glucose



### Uses

- First choice drug →
  - for all type 2 DM patients, except when not tolerated or contraindicated
  - Preferred oral hypoglycemics as they cause weight loss

## Adverse effects

1. Abdominal pain, anorexia, bloating, nausea, metallic taste, mild diarrhoea and tiredness
2. Vit B12 deficiency → due to interference with its absorption can occur with high dose of metformin

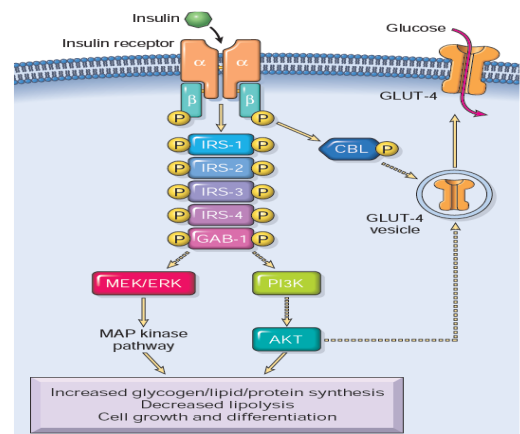
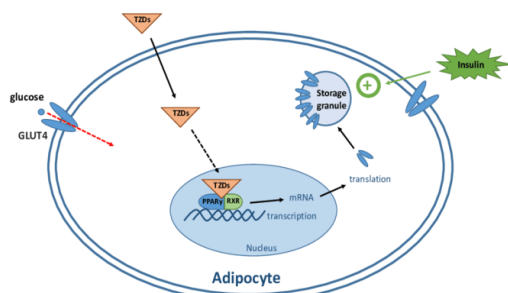
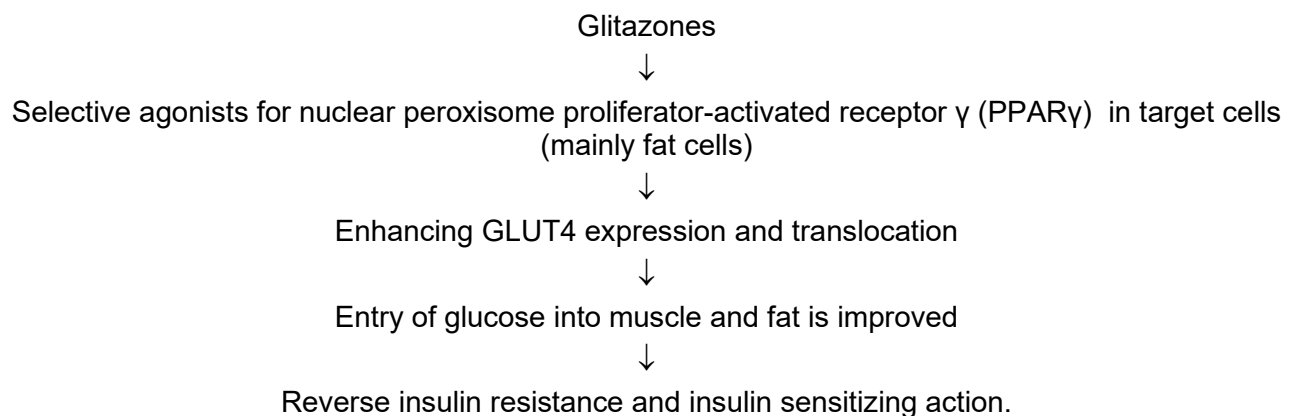


## THIAZOLIDINEDIONE

### Drugs

1. Pioglitazone
2. Rosiglitazone → banned in India since 2010 due to increase in risk of myocardial infarction, CHF, stroke and death.

### MOA

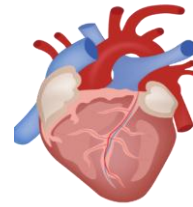


### Uses

1. Supplement SUs/metformin and in case of insulin resistance
2. Delay progression of prediabetics to overt type 2 DM

## Adverse effects

1. Fluid retention
2. Weight gain
3. Precipitation of CHF



## $\alpha$ - GLUCOSIDASE INHIBITORS

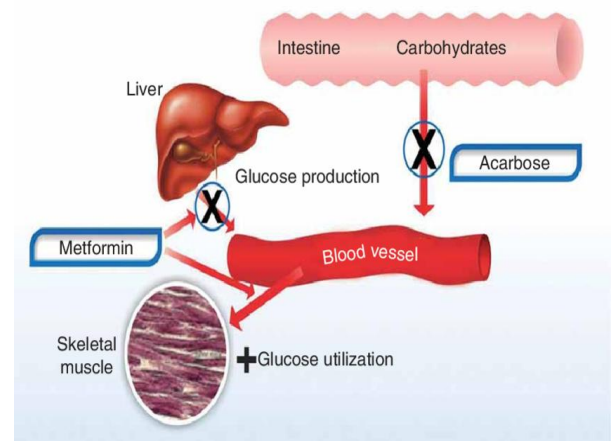
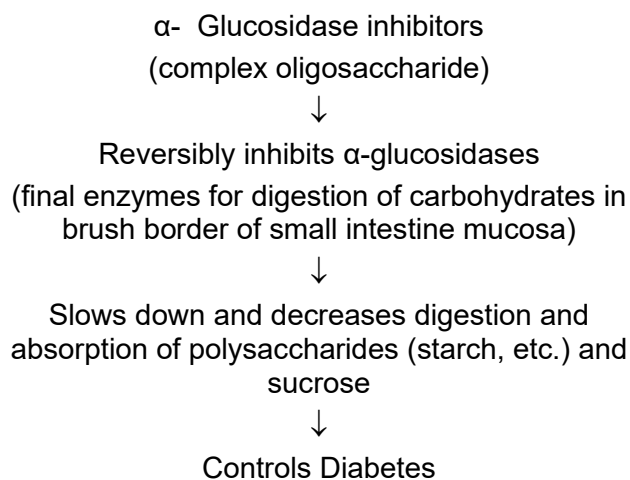
### Drugs

- Acarbose
- Miglitol
- Voglibose

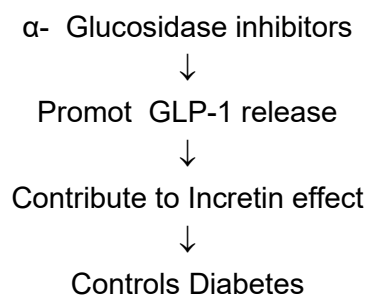
### MOA

- 2 MOA

#### 1<sup>st</sup> MOA



#### 2<sup>nd</sup> MOA



### Uses

- Used as an adjuvant to diet (with or without metformin/SU) in obese diabetics.



## Advantages

1. Postprandial glycaemia is reduced without significant increase in insulin levels.
2. Regular use lowers HbA1c modestly (by 0.4–0.8%), but change in body weight and lipid levels is minimal.
3. Long-term acarbose treatment in prediabetics reduces occurrence of type 2 DM as well as hypertension and cardiac disease

## Adverse effect

- Due to fermentation of unabsorbed carbohydrates
  - Flatulence
  - Abdominal discomfort
  - Loose stool



## α- GLUCOSIDASE INHIBITORS

### Drugs

- Pramlintide

### MOA

- Amylin is produced by pancreatic  $\beta$  cells

#### Pramlintide



1. Reduce glucagon secretion from pancreas  $\alpha$  cells
2. Delay gastric emptying → Retard glucose absorption
3. Acts on brain and promote satiety (centrally mediated anorectic action)

### Uses

- Used as an adjuvant to meal time insulin injection to suppress glycaemic peak in both type 1 and type 2 diabetics.
- Reduction in body weight is an additional benefit.

### Remember

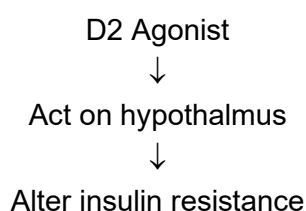
- Apart from insulin, the only drug approved for treatment of both type 1 as well as type 2 diabetes is pramlintide

## DOPAMINE D2 AGONIST

### Drugs

- Bromocriptin

### MOA



## Use

- To supplement diet + exercise or added to metformin or SU or both.

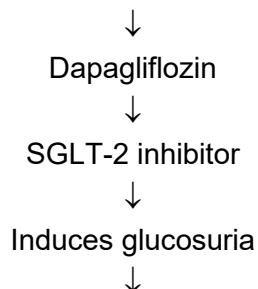
## SGLT-2 INHIBITOR

### Drugs

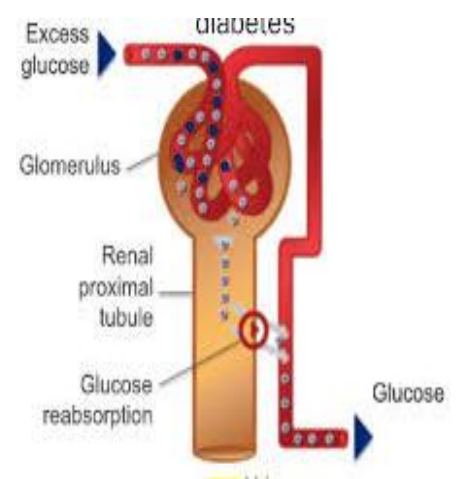
- Dapagliflozin
- Empagliflozin
- Canagliflozin
- Ertugliflozin

### MOA

- All the glucose filtered at glomerulus is reabsorbed in proximal tubules by SGLT-2 (Sodium-glucose Co-transport-2)



Lowers blood glucose in type 2 DM as well as causes weight loss.



### Uses

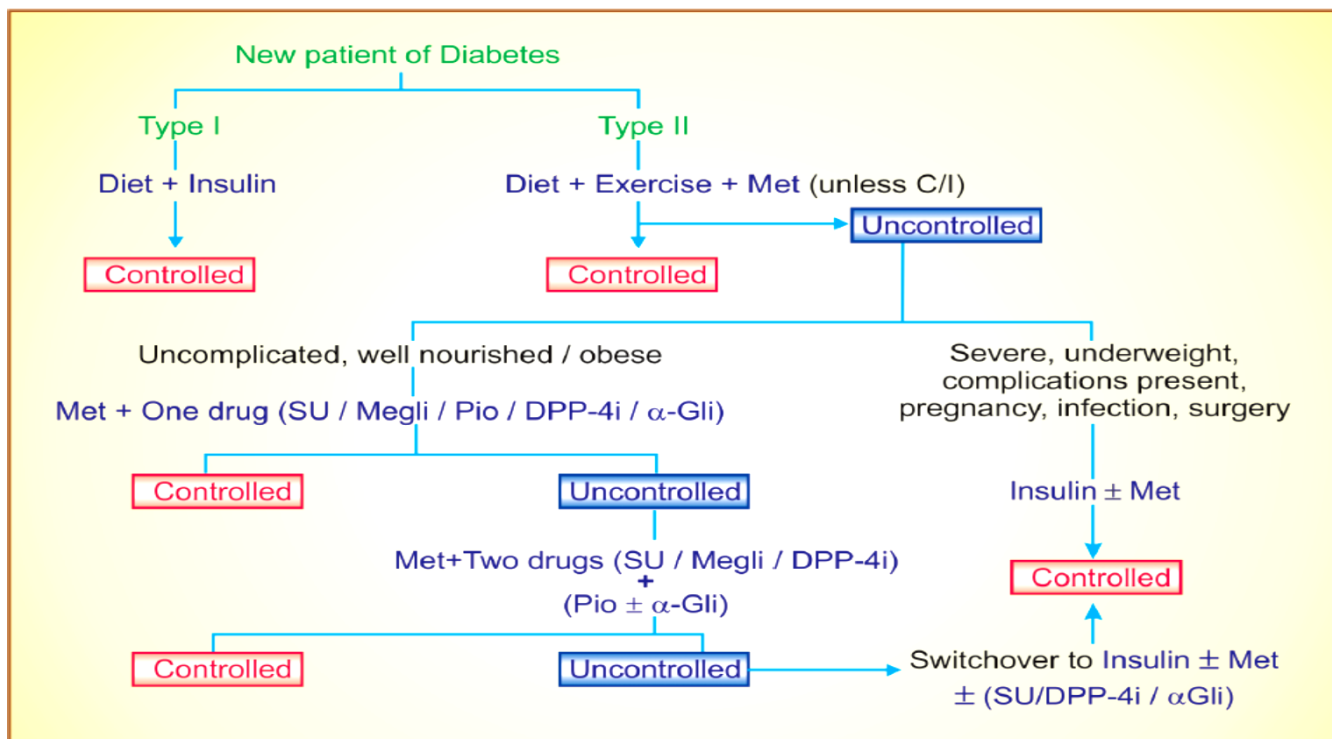
- **Type 2 Diabetes Mellitus** → As monotherapy or add-on to metformin.
- **Cardiovascular Benefits** → Reduce risk of Heart failure hospitalization
- **Renal Protection** → Slow progression of diabetic nephropathy.
- **Weight loss & BP reduction** → Secondary metabolic benefit

### Adverse effects

- Genital mycotic infections (e.g., candida)
- UTI



# MANAGEMENT OF DIABETES



## Type 1 (IDDM) DM

- All type 1 patients need immediate insulin therapy.
- Human insulin is preferred.

## Type 2 (NIDDM) DM

- Initial therapy in type 2 patients should be diet therapy for 2-3 months.
- Diet therapy is accompanied by exercise.
- But most patients need oral antidiabetics in addition
- Metformin → DOC for obese patients because it promotes weight loss, lowers insulin levels, improves lipid profile and has a lower secondary failure rate.
- If target glycemic goal is not reached on a single drug, second oral hypoglycemic may be added to metformin
- If control is still incomplete → either insulin or third oral hypoglycemic may be added

## Mnemonic

- **M**- Metformin preferred in
- **O**- Obese patients
- **S** - Sulfonylureas preferred in
- **T** - Thin Patients

## Indications of insulin use in Type 2 (NIDDM) DM

1. Diabetes not controlled on oral hypoglycemics.
2. Pregnancy
3. In complications like diabetic ketoacidosis and hyperosmolar coma → IV regular (soluble) insulin is preferred.
4. To tide over stressful conditions like infection and surgery.

## CORTICOSTEROIDS

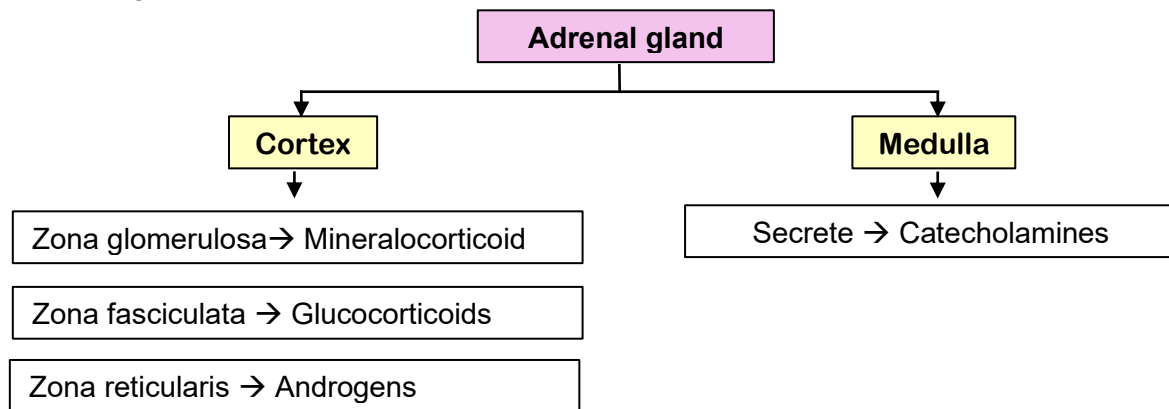
### OVERVIEW

- Natural corticosteroids
- HPA axis
- Biosynthesis
- Actions
- Classification
- Chemistry
- Uses
- Adverse effects
- Contraindications

### Natural Corticosteroids

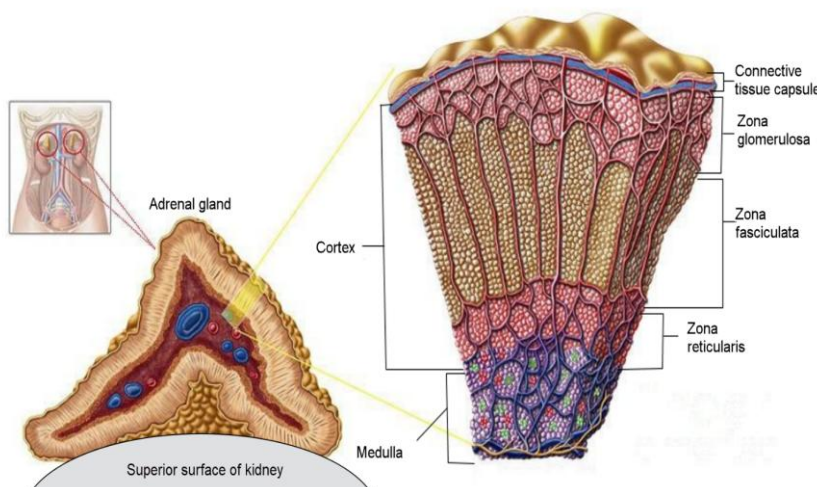
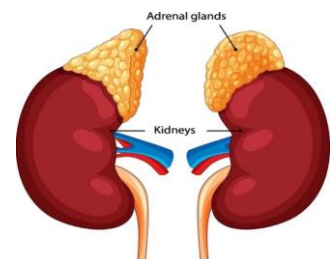
Corticosteroids are classified as:

1. Glucocorticoids
2. Mineralocorticoids
3. Androgens

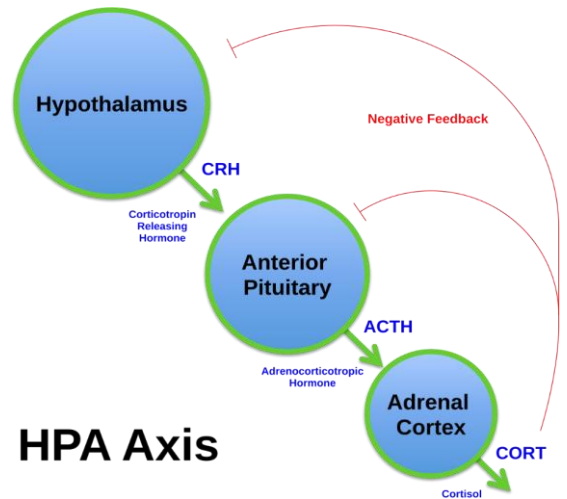
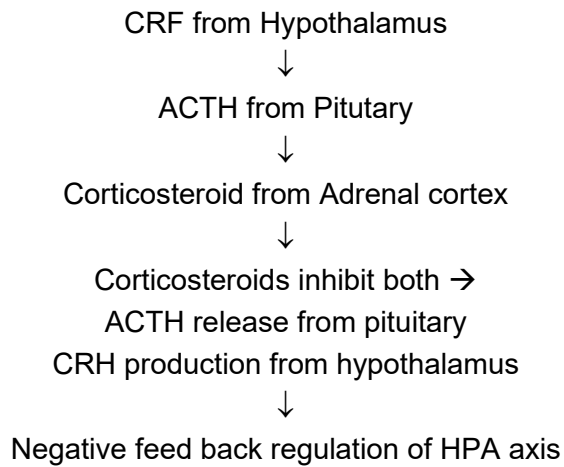


### Adrenal cortex

- Adrenal cortex has 3 layers →
  1. **Zona glomerulosa** → secretes Mineralocorticoid
  2. **Zona fasciculata** → secretes Glucocorticoids
  3. **Zona reticularis** → secretes Androgens



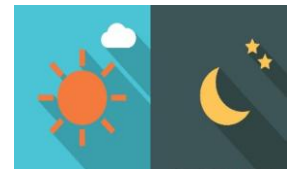
## HPA (Hypothalamic Pituitary Adrenal) Axis



### Levels of regulation of HPA axis

#### 1. Diurnal rhythm

- Maximum secretion at → 3-8 A.M
- Minimum at → 6 P.M. to 12 midnight



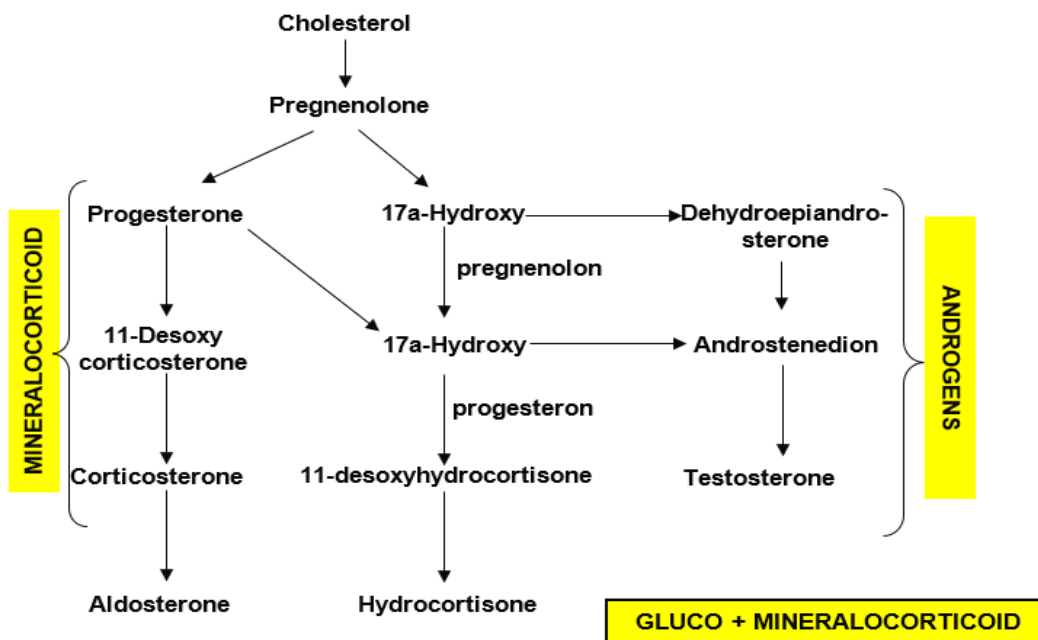
#### 2. Negative feed back regulation by glucocorticoids

**3. Stress** → such as injury, trauma, infection, surgery, hypoglycemia, cold, fever and pain → Marked increase in steroidogenesis



## Biosynthesis

- **Corticoids (both gluco and mineralo)** → 21 carbon compounds having a cyclopentanoperhydro- phenanthrene (steroid) nucleus
- **Synthesized in** → Adrenal cortical cells from cholesterol.



## Actions

- Mineralocorticoid actions
- Glucocorticoid actions

## Mineralocorticoid actions

1. Reabsorption of sodium
2. Excretion of potassium and H ion

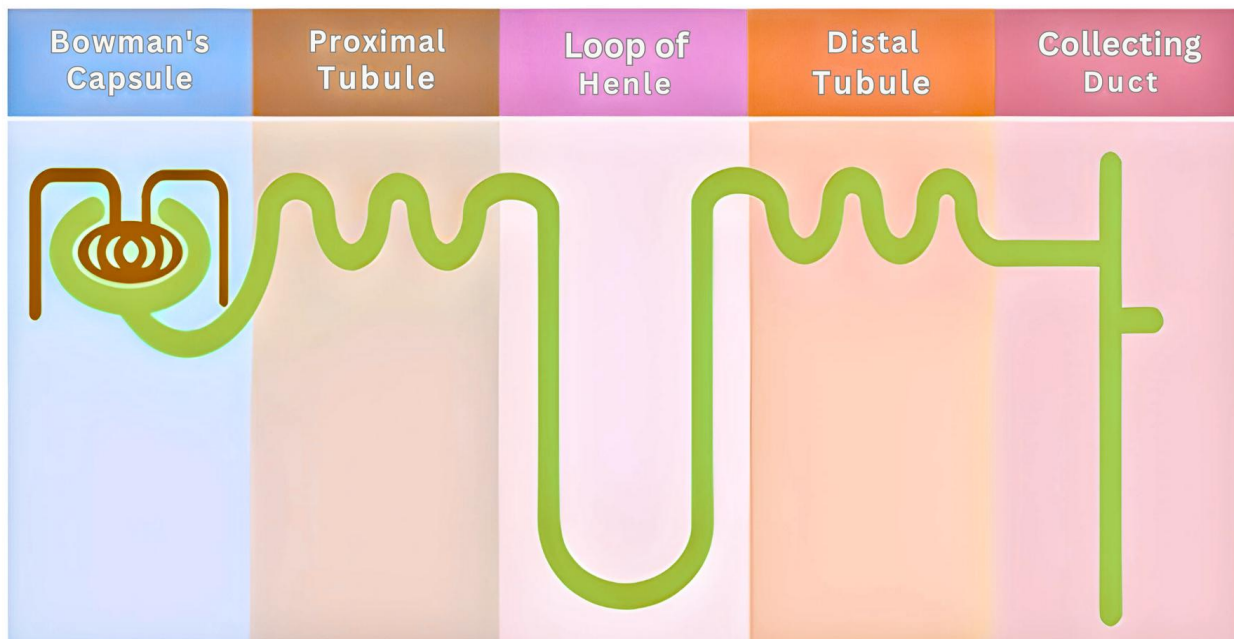
## Glucocorticoid actions

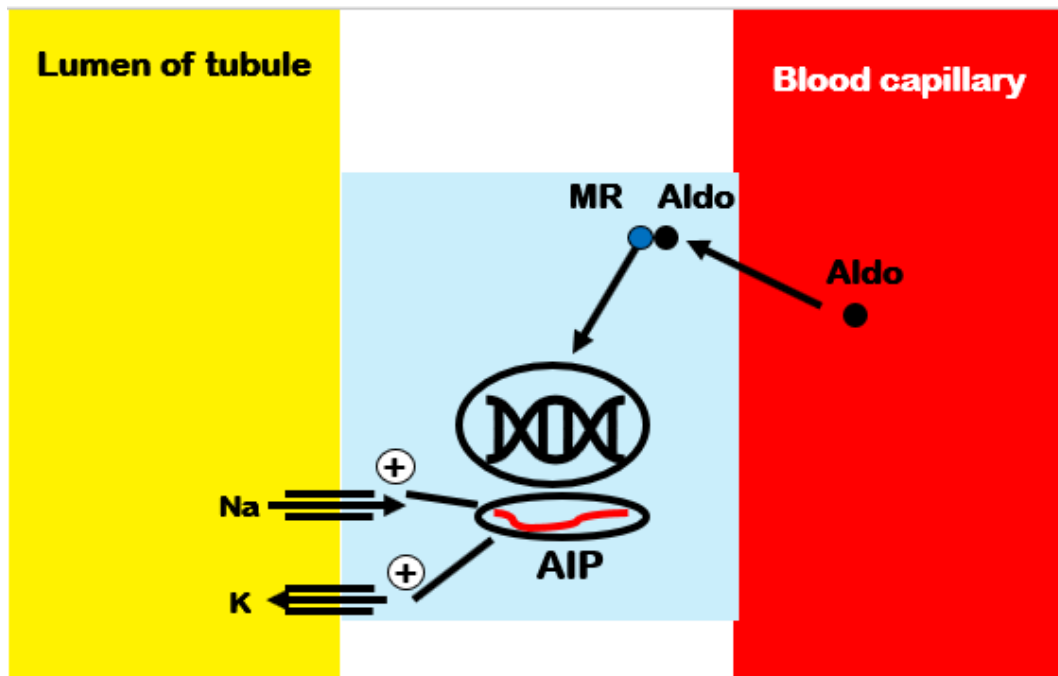
1. Carbohydrate metabolism
2. Protein metabolism
3. Fat metabolism
4. Calcium metabolism
5. Water excretion
6. CVS
7. Skeletal muscles
8. CNS
9. Stomach
10. Lymphoid tissue
11. Blood cells
12. Inflammatory responses
13. Immunological and allergic responses

## Mineralocorticoid actions

From collecting tubules of nephron → they promote

1. Reabsorption of sodium
2. Excretion of potassium and H ion





### Mineralocorticoid disorders

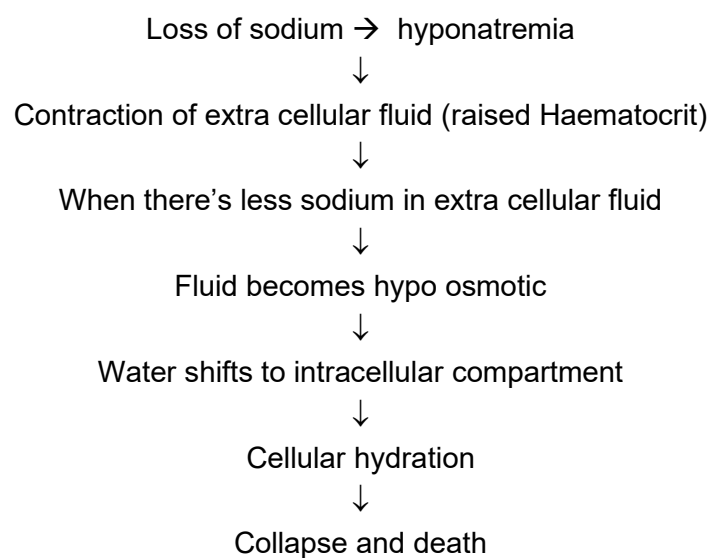
- Hypercorticism
- Hypocorticism

#### Hypercorticism

1. Hypokalemia
2. Alkalosis
3. Positive sodium balance with expansion of ECF volume

#### Hypocorticism

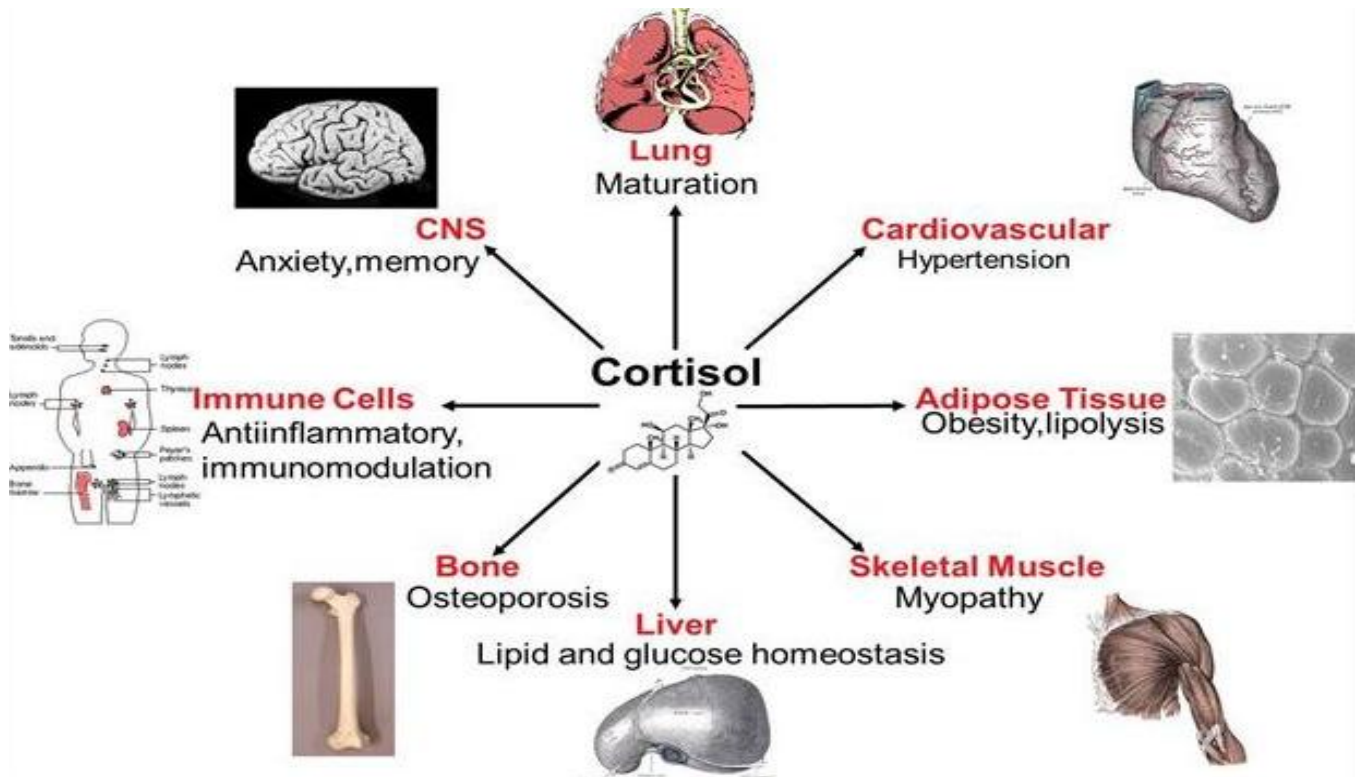
1. Hyperkalemia
2. Acidosis
3. Loss of sodium → Hyponatremia → contraction of extra cellular fluid



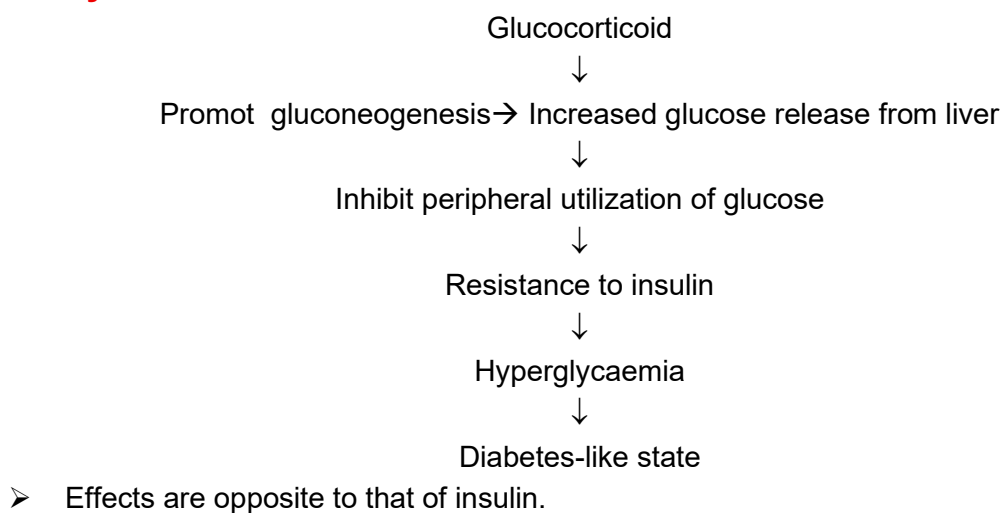
- These actions make adrenal cortex essential for survival.

## Glucocorticoid actions

1. Carbohydrate metabolism
2. Protein metabolism
3. Fat metabolism
4. Calcium metabolism
5. Water excretion
6. CVS
7. Skeletal muscles
8. CNS
9. Stomach
10. Lymphoid tissue
11. Blood cells
12. Inflammatory responses
13. Immunological and allergic responses



### 1. Carbohydrate metabolism



Glucocorticoids function appears to be aimed at maintaining blood glucose levels during starvation  
 ↓  
 So that brain continues to get its nutrient



## 2. Protein metabolism

- Glucocorticoids are catabolic

Glucocorticoid



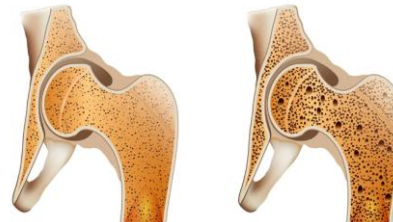
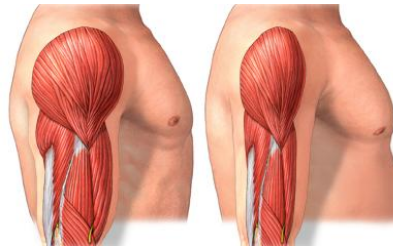
Cause protein breakdown



Amino acid mobilization from peripheral tissues to liver



**Muscle wasting**  
**Loss of osteoid from bone**  
**Thinning of skin**



Glucocorticoid



Cause protein breakdown



Amino acid mobilization from peripheral tissues to liver



Used up in gluconeogenesis  
Excess urea is produced  
Negative nitrogen balance

## 3. Fat metabolism

Glucocorticoids



Lipolytic effect



Mobilization of free fatty acids from adipose tissues



Fat depots in different areas of body respond differently



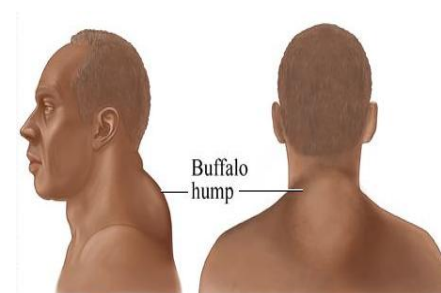
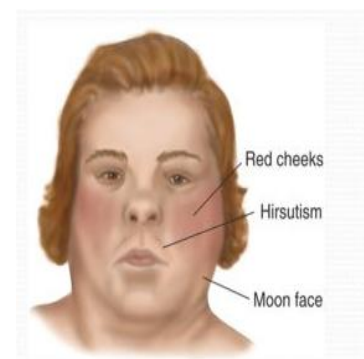
Redistribution of body fat occurs



Subcutaneous tissue over extremities loses fat which is deposited over face, neck and shoulder

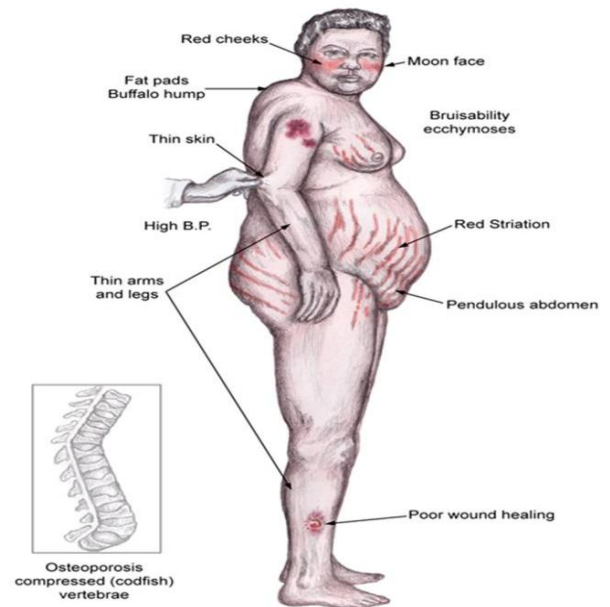


**'Moon face'**  
**'Fish mouth'**  
**'Buffalo hump'**

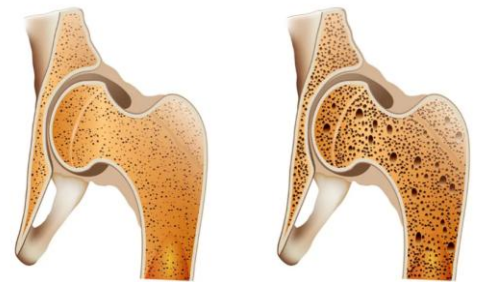
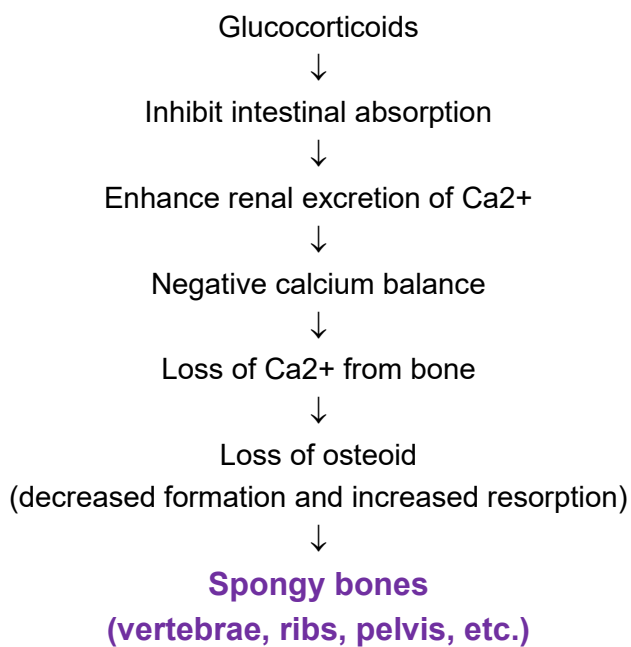


### Why redistribution of body fat occurs ???

- Peripheral adipocytes → less sensitive to insulin and more sensitive to corticosteroid
- Truncal adipocytes → respond mainly to raised insulin



### 4. Calcium metabolism



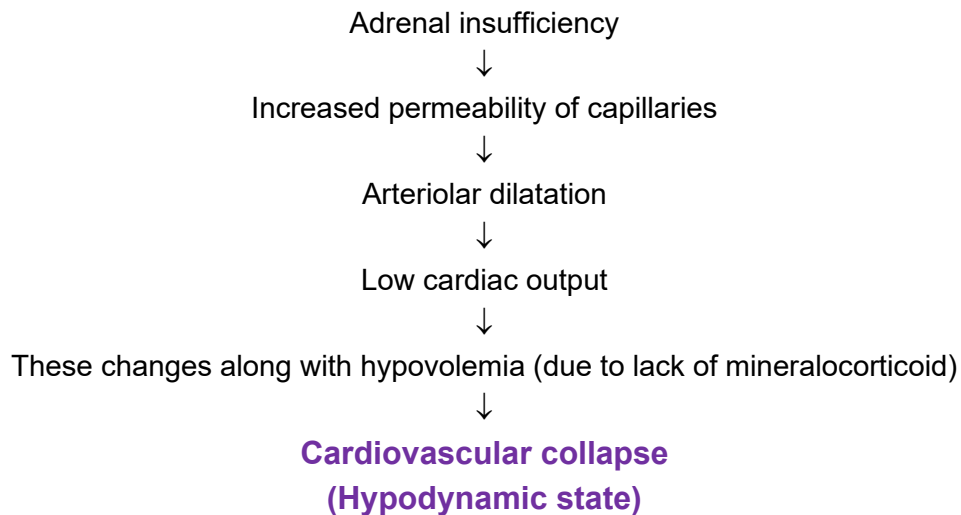
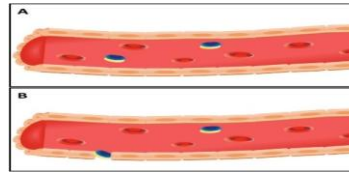
### 5. Water excretion

- Glucocorticoids → maintain normal GFR
- In adrenal insufficiency
- ↓
- Capacity to excrete a water load is markedly reduced
- ↓
- such patients are prone to water intoxication from i.v. infusions



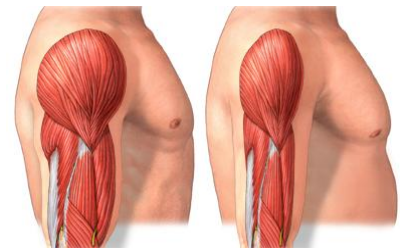
## 6. CVS

- Glucocorticoids→
  - Restrict capillary permeability
  - Maintain tone of arterioles
  - Myocardial contractility



## 7. Skeletal muscles

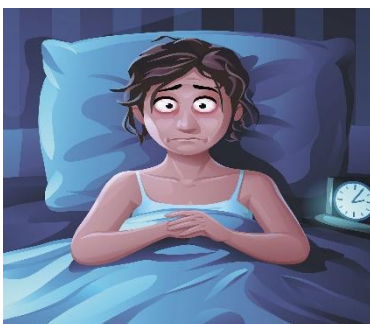
- Optimum level of corticosteroids is needed for normal muscular activity.
- Weakness occurs in both hypo- and hypercorticism
  - **Hypocorticism**→ Diminished work capacity and weakness are primarily due to hypodynamic circulation.
  - **Hypercorticism**→ Excess glucocorticoid action → Muscle wasting and myopathy→ Weakness



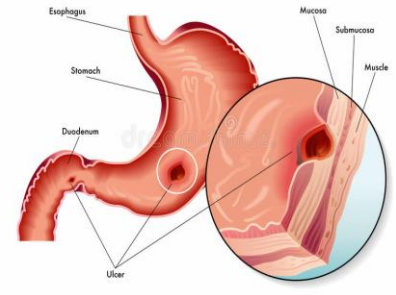
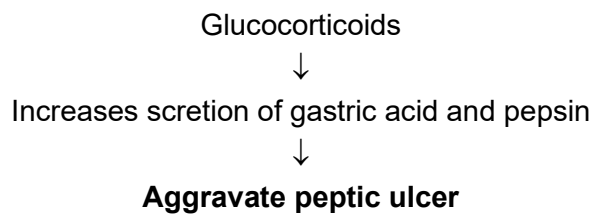
## 8. CNS

Glucocorticoids causes→

- **Mild euphoria** → sometimes progresses to cause increased motor activity, insomnia, hypomania
- **Lower seizure threshold** → Use in epileptics requires caution

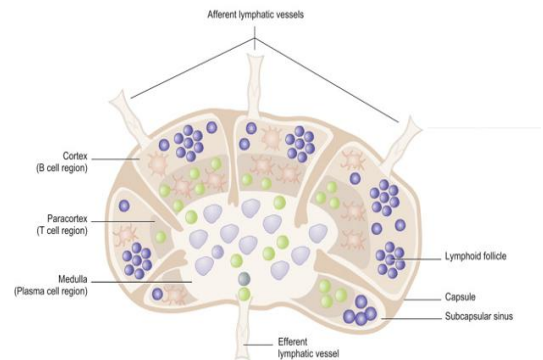


## 9. Stomach

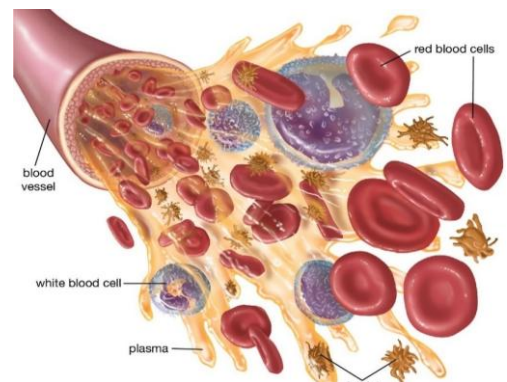
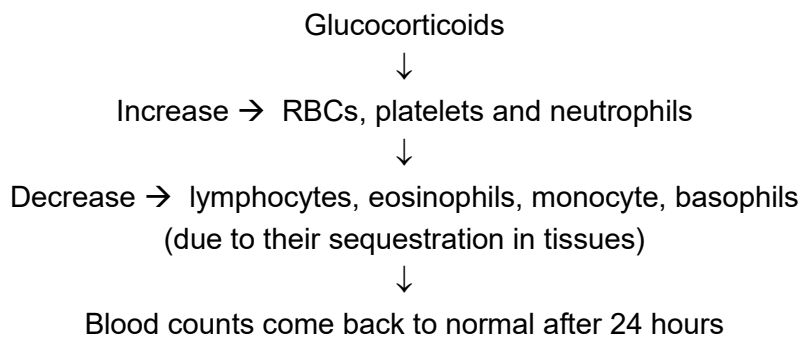


## 10. Lymphoid tissue

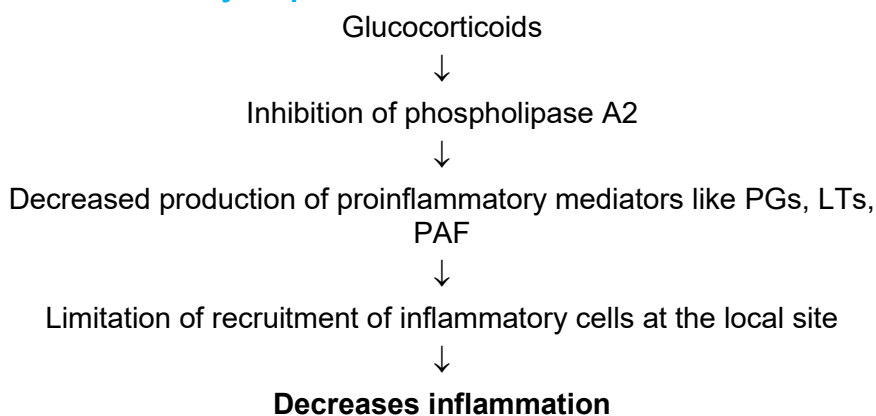
- Glucocorticoids → enhance rate of destruction of lymphoid cells
- T cells are more sensitive than B cells
- But in man effect on normal lymphoid tissue is modest.
- Marked lytic response is shown by malignant lymphatic cells → basis of their use in lymphomas.

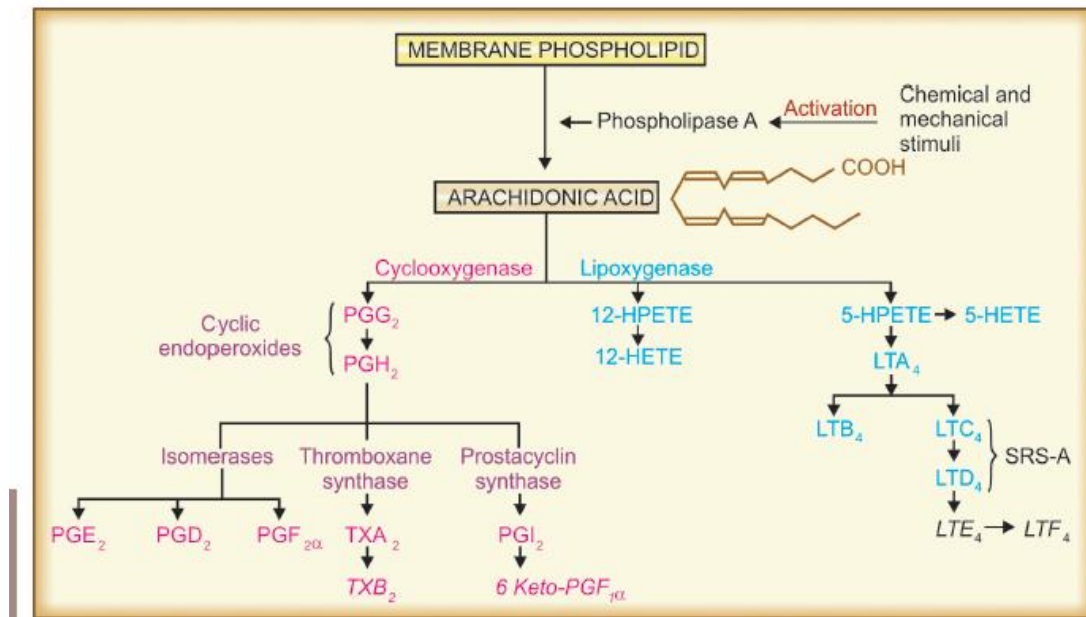


## 11. Blood cells



## 12. Inflammatory responses





Irrespective of the type of injury or insult

↓  
Inflammatory response is suppressed by glucocorticoids

↓  
Basis of most of their clinical uses

- Action is nonspecific and covers all components and stages of inflammation.
- Cardinal signs of inflammation → redness, heat, swelling and pain are suppressed.



## Remember

Corticoids are only palliative

↓  
Do not remove cause of inflammation

↓  
Underlying disease continues to progress while manifestations are dampened

↓  
They favour spread of infections because capacity of defensive cells to kill microorganisms is impaired.

↓  
Indiscriminate use of corticoids is hazardous

## 13. Immunological and allergic responses

Glucocorticoids

↓  
Suppress recruitment of leukocytes at site of contact with antigen

↓  
Suppress all types of hypersensitization and allergic phenomena

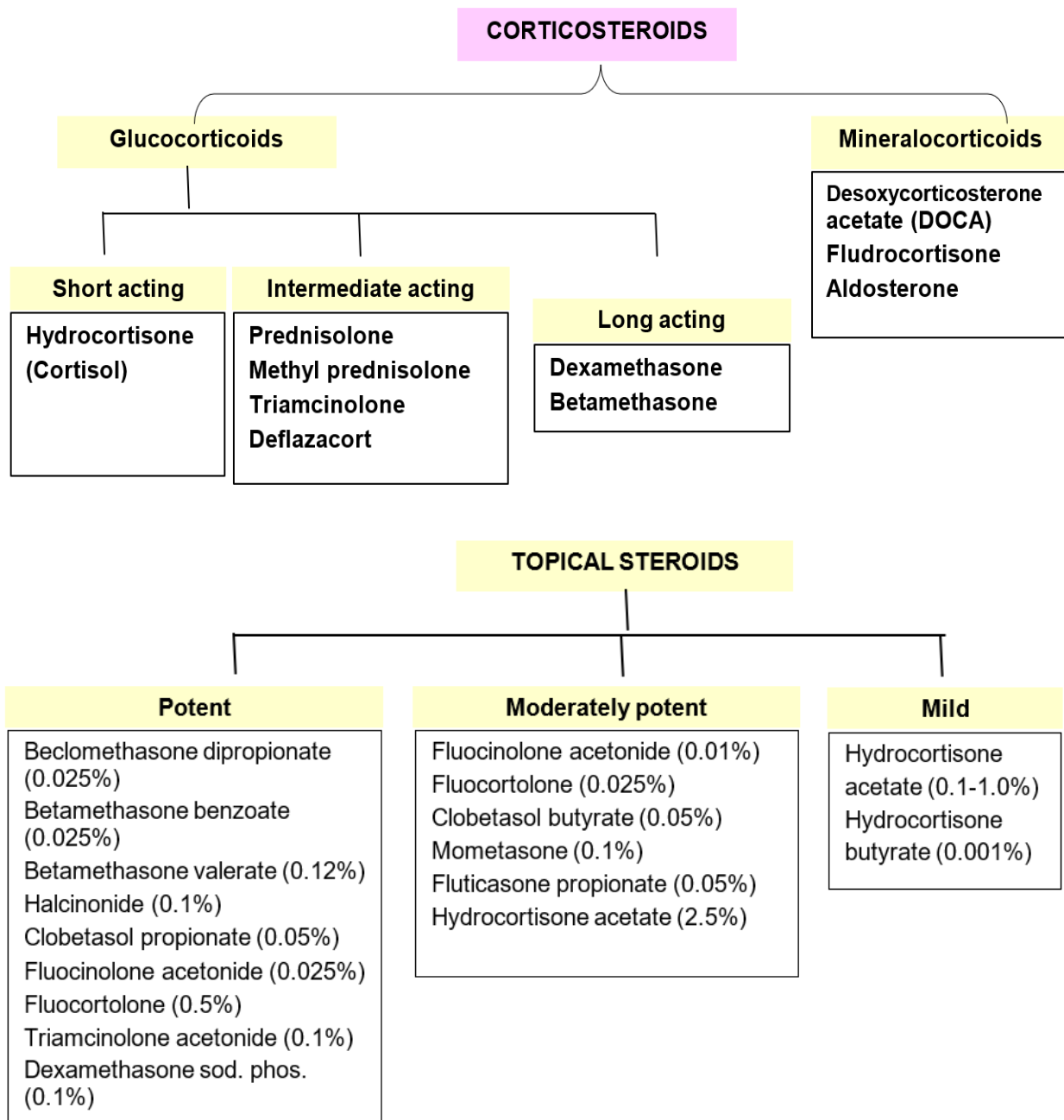
Glucocorticoids

↓  
Greater suppression of CMI in which T cells are primarily involved

↓  
Basis of their use in autoimmune diseases and organ transplantation



## Classification



### Inhaled preparations of steroid

- Beclomethason
- Budesonide
- Flunisolide
- Fluticasone
- Triamcinolone
- Ciclesonid

## A) Replacement therapy

1. Acute adrenal insufficiency
2. Chronic adrenal insufficiency (Addison's disease)
3. Congenital adrenal hyperplasia (Adrenogenital syndrome)

## B) Pharmacotherapy

### MALTI CO ABCESS HAI

- |                                     |                                         |
|-------------------------------------|-----------------------------------------|
| 1. <b>M</b> - Malignancies          | 9. <b>B</b> - Bronchial asthma          |
| 2. <b>A</b> - Arthritides           | 10. <b>C</b> - Cerebral edema           |
| 3. <b>L</b> - Lung disease          | 11. <b>E</b> - Eye disease              |
| 4. <b>T</b> - To test HPA axis      | 12. <b>S</b> - Severe allergic reaction |
| 5. <b>I</b> - Intestinal disease    | 13. <b>S</b> - Skin disease             |
| 6. <b>C</b> - Collagen disease      | 14. <b>H</b> - sHock                    |
| 7. <b>O</b> - Organ transplantation | 15. <b>A</b> - Adrenal insufficiency    |
| 8. <b>A</b> - Autoimmune disease    | 16. <b>I</b> - Infective disease        |

## A) Replacement therapy

1. Acute adrenal insufficiency
2. Chronic adrenal insufficiency (Addison's disease)
3. Congenital adrenal hyperplasia (Adrenogenital syndrome)

### 1. Acute adrenal insufficiency

- It is an emergency.
- Hydrocortisone or dexamethasone → given i.v., first as a bolus injection and then as infusion, along with isotonic saline and glucose solution.
- Amount of fluid infused i.v. is guided by monitoring central venous pressure, because these patients have reduced capacity to excrete water load.
- Short-term i.v. infusion of a vasopressor (dopamine) may be needed.
- Cause of adrenal insufficiency should be treated.



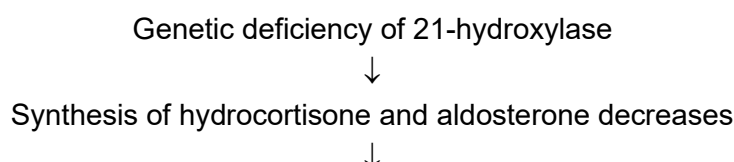
### 2. Chronic adrenal insufficiency (Addison's disease)

- Hydrocortisone → given orally along with adequate salt and water allowance.
- Some patients who continue to excrete excess Na<sup>+</sup> need additional mineralocorticoid: fludrocortisone is added.

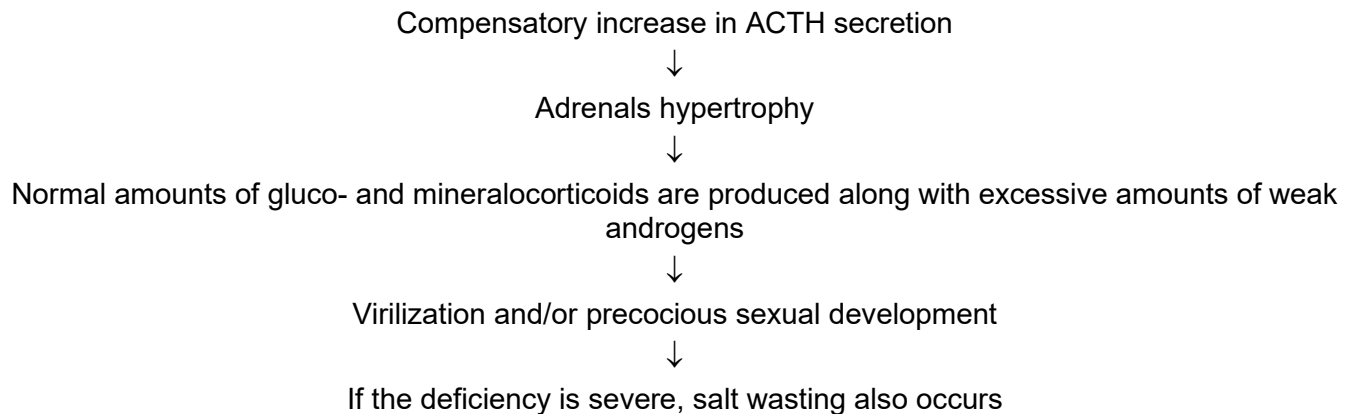


### 3. Congenital adrenal hyperplasia (Adrenogenital syndrome)

- Familial disorder due to genetic deficiency of steroidogenic enzymes, mostly 21-hydroxylase.
- Synthesis of hydrocortisone and aldosterone suffers.







### Treatment

- Hydrocortisone 0.6 mg/ kg daily in divided doses round clock to maintain feed back suppression of pituitary.
- If salt wasting persists → fludrocortisone 50–200 µg/ day may be added.

### B. Pharmacotherapy (for nonendocrine diseases)

- Systemic as well as topical corticosteroids have one of the widest spectrum of medicinal uses for their antiinflammatory and immunosuppressive properties.
- They have potential to cause dramatic improvement in many severe diseases as well as produce equally dramatic adverse effects if not properly used.
- Use in nonendocrine diseases is empirical and palliative, but may be life saving



### General principles

- (a) A single dose (even excessive) is not harmful → can be used to tide over mortal crisis, even when benefit is not certain.
- (b) Short courses (even high dose) are not likely to be harmful in absence of contraindications → starting doses can be high in severe illness
- (c) Long-term use is potentially hazardous → keep duration of treatment and dose to minimum
- (d) Initial dose depends on severity of disease
  - In severe illness → start with a high dose reduce gradually after symptoms subside
  - In mild cases → start with lowest dose and titrate upwards
- (e) No abrupt withdrawal → after a corticoid has been given for > 2 to 3 weeks → may precipitate adrenal insufficiency.
- (f) Infection, severe trauma, surgery or any stress during corticoid therapy → increase the dose.
- (g) Use local therapy (cutaneous, inhaled, intranasal, etc) wherever possible.

### MALTI CO ABCESS HAI

- |                                  |                                     |
|----------------------------------|-------------------------------------|
| 1. <b>M</b> - Malignancies       | 6. <b>C</b> - Collagen disease      |
| 2. <b>A</b> - Arthritides        | 7. <b>O</b> - Organ transplantation |
| 3. <b>L</b> - Lung disease       | 8. <b>A</b> - Autoimmune disease    |
| 4. <b>T</b> - To test HPA axis   | 9. <b>B</b> - Bronchial asthma      |
| 5. <b>I</b> - Intestinal disease | 10. <b>C</b> - Cerebral edema       |

- |                |                          |                |                       |
|----------------|--------------------------|----------------|-----------------------|
| 11. <b>E</b> - | Eye disease              | 14. <b>H</b> - | sHock                 |
| 12. <b>S</b> - | Severe allergic reaction | 15. <b>A</b> - | Adrenal insufficiency |
| 13. <b>S</b> - | Skin disease             | 16. <b>I</b> - | Infective disease     |

## 1. Malignancies

- Corticoids are an essential component of combined chemotherapy of →
  - Acute lymphatic leukaemia (ALL)
  - Hodgkin's and other lymphomas
- Because of their marked lympholytic action in these conditions.

## 2. Arthritides

- Rheumatoid arthritis
- Osteoarthritis
- Rheumatic fever
- Gout



## 3. Lung disease → Respiratory distress syndrome

Given during late pregnancy



corticoids accelerate lung maturation

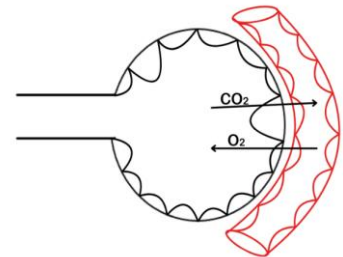


surfactant production in foetal lung



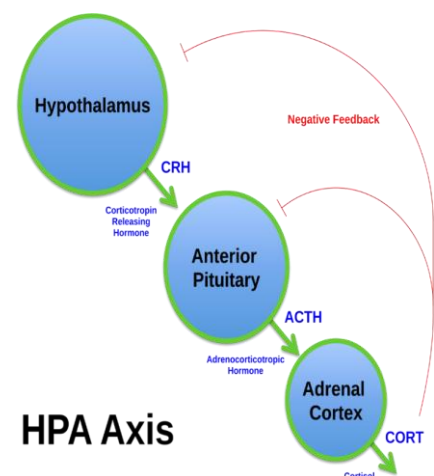
Prevent respiratory distress syndrome at birth

- Two doses of betamethasone 12 mg i.m. at 24 hour interval may be administered to the mother if premature delivery is contemplated.



## 4. To test HPA axis function

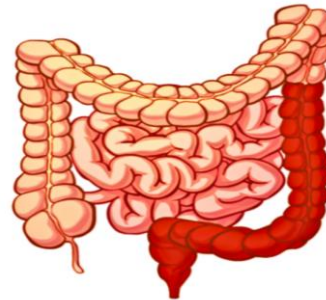
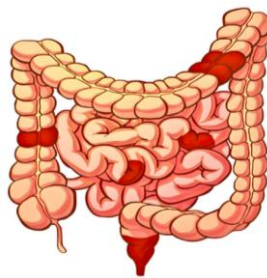
- Dexamethasone suppresses pituitary-adrenal axis
- Responsiveness of axis can be tested by measuring daily urinary steroid metabolite excretion after dosing with dexamethasone.



## 5. Intestinal diseases

- Ulcerative colitis
- Crohn's disease
- Coeliac disease

- Corticoids are indicated during acute phases → orally or as retention enema (for colonic involvement).
- Given in addition to sulfasalazine/ mesalazine + other measures



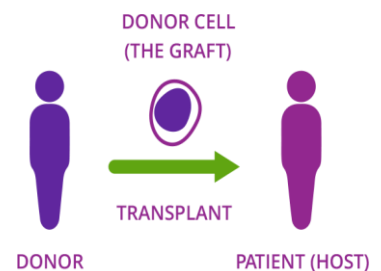
## 6. Collagen diseases

- Most cases of systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis, nephrotic syndrome, glomerulonephritis → need corticosteroid therapy.
- They may be life saving in these diseases.
- Therapy is generally started with high doses which are tapered to maintenance dose when remission occurs.



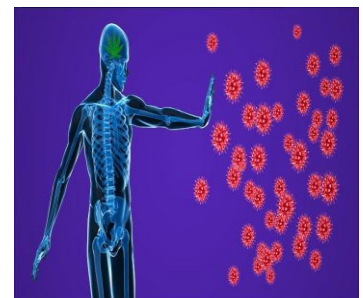
## 7. Organ transplantation and skin allograft

- **High dose corticoids** → given along with other immunosuppressants to prevent the rejection reaction.
- **Low maintenance doses** → generally continued over long term + maintenance doses of companion drugs.



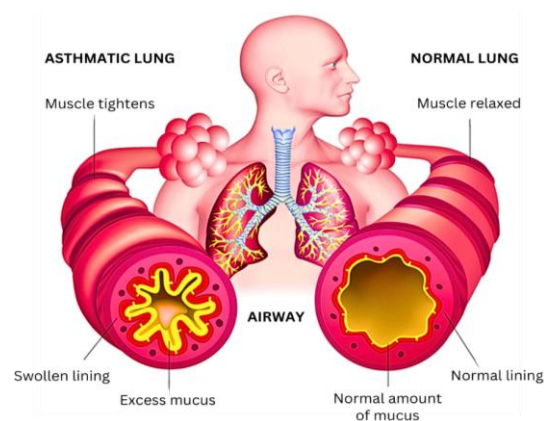
## 8. Autoimmune diseases

- Autoimmune haemolytic anaemia
- Idiopathic thrombocytopenic purpura
- Active chronic hepatitis
- **Prednisolone 1–2 mg/kg/day** → given till remission, followed by gradual withdrawal or low-dose maintenance depending on the response.



## 9. Bronchial asthma

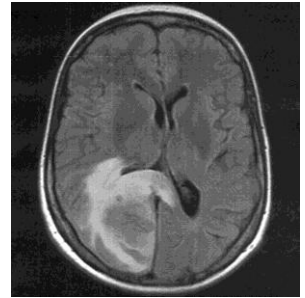
- **Status asthmaticus** → give i.v. glucocorticoid; withdraw when emergency is over.
- **Acute asthma exacerbation** → short-course of high dose oral corticoid, followed by gradual withdrawal.
- **Severe chronic asthma not controlled by inhaled steroids and bronchodilators** → add low dose prednisolone daily or on alternate days.





## 10. Cerebral edema

- Due to tumours, tubercular meningitis, etc., responds to corticoids.
- **Dexa-or betamethasone** → preferred because they do not have Na<sup>+</sup> retaining activity.



## 11. Eye diseases

- Ordinarily steroids should not be used in infective conditions.
- But if inflammation is severe, they may be applied in conjunction with an effective antibiotic.
- **Topical instillation as eye drops or ointment** → effective in diseases of the anterior chamber → allergic conjunctivitis, iritis, iridocyclitis, keratitis, etc.
- **Retrobulbar injection** → occasionally given to avoid systemic side effects



## 12. Severe allergic reactions

- Corticoids may be used for short periods in anaphylaxis, angioneurotic edema, urticaria and serum sickness.
- **IV injection of a glucocorticoid** → takes 1–2 hours to act and is not a substitute for Adr (which acts immediately) in anaphylactic shock and angioedema of larynx.
- **Topical use** → in allergic conjunctivitis and rhinitis



## 13. Skin diseases

- **Topical corticosteroids** → highly effective in many eczematous skin diseases.
- **Systemic therapy** → needed (may be life-saving) in pemphigus vulgaris, exfoliative dermatitis, Stevens-Johnson syndrome and other severe afflictions.



## 14. Shock

- Corticosteroids are primarily used in septic shock when there is poor response to fluids and vasopressors. They help by:
  - Reducing inflammation
  - Improving vascular responsiveness to catecholamines
  - Reversing relative adrenal insufficiency
- Commonly used: IV hydrocortisone (200 mg/day)

## 15. Adrenal insufficiency

- Acute adrenal insufficiency
- Chronic adrenal insufficiency (Addison's disease)

## 16. Infective diseases

- Administered under effective chemotherapeutic cover
- Corticosteroids are indicated only in serious infective diseases to tideover crisis or to prevent complications.
- They are indicated in conditions like → severe forms of tuberculosis (miliary, meningeal, renal, etc.), severe lepra reaction, certain forms of bacterial meningitis and Pneumocystis carinii pneumonia with hypoxia in AIDS patients



## Adverse Effects

- A) Mineralocorticoid
- B) Glucocorticoid

### A) Mineralocorticoid

1. Sodium and water retention → Edema
2. Hypokalaemic
3. Alkalosis
4. Progressive rise in BP.

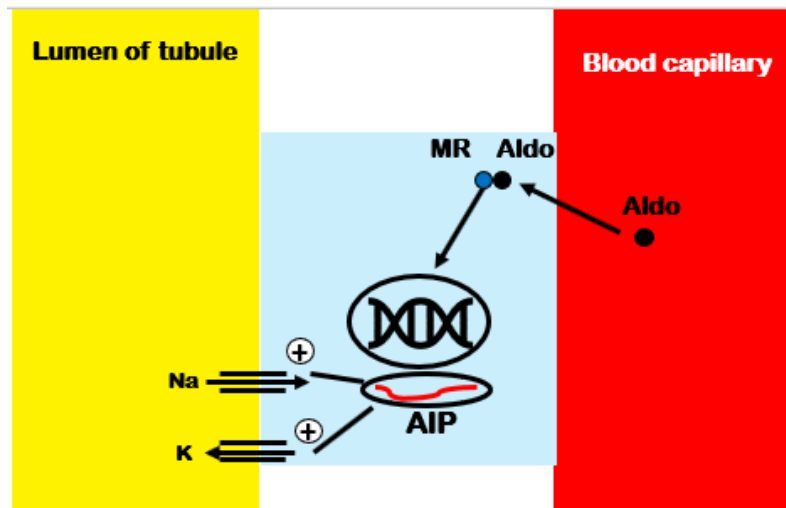
### B. Glucocorticoid

#### CORTICOSTEROIDS

- |                        |                                 |
|------------------------|---------------------------------|
| 1. Cushing's habitus   | 9. Teratogenic                  |
| 2. Osteoporosis        | 10. Emotional/mood disturbances |
| 3. Reduced growth      | 11. Rise in blood pressure      |
| 4. Thin skin           | 12. Obesity (truncal)           |
| 5. Immunosuppression   | 13. Increased hair growth       |
| 6. Cataracts           | 14. Diabetes                    |
| 7. Oedema              | 15. Striae                      |
| 8. Suppressed HPA axis |                                 |

### A) Mineralocorticoid

- |                                       |                            |
|---------------------------------------|----------------------------|
| 1. Sodium and water retention → Edema | 3. Alkalosis               |
| 2. Hypokalaemic                       | 4. Progressive rise in BP. |



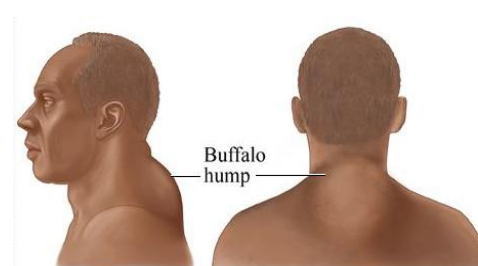
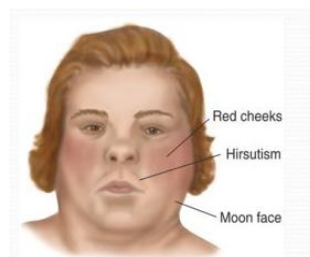
## B. Glucocorticoid

Mnemonic → **CORTICOSTEROIDS**

- |                                |                                         |
|--------------------------------|-----------------------------------------|
| 1. <b>C</b> ushing's habitus   | 9. <b>T</b> eratogenic                  |
| 2. <b>O</b> steoporosis        | 10. <b>E</b> motional/mood disturbances |
| 3. <b>R</b> educed growth      | 11. <b>R</b> ise in blood pressure      |
| 4. <b>T</b> hin skin           | 12. <b>O</b> besity (truncal)           |
| 5. <b>I</b> mmunosuppression   | 13. <b>I</b> ncreased hair grow         |
| 6. <b>C</b> ataracts           | 14. <b>D</b> iabetes                    |
| 7. <b>O</b> edema              | 15. <b>S</b> triae                      |
| 8. <b>S</b> uppressed HPA axis |                                         |

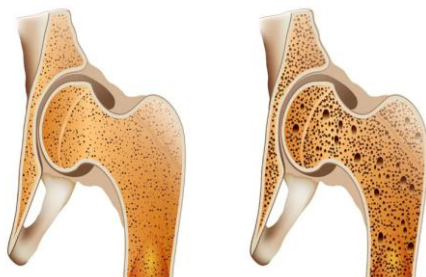
### 1. Cushing's

- Characteristic appearance with rounded face → Moon face
- Narrow mouth
- Supraclavicular hump



### 2. Osteoporosis

- Especially involving vertebrae and other flat spongy bones.
- Compression fractures of vertebrae and spontaneous fracture of long bones can occur, especially in elderly.



### 3. Reduced Growth

- a) Direct cellular effect of corticoids
- b) Large doses do inhibit GH secretion
  - Recombinant GH given concurrently can prevent growth retardation, but risk/benefit of such use is not known



### 4. Thin fragile skin

- Typically on thighs and lower abdomen, easy bruising, telangiectasis
- Cutaneous atrophy localized to site occurs with topical application as well.



### 5. Immunosuppression

- Susceptibility to infection
- This is nonspecific for all types of pathogenic organisms.
- Latent tuberculosis may flare
- Opportunistic infections with low grade pathogens (Candida, etc.) set in.

### 6. Cataract

- Posterior subcapsular cataract
- After several years of use, especially in children.



### 7. Oedema

- Na and water retention



### 8. Suppression of HPA axis

- Long term use (for more than 2 weeks) can lead to HPA axis suppression.

- Steroids should not be withdrawn abruptly because it may precipitate acute adrenal insufficiency.
- Many patients recover from HPA-axis suppression within several weeks to months but recovery may take one year or longer in some patients

## 9. Teratogenic

- Foetal abnormalities
  - Cleft palate and other defects are produced in animals, but have not been encountered on clinical use in pregnant women.
  - Intrauterine growth retardation can occur after prolonged therapy
  - Neurological/ behavioral disturbances
- Prednisolone appears safer than dexamethasone/ betamethasone, because it is metabolized by placenta, reducing foetal exposure



## 10. Emotional / Mood disturbances

- Mild euphoria accompanies high dose steroid treatment.
- This may rarely progress to manic psychosis.
- Nervousness
- Decreased sleep
- Mood changes occur in some patients.

## 11. Rise in BP

- Hypertension



## 12. Obesity (Truncal)

- Redistribution of body fat occurs
- Subcutaneous tissue over extremities loses fat which is deposited over face, neck and shoulder
  - Peripheral adipocytes → less sensitive to insulin and more sensitive to corticosteroid
  - Truncal adipocytes → respond mainly to raised insulin



## 13. Increased hair grow

- Hirsutism





## 14. Diabetes

- Hyperglycaemia, may be glycosuria, precipitation of diabetes



## 15. Straie

- Thinning of skin → Purple striae



## Contraindications

### MOTHER Please Pray For Children

- **M** - Mellitus(Diabetes Mellitus)
- **O** - Osteoporosis
- **T** - Tuberculosis
- **H** - Herpes simplex keratitis
- **E** - Epilepsy
- **R** - Renal failure
- **P** - Peptic ulcer
- **P** - Psychosis
- **F** - Fungal & viral infection
- **C** - Congestive Heart Failure

## Remember

|     | Glucocorticoids           | Duration of Action | G Activity    | M Activity | Potency (Eq. Dose) in mg |
|-----|---------------------------|--------------------|---------------|------------|--------------------------|
| 1.  | HYDROCORTISONE (CORTISOL) | Short              | 1             | 1          | 20                       |
| 2.  | CORTISONE                 | Short              | Minimum (0.8) | 0.8        | Least potent G. (25)     |
| 3.  | PREDNISONE                | Intermediate       | 4             | 0.5        | 5                        |
| 4.  | PREDNISOLONE              | Intermediate       | 5             | 0.5        | 5                        |
| 5.  | MEPREDNISONE              | Intermediate       | 5             | 0          | 4                        |
| 6.  | METHYLPREDNISOLONE        | Intermediate       |               |            | 4                        |
| 7.  | TRIAMCINOLONE             | Intermediate       |               |            | 4                        |
| 8.  | FLUPREDNISOLONE           | Intermediate       |               |            | 1.5                      |
| 9.  | PARAMETHASONE             | Long               |               |            | 2                        |
| 10. | BETAMETHASONE             | Long               |               |            | Most potent G            |

|                    |                 |    |     |                |                     |
|--------------------|-----------------|----|-----|----------------|---------------------|
|                    |                 |    |     |                | (0.6)               |
| 11.                | DEXAMETHASONE   |    |     |                |                     |
| Mineralocorticoids |                 |    |     |                |                     |
| 12.                | DOCA            |    | 0   | 20             |                     |
| 13.                | FLUDROCORTISONE | 10 | 250 | Most potent M. |                     |
| 14.                | ALDOSTERONE     |    | 0.3 | 3000 (max.)    | Not used clinically |

- Maximum glucocorticoid activity → **Dexamethasone**
- Maximum mineralocorticoid activity → **Aldosterone**
- Least potent glucocorticoid → **Cortisone**
- Most potent glucocorticoid → **Betamethasone**
- Glucocorticoid with max. mineralocorticoid activity → **Hydrocortisone**
- Glucocorticoid with min. glucocorticoid activity → **Hydrocortisone**
- Glucocorticoid with no mineralocorticoid activity → **Betamethasone, Paramethasone, Dexamethasone, Triamcinolone.**

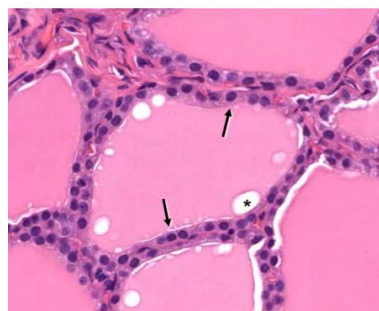
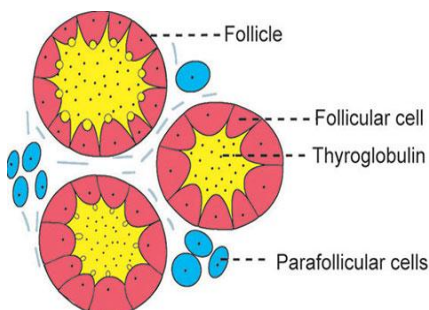
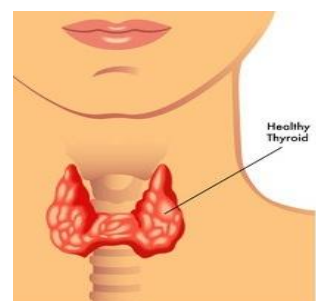
## THYROID HORMONES AND THYROID INHIBITORS

### NORMAL THYROID ANATOMY AND PHYSIOLOGY

- Anatomy of Thyroid Gland
- Thyroid hormones
- Chemistry
- Synthesis
- Regulation of Secretion

#### Anatomy of Thyroid Gland

- **Thyroid gland** → largest endocrine gland
- **Consists of** → 2 lobes and an isthmus
- **Weighs** → 15 to 25 g in adults.
- **Measures** → 5 cm x 3 cm x 2 cm
- **Each lobe** → conical in shape with apex directed upwards
- **Isthmus** → lies against II<sup>nd</sup> and III<sup>rd</sup> tracheal rings



## Thyroid hormones

- Term thyroid hormone denotes both →
  - **Thyroxine (T4)**
  - **Triiodothyronine (T3)**
 } **Follicular cells**
- **Calcitonin** → **C cells**

## Chemistry

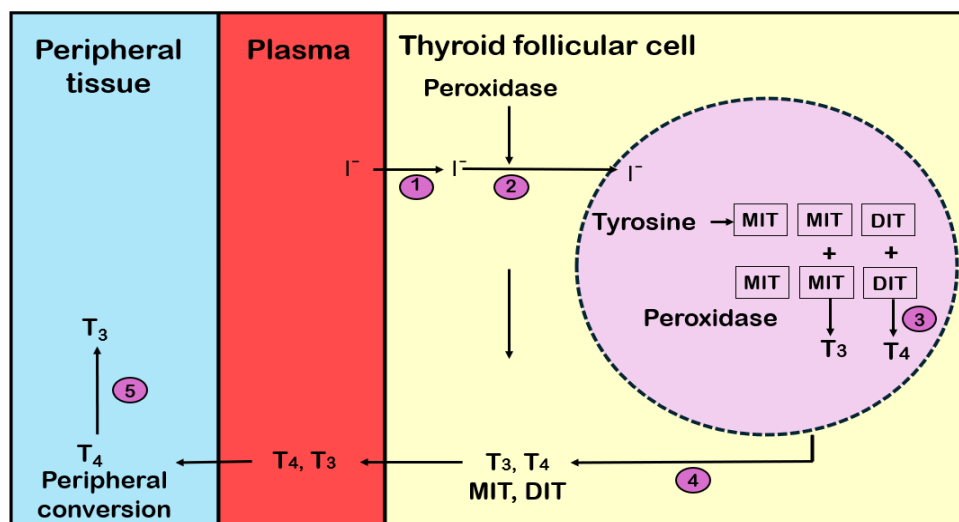
- Both T4 and T3 → iodine derivatives of thyronine.
- Thyronine → condensation product of two molecules of amino acid tyrosine
  - **T4** → 3, 5, 3', 5' - tetraiodothyronine
  - **T3** → 3, 5, 3'-triiodothyronine.

## Synthesis

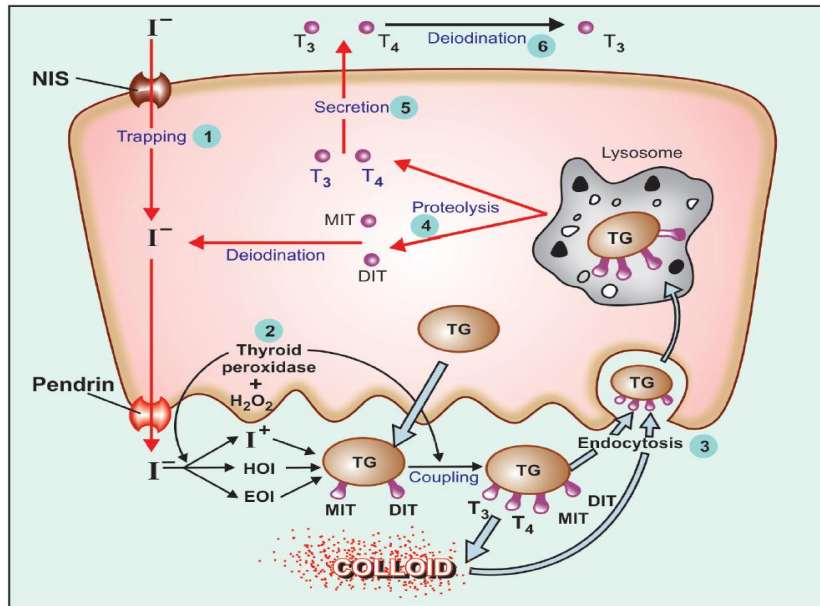
- Thyroid hormones are synthesized and stored in thyroid follicles as apart of thyroglobulin molecule.

## 5 Steps

1. Iodide uptake
2. Oxidation and iodination
3. Coupling
4. Storage and release
5. Peripheral conversion of T4 to T3







### 1. Iodide uptake

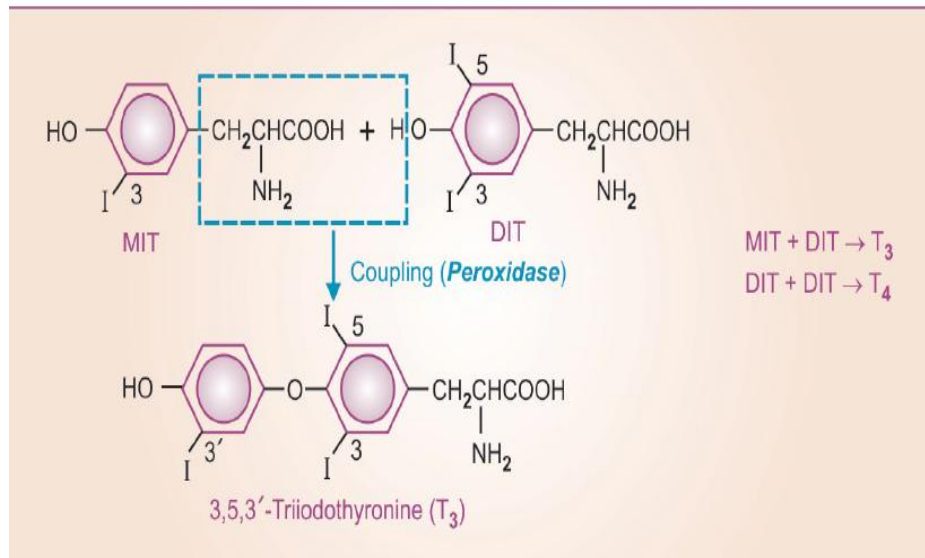
- **Thyroid cells (follicular cells)** → active transport system for iodine uptake → Na<sup>+</sup>: I symporter (NIS)
- **Trapping** → stimulated by TSH

### 2. Oxidation and iodination

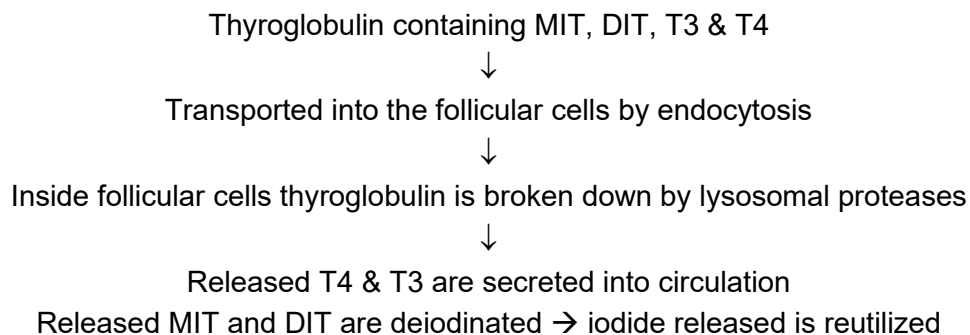
Iodide trapped by follicular cells  
 ↓  
 Transported to colloid  
 ↓  
 In colloid it is oxidised by membrane bound thyroid peroxidase to form oxidized forms of iodine →  
 Iodinium ion ( $I^+$ )  
 Hypoiodous acid (HOI)  
 Enzyme - linked hypoiodate (E-OI)  
 ↓  
 Oxidized forms of iodine combines with tyrosine residues of thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) → no enzyme is required  
 ↓  
 MIT and DIT are attached to thyroglobulin

### 3. Coupling

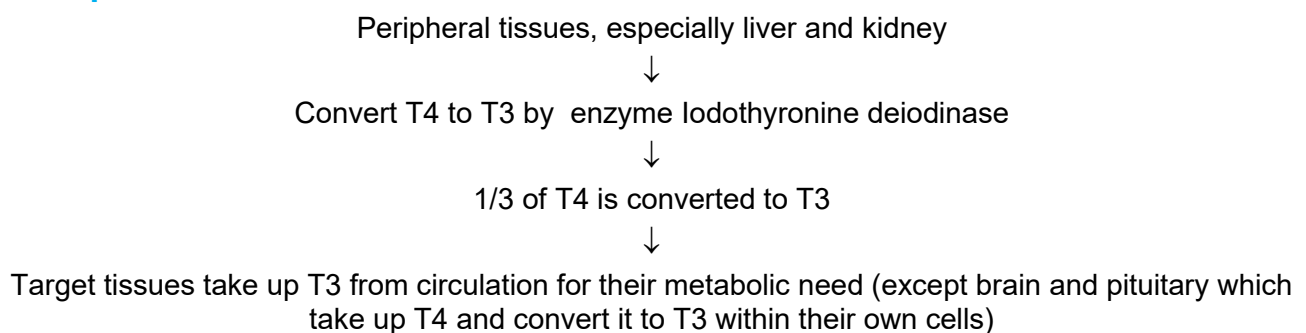
- Pairs of iodinated tyrosine residues couple together to form  $T_3$  and  $T_4$ .
- Catalysed by same membrane bound thyroid peroxidase.
  - **DIT + MIT =  $T_3$**
  - **DIT + DIT =  $T_4$**
- Normally more  $T_4$  is formed than  $T_3$
- Oxidation and coupling are stimulated by TSH



#### 4. Storage and release



#### 5. Peripheral conversion of T<sub>4</sub> to T<sub>3</sub>



#### Remember

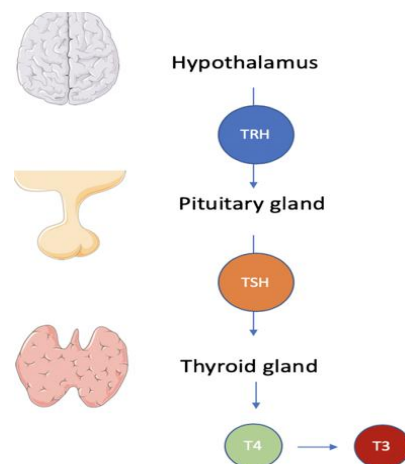
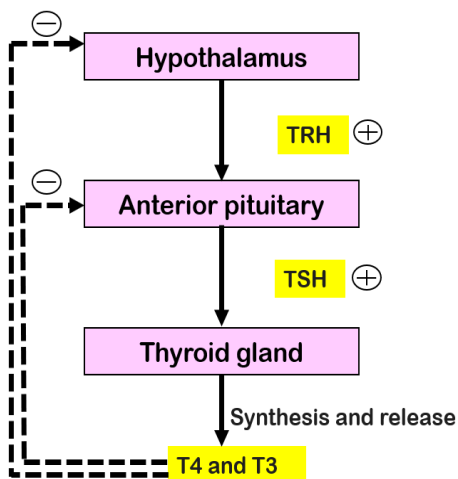
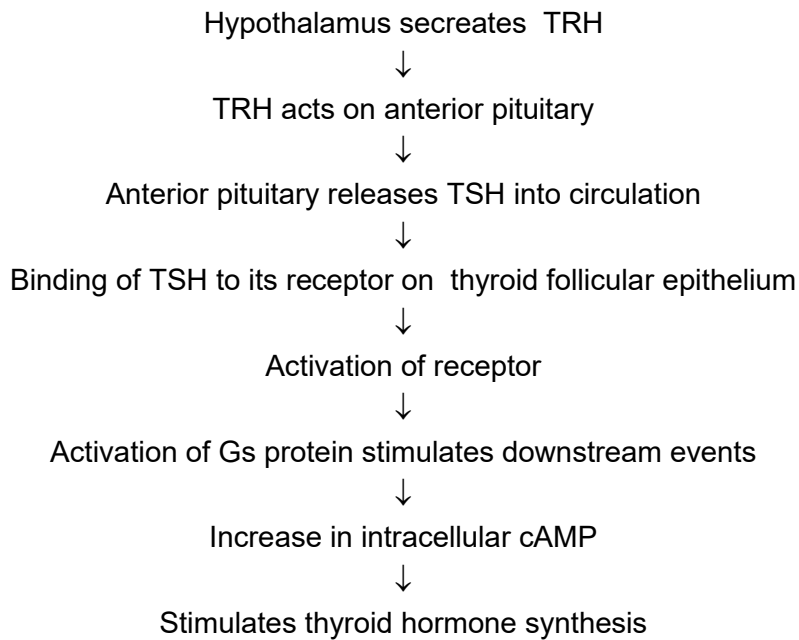
- T<sub>4</sub> has been called the prohormone of T<sub>3</sub>
- Most of the T<sub>4</sub> secreted by the thyroid is converted in the liver, kidney and pituitary to T<sub>3</sub> by the action of deiodinase → T<sub>3</sub> is considered the principal thyroid hormone which finally mediates the metabolic

| T3 (Triiodothyronine)                       | T4 (Thyroxine)                              |
|---------------------------------------------|---------------------------------------------|
| Formed by DIT + MIT = T3                    | Formed by DIT + DIT = T4                    |
| Relatively rapid onset of action            | Slower onset of action                      |
| Short duration of action (half-life: 1 day) | Long duration of action (half-life: 7 days) |
| More potent than T4                         | Less potent                                 |
| Useful to treat myxoedema coma              | Used for regular treatment of myxoedema     |

### Summary

- **T3** → Active hormone
- **T4** → Transport form

### Regulation of Secretion



- **Negative feedback** → by thyroid hormones is exercised directly on pituitary as well as through hypothalamus

## THYROID HORMONE

| Thyroid Hormone |  |
|-----------------|--|
| Classification  |  |
| MOA             |  |
| Actions         |  |
| Uses            |  |

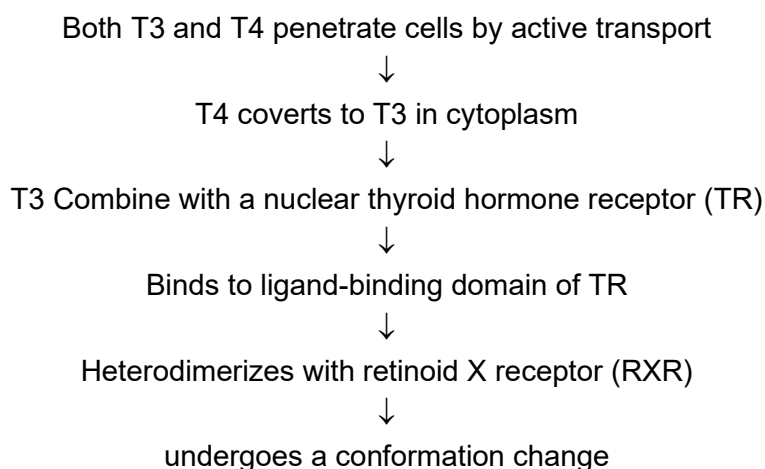
### Classification

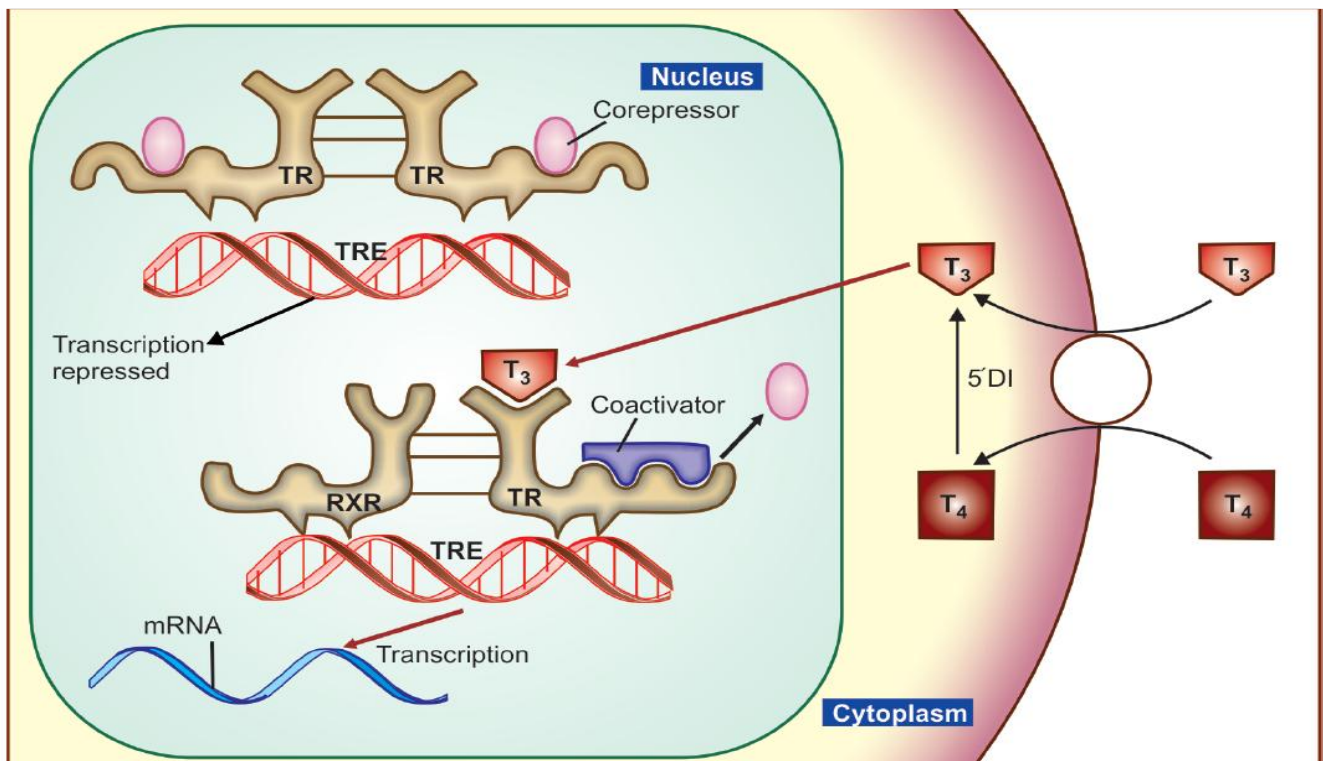
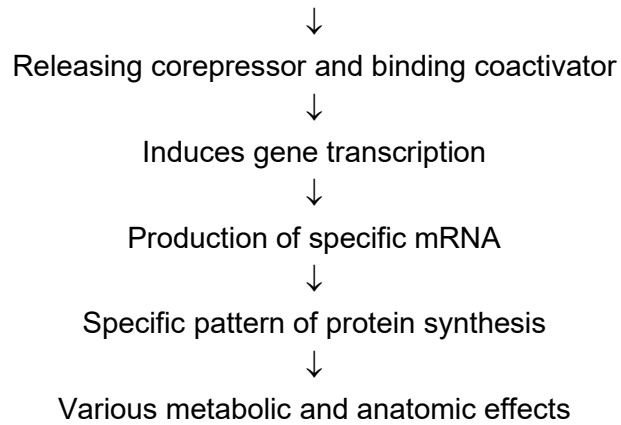
|                                                       |
|-------------------------------------------------------|
| Thyroid hormone                                       |
| Thyroxine (T4)<br>Triiodothyronine (T3, Liothyronine) |

| Liothyronine (T3)                                     | L-Thyroxine (T4)                               |
|-------------------------------------------------------|------------------------------------------------|
| More potent                                           | Less potent                                    |
| More active thyroid hormone.                          | Main circulating thyroid hormone.              |
| Short acting                                          | Long acting                                    |
| Beneficial in emergency situations like myxedema coma | Preferred for long term use in hypothyroidism. |

### MOA

- Both T3 and T4 produce majority of their actions by combining with a nuclear thyroid hormone receptor (TR) which belongs to superfamily of intracellular receptors





## Actions of thyroid hormone

1. Growth and development
2. Intermediary metabolism and BMR
3. Calorigenesis
4. CVS
5. Nervous system
6. Skeletal muscle
7. GIT
8. Kidney
9. Haemopoiesis
10. Reproduction

## 1. Growth and development

T4 and T3 → essential for normal growth and development.



Congenital deficiency of T4 and T3



Greatest effect on nervous system



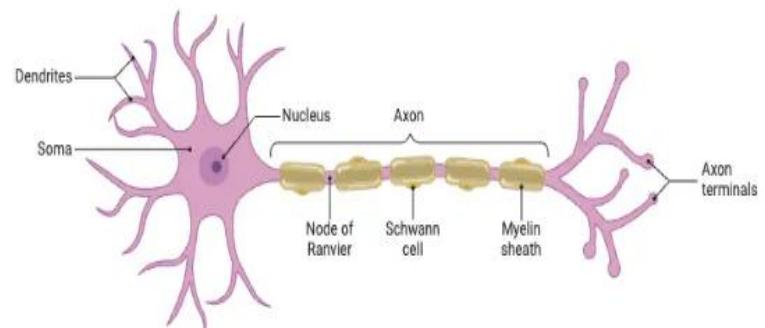
Paucity of axonal and dendritic ramification, synapse formation and impaired myelination



**Retardation and nervous deficit**



**Milestones of development delayed**



## 2. Intermediary metabolism and BMR

T3



Stimulation of cellular metabolism



Catabolic effect on lipid, carbohydrate and protein metabolism



**Increase BMR**



## 3. Calorigenesis

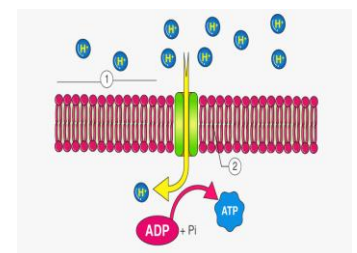
T3 and T4



Uncoupling of oxidative phosphorylation

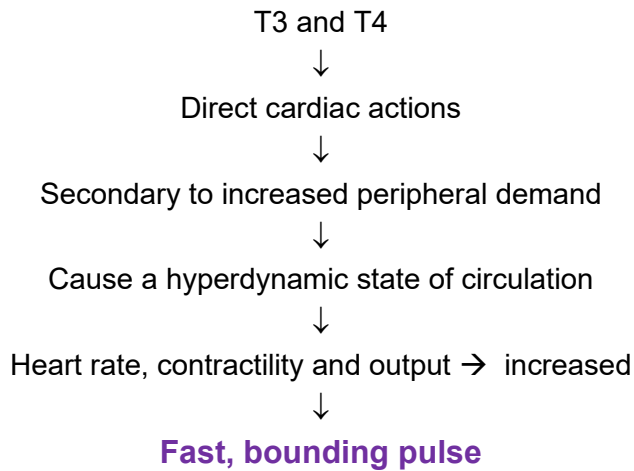


Excess energy being released as heat



**Important for maintaining body temperature**

#### 4. CVS



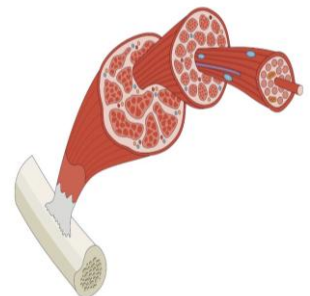
#### 5. Nervous system

- T3 and T4  
↓  
Profound functional effect on CNS
- **Cretinism** → Mental retardation
  - **Hyperthyroid individuals** → anxious, nervous, excitable, exhibit tremors and hyperreflexia



#### 6. Skeletal muscle

- **Myxoedema** → Muscles are flabby and weak
- **Thyrotoxicosis** → Increased muscle tone, tremor and weakness due to myopathy



#### 7. GIT

- T3 and T4  
↓  
Propulsive activity of gut is increased
- **Hypothyroid patients** → constipated
  - **Hyperthyroidism** → Diarrhoea

#### 8. Kidney

T3 and T4  
↓  
Increase rate of urine flow in hypothyroidism  
Do not cause diuresis in euthyroid individuals

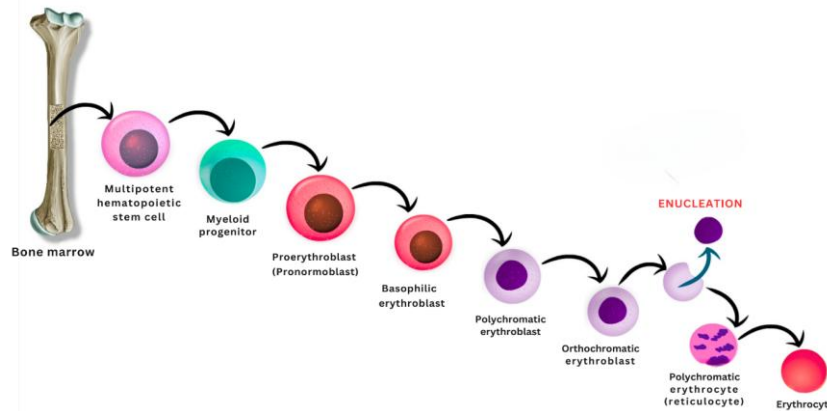




## 9. Haemopoiesis

T4  
↓  
Facilitatory to erythropoiesis

Hypothyroid patients → Anemia



## 10. Reproduction

Thyroid  
↓  
Indirect effect on reproduction  
↓

Required for maintenance of pregnancy and lactation

- Hypothyroidism →
  - Fertility is impaired
  - Women suffer from oligomenorrhoea

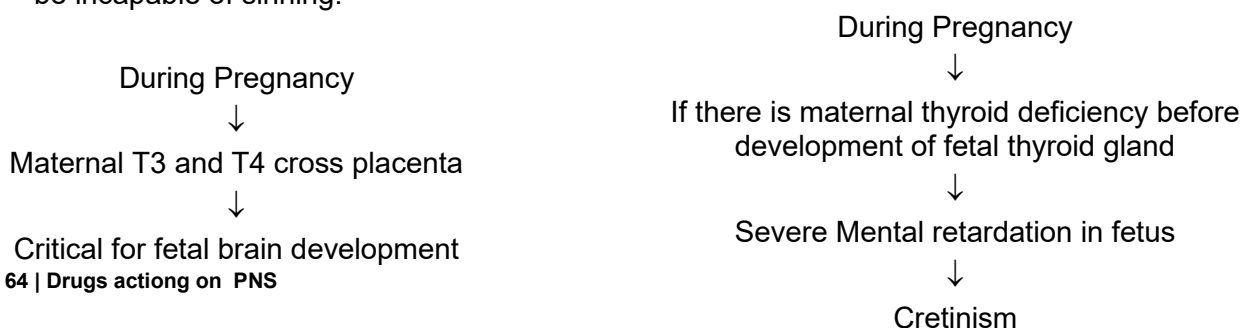


## Uses

1. Hypothyroidism of infancy or early childhood → Cretinism
2. Adult hypothyroidism → Myxoedema
3. Myxoedema coma
4. Goiter → Diffuse and nodular
5. Papillary carcinoma of thyroid

### 1. Cretinism

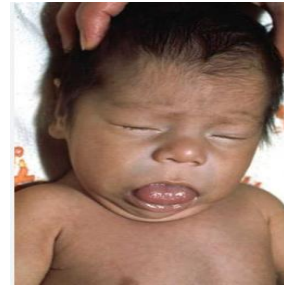
- **Cretinism** → hypothyroidism that develops in infancy or early childhood.
- Term cretin was derived from the French chrétien, meaning "Christian" or Christlike," and was applied to these unfortunates because they were considered to be so mentally retarded as to be incapable of sinning.





### Clinical features

- Severe mental retardation
- Puffy face
- Short stature
- Coarse facial features
- Protruding tongue
- Umbilical hernia



### Treatment

Thyroxine (8–12 µg/kg) daily



Should be started as early as possible



Response is dramatic



Physical growth and development → restored

Mental retardation that has already ensued → only partially reversible and further mental retardation is prevented

## 2. Myxedema

- **Myxedema** → hypothyroidism developing in older child or adult.

### Clinical features

- Slowing of physical and mental activity.
- Generalized fatigue, apathy, and mental sluggishness → mimic depression.
- Speech and intellectual functions are slowed.
- Frequently overweight.
- Decreased sympathetic activity → constipation and decreased sweating.
- Skin is cool and pale because of decreased blood flow.
- Cold intolerant
- Reduced cardiac output → shortness of breath and decreased exercise capacity
- Accumulation of matrix substances → Glycosaminoglycans and hyaluronic acid, in skin, subcutaneous tissue → nonpitting edema



### Treatment

- Start Thyroxine with a low dose → 50 µg daily and increase every 2–3 weeks to an optimum of 100–200 µg/day

### 3. Myxoedema coma

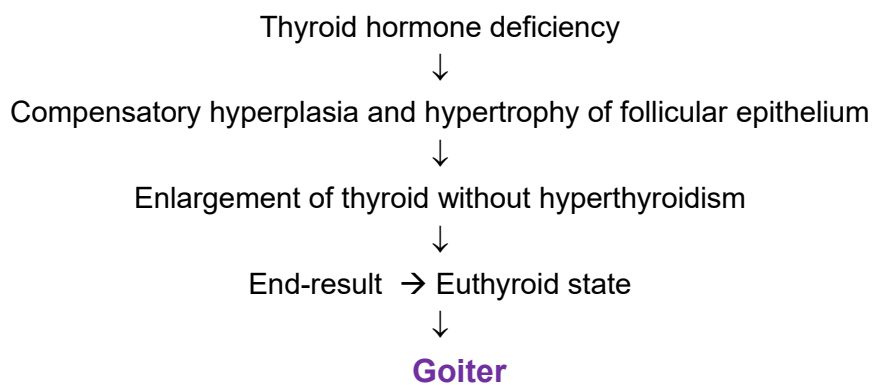
- It is an emergency
- Characterized by progressive mental deterioration due to acute hypothyroidism
- carries significant mortality.
- Rapid thyroid replacement is crucial.



#### Treatment

- DOC → L-thyroxine (T<sub>4</sub>) 200–500 µg i.v. followed by 100 µg i.v. OD till oral therapy can be instituted.

### 4. Goitre

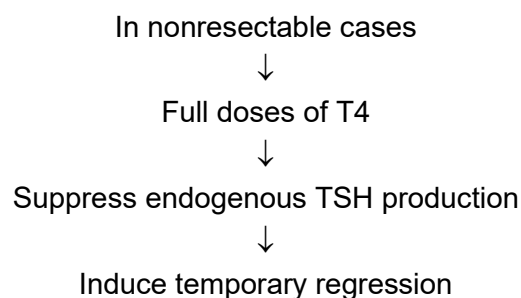
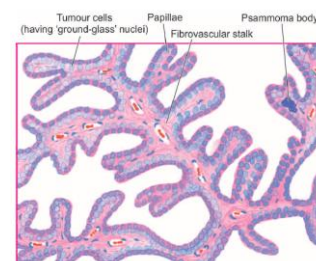


#### Treatment

- Treatment with T<sub>4</sub> despite no overt hypothyroidism
- Thyroxine therapy may be withdrawn after a year or so in some cases if adequate iodine intake is ensured.

### 5. Papillary carcinoma of thyroid

- TOC is surgery
- This type of cancer is often responsive to TSH.

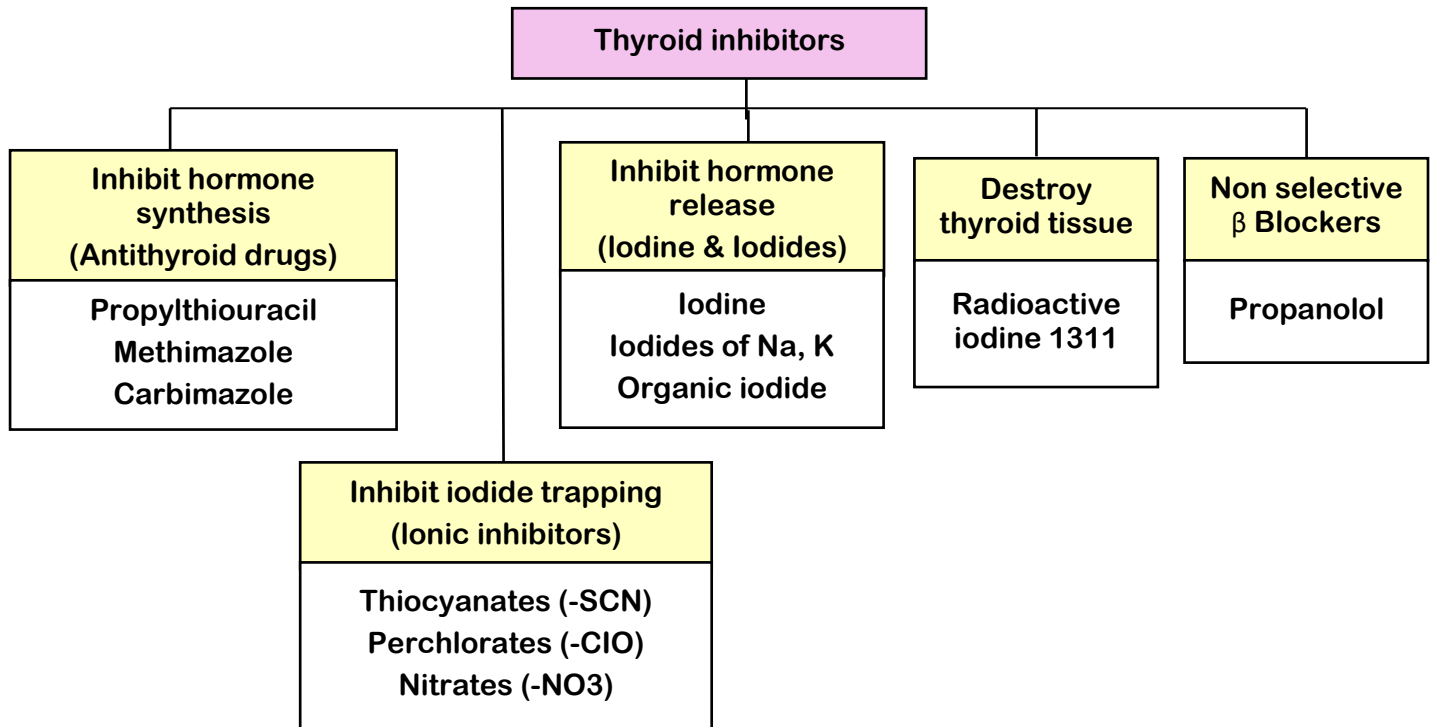


# THYROID INHIBITORS

## Introduction

- Drugs used to lower the functional capacity of hyperactive thyroid gland → Thyrotoxicosis

## Classification



| Thyroid Inhibitors |                                     |                     |                  |                    |                  |
|--------------------|-------------------------------------|---------------------|------------------|--------------------|------------------|
|                    | Thioamides/<br>Antithyroid<br>drugs | Ionic<br>Inhibitors | Iodine & Iodides | Radioactive Iodine | Beta<br>Blockers |
| Drugs              |                                     |                     |                  |                    |                  |
| MOA                |                                     |                     |                  |                    |                  |
| Uses               |                                     |                     |                  |                    |                  |
| Adverse<br>effects |                                     |                     |                  |                    |                  |

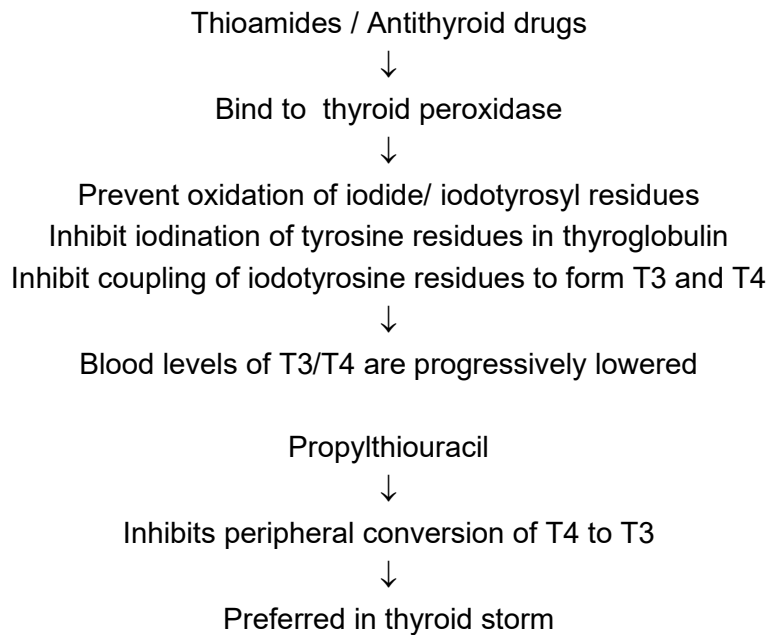
## THIOAMIDES/ANTITHYROID DRUGS

### Drugs

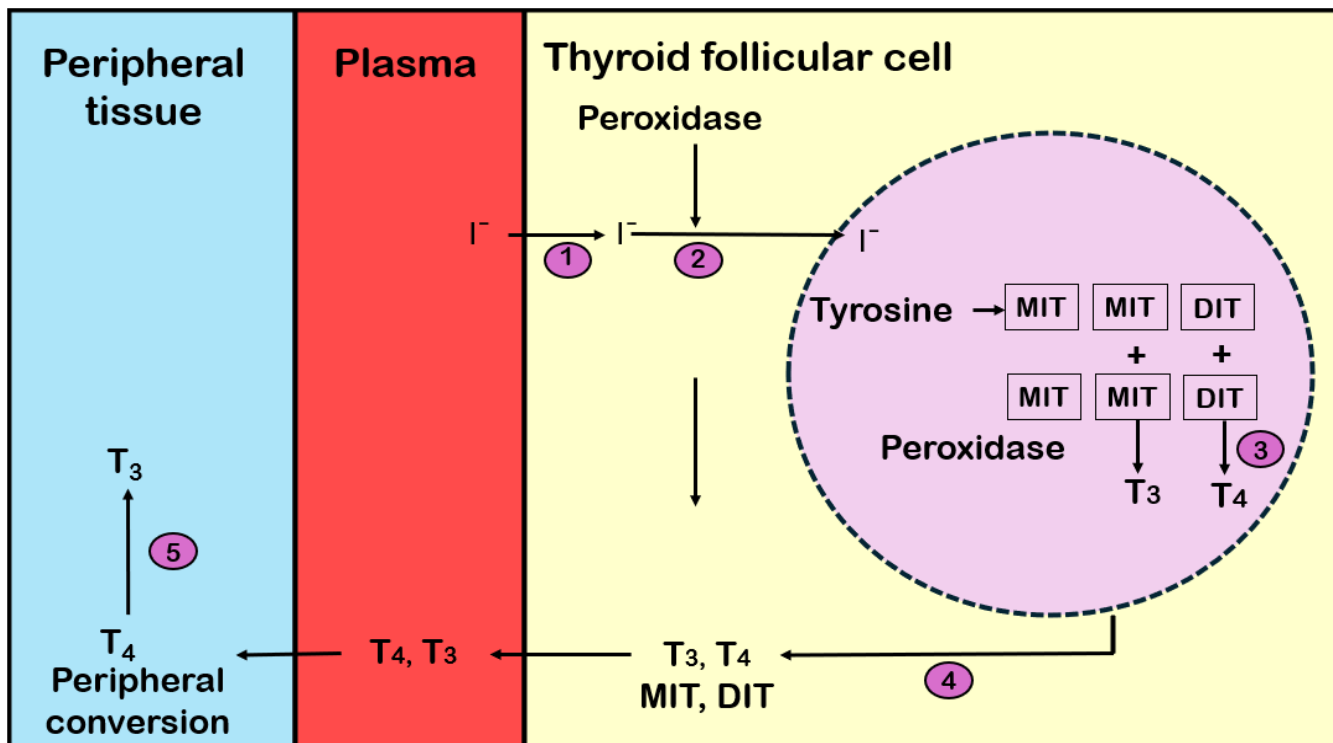
| Inhibit hormone synthesis<br>(Antithyroid drugs) |
|--------------------------------------------------|
| Propylthiouracil<br>Methimazole<br>Carbimazole   |

## MOA

- 2 MOA



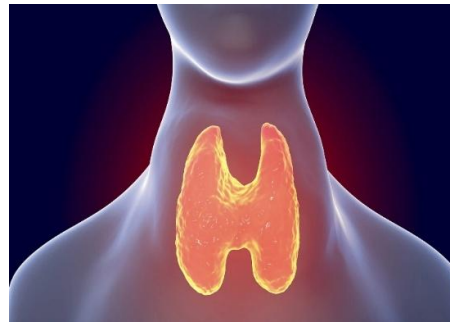
- Carbimazol and methimazole do not



| Propylthiouracil                           | Carbimazole                                   |
|--------------------------------------------|-----------------------------------------------|
| Less potent                                | More potent                                   |
| Highly bound to plasma proteins            | Less protein bound                            |
| Has short duration of action (4-8 hours)   | Has longer duration of action (12-24 hours)   |
| Inhibits peripheral conversion of T4 to T3 | Negligible action                             |
| No active metabolite                       | Gets converted to methimazole which is active |
| Passage across placenta is low             | Passage across placenta is low                |
| Levels in breast milk are low              | Levels in breast milk are low                 |

## Uses

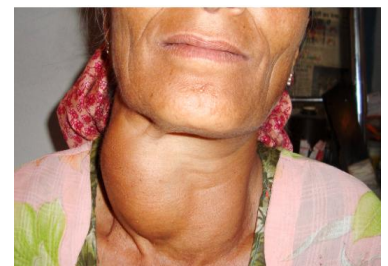
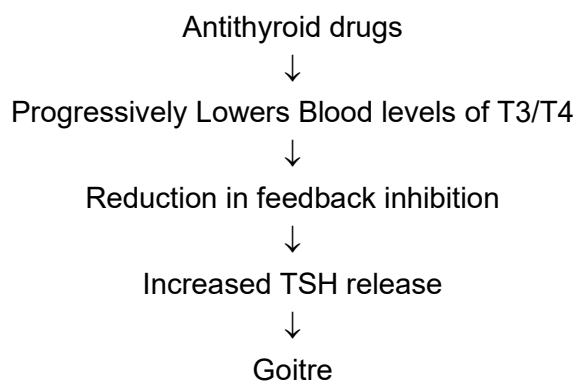
1. For control of thyrotoxicosis in patients with Graves' disease and toxic nodular goiter.
2. Propylthiouracil is DOC for hyperthyroidism in first trimester pregnancy and lactation (For all other patients, methimazole is preferred)
3. Used in young patients before performing thyroidectomy.
4. To make the patient euthyroid before application of radioactive iodine.



## Adverse effects

1. Goitre
2. Others

### 1. Goitre



- No goiter occurs if antithyroid drugs are given to hypophysectomised animals

## 2. Others

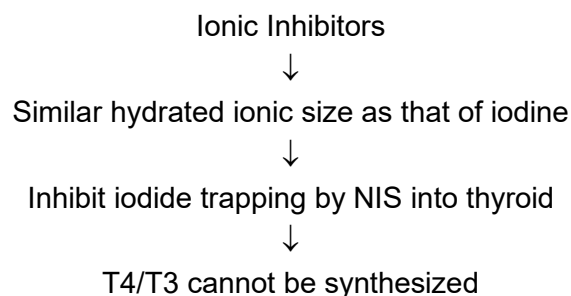
1. GIT intolerance
2. Maculopapular pruritic (most common)
3. Joint pain
4. Loss or graying of hair
5. Loss of taste
6. Liver damage
7. Agranulocytosis (most serious)

## IONIC INHIBITORS

### Drugs

|                                                                            |
|----------------------------------------------------------------------------|
| Inhibit iodide trapping<br>(Ionic inhibitors)                              |
| Thiocyanates (-SCN)<br>Perchlorates (-ClO)<br>Nitrates (-NO <sub>3</sub> ) |

### MOA



- Perchlorate is 10 times more potent than thiocyanate in blocking NIS, while nitrate is very weak

### Uses

- They are toxic and not clinically used now.

### Adverse effects

- **Thiocyanates** → liver, kidney, bone marrow and brain toxicity.
- **Perchlorates** → rashes, fever, aplastic anaemia, agranulocytosis.

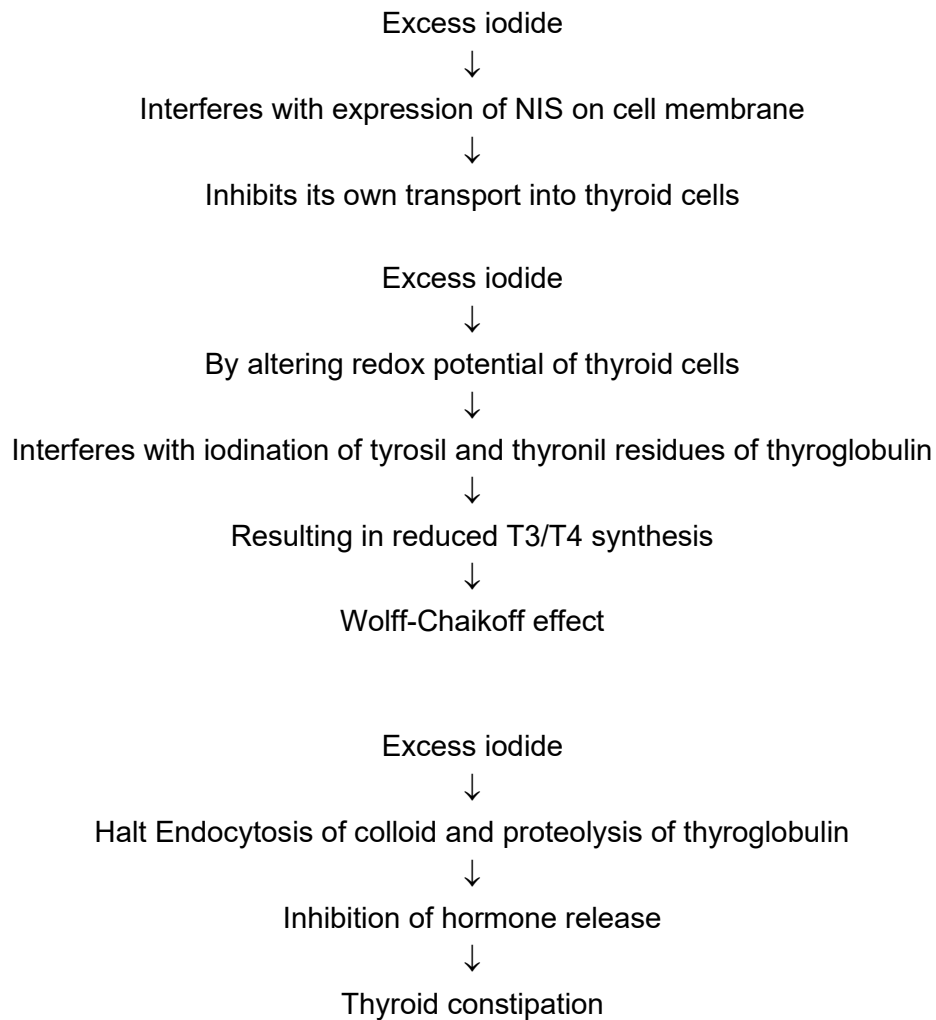
## IODINE & IODIDES

### Drugs

|                                               |
|-----------------------------------------------|
| Inhibit hormone release<br>(Iodine & Iodides) |
| Iodine<br>Iodides of Na, K<br>Organic iodide  |

**MOA**

- Though iodine is a constituent of thyroid hormones → it is the fastest acting thyroid inhibitor.
- 3 MOA

**Uses**

1. Preoperative preparation for thyroidectomy in Graves' disease
2. Thyroid storm
3. Antiseptic

**Adverse effects**

1. Acute reaction
2. Chronic overdose (iodism)
3. Goitre
4. Contraindicated in pregnancy

**1. Acute reaction**

- Occurs only in individuals sensitive to iodine
- Manifestations →
  - Swelling of lips

- Swelling of eyelids
- Angioedema of larynx (dangerous)
- Fever
- Joint pain
- Thrombocytopenia → Petechial haemorrhages
- Lymphadenopathy

## 2. Chronic overdose (iodism)

- Inflammation of mucous membranes
- Salivation
- Rhinorrhoea, sneezing, lacrimation
- Swelling of eyelids
- Burning sensation in mouth
- Headache
- Rashes



## 3. Goitre

Long-term use of high doses  
↓  
Cause hypothyroidism  
↓  
Goiter



## 4 Contraindicated in pregnancy

Given to pregnant or nursing mothers  
↓  
Foetal / infantile goiter and hypothyroidism



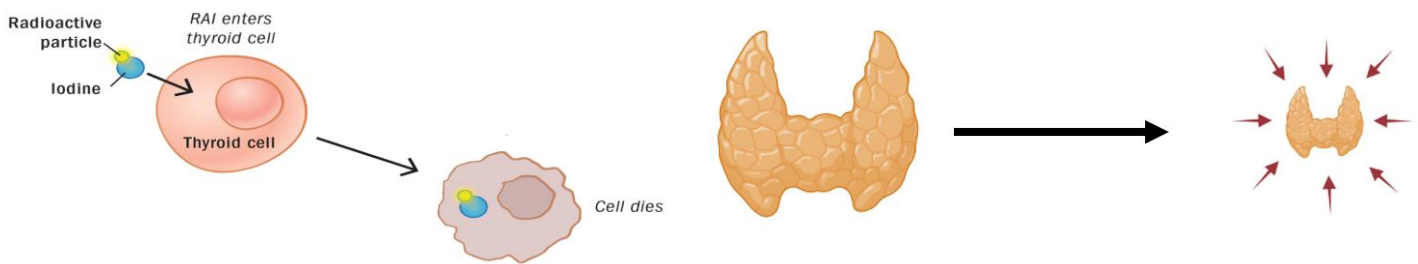
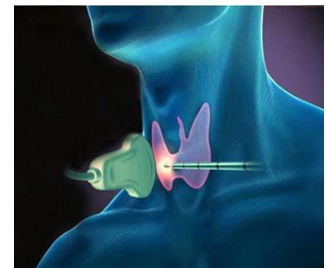
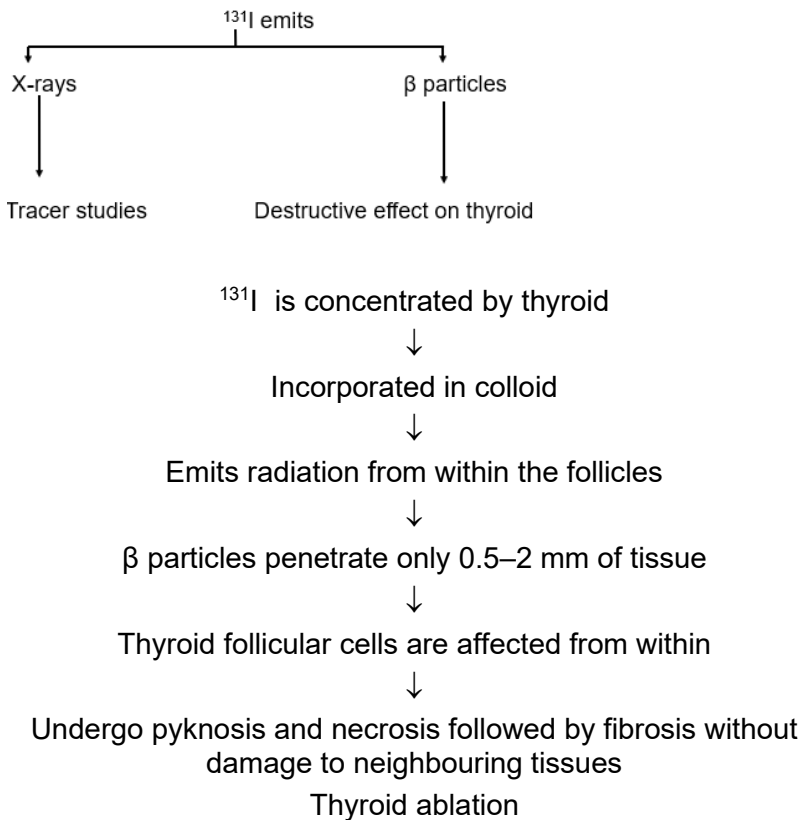
# RADIOACTIVE IODINE

## Drugs

- Stable isotope of iodine →  $I_{127}$
- Its radioactive isotope of medicinal importance is:  $I_{131}$
- Its physical half-life 8 days.
  1.  $I_{131}$  (half life - 8 days most commonly used.
  2.  $I_{123}$  (half life - 13 hours)
  3.  $I_{125}$  (half life - 60 days)
- Radioactive iodine is administered as sodium salt of  $I^{131}$  dissolved in water and taken orally



## MOA

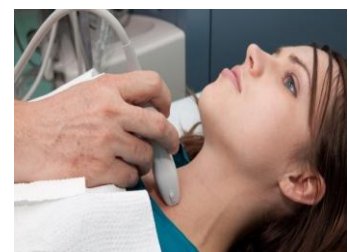


## Uses

- **Most common indication** → hyperthyroidism due to Graves' disease or toxic nodular goiter.
- **Average therapeutic dose** → 3–6 m curie → calculated on basis of previous tracer studies and thyroid size
- **Response is slow** → starts after 2 weeks and gradually increases, reaching peak at 3 months or so.

## Advantages

1. Treatment with  $^{131}\text{I}$  is simple, conveniently given on outpatient basis and inexpensive.
2. No surgical risk, scar or injury to parathyroid glands/recurrent laryngeal nerves.
3. Once hyperthyroidism is controlled, cure is permanent.



## Adverse effects

1. **Hypothyroidism** → About 5–10% patients of Graves' disease treated with  $^{131}\text{I}$
2. **Contraindicated during pregnancy** → foetal thyroid will also be destroyed → cretinism

## BETA BLOCKERS

### Drugs

- Propranolol
- Other Nonselective  $\beta$  blockers

### MOA

Nonselective  $\beta$  blockers (Propranolol)



Block sympathetic overactivity



Rapidly alleviate manifestations of thyrotoxicosis that are due to sympathetic overactivity, viz. palpitation, tremor, nervousness, severe myopathy, sweating



### Uses

1. While waiting response to carbimazole or  $^{131}\text{I}$ .
2. Along with iodide for preoperative preparation before subtotal thyroidectomy.
3. Thyroid storm (thyrotoxic crisis)

## ESTEROGEN AND RELATED DRUGS

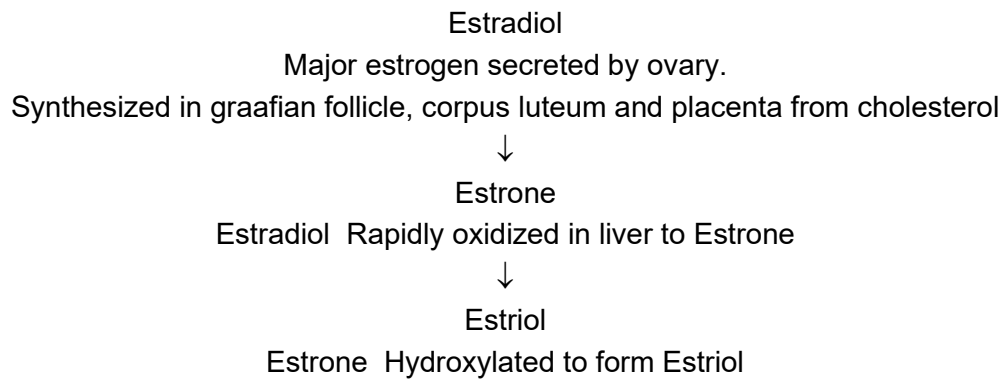
| Estrogen and Related Drugs |           |               |       |                      |
|----------------------------|-----------|---------------|-------|----------------------|
|                            | Estrogens | Antiestrogens | SERMS | Aromatase Inhibitors |
| Introduction               |           |               |       |                      |
| Classification             |           |               |       |                      |
| MOA                        |           |               |       |                      |
| Actions                    |           |               |       |                      |
| Uses                       |           |               |       |                      |
| Adverse effects            |           |               |       |                      |

# ESTROGENS

## Introduction

- Estrogens are endogenous sex hormones with major influence in females

## Forms



## Mnemonic → Estrogen forms

- Reproductive age** → Estradiol (husband and wife)
- Pregnancy** → Estradiol (husband, wife and baby)
- Postmenopause** → Estrone (only old lady left, husband died, baby married)

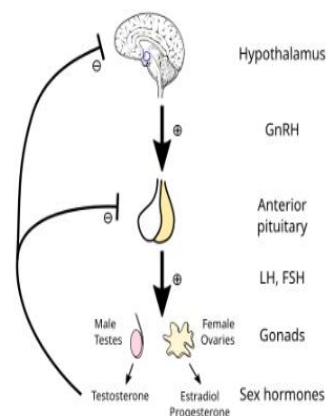
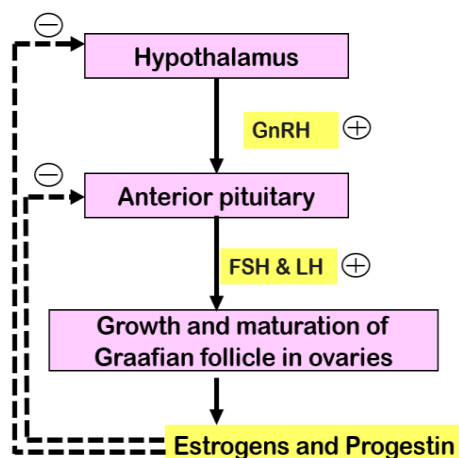


## Remember

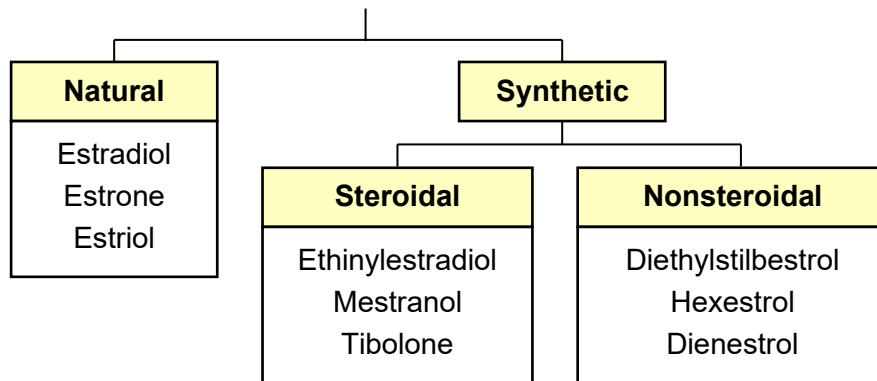
- Small quantity (2–20 µg/day) of Estradiol is derived in human males also from aromatization of testosterone in the testes and extraglandular tissues.

## Secretion

- Mainly secreted from → ovaries in females and testis in males.
- Also released from → Adrenals, Placenta, Liver, Fat, Skeletal muscles and Hair follicles

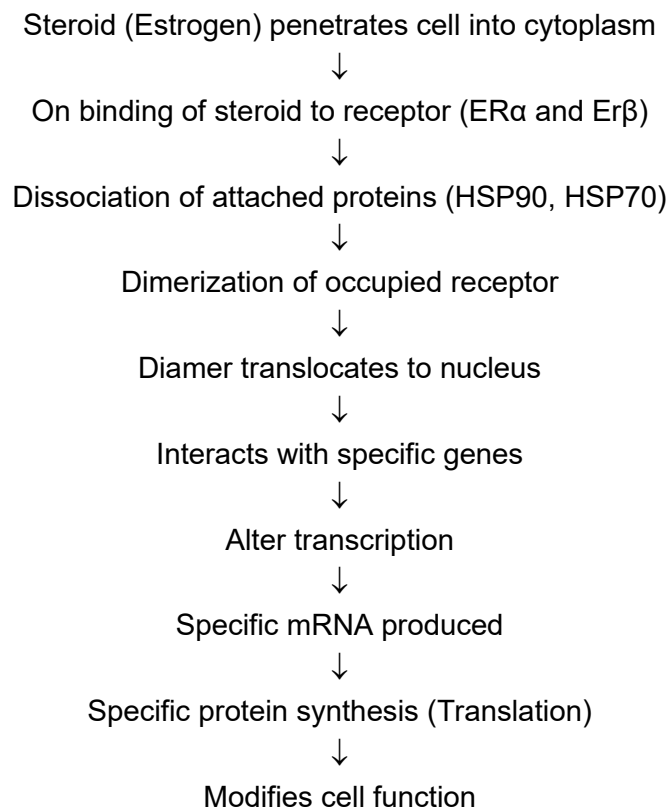


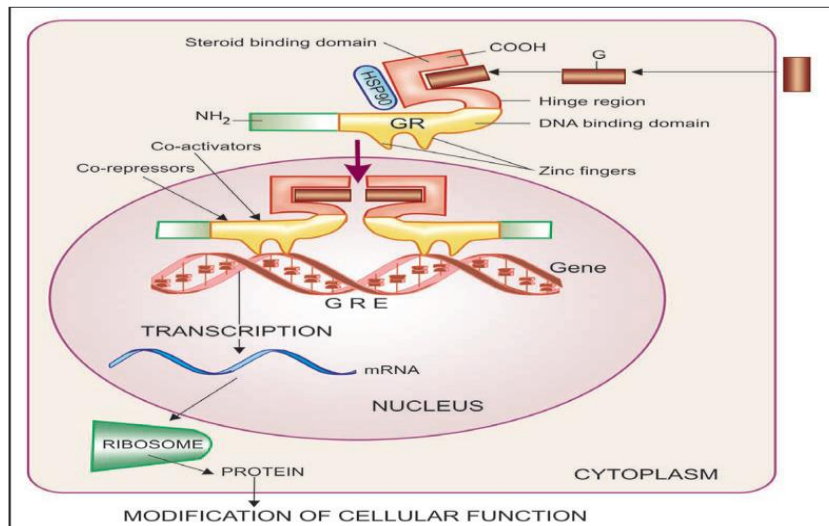
## Classification



## MOA

- Like other steroidal hormones.
- 2 types of estrogen receptors → ER $\alpha$  and ER $\beta$



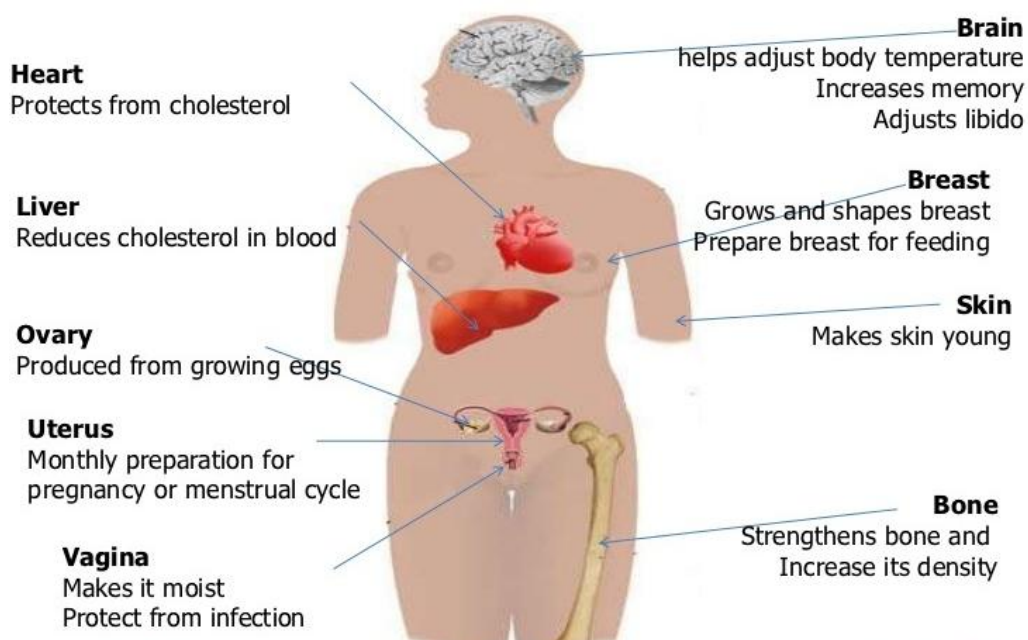
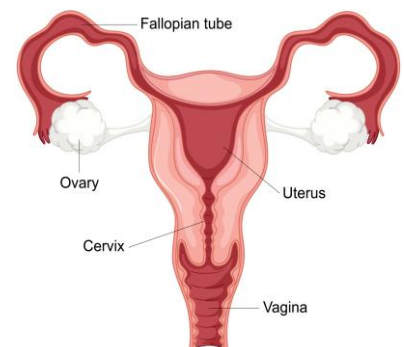


## Actions

1. Sex organs in females
2. Secondary sex characters in females
3. Skeletal growth
4. Metabolic effects

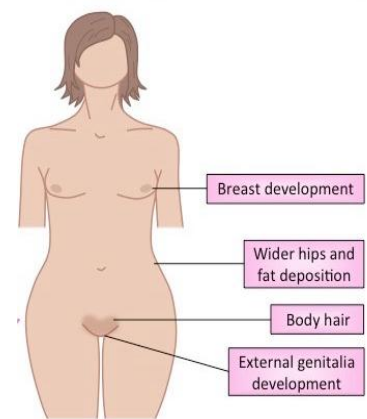
### 1. Sex organs in females

- a) Vaginal epithelium gets thickened, stratified and cornified.
- b) Proliferation of endometrium in preovulatory phase, and it is only in concert with estrogens that progesterone brings about secretory changes.
- c) Estrogens augment rhythmic contractions of fallopian tubes and uterus, and induce a watery alkaline secretion from cervix → favourable to sperm penetration.
- d) Sensitize uterus to oxytocin.



## 2. Secondary sex characters in females

- Estrogens produced at puberty cause growth of breasts → proliferation of ducts and stroma, accumulation of fat.
- Pubic and axillary hair appear
- Feminine Body contours and behaviour



## 3. Skeletal growth

- Promote skeletal growth
- Accelerate epiphyseal closures.

## 4. Metabolic effects

(a) **Weak anabolic effect** → retention of nitrogen and protein synthesis.

(b) **Lipid profile**→

- Increase in HDL
- Reduction in LDL.
- Raised HDL : LDL ratio is probably responsible for rarity of atherosclerosis in premenopausal women.

(c) **Bone**→

- Reduce number and activity of osteoclasts
- Enhance synthesis of osteoblasts
- Positive effect on bone mass.



## Mnemonic

### OESTROGEN SUX

**O**rgan development (sex organs)  
**E**ndocrine: FSH and LH regulation  
**S**econdary sex characteristics development  
**T**ropic for pregnancy  
**R**eceptor synthesis (of progesterone, oestrogen, LH)  
**O**steoporosis decrease (inhibits bone reabsorption)  
**G**ranulosa cell development  
**E**ndocrine: increases prolactin secretion, but then blocks its effect  
**N**ipple development  
**S**ex drive increase  
**U**terine contractility increase  
**O**Xytocin sensitivity increase

## Uses

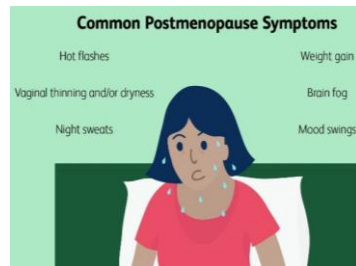
1. Post menopausal → Hormone Replacement Therapy (HRT)
2. To avoid undesired pregnancy as oral contraceptive
3. Replacement therapy in hypo-ovarian conditions
4. Menstrual disorders
5. Testosterone dependent carcinoma prostate
6. Osteoporosis



7. Acne
8. Hirsutism
9. PCOD

## 1. Post menopausal → Hormone Replacement Therapy (HRT)

- Reduction in estrogen secretion at menopause is responsible for so many problems.
- So HRT is given



### Benefits of HRT

#### (a) Prevention of bone loss

- Prevents bone resorption, reduces thinning and weakening of bones and risk of fracture.
- Calcium, vitamin D and weight bearing exercises support effects.
- Treatment needs early start with in 2-3 years.

#### (b) Prevention of vasomotor symptoms

- Estrogen reestablishes feedback on hypothalamic control of noradrenaline secretion.

#### (c) Protection against CVS complications

- Protection against CVS complications by reducing LDL and increasing HDL.

#### (d) Reversal of menopausal changes

- Reversal of menopausal changes on urogenital tract like dryness and itching of vagina, dyspareunia (pain during intercourse), pain during urination and urinary incontinence.

#### (e) Reduction of postmenopausal sleep disturbances.

#### (f) Neuroprotective effects → delay onset of Alzheimer's disease.

#### (g) Improvement in feeling of wellbeing

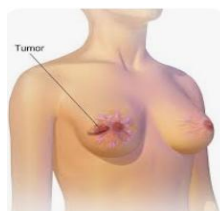
### Harmful effects of HRT

#### (a) Increase in risk of endometrial carcinoma

- Increase in risk of endometrial carcinoma due to continuous stimulation of endometrial hyperplasia.
- Therefore in patients, not undergone hysterectomy, progestin is combined.
- If uterus has already been removed estrogen alone is preferred since progestin unfavorably alter HDL/LDL ratio.

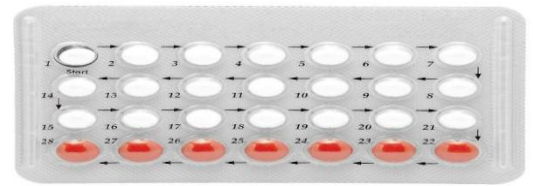
#### (b) Increase risk of breast cancer → progestin further increases the risk

#### (c) Gallstones formation



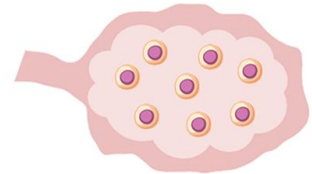
## 2. To avoid undesired pregnancy as oral contraceptive

- To avoid undesired pregnancy as oral contraceptive



## 3. Replacement therapy in hypo-ovarian conditions

- To mimic the natural cyclic pattern estrogen-progestin combination is used for 21 days and then progestin for 7-10 days.



## 4. Menstrual disorders:

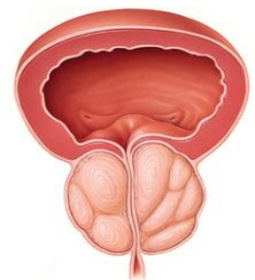
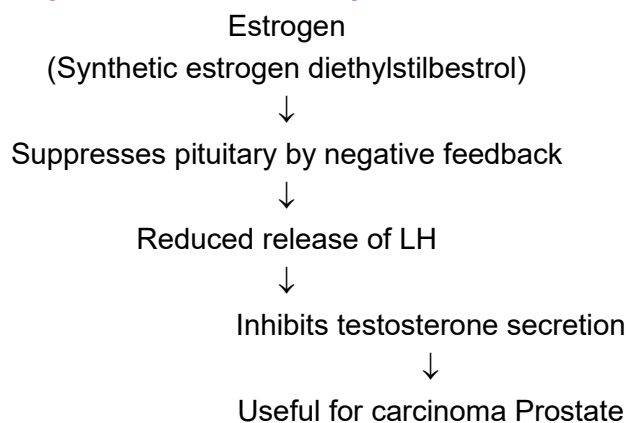
(a) **Amenorrhea** → if cause is failure of hormone production.

(b) **DUB** → a cyclical combination of estrogen and progestin, or a progestin alone. Danazol may also be effective.

(c) **Dysmenorrhea** → by suppressing ovulation in ovulatory cycles

(d) **Temporary regulation of menses**

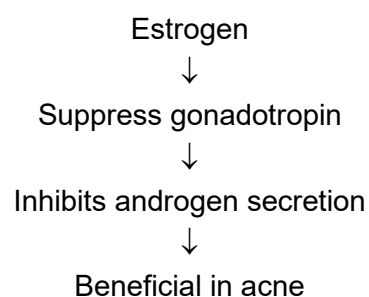
## 5. Testosterone dependent carcinoma prostate



## 6. Osteoporosis



## 7. Acne





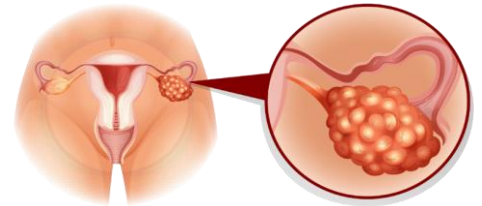
## 8. Hirsutism

- By inhibiting androgens.



## 9. Polycystic ovarian syndrome (PCOS)

- Syndrome of anovulation, increased androgens and hirsutism.
- There's an increase in LH that stimulates thecal cells to produce androgens.

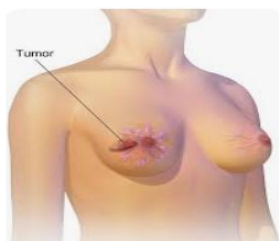


## Adverse Effects

1. Suppression of libido
2. Gynaecomastia and feminization when given to males.
3. Fusion of epiphyses and reduction of adult stature when given to children.



4. In postmenopausal women → estrogens can increase risk of endometrial carcinoma (5–15 fold). A progestin given concurrently blocks risk.
5. Estrogens can accelerate the growth of existing breast cancer, but low-dose estrogen only HRT does not appear to increase the risk of developing new breast cancer
6. Long-term estrogen therapy doubles the incidence of gallstones and Benign hepatomas



7. Migraine → worsened by estrogens.



8. Epilepsy → worsened by estrogens.



9. Endometriosis → worsened by estrogens.

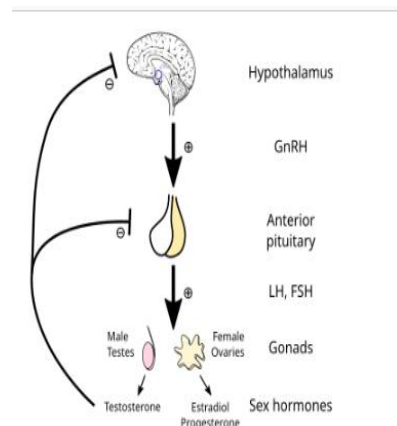
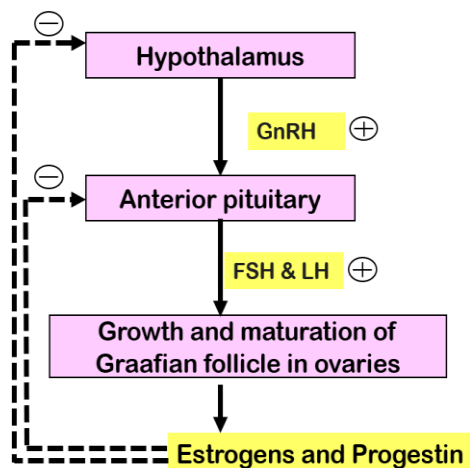
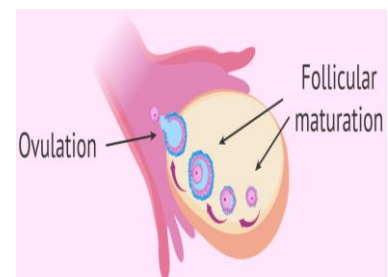
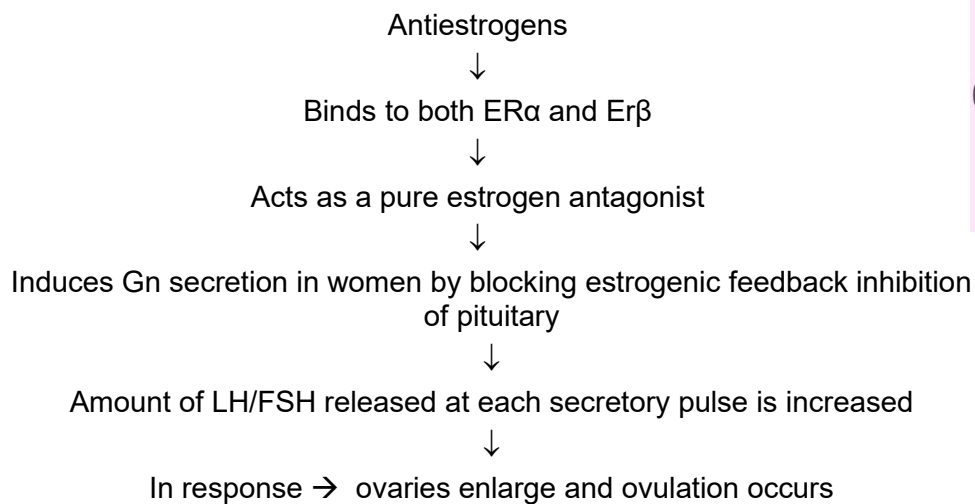


## ANTIESTROGENS

### Classification

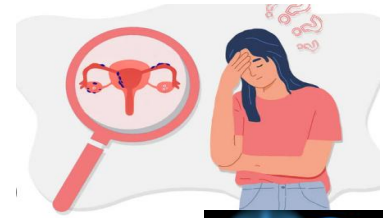
- Clomiphene citrate

### MOA



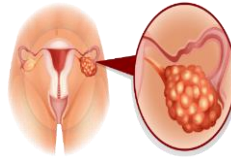
## Uses

- Infertility due to failure of ovulation: 50 mg once daily for 5 days starting from 5th day of cycle.
- Treatment is given monthly.



## Adverse effects

1. Polycystic ovaries
2. Multiple pregnancy
3. Risk of ovarian tumour increased
4. Hot flashes
5. Gastric upset



# SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

## Introduction

- They have both estrogen receptors agonistic as well as antagonistic actions

## Classification

1. Tamoxifen
2. Raloxifene

## MOA

- They have both estrogen receptors agonistic as well as antagonistic actions
  - Agonistic actions
  - Antagonistic actions

## Agonistic actions

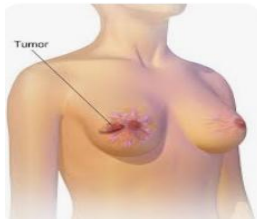
1. Improvement in lipid profile.
2. Inhibition of bone resorption.
3. High risk of thromboembolism.
4. High risk of endometrial carcinoma (with tamoxifen but not with raloxifene)

## Antagonistic actions

1. Reduced risk of Ca breast.
2. Increase in hot flashes.
3. Decrease risk of endometrial hyperplasia (only by raloxifene).

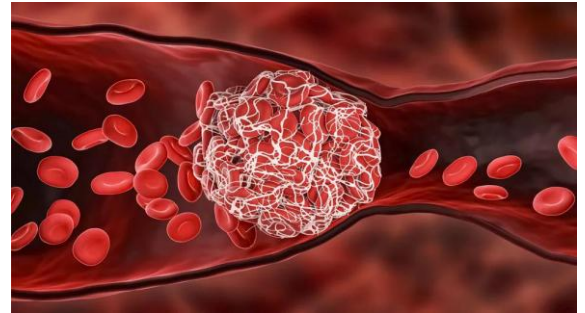
## Uses

1. **Carcinoma breast:** Tamoxifen is preferred.
2. **Osteoporosis:** Raloxifene is preferred.



## Adverse effects

1. Hot flushes
2. Vaginal bleeding
3. Vaginal discharge
4. Menstrual irregularities
5. Increased risk of venous thromboembolism is due to estrogenic action on clotting mechanism.



## AROMATASE INHIBITORS

### Classification

- Letrozole
- Anastrozole
- Exemestane

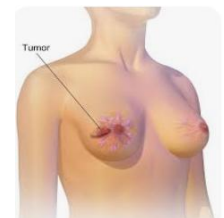
### MOA

In postmenopausal women  
↓  
Estrogen production do not occur in ovary  
↓  
Occur in peripheral tissue by Aromatization of testosterone

Aromatase Inhibitors  
↓  
Inhibits aromatization of testosterone in peripheral tissue including that within breast cancer cells  
↓  
Nearly total estrogen deprivation in postmenopausal women  
↓  
Useful in Postmenopausal Breast cancer

### Uses

- To prevent recurrence in Postmenopausal Breast cancer



## Adverse effects

- Hot flushes
- Bone loss



## PROGESTERON AND RELATED DRUGS

| Estrogen and Related Drugs |            |                |
|----------------------------|------------|----------------|
|                            | Progestins | AntiProgestins |
| Introduction               |            |                |
| Classification             |            |                |
| MOA                        |            |                |
| Actions                    |            |                |
| Uses                       |            |                |
| Adverse effects            |            |                |

### Uses

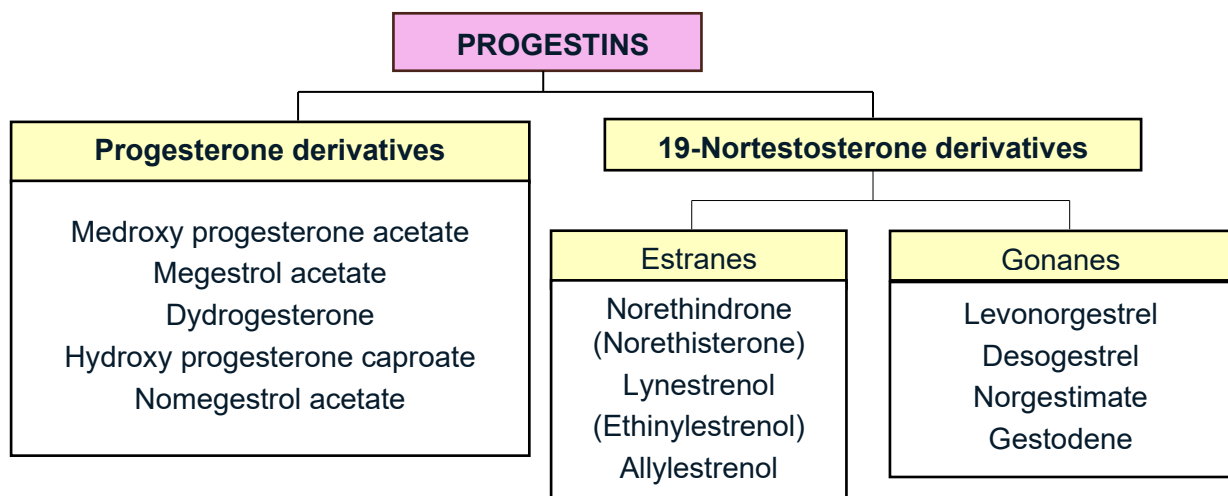
- To prevent recurrence in Postmenopausal Breast cancer

## PROGESTINS

### Introduction

- They are secreted by corpus luteum of ovary in second half of menstrual cycle and from placenta, adrenals and testes.

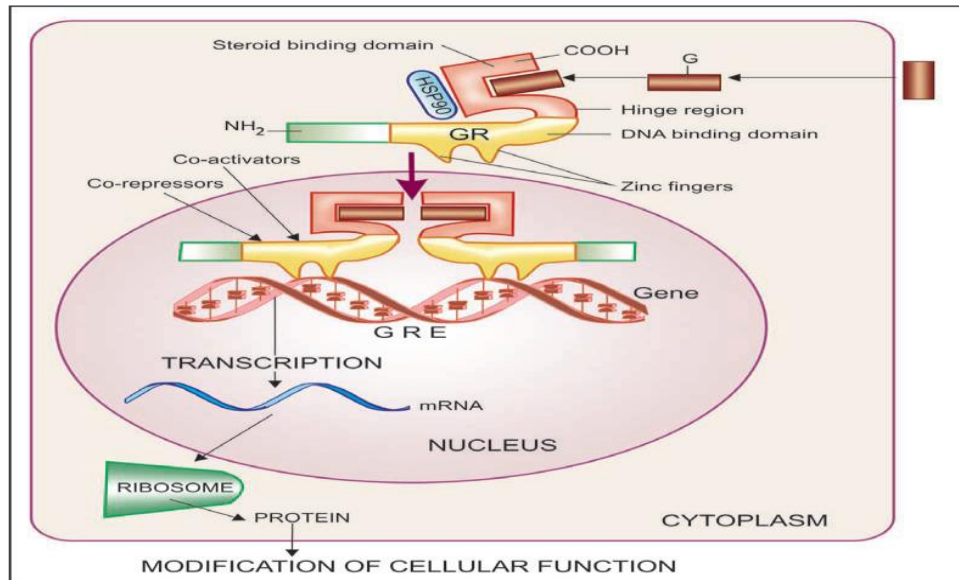
### Classification



### MOA

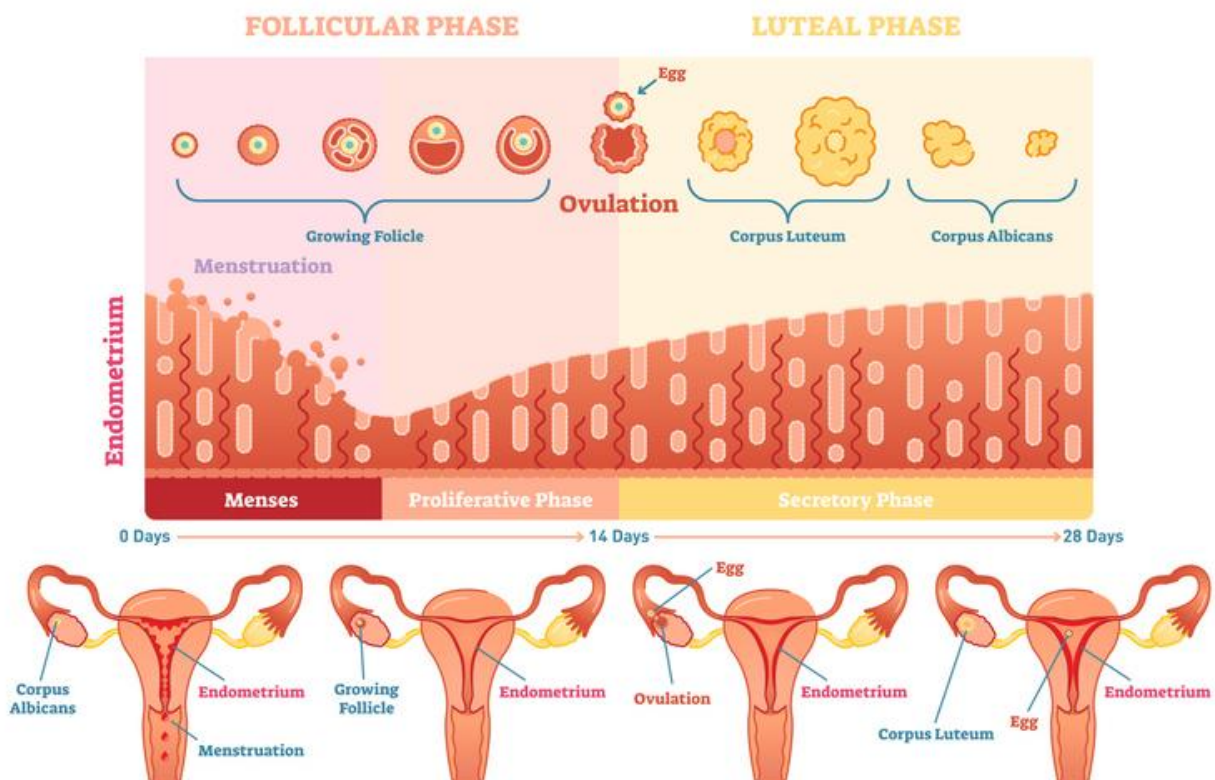
- Like other steroidal hormones.





## Actions

1. Secretory changes in endometrium are under influence of progestin → Proliferative phase is converted into secretory phase.
2. By suppressing uterine contraction and inhibition of immunological rejection it helps in implantation and maintenance of pregnancy
3. If pregnancy does not occur, the abrupt decline in concentration leads to shedding of endometrium and menses starts.



4. Stimulate scanty, viscid, secretion from endocervical gland of vagina.
5. Mid-cycle rise of basal body temperature (about 1° F) at event of ovulation.
6. Higher levels in second half of menstrual cycle (luteal phase) inhibit gonadotropin so there is inhibition of further ovulation.



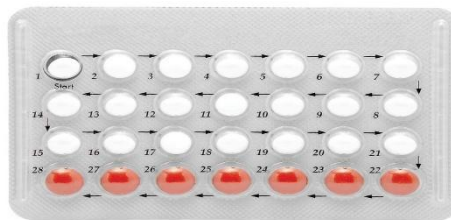
## Mnemonic

### PROGESTE

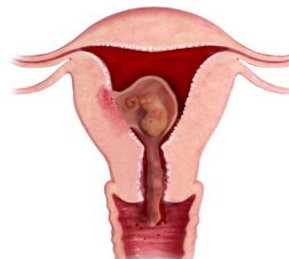
- **P**roduce cervical mucous
- **R**elax uterine smooth muscle
- **O**xytocin sensitivity down
- **G**onadotropin [FSH, LH] secretions down
- **E**ndometrial spiral arteries and secretions up
- **S**ustain pregnancy
- **T**emperature up
- **E**xcitability of myometrium down

## Uses

1. As HRT
2. As oral contraceptive
3. Menstrual disorders → amenorrhea, DUB, dysmenorrhea



4. Endometriosis
5. Endometrial carcinoma.
6. Threatened abortion and habitual abortion, if there's deficiency of progestin.
7. For postponement of menses: Norethisterone 5 mg for 3 days, started 3 days before the anticipated date. Bleeding occurs after 2-3 days of withdrawal. Combine oral pill users can continue their oral pills.



## Adverse Effects

1. Breast engorgement
2. Rise in body temperature

3. Mood swings → occur with higher doses.
4. Irregular bleeding or amenorrhoea can occur if a progestin is given continuously.
5. Long-term use of progestin in HRT → increase risk of breast cancer.
6. Blood sugar rise and diabetes precipitated by long-term use of potent agents like levonorgestrel.
7. Given in early pregnancy, progestins can cause masculinization of female foetus and other congenital abnormalities.

## ANTIPROGESTIN

### Classification

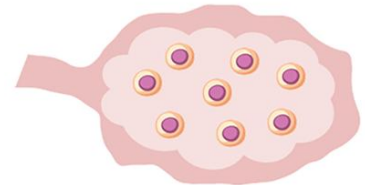
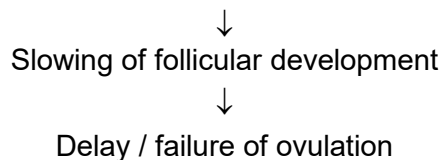
- Mifepristone

### MOA

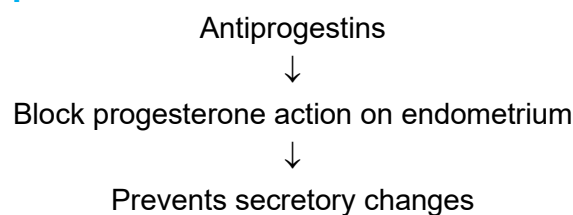
- Given during the follicular phase
- Given during the luteal phase
- Given later in the cycle
- Antiglucocorticoid action

### Given during the follicular phase

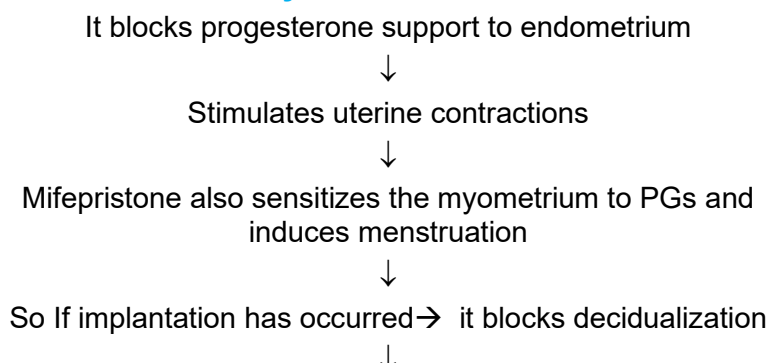
Its antiprogestin action results in attenuation of the midcycle Gn surge from pituitary



### Given during the luteal phase



### Given later in the cycle





Conceptus is dislodged



Abortion

## Antiglucocorticoid action

- It is also antagonist at corticosteroids receptor.

## Uses

1. Termination of pregnancy up to 7 weeks
2. Cervical ripenin
3. Postcoital contraceptive
4. Once-a-month contraceptive
5. Induction of labour
6. Cushing's syndrome

### 1. Termination of pregnancy up to 7 weeks

- 600 mg as single oral dose causes complete followed 48 hours later by a single 400 mg oral dose of misoprostol.
- This achieves >90% success rate
- Accepted nonsurgical method of early first trimester abortion.



### 2. Cervical ripenin

- Cervical ripening 24–30 hours before attempting surgical abortion or induction of labour → mifepristone 600 mg results in softening of cervix → procedure is facilitated.



### 3. Postcoital contraceptive

- Mifepristone 600 mg given within 72 hr of intercourse interferes with implantation and is a highly effective method of emergency contraception.



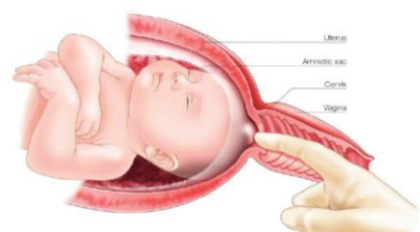
### 4. Once-a-month contraceptive

- A single 200 mg dose of mifepristone given 2 days after midcycle each month prevents conception on most occasions.



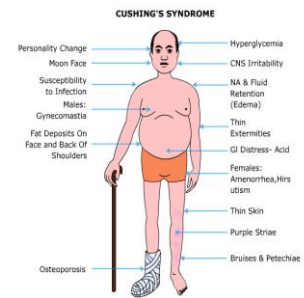
### 5. Induction of labour

- By blocking the relaxant action of progesterone on uterus of late pregnancy, mifepristone can promote labour.
- It may be tried in cases with intrauterine foetal death



## 6. Cushing's syndrome

- Mifepristone has palliative effect due to glucocorticoid receptor blocking property.
- May be used for inoperable cases



### Adverse effects

1. Long lasting vaginal bleeding
2. Abdominal pain, uterine cramps



## HARMONAL CONTRACEPTIVES

### Fertility

- By fertility is meant the actual bearing of children
- A woman's reproductive period is roughly from 15 to 45 years - a period of 30 years.



### Contraception

- Methods used to prevent pregnancy



### Contraceptive Methods

#### Spacing methods

1. Natural family planning methods
2. Barrier methods (condom, diaphragm, vaginal sponge)
3. Intrauterine contraceptive device (IUCD)
4. Hormonal contraceptive (OCPs, injectable)

#### Terminal methods

1. Male sterilization (vasectomy)
2. Female sterilization (tubectomy)

### An ideal contraceptive

Must have →

- Simplicity
- Acceptability

- Reversibility
- Lack of toxicity

## HORMONAL CONTRACEPTIVES

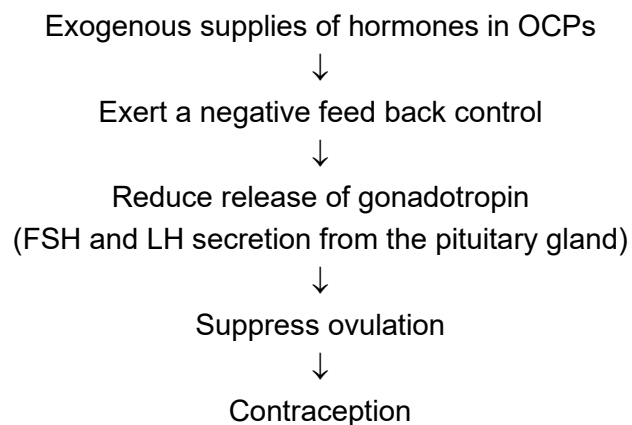
| Hormonal Contraceptives |  |
|-------------------------|--|
| Introduction            |  |
| MOA                     |  |
| Classification          |  |
| Uses/ Benifits          |  |
| Adverse effects         |  |
| Contraindications       |  |

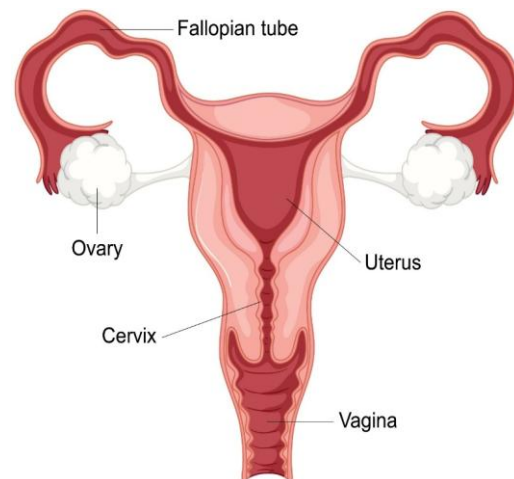
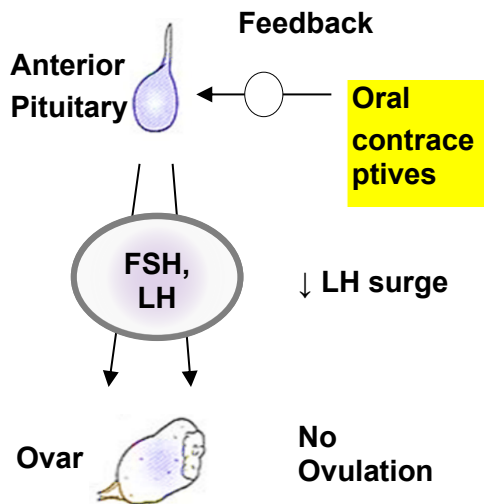
### Introduction

- These are hormonal preparations used for reversal or suppression of pregnancy.
- They contain different proportions of estrogens and/or progesterones.



### MOA





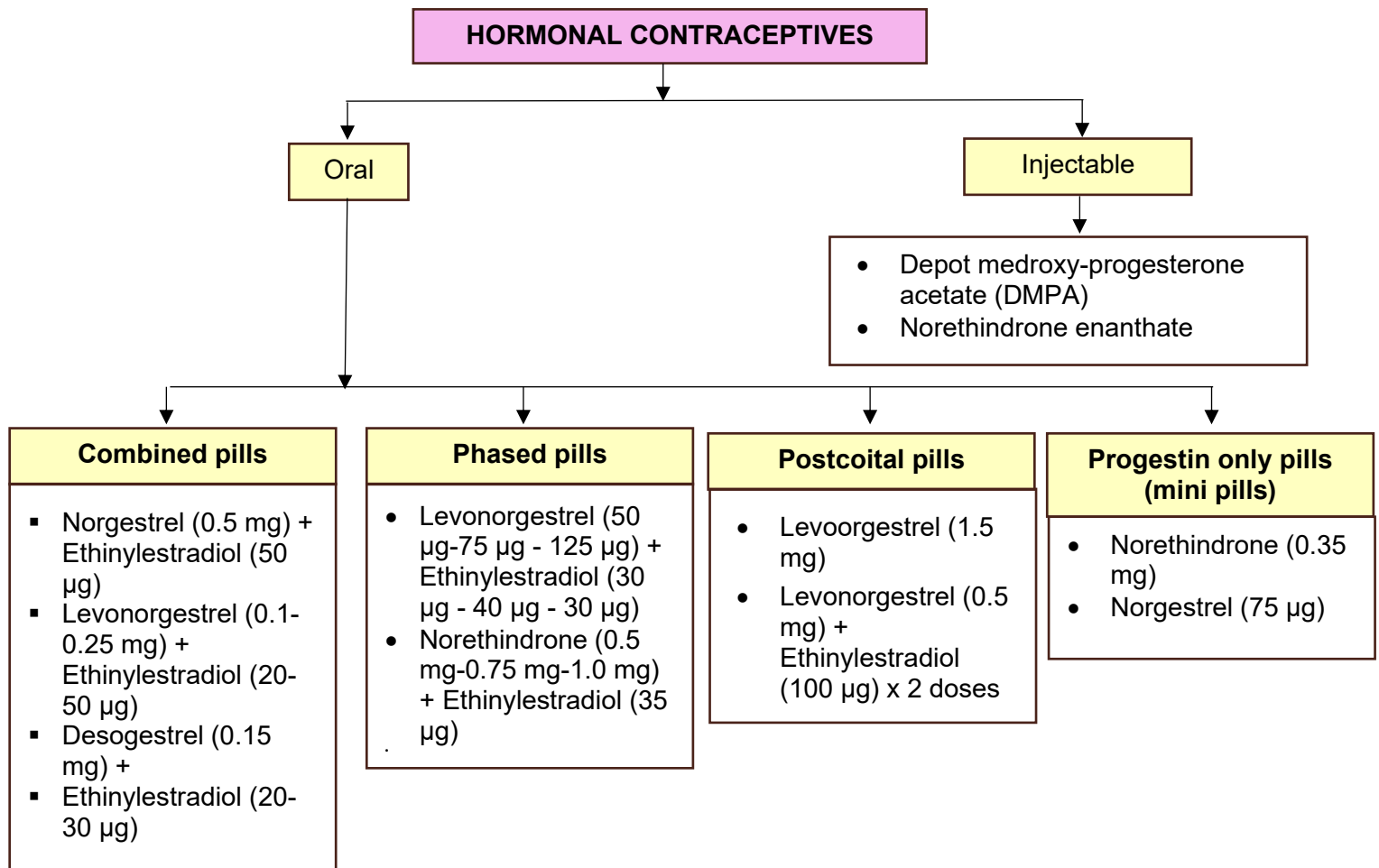
## Other MOA

Progestins in OCPs  
 ↓  
 Convert cervical mucus thick and viscid  
 ↓  
 Sperms are not able to penetrate it  
 ↓  
 Contraception

Estrogen and Progestins in OCPs  
 ↓  
 Alter maturation of endometrium  
 ↓  
 Making it unsuitable for implantation of fertilized ovum  
 ↓  
 Contraception

| Prevention of ovulation                                                                                                                                                                                                                                                                                          | Prevention of fertilization                                                                                          | Interference with Implantation                                                                                                                                                                                                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Progestin reduces frequency of LH secretory pulses, while estrogen primarily reduces FSH secretion.</li> <li>Both synergise each other to inhibit midcycle LH surge.</li> <li>As a result, follicles fail to develop and rupture and ovulation does not occur.</li> </ul> | <ul style="list-style-type: none"> <li>Thick cervical mucus, hostile to sperms may inhibit fertilization.</li> </ul> | <ul style="list-style-type: none"> <li>Endometrium is rendered either hyperproliferative, hypersecretory, or atrophic and out of phase with fertilization and not suitable for nidation. Thus, even if ovulation and fertilization occur, implantation does not occur normally.</li> </ul> |

## Classification



## ORAL CONTRACEPTIVES

- Agents used orally to prevent undesired conception.



### 1. Combined pills (classical or balanced)

- Combination of Estrogen and Progestin.
  - **Estrogen** → Ethinyl estradiol or Mestranol
  - **Progestin** → Norethisterone, Levonorgestrel, Norgestrel, Desogestrel
- Combination of a progestin →
  - Reduces risk of endometrial carcinoma
  - Continuous progestin suppresses the proliferative growth so menses are lighter and regular.

## Preparation

- Mala N** → Ethinyl estradiol 30 µg (0.03 mg) + Norgestrel 0.15 mg →

2. **Mala D** → Ethinyl estradiol 30 pg (0.03 mg) + Desogestrel 0.15 mg →
3. **New low dose OCP (femilon)** → Ethinyl estradiol 20 pg (0.02 mg) + Desogestrel 0.15 mg



|              | MALA – N                    | MALA - D                    | New low dose OCP (femilon)        |
|--------------|-----------------------------|-----------------------------|-----------------------------------|
| Estrogen     | Ethinyl estradiol (0.03 mg) | Ethinyl estradiol (0.03 mg) | Ethinyl estradiol 20 pg (0.02 mg) |
| Progesterone | Norgestrel (0.15 mg)        | Desogestrel (0.15 mg)       | Desogestrel 0.15 mg               |

## Schedule

- One tablet (containing estrogen and progesterone) is taken daily for 21 days starting on 5th day of menstruation.
- Next course is started 7-8 days after last pill or 5 days after starting of menses.
- Pill is to be taken regularly.
- If one dose is missed, double the next dose to minimize break through bleeding and stay on the schedule. If the dose is missed for 2-3 days, stop it and use other methods of contraception.
- Start next course from 5th day of menses.



## 2. Phased regimens

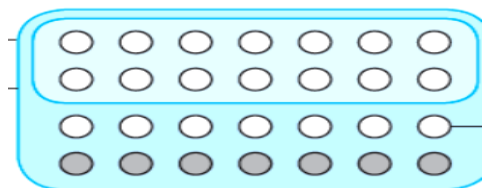
- Estrogen dose → kept constant
- Amount of progestin → low in first phase and progressively higher in second and third phases.
  - **First half of cycle:** Progestin/estrogen ratio is lower to allow endometrium to thicken
  - **Second half of cycle:** Progestin/estrogen ratio is higher to allow normal shedding of lining of the uterus

## 1. Biphasic Pills

- Day 1-10** → Ethinyl estradiol 35 mg + Norethindrone 0.5 mg
- Day 11-21** → Ethinyl estradiol 35 mg + Norethindrone 1 mg

## 2. Triphasic pills

- Day 1-7** → Ethinyl estradiol 35 mg + Norethindrone 0.5 mg
- Day 8-14** → Ethinyl estradiol 35 mg + Norethindrone 0.75 mg
- Day 15-21** → Ethinyl estradiol 35 mg + Norethindrone 1 mg





**Remember**

- The last 7 pills (in all types of OCPs with 28 tablets) do not contain any hormone but have 60 mg of elemental iron.

**3. Minipill (Progestin only pill)**

- A low dose progestin pill is taken daily without any gap.
- They eliminate estrogen side effects.
- But they are having low efficacy (97-98%)
- Risk of irregular cycles.
- Suitable → during lactation and for patients with contraindication to estrogens.
- Preparations → Norethindrone 0.35 mg or Norgestrel 75 mg

**4. Postcoital (emergency) contraception**

- Post-coital contraception is advocated as an emergency method; for example, after unprotected intercourse, rape or contraceptive failure
- Failure rate for post-coital contraception → < 1 %

**Method of choice for emergency contraception**

- **In India** → Levonorgestrel 0.75 mg tablet is approved for emergency contraception
- **Schedule** → one tablet of 0.75 mg within 72 hours of unprotected sex and the 2nd tablet after 12 hours of 1st dose

**Alternative methods**

- 2 oral contraceptive pills containing 50 mcg of ethinyl estradiol within 72 hours after intercourse, and the same dose after 12 hours
- 4 oral contraceptive pills containing 30 or 35 mcg of ethinyl estradiol within 72 hours and 4 tablets after 12 hours
- Yuzpe method → Levonorgestrel 0.5 mg + ethinyl estradiol 0.1 mg → within 72 hours of unprotected intercourse and repeated after 12 hours
- Mifepristone 10 mg once within 72 hours

**INJECTABLE HORMONES / DEPOT FORMULATIONS**

- Agents used injectable route to prevent undesired conception.

**DMPA (Depot Medroxy Progesterone Acetate)**

**Introduction** → A Progestogen only Injectable contraceptive (Depot formulation)

**Dose** → 150 mg i/m every 3 months

**Advantages** →

- Highly effective
- Long lasting and reversible
- Does not affect lactation

#### Side effects→

- Disruptions of normal menstrual cycles
- Amenorrhoea

## NET-EN: Norethisterone Enanthate

**Introduction** → Progestogen only Injectable contraceptive (Depot formulation)

**Dose** → 200 mg i/m every 2 months

#### Advantages→

- Highly effective
- Long lasting and reversible
- Does not affect lactation

#### Side effects→

- Disruptions of normal menstrual cycles
- Amenorrhoea

## Uses / Benefits of oral contraceptives

1. Reduction in menstrual blood flow and its irregularity as well as a reduce potential for anemia.
2. Relief from dysmenorrhea and premenstrual tension.
3. Reduced risk of ovarian cyst and pelvic inflammatory disease (PID).
4. Reduced risk of uterine and ovarian carcinoma.



## Mnemonic

### Other BENEFITS

OCPs decrease the risk of:

|       |   |                                                |
|-------|---|------------------------------------------------|
| Other | - | Ovarian cyst                                   |
| B     | - | Benign breast disease                          |
| E     | - | Ectopic pregnancy                              |
| N     | - | Neoplasia (Ovarian, Endometrial, Colon cancer) |
| E     | - | Endometriosis                                  |
| F     | - | Fibroid                                        |
| I     | - | Iron deficiency anemia                         |
| T     | - | Tension (Pre-menstrual tension syndrome)       |
| S     | - | Skeletal (RA and Osteoporosis)                 |

## Adverse effects

- A. Effects due to estrogen component
- B. Effects due to progestin
- C. Effects due to both estrogen as well as progestin
- D. Adverse effects with long-term use or high doses



### A. Effects due to estrogen component

1. Nausea and vomiting → usually subside with continuous use and risk is minimized by giving with milk at bedtime and starting with low dose.
2. Dizziness and headache.
3. Fluid retention.
4. Cervical mucorrhea.
5. Chloasma → increase pigmentation of face and forehead



### B. Effects due to progestin

1. Acne, Oily skin
2. Weight gain (acyclic due to increase appetite; with estrogen there's cyclic weight gain due to fluid retention.)
3. Irritation, depression
4. Decrease libido
5. Amenorrhea



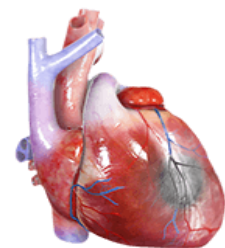
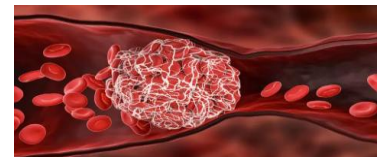
### C. Effects due to both estrogen as well as progestin

1. Breast tenderness and engorgement
2. Break through bleeding → inter-menstrual bleeding → it is due to insufficient dose that is not able to maintain the endometrium.

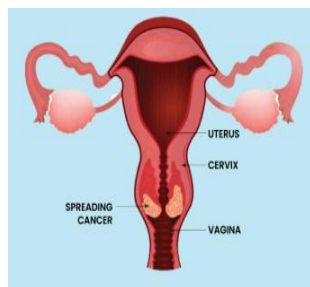
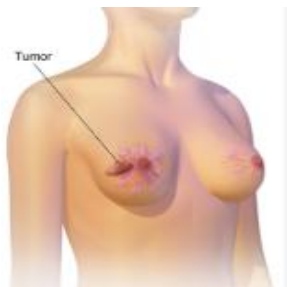


### D. Adverse effects with long-term use or high doses

1. Hypertension → due to salt and water retention.
2. Thromboembolism → due to enhancement in platelet aggregation and clotting factor and therefore they are discontinued for a month before and two months after major elective surgery.
3. Increase risk of myocardial infarction
4. Carcinogenicity → increase risk of carcinoma breast and cervix.
5. Carbohydrate intolerance → it may unmask latent diabetes.
6. Gall stones → due to increase cholesterol in bile. (Estrogens stimulate liver to remove more cholesterol from blood and divert it to bile. It disturbs the ratio of cholesterol to bile salts and thereby cholesterol solubility is reduced and so : gall stone formation occurs.).



## 7. Aggravation of migraine, epilepsy and asthma.



## Mnemonic

### CONTRACEPTIVES:

Cholestatic jaundice  
 Oedema (corneal)  
 Nasal congestion  
 Thyroid dysfunction  
 Raised BP  
 Acne/Alopecia/ Anaemia  
 Cerebrovascular disease  
 Elevated blood sugar  
 Porphyria/ Pigmentation/ Pancreatitis  
 Thromboembolism  
 Intracranial hypertension  
 Vomiting (progesterone only)  
 Erythema nodosum/ Extrapyrimal effects  
 Sensitivity to light

## Contraindications

- Absolute Contraindications
- Relative Contraindications

## Absolute Contraindications

|         |                                                                                                             |
|---------|-------------------------------------------------------------------------------------------------------------|
| Banks   | Known or suspected Breast cancer                                                                            |
| Have    | Hypertriglyceridemia/ Hypercholesterolemia                                                                  |
| Various | Vaginal bleeding (Undiagnosed abnormal)                                                                     |
| Schemes | Smokers over age of 35 years                                                                                |
| To      | Thrombophlebitis/Thromboembolic disorders, (present H/O, past H/O, family H/O) Cerebral and Cardiac disease |
| Provide | Pregnancy                                                                                                   |
| Home    | Hypertension (Moderate to severe) (> 160/110 mm Hg)                                                         |
| Loans   | Impaired Liver function/infective hepatitis                                                                 |
| During  | Diabetes mellitus with vascular disease                                                                     |
| May     | Migraine with aura                                                                                          |

## Relative Contraindications

- Migraine without Aura
- Diabetes mellitus/Gestational diabetes
- Hypertension (mild)

- Smoking
- Uterine leiomyoma
- Elective surgery (OCP should be stopped 4 weeks before any scheduled surgery)
- Seizure disorders
- Obstructive jaundice in pregnancy
- Sickle cell disease
- Gall bladder disease
- SLE
- Mitral valve prolapse
- Hyperlipidemia
- Hepatic disease.

## CENTCHROMAN (SAHELI)

### Introduction

- Synthetic NON-STEROIDAL oral contraceptive
- **Brand name:** Saheli
- **Developed by:** Central Drug Research Institute (CDRI), Lucknow, India
- **Chemical in Centchroman:** Ormeloxifene



### MOA

- **Selective estrogen receptor modulators (SERMs)** → a class of medication which acts on the estrogen receptor

### Dosage & frequency

- 1 tablet (30 mg) twice a week X 3 months, then 1 tablet per week

### Uses

1. As a contraceptive
2. Treatment of dysfunctional uterine bleeding
3. Centchroman has also been found effective as an anti-breast cancer agent

### Contraindications

1. PCOD (Stein Leventhal Syndrome)
2. Cervical hyperplasia
3. Recent history of jaundice
4. Severe allergic disease

### Remember

- Centchroman is also known as 'once-a-week pill'
- Centchroman is the 'only anti-implantation agent approved for clinical use' globally
- Centchroman has also been found effective as an anti-breast cancer agent

## MALE CONTRACEPTIVE

### Introduction

- Only way to suppress male fertility by drugs is to inhibit spermatogenesis.

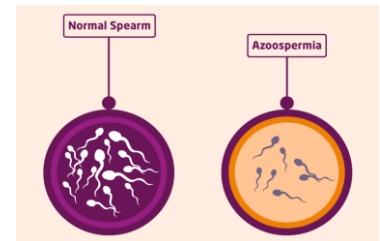


### Drugs

- Gossypol** →
  - It is a nonsteroidal compound
  - Obtained from cotton seed; has been studied in China.
  - It is effective orally
  - Causes suppression of spermatogenesis and reduces sperm motility—infertility develops after a couple of months.

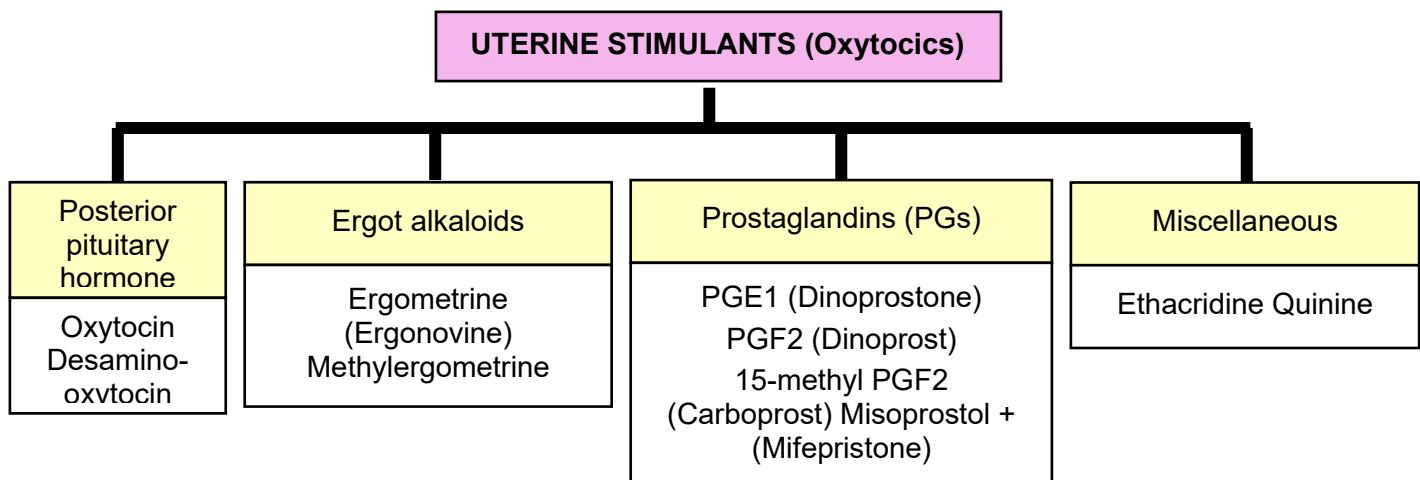
### Adverse effects

- It is effective in producing azoospermia or severe oligospermia, but as many as 10 % of men may be permanently azoospermic after taking it for 6 months.
- Gossypol could be toxic



## UTERINE STIMULANTS (OXYTOCICS)

### Classification



| Uterine Stimulants (Oxytocics) |                             |                 |
|--------------------------------|-----------------------------|-----------------|
|                                | Posterior pituitary hormone | Ergot alkaloids |
| Introduction                   |                             |                 |
| Drugs                          |                             |                 |
| Pharmacological Actions        |                             |                 |
| Uses                           |                             |                 |
| Adverse effects                |                             |                 |
| Contraindications              |                             |                 |

## POSTERIOR PITUITARY HORMONE

### Introduction

- Posterior pituitary hormone

### Drugs

- Oxytocin
- Desamino-oxytocin

### Oxytocin

- Oxytocin → prototype
- Oxytocin is a peptide hormone released from posterior pituitary.
- It stimulates smooth muscles of uterus and mammary gland.
- Oxytocin induced contraction resembles in amplitude, frequency and duration to the contractions seen during labor.
- It is not the concentration, but the sensitivity to oxytocin that is increased as the pregnancy progresses.
- In absence of oxytocin prolonged labor had been observed and there is absence of milk ejection reflex.



### Pharmacological actions

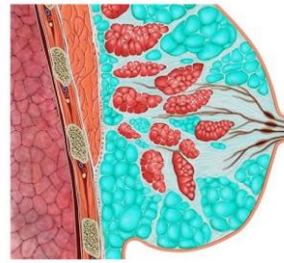
1. Action on uterus
2. Action on mammary glands

#### 1. Action on uterus

- It stimulates both frequency as well as force of contraction.
- This effect is highly dependent on presence of estrogens.
- Response increases as pregnancy progresses.

## 2. Action on mammary glands

- Contraction of myoepithelium of mammary glands, which forces milk from alveolar channels to large sinuses where it is available to suckling infants (milk ejection reflex).
- It does not improve production of milk, only aids in ejection of milk.

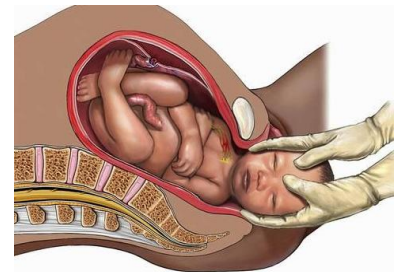


## Uses

1. Induction of labor → When continuation of pregnancy is risky for mother or fetus for example with premature membrane rupture, isoimmunization, IUGR, and placental insufficiency (diabetes, preeclampsia, eclampsia).
2. Abortion
3. Uterine inertia
4. Post partum hemorrhage (PPH)
5. To relieve breast engorgement → But not useful for inadequate milk production since there's no galactopoietic effect.

## Risk associated with induction of labor

- Premature baby
- Uterine rupture
- Fetal asphyxia secondary to over stimulation.



## Precautions taken before oxytocin

- Before medical induction → it is necessary to assess the fetal maturity and to rule out fetopelvic disproportion.
- Fetal maturity is assessed by assessment of lungs maturity, which is judged by Lecithin - sphingomyelin ratio in amniotic fluid that should be more than two.

## Adverse effects

1. Over stimulation of uterus may lead to uterine rupture and fetal asphyxia → monitoring of timing and length of contraction is necessary.
2. Fall in BP
3. Water intoxication
4. Fetal dysarrhythmias.

## Contraindications to medical induction of labor

- Fetal immaturity
- Fetopelvic disproportion
- Abnormal fetal position
- Fetal distress
- Placental abnormality
- Previous uterine surgery



# ERGOT ALKALOIDS

## Introduction

- Only amine ergot alkaloid ergometrine (ergonovine) and its derivative methylergometrine are used in obstetrics

## Drugs

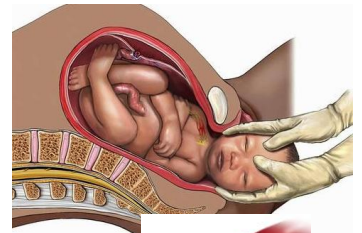
- Ergometrine (Ergonovine)
- Methylergometrine

## Pharmacological actions

- Uterus
- CVS

### 1. Uterus

- Increase force, frequency and duration of uterine contractions.
- Gravid uterus is more sensitive, especially at term and in early puerperium.



### 2. CVS

- Ergometrine and methylergometrine are much weaker vasoconstrictors than ergotamine and have low propensity to cause endothelial damage.
- Though they can raise BP, this is not significant at doses used in obstetrics.



## Uses

- To control and prevent postpartum haemorrhage (PPH) →
  - Only in those expected to bleed more, e.g. grand multipara, uterine inertia.
  - Multiple pregnancy should be excluded before injecting.



## Adverse effects

- Nausea
- Vomiting
- Rise in BP
- Decrease milk secretion if higher doses are used for many days postpartum → due to inhibition of prolactin release (dopaminergic action).

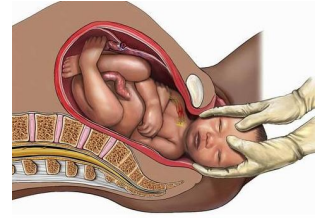
## Differences between Oxytocin and Ergotamine

| Character          | Oxytocin                                    | Ergometrine                                                             |
|--------------------|---------------------------------------------|-------------------------------------------------------------------------|
| Contractions       | Resembles normal physiological contractions | Tetanic contraction; doesn't resemble normal physiological contractions |
| Uses               | To induce & augment labor. PPH              | Only in PPH                                                             |
| Onset and Duration | Rapid onset<br>Shorter duration of action   | Moderate onset<br>Long duration of action                               |

## UTERINE RELAXANTS (TOCOLYTICS)

### Introduction

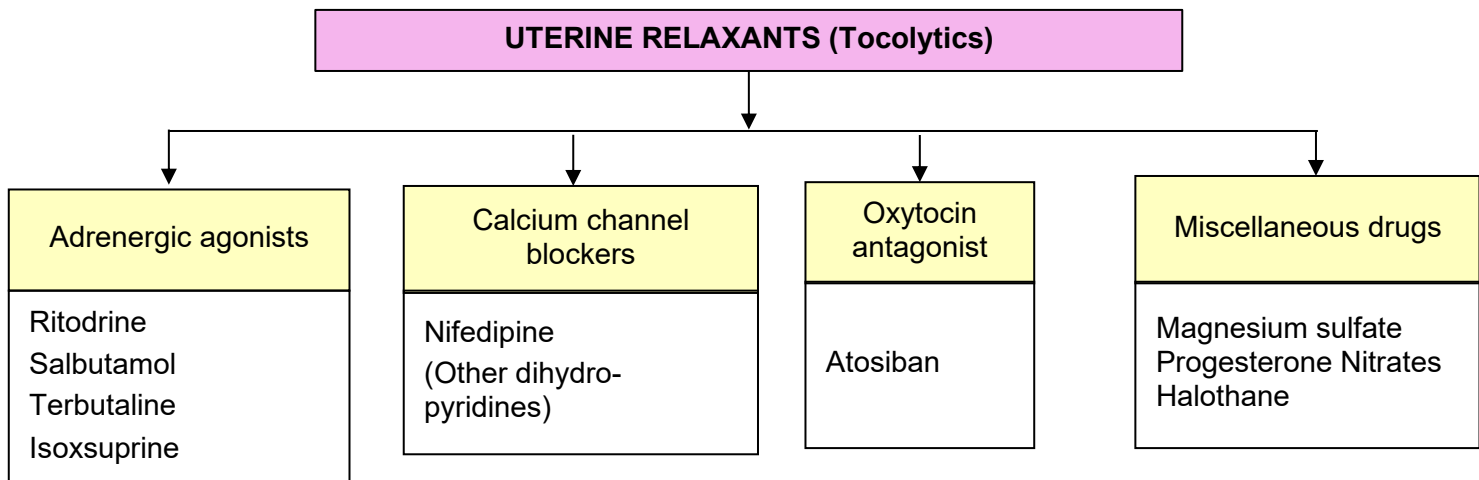
Tocolytics  
↓  
Relax uterine smooth muscle  
↓  
Used to delay labor to prevent premature delivery



### Conditions

1. Cervical dilatation is not more than 4 cm.
2. Membrane is not ruptured.
3. There is no placental separation.
4. There is no fetal distress.
5. There's no severe eclampsia or preeclampsia.

### Classification



| Uterine Relaxants (Tocolytics) |                     |                          |
|--------------------------------|---------------------|--------------------------|
|                                | Adrenergic agonists | Calcium channel blockers |
| Introduction                   |                     |                          |
| Drugs                          |                     |                          |
| Uses                           |                     |                          |
| Adverse effects                |                     |                          |



## ADRENERGIC AGONISTS

### Introduction

- $\beta_2$  selective agonist
- More prominent uterine relaxant action
- Approved to suppress premature labour
- Treatment beyond 48 hours is not recommended, since risk to mother increases and benefit is uncertain.

### Drugs

- Ritodrine
- Salbutamol
- Terbutaline
- Isoxsuprine

### Uses

- Delivery can be postponed in about 70% cases by few hours to few weeks.



### Adverse effects

- **CVS** → hypotension, tachycardia, arrhythmia
- **Metabolic** → hyperglycaemia, hyperinsulinaemia, hypokalaemia
- **Foetal pulmonary edema**
- **Neonate** → develop hypoglycaemia and ileus.

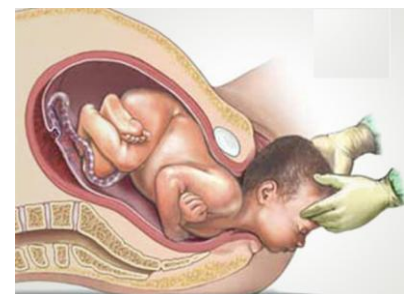
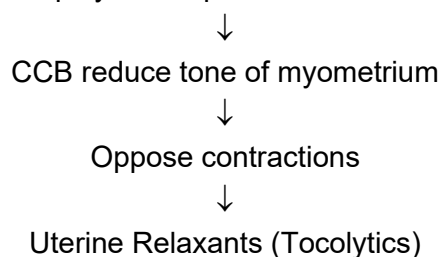
### Contraindications

- It should not be used if mother is →
  - Diabetic
  - Having heart disease
  - Receiving  $\beta$  blockers or steroids.

## ADRENERGIC AGONISTS

### Introduction

Influx of  $\text{Ca}^{2+}$  ions plays an important role in uterine contractions



## Drugs

- Nifedipine
- Other dihydro-pyridines

## Uses

- Postpone labour if used early enough.

## Adverse effects

- **CVS** → Tachycardia and hypotension
- **Reduced placental perfusion** → foetal hypoxia

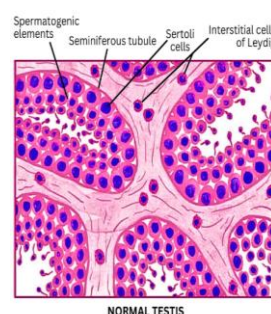
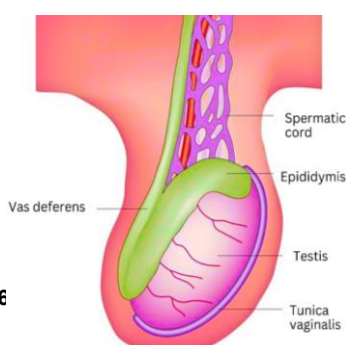
# ANDROGENS AND RELATED DRUGS

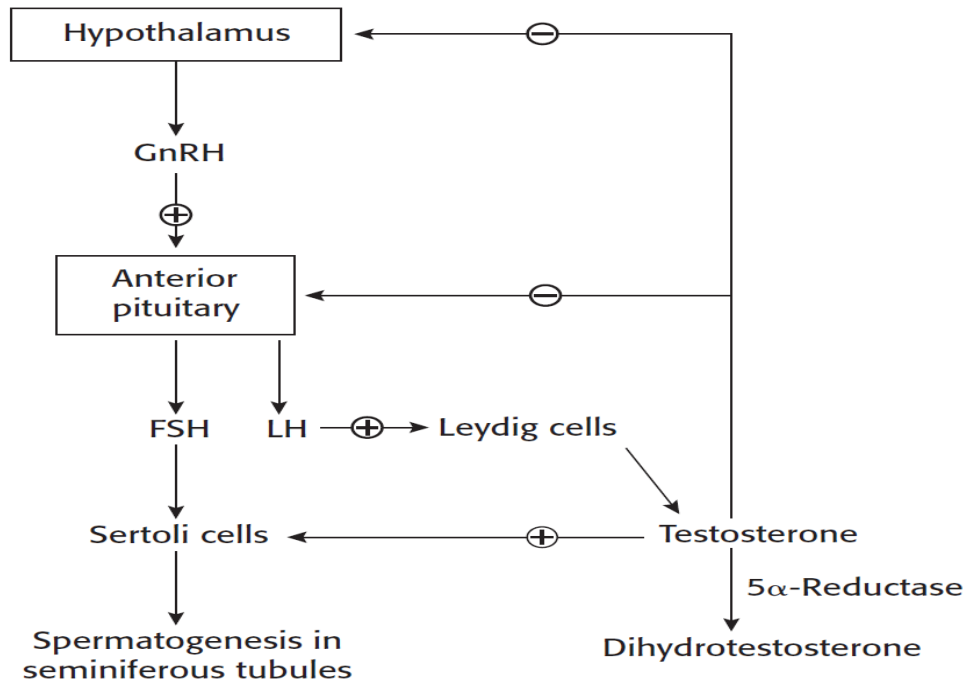
| Androgens and Related Drugs |           |               |
|-----------------------------|-----------|---------------|
|                             | Androgens | AntiAndrogens |
| Introduction                |           |               |
| Classification              |           |               |
| MOA                         |           |               |
| Actions                     |           |               |
| Uses                        |           |               |
| Adverse effects             |           |               |

# ANDROGENS

## Introduction

- Testosterone → main androgen in men.
- It is synthesized by Leydig cells (interstitial cells) of testes under the influence of interstitial cell-stimulating hormone ICSH (LH) of anterior pituitary.
- FSH is responsible for spermatogenesis.





## Classification

### Natural androgens →

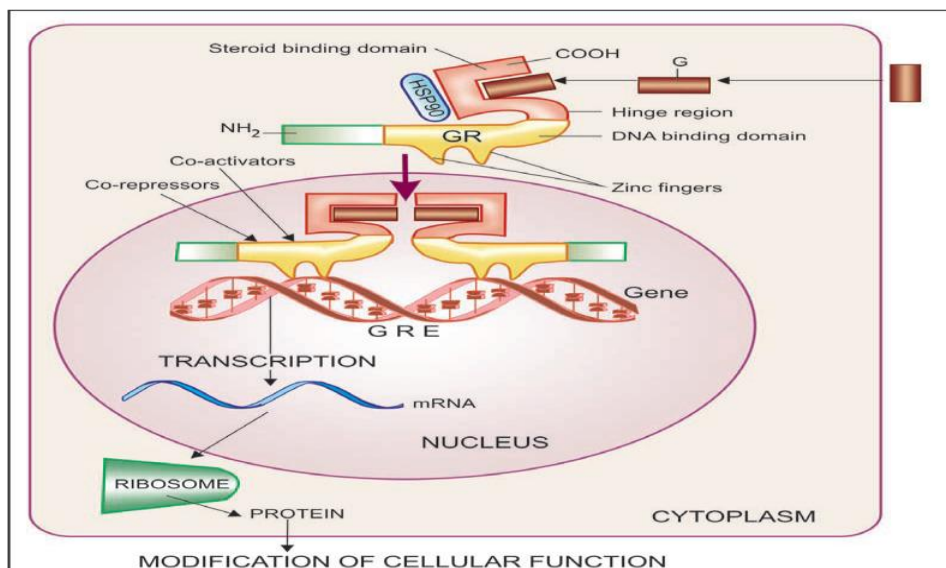
- Testosterone
- Dihydrotestosterone
- Dehydroepiandrosterone
- Androstenedione

### Synthetic androgens →

- Methyltestosterone
- Fluoxymesterone
- Esters of testosterone in form of cypionate (i.m.), propionate (i.m.), enanthate (i.m.) and undecanoate (oral, i.m.)

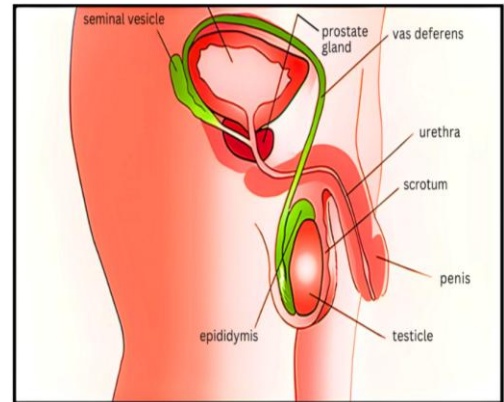
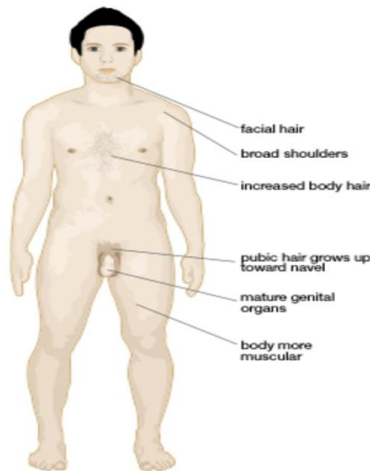
## MOA

- Like other steroidal hormones.



## Actions of Testosterone

1. Responsible for the development of male secondary sexual characteristics
2. Maturation of reproductive organs (androgenic action)
3. Increase in mass and strength of skeletal muscle (anabolic action)
4. Erythropoiesis



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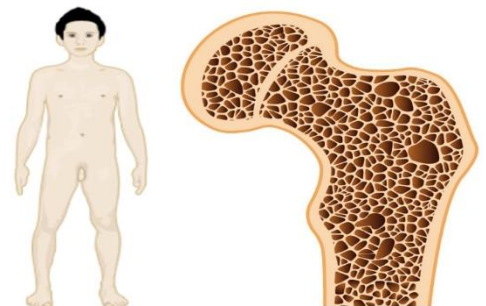
## Pharmacokinetics

- Testosterone is extensively metabolized in liver after oral administration → given by intramuscular (i.m.) route.



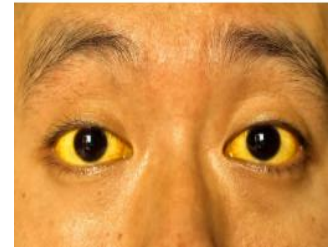
## Uses

1. Androgens are mainly used in replacement therapy in males with hypogonadism due to testicular failure, hypopituitarism
2. Osteoporosis in elderly males.



## Adverse Effects

1. **In females** → androgens cause virilization → hirsutism, menstrual irregularities, breast atrophy, acne and deepening of voice.
2. **In children** → impairment of growth due to premature closure of epiphyses.
3. **Sodium and water retention** → oedema.
4. **Cholestatic jaundice** → mainly with methyltestosterone.



## Contraindications

1. **Pregnancy** → Androgens should not be used during pregnancy because of fear of virilization of female fetus.
2. Carcinoma of prostate
3. Breast cancer in men.

## ANTIANDROGENS

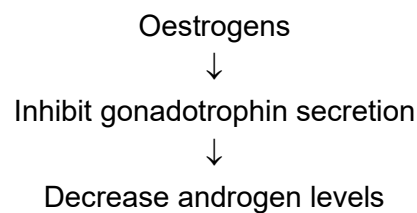
### Classification

1. **Physiological antagonist:** Oestrogens.
2. **Testosterone synthesis inhibitors:** Ketoconazole, spironolactone.
3. **Androgen-receptor antagonists:** Flutamide, bicalutamide, cyproterone, spironolactone.
4. **5 $\alpha$ -reductase inhibitors:** Finasteride, dutasteride.

### MOA, Uses, Adverse effects

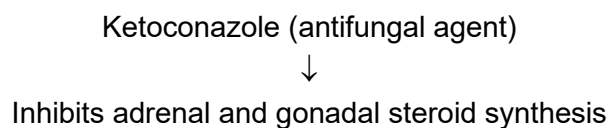
#### Oestrogens

##### MOA →



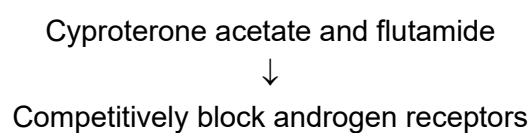
#### Ketoconazole

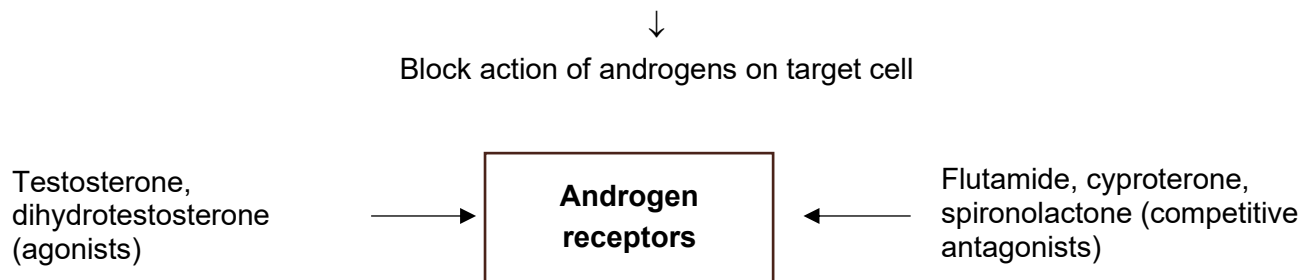
##### MOA →



#### Cyproterone acetate and flutamide

##### MOA →





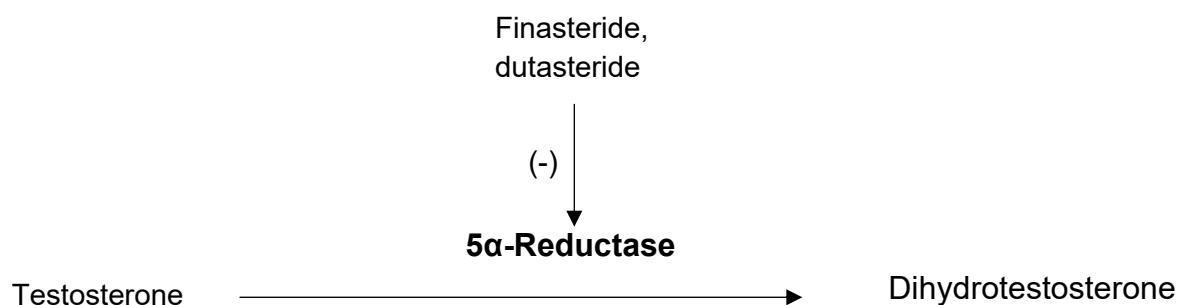
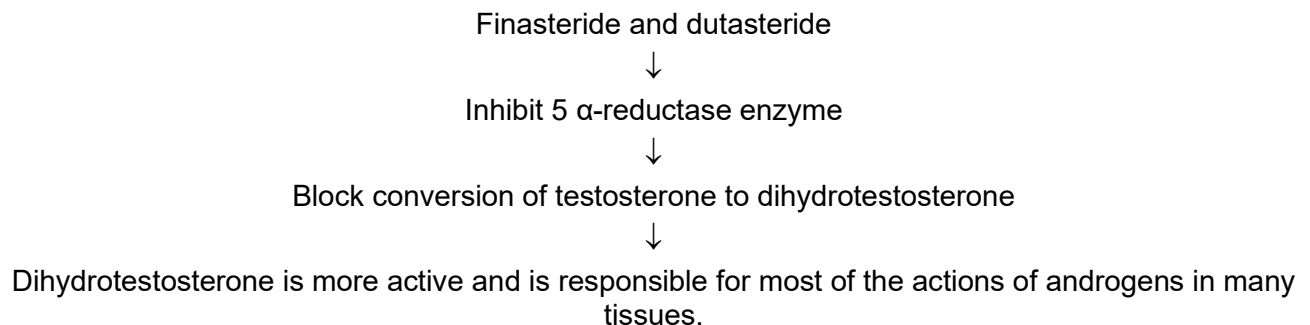
## Uses

### Adverse effects

- Impotence
- Hot flushes
- Gynaecomastia
- Hepatic damage
- Decreased spermatogenesis

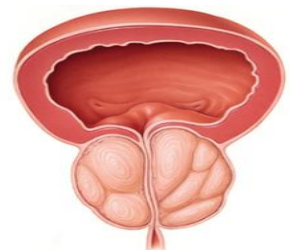
## Finasteride and dutasteride

### MOA→



## Uses

- Decrease the size of prostate and improve urinary flow rate.
  - Less effective when compared to surgery and α 1-blockers in treatment of BPH.
  - Combined use of finasteride and α 1-adrenergic blockers results in better effect.
  - Prolonged treatment is necessary to sustain benefit.



## Adverse effects

- Impotency
- Decrease libido
- Skin rashes